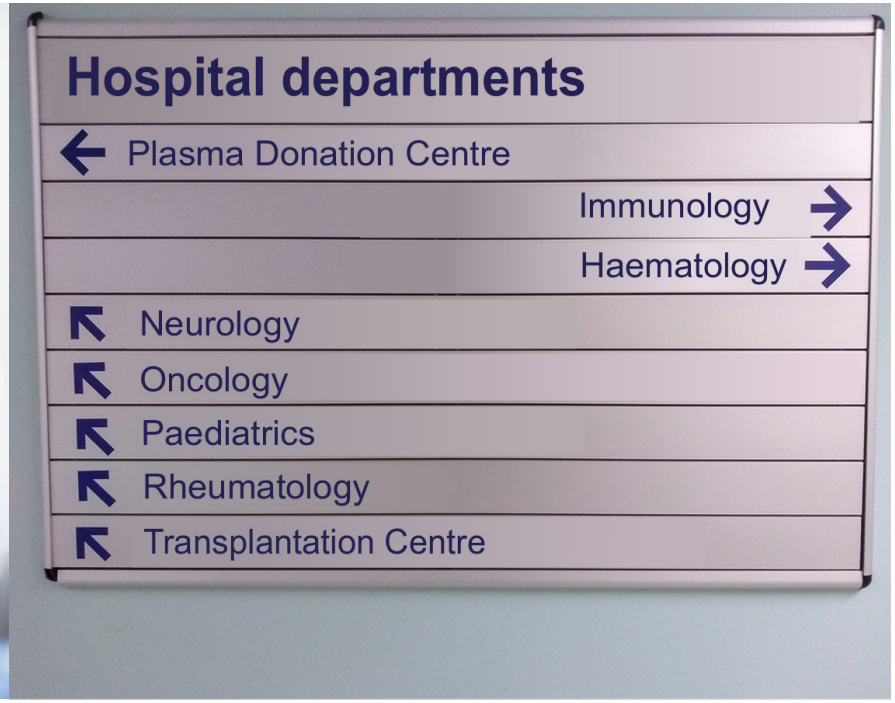
KCE REPORT 327

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

POLYVALENT IMMUNOGLOBULINS – PART 1: A RAPID REVIEW



KCE REPORT 327
HEALTH TECHNOLOGY ASSESSMENT

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POLYVALENT IMMUNOGLOBULINS – PART 1: A RAPID REVIEW

JOLYCE BOURGEOIS, NICOLAS FAIRON, LORENA SAN MIGUEL

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COLOPHON

Title:	Polyvalent immunoglobulins – Part 1: A rapid review
Authors:	Jolyce Bourgeois (KCE), Nicolas Fairon (KCE), Lorena San Miguel (KCE)
Information specialist:	Nicolas Fairon (KCE)
Project facilitator:	Els Van Bruystegem (KCE)
Senior supervisor:	Leen Verleye (KCE)
Reviewers:	Dominique Roberfroid (KCE), Charline Maertens (KCE)
External experts:	Marc Van De Casteele (RIZIV – INAMI - Rijksinstituut voor ziekte- en invaliditeitsverzekering – Institut national d'assurance maladie-invalidité), Martine De Witte (RIZIV-INAMI), Joël Daems, (RIZIV – INAMI), Laure Geslin ((FAGG – AFMPS – Federaal agentschap voor geneesmiddelen en gezondheidsproducten – Agence fédérale des medicaments et des produits de santé), Margaretha Haelterman (FOD Volksgezondheid – SPF Santé Publique), Marlène Jagut (Sciensano), Nicolas Mavroudakis (ULB – Université libre de Bruxelles, Hôpital Erasme), Rik Schrijvers (UZ Leuven), Peter Van den Bergh (Cliniques universitaires Saint-Luc, Bruxelles), Jeroen Van der Hilst (Jessa ziekenhuis, Uhasselt)
International experts:	Jo Cameron (Immunoglobulin Governance National Blood Authority, Australia), Gaelle Guyader (National Agency for the Safety of Medicines and Health Products, France), Brian O'Rourke (CADTH – Canadian Agency for Drugs and Technologies in Health), Brent Fraser (CADTH – Canadian Agency for Drugs and Technologies in Health), Sylvain Grenier (Plasma Protein Products Formulary Program with the Canadian Blood Services), Rob Coster (National Programme of Care Manager-Blood and Infection, NHS England)
External validators:	Michel Delforge (Hematology, Universitair ziekenhuis Leuven), Sara Khangura (CADTH – Canadian Agency for Drugs and Technologies in Health), Wim Penninckx (FAGG – AFMPS – Federaal agentschap voor geneesmiddelen en gezondheidsproducten – Agence fédérale des medicaments et des produits de santé)
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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AEs:	Adverse Events
AMR	Antibody Mediated Rejection
ANSM	L'Agence nationale de sécurité du médicament et des produits de santé (in France)
BPIDG	Belgian Primary Immunodeficiency Group
CAAs	Coronary Artery Abnormalities
CCA	Cost Consequences Analysis
CEA:	Cost effectiveness analysis
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CLL	Chronic Lymphocytic leukaemia
CMA	Cost Minimisation Analysis
CMV	Cytomegalovirus
CUA	Cost Utility Analysis
DAS	Disease Activity Score
DDD	Defined Daily Dose
EUnetHTA	European Network for health Technology Assessment
FAMHP-FAGG	Federal Agency for Medicines and Health products
GBS	Guillain-Barre Syndrome
GVHD:	Graft versus host disease
HTA	HTA: Health Technology Assessment
ICH	Intracranial Haemorrhage
Ig	Immunoglobulin
INAHTA	International Network of Agencies for Health Technology Assessment
ITP	Immune thrombocytopenia purpura

ITT	Intention to Treat
IUPT	Intrauterine Platelet Transfusions
IVIg	Intravenous Immunoglobulin
KD	Kawasaki Disease
LoS	Length of Stay
MA	Meta-Analysis
MFAs	Myocardial Function Abnormalities
MG	Myasthenia Gravis
MM	Multiple Myeloma
MMN	Multifocal motor neuropathy
MMRC	Modified Medical Research Council
MORSE report	Monitoring Of Reimbursement Significant Expenses - report
NBA	National Blood Authority (Australia)
NHS England	National Health Service England
NIHDI-RIZIV-INAMI	National Institute of Health and Disability Insurance
PE	Plasma Exchange
PID	Primary Immunodeficiency
PP	Per protocol
PTP	Post transfusion purpura
QALYs	Quality-Adjusted Life Years
QMGS	Quantified Myasthenia Gravis Score
QoL	Quality of Life

RCT	Randomised controlled trial
RoB	Risk of Bias
RR	Relative Risk
SCIg	Subcutaneous Immunoglobulin
SID	Secondary Immunodeficiency
SR	Systematic Review
STSS	Streptococcal toxic shock syndrome
TSS	Toxic shock syndrome
WTP	Willingness to Pay

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Background

Immunoglobulins (Ig), also called antibodies, naturally circulate in the human blood. They are a part of the humoral immune response towards pathogens such as viruses and bacteria.

Ig, once purified from blood plasma of healthy humans, can also be used as a drug therapy[1]. Most of the time they are administered intravenously (IVIg), but subcutaneous use (SCIg) is emerging.[2,3] These agents were initially used as replacement therapy for patients with malfunctioning immune systems who could not adequately produce Ig to combat infections (agammaglobulinemia-hypogammaglobulinemia). Since the 1980's Ig are increasingly linked to anti-inflammatory and immune modulating properties[4] and as a result, they slowly became an important treatment option in a number of inflammatory- and autoimmune diseases (such as Guillain Barre Syndrome, CIPD,…). The increase in potential indications, makes the demand for Ig grow, while their supply remains limited by the number of blood donors. To obtain an ideal mix of circulating antibodies targeting many different pathogens, Ig are manufactured by fractioning human plasma from a pool of at least a thousand blood donors. The limited availability of donors, and as a consequence of Ig, makes it crucial to assess the available evidence in order to gain a better understanding of the disorders/indications or types of patients that could benefit the most from this therapy.

1.2 International context

During the late 1990s, worldwide product shortages of Ig occurred due to increased demand, reduced supply and product recalls based on possible contamination of blood donors.[5,6] More recently, 2018 has been a year of instability in the provision of Ig products to patients (e.g. withdrawal of the IVIg product Kiovig® and Subcuvia® by Shire Pharmaceuticals).[7]

For the future, factors such as market forces resulting in companies allocating Ig products to other countries, the limited supply of blood donors, and technical, as well as regulatory issues that could affect Ig availability, must be kept in mind in order to better respond to possible shortages.

Several countries have launched initiatives to encourage appropriate use of IVIg/SCIg. Guidelines on indications to help limit non-evidence based use of IVIg/SCIg have been recently developed in collaboration with prescribers and stakeholders in Canada,[8] and Australia.[9] In some cases, a priority list of indications to be covered in case of shortage has been drafted (e.g. in England[10] and France[11]). Other initiatives currently in place include monitoring the use of Ig in different ways: for example, in England, this is done by means of a registry (i.e. the National Immunoglobulin Database,[12] while in France this is facilitated by a monthly status of Ig provision[13]).

In order to draw lessons from international initiatives, a chapter of this report is dedicated to describing these recent initiatives pursued in countries other than Belgium (see chapter on International Comparison).

1.3 Belgian context

Since Ig are sometimes the only possible treatment for serious illnesses, ensuring an adequate supply in Belgium is of great interest to the Belgian Health authorities. Since 2014 the 'Law of 5 July 1994 on blood and blood derivatives of human origin' was updated with an article 20/1 on the self-sufficiency of plasma derivatives, including a tender procedure and to secure/ensure a national strategic stock.[14] In 2018, a public contract was awarded to a company that purchases Belgian blood and plasma, and processes it into blood derivatives such as albumin and Ig. As far as albumin is concerned, 100% sufficiency must be foreseen by this company. However, supply for IVIg is more challenging and is expected to reach only 50% with the collected plasma and blood.[15] The remaining 50% is contracted directly by hospitals and processed from plasma from other countries (via commercial tenders). This means that for this commercial part of IVIg and for SCIg for which no tender is currently in place, there is high dependency on the international market. At the beginning of 2019, stock ruptures were notified (Iqymune®, Pangyza®[a]), which coupled with the increasing use of Ig for several indications, resulted in a potential risk of shortages, and high pressure on prices. Available IVIg and SCIg products in the Belgian market, as well as recent stock ruptures and market withdrawals are described in Supplement 1.

Ig use and its associated costs continue to rise year after year; from around 40 million euros in 2007 till 80 million euros in 2016 (see Figure 1).[16]

Despite the fact that in Belgium, only licenced indications (authorized by the European Medicine Agency or the national agency FAMPH) are considered for reimbursement, a Belgian study published in 2011 found off-label use to account for 46% of all patients treated with IVIg in the year 2007 (based on a IMS Health analysis of a nationally representative sample of 47 Belgian hospitals),[17] although the methodological limitations (recognised by its author) of the study are likely to have overestimated to a certain extent off label use.

To facilitate a more evidence-based practice approach in Belgium, one KCE report was already published on this subject in 2009 (KCE report 120B).[18] Similarly, recommendations by the Superior Health Council were drafted in 2010 highlighting the most appropriate indications for IG use.[19]

Consequently, some changes were made to the list of reimbursed conditions issued on 1st January 2014,[20] as well as on 1st April 2017,[21] and more recently on the 1st of September 2019.[22]

In 2014 some adjustments with logistical consequences were made: for primary immunodeficiency disease, diagnosis and clinical re-evaluation must be made by a physician from 'The Belgian primary immunodeficiency group[b]' (BPIDG), recognised by the NIHDI, and for the indication Multifocal Motor Neuropathy diagnosis must be completed in a Neuromuscular Reference Centre (NMRC), approved by the NIHDI.

[a] Since January 2020 there is an interruption of commercialisation of Panzyga® in Belgium

[b] The BPIDG group is composed of many people (physicians, laboratory technicians, researchers,...) involved in the diagnosis and treatment of primary immune deficiencies. Within this group there are mandated physicians for the diagnosis of Ig (www.bpidg.be)

In 2017, the indication 'acquired hypogammaglobulineamia' was deleted from this list to discourage the use of Ig in recurrent pulmonary infections not due to primary immunodeficiency.

Since the supply problems in 2018 arose, physicians experienced more difficulties to guarantee Ig for their patients based on the strict reimbursement criteria (e.g. not all Ig on the market are licenced for the same indications). A task force with physicians, hospital pharmacists and authorities was set up to formulate recommendations. [23] For clinicians they made following recommendations:

1. Switch to SCIg when clinically possible.[c]
2. Prescribe rationally and only within the reimbursable indications. It is important to limit improper or off-label use as much as possible.
3. No unnecessary stockpiling.

In addition reimbursement criteria were harmonized (for some IVIg products) allowing a greater flexibility among the different brands for the 8 defined reimbursed indications (e.g. physicians can also switch medication to another brand when stock ruptures occur).[22]

An overview of currently reimbursed indications (see Table 1) shows that each of them is subject to specific requirements aimed at optimising the use of these scarce and expensive products[d]. In Belgium only licenced indications (authorized by the EMA or the national agency FAMHP) are considered for reimbursement. Exceptions are possible via special programs in which a commission decides on possible reimbursement for individual cases (see also chapter 4 on the International Comparison).

The Belgian authorities have requested the support of KCE in completing an update of the 2009 report[18] and more specifically, to offer recommendations regarding the indications in which Ig are most effective, as well as approximations to the required quantity of Ig needed to respond to patient needs in those indications.

[c] A switch to SCIg is not possible for every indication, since their (reimbursed) use is limited to PID and some SID indications

[d] Webtool per pharmaceutical product which lists the conditions needed to be fulfilled to obtain reimbursement https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/nl/Public/ProductSearch

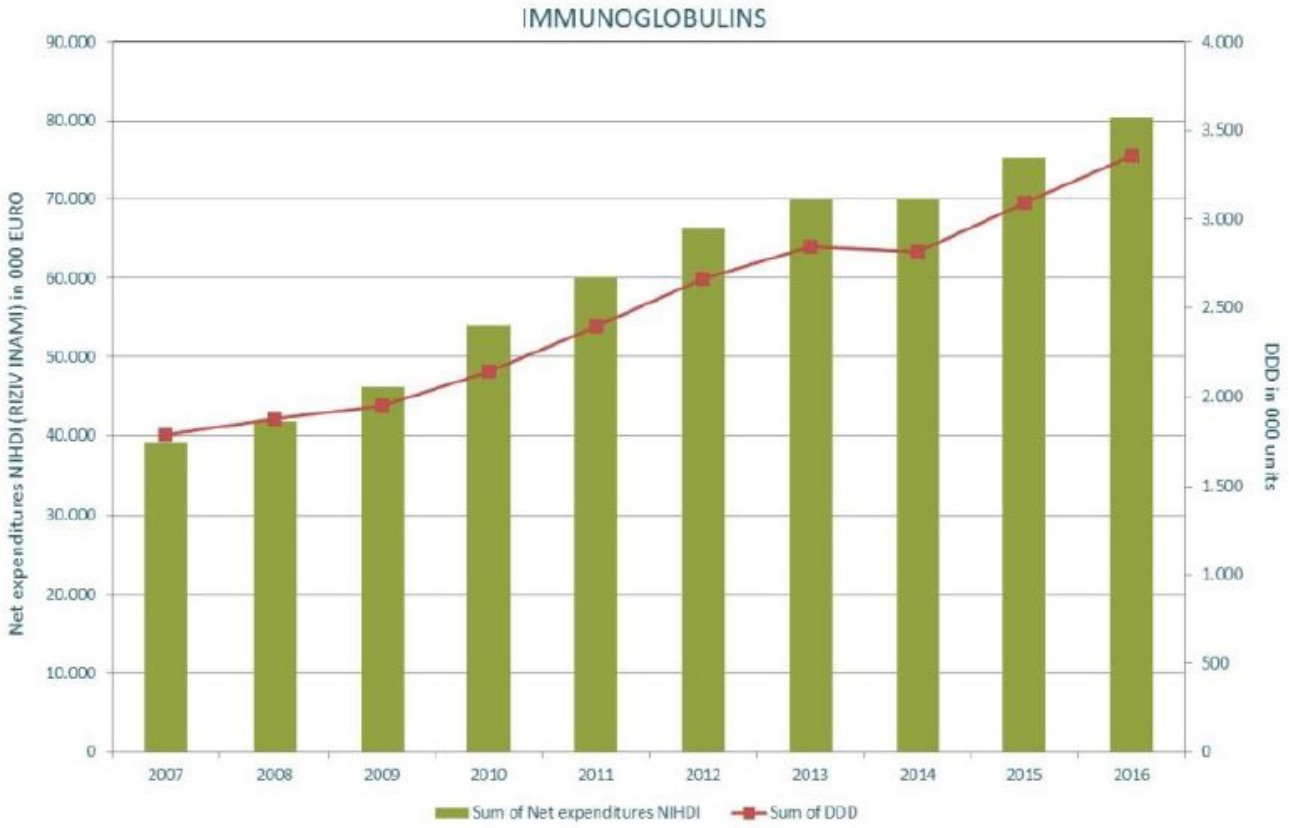
Table 1 – Reimbursed indications for immunoglobulin use in Belgium - September 2019

reimbursed indication	condition/ prerequisite	validity	product
Primary immunodeficiency syndromes (PID) **a) congenital defects in the production of antibodies resulting in low titers** **b) congenital Specific Polysaccharide Antibody Deficiency** **+** **recurrent clinically significant infections for which antibiotics were indicated**	1. Specialist documents laboratory results 2. Diagnosis and need for IVIg/SCIg confirmed by a doctor from BPIDG[1] 3. Specialist completes reimbursement request form[2] 4. Documentation[3] of therapy efficiency	12 months, after which clinical re-evaluation needs to be done by a doctor from BPIDG[1]	INTRAVENOUS: Iqymune ® , Multigam ®, Nanogam ®, Octagam ®, Panzyga ® [6], Privigen ®, Sandoglobuline ® SUBCUTANEOUS: Gammanorm ®, Hizentra ® (not for HSCT)
Secundary hypogammaglobulinemia due to **a) B cell malignancy (cancer) such as Multiple Myeloma or Chronic lymphocytic leukemia** **b) iatrogenic B cell deficiencies due to chemotherapy, or monoclonal antibodies** **c) allogenic or autologous hematopoietic stem cell transplantation** **+** **recurrent clinically significant infections for which antibiotics were indicated**	1. Specialist documents diagnosis 2. Specialist completes reimbursement request form[2]	12 months	
Idiopathic thrombocytopenic purpura **+** **serious bleeding or risk of bleeding**	1. Specialist documents diagnosis 2. Specialist completes reimbursement request form[2]	12 months	INTRAVENOUS: Iqymune ® , Multigam ®, Nanogam ®, Octagam ®, Panzyga ®[6], Privigen ®, Sandoglobuline ®
Kawasaki disease			
Syndrome Guillain Barre or variants **+** **progressive muscle weakness/symptomatology**	1. Diagnosis confirmed by lumbar puncture and GBS DS score[4] 2. (Paediatric) neurologist or neuropsychiatrist completes reimbursement request form[2]		
Invasive streptococcal group A infection (streptococcal toxic shock syndrome) **+ when failing of other therapeutic options**	1. Specialist documents diagnosis 2. Specialist completes reimbursement request form[2]	12 months	INTRAVENOUS: Iqymune ® , Multigam ®, Nanogam ®, Octagam ®, , Privigen ®, Sandoglobuline ®
Multifocal motor neuropathy (MMN)	1. Diagnosis made in a neuromuscular reference center[5], including an electromyographic examination	6 months	INTRAVENOUS: Iqymune ® , Multigam ®,

reimbursed indication	condition/ prerequisite	validity	product
+ **distortion daily functioning**	2. Neurologist or neuropsychiatrist completes reimbursement request form[2]	dosis max 2g/kg/3 weeks	Nanogam ®, Octagam ®, Privigen ®, Sandoglobuline ®
Chronic Inflammatory Demyelinating polyradicolopathy (CIDP) **+** **distortion daily functioning** **+** **contra-indication or ineffectiveness of oral corticoid treatment**			

1: BPIDG = 'The Belgian primary immunodeficiency group'. 2: For IV preparations: the reimbursement request form must be sent to the hospital pharmacy, where it is kept for the insurance doctor. For SCIg preparations: the reimbursement request form must be sent to the advisory physician from the sickness funds who issues an authorization. 3: Documentation means that the physician must make a detailed report, showing that the therapy has been effective and that treatment continuation is necessary. This report must be added to the patient's medical file. 4: GBS DS: Guillain-Barre Syndrome Disability Score; a score ranging from 0 healthy to 6 dead and for which a score of ≥ 3 indicates Immunoglobulin use. 5: Diagnostic criteria following the most recent guidelines of the 'European Federation of Neurological Societies'. 6: Since January 2020 there is an interruption of commercialisation of Panzyga® in Belgium.

Figure 1 – Evolution of annual reimbursement expenses in hospitals and consumption (DDD) of Ig (IVIg and SCIg)



Morse report 2018- based on data from 2016: including ambulant and hospitalised patients[16]

1.4 Project scope

The aim of this research is to offer recommendations on the indications for which Ig appear to be most effective, and to offer approximations to the required quantity needed to respond to current and future patient needs in those indications. The research is divided into five research questions. The reporting on these questions will be conducted in 2 different phases/reports. The first phase, captured in this report, focuses on a review of the available literature, while the second phase, which will be captured in a further document expected to be published in 2020, will offer a more detailed data analysis of the Belgian situation.

Project research questions:

- Phase 1:
  - Research Question 1: In what indications are intravenous and subcutaneous polyvalent Ig proven to be effective and safe?
  - Research Question 2: Are polyvalent Ig also cost-effective in those indications?
  - Research Question 3: How do the indications reimbursed in Belgium compare to those reimbursed in other countries?
- Phase 2:
  - Research Question 4: What is the prevalence of the most frequent indications in which Ig is used?
  - Research Question 5: What is the use/consumption of Ig in Belgium, categorized per indication, and what are the possible trends for the coming years?

2 THE EFFECTIVENESS AND SAFETY OF IMMUNOGLOBULINS BY INDICATION

2.1 Background

Although polyvalent Ig are licenced (authorized by the European Medicine Agency - EMA - or the national agency FAMPH) for a restricted list of indications, their use currently exceeds these licenced indications due to their therapeutic properties:

- As antibody replacement therapy for people with malfunctioning immune systems (within the range of 0.2-0.8 g/kg/month).[24]
- In higher doses (1-2g/kg), Ig can modulate the immune system and can therefore be used in various auto-immune conditions and inflammatory diseases (Kawasaki disease, immune trombocytopenia ITP, Guillain Barré syndrome, …). Most often, it is not used as first line treatment, but rather as an alternative or as an add-on when other conventional therapies have failed or when there is a need for a cortisone-sparing therapy.

In most European countries, the list of licenced indications is the same, partly due to the centralised EMA registration procedure which harmonised the two replacement therapy indications (PID and SID) and the five indications when Ig is used as an immunomodulatory agent. For IVIg and SCIg, this means that when an Ig product can show efficacy in a sample of PID patients its licence/registration is also valid for SID. Moreover for IVIg products, when efficacy is established in immune trombocytopenia (ITP), the licence/registration is extended to other immunomodulating indications GBS, Kawasaki, MMN and CIPD, without the need to perform separate clinical trials (this new EMA guideline came into effect in 2019).[25, 26]

Mostly because of the immunomodulating properties the list of possible indications and off-label use keeps growing. The exact working mechanism of Ig is not fully elucidated. Therefore, Ig are often used and tested for a broad spectrum of illnesses linked to a malfunctioning immune system. Therapeutic areas are scattered over haematology neurology, dermatology, oncology, rheumatology, pediatrics,…

Almost all indications for which Ig are used are classified as rare diseases[e]. The field of rare diseases suffers from a deficit of medical and scientific knowledge. It is not easy to conduct a study for a rare disease, primarily due to the limited number of individuals who will be eligible to participate in any given study, and uncertainty about or heterogeneity in the natural history of the disease[27]. Therefore proving efficacy and safety in order to obtain a licence may be challenging in these diseases. This, coupled with the fact that Ig appear to have a relatively beneficial safety profile, has resulted in relatively frequent off-label[f] use.[28-30]

This report aims at updating a former KCE report, published in 2009[18] by analysing the existing evidence for different clinical indications.

2.2 Methods

2.2.1 Overview of general methodology

Given the limitations on time and resources available for this project and the expected broadness of the topic, the research team decided to pursue a rapid review, instead of a classic full HTA. A step-wise approach was applied by which good quality SRs were used as the starting point of our review and then updated by the identification of more recent primary studies, limiting the search for primary studies to RCTs. This approach was considered an efficient way to re-use previously validated research and to focus the efforts of the research team on updating the evidence when necessary and checking its current validity.

The following research phases were pursued:

1. Phase 1: Internal scoping review: This phase involved the research team as well as other internal KCE experts not directly working in this project, which were consulted throughout this phase, when needed. The scoping review consisted of three steps:

a) Scoping review: a broad search for systematic reviews (SRs) on the use of Ig was completed, in order to better understand the clinical indications for which Ig have been studied (no limit on indications). The clinical research question was formulated using the PICOS (Participants-Interventions-Comparator-Outcomes-Study Design) framework (see Table 2). Because polyvalent Ig are used for a wide range of indications covering different medical domains such as haematology, neurology, immunology, dermatology, paediatrics… the search strategy items were defined broadly (e.g. no restriction on population and age, different comparators and outcomes dependent on the indication/disease). More details on this general search are offered in section 2.2.2, of this report, and full copies of all search strategies are available (Appendix Search strategy).
b) International comparison: Information for countries in which recent reviews on Ig use have been pursued, was gathered via searching official government bodies and HTA agency websites, and contacts with national experts in order to complement our scoping review and ensure a relevant selection of clinical indications. The details on this international comparison are described in chapter 4 of this report.
c) Selection of indications: the large number of (frequently rare) potentially interesting diseases that resulted from the scoping phase, made it unfeasible for the research team to pursue a full systematic review of all clinical studies published up to this date. Instead, a limited number of indications were “selected” as being the most interesting for the purpose of our rapid review research. These selected indications included:
   i) All indications currently reimbursed in Belgium.

[e] Rare diseases are diseases which affect a small number of people compared to the general population. In Europe, a disease is considered to be rare when it affects 1 person per 2000.(www.orpha.net)

[f] Off-label use is the use of a medicinal product for another indication, another patient group, another dose, dose interval or by another route of administration than indicated in the package insert. It does not mean that it is not a clinically relevant indication, but that the manufacturer did not test and/or register their product for use in that indication.

ii) Indications not reimbursed in Belgium but commonly recognised/reimbursed in at least 3 out of the 4 countries analysed in our international comparison chapter (i.e. Australia, Canada, England and France) (see chapter 4 for more details).

2. Phase 2: Identification of indication-specific "core" SRs for the selected indications: This phase consisted of two steps:

   a) Once the selected indications were established, indication- specific searches for SRs were carried out, in order to better structure the work and update the previous, general search (performed in October 2018). Search strategies are detailed in an appendix (Appendix Search Strategy 1.3). Similarly, indication-specific study selection flow charts, with reasons for exclusion are also presented as an appendix (Appendix Search Strategy section 2 and 3).

   b) Quality appraisal of SRs: the quality of the identified indication-specific SRs was checked (according to the AMSTAR checklist) and only those with high or moderate quality were considered. From those, the one with the highest quality (the "core" SR) was described in detail.

      If more than one good or moderate quality SR was found covering the same ground (i.e. same population and comparisons), the most recent was in principle preferred, but first, the conclusions of the SRs were confronted to ensure the evidence base was the same (no relevant RCTs missed in the more recent SR), and the conclusions were similar. If any inconsistencies were found in the evidence base, SRs focusing on RCTs (if available) or being more inclusive (more relevant studies identified via their search), were included in our analysis.

      If more than one good or moderate quality SR covering different questions and PICOs were found (e.g. different sub-populations, different comparators or formulations), these were all included and described in our analysis.

      If the identified SRs included both RCTs and non-randomised studies, their overall results were presented, but whenever possible, a detailed description of the results from RCTs (or from high quality/low risk of bias studies) was provided.

3. Phase 3: Updating the "core" SRs: the search date of the "core" indication-specific SR was used to perform an update of the literature (limited to RCTs). The PICO was in this case based on that of the "core" SR, and the search performed used similar terminology, although it did not follow precisely the search strategy of the core SR (often, more sensitive searches without any filters applied in single indication SRs, while for the purpose of our broad scope review, highly sensitive searches would have been too time consuming). Detailed searches are presented in an appendix (Appendix Search Strategy 1.3).

   Given the number of selected indications needed to be covered, a conscious decision was made to avoid systematically updating the MAs included in the core indication-specific SR identified via our literature review, with more recent RCTs. Instead, a formal assessment of the need for updating the MAs was carried out, and only if the new evidence published after the SR appeared to contradict, or have the potential for changing the overall conclusions of the SR, the research team would update the MAs. In all other cases, the results of the more recent RCTs would still be described in detail and their quality assessed via the RoB tool of the Cochrane group[31], in order to offer a more complete view of the available evidence, but no update of MAs would be performed.

   This method, was inspired on the Ottawa method[32] for rapid reviews, and was thought to provide a transparent, easily reproducible and consistent way to approach broad topics such as the one here covered.

   Only in cases in which no evidence of SR or RCTs was found for the "selected" indications, an overview of any non-systematic reviews that may have been captured during our indication-specific searches was provided for completeness.

4. Phase 4: Overview of SRs for non-selected indications: For all "non-selected" indications (not reimbursed in Belgium or not-recognised in at least three out of the four countries analysed in our international comparison), for which SRs were found via the general SR search performed during our scoping review, an overview of the high or

moderate quality SRs identified was provided (no update on RCTs performed). The results are reported in chapter 2.3.4.

5. Phase 5: Expert consultation: In view of the limitations linked to rapid reviews in general, and to the methodology here applied in particular, and the fact that the field of Ig is rapidly evolving, an expert consultation (via a short online survey) was pursued. Experts were identified via their publication record or their participation in Belgian or European disease networks. The survey aimed at ensuring no important studies had been missed and no important indications had been omitted. A copy of the short online survey is provided in appendix (Supplement chapter 4) for information.

Table 2 – Clinical Research Question

PICOS item	Inclusion	Exclusion
Population	All human populations	
Intervention	• Polyvalent Ig for intravenous and subcutaneous/intramuscular use. • Monotherapy or as combination (add-on)	• Hyper immune plasma: polyclonal or monoclonal Ig targeted against specific (epitopes) of pathogens, • Orally administered Ig • Allergen immunotherapy
Comparator	Different comparators depending on indication (e.g. placebo, plasma exchange, monoclonal antibodies, anti-inflammatory medication …)	
Outcomes	Different outcomes considered: - clinical effectiveness: mortality, morbidity (infections), disease progression, symptom relief, patients' QoL - adverse events,	Results from laboratory testing or proxy measurements.
Study Design	Systematic reviews (controlled studies) Randomized controlled trials (RCTs)	Non controlled studies, case reports
Type of publication	Articles, reviews, health technology assessment (HTA) reports	Letters, editorials, conference proceedings, abstracts

2.2.2 Literature search and selection of indications

Searches for SRs

As previously mentioned, the large number of indications for which Ig can currently be used, and the complexity of carrying out a full systematic search on primary studies in this field, made the research team to pursue the step-wise approach previously described, by which first, SRs or meta analyses (MAs) were searched for in order to identify the most recent, high or moderate quality SRs (according to AMSTAR 1) - http://amstar.ca) per indication, (the "core" indication-specific SR) which was then used as a starting point of our review.

In order for SRs to be considered for inclusion, these had to have carried out their searches in a minimum of two different databases (including MEDLINE and/or EMBASE). For the purpose of our review, SRs with an AMSTAR score of 8-11 were considered of high quality, those with a score of 4-7 were considered of moderate quality, while those with a score below 4 were classified as low quality. Low quality SRs were excluded from our analysis.

The SRs search was limited from 2008, the year when the search of the previous KCE report [18] and that of the superior health council [19] were performed (see appendix for details), but any studies identified in the previous KCE report were also considered.

For systematic reviews (SR), the following electronic databases were searched:

- Medline
- EMBASE
- Cochrane Library: Cochrane Database of Systematic Reviews
- HTA database and DARE

Two authors developed the selection criteria for the SRs based on the PICOS inclusion and exclusion criteria (described in Table 2). One reviewer screened title and abstract of the studies identified via our search. Potentially relevant articles were retrieved and full text was assessed. When there were doubts, a second reviewer was consulted and in case of disagreements, discussions were held until a consensus was reached. The selection did not take into account inclusion criteria related to comparator or outcomes because of the wide spectrum of indications in this overview.

Searches for primary studies (RCTs)

For the selected indications (reimbursed in Belgium or reimbursed/recognised in at least 3 of the 4 countries analysed in our international comparison), for which recent, good or moderate quality SRs were found, an update was performed, by searching all RCTs published after the search date reported in the core SRs. In case no core SR could be identified, the search was carried out with the date limit of 2008.

Databases consulted for primary studies (limited to RCTs) were the following:

- Medline
- EMBASE
- CENTRAL

Primary studies (RCTs) identified per indication were selected based on the inclusion criteria of the specific "core" SRs identified.

An expert information specialist carried out the searches. Search strategies are documented in appendix. Similarly, indication-specific study selection flow charts and a list of excluded studies with reasons for exclusions are also presented (Appendix Search Strategy- chapter 2 and 3).

Searches for relevant grey literature

References from all included studies were hand searched for further relevant studies. In addition to this, the EUnetHTA Pop database as well as the websites of the members of INAHTA (excluding the ones already members of EUnetHTA) were consulted to identify any relevant HTA reports on Ig that may have been published by other HTA agencies.

Searches for ongoing studies

Finally, a search for ongoing RCTs was done in the available trial registers in ClinicalTrials.gov, Netherlands Trial Registry (NTR), and the EU Clinical Trials Register. Relevant studies on efficacy were defined based on the PICOS (Table 2), including only RCTs comparing Ig versus placebo or other active comparators. Relevant studies on safety, not limited to RCTs were also identified. Details can be found in Appendix Search Strategy 1.4.

2.2.3 Quality appraisal and data extraction

As previously mentioned, the quality of SRs was assessed with the AMSTAR 1 tool[g] (8-11 – high quality; 4-7 – moderate quality; 0-3 - low quality). Two researchers individually performed the AMSTAR assessment and compared their results. Any disagreements were discussed until consensus was reached. In addition to the AMSTAR, authors decided to categorised any SRs for which only 1 database was consulted as being of "low quality". Low quality SRs (either classified as such according to the AMSTAR, or having consulted only 1 database) were excluded from the analysis.

The quality of the primary RCTs was assessed using the Cochrane Collaboration's tool for assessing risk of bias[h]. These assessments were split between two researchers (not carried out in duplicate). A third researcher was involved in the process to discuss any doubts that came up during the exercise.

Full quality appraisals for both SRs and RCTs are available in an appendix (Supplement 3.1 and 3.2).

2.2.4 Assessing efficacy

Ig are used as an antibody replacement therapy for people with a malfunctioning immune system or as an immunomodulation therapy used in various auto-immune conditions and inflammatory diseases.

Depending on the indication for which Ig are used, different outcomes are studied, i.e. for antibody replacement therapy the rate of infections is a primary outcome whereas for auto-immune disease, symptomatic improvement is the focus. Therefore, different outcomes are analysed and discussed per indication.

2.2.5 Assessing safety

Although the main focus of our review was on the efficacy of Ig, safety data was extracted whenever possible from the body of evidence found.

First, any SRs identified via the general search for SRs carried out during our scoping review phase covering general safety aspects of Ig are described (See section 2.3.1).

Furthermore, safety results obtained from the indication-specific SRs or RCTs, are reported per indication (see data extraction tables in appendix 2 for more detail). An important limitation of our approach is that given the fact that only RCTs were retained for updating the existing SRs, safety is most often studied over a short period and thus, reflects only short term horizons, which may be appropriate in some cases (e.g. acute illnesses), but are unlikely to offer a complete view of all possible long term AEs linked to the use of these agents. Similarly, larger pools of patients are often captured in observational studies or registries, so having excluded these from our searches, represents a key limitation that challenges the identification of rare AEs or harms, in particular when the focus is on rare indications.

g https://amstar.ca/Amstar_Checklist.php

h https://www.bmj.com/content/343/bmj.d5928

2.3 Results

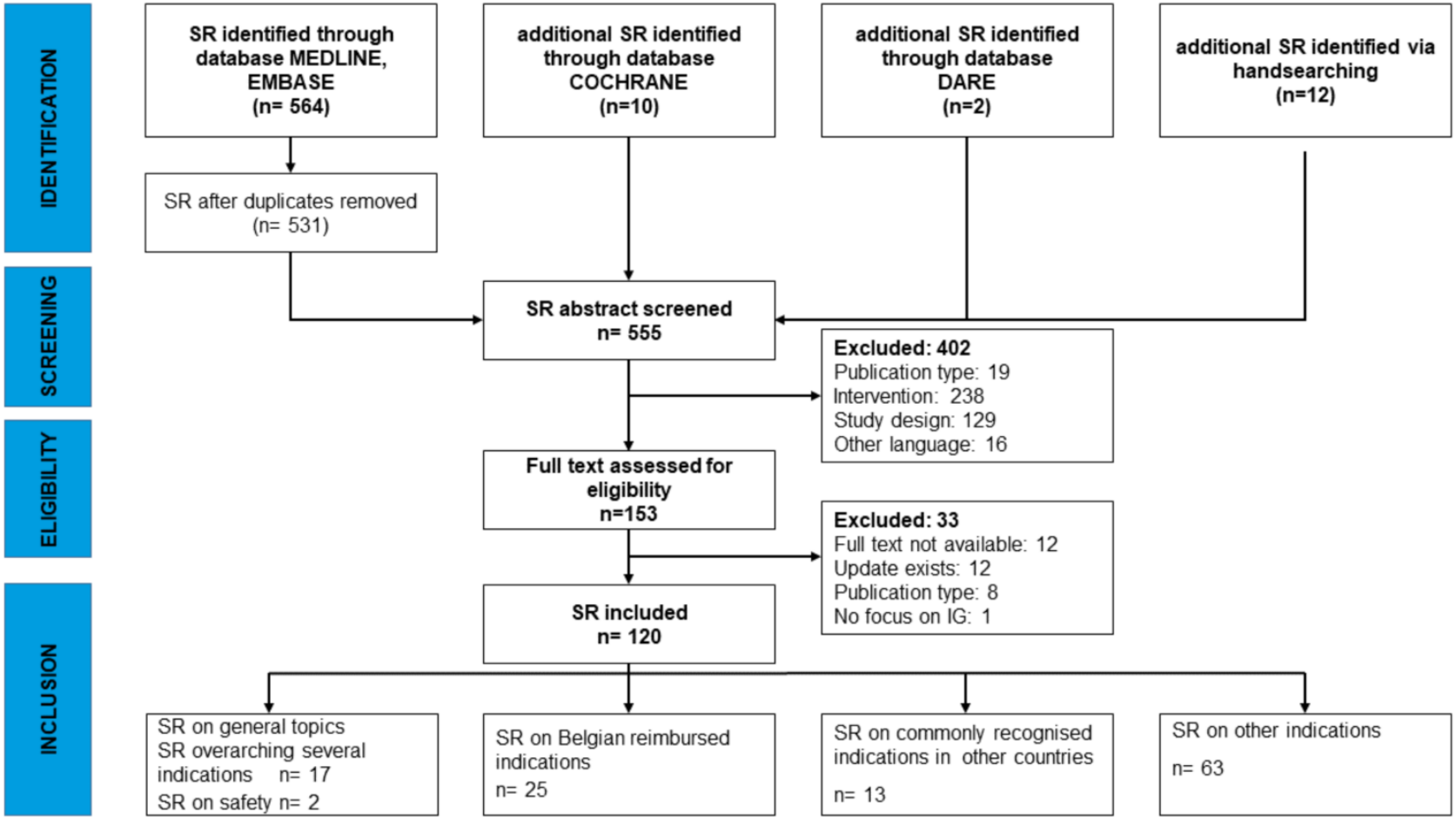
The literature search yielded 588 SRs (564 from MEDLINE and EMBASE, 10 additional Cochrane systematic reviews via the Cochrane Library, 2 additional via the DARE database, and 12 through hand searching references, or searches in the grey literature).

After eliminating duplicates, 555 titles and abstracts were screened and 153 references were considered potentially eligible. From these, 12, were excluded because their full text was not found, while 12 more, were found to be early versions of updated SRs and thus, were also ruled out. Finally 8 SRs were excluded on the basis of publication type (e.g. poster and abstracts), and one because of its focus (not on Ig). Therefore, 120 SRs were finally considered.

Figure 2 shows the PRISMA flowchart for our literature search for SRs. These 120 SRs were used as our starting point to assess the indications in which Ig have been studied. From these 25 SRs covered Belgian reimbursed indications (see section 2.3.2), 14 SRs were on indications not reimbursed in Belgium but commonly recognised in other countries (3 out of the 4 countries analysed in our international comparison; see chapter 4), 19 reviews had a more general focus (e.g. focus on AEs of Igs) or covered more than one indications (e.g. dermatology, neurology, etc). The latter were used for describing general AEs for Ig use and for reference checking purposes, to ensure no relevant studies were missed from our indications-specific review. The remaining 63 reviews were on a wide range of other indications, for which an overview is offered in 2.3.4.

High quality SRs were present for the most well-known indications whereas there were few high quality studies for more recent indications such as dermatological diseases (Pemphigus of Pemphigus vulgaris, foliculae, urticaria).

Figure 2 – PRISMA flowchart of general literature search for Systematic Reviews (Internal Scoping Phase)



2.3.1 General Safety

In general, AEs in this field, may be related to the Ig treatment, their manufacturing process, or the administration methods used. IV therapy is linked to more systemic side effects, probably caused by the sharp peaks in serum concentration that occur immediately after IV infusion, whereas for subcutaneous (SC) use there is a slower augmentation. Ig therapy can result in systemic reactions such as severe headache, transient flu-like symptoms, fever, change in blood pressure, tachycardia, which may in some cases, be avoided by lowering the infusion speed, or switching to SCIg[33]. Infusion-related risks of AEs have been reduced considerably in recent years, due to improved manufacturing processes.[34] Next to the systemic AEs, there are also local side effects. Mild local reactions appear to be more frequent with SCIg use.[34]

Other, more serious side effects mentioned in the literature include anaphylactic reactions (2–27 % of all infusions)[35], thromboembolic events, aseptic meningitis, hemolysis, and renal failure, which are mainly linked to the use of high-dose IVIg.[36] Serious AEs appear to be rare.

Because Ig is a blood product there is a chance of transmission of blood-borne viruses. Viral transmission due to Ig administration has not been reported since the last outbreak of hepatitis C (HCV) in 1994. Rigorous donor screening measures as well as new manufacturing techniques requiring the implementation of dedicated pathogen reduction steps ensure that Ig therapies are safe from established and emerging pathogens.[6]

2.3.1.1 Results

The studies found via our search, most often looked at AEs as a secondary outcome, with considerable variation in methods and quality of reporting. However two studies found via the general SR search, focused on AEs. More specifically on thromboembolic events in different indications[37] and necrotising enterocolitis, specifically in hemolytic infants.[38] These are described in some detail below (as well as in Supplement 2.1).

Studies with a focus on AEs from general search

The SR by Ammann et al. (AMSTAR 8/11), focused on thromboembolic events (TEEs). The SR focused only on RCTs with a low RoB, and included 31 studies overall, on 4129 patients[37]. The median length of follow-up was 9 months and the median of the trial mean ages was 47 years (ranging from 29 to 70 years). The main outcome of interest was the rate of serious TEEs (i.e. acute myocardial infarction; ischemic stroke or venous thromboembolism). Arterial and venous TEEs were analysed as secondary outcomes.

Based on a MA of the 31 RCTs, (n=2318 treated with IVIg and n=1811 treated with a control), 12 patients (0,52%) treated with IVIg experienced serious TEEs, versus 8 (0,44%) in the control group. This resulted in a pooled risk difference of 0,0% (95%CI: -0,7% ; 0,7%), with no significant evidence of heterogeneity across studies. Similarly, no significant increase in risk was observed when arterial and venous TEEs were analysed separately.

A number of hypothesis were tested to assess the sensitivity of the results obtained, (e.g. dose of IVIg; patient age, year of study publication; length of follow up and whether studies excluded patients with a prior risk of cardiovascular disease or TEEs). None of the hypothesis showed to have an important weight on the results. Although overall, the risk appears to be low, the authors ask for a cautious interpretation of their results, mainly due to the young age of the population studied, as well as a potential underreporting of AEs in the studies analysed.

The SR by Yang et al. (AMSTAR 6/11) focused on a specific population of haemolytic infants/newborns. All 5 trials included in the meta-analysis were observational studies but were rated as having a good quality (Jadad quality scores ≥ 3). The outcomes studied were necrotising enterocolitis (NEC) and mortality. For NEC, the MA showed that there was a significant difference when comparing IVIg versus the control group (OR: 4.53; 95%CI, 2.34-8.79; $p < 0.00001$; 5 studies, n=1355). For mortality, no significant differences were found (OR: 0.86. 95% CI, 0.15- 5.13; $p = 0.87$).

Safety findings from indication-specific searches

As already mentioned, studies found via our indication-specific searches, looked at AEs as a secondary outcome with considerable variation across trials in methods and quality of reporting.[37] In order to avoid repetition, we summarise in this section the main findings regarding AEs linked to three common comparisons:

1. Ig compared to placebo.
2. High versus low doses of Ig.
3. IVIg versus SCIg.

AEs of Ig compared to other active treatment alternatives are reported later on, on a per indication basis, as described in the SRs and RCTs identified and included in this review (see extraction tables in appendix 2 for more detail).

AEs of Ig versus placebo or no treatment

Although as expected, IVIg treated patients appear to experience more side effects when compared to placebo or no treatment,[39, 40] differences are not always significant.[41]

Moreover, IVIg-related AEs, when experienced, were mostly mild and temporary. The most commonly reported side effects included fever, chills, nausea and vomiting, headaches, myalgia, rash or hypotension, which only in exceptional cases led to discontinuation of treatment.[42,43,44, 41,40, 45]

AEs High dose vs low dose Ig

Overall eleven studies looking at different dosages, were identified in the review of which 9 reported on AEs. Four studies reported that AE were less frequent with low doses of IVIg [46,47,48] or SCIg.[49] Other RCTs reported that there was no significant difference between high and low dose.[50,51-54]

SCIg vs IVIg

Studies found comparing the safety of different Ig formulations showed for IVIg and SCIg to be similar in that respect, with non-significantly different rates of AEs. These were generally mild and rarely impeded treatment continuation. Nevertheless, more systemic reactions were linked to IV use, while more temporary local reactions were observed with SCIg.[35,55, 56,57,58,3]

Serious AEs

In the SRs and RCTs analysed, the following serious AEs were reported for IVIg: haemolysis (n=1) (in Hodson 2007 for solid organ transplant), haemolytic anaemia (n=4) (3 in Markvarden 2017 for CIPD and 1 in Barth 2011 for MG), 1 pulmonary embolism (Hahn 2013 for MMN), 1 allergic skin reaction with shock (Alejandria), 1 pancreatitis, 1 vitreous hemorrhage, 1 Ecoli pneumonia (Lederer 2014 for lung transplantation), 1 death due to aggravation of HepC infection (Amagai 2009 Pemphigus), 1 aseptic meningitis with generalized seizures (Lioger for children with ITP), 1 severe reduction in muscle strength and 1 severe increase in serum creatine kinase (Miyasaka 2011 poly/dermatomyositis), 8 HSCT patients with hepatic Veno-occlusive disease, 6 deaths (Darenberg for TTS), 1 deterioration in mental state (in Hodson 2007 for solid organ transplant), 1 with side effects resembling aseptic meningitis (Etimov 2013), 1 death after cardiac arrest 1 month after IVIg treatement (Etimov 2013), 1 death three months after treatment due to respiratory failure (Etimov 2013) urinary sepsis (n=1), fever (n=1), urinary tract infection (n=2), hyponatremia (n=1) (Moreso 2018)

For SCIg: 1 extensive skin reaction (Vacca 2018)

Conclusions

Studies most often looked at AEs as a secondary outcome with considerable variation across trials in methods and quality of reporting:

- **The most commonly reported side effects included fever, chills, nausea and vomiting, headaches, myalgia, rash or hypotension, which only in exceptional cases led to discontinuation of treatment.**
- **IVIg versus SCIg studies report more systemic AEs linked to IVIg use and more local reactions with SCIg.**

Two studies looked at more serious AEs as their main focus

- **Thromboembolytic events appear to be rare (MA of 31 RCTs, all with a low risk of bias; n= 4129).**

Necrotising enterocolitis in haemolytic infants/newborns is significantly more frequent with IVIg versus controls, but no significant differences were found on mortality (MA of 5 observational studies, all of high quality according to the Jadad scale; n=1355).

2.3.2 Indication-specific results - Reimbursed indications

Table 3 gives a summary on the available evidence for indications currently reimbursed in Belgium. More details on the SRs and primary studies, included in our review can be found in the extraction tables in the Supplement 2.2 and 2.4.

Table 3 – Summary table on available evidence for indications currently reimbursed in Belgium

Indications	Main findings	Evidence identified
Primary Immunodeficiency Disease (PID)	IVIg recognised as "standard" therapy	SR of moderate quality including observational studies and 2 crossover RCTs showing a dose-response (n=42)
	Positive dose response seen for IVIg: dose increments and higher Ig through level are associated with lower incidence of pneumonia	MA of moderate quality (n= 676) including 15 observational studies and two cross-over RCTs (n= 42)
	SC and IV Ig are equally effective in terms of annual number of infections.	2 crossover RCTs (n=41) and 3 observational studies (n=55)
Secondary hypogammaglobulinemia (SID)	**a) caused by haematological B cell malignancy (MM and CLL).**	
	Used prophylactically, IVIg sig. reduce the incidence of infections in MM and CLL patients with hypogammaglobulinemia, subject to recurrent infections, vs placebo or no treatment.	IVIg - MA of 3 RCTs with low RoB (n=205)
	SCIg sig. improve infection rates in patients with MM and hypogammaglobulinemia vs no treatment. Shorter LoS at hospital, less days on antibiotics and a better QoL was observed.	SCIg - 1 RCT, high RoB (n=46)
	b) caused by drug therapy (iatrogenic hypogammaglobulinemia)[1]	
	No SR or RCT evidence identified	
	c) caused by immunosuppressive therapy in haemotopoietic stem cell transplantation (HSCT)	All-cause mortality: MA of 8 RCTs, 7 unclear RoB, 1 low RoB (n=1418)
	Used prophylactically for autologous and allogenic HSCT transplantation, IVIg is not sig. more effective in terms of all-cause mortality and reduction of infection than placebo or no treatment	Reduction of infection: MA of 5 RCTs, all with unclear RoB, (n=699)
	IVIg increases the risk for veno-occlusive disease (VOD)	VOD: MA of 4 RCTs, 3 with unclear RoB, 1 low RoB (n=447)
	In a paediatric population, similar results were observed within the first 100 days after allogeneic HSCT, between IVIg and Ig-M enriched IVIg, in terms of infection prevention, AEs related to Ig use, acute GVHD incidence, and veno-occlusive disease incidence.	Pediatric population: 1 RCT, with unclear RoB (n=59)

Indications	Main findings	Evidence identified
	d) **caused by immunosuppressive therapy in Solid organ** transplants[1] CMV disease and all-cause mortality was not reduced with IVIg vs placebo or no treatment. Antiviral treatment showed a small but significant decrease in the risk of CMV disease compared to Ig In lung transplanted patients with hypogammaglobulinemia, monthly use of IVIg reduced neither the incidence of bacterial or other infections, nor all-cause mortality, compared to placebo	CMV disease: MA of 5 RCTs including kidney, heart, liver, pancreas transplant, all with unclear RoB (n=175) All-cause mortality: 1 RCT on kidney transplant, unclear RoB (n=34) Antiviral: MA of 4 RCTs, all with unclear RoB (n= 392) Lung transplant: 1 RCT, low RoB (n= 10)
	e) Other causes of secondary hypogammaglobulinemia (such as excessive protein loss) No SR or RCT evidence identified	
Chronic Inflammatory demyelinating polyradiculoneuropathy	The administration of IVIg sig. improves disability vs placebo in the short term (2 to 6 weeks)	MA of 5 RCTs with low RoB (n=235)
	Compared to other therapies such as oral prednisolone; IV methylprednisolone or PE, no sig. differences in effectiveness or AEs were observed	IVIg vs. prednisolone: 1 RCT; unclear RoB (n=20); IVIg vs. IV methylprednisolone: 1 RCT low RoB (n= 45); IVIg vs. PE: 1RCT high RoB (n=32) MA of 1 RCT with low RoB and 3 observational studies, (n= 88)
	SCIg is as effective as IVIg, as a first line therapy in treatment-naive patients, as well as a maintenance therapy in both low (0.2 g/kg) or high doses SCIG (0.4 g/kg)	Naïve patients: 1 crossover RCT; unclear RoB, (n=20) Maintenance: 1 RCTs; low RoB, (n=29) Low vs. high as maintenance: 1 RCTs; low RoB, (n=172)
Streptococcocal toxic shock	IVIg reduce all-cause mortality compared to standard care in a subgroup population (i.e. clindamycin-treated patients with streptococcal toxic shock syndrome) IVIg reduces all-cause mortality compared to placebo in adults with sepsis and septic shock. No subgroup analysis was performed in STSS patients and thus, no conclusions on that regard could be made.	MA of 5 studies: 1 RCT with unclear RoB, terminated prematurely due to slow recruitment (n=21) and 4 nonrandomised studies (n=144) MA of 11 RCTs on adults: all of high quality (Jadad ≥3, (n=2025). Only global results available. No subgroup analysis for STSS patients

Indications	Main findings	Evidence identified
Kawasaki disease	IVIg + salicytate sig. reduces CALs, hospitalisation and duration of fever compared to salicytate alone.	MA of 16 RCTs (12 low RoB; 4 unclear RoB)
	Unclear clinical benefit in IVIg-refractory KD patients vs other therapeutic options (i.e. infliximab or glucocorticosteroids)	Vs Infliximab: MA of 3 RCTs, mixed RoB (n=98) Vs glucocorticosteroids: MA of 2 RCTs; unclear RoB (n=37)
Multifocal Motor Neuropathy	IVIg showed sig. improvements in muscle strength and non-sig. improvements in disability vs placebo	Vs placebo: MA of 4 RCTs; 3 low RoB; 1 unclear RoB (n=34); 1 cross over RCT, unclear RoB (n=44)
	Non sig. differences, in mean changes in muscle strength, or patient's QoL between SCIg and IVIg	IV vs SCIg: 1 cross over RCT; low RoB (n=9)
	IqYmune is non-inferior to Kiovig in terms of efficacy or safety	Different brands: 1 RCT; low RoB (n=22)
Idiopathic thrombocytopenic purpura	IVIg in children with acute ITP is sig. more effective than corticosteroids	Vs corticosteroids: MA of 5 RCTs; low quality (n=289)
	IVIg is sig. more effective (at increasing platelet counts) than anti-D IG at 24-72 hours	Vs anti-D Ig: MA of 8 RCTs; High and unclear RoB (n=484)
	No significant differences were found in efficacy or safety when comparing a single dose of IVIg to careful observation in children newly diagnosed with ITP	Vs observation : 1 RCT; low RoB (n=206)
	High vs low dose: AEs are sig. less frequent with low doses of IVIg (0,2g/Kg/day over 5 days) vs high doses (0,4-0,5g/Kg/day over 4-5 days) in acute ITP, while there are no sig. differences in efficacy.	SR of 13 RCTs; low quality (n=646)
	Unclear benefits of IVIg vs other interventions in children with chronic ITP or in adults	Children with chronic ITP: SR including RCTs; high RoB (n=95) Adults: SR including 2 RCTs; unclear to low RoB (n=159)
Guillain-Barre Syndrome	Non-significant differences in improvements of disability scores with IVIg vs plasma exchange Changes in muscle strength are not significantly different between IVIg versus PE	IVIg vs PE: MA of 5 RCTs; mixed RoB (n= 536) RCTs: 1 with low RoB (n=40), and 1 with high RoB (n=37)
	Giving Ig after plasma exchange does not offer additional clinical benefit	PE+IVIg vs PE: 1 RCT; low RoB (n=149)

AEs: Adverse Events; CLL: Chronic Lymphocytic leukaemia; CMV: Cytomegalovirus; Ig: Immunoglobulins; GVHD: Graft versus host disease; IVIg: Intravenous Immunogobulins; MM: Multiple Myeloma; LoS: Length of Stay; MA: Meta-analysis; PE: Plasma Exchange; QoL: Quality of Life; RCT: Randomised Controlled Trial; RoB: Risk of Bias; SCIg: Subcutaneous Immunoglobulins; SR: Systematic Review; 1: This indication as such is not included in the Belgian reimbursement criteria, but is often considered in the category of secondary immune deficiencies.

2.3.2.1 *Primary Immunodeficiency Disease (PID)*

Primary Immunodeficiency Disease (PID) is a collective term for intrinsic immune system defects caused by genetic disorders; in contrast to immune disorders caused by infection, chemotherapy, or immunosuppressive therapy. While there are over 300 recognized PIDs, most are very rare. Some of the more frequently seen forms of PID include common variable immunodeficiency (CVID), severe combined immunodeficiency (SCID), X-linked agammaglobulinemia (XLA) and Wiskott-Aldrich syndrome. Many of the PIDs involve defects in antibody production with an increased susceptibility to chronic, serious or recurrent infections such as ear or lung infections, skin infections or intestinal infections that often respond poorly to standard treatments such as antibiotics. The prevalence of PID in Belgium is between 2 and 3/ 100 000[59]. The majority of PIDs are diagnosed in children under the age of one, although milder forms may not be recognized until adulthood. It is estimated that more than half of the PID patients in Belgium have not yet been diagnosed[i].

Treatment often consists of prophylactic administration of antibiotics. For those patients with a low antibody count and experiencing recurrent infections, replacement therapy (IVIg or SCIg) is recommended. In more severe forms, stem cell transplantation or gene therapy is necessary. Standard IVIg therapy involves 1 infusion per month at a dose of around 400mg/kg (and an extra loading dose at the start of the treatment of 400mg/kg), whereas SCIg is administered weekly or biweekly. Although the pharmacokinetic parameters are not the same for IVIg and SCIg, in most clinical practice, the cumulative monthly dose administered is the same. However, in the US, higher doses of SCIg are necessary to comply with the FDA requirement to obtain the same area under the curve of serum IgG over time, whereas in Europe the through level is a more important pharmacokinetic parameter and does not require higher doses.[35] When there is proof of clinical effectiveness, the treatment period is most of the time lifelong. Therefore, guidelines highlight the importance of regular reassessments of the effect of the Ig replacement therapy. Since 2014 a clinical re-evaluation every 12 months, by (or in consultation with) a doctor who is part of "The Belgian Primary Immunodeficiency Group" is necessary to comply with Belgian reimbursement criteria[j].

Results

Overall five SRs (of which one already captured in the former KCE report) and two more recent RCTs were retained and analysed for PID. Details describing exclusions are reported in an appendix (Search Strategy chapter 3). Details on included studies can be found in the extraction tables (Supplement-chapter 2).

Former KCE report

The literature review presented in the previous KCE report on this topic was mainly based on a moderate quality SR (AMSTAR 4/11),[60] highlighting a lack of RCTs comparing Ig with no treatment, or placebo. The only RCTs identified were dosing studies that showed that higher Ig doses and plasma through levels provide better protection against infections[52, 61] and studies on different formulations (IVIg caprylate/chromatography or solvent/detergent treated product)[62] *or* administration forms (IV or SC) showing therapeutic equivalence[63].

Ig is nevertheless, considered an established effective treatment in PID patients, on the basis of evidence coming from observational studies[60] and is currently considered unethical to withhold Ig in PID patients. In the SR by Wood et al., the primary efficacy endpoint was the rate of serious bacterial

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[i] http://bpidg.be/nl/pid/

[j] https://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/specialiteiten/wijzigingen/Paginas/immunoglobulinen.aspx#.XYnAfkYzY2w

infections (SBI)[k] or severe infections, while a secondary endpoint was serum Ig levels.

SR review

Our search for more recent SRs on Ig replacement therapy in this indication returned 4 relevant SRs.[3, 35, 64, 65] In line with previous findings, these SRs did not focus on studying the efficacy of IVIg, placebo or no treatment, but rather on comparing different administrations: IVIg versus SCIg,[3, 35, 65] or on measuring the correlation between dose and clinical outcomes.[64]

IVIg versus SCIg

The highest quality SR comparing IVIg and SCIg (AMSTAR 8/11),[35] included 2 RCTs[63, 66] (on 41 patients) and 17 nonrandomized studies in PID patients and used descriptive analysis to conclude that there were no differences between the two administrations in terms of infection rates and safety. No pooling of the results could be performed because of the lack of details of the studies and the low grade of evidence for all outcomes. The primary endpoint serious bacterial infection (SBI) was only reported in 3 observational studies, which found no SBIs amongst their patients. There was no difference in annual number of infections (Based on 2 small RCTs with an unclear risk of bias, n=41[63, 66] and 3 observational studies, n=55). There was great heterogeneity between the studies as some only counted bacterial infections while others included viral infections. Eleven studies (n=284), including the 2 RCTs (n=41) that reported IgG trough levels showed higher levels during SCIg treatment compared to IVIg. No serious AEs were observed in the Lingman-Framme SR (4 observational, n=88 and 1 RCT, n=30). Local adverse events such as redness, itching and swelling were more frequent in SCIg treated patients (based on 3 observational studies, n=75 and 1 RCT with an unclear risk of bias, n=30).

A SR with a moderate quality (AMSTAR 5/11),[3] comparing IVIg and SCIg, included observational studies and RCTs. Their classification of studies into RCT or observational studies does not appear to be correct. However, they include the two cross-over RCTs[63,66] also mentioned in the Lingman-Framme SR. The primary outcome is the IgG through level and the serious infection rate, for which a meta-analysis is performed. The serum IgG through level is higher in SCIg compared to IVIg (mean difference= 1.00, range (0.84–1.15; p<0.01), 17 studies n=1026). The serious infection rate indicated non-sign preference of SCIg over IVIg (OR=0.59 95%CI 0.36–0.97; p<0.04, 9 studies, n=269). Also AEs were analysed but only for the systemic AEs a meta-analysis was performed, indicating a significant preference for SCIg (OR= 0.09, 95%CI 0.07–0.11; p<0.001, 15 studies, n=376).

A SR with a moderate quality (AMSTAR 5/11),[65] comparing IVIg and SCIg, included 24 studies and is described because it includes a MA on AEs. Their classification of studies into RCT or observational studies does not appear to be correct. However they include the cross-over RCT also mentioned in the Lingman-Framme SR.[63] The primary outcome was IgG trough level for which a meta-analysis was performed. SCIg achieves higher serum IG levels (mean diff = 0,336 (0,205-0,467; p<0,01, 15 studies, n=446). Because of differences in measuring the outcome 'infection rate', only a descriptive analysis of studies was carried out. A meta-analysis on AEs reported a non-significant odds ratio of 0.497 (95%CI 0.180-1.371, 13 studies, n=431) in favour of SCIg.

Dosing

A SR with a meta-analysis on different doses of IVIg (AMSTAR 6/11,[64] including 2 crossover RCTs (n=42)[61,63] and 15 observational studies (n=634)), found that IVIg dose increments of 100mg/kg dose and higher Ig trough level were associated with a significant reduction in pneumonia incidence (incidence rate ratio=0.726, 95%CI 0.658-0.801).

[k] number of serious bacterial infections, defined by US Food and Drug Administration (US FDA) as bacterial pneumonia, meningitis, osteomyelitis, septicemia, and peritonitis

Primary studies

Our search for more recent primary studies identified two RCTs, one comparing low and high doses (bio-equivalence study) of Ig and one on different administration forms.[50, 67]

A crossover RCT with a low risk of bias[50] randomised 33 adult patients to high dose (10% IVIg) versus low dose (5% IVIg) to study bioequivalence and safety of different concentrations. The primary endpoint was the pharmacokinetic parameters and not the clinical efficacy such as infection rate. In terms of AEs there was a higher proportion of general AEs in the higher concentrated dose, but when focusing on product related AEs the proportion was similar (34.0% of the high dose treated patients versus 36.4% in the low dose).

A crossover RCT with a high risk of bias randomised 30 patients to either self-administration of small volumes of SCIg at home, every other day, using a syringe (rapid push) versus administration of larger volumes by pump once a week.[67] On the primary outcome 'quality of life' and 'treatment satisfaction' no statistical significant differences were observed. In terms of AEs, two were related to the study drug and led to treatment discontinuation (one patient experienced general reactions after pump infusion, while another reported pruritus on rapid push syringe and switched back to the pump). All other AEs were mild and local. The proportion of local AEs such as swelling, pain or pruritus was the same with both administrations (67.2% versus 71.8%, p=0.11).

Conclusion

- **Ig use for PID patients experiencing a low level of antibodies (hypogammaglobulinemia) is considered established based on observational studies (SR of moderate quality). Although there is no formal evidence on efficacy based on RCTs comparing Ig to placebo or no treatment or other active treatments, Ig replacement is considered unethical to withhold. Some dose-response studies show that dose increments and higher Ig trough level were associated with a reduction in pneumonia incidence (MA of moderate quality (n= 676) including 15 observational studies and two cross-over RCTs (n= 42), unclear risk of bias).**

  IVIg versus SCIg

  - **SC administration of Ig is as effective as IV for PID. The pharmacokinetic outcome 'IgG through level' is repeatedly reported to be higher in SCIg treated patients compared to IVIg (MA of 15 observational studies n=446, of moderate quality and a MA of 16 observational studies and 1 crossover RCT, n=1026, with moderate quality).**
  - **For the primary outcome, (serious) infection rate, pooling of results was not ideal because of the heterogeneity seen in the reporting of the outcomes across different studies. However all studies comparing IVIg to SCIg found no difference in infection rate (SR of high quality, descriptive analysis based on 2 crossover RCTs with an unclear risk of bias (n=41) and 3 observational studies (n=55). A moderate quality MA pooled the data of 2 crossover RCTs (n=41) and 7 nonrandomized trials (n=228) and found similar outcomes.**
  - **Recent primary studies are focussing on new ways on enhancing the comfort of administering Ig, for example at the home base (instead of hospital) and on limiting treatment duration.**

2.3.2.2 Secondary hypogammaglobulinemia (SID)

In contrast to primary immunodeficiency's originating from a genetic malfunction, secondary antibody failure (secondary hypogammaglobulinemia) can have different aetiologies. Secondary hypogammaglobulinemia can be an intrinsic aspect of a disease (mostly haematological cancers affecting the immune system, or excessive loss of Ig due to nephrotic syndrome, protein losing enteropathy, severe burns) or can be iatrogenic due to some specific drug use that affects the immune system, mostly targeting B cells (e.g chemo-immunotherapy; immune-

suppressive therapy in autoimmune diseases; transplantation). This hypogammaglobulinemia can lead to a higher susceptibility to bacterial, fungal, and viral infections, for which prophylactic Ig replacement therapy can be indicated.

Although the clinical presentation of recurrent infections is similar in both PID and SID, the treatment can differ, because in SID, sometimes the elimination of the causal mechanism is possible[68]. However when Ig is deemed necessary, the same dosages used in PID apply for SID: for IVIg an infusion once per month of a dose of around 400mg/kg and for SCIg a weekly or biweekly dose of 400mg/kg

Belgian reimbursement criteria define eligible patients for Ig treatment as those experiencing secondary hypogammaglobulinemia (caused by either haematological B cell malignancy, e.g. Multiple myeloma or Chronic Lymphocytic leukaemia, or by drug therapies targeting B cells), and presenting a life-threatening or recurrent clinical significant infection for which antimicrobial treatment is necessary. Also eligible are patients with a hematopoietic stem-cell transplantation experiencing a hypogammaglobulinemia and life-threatening, or recurrent clinical significant infection, for which antimicrobial treatment is necessary.

Secondary hypogammaglobulinemia caused by haematological B cell malignancy

The most common haematological B-cell malignancy cancers for which Ig is investigated are Multiple Myeloma (MM) and Chronic Lymphocytic leukaemia (CLL).

In Multiple Myeloma, also called “Kahler’s disease” there is a proliferation of a type of white blood cell, a plasma cell, which may lead to an excess production of 1 particular antibody. The proliferation of the plasma cell in the bone marrow can lead to bone pain and osteoporosis, and can suppress the remaining normal plasma cells. The latter may results in a shortage of normal antibody production (hypogammaglobulinaemia) with an increased risk of infections. In Belgium 837 new diagnosis of MM were made in 2017 (age adjusted incidence rates of around 6.5 per 100 000 person years in 2017 for males and 4.5 for females), mainly in patients older than 60 years.[69]

Age adjusted incidence rates of around 4.6 per 100 000 (3.6 to 5.7) have been reported for Western Europe.[70]

Chronic Lymphocytic Leukaemia (CLL) is the most common leukaemia in adults, mostly older adults. The term chronic indicates it is a slow-growing disease. In CLL there is a proliferation of abnormal white blood cells (lymphocytes) in the bone marrow, crowding out normal blood-forming cells. Lymphocytes are important in the development of the different aspects of the immune response. A shortage of normal cells can lead to an increased risk of infections. In Belgium 1035 new diagnosis of lymphoid leukaemia were made in 2017 (age adjusted incidence rate of 8.9 per 100 000 person years in 2017).[69]

It is important to consider that not all MM or CLL patients develop hypogammaglobulinemia and are eligible for Ig treatment. Some remain asymptomatic for whom monitoring is required. In these malignancies, hypogammaglobulinemia can be an intrinsic aspect of the disease or may follow chemo-immunotherapy treatment regimens (iatrogenic hypogammaglobulinemia see further). Prophylaxis to prevent potentially dangerous infections due to the affected immune response can be provided with antibiotics or with Ig replacement therapy.

Results

The results are based on one SR (which was also included in the former KCE report) and one, more recent RCT. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement 2).

Former KCE report

One high quality Cochrane SR published in 2008 was included (AMSTAR 10/11).[45] This SR included 9 RCTs comparing IVIg to placebo or no treatment, from which the results of 7 RCTs on MM and CLL were combined in a MA[71,72,73-75,76,77]. Two RCTs consisted of crossover studies and were excluded from the MA[78,79]. The primary endpoints were all-cause mortality and clinically documented infections. The MA did not find an impact on all-cause mortality between Ig and the control (2 RCTs with a low risk of bias including 163 patients- RR 1.36 (95% CI 0.58 to 3.19), but Ig significantly

reduced the risk for developing clinically documented infections by 51%, (3 RCTs with a low risk of bias including 205 patients - RR 0.49 (95% CI 0.39 to 0.61). The RCTs included in this MA included patients with hypogammaglobulinemia and experiencing recurrent infections, limiting the generalisability of the results to this subgroup and not considering the whole population suffering from lymphoproliferative disorders (MM and CL).There were significantly more side effects in patients receiving IVIg (fever, chills, nausea and vomiting, headaches, myalgia, rash and hypotension without anaphylaxis): RR=2.37 (95% CI 1.74 to 3.24) (3 studies, n=205). However, the significance disappeared when focusing on AE leading to study discontinuation (5 patients in the IVIg treated population and none in the control group (RR= 5.43 (95% CI 0.70 to 42.24).

More recent SR

No new, relevant SR were identified.

Update on RCTs

One additional RCT was identified via our search for primary studies.[80] This RCT with a high risk of bias, compared SCIg versus no treatment (46 myeloma patients with hypogammaglobulinemia low serum Ig <500 mg/dL) and reported on 'severe' infection rates (primary outcome) and secondary outcomes such as length of hospitalisation, days on antibiotics, and health related quality of life. SCIg-treated patients showed a significantly lower total number of infections per year ($p < 0.001$) as well as severe infections ($p< 0.01$), although no further data on their primary outcome results were provided. Also a significant impact on secondary endpoints was observed: mean days per year of hospitalization due to severe infections were 8 in SCIg vs. 121 in the control group ($p <0.001$), the mean number of days on antibiotics: 28 for SCIg vs. 217 for the control ($p <0.001$). Patients receiving SCIg consistently reported improvements in QoL measures, including improvements in their feeling of general well-being (SF-36) and in the impact of MM on both their own and their family's activities. Only for incidence of pain were similar responses recorded in both arms of patients, though not statistically significant. Most reported side-effects were mild, although in three patients they required treatment discontinuation (2 local reactions and 1 extensive skin reaction).

Secondary hypogammaglobulinemia caused by drug therapy (iatrogenic hypogammaglobulinemia)

Chemo-immunotherapy targeting B cells, or immune-suppressive therapy in autoimmune diseases or in transplantation intentionally target the immune system and therefore can cause hypogammaglobulinemia, especially when used as maintenance therapy.[68]

One of the most frequently used drug able to induce iatrogenic hypogammaglobulinemia is the anti-CD20 monoclonal antibody 'rituximab'. Originally introduced in clinical practice for the treatment of haematological malignancies, it has become a commonly used immunomodulatory strategy for the treatment of many refractory or poorly controlled autoimmune or inflammatory disorders.[81]

More recently developed drugs can also have an impact on the immune homeostasis, and regulatory functions of normal B cells.

Immunosuppressant drugs used to suppress one's immune system in bone marrow- or solid organ transplantation are also linked to hypogammaglobulinemia.[82] These two specific indications are described in separate subsections (see 2.3.2.2.3 and 2.3.2.2.4).

Results

Except for the immunosuppressive therapy linked to Haematopoietic Stem Cell Transplantation and solid organ transplantation which are described in other sections (see sections c and d below), no SR or RCT evidence was identified via our searches for SID linked to drug therapy.

Secondary immunodeficiency in haemopoietic stem cell transplantation (HSCT)

Patients with certain cancers of the blood or bone marrow, such as multiple myeloma or leukaemia may need a hematopoietic stem-cell transplantation. It may be autologous (the patient's own stem cells are used), or allogeneic (the stem cells come from a donor). Patients receive high doses of chemo-radiotherapy about 1 week before the transplantation to destroy the malignant cancer cells. In the case of allogenic transplantation, the patient receives immunosuppressive therapy after the transplantation to supress

their immune response and to enhance the uptake of the transplanted donor cells. During this period of immunological incompetence, HSCT recipients are highly susceptible to bacterial, viral and fungal infections. This period of immunological incompetence usually starts from 1 week before allogeneic transplantation and lasts around 6 to 12 months after.

The incidence of HSCT in Belgium is between 3 and 4 per 100 000 for allogenic transplantations and more than 4 per 100 000 for autologous transplantations (based on 2014 survey data of the European Society for Blood and Marrow Transplantation (EBMT)[l] including 18 Belgian centres).

Results

Overall one SR (already captured in the former KCE report)[45] and one more recent RCT[83] were retained and analysed for post-haemopoietic stem cell transplantation. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement 2).

Former KCE report

One high quality Cochrane systematic review published in 2008 was included (AMSTAR 10/11).[45] This SR also covered the indication of SID due to haematological cancers (see above).

This Cochrane SR on prophylactic IVIg use as such (and not as treatment of suspected or documented infections) included 21 RCTs with polyvalent IVIg after allogenic or autologous HSCT; one compared IVIg to placebo,[84] one compared different doses and placebo[48], ten compared IVIg to no treatment,[85-94] three compared IVIg to a specific hyper immune IVIg, e.g. CMV-IVIg[95-97], and six compared different products or different doses.[47, 98-102] In the group of polyvalent IVIg, standard IVIg as well as IgM enriched IVIg were considered. No separate analysis for standard and IgM enriched Ig was made in the MAs. Primary outcomes included all-cause mortality, and clinically documented infections, and secondary outcomes included CMV or bacterial infections, acute Graft versus Host Disease (GVHD) and AEs. The quality of the included RCTs, as reported in the SR by the authors, was unclear based on allocation concealment. Only the studies by Cordonnier 2003 and Fillipovich 1992 had low risk of bias.

Compared to placebo or no treatment, there was no difference in the risk for all-cause mortality between the study groups (RR=0.99, 95% CI 0.88 to 1.12, 8 RCTs, n= 1418, all with an unclear risk of bias, except one RCT of 200 patients, with a low risk of bias), no reduction in the occurrence of clinically documented infections (RR=1.00, 95% CI 0.90 to 1.10, 5 RCTs, n=699 all with an unclear risk of bias), and no decrease in occurrence of acute GVHD (RR=0.93, 95% CI 0.83 to 1.04, 7 RCTs, n=989).

Comparing IVIg to the hyper immune CMV-IVIg, all-cause mortality did not differ significantly (RR=1.46, 95% CI 0.92 to 2.32, 3RCTs, all with an unclear risk of bias, n=212); whereas the risk for CMV infection was significantly higher with polyvalent IVIg (RR=1.42, 95% CI 1.07 to 1.89, 3RCT, n=212). There was no significant impact on GVHD (RR=1.23, 95% CI 0.87 to 1.75, 2RCT, n=163).

Comparing low dose IVIg (250 mg/kg) versus higher doses (500 mg/kg), there was a slight decrease in the occurrence of clinically documented infections with the lower dose (RR=0.89, 95% CI 0.81 to 0.97), while there was a slight increase (RR=1.28, 95% CI 1.04 to 1.57) in microbiologically documented infections. This discrepancy between clinically and microbiologically documented infections could stem either from the small number of trials (only two for each comparison) or from the different definitions, (i.e. there is not necessarily an overlap between the two outcomes). There was a higher rate of acute GVHD with the low dose Ig regime when compared to the higher dose (RR=1.32, 95% CI 1.13 to 1.55).

The Cochrane MA[45] found that there was a significant increase in the risk for veno-occlusive disease (4 RCTs including 447 patients- RR=2.73, 95% CI 1.11 to 6.71), and in mild AEs which did not require to discontinue treatment (fever, chills, nausea and vomiting, headaches, myalgia, rash - 5 RCTs including 728 patients – RR=8.12, 95% CI 3.15 to 20.97). Raanani et

[l] www.ebmt.org

al. concluded that routine prophylaxis is not supported neither for allogenic nor for autologous HSCT.

A major limitation of this review is that the majority of the studies are old, with many of them reporting on patients treated in the 80's and 90's. The techniques and supportive treatments for patients undergoing transplantation for haematological malignancies have changed considerably during the last two decades which might need to be kept in mind when interpreting the results here mentioned.

More recent SR

No new relevant SRs were identified.

Update on RCTs

Only one RCT with an unclear risk of bias[83] on prophylactic use comparing IVIg versus IgM-enriched IVIg in paediatric patients following allogenic HSCT, was found. This paediatric RCT on 59 patients reported on the following endpoints: infection, frequency of CMV reactivation or CMV disease, acute GVHD, VOD and AEs within the first 100 days after transplant. This RCT concluded that there was no significant difference between the utilization of Ig-M enriched IVIg and IVIg within the first 100 days after allogeneic HSCT in terms of infection prevention: bacteraemia episodes (65.6% in Ig-M enriched vs. 55.6% IVIg, p=0.429), septicaemia episodes (1 patient in Ig-M enriched vs. 2 in IVIg, p=0.588), local infections (43.7% vs. 55.6%, p=0.635), CMV reactivation (21.9% vs. 29.6%, p=0.496), acute GVHD (28.1% vs. 14.8%, p=0.219). There was no difference in veno-occlusive disease incidence (3 patients in Ig-M enriched IVIg vs. 2 IVIg in, p=1.0) or other AEs related to Ig use such as fever, nausea, tremor, hypertension (4 in Ig-M enriched vs 1 in IVIg, p=0,231).

Secondary hypogammaglobulinemia in Solid organ transplantation

Often, immunosuppressive therapy is necessary for 6 to 12 months after transplantation. The exact regimen and agents used vary by patient or transplant centre. This therapy can induce hypogammaglobulinemia which make patients after solid organ transplant susceptible to infections (iatrogenic hypgammaglobulinemia). Opportunistic infections such as cytomegalovirus (CMV) are a major cause of disease and death in transplanted patients.[82] Ig and the hyperimmune CMV-Ig can have a role as prophylaxis as they can neutralise the infective agent, although their use has recently been reduced in favour of antivirals such as valganciclovir, ganciclovir, acyclovir, valaciclovir, which have become first-line treatment for these patients.[103]

This indication as such is not eligible for reimbursement. This indication may be eligible for reimbursement in Belgium if the patient suffers from life-threatening or recurrent clinically significant infections requiring antibiotic treatment. Since November 2019, a hyperimmune CMV-Ig (Megalotect®) is reimbursed for lung and heart transplant patients, when no other therapeutic option is available.

The primary outcome in this indication is the decrease in the prevalence of severe infections.

Therapy with Ig for antibody medicated rejection is described in a separate section (see section 2.3.3.6) as this reflects another immunological mechanism (neutralising the immune response of the host towards the donor-organ).

Results

The results are based on one Cochrane SR (already included in the former KCE report),[104] and one additional RCT.[105] Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement 2).

Former KCE report

One high quality Cochrane SR already identified by the former KCE report was included.[104] This SR investigated the effectiveness of prophylactic IVIg or hyperimmune CMV-Ig (in the absence of proven infections) on the outcome CMV disease and all-cause mortality in solid organ transplants. Twelve studies (704 enrolled patients) compared hyperimmune CMV IgG with placebo or no treatment. Six studies (189 enrolled patients) compared polyvalent IgG with placebo[106] or no treatment.[107-111] Of these Preiksaitis et al. did not report any outcome data relevant to this review. Four studies (204

enrolled patients) compared different IgG preparations; three compared CMV IgG with IgG, and one compared two CMV IgG preparations.[112] Four studies (441 enrolled patients) compared ganciclovir[113-115] or acyclovir[116] with IgG. Four studies (294 enrolled patients) compared ganciclovir [117-119] or acyclovir[120] combined with IgG to antiviral medication alone.

For the outcome CMV disease, a MA of 5 RCTs on polyvalent IVIg concluded that there is no added value of IVIg compared to placebo or no treatment (5 RCTs on CMV disease, n=175; RR=0.83 95%CI 0.54 -1.28). For the outcome all-cause mortality, 1 RCT in kidney transplants was identified, which did not showed a statistical difference of IVIg compared to placebo (n=34; RR=0.47, 95%CI 0.02, 10.69). Also for hyperimmune CMV-Ig, no statistical significant effect was seen on CMV disease, CMV infection and all-cause mortality compared to placebo or no treatment. Therefore there was a MA performed, combining both the polyvalent IVIg and hyperimmune CMV-Ig products, also concluding no statistical significance for CMV disease (16 RCTs, n= 770, RR=0.80 95%CI 0.61, 1.05), CMV infection (15 RCTs, n=775, RR= 0.94 95%CI 0.80, 1.10), all-cause mortality (8 RCTs, n= 502, RR= 0.57 95%CI 0.32, 1.03) compared to placebo or no treatment.

Comparing Ig to antiviral treatment, there is a slightly significant decreased risk of CMV disease with antiviral therapy (4 RCTs, n=392: RR 0.68, 95% CI 0.48 to 0.98). There was no significant difference in all-cause mortality between antiviral medications and IVIg (2 RCTs, RR 0.70, 95% CI 0.37 to 1.33).

In the 4 RCTs investigating Ig as add-on to antiviral treatment, there was no significant impact on the outcomes CMV disease (4 RCTs, n=298: RR 1.17, 95%CI 0.74 to 1.86), CMV infection (4 RCTs, n=298: RR 1.16, 95% CI 0.89 to 1.52) and mortality (2 RCTs, n=218; RR 0.92, 95% CI 0.37 to 2.29) compared to antiviral treatment alone.

According to the authors of the Cochrane review, all the above mentioned RCTs have an unclear risk of bias, because the allocation concealment was not well described.

Most studies in the SR did not report on AEs, or reported no AEs. In the studies that did report AEs, fever, chills, flushing, anxiety, nausea, breathlessness, cramps and backache were the most common, but none of these mild effects required treatment cessation. One patient treated with Ig showed deterioration in mental state the day after the first infusion; the patient recovered but no further Ig was administered. One patient developed haemolysis with Ig.

More recent SR

No new relevant SRs were identified.

Update on RCTs

Our search for more recent primary studies identified one RCT with a low risk of bias in 10 patients with hypogammaglobulinemia after lung transplantation, comparing IVIg (400mg/kg every 4 weeks) to placebo [105]. It was a crossover study with two 12 week treatment periods separated by a 12 week washout period. The primary endpoint was the number of bacterial infections. Secondary outcomes included overall number of infections, through IgG level, hospital admissions, antimicrobial use, serious bacterial infections, acute rejection, spirometry and mortality. AEs were also described but no statistical analysis was provided on this outcome.

The number of bacterial infections did not differ significantly (3 with IVIg and 1 with placebo, OR=3.5, 95%CI 0.4-27.6, p=0.24), neither did the overall number of infections including viral and fungal (7 with IVIg and 3 with placebo, OR=2.7, 95%CI 0.95-7.6, p=0.06). All other secondary outcomes did not differ significantly, except the IgG through level which was higher with IVIg (mean of 765 vs 486, p<0.001). During IVIg treatment, chills, flushing and nausea were reported. In this same treatment group, 3 serious AEs were also seen (pancreatitis, vitreous hemorrhage, Ecoli pneumonia) compared to only 1 serious AEs with placebo (hospital admission for thymoglobulin infusion). Bronchoscopy was frequent with similar rates in both groups, while cough and neck stiffness was more common with IVIg.

Other causes of secondary hypogammaglobulinemia

Several diseases can cause excessive loss of Ig, via the gastrointestinal tract such as protein losing enteropathy or via renal loss in nephrotic syndrome or via the skin in severe burns.[121]

Treatment of these disorders consists mainly in the management of the underlying disease, no comparative clinical studies are available regarding the potential role that Ig replacement therapy could play in these diseases.

The limited evidence calls for a more pragmatic approach. Only for patients who suffer from severe or recurrent infections, guidelines recommend to first assess the effect of prophylactic antibiotics[24], and only in cases where antimicrobial treatment has failed and there is either evidence of specific antibody failure (as tested with the pneumococcal polysaccharide and polypeptide antigen vaccines) or serum IgG level of lower than 4 g/l, IVIg are recommended.

IVIg compared to SCIg

Results

The results are based on two SRs comparing IVIg versus SCIg in patients with SID regardless of the aetiology.[35,57] Both SR only included observational studies.

The SR performed by Lingmann framme in 2013 includes studies with patients with PID (2 RCTs and 17 observational) and patients with SID (1 observational). The results were presented separately (see section on PID). For SID, 1 retrospective study compared SCIg in 12 patients with SID after HSCT versus 46 with IVIg.[122] This study found that SCIg patients experienced significantly fewer AEs, were no more affected by infections than children who underwent IV substitution (infection rates for SCIg: 6.4 (range 3–13) and for IVIg: 5.5 (0–23), NS) and considered SCIg as their preferred treatment option.

The other SR by Health Ontario 2017 included 16 observational studies of which 13 studies on PID patients, two studies only including patients with SID[81,122] and one including both PID and SID patients.[123] No separate MA was performed for patients with SID. Therefore, a description of the studies including SID patients and their outcome is offered here.

The study of Sundin was already described above. The study by Compano compared the outcomes obtained with SCIg in 33 patients previously treated with IVIg. The pharmacokinetic outcome Ig through level was significantly higher in SCIg treated patients compared to IVIg (IVIg (mean of 660 (SD173) versus 474 (SD116)), and no differences were seen in the annual incidence of serious infections per patient (SCIg: 0.11; IVIG: 0.10), or in the annual incidence of infections per patient: (SCIg: 1.76; IVIG: 2.29). The study by Hoffmann included 82 patients with hypogammaglobulinemia of which nine patients (11%) had SID with chronic lymphocytic leukaemia (4 patients) and non-Hodgkin lymphomas (3 patients) being the most frequent underlying diseases. No separate analysis of PID and SID was possible. In terms of AEs, no separate analysis was made between PID or SID studies. Overall, 9 of the 16 studies gave information on AEs. One anaphylactic reaction (hypersensitivity) was reported in a patient receiving hospital-based IVIg, while one vagal reaction was seen in a patient who received SCIg. No further severe reactions were reported. Mild systemic reactions including fever, chills, headache, dizziness, nausea or vomiting, diarrhoea, allergic reaction, and malaise.

Conclusion

1. SID linked to haematological cancer (MM and CLL):
   - IVIg significantly reduces the incidence of clinically documented infections in MM and CLL patients with hypogammaglobulinemia, and subject to recurrent infections compared to placebo or no treatment (Based on a MA including 3 RCTs with a low risk of bias, n=205).
   - A recent RCT showed that SCIg significantly improved infection rate, and reduced length of hospitalisation due to infections, compared to no treatment in patients with MM and hypogammaglobulinemia. QoL was also significantly higher in the SCIg treated group (1 RCT with a high risk of bias, n= 46 myeloma patients).
2. SID linked to drug therapy (chemotherapeutics-immunosuppressants):
   - No SR or RCT evidence was identified.
3. SID in haematopoietic stem cell transplantation (HSCT):
   - The prophylactic administration of Ig after autologous and allogenic HSCT transplantation (without proven infection or low Ig levels), does not appear to be significantly more effective than placebo or no treatment at reducing all-cause mortality (MA of 8 RCTs, n=1418, all with an unclear risk of bias, except one RCT, n=200 patients, with a low risk of bias) or infections (MA of 5 RCTs, n=699, all with an unclear risk of bias).
   - There is a similar efficacy on all-cause mortality between IVIg and hyperimmune CMV-IVIg for prophylactic use after autologous and allogenic HSCT transplantation (MA of 3 RCTs, n=212, all with an unclear risk of bias).
   - IVIg increase the risk for veno-occlusive disease versus placebo or no treatment (MA of 4 RCTs, n=447, 3 with an unclear risk of bias and 1, n= 200, with a low risk of bias).
   - In a paediatric population, similar efficacy was observed within the first 100 days after allogeneic HSCT, between IVIg and Ig-M enriched IVIg in terms of infection prevention, treatment related AEs, rate of acute GVHD, and rate of veno-occlusive disease (1 RCT, n=59, unclear risk of bias).
4. SID in Solid organ transplantation:
   - For the prevention of opportunistic infections in transplanted patients, IVIg neither reduced CMV disease compared to placebo or no treatment (MA of 5 RCTs, n=175, all with an unclear risk of bias), nor reduced all-cause mortality compared to placebo (1 RCT, n=34, with an unclear risk of bias).
   - Comparing Ig to antiviral treatment, the antiviral treatment showed a slightly significant decreased risk of CMV disease (MA of 4 RCTs, n= 392 including patients with kidney, heart, liver and pancreas transplantation, all with an unclear risk of bias).
   - In lung transplanted patients with hypogammaglobulinemia, monthly use of IVIg did not reduce the incidence of bacterial or other infections compared to placebo (1 RCT, n= 10, low risk of bias).
5. SID due to other causes (e.g. excessive protein loss):
   - No SR or RCT evidence was identified.

2.3.2.3 *Chronic Inflammatory demyelinating polyradiculoneuropathy*

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a neurological disorder characterized by progressive weakness and impaired sensory function in the legs and arms, lasting for a minimum of 2 months. CIDP is an immune mediated disorder. The disorder is caused by damage to the myelin sheath (the layer of fat covering and protecting nerve fibres) of the peripheral nerves. CIDP is closely related to Guillain-Barre syndrome and it is considered the chronic counterpart of that acute disease.

The Belgian Neuromuscular Disease Register has estimated a prevalence of 3.32/100 000 inhabitants and an annual incidence of 3.70 per million population in Belgium.[m] These numbers are within the range internationally defined of 1 to 9 per 100,000 adults.[124]

Treatment for CIDP includes corticosteroids such as prednisone, which may be prescribed alone or in combination with immunosuppressant drugs. Plasmapheresis (plasma exchange) and IVIg therapy can also be considered first-line. As IVIg is used in these cases for its immunomodulary properties, instead of using it as replacement therapy, a higher induction dose (mostly 2g/kg over 2 days) followed by a maintenance dose (around 0.4–1 g/kg, 2–6 weekly) is administered. Physiotherapy may improve muscle strength, function and mobility, and minimize the shrinkage of muscles and tendons, and distortions of the joints.

Results

Overall 4 SRs were retained. One captured in the former KCE report,[40] and one being an update of that same review.[124] Two other good quality SRs were described as they included additional RCTs. The search for more recent RCTs identified three relevant studies. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement 2).

Former KCE report

A Cochrane review of high quality (AMSTAR: 10/11) published in 2009,[40] included 7 RCTs, of which 5 compared IVIg to placebo (n=269, all low risk of bias),[125-129] a further RCT compared IVIg to plasma-exchange (n=20, cross-over with an unclear risk of bias[130]) and the last one compared IVIg to corticosteroids (1RCT, n=32, cross-over, with a low risk of bias[131]). Since different disability scales were used in the studies (six-point Rankin disability scale, Medical Research Council (MRC) sumscore, etc), the primary outcome was defined as the proportion of patients experiencing an improvement in disability within six weeks after the onset of treatment. Another relevant outcome considered was the relapse rate. Secondary outcomes included change in mean disability score on the scale used in the original study, change in the mean disability score at 24 weeks or more, as well as (serious) side effects.

The MA results indicate that Ig improves disability for at least two to six weeks compared to placebo (RR=2.40, 95% CI 1.72 to 3.36, 5 RCTs, n=235, high quality as assessed by the authors via GRADE). In three trials, including 84 participants, the disability score could be transformed to the modified Rankin score, on which improvement of one point after IVIg treatment compared to placebo was barely significant (RR 2.40, 95% CI 0.98 to 5.83) (moderate quality evidence as assessed by the authors via GRADE). Only one placebo-controlled study (n = 117), with a low risk of bias, included in this review had a long-term follow-. The results of this study suggest that IVIg significantly improves disability compared to placebo over 24 weeks, with a mean change from baseline disability of 1.1 (SD 1.8) in the IVIg treatment group and 0.3 (SD 1.3) in the placebo treatment group (mean difference: 0.8, 95%CI 0.23 to 1.37).

Compared to prednisolone, the proportion of participants with a significant improvement did not differ significantly (RR=0.91, 95% CI 0.50 to 1.68, 1 RCT, n=32). The comparisons of IVIg with plasma exchange revealed no difference on the study specific Neurological Disability Scale (1 cross-over

[m] Calculation based on data of 2017 in the Belgian Neuromuscular Disease Registry by Sciensano

RCT, n=19). However, no info on the proportion of treatment responders was available, therefore, no reporting on the primary outcome was possible.

There was a significant increase in the risk of side effects with IVIg treatment compared to placebo (RR=2.61, 95% CI 1.80 to 3.78, 3RCTs, n=308, high quality as assessed by the authors via GRADE). However, when only severe side effects were considered results became non-significant (RR=0.82, 95%CI 0.36 to 1.87, 3 RCTs, n=315). In the study comparing IVIg to prednisolone, there was no significant difference for serious side effects (one receiving IVIg and two receiving prednisolone, RR=0.45, 95% CI 0.04 to 4.69) or side effects in general (headache, indigestion, fever, rash, hypotension, urticaria and psychosis) (RR=1.47, 95% CI 0.86 to 2.53).

SR review

Our review for more recent SRs found three relevant SRs.[124,132,133]

The Cochrane update[124] (AMSTAR 10/11) including 8 RCTs[125,126,127-131,134] of which one was an RCT[135], not already included in the Etimov 2009. This RCT with a low risk of bias, included 46 patients, and compared IVIg to IV methylprednisolone (IVMP) and was not included in the meta-analysis, because other outcomes were used. Therefore, the results of the MA do not change and can be found in the text above on the former KCE report. In this additional RCT,[135] the primary outcome was the difference in the number of patients discontinuing either therapy owing to inefficacy or intolerance. More patients stopped methylprednisolone (11 [52%] of 21) than IVIg (three [13%] of 24; relative risk 0·54, 95% CI 0·34–0·87; p=0·0085). The authors of the study were contacted to be able to extract results to report on the primary outcome of the SR [124]. The proportion of participants showing an improvement on disability did not differ significantly between the two treatment arms (RR 1.46, 95% CI 0.4 to 5.38). During the six months' follow-up, there were no statistically significant differences in frequencies of serious side effects (2 reported in the IVIg group versus none in the methylprednisolone). Furthermore, the proportion of participants developing any adverse event did not differ between the groups (RR 0.66, 95% CI 0.39 to 1.13). In the IVIg group, one participant died because of cardiac arrest one month after last IVIg treatment, and a further one died of respiratory failure three months after last IVIg treatment, RR of 4.4 (95% CI 0.22 to 86.78).

The review of Gaebel 2010 (AMSTAR 9/11) includes 9 RCTs taking into account 2 extra RCTs which were excluded in the Cochrane SR, one because it was a proof of concept study with selection bias (only IVIg responders)[136] and the other because of attrition bias (only half of included patients assessed at 6 months).[137] Based on a MA of 4 RCTs, IVIg was statistically superior to placebo in reducing disability and impairment. The effectiveness of IVIg was similar to that of plasma exchange and oral prednisolone.

The review of Oaklander 2017 (AMSTAR 9/11) was a review of SRs on all possible treatments for CIPD, and the results on Ig was based on the Etimov 2013 SR, supplemented with findings from an unpublished randomised open trial (Camdessanché 2014), comparing IVIg to oral prednisone and finding no difference in disability (RR 1.65, 95% CI 0.94 to 2.90). The conclusion of this review of reviews was that there is moderate quality evidence supporting the short-term efficacy of IVIg.

Primary studies

Our search for primary studies published after the literature search of Etimov 2013 (search date 2012) identified three new RCTs analysing SCIg use.[49,55,58] These three studies had different objectives and comparisons and thus, no pooling of results was pursued.

The RCT by Markvardsen et al.[55] (low risk of bias), randomised 29 patients, who were already in maintenance therapy with IVIg (IVIg responders) to SCIg or placebo. The primary outcome was change in muscle strength evaluated at isokinetic dynamometry. In the SCIg group there was an increase of isokinetic muscle strength of 5.5+-9.5% ($p < 0.05$) as compared with a decline of 14.4+-20.3% ($p < 0.05$) in the placebo group. The authors concluded that SCIg treatment in CIDP is feasible and effective. In terms of side effects, six SCIg treated patient reported mild and localised AEs such as local redness, itching and rash, compared to two cases in the placebo group.

In 20 treatment-naive patients with CIDP, a crossover RCT[58] – unclear risk of bias) showed that SCIg and IVIg improve motor performance to a similar degree: Isokinetic muscle strength increased by 7.4+-14.5% ($P = 0.0003$) during SCIg, and by 6.9+-16.8% ($P = 0.002$) during IVIg, the effect being

similar in both groups (P = 0.80). IVIg resulted in an earlier maximal improvement (after 2 weeks) than SCIg treatment (after 5 weeks). In terms of reported side-effects, three patients in the IVIg group experienced haemolytic anaemia, of which one needed hospitalisation. Other side effects were mild with two fever and nausea, two a dermatological reaction and six a headache. In the SCIg group, three patients reported local skin reactions and two had nausea. There were in total six dropouts but no information was available on whether this was related to side effects. The authors suggest that SCIg can be used as first-line treatment in patients with newly diagnosed CIDP.

The most recent RCT- the PATH-study[49] (low risk of bias), investigated the efficacy of two different doses of SCIg (0.2 g/kg or 0.4 g/kg) as maintenance therapy in a population of IVIg responders compared to placebo (57 placebo, 57 low-dose group, and 58 high-dose group for 24 weeks). The primary outcome was the proportion of patients who had a CIDP relapse or were withdrawn from the study for any reason. Both SCIg groups had significant lower relapse rates compared to placebo. Absolute risk reductions were 25% (95% CI 6–41) for low-dose versus placebo (p=0·007), 30% (95%CI 12–46) for high-dose versus placebo (p=0·001), and 6% (95%CI –11 to 23) for high-dose versus low-dose (p=0·32), suggesting that SCIg, low and high dose can be used as a maintenance treatment for CIDP. In terms of side effects, 11 serious AEs were encountered, of which one in a placebo treated patient, five in patients treated with a low dose and five in those treated with high doses. One acute allergic skin reaction occurred in the low-dose group which led to treatment discontinuation. No haemolysis or thrombosis occurred during the SC treatment period.

Conclusion

- **The administration of IVIg for CIPD is effective in improving disability compared to placebo in the short term (2 to 6 weeks) (based on a high quality meta-analysis of 5 RCTs, all with a low risk of bias (n=235)).**
- **Compared to other therapies such as oral prednisolone (1 crossover RCT, unclear risk of bias, n=20), IV methylprednisolone (1 RCTs, low risk of bias n= 45) or plasma-exchange (1 crossover RCT, high risk of bias n=32), no significant differences in improvement or in AEs was observed.**
- **SCIg is as effective as IVIg:**
  - **as first line therapy in treatment-naive patients (1 crossover RCT, unclear risk of bias, n=20);**
  - **as maintenance therapy (1 RCTs, low risk of bias, n=29);**
  - **as maintenance therapy in both low (0.2 g/kg) or high dose (0.4 g/kg) (1 RCTs, low risk of bias, n=172).**

2.3.2.4 Streptococcal toxic shock syndrome

Sepsis is the inflammatory response of the body to severe infection, which can be caused by a variety of micro-organisms including bacteria, viruses and fungi. Signs of sepsis include fever, hypothermia, rapid heart rate and respiration; and a laboratory finding of increased or decreased white blood cell count[138].

Septic shock is a subset of severe sepsis, defined as persistence of sepsis-induced hypotension, despite adequate fluid resuscitation, which can lead to death.

Toxic shock syndrome (TSS) is a septic shock caused by the toxins released by bacteria, either the Streptococcus pyogenes or Staphylococcus aureus type. These are superantigen toxins that non-selectively activate the immune system (T cell) which causes a cytokine storm, followed by a multisystem disease. Streptococcal toxic shock syndrome (STSS) is a

severe life-threatening condition complicating invasive infections by streptococci, mainly group A streptococcus (GAS, S. pyogenes), which are a frequent cause of pharyngitis and skin infections such as cellulitis and impetigo as well as necrotising fasciitis. It has a rapid onset and death may occur within 2 days. The staphylococcus aureas type symptoms include high fever, accompanied by low blood pressure, malaise and confusion, which can rapidly progress to stupor, coma, and multiple organ failure.

In spite of medical progresses in the care of patients with septic shock during the last decades, this condition remains associated with high mortality. Early recognition and multidisciplinary management are key to the care of patients with streptococcal toxic shock syndrome. This may require: rapid diagnosis of infectious source(s) and antibiotics to treat the infection, intensive support of failing organs with oxygen to help with breathing and fluids to help prevent dehydration and organ damage, and in severe cases, surgery to remove any dead tissue. Polyvalent IVIg is recommended by some experts as an adjunctive treatment for STSS, because it contains antibodies that can neutralize the bacterial toxins.[139] In Belgium only the streptococcal toxic shock is recognised for reimbursement and will be analysed in this section. Ig for sepsis or septic shock are covered in the chapter on “other indications”.

The incidence of invasive group A streptococcal infections in industrialised countries is in the order of 3 per 100,000.[140]

Results

Only one relevant SR was identified for streptococcal toxic shock syndrome. Our search for more recent RCTs did not find any pertinent studies on this specific indication. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement 2). There are SR identified that covered sepsis and septic shock, also including STSS patients, however no specific analysis or conclusion was made for that specific subgroup. The use of Ig in patients, including neonates, with sepsis or septic shock will be treated in the chapter 2.3.4 on ‘other indications”.

The former KCE report

The former KCE report did not report on the specific indication of streptococcal toxic shock syndrome, but more general, on sepsis and septic shock. The conclusions were based on a Cochrane review looking at sepsis and septic shock[141] and 2 meta-analysis from 2007.[142,143] All those SRs also included studies with STSS patients, but no specific analysis or conclusion was made for that specific subgroup.

More recent SR

Our search for SR (search date from 2008) identified one relevant SR on streptococcal toxic shock in a subgroup of patients already treated with the antibiotic clindamycin.[144]

This SR was published in 2018 (AMSTAR 7/11)[144] and included a MA of four nonrandomised studies, comparing IVIg to standard care,[145-148] and one RCT comparing IVIg to placebo[149] (n=21 with an unclear risk of bias). The primary outcome studied was mortality at 30 days and their results showed a reduction from 33.7% to 15.7% (RR, 0.46; 95%CI 0.26–0.83; n=165). AEs were not reported in this SR.

Update primary studies

Our search for primary studies published since the SR of Parks et al. 2018 (search date 2017) returned no relevant RCTs on streptococcal toxic shock syndrome.

Conclusion

- **IVIg in clindamycin-treated patients with streptococcal toxic shock syndrome, seem to reduce all-cause mortality compared to standard care (based on a moderate quality MA including 1 RCT with unclear risk of bias, that terminated preliminary due to slow recruitment, n=21, and 4 nonrandomised controlled studies, n=144).**
- **There are SRs covering sepsis and septic shock which also included STSS patients, demonstrating a significant decrease of all-cause mortality compared to placebo (11 RCTs of high quality Jadad ≥3, n=2025). However, no specific analysis or conclusion was made for the specific subgroup of STSS.**

2.3.2.5 Kawasaki disease

The Kawasaki syndrome (KD) is an acute vasculitis affecting infants and young children (usually aged below 5), involving the coronary arteries. Its main cause is unknown. The main complications it may bring are coronary artery abnormalities (CAA) that may occur from the second week of illness during the convalescent stage. Due to the potential severity of these complications (even if rare), KD is most often treated in the hospital setting. IVIg is recognised as the gold standard and usually given as a single, high dose, which can be repeated after 24 hours if temperature is not controlled. Most often IVIg is given in combination with high dose aspirin, with the later continuing at low doses for a period of around 2 months in order to prevent cloting. Early diagnosis is considered critical to achieve optimal treatment result

KD occurs worldwide, with the highest incidence in Japan, and it mostly affects boys. The annual incidence for children aged below 5 years in Europe is 1/12,500-1/11,000.[n]

Results

Overall 4 SRs (one from the former KCE report and two more recent) were retained and analysed for Kawasaki disease. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement 2).

Previous KCE report

The KCE report from 2009 identified a high quality (AMSTAR 9/11) cochrane review published in 2003,[41] which included overall 16 RCTs to evaluate the efficacy of IVIg in children (aged below 19), diagnosed with Kawasaki disease. All studies identified, compared IVIg combined with salicytate (aspirin), versus salicytate alone. Different doses of IVIg were also compared. Two primary outcomes were studied: mortality and coronary artery abnormalities (CAAs), and myocardial function abnormalities (MFAs). Secondary outcomes included duration of fever, hospitalisation time and incidence of AEs.

Regarding mortality, and despite the fact that it was chossen as a primary outcome, the authors of the SR saw that very few studies offered information on that regard. Overall, only one death was reported in one of the 16 studies included. This happened in a child on the IVIg 400,g/kg group, during the sub-acute phase, and was due to a giant aneurysm. Given the scarcity of data, no conclusion could be made on mortality.

Regarding CAAs, the authors performed a MA, of 10 RCTs (n=970) which showed a statistically significant decrease in new CAA, in favour of IVIg plus salicylate over salicylate alone at day 30 (RR: 0,74; 95% CI 0,61-0,90). Sensitivity analyses confirmed these results in favour of the IVIg group. No significant differences were found after day 30. A subgroup analysis of 6 RCTs (n=521), excluding children with CAAs also found a significant reduction of new CAAs in the group treated with IVIg (RR: 0.67; 95% CI 0.46 to 1.00).There was also a significant decrease in duration of fever and hospitalization in cases treated with IVIg, while no statistically significant

[n] Orphanet - https://www.orpha.net/consor/cgi-bin/index.php?lng=EN

increase in AEs was observed in any of the 9 RCTs (n=1787) which captured this outcome. No severe AEs were reported.

MAs on dosing regimes (2 RCTs, n=253) showed a significant reduction in the number of CAAs (RR: 4,47; 95% CI: 1,55-12.86), with a single high dose of 2/gr/kg, compared to a low dose regime over a longer time period (i.e. 400mg/kg/day for 5 days).

More recent SRs on Immunoglobulins in KD

1. General KD population

Our review for more recent SRs (i.e. published in March 2003 or later), found no SRs focusing on the general KD population. However, two SRs focusing on refractory or IVIg resitant KD[150-152] were included in this review for completeness.[151] A further relevant SR was identified via a hand search. This focused on dose comparisons.[153] The three SRs retained presented a different focus and thus, no pooling of results was done. Instead, their results are described below.

2. Dose comparisons

A moderate-quality SR and meta-analysis (AMSTAR 6/11) by Chen et al.,[153] published in 2012, looked at the efficacy and safety of different does of Ig. They included 28 RCTs involving 2596 patients and compared the following dose regimes:

- 1gr/kg over 1-2 days versus 2 gr/kg on a single infusion (9 RCTs).
- 1gr/kg over 1-2 days versus 400 mg/kg for 4-5 days (11 RCTs).
- 2gr/kg over 1-2 days versus 400 mg/kg for 4-5 days (9 RCTs).

The main outcome studied was the incidence of CAAs (i.e. coronary artery dilatation and/or coronary aneurysm). Secondary outcomes included time for fever disappearence and AEs.

The authors mention that a single infusion of 2g/kg of IVIg results in a significant lower incidence of CAAs during the acute phase, and 6 months after treatment, when compared to a dose of 400 mg/kg over 4-5 days. This appears to confirm the findings from Oates-Whiteheat et al.[41] However, when looking at the quantititive data reported in this manuscript, it was noted that the 95%CIs for the RRs of CAAs crosses 1, thus, indicating non-significant results, contrarily to what the authors report: RR 0,76; 95%CI: 0,54, 1,06; p<0,05, reported for the acute phase, and RR 0,49; 95%CI: 0,18, 1,30; p<0,009, for 6 months after treatment .

An attempt was made to contact the authors of the study in order to clarify these results, but no answer was received before the publication of this report.

The same manuscript concluded that differences in the incidence of CAAs were non significant at 1 year and during the subacute phase.

No significant differences were found on CAAs between the 1gr/kg for 1-2 days and the 400mg/kg for 4-5 days regimens.

The mean time to resolve fever appeared to be significantly lower for the two high-dose regimes, compared to the 400mg/kg over 4-5 days: Mean differences, in days: -1,51; 95%CI:-1,95, -1,07; p<0,001, for 2g/kg in a single infusion versus 400mg/kg over 4-5 days, and -1,17; 95%CI:-1,47, -0,87; p<0,001, for 1g/kg over 1-2 days versus 400mg/kg over 4-5 days.

Non significant differences in any of the outcomes studied were identified when the two high-dose regimes were compared (i.e. 1gr/kg over 1-2 days versus 2gr/kg as single infusion).

Regarding AEs, no significant differences were observed between the different groups that were compared in this SR and none of the included RCTs reported any severe AEs. Only mild, short lived AEs such as chills, rash, shock, irritability, and palpitation were registered.

3. Evidence for sub-groups: Refractory KD patients

A very recent review,[150] of good quality (AMSTAR 9/11) compared different standard treatment options (i.e. infliximab or IVMP versus 2nd IVIg infusion), in patients with refractory KD according to the Japanese MoH or the American Heart Association. This review included overall 12 studies of which 9 were RCTs. Four RCTs, compared a 2nd infusion of IVIg versus infliximab, while the remaining 5 compared a 2nd infusion of IVIg versus IVMP. Two primary outcomes were studied: reduction in coronary arterial lesions (CAAs) and treatment resistance. Secondary outcomes included antipyretic effects and AEs. The MAs performed for IVMP studies did not

separate RCTs from non RCTs and included small studies considered of relatively low quality by the authors of the review (based on the cochrane RoB assessment tool) and thus, only the results on the comparison infliximab versus IVIg (whose MAs for clinical effectiveness included only RCTs) are considered in this report.

A MA of 3 RCTs on 98 patients showed no significant differences between infliximab and IVIg in reducing the incidence of CAAs (RR 0,85; 95%CI: 0,43, 1,69; p=0,46).

The pooled analysis of treatment resistance did not identified either any significant differences between these two treatment approaches (RR 0,43; 95%CI: 0,21, 0,89; p=0,667).

Total rates of AEs also appeared to be similar (RR 1,06; 95%CI: 0,69, 1,63; p=0,910). Only one analysis showed significant results in favour of infliximab for its antipyretic effects when compared to a 2nd infusion of IVIg (RR 1,52; 95%CI: 1,16, 1,99). The quality of the evidence was considered high for the primary outcomes and moderate for secondary outcomes.

A moderate-quality review (AMSTAR 6/11) published in 2015 by Yang et al.[152] focused instead on the comparison of glucocorticosteroids compared to a second IVIg infusion in IVIg-resistant Kawasaki disease patients. The review included 4 studies involving 127 patients overall (52 treated with a second dose of IVIg and 75 with glucocorticosteroids). Only two of these studies were RCTs, both with a very small sample size and authored by the same researcher.[154,155] Effectiveness was defined as coronary artery damage and time to recover body temperature.

Only the subgroup MA analyses performed on the results of the two RCTs, have been included in our review. These involved 37 patients overall and showed that body temperature in KD resistant patients was more effectively restored with glucocorticosteroids compared to a 2nd IVIg infusion RR 0,39; 95%CI: 0,20, 0,74; p=0,004. However, no statistically significant differences were found on the incidence of CAAs between one therapeutical approach or another RR 1,24; 95%CI: 0,28, 5,59; p=0,78.

Regarding AEs, glucocorticosteroids (i.e. Methylprednisolone pulse therapy) registered AEs including hypertension, hypothermia, bradycardia, thrombosis, and even gastrointestinal bleeding. However, these AEs were mostly temporary and children recovered without pursuing any treatment. A direct comparison of AEs with Ig treatment versus glucocorticosteroids was not offered in this SR.

Update primary studies

No new relevant RCTs on Kawasaki disease (general population or sub-groups), comparing Ig directly with another therapeutically option appear to have been published, after the search date of the core SR by Oates-Whiteheat et al. previously summarised.[41]

Conclusions

- **IVIg (in combination with aspirin) has been shown to be effective at reducing CAAs and the duration of fever in RCTs involving KD patients (1 SR of 16 RCTs, 12 with a low risk of bias and 4 with an unclear risk of bias).**
- **High single doses of IVIg (i.e. 2g/kg in a single dose) have been shown to be more effective than lower doses, given over longer administration periods (i.e. 400mg/kg/day for 5 days). (1 MA of 2 RCTs with an unclear risk of bias, n=253; and 1 SR of 28 RCTs with an unclear risk of bias; n=2596).**
- **Despite the proven efficacy of IVIg in this field, a minority of IVIg-refractory KD patients appear to still raise concerns with some recent reserch being devoted to this subpopulation:**
  - **No clear conclusions regarding the clinical effectiveness of Ig versus alternative therapeutic options (Ig vs infliximab – 1 MA of 3 RCTs, 1 of high, 1 unclear and 1 with a low-risk of bias, n=98; Ig vs glucocorticosteroids – 1 MA of 2 RCTs, with a moderate risk of bias; n=37) can be drawn from the research carried out up to this date in IVIg-refractory KD patients.**

2.3.2.6 *Multifocal Motor Neuropathy*

Multifocal motor neuropathy (MMN) is a rare disease affecting the body's motor nerves. It is characterized by progressive, muscle weakness and atrophy, exempt of sensory impairment. Symptoms may include weakness in the hands and lower arms; cramping; and or involuntary contractions or twitching. MMN is known to be due to an abnormal immune response, but its cause remains to this date unclear.

Most people are treated with IVIg which has shown to be effective and to improve symptoms over a short time period, although a maintenance dose (usually once monthly) is required.

Most people are diagnosed in their 40s or 50s, but it is a disease that can affect all ages.

Prevalence estimates for MMN range from 1 to 9 cases per 100 000 inhabitants.[o] In Belgium, there is a prevalence of 0.69 for 100.000 habitants and an incidence of 1.06 per million population in a year.[p]

Results

Overall 1 SRs (already captured in the former KCE report) and four more recent RCTs were retained and analysed for MMN. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement 2).

Former KCE report

The KCE report from 2009 identified a Cochrane review of high quality (AMSTAR 10/11) published in 2005, and updated in 2007[42] which included 4 small size RCTs involving overall 34 patients with confirmed or probable MMN. These studies compared the efficacy of IVIg versus placebo. Since different disability scales were used in the studies, the primary outcome was defined as the proportion of patients experiencing an improvement in disability between week 2 and 4 week after treatment, compared to baseline.

Secondary outcomes included muscle strength and frequency of AEs. MAs of the study results showed that muscle strength improved in 21/27 patients (78%) treated with IVIg and only in 1/27 (4%) of the patients in the placebo group (RR: 11,00; 95%CI: 2,86-42,25). Disability improved in a higher proportion of patients treated with Ig (39%) than with placebo (11%), but the difference was in this case, non-significant (RR: 3,00; 95%CI: 0,89-10,12). Mild, temporary AEs were reported in 71% of IVIg patients, but no serious AEs were observed.

More recent SRs on Immunoglobulins in MMN

Our search for more recent SRs (i.e. publication in 2008 or later) did not find any relevant reviews focusing on efficacy/effectiveness or safety of Ig in this indication.[28, 156-163]

One review by INESSS from 2017[164] was identified via hand searching. This included both SRs and primary studies to assess the clinical evidence on Ig in neurology in general, and was kept for reference checking purposes only.

Update primary studies

Our searches identified four relevant RCTs published after the search date of the update to the SR by van Schaik et al. (i.e. March 2007) with very different objectives.[43,56,165,166] For all others, reasons for exclusion included: study design,[167-172] focus/research question,[173] and publication type.[174, 175]

From the four primary studies retained, only one focused on the efficacy of IVIg versus placebo.[43] The other three focussed on comparing different Ig formulations (i.e. IV versus SC);[56] comparing two different brands of IVIg (IqYmune versus Kiovig);[166] and comparing the administration of multiple small dosages of SCIg with a large volume infusion of SCIg, facilitated by pre-treatment with hyaluronidase.[165] Given the different focuses of these studies, no attempt to pooling their results was made, and instead, a description of their aims method and results is provided below.

[o] Orphanet - https://www.orpha.net/consor/cgi-bin/index.php?lng=EN

[p] Calculation based on data of 2017 in the Belgian Neuromuscular Disease Registry by Sciensano

Hahn et al.[43] (unclear risk of bias), performed a cross over double blind RCT involving 44 patients pre-treated with IVIg for a minimum of 3 months. The aim was to assess the efficacy of IVIg by comparing the outcomes in patients randomised to IVIG followed by placebo for 12 weeks each, to those of patients randomised to placebo followed by IVIg for the same treatment period. Primary outcomes included mean maximal grip strength of the more affected hand, and disability. The study also looked at AEs. The results showed that:

- Mean maximal grip strength of the more affected hand declined 31.38% during placebo treatment and increased 3.75% during IVIg therapy (p=0.005).
- In 35.7% of participants, disability scores for upper limbs worsened during placebo, while these scores improved in 11,9% of participants during IVIg treatment (p=0.021).
- Sixty-nine percent of patients switched prematurely from placebo to open-label IVIG. Regarding safety, one severe AE (pulmonary embolism) linked to IVIg therapy occurred. In addition 100 non-serious reactions were captured during the study.

A further study[56] (low risk of bias), consisted of a cross over, single blinded RCT involving just 9 IVIG responsive patients who were randomised to receive either SCIg or IVIg for a period equivalent to three IVIG treatment intervals before crossing over to the other treatment. Primary outcomes were strength of the affected muscles and quality of life. AEs were recorded by nurses in a diary throughout the study. The study showed that:

- No significant differences (p=0,86) in mean changes in the strength of the affected muscles were observed (3.6%; 95% CI: -3.6% to 10.9% during the SCIg period versus 4.3%; 95% CI: -1.3% to 10.0% during IVIg treatment).
- No significant differences were seen in patient's QoL. Although the possibility to follow treatment with SCIg at home was perceived as an advantage, the fact that SCIg administration required more frequent doses, made IVIg more attractive for others.

Mild AEs were more common with SCIg, but all were temporary and did not prevent patients from continuing treatment. Two moderate AEs were recorded: one for a patient on SCIg who had a sustained erythema and oedema for a few weeks and one for a patient on IVIg who experienced a local infection on the catheter site. No systemic AEs were registered.

Léger et al.[166] (low risk of bias), evaluated the non-inferiority of IqYmune versus Kiovig, in a randomised, double-blind cross over RCT involving 22 adults with probable or definite MMN (according to the EFNS/PNS) 2010 guidelines. Patients had to be following a treatment with a stable maintenance dose 1g/kg over 1-3 days to 2g/kg over 2-5 days, every 4-8 weeks) of any brand of IVIg (Kiovig excluded) for a minimum of 3 months prior to their enrolment. The 22 participants were randomised to receive either Kiovig first for 21-25 weeks, followed by IqYmune for a further 21-25 weeks (n=12), or IqYmune, followed by Kiovig (n=10). Dosing and frequencies were kept the same as in the pre-randomisation phase. Baseline characteristics, appeared to be similar between the two groups.

The primary outcome was efficacy measured by means of the MMRC sum score of 10 muscle groups (score from 0 to 100). Other muscle strength measurements were captured as secondary outcomes. Frequency and type of AEs were registered throughout the study. The results showed:

- No significant difference was found between IqYmune and Kiovig in terms of MMRC sum score for either the ITT analysis (difference -0,01 (95%CI -0,51; 0,48; p=0,96), or the PP analysis (difference -0,14 (95%CI -0,60; 0,31; p=0,51).
- No significant differences were found either for any of the secondary outcome measurements.
- Regarding safety, no significant differences were found between the two arms in the incidence of common AEs and no AEs was considered serious. Overall, 52% of participants receiving Kiovig and 46% of those receiving IqYmune experienced AEs (mainly headaches and/or fatigue). No thromboembolic events were registered.

Finally, the most recent study,[165] a non-inferiority, observer-blinded cross over randomised trial, with an low risk of bias, compared conventional infusions via multiple small dosages of SCIg versus large volume infusions

of SCIg, facilitated by pre-treatment with hyaluronidase. Twenty adults diagnosed with MMN according to the criteria of the EFNS/PNS, receiving maintenance therapy with conventional infusions of SCIg were randomised to continue with the conventional approach (i.e. SC infused at a concentration of 16% Ig at the abdomen or the thighs, at an average infusion speed of 20ml/hour and a maximum infusion volume of 20 ml per site), or receive an injection of hyaluronidase (at a dose of 80U/gram IgG), followed by infusion of a 10% Ig (maximum volume infused per site 600ml at a rate of 300ml/hour). The study period was 48 weeks overall, with patients receiving 24 weeks of each treatment. The primary outcome was isometric muscle strength, while secondary outcomes included: disability, manual assessment of muscle strength, grip strength, dexterity, walking performance, and QoL, as well as patients' preferences. AEs were registered throughout the study. Two patients left the hyaluronidase+ SCIg before the end of the study, and a further patient received only half of the prescribed dose. Data was analysed according to ITT. Results showed:

- Median isometric strength values following treatment were not significantly different for those receiving hyaluronidase+ SCIg (100,8%; 95%CI: 94,5%-7,1%) versus those on conventional SCIg (105,9%; 95%CI: 99,8%-112,0%); p=0,10. Inferiority testing confirmed non inferiority (p=0.0014).
- No statistically significant differences were found for any of the secondary outcomes studied.
- Higher relative frequency of local AEs per infusion was seen in the hyaluronidase+ SCIg (0,63; IQR: 0,23-1,00), versus conventional SCIg (0,09; IQR: 0,0-0,22); p=0,005. However, given the higher number of infusions linked to conventional SCIg use, the absolute number of local AEs was similar in both arms.
- No serious AEs were detected.

Conclusions

- **Existing evidence (mostly limited to small sample size studies) suggest IVIg may be efficacious in MMN patients (1 MA of 4 RCTs, 3 with a low risk of bias and 1 with an unclear risk of bias; n=34; and 1 cross over RCT, with unclear risk of bias, n= 44).**
- **Only one, small, cross over RCT compared the efficacy of different formulations (IV versus SC) in MMN patients. The study found no significant differences, in terms of mean changes in muscle strength, or patient's QoL between the two administration groups (1 RCT, low risk of bias, n=9).**
- **One small cross over RCT showed IqYmune to be non inferior to Kiovig in terms of efficacy measured by means of the MMRC sum score of 10 muscle groups. The frequency and severity of AEs were also not signifcantly different (1 RCT, low risk of bias, n=22).**
- **One small cross over RCT showed large volume infusions of SCIg, facilitated by pre-treatment with hyaluronidase to be non-inferior to conventional infusions via multiple small dosages of SCIg in terms of efficacy (measured as isometric strength values). Total number of AEs appeared not to be significantly different (1 RCT, low risk of bias, n=20).**

2.3.2.7 Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) is an auto-immune disorder characterized by an auto-antibody induced destruction of platelets by the reticuloendothelial system. It is defined by too few platelets in the blood, normal bone marrow and the absence of other causes of thrombocytopenia. It causes a characteristic purpuric rash and can lead to easy or excessive bruising and bleeding. Most often the disease manifests as an acute condition in children (usually after an infection), while in adults the disease is often long term (chronicity, defined as lasting over 6 months), and has an unknown cause.

Prevalence has been reported to be of around 10-50 per 100,000 inhabitans, while the annual incidence in adults is estimated to be between 1,6 and 3,9/ 100,000 inhabitants, with a female to male ratio of 1.3:1.[q]

The acute form often has a spontaneous resolution within two months, although 15-20% of children with acute ITP, may develop a chronic form of ITP. The most severe complication of ITP is intracranial haemorrhage, which although relatively rare, is life-threatening.

In mild cases, careful observation may be enough, but very low counts or significant bleeding would usually require treatment with corticosteroids, Ig, anti-D Ig, or immunosuppressive medications. The treatment goal is to prevent serious and potentially fatal bleeding. Refractory ITP (not responsive to conventional treatment) may require the surgical removal of the spleen.

Results

Overall 4 SRs (one already captured in the former KCE report) and 3 more recent RCTs were retained and analysed for ITP. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement 2).

Former KCE report

The previous KCE report found one SR of high quality, (AMSTAR 9/11) published in 2008 by CADTH (Canadian Agency for Drugs and Technologies in Health - https://www.cadth.ca),[176] including 28 RCT: 15 in children with acute ITP, 4 in children with chronic ITP, 7 RCTs in adult ITP and 2 RCT in mixed populations. In the included studies, IVIg were compared with steroids, anti-D Ig, or close observation. The studied outcomes included reduction in bleeding, deferred splenectomy, and time to a platelet count of greater than or equal to 20x109/L or greater than or equal to 50x109/L.

Results showed that IVIg (0.8 to 1 g/kg/day over one to two days) in children with acute ITP is more efficacious when compared to corticosteroids in terms of early improvement of thrombocytopenia to platelet counts greater than or equal to 20x109/L, with relative risks and 95% CI as follows:.

- at 24 hours (RR: 1.55; 95%CI: 1.19, 2.03; 5 RCTs, n=289).
- at 48 hours (RR:1.33; 95%CI: 1.14, 1.55; 5 RCTs, n=288).
- at 72 hours (RR: 1.17; 95%CI: 1.06, 1.30; 4 RCTs, n=246).

No clear conclusions could be drawn regarding the potential clinical benefit of IVIg versus other interventions in children with chronic ITP or for the long-term management of adult ITP. Most of the studies included were rated by the authors as being of poor quality.

Regarding safety, incomplete AE reporting impeded the authors from completing a qualitative or quantitative analysis. Frequently reported IVIg related AEs included headache, vomiting, fever and chills, meningismus and aseptic meningitis, and rash. Commonly reported corticosteroid related

AEs were increase in body weight, cushingoid features, dyspepsia, glycosuria, hypertension, headache, and behavioural changes. No trials reported thrombotic events or infectious complications.

More recent SRs on Immunoglobulins in ITP

Our search for more recent SRs resulted in three SRs retained for further analysis.

The first of these, a high quality study (AMSTAR 9/11) in children (younger than 18 years) with ITP, compared different IVIG regimes versus a standard single dose of 50 g/kg of anti-D Ig.[177] Overall 11 studies involving 558 children were included. The primary outcomes studied included platelet response and bleeding. Other outcomes considered were splenectomy, disease course (i.e. prevention of chronicity), mortality, and safety.

[q] Orphanet - https://www.orpha.net/consor/cgi-bin/index.php?lng=EN

The MA of 8 of these RCTs (7 on acute and 1 on chronic ITP; n=484) showed that anti-D was significantly inferior to IVIG at increasing platelet counts, both for a thresholds of >20 × 10_9/L at 24-72 hours (response rate ratio for anti-D vs IVIg: 0.85, 95% CI 0.78-0.94). A similar results was obtained for a threshold of >50 × 109/L at 72 hours, based on 4 RCTs involving 282 patients (response rate ratio for anti-D vs IVIG: 0.75, 95% CI 0.61-0.92), although some heterogeneity was found between the studies for this comparison. Sensitivity analyses confirmed the clinical advantage of IVIG when platelet response was defined as >20 × 109/L, while showed inconsistencies when using the higher threshold (i.e. >50 × 109/L).

Bleeding response was assessed in 4 studies only and the presence of some heterogeneity impeded clear conclusions on this regard.

Regarding treatment related AEs, general symptoms such as fever, chills, nausea, or headache were registered in 134 of 477 children (7 RCTs) and appeared to be less frequent with anti-D infusion than with IVIg (Peto OR 0.39, 95% CI 0.25-0.62).

In terms of safety, a significantly higher risk of haemolysis was observed after anti-D treatment, while a serious AEs was reported for IVIg (i.e. 1 aseptic meningitis with generalized seizures 24 hours after infusion. No deaths were reported in any study.

The authors highlighted that the overall quality of the studies was low (according to the Cochrane RoB criteria).

No SRs focused on the adult population were identified via our search.

One SR of moderate quality (AMSTAR: 6 /11) published in 2010 by Qin et al.,[46] compared low-doses of IVIg (mostly 0,2g/Kg/day over 5 days) versus high doses (mostly 0,4-0,5g/Kg/day over 4-5 days) for the treatment of acute ITP. The SR included 13 RCTs involving overall 646 patients. Outcomes considered included: Effective rate, time of cessation of bleeding, time of platelet count beginning to rise, platelet count at different points in time, AEs and rate of chronification. The results showed non-significant differences in any of the studies outcomes with the exception of AEs which appeared to be significantly less frequent with low doses of IVIg: (OR: 0.39; 95% CI: 0.18–0.83; P=0.01).

A final SR specifically focused on cost effectiveness studies was found[178]. This was used for reference checking purposes in our review of economic evidence section.

Update primary studies

Our search for primary studies identified 3 relevant RCTs, all carried out in paediatric populations.
Koochakzadeh et al. 2018;[179] (low risk of bias), undertook a double blind RCT involving 98 children with acute ITP, randomised to compare IVIG (1 g/kg/day for 8 to 12 hours in 2 days) and anti-D at 75 µg/kg. Outcomes studied included platelet count, haemoglobin level, and AEs, observed on days 1, 3, 7, 14, and 21 after treatment. Results showed that:

- Platelet count increased in both groups (P < 0.001), with non-significantly different results between the two treatments (P > 0.05).
- Heamoglobin levels decreased significantly after treatment in both groups (P < 0.001), with a non-significantly different effect between groups.
- No significant differences were observed between the two groups in terms of treatment-related AEs, including fever and chills (4.1% with anti-D group versus 10.4% with IVIg), severe haemolysis (4.5% with anti D group versus 0% with IVIg) and headaches (6.25% with anti-D group versus 4.1% with IVIg group).

A further RCT by Heitink et al., published in 2018;[44] (low risk of bias), compared a single injection of IVIg (0,8g/kg) versus careful observation in 206 children aged 3 months to 16 years, newly diagnosed with ITP, with platelet count ≤20x10_9/L and mild to moderate bleeding. No pre-medication was used and the primary outcome was defined as the development of chronic ITP (i.e platelet count <150x10_9/L after 6 months, and <100x10_9/L at 12 months). Other outcomes studied included recovery rates, bleeding scores and AEs and HRQoL. Results showed that:

- 18,6% of IVIG patients developed chronic ITC (defined as platelet count <150x10_9/L after 6 months), versus 28,9% in the observation group, but the difference was non-significant (RR: 0,64; 95%CI: 0,38-1,08).

- When the definition of chronic was taken as platelet count <100x10$_9$/L at 12 months, 10% of IVIG patients versus 12% in the observation group developed chronic ITP (RR: 0,83; 95%CI: 0,38-1,84).
- Complete response was significantly higher for IVIg at 3 months with a RR of 1,24 (95%CI: 1,04-1,47; p=0,01), but the difference was non-significant at 6 months.
- More grade 4-5 bleeding was observed in the observation group (9% - 10 cases) versus the IVIg group (1% - 1 case). Treatment related AEs such as allergies, nausea vomiting or headache were more common in the IVIg group (n=5) compared to none in the observation group. Other severe AEs (i.e. infections and observation after mild traumatic head injury) were also more common in the observation group (n=6 versus 4 in the IVIg group).

An open label RCT by Elalfy et al, published in 2017;[180] (unclear risk of bias), studied IVIg from mini-pools of 20 plasma donations (1g/kg over 6-8 hours), versus standard IVIg (1g/kg at a single dose) and observation in 72 patients children with IT (n= 24 in each arm). The outcomes studied included complete response, time to response and AEs. The results showed that:

- Mini-pool IVIg presented non-significant differences in platelet count and bleeding episodes on day 28, compared to standard IVIg and was significantly more effective than observational (p<0.001).
- Response rates were 75,4% (18/24); 83,4% (20/24) and 50% (12/24) for the mini pool IVIg, the conventional IVIg and the observation groups respectively.
- AEs were more common in the Ig groups (8 comparable AEs reported in each of these groups), versus the observation group, in which 6 AEs were reported. However no unexpected AEs were seen and mini pool IVIg appeared to be well tolerated.

Conclusion

Conclusions on children:

- **IVIg (0,8-1,9/kg/day) in children with acute ITP appears to be more efficacious when compared to corticosteroids (1 MA of 5 RCTs, of low quality, n=289).**
- **IVIg (different doses) were more efficacious (at increasing platelet counts) than anti-D Ig (1 dose of 50g/kg) at 24-72 hours (MA of 8 RCTs, of high or unclear risk of bias, n=484). AEs appear to be less frequent with anti-D Ig. (MA of 7 RCTs, with high or unclear risk of bias, n=477).**
- **A single infusion of IVIg is more efficacious (higher response rates and and lower rate of chronic ITP), and safer (less frequent AEs) than careful observation, in children with acute ITP but differences did not reach statistical significance (1 RCT, with a low risk of bias, n=206).**
- **IVIg made from a mini pool of 20 plasma donours appeared not to be significantly difference in terms of platelet count response rates or rate of AEs when compared to conventional IVIg, in children with newly diagnosed ITP, while it was more efficacious (at increasing platelet count and decreasing bleeding episodes), but presented more frequent AEs when compared to observation. (1 RCT, with an unclear risk of bias, n=72, 24 in each arm).**
- **AEs appeared to be significantly less frequent with low doses of IVIg (0,2g/Kg/day over 5 days) versus high doses (0,4-0,5g/Kg/day over 4-5 days) in children with acute ITP (1 SR of 13 RCTs, of low quality, n=646), but no significant differences were found in efficacy.**

No clear conclusions could be drawn from the available evidence regarding the potential clinical benefit of IVIg versus other interventions in children with chronic ITP or in adults.

2.3.2.8 Guillain-Barre Syndrome

Guillain-Barre syndrome is a rare, acute disease of the peripheral nerves. It often appears days or weeks after an infection (of the respiratory or digestive tracts) and is characterized by rapid development of weakness and numbness of the limbs and often also of the facial, swallowing or breathing muscles. Treatment must be quickly put in place to limit nerve damage and most often patients are hospitalised. Although there is no cure for this syndrome there are two well recognised treatments, IVIg and plasma exchange (or plasmapheresis), which are thought to be equally effective at reducing symptoms and time to recovery.

Guillain–Barré syndrome is rare, with a prevalence of around 1-9/100,000 and an overall annual incidence between 1/91,000 and 1/55,000. In Belgium there is a prevalence of 0.86 for 100.000 habitants and an incidence of 0.99 per million population in a year[r]. In Europe and North America, acute idiopathic demyelinating polyneuropathy (AIDP) is the most frequent form of GBS (accounting for around 90% of cases) and as a consequence, it is not uncommon to see both terms used as synonyms[s].

Results

Overall 2 SRs were retained for GBS. The first, was already captured in the former KCE report, while the second was an updated version of the same review. The search for more recent RCTs identified two relevant studies. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement 2).

Former KCE report

The previous report identified one good quality Cochrane review, updated in 2004,[181] looking at the efficacy of plasma exchange versus placebo. The overall result of this review highlighted that plasma exchange significantly improves recovery in patients suffering from GBS. Following these results plasma exchange was established as first line therapy for GBS patients.

A further high quality Cochrane SR (AMSTAR 9/11), this time focused on Ig use, was also captured in the 2009 report. Originally published in 2001, it was updated in three occasions, with the last update dating from 2007.[182] The review compared Ig with plasma exchange, and included 6 RCTs overall. The primary outcome studied was change in a seven-grade disability scale 4 weeks after randomisation.

A meta-analysis of 5 of these RCTs, (n=536 mostly adult patients) unable to walk unaided, showed that Ig started within two weeks from onset offered a similar disability improvement rate compared to plasma exchange, (WMD: -0.02 (95% CI: -0.25 to 0.20) of a disability grade more improvement in the IVIg. There were no significant differences in other (secondary) outcomes, including: mortality, time from randomisation until recovery of unaided walking, time from randomisation until discontinuation of ventilation (for patients on ventilation), death or disability (inability to walk without aid) after 12 months, treatment related fluctuations or relapses, and AEs.

Giving Ig after plasma exchange did not appear to offer an additional benefit.

A new update by the same authors was published in 2014 and is discussed below in more detail (see section on more recent SRs on Ig in GBS).

More recent SRs on Immunoglobulins in GBS

Our search for more recent SRs identified a high quality Cochrane review and meta-analysis (AMSTAR 9/11) published in 2014[183] which was retained for its relevance. Two other SRs originally retained for analysis,[184, 185] offered no additional RCTs and were less detailed in their reporting than Hughes et al. Therefore, no further analysis was done on them. The SR published in 2007 by INESSS on Ig use in neurology[186], was used for reference checking purposes, in order to ensure no relevant studies had been missed.

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[r] Calculation based on data of 2017 in the Belgian Neuromuscular Disease Registry by Sciensano

[s] Orphanet - https://www.orpha.net/consor/cgi-bin/index.php?lng=EN

The Cochrane review by Hughes et al.[183] included overall 12 RCTs looking specifically at the efficacy of IVIg in adults or children with Guillain-Barre syndrome.

Of these studies, 7 compared the effectiveness of IVIg (most frequently at a dose of 2g/kg over 4 or 5 days) versus that of plasma exchange in severe cases (n=623). The primary outcome in the MA was change in disability at 4 weeks after randomisation. Secondary outcomes included mortality, the proportion of patients disable at 12 months, the proportion of patients with ≥1 disability grade improvement at week 4 and the proportion of patients experiencing a relapse at week 12. The results of the MA showed no significant differences between IVIg and plasma exchange with regard to change in disability at week 4 (5 RCTs, n= 536). No significant differences were captured either for any of the secondary outcomes.

AEs appeared not to be significantly more frequent with IVIg, (RR: 0.84, 95% CI: 0.54 to 1.30, based on 4 RCTs, n=388), but patients on IVIg, were more likely to complete their treatment (compared to those on plasma exchange). The authors also showed that the addition of IVIg after plasma exchange therapy does not provide additional benefit over plasma exchange alone, in terms of change in disability at week 4 (MD: -0.20; 95%CI: -0.54, 0.14 , 1 RCT, n=249).

The evidence was rated as of having a moderate quality and a variable risk of bias.

Update primary studies

Our review of primary studies published after the Cochrane review by Hughes et al.[183] only identified[187-189] two small trials carried out in India, which had a special focus on costs but also reported on clinical outcomes. The first of these, a study with a high risk of bias,[190] compared IVIg (at a dose of 2/g/kg over 5 days) with plasma exchange in 37 participants. Their main outcomes were muscle strength and costs. Results indicate that:

- Muscle strength was not statistically different between the IVIg and the plasma exchange groups neither at hospitalisation, nor at discharge.
- Mean costs of plasmapheresis (US$2 585) appeared to be significantly lower than those of IVIg (US$4 385).
- Complications were not significantly different in the two groups.

The second primary study,[191] consisted of an RCT with a low risk of bias, aimed at comparing costs and outcomes (differences in disability) of IVIg and plasma exchange as first line treatments for 40 Guillain Barre Syndrome patients with a disability score at enrolment of 4-5. Results showed that:

- No significant differences were observed in disability scores over the treatment period, while costs appeared to be lower in the plasma exchange group (US$2 041), versus the IVIg group (US$4 298).
- AEs were not significantly different in both treatment arms.

Conclusions

- **Changes in disability scores are no significantly different when comparing IVIg and plasma exchange (MA on 5 RCTs of moderate quality, and variable risk of bias; n= 536 and 1 RCT with a low risk of bias, n=40).**
- **Giving Ig after plasma exchange did not appear to offer an additional benefit (1 RCT with a low risk of bias).**
- **Changes in muscle strength are not significantly different with IVIg versus plasma exchange (1 RCT with a high risk of bias, n=37).**
- **Plasma exchange appears to offer a significantly cheaper alternative to IVIg (2 RCTs, 1 with a low risk of bias and 1 with a high risk of bias, n=77).**

2.3.3 *Indication-specific results - Commonly recommended indications in other countries*

Indications commonly covered in (at least 3 out of the 4) countries analysed in our international comparison, (i.e. Australia, Canada, France and England) are:

- Myasthenia Gravis
- Dermatomyositis and Polymyositis
- Antibody mediated rejection in Solid Organ Transplant
- Feto/Neontal Thrombocytopenia
- Pure red cell aplasia
- Post transfusion purpura
- Pemphigus vulgaria and foliculae.

Table 4 offers an overview of the relevant SRs identified and included in our review for these indications, which are not currently reimbursed in Belgium. In appendix 2.2 and 2.3, the extraction tables for the SR and RCTs are given.

Table 4 – Summary table on available evidence for indications commonly recognised in other countries

Indications	Main findings	Level of evidence
Myasthenia Gravis	Severe or worsening MG with exacerbations, IVIg significantly reduce symptoms compared to placebo IVIg have similar effects on functional parameters and QoL compared to PE Low dose (1g/kg) is as effective as high dose (2g/kg) IVIg (non sig. differences in mean change in muscle score)	IVIg vs. placebo: 1 RCT, low RoB, (n=51). IVIg vs. PE: 2 RCTs; low RoB, (n=171) Low-dose vs high dose: 1 RCT; low RoB, (n=173)
	Patients undergoing surgery (e.g. thymectomy) for preventing MG crises. Positive effects on intubation and surgery time in patients seen with IVIg vs PE. No differences (in MG crises or other post-operative outcomes) found in well-controlled patients vs placebo	MG crisis after surgery: IVIg vs. PE: 1 RCT-high RoB, (n= 24) IVIg vs. placebo: 1 RCT-low RoB, (n=47)
	In chronic stable MG, there is insufficient evidence from RCTs to determine whether IVIg is more efficacious than a placebo. Similar efficacy was observed when comparing IVIg to PE	Chronic stable MG: IVIg vs. placebo: 1 RCT; unclear RoB (n=15) IVIg vs PE: 1 RCT, high RoB (n=12)
	For Lambert-Eaton MG, a short-term positive effect in muscle strength is observed for IVIg vs placebo.	Lambert Eaton: 1 crossover RCT; unclear RoB, (n=10)
	Discrepant results on IVIg for steroid resistant patients with dermato-or polymyositis.	Derma: 1 cross over RCT; n=15; low RoB

Indications	Main findings	Level of evidence
Dermatomyositis and Polymyositis	IVIg appear to offer significant improvements in muscle strength in patients with steroid-resistant dermatomyositis	
	Non-significant improvements in muscle strength were seen in Japanese patients with steroid-resistant dermatomyositis or polymyositis.	Derma and Poly: 1 cross over RCT; n=26; unclear RoB
Solid organ transplant (preventing antibody mediated rejection)	Prevention of graft failure (antibody mediated rejection). Evidence limited to kidney transplantation and in different subpopulations, limiting generalisability.	
	Re-transplantation: sig. increase in 5-year graft survival with IVIg added to the quadruple-immunosuppressive therapy. No sig. effect on overall survival (mortality)	Re-transplantation: 1 RCT, unclear RoB, (n=41).
	Steroid-resistant rejections: No sig. differences in rejection rates with IVIg vs monoclonal therapy	IVIg vs. monoclonal (OKT3): 1 RCT; high RoB, (n=30)
	Highly sensitised patients: sign. decrease in anti HLA-antibodies was seen in IVIG vs placebo, which reduced waiting times before transplantation (4.8y for IVIg vs 10.3y for placebo p=0,049). No impact on outcomes such as graft survival or overall survival at 30 months after transplantation	Highly sensitised patients: 1 RCT; low RoB, (n=101).
	In chronic AMR, no impact of IVIg (even in combination with rituximab) on renal function parameters vs placebo.	1 RCT; low RoB, (n=25)
Fetoneonatal Thrombocytopenia	IVIg recognised as “standard” therapy	No RCTs. 27 observational studies (n= 241)
	Pregnant women with FNAIT, but with no prior babies with intracranial haemorrhages: IVIg have a similar effect on outcomes (intracranial haemorrhage, fetal/neonatal platelet count or preterm birth) cpmpared to corticosteroids	IVIg vs. corticosteroids: 1 RCT; unclear RoB , n=39.
	Low dose IVIg (0,5g/kg/week) does not sign. differ compared to high dose IVIg (1g/kg/ week)	Low dose vs high dose: 1 underpowered RCT; low RoB; (n=23)
Pure red cell aplasia	Given the lack of evidence from SRs or RCTs, no conclusions could be drawn regarding the use of Ig for pure red cell aplasia (PRCA). Some positive findings in a subgroup of immunocompromised patients with PRCA diagnosed with parvovirus B19, and a subgroup of patients with hypogammaglobulinemia	Only retrospective case series on specific subgroups exist. Parvovirus B19 (>100 cases); Patients with hypogammaglobulinemia (11 cases)
Post transfusion purpura/Thrombocytopenia	Given the lack of evidence from SRs or RCTs, no conclusions could be drawn regarding the use of Ig for post-transfusion purpura (PTP).	Only retrospective case series exist
	Evidence from RCTs in steroid resistant patients only:	

Indications	Main findings	Level of evidence
Pemphigus Vulgaris, Foliculae	IVIg at a dose of 400g/kg for 5 days sign. reduces disease progression compared to placebo This effect was not seen at a dose of 200mg/kg for 5 days	Disease progression: 2 RCTs; low RoB; (n=117) Low dose vs high dose: 1 RCT; low RoB, (n=61)
	IVIg reduces symptoms in the short term (day 1- 15) , and the effect is sig. larger in the more severe patient subgroup compared to placebo	Symptom reduction: 1 RCT with a low RoB n=61 Severe subgroup: 1 RCT with a low RoB n=56

Ig: Immunoglobulins; IVIg: Intravenous Immunoglobulins; MG: Myasthenia Gravis; PE: Plasma Exchange; QoL: Quality of Life; RCT: Randomised Controlled Trial; RoB: Risk of Bias; SR: Systematic Review; FNAIT: FetoNeonatal Allo Immune Trombocytopenia

2.3.3.1 Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disease, where auto-antibodies can be found against receptors responsible for transmission of signals for muscle contraction. As a result, the signal from the nerve to the muscle can no longer be passed on, which leads to clinical symptoms of muscle fatigue and weakness that can be generalized across multiple muscle groups but mostly skeletal muscles (and not smooth muscles and heart muscle). Myasthenia may have a stable course (called chronic) or be associated with exacerbations. Usually, the start is characterized by ocular symptoms, which in most cases changes to a generalized form. Involvement of respiratory musculature can be life-threatening because of swallowing difficulties or respiratory failure and is called a MG crisis.

Specific forms of Myasthenia gravis include Lambert-Eaton myasthenic syndrome (LEMS).

Although there is no cure for this syndrome there are well recognised treatments: cholinesterase inhibitors, corticosteroids and immunosuppressiva to reduce the production of antibodies, and thymectomy as the thymus is thought to trigger antibody production. As an adjuvant therapy, indicated to treat a sudden worsening of symptoms, or as a disease stabilizing regimen to reduce risk of postoperative respiratory complications, IVIg and plasma exchange (PE also called plasmapheresis PP) are thought to be equally effective at reducing symptoms and time to recovery. However IVIg is considered to be easier in terms of administration and side effects compared to PE.[192]

An immunomodulation dosage of 2g/kg spread over 2 to 5 days is often considered.[193]

The incidence is estimated to be between 0,4 and 3,03 /100,000.[t] In Belgium the prevalence is estimated to be 1.78 for 100.000 habitants and the annual incidence of 2.03 per million population.[u]

[t] Orphanet: https://www.orpha.net/consor/cgi-bin/Disease_Search_Simple.php?lng=EN

[u] Calculation based on data of 2017 in the Belgian Neuromuscular Disease Registry by Sciensano

Results

Overall 6 SRs (one already identified in the former report) and 3 more recent RCTs were retained for MG and are described below. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement chapter 2).

Former KCE report

The former report based its results on a Cochrane systematic review from 2008[194], including 6 RCTs. Although a meta-analysis was not possible due to heterogeneity in comparators and outcomes, the authors concluded that Ig is more effective than placebo and as effective as other therapies (plasma exchange and steroids) for severe MG exacerbation and MG worsening, but this benefit was not shown in mild and moderate disease. An updated version of this Cochrane SR was identified via our SR search and is described below.

More recent SRs on Immunoglobulins in MG

Our search for more recent SRs yielded five relevant SRs.[185,186,192,195,196] We describe the Cochrane SR in more detail, as it was the one with the highest AMSTAR score, as well as Ortiz-Salaz 2016, because it performed a MA comparing IVIg to Plasma-exchange.

A Cochrane high quality SR (AMSTAR 8/11) published in 2012,[192] which is an update of the Cochrane review of 2008 by the same authors, included 5 RCTs for acute worsening MG (n=428)[53,197-200] and 2 for chronic stable MG (n=27).[201,202] For acute worsening/exacerbation, the primary outcome was mean change in a muscle strength score after 15 days. For chronic stable MG, the primary end point was an improvement by at least one grade in a functional scale, at least six months after the start of treatment.

Pooling of data for a MA was not possible because of high heterogeneity. A description of the included studies was provided.

- IVIg compared to placebo in acute worsening
  - Only 1 RCT was identified comparing IVIg to placebo (low risk of bias, n=51).[200] The mean change on day 14 in the quantified myasthenia gravis score (QMGS) was -2.5 (SD= 3.4) in the IVIg group and -0.9 (SD=2.4) in the placebo group, resulting in a mean difference of -1.60 (95% CI -3.23 to 0.03) (P = 0.05). This result was borderline statistically significant in favour of IVIg. A subgroup analysis showed a pronounced significant effect in the moderate to severe MG (IVIg n=13; placebo n=15): on day 14 the mean difference in Quantitative Myasthenia Gravis score (QMGS) was -3.40 (95% CI -5.74 to -1.06) (P = 0.004) in favour of IVIg. No serious adverse events were observed, and headache was the most frequent side effect, occurring in 75% of patients in the IVIg group and in 19% of patients in the placebo group (P <0.001).
- IVIg compared to Plasma exchange (PE) in acute worsening
  - In the RCT comparing IVIg and plasma exchange for myasthenia worsening (low risk of bias, n=84),[197] the mean change in QMGS was not significantly different between the two treatment groups at day 14 (3.2+- 4.1 and 95% CI (2–4.5) for IVIg group and 4.7 +- 4.9 (95% CI 3.2–6.2) for the PLEX group (p = 0.13). Clinical relevant response was defined as those who had a decrease in QMGS of > 3.5. Adverse events in the IVIg group were mostly headache, nausea, allergic reaction and 1 reported haemolytic anemia and hypothension. In the PE group, adverse events such as vasospasm, citrate reaction, and one myocardial infarct were seen.
  - In the unblinded Gajdos 1997 trial comparing IVIg and plasma exchange (n=87, low risk of bias),[198] the mean change in a muscle strength score between day 0 and day 15 was not significantly different between the two treatment groups: 15.60 in the IVIg group versus 16.60 in the PE group, MD -1.00 in favour of IVIg (P = 0.77).
- IVIg compared to methylprednisolone in acute worsening
  - In a unpublished underpowered trial (n=33, unclear risk of bias)[199] comparing IVIg and methylprednisolone, the mean (SD) change in the total QMGS was 1.87 (2.82) in the IVIg and 2.53 (2.79) in the methylprednisolone group (P =0.51).

- Low dose (1g/kg) versus high dose (2g/kg) in acute worsening
    - In the trial comparing two doses of IVIg (low risk of bias, n=173),[53] the mean change in MMS between day 0 and day 15 was not significantly different between the two treatment groups, 15.49 points (95%CI 12.09 to 18.90) in the 1g/kg IVIg group and 19.33 points (95% CI 15.82 to 22.85) in the 2 g/kg IVIg group, MD 3.84 (95% CI -0.98 to 8.66) (P= 0.12) in favour of IVIg 2g/kg.
- Chronic myasthenia gravis
    - In the RCT of IVIg versus placebo (n=15, unclear risk of bias),[202] mean (SD) change in the QMGS from day 0 to day 42 was 0.00 (3.8) in the IVIg group and -1.6 (2.7) in the placebo group, MD -1.60 (95% CI -1.92 to 5.12)(P = 0.37).
    - In the other trial (n=12, high risk of bias)[201] comparing the clinical effect of plasma exchange or IVIg from baseline to one and four weeks, no significant difference could be detected (data was not published).

A lot of people with a crisis were excluded from the studies. So it is still not clear whether the conclusion concerning the efficacy of IVIg in the treatment of MG worsening or exacerbation is also valid if the patient is in MG crisis. Adverse events related to IVIg were observed in all the trials, mostly fever or chills (13.8%), headaches (17.4%), nausea (6.9%), allergic reaction (1.3%).These adverse events would be considered subjectively as less severe than with plasma exchange where arterial bleeding, bleeding disorders, septicaemia and venous thrombosis were reported (Gajdos 1997; Ronager 2001) but, given the available data, no statistical comparison is possible.

A SR of 2016 (AMSTAR 7/11)[185] included a meta-analysis on efficacy and safety,[197,198,201,203] comparing IVIg to PE. The primary outcome was changes in the myasthenia muscle score, or quantitative myasthenia gravis score between day 1 and 15 days after the start of treatment. The authors concluded that there is no evidence for superiority in the efficacy of IVIg or PE (OR=0.561, 95%CI 0.224-1.408, p=0.218) (based on 3 RCTs, n= 201). The frequency of AEs was assessed based on 4 RCTs and did not find an impact (OR, 0.65; 95%CI: 0.16–2.57, P = 0.543, n=213). In contrast to the Cochrane SR, the SR of Ortiz-Salaz included an extra RCT[203] for assessing AEs. This RCT compared QMGS between IVIg (n=15), immunoadsorption (n=10) and PE (n=15). The QMGS decreased in all three groups after treatment, along with symptom improvement. However, it decreased more in the immunoadsorption and PE groups, than in the IVIg group (60.8+-3.5% vs.42.4+-4.2% vs. 23.8+-3.7%, P<0.01). This study was excluded from the Cochrane review because few data were available and the authors gave no response to a request for further information.

Also a Cochrane review on treatment of Lambert Eaton myasthenia gravis[195] was published in 2011 (AMSTAR 7/11); only 1 cross-over RCT[204] (n=10) was identified. It had an unclear allocation concealment for which it was considered as unclear risk of bias. The RCT reported significant improvement in myometric limb strength compared to placebo. Clinical improvement lasted for up to eight weeks. No muscle strength score such as the QMGS was used to measure treatment effect. Individual participant data were not available. Adverse events reported from IVIg treatment during the single randomised trial include acute meningitis in one participant and self-limiting headache in four other participants.

A CADTH report from 2018, performed a rapid review and identified four SRs[184, 185, 192,186] and two RCTs[205, 206] that were not yet included in a SR.

The INESSS report from Quebec was based on the Cochrane Gajdos 2012 and two primary studies.[205, 206] These more recent RCTs are described under primary studies.

Update primary studies

Our search for more recent primary studies since the last good quality SR[192] (search date sept 2011), identified two relevant RCTs.[205, 206] A further, newly published RCT[207] and one RCT with unpublished results[208] was found via hand searching. Only the RCT with published results will be discussed.

One of the included RCTs was a publication with extra information on the outcome ‘quality of life’ on the already analysed study of Barth et al 2011.[206] This follow-up study confirmed that IVIg and PE both improve quality of life, with non-significant differences observed between the two interventions (questionnaire QoL-15: IVIg −5.7±8.5, PE: −7.0±7.6, p=0.52).

Other recent RCTs focused more on a subgroup, namely patients undergoing a thymectomy or other surgery and where a MG crisis can be evoked – described below.

IVIg as pre-operative treatment to reduce risk of MG exacerbation or crisis.

One non-blinded RCT (high risk of bias, n= 24)[205] was identified comparing IVIg (n=12) to PE (n=12) in patients in preparation for thymectomy and focusing on post-operative outcomes. Although, no firm conclusion can be drawn due to the quality and small sample size, the IVIg treated patients in this study had no intubation time compared to 13h intubation time in the PE group (p=0.01) and had a shorter duration of surgery (3.46+-0.68h versus 4.17+-1.03, p=0.05).

Another RCT (low risk of bias, n=47)[207] in well controlled patients compared IVIg (n=25) to placebo (n=22) as a preoperative treatment for preventing a Myasthenia Crisis (MC) during or after surgery. There were no significant difference in the primary outcome MC: one patient in the placebo group presented with MC, which required non-invasive ventilation for 6 days. Other reported outcomes such as QMG score, hospitalisation, operation and duration, did not differ significantly. Therefore the authors concluded that in well-controlled MG patients preoperative IVIg is not justified.

Conclusions

Due to heterogenecity in patients, comparators and outcomes, the conclusion was broken down accordingly.

<u>For severe or worsening MG with exacerbations</u>:

A small RCT showed impact on reduction of symptoms of IVIg compared to placebo (1 RCT, low risk of bias, n=51).

IVIg has similar effects on functional parameters and quality of life, compared to plasma exchange (2 RCTs with a low risk of bias, n=171).

Low dose (1g/kg) or high dose (2g/kg) of IVIg does not impact outcomes differently (1 RCT- low risk of bias, n=173).

<u>For prevention of MG crisis in pre-operative patients:</u>

A high risk of bias study found a small postive effect of IVIg compared to PE on intubation and surgery time in patients undergoing thymectomy (1 RCT with a high risk of bias, n= 24).

In well controlled (stabilised) patients, a low risk of bias study concluded there was no difference in MG crisis or other post-operative outcomes compared to placebo (1 RCT with a low risk of bias, n=47), suggesting to omit this therapeutic option.

<u>In chronic stable myasthenia gravis:</u>

There is insufficient evidence from RCTs to determine whether IVIg is efficacious (1 RCT with an unclear risk of bias n=15). IVIg seems comparable in efficacy and safety compared to Plasma exchange (1 RCT with a high risk of bias n=12).

<u>For Lambert-Eaton MG</u>:

Only a small crossover RCT (unclear risk of bias, n=10) found a short term postive effect for 8 weeks on musle strenght compared to placebo.

2.3.3.2 *Dermatomyositis and polymyositis*

Dermatomyositis (DM) and polymyositis (PM) are idiopathic inflammatory diseases, characterized by chronic inflammation of skeletal muscle which can result in progressing muscle weakness with significant disability. They may both occur in association with gastrointestinal, pulmonary and cardiac dysfunction, while only dermatomyositis has skin involvement. These diseases are thought to result from an auto-immune process. They are categorised a broad group of idiopathic inflammatory diseases, also including Inclusion Body Myositis.

Treatment is aimed at alleviating symptoms and often based on long-term treatment of corticosteroids. There is a frequent need to use additional treatment both to improve the disease response and to reduce the side effects of corticosteroids. Additional treatment includes immunosuppressant and immunomodulating agents such as methotrexate or azathioprine. The role of IVIg is uncertain but can be a possibility.

Prevalence of polymyositis in Belgium is 0.51 for 100.000 habitants, and an incidence of 0.97 per million population in a year.[v] The prevalence of dermatomyositis in Belgium is 0.19 for 100.000 habitants, and an incidence of 0.35 per million population in a year.[w] Both diseases occur twice as common in women, as in men.[w]

Results

Overall 5 SRs (one already identified in the former report) were retained for dermatomyositis and/or polymyositis. No relevant additional RCTs were found. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement chapter 2).

Former KCE report

The KCE report from 2009 identified a high quality (AMSTAR 9/11) Cochrane review published in 2005,[209] aimed at assessing the effectiveness of immunosuppressant and immunomodulatory agents in the treatment of dermatomyositis and polymyositis. This SR identified one small US cross-over RCT[210] (low risk of bias), evaluating the efficacy of IVIg (2g/kg over 2 days, per month) versus placebo, in 15 patients with confirmed, treatment resistant dermatomyositis, over a period of 3 months. Both groups received continuous treatment with prednisolone. Clinical response was evaluated as changes in muscle strength using the MRC scale. This RCT found statistically significant improvements in muscle strength from 76.6 ± 5,7 to 84.6 ± 4,6 in the IVIg group, versus no significant difference in the placebo group (78,6 ± 6,3 to 78,6 ± 8,2). The weighted mean difference was 9.50 (95% CI: 4.33 to 14.67).[211] The authors of the SR concluded that the limited evidence on IVIg suggests that it could be a beneficial second-line therapy for patients with DM.

More recent SRs on Immunoglobulins in DM and PM

Four relevant SR were retained.

Vermaak et al.[212] (AMSTAR 7/11) and the review by INESSS (AMSTAR 10/11)[186] had the same evidence base. They looked at the evidence for immunotherapy in adult patients with definite or probable dermatomyositis or polymyositis. In addition to the RCT by Dalakas et al., a more recent Japanese cross over RCT was included. No pooling of the results was performed. This more recent RCT (unclear risk of bias),[213] looked at the efficacy of IVIg (2g/kg over 5 days) versus placebo, in patients with dermatomyositis (n=10) or polymyositis (n=16) resistant to treatment with corticosteroids. The primary outcome was the same in both RCTs (muscle strength score), measured by means of the same scale but the time frame of the study was shorter in the Japanese study, which had a crossover of patients after 8 weeks versus the three months of the US study. Although patients in the IVIg group experienced a significant improvement in mean

[v] Calculation based on data of 2017 in the Belgian Neuromuscular Disease Registry by Sciensano

[w] Orphanet - https://www.orpha.net/consor/cgi-bin/index.php?lng=EN

muscle strength over the eight weeks of 11,8 ± 8,0 (p<0,0004) in the IVIg group, improvements were also seen in the placebo group (9,9 ± 8,3 (p<0,0007), which lead to a non-significant mean muscle score difference between the two groups (mean difference: 1.9, 95%CI -4.8 – 8.5). Although shorter time to improvement was seen in the IVIg group, the difference did not reach statistical significance.

The discrepant findings of both RCTs made it impossible to draw clear conclusions. Reasons that may explain the differences between the results in these two RCTs include on the one hand, the focus of the RCT by Dalakas et al. on patients with dermatomyositis, versus Miyasaka's RCT which also included patients with polymyositis, and on the other hand the ethnicity of the patient population (Miyasaka's including Japanese patients).

In terms of safety, the RCT by Dalakas et al. reported no withdrawals from toxicity in either of the groups, and good tolerability, while the study by Miyasaka et al captured AEs in 42,3% of patients overall, with 2 serious AEs in one patient (increased creatinine kinase and muscle weakness) thought to be due to the IVIg treatment.

Additionally, via hand searching two additional SRs analysed Ig for polymyositis and dermatomyositis were found,[214,215] but had the same evidence base (similar RCTs included in Vermaak and INESSS) and presenting similar conclusions. Therefore, these were not analysed further.

Update primary studies

Our search for more recent primary studies published after January 2016 (search date of the INESSS SR), identified no relevant RCTs in dermatomyositis and/or polymyositis.

Conclusions

Discrepant findings for IVIg versus placebo in patients suffering from treatment resistant dermato- and polymyositis and no clear conclusion could be made:

- **One small US cross-over RCT found that IVIg in addition to prednisolone therapy may offer significant improvements in muscle strength in confirmed patients with corticoresistant dermatomyositis (low risk of bias, n=15).**
- **One small Japanese cross over RCT, in patients with dermatomyositis (n=10) or polymyositis (n=16) saw no significant differences in muscle strength changes between the two study arms in corticoresistant patients (unclear risk of bias, n=26).**

2.3.3.3 Pemphigus (Immunobullous disease)

Pemphigus diseases are a heterogeneous group of potentially life-threatening autoimmune bullous disorders, clinically characterized by blistering and erosions of the skin and/or mucous membranes. Auto-antibodies are formed against a protein 'desmoglein' causing the disruption of intercellular junctions and the loss of cell-to-cell adhesion. In about half of patients, oral lesions are seen first.

The most common forms are pemphigus vulgaris (PV) and pemphigus foliaceus (PF), accounting for 70 and 20 % of cases, respectively. Annual incidence rates range from 0.76 to 32 cases per million.[216]

Treatment of pemphigus is aimed to induce and maintain remission. This is achieved with immunosuppressive agents such as systemic glucocorticoids, usually administered for a long duration and often in a combination with corticosteroid-sparing immunosuppressant agents such as azathioprine, mycophenolate mofetil/mycophenolic acid and rituximab. In severe or treatment-refractory cases, immunoadsorption or high-dose IVIG, 2g/kg every 4 to 6 weeks, are possible.[217]

Results

Overall 2 SRs were retained for pemphigus, basing their conclusion on 2 RCTs. No additional recent RCTs were found. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement 2).

Former KCE report

The former KCE report did not investigate this indication.

More recent evidence on Immunoglobulins in pemphigus

The two included SRs were identified via hand searching.[215, 216]

One of these, (AMSTAR 4/11)[216] investigated several therapies for pemphigus and included 1 RCT on IVIg compared to placebo [51]. The primary outcome of the SR was the proportion of patients achieving complete response. However, it was not possible to report on this predefined primary outcome as the only included RCT used other outcomes. Nevertheless, a descriptive analysis of the RCT results was offered. Amagai et al. 2009 (low risk of bias) performed an RCT, randomising 61 patients with pemphigus vulgaris or pemphigus foliaceus, who did not respond to prednisolone, to 200mg/kg IVIg or 400mg/kg IVIg, or placebo. Efficacy was evaluated with 'time to escape from protocol' (TEP) as a novel primary end point, allowing physicians the flexibility to rescue patients with other treatment when needed. TEP was defined as the time period a patient followed the protocol without requiring additional treatment. Secondary outcomes were the pemphigus activity score, antidesmoglein enzyme-linked immunosorbent assay scores, and AEs. Time to escape from protocol was significantly prolonged in the 400-mg group but not in the 200 mg group, when these groups were compared to placebo; and a significant dose-response relationship among the 3 treatment groups was observed (P<0.001).

There was no significant differences in the rate of AEs between the 3 treatment groups (6/21, in the 400-mg group, 7/20 in the 200-mg group, and 5/20 in the placebo group). However there was one serious AE linked to the treatment in the 200mg group (dead due to aggravation of Hepatitis C).

The most recent SR with the high quality[215] (AMSTAR 8/11) did found 1 additional RCT from the same research group.[218] No pooling of the results was done and a descriptive analysis of this RCT was performed. This RCT[218] (low risk of bias) randomised 56 patients with steroid-resistant bullous pemphigoid (BP) (no symptomatic improvement with prednisolone) to 400mg/kg IVIg or placebo. The primary outcome was disease activity score on day 15 (DAS15). Secondary outcomes were changes in the DAS over time, the anti-BP180 antibody titer, time to treatment reduction, oral steroid dosage/day and AEs. There was no significant difference in the DAS15 score between IVIg and placebo (p = 0.089). However, posthoc analysis (covariance of DAS score on day 1) did found a significant better DAS15 compared to placebo (p=0.041). A posthoc analysis in the severe patient subgroup (with a DAS score of more than 40 on day 1), showed that IVIg treatment provided significantly better values than the placebo group on days 8, 15, and 22 (p<0.05). The secondary outcome "change in disease activity over time" found a significant higher decrease for IVIg compared to placebo from day 1 to 15. However this effect was not maintained through day 57.

Update primary studies

Our search for more recent primary studies published after the CADTH report (search from 2017), identified no relevant RCTs in this indication.

Conclusions

Only for steroid resitant patients, RCTs were performed, indicating it is not a first line therapy.

- **In steroid resistant patients with pemphigus, the use of IVIg (400mg/kg) is effective in limiting the disease progression compared to placebo (2 RCTs with a low risk of bias, n=117). This effect was not seen in a dosage of 200mg/kg (1 RCT with a low risk of bias, n=61).**

- **There is limited evidence that it reduces symptoms (1 RCT with a low risk of bias n=61), more specifically in the short term (day 1-day 15) and in the more severe patient subgroup (posthoc analysis of 1 RCT with a low risk of bias, n=56).**

2.3.3.4 Post-transfusion Purpura

Post transfusion purpura (PTP) is characterized by profound thrombocytopenia occurring 5–10 days after a blood transfusion. Most patients achieve remission after 1–4 weeks but about 15% have a life threatening bleeding.[219] The reason for the PTP is the presence of potent alloantibodies of the recipient specific for one or more human platelet-specific antigens of the donor, but eventually also attacking the patient's own platelets.

For the cases that do not resolve after four weeks, treatment with IVIg, steroids, or plasma exchange is recommended.[220] The use of high dose Ig is based on a case series in 1988[221]. Of the 17 PTP cases, 16 had a good or excellent response to IVIg attaining normal platelet counts within a few days; only one failure was observed. Five patients relapsed, but attained complete remission after a second dose of IgG. No adverse reactions were observed. The authors conclude that IVIg is the treatment of choice for PTP.[221]

Results

No relevant SRs or RCTs were found in post-transfusion purpura. Details describing exclusions are reported in appendix Search Strategy chapter 3.

Former KCE report

This indication was not considered in the previous KCE report.

More recent evidence on Immunoglobulins in PTP

Our search for recent literature on PTP did not identify any relevant studies, though two case reports were captured confirming earlier results.[222,223] It appears that the inclusion and consideration for reimbursing/recognising this indication in the countries analysed in our international comparison is based on a case series where IVIg appeared to offer benefit for these patients.[221]

Conclusion

- **Given the lack of evidence from RCTs or observational studies, no conclusions could be drawn regarding the use of Ig for post-transfusion Purpura.**
- **Only retrospective case series exist.**

2.3.3.5 Pure Red cell aplasia (Erythroblastopenia)

Pure red cell aplasia is defined by a marked reduction or absence of erythroid precursors from the bone marrow leading to severe anemia. Depending on the cause, the course can be acute and self-limiting or chronic with rare spontaneous remissions. Congenital (Diamond-Blackfan anemia) as well as acquired forms exist. Acquired anemia may be primary or secondary to a variety of neoplastic, autoimmune, or infectious diseases especially B19 parvovirus; or to exposure to various drugs.[224] Most cases of PRCA are considered to be autoimmune-mediated.

First line treatment are glucocorticoids (prednisolone). In patients unresponsive to corticoids, immunosuppressants are used as well as hematopoietic stem cell transplantation. Because of the diversity of the pathogenicity, different treatment approaches are necessary.

The specific subgroup of PRCA associated with B19 parvovirus in immunocompromised patients (e.g. transplant patients on immunosuppressive therapy) can be an indication for IVIg as specific therapy, based on several case series.[225] In the general population B19 parvovirus is highly prevalent (50-75% of the general population have antibodies), therefore IVIg products have high amount of specific antibodies. No optimal dosing strategy exists but as reported in a retrospective study on 133 cases, most cases use 2g/kg usually divided over 5 days (400 mg/kg/d (similar as in immune thrombocytopenic purpura).[225] PRCA corrected after a first course of intravenous Ig in 93% of patients, but approximately one-third relapsed, at mean time to relapse of 4.3 months.[225]

Results

No relevant SRs or RCTs were identified in pure red cell aplasia. Details describing exclusions are reported in appendix Search Strategy chapter 3.

Former KCE report

This indication was not considered in the previous KCE report.

More recent evidence on Immunoglobulins in PRCA

Our search for recent literature on PTP did not identify any relevant SR or RCTs, though 2 non-systematic reviews[225, 226] were captured. Given the lack of SR and RCTs a brief description of the reviews found is offered below.

One review focused on IVIg treatment in patients with pure red cell aplasia (PRCA) related to human parvovirus B19 infection[225] in 10 patients in their own institution and 123 cases found in the literature. Among 133 patients with parvovirus B19 PRCA who received IVIg, 63 had undergone solid-organ transplant and 39 had human immunodeficiency virus infection. Hemoglobin level was corrected after the first IVIg course in 124 patients (93%); disease relapsed in 42 (33.9%), at a mean of 4.3 months. Adverse events were seen in 18/133 patients: acute renal failure in 9 (including 6 kidney transplant recipients); fever, rash, and joint pain in 7; and left ventricular failure in 2 patients.

The most recent review investigated all therapy for PRCA patients (with different etiology) and found that 3 of the 4 patients receiving IVIg for parvovirus linked PRCA responded with durable remissions. Also patients with hypogammaglobulinemia, even in the absence of diagnostic signs of B19, had all a positive response (11/11) and could benefit from IVIg therapy. Patients with PRCA resulting from another etiology (e.g idiopathic) did not had the same responses.[226]

It appears that the inclusion and consideration for reimbursing/recognising this indication in the countries analysed in our international comparison is based on case reports where IVIg appeared to offer benefit for these patients.[227] It should be noted that most countries recognise pure red aplasia only when it follows an infection by Parvovirus B19 or when it is linked to an auto-immune process. This is justified in view of the limited evidence which appears to focus in these particular populations.[226, 228]

Conclusions

- **Given the lack of evidence from RCTs or observational studies, no conclusions could be drawn regarding the use of Ig for pure red cell aplasia (PRCA).**
- **Only retrospective case series on specific subgroup of PRCA exist:**
  - **On the subgroup of immunocompromised patient with a diagnosed parvovirus B19 (>100 cases described in a nonsystematic review).**
  - **On the subgroup of patients with hypogammaglobulinemia (11 cases described in a nonsystematic review).**

2.3.3.6 Antibody Mediated Rejection in Solid Organ Transplant

Graft rejection is an immunological process where the recipient's immune system attacks the donor-organ. There are different mechanisms of rejection, depending on which part of the immune system is primarily activated, either the cellular T cell response or the humoral antibody mediated response. Acute T cell–mediated rejection typically responds well to increased immunosuppression. For the prevention of Antibody mediated rejection (AMR) where the recipient produces donor-specific antibodies (targeted against HLA molecules which are present on all human cells except on red blood cells, against blood group antigen (ABO)-isoagglutinins present on red blood cells, or against endothelial cell antigens), that attack the donor organ, the immunomodulating properties of Ig may be indicated.

Ig can be indicated in before and after transplantation.

Before transplantation, patients with high levels of pre-formed anti-HLA (anti-Human Leukocyte Antigen) antibodies have an increased risk of transplant rejection and poorer graft survival and consequently need a desensitisation phase. These circulating antibodies result from exposure to

nonself HLA antigens; usually from previous transplants, blood transfusions, or pregnancy. Recent desensitization protocols using the combination of plasmapheresis (PP) or immunoadsorption to remove donor-specific anti-HLA antibodies (DSA) and/or IVIg and rituximab to downregulate antibody-mediated immune responses.

After transplantation, the development of de novo donor-specific antibodies increase the possibility of rejection, which can occur either acutely (i.e. from during the procedure up to three months afterwards) or chronically (i.e. more than three months afterwards). The therapeutic strategy is to neutralise and stop the production of the donor specific antibodies. Next to specific drugs targeting the process of Bcell activation and antibody production, there is the option to physically remove the antibodies from the circulation with plasmapheresis, and/or to use IVIg.[229]

In Belgium, there were 474 kidney transplants, 190 heart and/or lung transplants and 273 liver transplants performed in 2018.[x]

For the use of Ig in patients with a hypogammaglobulinemia and therefore an increased risk for opportunistic infections such as cytomegalovirus (CMV) due to the immunosuppressive therapy after transplantation (mostly till 6 months after transplantation), the details can be found in section 2.3.2.2.4 SID after solid organ transplantation.

Results

The results are based on 3 SRs and 3 RCTs (the latter already included in the former KCE report). Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement 2).

Previous KCE report:

For the prevention of rejection, the former KCE report found no SRs, but three RCTs involving kidney transplants.[230-232]

The first RCT[232] (unclear risk of bias), conducted in 41 patients receiving a second kidney transplant and treated with immunosuppressant therapy, showed a significantly higher 5-year graft survival rate in patients treated with IVIg, compared to those in the control group (68% in the IVIg, 50% in the control group, P=0.0017). No AEs were reported.

A further RCT[230] (high risk of bias), involving 30 patients with steroid resistant rejection, compared IVIg to monoclonal anti-CD3 (OKT3) therapy. The incidence of rejections did not differ significantly between the two patient groups (5/11 with IVIg versus 9/12 with OKT3, p=0.4).

A third RCT[231] (low risk of bias), conducted in 101 patients with end-of stage renal disease and with high level of anti-HLA antibodies prior to transplantation, compared IVIg to placebo. The outcomes reported were antibody levels before transplantation as an indicator for sensitisation, transplantation rates, graft survival, overall survival, and AEs. IVIg significantly decreased anti-HLA antibody levels (p=0.033), but did not eliminate sensitisation. Waiting times (to be transplanted) improved significantly in IVIg treated patients (4,8 years with IVIG vs 10,3 years with placebo, p=0,049). In the 27 patients undergoing transplantation, two-year graft survival did not differ (80% IVIg vs 75% placebo, p=0,57), neither did the all-cause mortality after 30 months (p=0.22).

These studies showed some benefit, however, they failed to show a statistically significant reduction of transplant rejection.

More recent SRs on Immunoglobulins in AMR in Solid Organ Transplantation

Three relevant publications were identified,[233,234,235] of which one is an updated version[234] of a SR.[233] Only the updated version of the SR will be described below.

Wan et al. 2018[234] (AMSTAR 9/11) focused on several treatments for AMR in kidney transplantation and included all controlled studies. Amongst them, two retrospective studies of very low quality[236, 237] comparing IVIg combined

[x] Numbers based on data in http://statistics.eurotransplant.org/

with PE [236] or IVIg plus PE plus rituximab[237] versus no treatment were found. These two non-RCTs reported discordant findings on the primary outcome 'graft survival'. Lee et al. (n=75) found a significant decrease in graft failure (HR=0.26, p<0.001, no 95%CI reported) compared to no treatment, while Einecke et al. (n=71) found no difference between PE+IVIg+rituximab and no treatment (RR=0.86 95%CI 0.6-1.22). Wan et al. concluded that PE and IVIg have become the standard of care despite limited low-quality evidence. Only the study by Lee et al. reported on mortality and found 1 death in the IVIg group compared to 2 in the control.

The CADTH report[235] (AMSTAR 8/11) focused on IVIg or SCIg use for AMR in solid organ transplantation and limited their search to the period 2012-2017. They found only 1 RCT[238] comparing IVIg to placebo and 1 non-randomized retrospective observational study comparing IVIg to methylprednisolone. They reported on those two studies without combining results. Below we describe the results of the RCT.

The RCT (low risk of bias, n=25)[238] in patients with chronic AMR within 6 months after transplantation, investigated IVIg combined with rituximab versus placebo and reported on graft function (change in eGRF after 1year) and secondary outcomes related to renal function (evolution of proteinuria, renal lesions and donor-specific antibodies) and AEs. There was no statistical difference neither in eGRF after 1year (a decline of -6,6+-12,0 for the placebo and -4,2+-14,4ml/min per1,73m² (p=0,457)), nor in daily proteinuria (+0.9+-2.1 vs. 0.9+-2.1 g/day, p=0.378). The total number of AEs were similar in placebo and the treatment group (28 vs. 26). Serious AEs needing hospitalisation were observed in four patients in the placebo group and five in the treatment group (urinary sepsis (n=1), fever (n=1), urinary tract infection (n=2), hyponatremia (n=1)).

Both studies included in the CADTH report focused on kidney transplantation and were of limited quality suggesting that the clinical effectiveness of IVIg remains unclear.

Primary studies:

Our search for primary studies published after the search date of the most recent, good quality SR (CADTH et al 2018 - search from 2017), identified no additional RCTs.

Conclusions

For the prevention of graft lost (antibody mediated rejection), only RCTs on kidney transplantation are available. Furthermore, the available studies cover different subpopulations. Both these factors limit the generalisability of the results.

- **Patients undergoing a re-transplantation can have an increased 5-year graft survival when IVIg is added to the quadruple-immunosuppressive therapy. However, there is no significant effect on overall survival (mortality) (1 RCT of 1996, unclear risk of bias, n=41).**
- **In patients experiencing steroid-resistant rejections, IVIg has the same rejection rates as monoclonal therapy (1 RCT, high risk of bias, n=30).**
- **Sensitisation (presence of anti HLA-antibodies) significanlty decreases in patients with IVIg compared to placebo, which reduces waiting times of highly sensitised patients before transplantation (4,8 years with IVIg versus 10,3 years for placebo p=0,049). However, there is no impact on outcomes such as graft survival or overall survival, measured 30 months after transplantation (1 RCT, low risk of bias, n=101).**
- **In patients with chronic AMR, a recent (2018) RCT (low risk of bias, n=25) shows no efficacy of IVIg (even in combination with rituximab) on renal function parameters compared to placebo .**
- **A recent SR did not find any RCTs and concluded that PE and IVIg have become the standard of care for acute antibody mediated rejection, despite limited, low-quality evidence.**

2.3.3.7 *Fetoneonatal trombocytopenia*

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) may lead to severe bleeding complications such as intracranial haemorrhage, in the foetus or newborn. The thrombocytopenia is caused by maternal alloantibodies against fetal platelet antigens that the foetus has inherited from the father. As maternal screening is not routinely performed, and first pregnancies can be affected, most cases are diagnosed at delivery of a first affected pregnancy.

The incidence of FNAIT in Caucasian populations, based on population surveys, is between 1 in 1000 and 1 in 1500 live births. However, in the absence of neonatal screening, it is likely that the true incidence is higher.[239]

Postnatal treatment of severe foetal thrombocytopenia considers the administration of antigen-negative platelets until the platelet count recovers, usually 7 to 10 days following birth.[239]

Antenatal management for secondary prophylaxis in a subsequent pregnancy could include serial foetal blood sampling (FBS) and intrauterine platelet transfusions (IUPT), and maternal IVIg infusion, with or without additional corticosteroid therapy on a weekly basis until delivery, but optimal management has not been determined. Serial foetal blood sampling (FBS) and intrauterine platelet transfusions (IUPT) are invasive treatments, associated with a relatively high complication rate, consisting mainly of preterm emergency caesarean section in around 11% per treated pregnancy.[240]

Data on the efficacy of IVIg for primary prophylaxis of FNAIT are lacking.

Results

Results are based on 3 SRs (one already captured in the previous KCE report). No additional (more recent) RCTs were identified. Details describing exclusions are reported in appendix Search Strategy chapter 3. Details on included studies can be found in the extraction tables (Supplement chapter 2).

Former KCE report

The former KCE report found a SR[241] including RCTs that did not assess the efficacy of IVIg but compared IVIg to IVIg plus steroids. There were no RCTs identified comparing IVIg to placebo or no treatment. The conclusion was based on observational research (26 studies, though no MA was performed), suggesting a benefit for IVIg.

More recent SRs on Immunoglobulins in FNAIT

Our search identified two SRs,[239, 240] one of which provided an update of the Cochrane SR already included in the former KCE report.

This updated Cochrane SR (AMSTAR 10/11)[239] included four small RCTs in 3 publications.[242-244] The study of Berkowitzh 2006 included 2 RCTs, one for high risk pregnancies (women who already had a baby with intracranial haemorrhage), and one for standard risk (woman who did not have a prior baby with haemorrhage). No pooling of results from the 4 RCTs was possible due to a lack of complete data sets and important differences in interventions. Three trials (quality of these trials was considered adequate by Cochrane risk of bias) involving 167 people in total compared IVIg plus a corticosteroid (prednisone in two trials and dexamethasone in one trial) versus IVIg alone. In these trials there was no information on fetal/neonatal mortality. ICHs were reported in both treatment arms in Berkowitz 2007, 1/36 with IVIg combined with prednisolone versus 1/37 with IVIg alone, but the relative risk of experiencing an ICH was not statistically significant between the two treatment groups (RR 1.03, 95% CI 0.07 to 15.82). In the trial, focusing on high risk pregnancies[243] (Berkowitz 2006 (high), one ICH was observed in the group treated with IVIg alone and none in the prednisolone group. No ICHs were found in the third trial.[242]

In all the included trials the difference in mean platelet count at birth between the two groups was not statistically significant. Similarly, the difference in mean gestational age at birth between the two groups was non-significant (MD -0.20 weeks; 95% CI -5.71 to 5.31 (Berkowitz 2007) and MD -0.50 weeks; 95% CI -2.69 to 1.69 (Bussel 1996a). One RCT[243] with an unclear risk of bias involving 39 pregnant woman who did not have a prior baby with haemorrhage (considered pregnancies with a standard risk) compared a corticosteroid (prednisone) versus IVIg alone. The treatment started at

approximately 20 weeks' gestation. There were no statistically significant differences between the treatment arms for predefined outcomes: Fetal/neonatal death (RR 0.95; 95% CI 0.06 to 14.13), platelet count at birth ((MD) -36.30 x 10*9/l, 95%CI -85.77 to 13.17). There were two ICHs in this study, but the trial did not report the treatment arm in which the two ICHs occurred.

Although there were no RCTs comparing IVIg to no treatment or placebo, a table summarizing 27 observational cohorts (n=241) was included in the Cochrane review.[239]

No AEs for the mother were reported in any of the 4 trials. Fetal blood sampling was performed in all trials. However, AEs associated with the fetal blood sampling technique were reported in 1 trial.[244] There was no statistical difference in the probability of experiencing an adverse outcome following FBS between IVIg versus IVIg plus prednisolone (RR 0.97, 95% CI 0.41 to 6.58).

The more recent SR[240] had a lower quality (AMSTAR 5/11) and included 4 RCTs,[54, 242-244] as well as 5 prospective and 17 retrospective studies. In this SR only 1 extra RCT was identified compared to the Cochrane review by Rayment et al. This open label RCT[54] compared 1g/kg IVIg (n=11) to 0.5g/kg (n=12), but failed to demonstrate non-inferiority of the low dose due to recruitment problems. No intracranial haemorrhage occurred and other outcomes such as platelet count and AEs did not differ.

Update Primary studies

Our search for more recent primary studies did not identify any additional RCTs not already covered in the SRs previously described.

Conclusions

- **IVIg is considered as "standard" therapy though no RCTs comparing antenatal IVIg therapy to no treatment or placebo exist (based on data of 27 observational cohorts, n= 241).**
- **Adding corticosteroids to IVIG is not proven to have an added benefit. Three RCTs (all with a low risk of bias) on FNAIT compared IVIg to IVIg + corticosteroids (n=167), and found no differences in outcomes such as intracranial hemorage, fetal/neonatal platelet count or preterm birth.**
- **In pregnant woman with no prior baby with intracranial hemorrage, IVIg has similar effects on outcomes such as intracranial hemorage, fetal/neonatal platelet count or preterm birth compared to corticosteroids (1 RCT with a low risk of bias, n=39).**
- **The most recent RCT (n= 23, low risk of bias) intended to show non-inferiority of a lower dose. Although underpowered, the study did not found differences of a lower weekly dose of 0,5g/kg compared to the standard 1g/kg/ week.**

2.3.4 Other indications for which evidence exists

The experts who responded to our online survey (see Supplement chapter 4 for more details) confirmed that the main indications for Ig use (based on evidence) had been covered in our selection and that for those selected indications, no major studies had been missed. However, they also identified other potentially interesting indications for which very limited evidence exists at present, but that would still be worthwhile mentioning. Reference is made to these indications in this section, if and when relevant.

This section offers a description of other (non-selected) indications for which there is evidence from SRs of a positive effect and for those in which there is evidence of no benefit. For the indications were conclusions are unclear, results from the SRs are summarised in an appendix (2.5).

2.3.4.1 *Evidence of a positive effect*

Sepsis and septic shock in adults

Sepsis and septic shock are life-threatening because they induce multiple organ failure. Ig have been used as adjuvant therapy. There are several studies on adults as well as neonates, each presenting different outcomes. Below we describe the results for the adults for which a positive effect is observed in contrast to the findings for neonates.

The most recent SR (AMSTAR 6/11)[245] covers all RCTs on adults previously included in a Cochrane SR,[138] supplemented by 1 additional RCT[246] (n=33 patients, IgM enriched IVIg compared to placebo). The total number of RCTs covered in this recent SR is 18 (9 RCTs on polyclonal IVIg and 9 RCTs on IgM enriched IVIg). The primary outcome is all-cause mortality. The pooled analysis for standard polyclonal IVIg compared to placebo or no treatment shows the former to offer a significant reduction in all-cause mortality (OR=0,45, 95%CI 0,24-0,87; n=1736, 9 RCTs). The pooled analysis for IgM enriched IVIg also showed a significant decrease in all-cause mortality compared to placebo or no treatment: OR=0,55 (95%CI 0,38-0,81; n=597, 9 RCTs). A sensitivity analysis showed that high quality studies (Jadad score ≥3) also reported a significant decrease, but with a high level of heterogeneity (OR=0.51, 95%CI 0,31-0,84, 11 RCTs, n=2025, heterogeneity I^2=58.43). Therefore there is some reluctance to consider it as a widespread standard therapy.[245]

Stiff man's Syndrome

Stiff-man syndrome (SMS), is a rare neurologic condition which causes severe, irregular muscle rigidity and spasms leading to progressive rigidity and stiffness. The stiffness primarily affects the truncal muscles and patients commonly suffer from chronic pain, impaired mobility, and lumbar hyperlordosis. The cause of this syndrome remains unknown, although most patients with this condition, have high amounts of glutamic acid decarboxylase antibodies (GAD). Benzodiazepines are the most common first line treatment; they are used for symptom relief from stiffness, but the condition often worsens over time and doses need to be increased which makes tolerability a frequent problem. Treatments that target the autoimmune response, such as IVIg, are sometimes used as second line treatment.

Our search found 1 SR of high quality (AMSTAR 10/11),[186] which included a small cross over RCT (low risk of bias) conducted between 1996-99, involving 16 patients, not responding well to their therapy (mostly on benzodiazepines but some on anti-epileptics). Patients were randomised to IVIg (2g/kg over 2 days every month) or placebo for 3 months.[247] Results showed a significant improvement in stiffness scores during the first three months in the IVIg treated group (from 4,6 to 3,0 on a scale ranging from 0 to 6, with higher scores indicating more stiffness). Stiffness scores remained constant during the washout period (at 3,0) and worsened during the placebo period (from 3,0 to 4,0). In the placebo group, stiffness scores remained constant during the first three months, and the additional month of washout (at 4,7). Stiffness scores improved significantly after cross over and treatment with IVIg (from 4,7 to 2,0). Length of treatment effect appeared to differ from one patient to another (from 6 weeks to 1 year).

2.3.4.2 *Evidence of no benefit*

Post-polio Syndrome

Post-polio syndrome (PPS) is a condition that affects polio survivors, years after recovery from an initial acute attack of the poliomyelitis virus. A weakening in muscles and a gradual decrease in the size of muscles (muscle atrophy), previously affected by the polio infection, are observed. The most common symptoms include slowly progressive muscle weakness, fatigue (both generalized and muscular).

Two SRs[248, 249] concluded that IVIg was no better than placebo for post-polio syndrome, based on 3 RCTs.[250-252] No significant beneficial effect on activity limitations in the short or long term, pain, fatigue, or muscle strength (see table in appendix 2.4).

However there is one ongoing study identified in this specific indication. Completion of this trials is expected for 2021 (trial number NCT02176863, see section 2.3.5 Ongoing trials).

Sepsis in neonates

Among neonates with sepsis, there is evidence that standard polyclonal IVIg, as adjunctive therapy, does not reduce mortality. A Cochrane review from 2013[138] identified 8 RCTs and performed a MA. The primary outcome mortality was not impacted (RR=1.00; 95%CI 0.92 to 1.08; 5 RCTs n = 3667). A sensitivity analysis only including studies with a low risk of bias confirmed the finding (RR=1.01, 95%CI 0.93 to 1.09, 3 RCTs, n= 3561). Ig-M enriched IVIg in neonates compared to placebo or to no treatment did not reduce all-cause mortality (RR=0.57, 95%CI 0.31 to 1.04, 3 RCTs, n=164).

Myocarditis

Acute myocarditis is a disease that occurs in individuals of all ages. It is presumed to start usually as a viral infection, although autoimmune and idiopathic forms also occur. If ongoing infection is the primary problem, IVIg could be efficacious if it contains antibodies to the pathogen.

A good quality SR (AMSTAR 11/11)[253] identified 2 RCTs, one on adults[254] and one on children.[255] The primary outcome is event free survival, defined as no death, no requirement for cardiac transplant or placement of a left ventricular assist device. The RCT on adults (unclear risk of bias) randomised 62 adults to 2g/kg IVIg or placebo and found no significant difference in the odds for event-free survival (OR 0.52, 95% CI 0.12 to 2.30). Similar improvements in Left ventricular ejection fraction and in functional status seen at 6 and 12 months in both groups (MD 0.00, 95%CI -0.07 to 0.07 at six months; MD 0.01, 95% CI -0.06 to 0.08 at 12 months). Infusion related AEs were frequent but mild.[254]

One RCT (with a high RoB) randomised 83 children with acute encephalitis and myocarditis to IVIg or no treatment and showed no significant impact on odds for event-free survival (OR=7.39, 95% CI 0.91 to 59.86). However a significant effect was seen on the outcome left ventricular ejection fraction (49.5% with IVIg vs 35.9% with placebo - risk difference: 13.6%, 95% CI 5.1 to 22.1%; P value = 0.001).[255]

Until higher-quality studies have demonstrated benefit in a particular group of patients, IVIg for presumed viral myocarditis should not be provided as routine practice in any situation. Indeed there is a recent placebo controlled study comparing IVIg and placebo terminated, but for which no results on the primary outcome change cardiac ejection fraction presence of the heart in 6 months were published (IVIg) for Parvovirus B19(PVB19) Mediated Cardiomyopathy –trial number:NCT00892112- 2.3.5 Ongoing trials).

Alzheimer's disease (AD)

Alzheimer is a chronic neurodegenerative disease associated with intracerebral accumulation of aggregated amyloid-beta (Aβ) and tau proteins, as well as neuroinflammation, leading to increasing memory problems and other disturbances of the cognitive domain that make activities in daily life difficult or even impossible.

The presence of natural anti- Aβ antibodies in IVIg, the favourable safety profile and inherent anti-inflammatory/immunomodulatory properties make IVIg a potential AD treatment.

The most recent SR is a rapid review from CADTH[196] identifying a SR from INESSS[186] and three RCTs comparing IVIg to placebo.[256-258] In one RCT (high risk of bias, n= 56) the primary outcome was a pharmacokinetic parameter (AUC of plasma Aβ) and was not significantly different between placebo and different doses of IVIg.[256] In the two other RCTs with clinical outcomes such as change in cognitive performance between baseline, 12 and 24 months after the first infusion, no significant differences were found between IVIg and placebo (1 RCT of low risk of bias, n=383;[258] and 1 RCT of high risk of bias, n=50.[257] The SR concluded that IVIg is a not possible treatment for Alzheimer's disease (due to inadequate efficacy, a lack of pathophysiological justification or potentially harmful effect) when compared with placebo or no intervention.[186]

2.3.4.3 Indications for which evidence is unclear

No conclusions could be made in favour or refuting the use of IVIg, due to too little evidence, low quality evidence or conflicting results: inclusion body myositis, Sydenham's chorea, Paraneoplastic neuropathy, Paraprotein neuropathy, encephalitis, relapsing remitting MS, epilepsy, Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), Neuromyelitis optica/Devic's disease, Carditis (in acute rheumatic fever), Wegener's granulomatosis (system vasculitis),

Preventing infection (in nephrotic syndrome), Preventing infection in preterm/low birthweight, Preventing Hepatitis A, Necrotising soft tissue infections, Dengue Shock Syndrome, Severe or recurrent clostridium difficile colitis, Atopic dermatitis, Toxic epidermal necrolyse, Stevens Johnson Syndrome, Mycoplasma pneumoniae-associated mucocutaneous disease, Chronic urticaria, Recurrent miscarriage, Von Willebrand disease, Haemolytic disease in newborns.

Experts answering our survey highlighted interesting indications for Ig although they were conscious of the limited evidence: “Auto-immune encephalitis; Rasmussen encephalitis; Susac syndrome; acute neuritis optica, severe infections related to hypogammaglobulinemia (SID not linked to haematological cancers such as protein losing enteropathy)” and Systemic capillary leak syndrome (SCLS). Most of the indications are indeed also recommended in other countries, but most of the time not as a priority.

Our literature search showed that for Rasmussen encephalitis, there is one RCT with a high risk of bias, comparing IVIg to tacrolimus and no treatment (historical control group) in 16 patients.[259] IVIg was as effective as tacrolimus in reducing seizures, both active therapies were significantly better than no treatment. For an autoimmune encephalitis subtype, Anti-NMDA receptor encephalitis, our search identified SRs[186] referring to 1 large observational cohort[260] which found response to treatment with a combination of IVIg, steroids, and plasmapheresis in 52% (n=241 out of 462) at 4 weeks. Another SR on 83 case series (n=432)[261] found no statistically significant difference between the 3 types of first-line treatment administered alone (IVIg, corticosteroids and plasma exchanges or immunoadsorption), nor between the different combinations comprising 2 of these 3 treatments. The conclusion of this good quality SR (AMSTAR 10/11) was that the available evidence does not allow a judgment to be made regarding the efficacy of IVIg. Other countries recommend autoimmune encephalitis including Rasmussen encephalitis as a possible indication for Ig use, however not as a priority (France, Australia, England, and all the provinces guidelines of Canada).

For neuromyelitis optica two SRs[186,196] identified 5 case series and one preliminary ended RCT without results[262] was found indicating insufficient to draw any conclusions on the clinical value of Ig in neuromyelitis optica. For acute neuritis optica, our SR search did not pick up any evidence. However, there is an RCT randomizing 68 patients to IVIg or placebo which did not find any significant difference on the outcome contrast sensitivity after 6 months or on visual function measures and MRI, at any time during follow-up.[263] Therefore IVIg is not supported for acute neuritis optica, not linked to the syndrome of neuromyelitis optica/Devic’s disease. Other countries recommend neuromyelitis optica (Australia, two of the Provinces guidelines of Canada) but explicitly not support the use for acute neuritis optica (Australia, one Province guideline of Canada).

Susac syndrome is a rare, microangiopathic disorder characterised by encephalopathy, hearing loss and retinal artery branch occlusions. Our literature search did not identify any relevant SRs. Some case series have identified a positive effect possibly linked to IVIg.[264] In Australia, it is only recommended in exceptional circumstances as well as in the Canadian province guideline of Saskatchewan/Manitoba/Alberta.

Systemic capillary leak syndrome (SCLS), also known as Clarkson syndrome, is an extremely rare condition that is characterised by recurrent life-threatening attacks of reversible capillary hyperpermeability accompagnied by loss of plasma into the extravascular space resulting in oedema, haemoconcentration, hypoproteinemia and shock. Since the initial description of the disease by Clarkson et al in 1960, around 250 cases have been reported worldwide.[265] In more than 85% of patients, monoclonal IgG gammopathy was observed, which means that there is a high titer of a specific Ig in the blood.[266] Most of the time this Monoclonal Ig G gammopathy does not have symptoms (MGUS-Monoclonal gammopathy of undetermined significance), but sometimes it can progress to more-serious diseases, including some forms of blood cancer. Optimal management remains unclear, although in recent years, a growing number of case reports suggested that IVIg might prevent attack recurrence.[267] A European Clarkson disease (EurêClark) registry was set up in 1997. A registry based retrospective study analysed 69 patients of which 48 (73.8%) received IVIg. Multivariate analysis found preventive treatment with IVIg (hazard ratio 0.27; 95% confidence interval, 0.10-0.70; P = .007) and terbutaline (hazard ratio 0.35; 95% confidence interval, 0.13-0.96; P = .041) to be independent predictors of mortality.[268] The Rapid review literature search did not identify a SR or RCT. In Australia, Ig for capillary leak syndrome is only allowed in

exceptional cases as it is considered there is insufficient data. In France, it is also reserved for emergencies. In England, this indication is not captured in the priority list. In Canada, only in one provincial guideline IVIg may be considered for prophylaxis of systemic capillary leak syndrome, in addition to other therapies (based on case reports and expert opinion).

Conclusion

- **Next to the reimbursed or commonly reimbursed indications, there are still indications for which some evidence of an effect exist: sepsis, septic shock for adults and stiff man syndrome.**
- **For some indications, evidence shows there is no benefit: sepsis in neonates, postpolio syndrome, viral myocarditis, Alzheimer's disease.**
- **But for a large number of indications the results are unclear due to: a lack of evidence, the existence of evidence with low quality or conflicting results.**

2.3.5 Ongoing trials

In Table 5 there is an overview of ongoing studies assessing efficacy (see Appendix Search strategy). Thirty nine relevant ongoing RCTs focusing on efficacy were identified. Most RCTs were on IVIg (33), five on SCIg, and one comparing SCIg to IVIg. Most of them compared IVIg or SCIg (or a combination) to placebo (n=19) or standard of care (n=9) and covered diseases not licensed to this date in Belgium (ranging from neurological conditions to respiratory conditions such as COPD, bronchiectasis or Idiopathic pulmonary fibrosis or infertility).

Five studies compared IVIG or SCIG to an active comparator and mostly in patient with a licenced indication (ITP, Kidney transplant, Kawasaki disease, Henoch-Schönlein Purpura vasculitis). There was one RCT comparing IVIg to SCIg in patients with CIPD, and one RCT comparing a new IVIg (sialic acid-enriched (sIVIg)) to an established IVIg product for ITP.

A specific mention should be made for trials targeting an indication or population (subgroup) for which there is currently a lack of published evidence of RCTs.

Thus, our search identified one ongoing study in Kawasaki disease (KIDCARE NCT 03065244), focusing on IVIg refractory patients, the subgroup population in which, as previously described in our review of the published evidence on KD, there is currently inconclusive evidence. This trial aims at recruiting 250 Kawasaki disease patients with persistent fever after the first IVIg infusion, and to compare the results (primary outcome elimination of fever) between a second IVIg infusion and Infliximab. The study is expected to be completed next year.

Similarly, two ongoing RCTs on dermatomyositis were found: the "ProDERM Study" comparing IVIg with placebo in 95 patients (completion expected by the end of 2019), and a further one comparing SCIg versus placebo in 126 patients (completion expected by January 2023).

Ongoing studies on sepsis/septic shock and specifically for the subgroup of children with staphylo or streptococ toxic shock were also identified. For the latter, one study on 156 children is planned to be completed in 2022.

In ITP, one RCT on 74 adults with ITP was found. This was aimed at comparing IVIg versus Eltrombopag for preventing bleeding in patients undergoing surgery. Completion is expected by the end of 2019.

There were also five RCTs on dosing regimens (on increasing doses, dosing intervals, and on tapering doses), all for the licenced indications CIPD or PIDD.

In Table 6, there is an overview of the ten relevant ongoing studies assessing safety of IVIg or SCIg products, 4 on IVIg and 6 on SCIg products and almost all for licenced indications (PIDD, SIDD, CIPD, ITP and systemic sclerosis). None of these trials included a control group.

Table 5 – Ongoing RCTs assessing efficacy

Trial-ID	Indication	Title	Sample size	Intervention	Comparator	Anticipated end date
IVIG						
NCT01757418	Sickle Cell	IV Gammaglobulin for Sickle Cell Pain Crises	94 participants	IVIG	Normal saline	July 2023
NCT01621204	ITP	A Trial of Eltrombopag or IV Immune Globulin Before Surgery for Immune Thrombocytopenia Patients	74 participants	Eltrombopag	IVIG	Dec/19
NCT02308982	Encephalitis	Investigating the Role of Early Intravenous Immunoglobulin Treatment for Children With Encephalitis	308 participants	IVIg: Privigen®	Placebo	February 2020
NCT03194815 **2016-000118-31**	Acute psychosis associated with anti-neuronal membranes/Autoimmune Encephalitis	A Randomised Phase II Double-blinded Placebo-controlled Trial of IV Ig and Rituximab in Patients With Antibody-associated Psychosis (SINAPPS2)	80 participants	IVIg + Rituximab	Placebo	Dec/21
NCT02176863 **2013-004503-39**	Post-polio Syndrome	Study of the Efficacy and Safety IVIg (Human) Flebogamma® 5% DIF in Patients With Post-polio Syndrome (FORCE)	210 participants	IVIg: Flebogamma 5 % DIF ®	Placebo	June 2021
NCT02728752 **2016-002902-37**	Dermatomyositis	Study Evaluating Efficacy and Safety of Octagam 10% in Patients With Dermatomyositis (Idiopathic Inflammatory Myopathy) (IIM) ProDERM study	94 participants	IVIg: Octagam 10% ®	Placebo	October 2019
NCT03401073	Small Fiber Neuropathy	A Double-Blind, Placebo Controlled Trial of IV Immunoglobulin Therapy in Patient With Small Fiber Neuropathy Associated With Autoantibodies to TS-HDS and FGFR3	20 participants	IVIg	Placebo: NaCl 0.9%	June 2020
2015-002624-31	Small Fiber Neuropathy	IVIg therapy for small fiber neuropathy: a randomised, double-blind, placebo-controlled study on efficacy and safety.	60 participants	IVIg: Gamunex®	Placebo	1 year
NCT03700138	Sjögren's Syndrome Associated Painful Sensory Neuropathies	IVIg for the Treatment of Primary Sjögren's Syndrome Associated Painful Sensory Neuropathies (TINISS)	24 participants	IVIg: Privigen®	Placebo: NaCl 0,9%	Dec/20
NCT01785056	Systemic Sclerosis	IVIg Treatment in Systemic Sclerosis	14 participants	IVIg: Privigen®	Placebo: Albuminar®-5	January 2019

Trial-ID	Indication	Title	Sample size	Intervention	Comparator		Anticipated end date
NCT03342638	Multiple Sclerosis, Relapsing-Remitting	Maximizing Outcome of Multiple Sclerosis Transplantation (MOST)	200 participants	IVIg + treatment regimen (methylpredisolon, cyclophoshamide, mesna, rATG, G-CSF, autologous stem cells)	treatment regimen (methylpredisolon, cyclophoshamide, mesna, rATG, G-CSF, autologous stem cells)		January 1, 2024
NCT02915263	Diabetes	The Efficacy Of IV Immunoglobulin Therapy In Treatment Induced Neuropathy Of Diabetes	20 participants	IVIg-C	Placebo: NaCl 0.9%		Sep/19
NCT03684018	CIDP	Single vs. Multiple PrIVIgen Dose Regimens in Pediatric CIDP	30 participants	IVIg: IgPro10 (single dose)	IVIg: IgPro10 (multiple dose)		January 2023
NCT02638207 2015-005443-14	CIPD	Prospective, double-blind, randomized, multicenter phase III study evaluating efficacy and safety of three different dosages of NewGam in patients with chronic inflammatory demyelinating poly(radiculo)neuropathy (ProCID)	142 particpants	IVIg: Newgam® 0,5g/kg	IVIg:Newgam® 1g/kg	IVIg: Newgam® 2g/kg	sep/19
2012-005150-34	CIPD	Dose response trial of IV immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy (DRIP-study)	17 participants	IVIg: Kiovig® high frequency low dosage (as maintenance)	IVIg: Kiovig® low frequency high dosage (as maintenance)		not specified
NCT03919773	Postural tachycardia syndrome patients with evidence of autoimmunity.	IVIg (Gamunex-C) Study of Treatment for Autoimmune Neuropathic Dysautonomia/Postural Tachycardia (POTS)	20 participants	IVIg crossover	Placebo: albumin		Dec/20
NCT04033276	Kidney Transplant antibody-mediated rejection (AMR)	IVIg/Rituximab vs Rituximab in Kidney Transplant With de Novo Donor-specific Antibodies	50 participants	Rituximab	high-dose IVIg + Rituximab		January 2021
NCT03380936	Kidney Transplant antibody-mediated rejection (AMR)	Pilot Study of Treatment for Subclinical AMR (Antibody-mediated Rejection) in Kidney Transplant Recipients	50 participants	Tacrolimus	PE + IVIg + rituximab		Nov/21
NCT02659891	Kidney Transplant	IVIg to Treat BK Viremia in Kidney Transplant Recipients	60 participants	IVIg: Privigen®	Placebo		Dec/19
NCT02690038	COPD	Feasibility and Safety of Immunoglobulin (Ig) Prophylactic Treatment in COPD Patients With Frequent Exacerbations: A Pilot Study	48 participants	IVIg	Placebo: Normal Saline		June 2020

Trial-ID	Indication	Title	Sample size	Intervention	Comparator	Anticipated end date
NCT03018652	COPD	Feasibility and Safety of Immunoglobulin (Ig) Treatment in COPD Outpatients With Frequent Exacerbations: Pilot Study 1	22 participants	IVIg	Placebo: normal saline	June 2020
NCT03584802 **2018-002632-24**	Severe Acute exacerbation for Idiopathic pulmonary fibrosis (IPF)	Therapeutic Plasma Exchange, Rituximab and IV Ig for Severe Acute Exacerbation of Idiopathic Pulmonary Fibrosis Admitted in ICU: an Open, Randomized, Controlled Trial	40 participants	Plasma exchange + IVIg + Rituximab	Standard of Care (mostly corticosteroids)	March 1, 2021
NCT03286556	Idiopathic Pulmonary Fibrosis	Study of Therapeutic Plasma Exchange, Rituximab and IV Immunoglobulin for Acute Exacerbations of Idiopathic Pulmonary Fibrosis (STRIVE-IPF)	51 participants	Plasma exchange + IVIg + rituximab	Standard of Care (Antibiotics and steroids)	September 30, 2022
NCT02184741	Recurrent Miscarriage	A Randomized, Placebo-controlled, Double-blinded Study With GB-0998 for Unexplained Primary Recurrent Miscarriage	80 participants	IVIg: GB-0998 (Venoglobulin®I 2.5g/50ml)	Placebo	June 2021
2014-005419-18	Pregnancy loss	Clinical trial, phase III, randomised double blind placebo controlled with IV immunoglobulin human for the treatment of repeat abortion with immune etiology	66 participants	IVIg	Placebo	2 years
NCT03289403	Infertility-Autoimmune Thyroiditis	The Role of Immunomodulatory Treatment in Success of ICSI in Patients With Autoimmune Thyroiditis	100 participants	thyroxine + immunomodulatory drugs (Prednisolone + hydrochloroquine) In case no response to immunomodulatory drugs ==> Ig	thyroxine (and no immunomodulatory drugs)	Sep/19
NCT04041765	Neonatal Sepsis	Efficacy of Prophylactic IgM-Enriched Immunoglobulin for the Management of Early-Onset Neonatal Sepsis in Very Low Birth Weight Preterm Neonates; A Randomized Controlled Trial	70 participants	IgM-enriched IVIg given with dose of 0.25g/kg/ 3 days + Antibiotics	antibiotics	Aug/20
NCT02899702	Toxic Shock Syndromes in Children	Effectiveness of IVIg in Toxic Shock Syndromes in Children (IGHN2)	156 participants	IVIg: Privigen®	Placebo: Albumin	Apr/22
2017-000826-36	Nephrotic syndrome	Efficacy and safety of immunoglobulin associated with rituximab versus rituximab alone in Childhood-Onset steroid-dependent nephrotic syndrome	90 participants	IVIg: Privigen® + rituximab	rituximab	3 years
2016-001788-34	Sepsis / Septic shock	Prospective, randomized study concerning personalized medicine with Pentaglobin® after	200 particpants	IgM-enriched IVIg: Pentaglobin®	Standard of Care	3 years

Trial-ID	Indication	Title	Sample size	Intervention	Comparator		Anticipated end date
		interventional infectious source control in peritonitis patients					
NCT03065244	Kawasaki disease	KIDCARE (Kawasaki Disease Comparative Effectiveness Trial) (KIDCARE)	250 participants	IVIg (crossover)	Infliximab		Sep/20
NCT02540720	Henoch-Schoenlein Purpura (vasculitis affecting small vessels)	The Research of Standard Diagnosis and Treatment for Severe HSP in Children	30 participants	Dexamethasone	Dexamethason + gammaglobulin	Dexamethason + Hemoperfusion	July 2020
NCT03647852	Henoch-Schönlein Purpura (IgA vasculitis)	Clinical Study on Strategy for Refractory Henoch-Schönlein Purpura	150 participants	IVIg (+ blood purification)	methylprednisolon (+blood purification)		October 30, 2021
SCIG							
NCT03939533	PIDD	Study to Monitor SC Human Ig Administered at Modified Dosing Regimens in Patients With Primary Immunodeficiency Diseases	65 participants	SCIg: Cutaquig® weekly and increase volumes every 4 week	SCIg: Cutaquig® weekly and increase infusion rate every 4 weeks	SCIg: Cutaquig® every 2 weeks increased dose (twice their body beight)	March 2021
NCT04044690	Dermatomyositis	A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of IgPro20 in Adults With Dermatomyositis (DM)	126 participants	SCIg: IgPro20 (Hizentra®)	Placebo		January 2023
NCT02549170 **2014-005496-87**	CIPD	A Phase III Study to Evaluate the Efficacy, Safety, and Tolerability of Immune Globulin Infusion 10% (Human) With Recombinant Human Hyaluronidase (HYQVIA/HyQvia) and Immune Globulin Infusion (Human), 10% (GAMMAGARD LIQUID/KIOVIG) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)	232 participants	SCIg: Hyqvia® as maintenance therapy	0.25% albumin placebo solution with rHuPH20		December, 2021
2018-003592-34	CIPD	Randomized, parallel study of SC versus IV immunoglobulin in treatment-naïve patients with chronic inflammatory demyelinating polyneuropathy	60 participants	SCIg: Hizentra®	IVIg: Privigen®		6 year
2017-002024-24	CIPD	Randomized, cohort study of standardized reduction of SCIg treatment in patients with chronic inflammatory demyelinating polyneuropathy	60 participants	dose reductions: SCIg: Gammanorm®			1 year

Trial-ID	Indication	Title	Sample size	Intervention	Comparator	Anticipated end date
				, Hizentra® , Subcuvia®		
NCT03737617	Bronchiectasis	Ig Replacement Therapy for Immunoglobulin G Subclass 2 Deficient Patients With Bronchiectasis	20 participants	SCIg: Cuvitru 20 %	standard of care	December 1, 2021

Table 6 – Ongoing trials assessing safety

trial ID	Indication	Title	Sample size	Intervention	Comparator	Anticipated end date
NCT03866798	ITP	Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients With Chronic Immune Thrombocytopenia (ITP)	20 participants	IVIg: Panzyga	none	March 2022
2018-003534-32	ITP	A 4-part Phase 1/2 study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of M254 in healthy volunteers and in patients with immune thrombocytopenic purpura	93 participants	IVIg: hypersialylated Ig	IVIg: Privigen®	2 years
2009-012036-32	PIDD	Safety study of IGNG, a new liquid preparation of human normal immunoglobulin for IV use, when administered to primary immunodeficient patients, at a progressively increased flow rate	25	IVIg	none	1 year
2007-001410-17	PIDD	Long-term safety and efficacy study of IGNG, a new liquid preparation of human normal immunoglobulin for IV use, administered in current practice to primary immunodeficient patients	25	IVIg	none	2 years
SCIG						
NCT03677557	PIDD or SIDD	Safety, Tolerability, Patient Satisfaction and Cost of 16.5% SCIg (Cutaquig®) Treatment in Patients Who Did Not Tolerate Other 20% SCIg Product(s)	30 participants	SCIg: 16,5% Cutaquig	none	July 10, 2019
NCT01888484 **2013-003877-87**	PIDD	Clinical Phase III Study to Evaluate the Pharmacokinetics, Efficacy, Tolerability and Safety of SC Human Ig (Octanorm 16.5%) In Patients With Primary Immunodeficiency Diseases	64 participants	SCIg: Octanorm 16.5%	none	July 2020

NCT03116347 **2016-003438-26**	PIDD	Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric PIDD Subjects	40 participants	SCIg: Hyqvia, Kiovig, Cuvitru	none	April 28, 2023
NCT03277313	PIDD	Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric PIDD Subjects	44 participants	SCIg: Hyqvia	none	October 30, 2023
NCT02955355 **2016-000374-37**	CIPD	Long-Term Tolerability and Safety of HYQVIA/HyQvia in CIDP	149 participants	SCIg: Hyqvia	none	September 30, 2024
2018-003149-41	Systemic sclerosis	A Multicenter, Randomized, Open-label, Crossover, Phase 2 Study to Evaluate the Safety and Pharmacokinetics of IgPro20 (SCIg, Hizentra®) and IgPro10 (IVIg, PrIVIgen®) in Adults with Systemic Sclerosis (SSc).	26 particpants	SCIg: Hizentra IVIg: Privigen	none	2 years

3 SYSTEMATIC LITERATURE REVIEW OF ECONOMIC STUDIES

3.1 Introduction

This chapter provides a rapid review of published studies evaluating the use of polyvalent Ig (IV or SC) in different indications, from an economic perspective. It builds on the KCE report 120, published in 2009.[18]

The aim is to offer an update on any new economic studies that may have been published since then, and adapt the critical assessment.

3.2 Methods

3.2.1 Search strategy

The systematic search carried out at the beginning of June 2019, looking at any full economic evaluations published from 2008 (search date used in previous report.

The following databases were consulted: Medline (through OVID), Econlit (through OVID), NHSEED (CRD) and NHSHTA (CRD) in order to retrieve recent primary full economic evaluations (studies comparing both costs and outcomes) and reviews of economic evaluations (i.e. secondary economic evaluations). An overview of the update to the original search strategy is offered in the appendix on the search strategy 1.5.

Furthermore, the websites of Health Technology Assessment (HTA) institutes listed on the INAHTA website (International Network of Agencies for Health Technology Assessment) and NICE (National Institute for Health and Care Excellence) were consulted to capture any recent reports (published from 2008) on the use of Ig. Articles published in English, Dutch, French, German, Portuguese and Spanish, were considered.

3.2.2 Selection procedure

To identify potentially relevant studies for our analysis we first went through all titles and abstracts in order to exclude any obvious studies that did not match our research subject. All articles that appeared to be interesting, or for which there were some doubts, were read in full in order to select those relevant for inclusion in our review.

Reference lists of the selected primary and secondary economic evaluations found via our search were checked for additional references worth adding to our analysis.

Study selection was completed by one researcher but any doubts that came up during the exercise were solved in collaboration with a second reviewer.

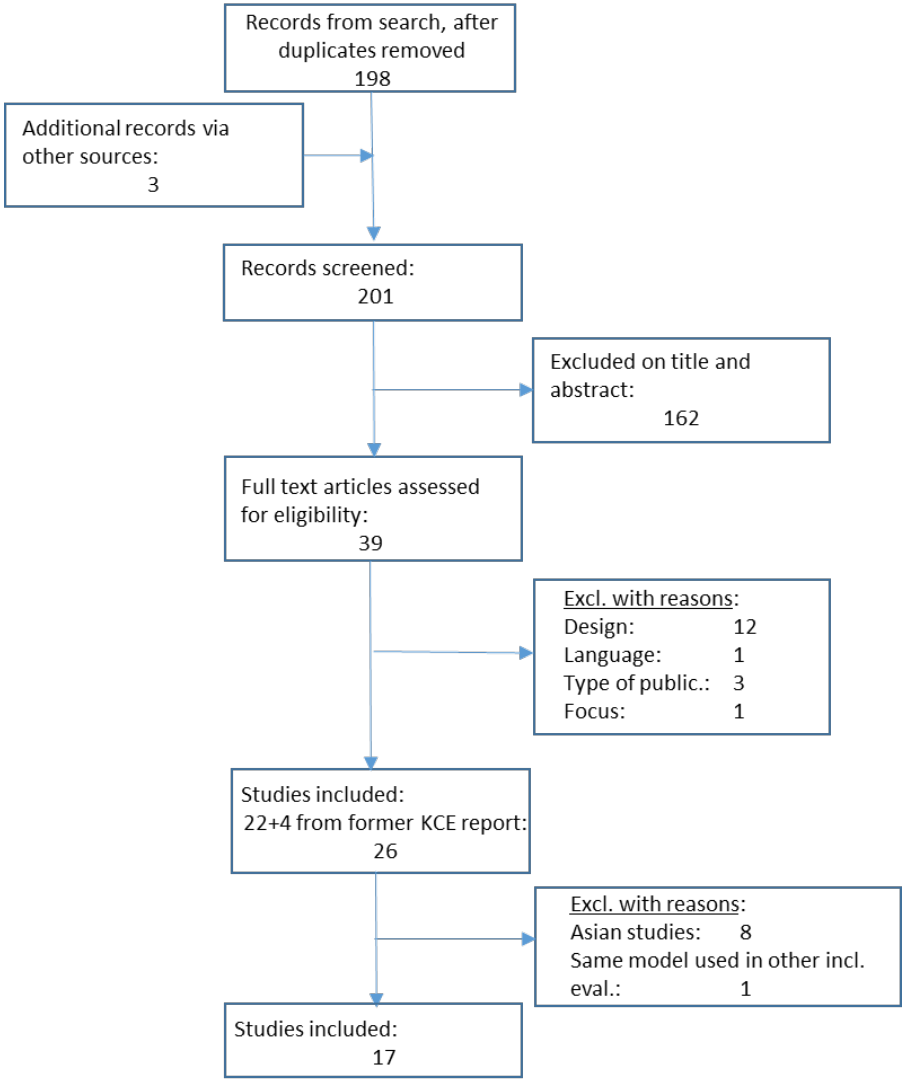
All studies finally included in our review were critically appraised by using an in-house structured data extraction excel sheet based on the check list originally developed by Drummond et al.[269]

A copy of this template is provided as in Supplement 5.1

3.2.3 Selection criteria

All full economic evaluations looking at polyvalent Ig for IV and SC/IM use published between 2008 and May 2019 (incl.), were included in our review and added to the original list of studies on Ig already identified in our 2009 report.

Figure 3 – Flow chart of study selection for review on economic evaluations



Cost descriptive analyses or cost comparisons not taking into consideration effectiveness in any way were discarded. Cost studies based on less than 10 patients were also discarded. Similarly, publications in the form of letters, editorials or notes and abstracts were excluded, since these would not offer enough information to include them in our analysis and critically appraise their findings. An overview of the inclusion/exclusion criteria is given in Table 7 and a flow chart for study selection is offered in Figure 3.

Table 7 – Selection criteria for economic evaluations

Selection criteria	Inclusion criteria	Exclusion criteria
Population	All patients treated with Ig	None
Intervention	Polyvalent Ig (IV, SC or IM formulations)	Not hyper immune plasma, polyclonal or monoclonal Ig targeted against specific (epitopes) pathogens. No other formulations (i.e. oral Ig).
Comparator	All	No treatments excluded a priori
Design	Full economic evaluations (primary or secondary)	Cost descriptive analysis, cost comparisons
Type of publication	Articles or reviews	Letters, editorials, notes, abstracts

Ig – Immunoglobulins; IV – Intravenous; SC –Subcutaneous; IM –Intramuscular

Our search returned 198 citations, after eliminating duplicates. Of those, 161 did not meet our inclusion criteria based on a review of their title and/or abstract. Of the 37 citations left, 12 were excluded after reading their full text because of their design.[35, 270-280] A further study was excluded on the basis of its focus.[281] Other reasons for exclusion included the type of publication[282-284] and language.[285] This left us with 20 relevant studies. In the 2009 KCE report, 5 primary cost studies were identified. One of these studies,[286] was excluded because it was considered too old to be informative for the purposes of our analysis (published in 1993). This left us with 4 additional sources that added to the 20 found via our search gave us a total of 24 relevant studies. An exploration of the references of articles resulted in three additional studies.[190,191,287] The overall number of studies was 27.

Given the important number of economic evaluations found, and the purely informative nature of this review (modelling not in the scope of this review), the research team decided to exclude Asian studies, which are less likely to be representative of common medical practices in Western European countries such as Belgium. Therefore, eight Asian studies were excluded from our selection. Three of them were carried out in Thailand, two by the same autor,[178, 288, 289] two in Japan;[290, 291] two in India[190, 191] and one in Iran.[292]

In addition to this, after careful reading of evaluations that were left, it was noticed that two of the evaluations carried out in Canada for CIDP[287,293] made use of the same model and referred to the same evaluation, even if the absolute ICERs differed slightly probably due to different assumptions. The overall conclusions did not change and thus, in order to avoid repetition, the study by [287] et al. was excluded and instead we appraise the evaluation by Blackhouse et al., which was published a year later, in a peer reviewed journal.

Our literature selection process is illustrated in a flow chart (Figure 3). Out of the economic evaluations left, one[294] consisted of a HTA report which included the development of an original cost model and thus, was included in our analysis.

References of any reviews found (even if not systematic), focusing on economic evaluations were hand searched, in order to ensure no relevant primary economic evaluations had been missed from our review.

Table 8 offers and overview of the 17 studies on Ig finally included in our review.

3.3 Overview of economic evaluations

As shown in Table 8 eight studies were undertaken in Europe. Of these one study was carried out in Belgium,[295] while a further was done in 9 different European countries amongst which Belgium was included.[296] Six more studies were carried out in Canada,[293, 297-301] two in the USA[302, 303] and one in Australia.[304]

Seven out of the 17 studies date from 2012 or later.

Table 8 – Overview of economic evaluations on Immunoglobulins

Author	Year	Country	Type of evaluation	Perspective	Discount rate (%)	Indication
Windegger[304]	2019	Australia	CUA	Healthcare system	5%	SID
Furlan[298]	2016	Canada	CMA	Healthcare payer and Hospital	NA	MG
Perraudin[305]	2016	Switzerland	CMA	Societal	NA	PID
Lazzaro[306]	2014	Italy	CMA	Societal	NA	CIDP
Martin[299]	2013	Canada	CMA	Health care system	NA	PID
Blackhouse[297]	2012	Canada	CUA	Healthcare payer	5%	Acute ITP
Soares[294]	2012	UK	CUA	Healthcare system	3,5%	Sepsis and toxic shock
Connolly[295]	2011	Belgium	CMA	Societal	NA	PID
Heatwole[307]	2011	Netherlands	CMA	Healthcare system	NA	MG
Winters[303]	2011	USA	CMA	Hospital	NA	GBS
Beaute[308]	2010	France	CMA	Healthcare payer	NA	PID
Blackhouse[293]	2010	Canada	CUA	Healthcare system	5%	CIDP
Maroto Hernando[309]	2009	Spain	CCA	Societal	NA	Common variable immunodeficiencies
Xie[301]	2009	Canada	CUA	Healthcare system	5%	Chronic ITP
O' Brien[302]	2007	USA	CUA	Societal	NA	Acute ITP
McCrone[296]	2003	Europe (incl. BE)	CUA	Societal	NA	CIDP
NagPal[300]	1999	Canada	CMA	Healthcare system	NA	GBS

CCA: Cost consequences analysis; CEA: Cost effectiveness analysis; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; CMA: Cost minimisation analysis, CUA: Cost utility analysis; GBS: Guillain-Barre Syndrome; ITP: Immune thrombocytopenia purpura; MG: Myasthenia Gravis; PID: Primary Immunodeficiency; SID: Secondary immunodeficiency.

3.3.1 Type of economic evaluation

Seven of the studies performed cost-utility analyses (CUA) (see Table 8 for references) and expressed their outcomes in quality-adjusted-life-years (QALYs). One consisted of a cost consequences analysis (CCA) in which costs and outcomes were presented separately,[271, 309] and the remaining 9 studies were cost minimisation evaluations (CMA), in which the authors first, justified their choice of evaluation type, by presenting references of studies showing similar effectiveness between the therapies they aimed to compare, and then, focused purely on costs.

3.3.2 Time frame of analyses and discounting

Only three studies included in this analysis looked at costs and outcomes over a patient's lifetime,[294, 297, 301] a further four, used time horizons between 3-10 years.[293, 299,304,305] The remaining 9, looked at short term horizons which varied greatly from just few infusions to 1 year (See Table 9 for details).

Although a lifetime framework is considered the gold standard in economic evaluations, the acute nature of some of the diseases (eg Kawasaki or acute ITP) here analysed, may justify a more limited time horizon. Other diseases, such as PID or CIDP, in which chronicity requires long-term treatment, longer time frames are needed to offer an appropriate comparison.

Of the seven studies looking at horizons longer than a year, two did not apply discounting.[299,305] The remaining five studies discounted costs and outcomes and gave details on the rates used, which reflected different national recommendations.

Four of them used 5% for both costs and outcomes,[293, 297, 301, 304] and based their choice, in the case of the Australian study on standard practice in Australian economic evaluations, while the three Canadian studies followed their national guidelines.

3.3.3 Perspective

Seven studies were performed from a healthcare services perspective (see Table 8 for details), while a further two used a third party payer perspective. One evaluation was performed from a hospital perspective, while another was completed from both a healthcare payer and a hospital perspective.[298] Finally, six studies offered a societal perspective taking into consideration productivity costs (lost wages or time), estimated by the human capital approach in all cases.

3.3.4 Indications and Population

Various different indications, mainly covering those well established and commonly reimbursed have been studied from an economic perspective. PID was investigated in four studies,[295,299,305,308] with a further one looking at common variable immunodeficiencies.[309] Two studies covered GB syndrome[300,303] and[310] CIDP was described in three evaluations.[293,296,306]

Single evaluations were found for SID[304] and severe sepsis and septic shock,[294] while three studies covered ITP. Two of the latter focused on children with acute ITP[297,302] and a further one, on adults with persistent (chronic) ITP.[301]

All of the above represent indications already reimbursed in Belgium. Only two studies focused on other diseases, more specifically on moderate to severe MG patients.[298,307] Although MG is not currently reimbursed in Belgium, it is frequently recognised or reimbursed in other countries (see chapter on international comparison for more details).

3.3.5 Comparators

Three groups of comparisons were performed in the evaluations included in this review:

First, *comparisons between IVIg and other active therapies used in the specific indications studied*

Four studies compared IVIg with plasma exchange in those indications in which plasma exchange is commonly used (i.e. MG and GBS).[298, 300, 303, 307]

The three studies looking at ITP (chronic or acute) compared IVIg mainly to prednisolone,[297, 301, 302] although methylprednisolone and observation were also included in two of these evaluations.[297, 302]

Two studies looked at IVIg versus corticosteroids, both in populations suffering from CIDP.[293, 296]

The only study which looked at severe sepsis focused on IVIg as an add-on to standard therapy versus standard therapy alone.[294]

Second, *comparisons between IVIg and SCIg*

Overall, six evaluations compared these two different formulations of Ig, four in PID,[299, 305, 308, 309] one in CIDP,[306, 310] one in SID.[304]

Third, one single study, a Belgian evaluation, focused on *comparing different brands of Ig*. In this case, three products were compared. These were Kiovig, Multigam and Sandoglobulin.[295]

3.3.6 Cost and outcome inputs

Different sources were consulted to derive costs. In addition to the published literature, hospital expenses and patient records, national/provincial administrative data and medical reimbursement fees/tariffs were also used.

For the cost of therapies, studies mentioned formularies, national tariffs or blood service suppliers as their main sources.

Some of the evaluations, focused purely on costs surrounding infusions/acute episodes reflecting a short-term view that may be more justifiable, in those studies looking at (often) acute illnesses/crises (such as MG or GBs). Two of these studies focused on MG[298,307] a further two considered GBS,[300,303] but the last two studied PID,[299,308] an indication for which longer time horizons would have been more appropriate. Costs considered in these studies included hospital costs, physician fees, cost of supplies and therapies, and infusion related costs. Only one of these evaluations mentioned explicitly the inclusion of costs linked to the management of short term AEs.[307] Transport costs were considered in two of the studies.[307,308] Cost sources for these studies relied mostly on hospital accounting and reimbursement tariffs.

Other studies offered a broader costing view including also costs of follow up and management of AEs.[293, 304]

Finally, six studies covered productivity or time costs linked to patients and or family carers.[295, 296, 302, 305, 306, 309] Calculations on productivity costs were based on national statistics on salaries.

Regarding outcomes, an important number of the studies here included performed CMA and thus, focus purely on the cost side of the analysis. Nevertheless, they all offered references of studies showing an equivalence (non-significant differences) in the effectiveness of Ig versus the relevant comparators.

For the CUA, authors of the evaluations based their inputs on the literature. Although the response rates relied often on MAs of RCTs, estimations of utilities tended to be based on single, small studies. One of the evaluations, focused on CIDP, consisted on an RCT with a very small sample size (n=25),[296]

The only CUA comparing IVIg to SCIg, captured outcomes from their study and relied on very few patient charts to draw their conclusions (n=13).[304]

3.3.7 Modelling

Most CMAs included in this review, made use of itemised micro-costing approaches to compare the costs of the different treatment groups analysed over very variable time frames. Only two of these CMA[295, 305] used decision analytic models to pursue their cost comparisons. All CUA studies consisted of modelling exercises. One of them, focused on CIDP, used multiple regression models to compare the costs and outcomes captured during a cross over study.[296] The remaining consisted of decision trees and Markov models. Health states used were based on the literature and the cycle lengths varied greatly form one study to another (from weekly cycles in the study on SID by Winderger et al.[304] to yearly cycles in the study by Soares et al.[294] on severe sepsis, as well as those by Blackhouse et al.[297] and Xie et al.[301] in children with acute ITP and adults with chronic ITP respectively). Direct comparisons were difficult due to the differences in populations, indications and therapies compared.

3.3.8 Results

3.3.8.1 Incremental costs

Table 9 shows the mean costs reported in the 17 studies included in our review. Comparisons between studies are difficult primarily because of the different costs borne in mind, differences in cost definitions, in time horizons, in practices and in prices.

The evaluations comparing IVIg with other active therapies, showed in all cases but one, incremental costs linked to the use of IVIg. The absolute increments varied greatly and can be seen in Table 9.

The exception was one study, comparing IVIg versus plasma exchange in moderate to severe MG, which found plasma exchange to be more expensive, reporting an incremental cost of $22,326. These differences appeared to be mainly driven by longer hospital (and ICU) stays for patients on plasma exchange compared to those on IVIg. Differences were based on historical data from 4 US hospitals on 54 patients. This study found a mean ICU stay of 14 days with IVIg, versus 17,4 days for those on plasma exchange. The overall hospitalisation period also varied greatly (a mean LoS of 17,7 days with IVIg versus 25,7 with plasma exchange). The results were also highly dependent on IVIg dosing and the authors warned that prospective studies would be needed before clear conclusions could be made.[307]

There was consistency in the results obtained from evaluations comparing different Ig formulations (IV and SC) showing greater overall costs linked to IVIg versus SCIg. Amongst these, three studies were carried out from a societal perspective and thus, considered productivity and time lost by patient and carers.[305, 306, 309]

The only study which compared different brands of IVIg appeared to favour the use of Kiovig when compared to Multigam: +€56 and Sandoglobulin: +€101, but this offered a very limited analysis looking at the cost for one infusion, which could then be extrapolated to consider higher numbers of infusions and longer time frames.

Table 9 – Costs in economic evaluations of Immunoglobulins (Ig)

Author	Costing yr	Time horizon	Test/Comparator	Population	Costs included	Cost source	Mean incremental cost*
Comparisons Ig versus other active treatments or standard care							
Furlan 2016	2014	Unclear - probably whole treatment period	IVIg/PE	Adults with moderate to severe MG, requiring a change in treatment	Hospital costs, physician fees and cost of blood products	Hospital expenses/patient (from RCT). Physician fees from the Ontario Health Insurance and official prices	CAN$2 039 (≈€1 393)
Blackhouse 2012	2008-2009	Lifetime	IVIg/Anti-D/ prednisone/ IV methylpred/observation	Hospitalised children with ITP and platelet count <20,000/µL.	Drug costs; hospitalisation costs for ITP; hospitalisation and management costs for intracranial haemorrhage (ICH)	Canadian Formularies, Ontario Case Costing Project and other Canadian public sources	CAN $236 (≈€161) IVIg vs prednisone
Soares 2012	2009	Lifetime	IVIg + standard care/standard care	Patients with severe sepsis	Costs of IVIg and LoS in hospital (critical-care unit and other wards). Cost of managing survivors after the initial hospitalisation	National Schedule of Reference Costs 2007/08, formularies and literature	£9 308 (≈€11 010) IVIg +standard vs standard alone
Heatwole 2011	NA	Short term	IVIg/PE	Myastenia gravis	Cost of therapy; hospitalization; AEs. Ambulance costs, standard initial chest X-rays and lab tests not included	Local cost, accounting data and a literature review	- US$22 326 (≈ -€20 100)
Winters 2011	2010-2011	5 infusions - short term horizon	IVIg/PE	GBS patients	Supplies; nursing costs, central venous catheter; hospital costs, TPE equipment and infusion costs	Hospital accounting/financial data and reimbursement rates	US$5 692 (≈€5 125)

Author	Costing yr	Time horizon	Test/Comparator	Population	Costs included	Cost source	Mean incremental cost*
Blackhouse 2010	2008	5 years	IVIg/corticosteroid	CIDP	Costs of IVIg infusion, costs of corticosteroids, AEs	Canadian Blood Services, formularies and reimbursement rates. Nursing costs from national salary stats	CAN$121 869 (≈€83 327)
Xie 2009	2007	Lifetime	IVIg/oral prednisolone	Adults with persistent, chronic ITP	IVIg costs, prednisone costs, and splenectomy costs. No costs of administration or distribution included	Formularies national costing and literature	CAN $8 080 (≈€5 525)
O' Brien 2007	2004	Unclear - probably whole treatment period	IVIg/anti-D; methylpred/prednisone	Acute Childhood ITP	Medication, infusion, AEs, Intracranial hemorrhage, lost wages (parents)	Cost data and QoL measures from hospital sources and published data, tariffs and reimbursement rates	US$457 (≈€412) vs anti-D; US$1 146 (≈€1 033) vs methylpred; US$1 706 (≈€1 537) vs prednisone
McCrone 2003	2000-2001	6 weeks	IVIg/Prednisolone	CIDP	Accommodation, employment, income, informal care/services (by friends and family); hospitalisation, outpatient, costs of therapies	UK costs were used	€ 3 754
NagPal 1999	1997	48 weeks	IVIg/PE	Acute GB syndrome	Supplies and therapy costs, staff costs, overhead costs and hotel costs	Pharmacy and supply costs, hospital costs, insurance charges and provincial salaries	US$3 961 (≈€3 566)
Comparisons IV versus SC Ig							

Author	Costing yr	Time horizon	Test/Comparator	Population	Costs included	Cost source	Mean incremental cost*
Windegger 2019	2018	10 years	IVIg/SCIg	Adult patients with SID	Ig; consumables; pumps; training; haematology fee; pathology tests; costs of bronchiectasis; infection costs	Accounting data from hospital and health services	AU$7 215 (≈€4,456) IVIg vs SCIg;
Perraudin 2016	2015	3 years	Monthy IVIg/weekly SCIg	Any PID patients	Ig, staff time, infusion pump, disposables; Non medical costs: transport and productivity costs.	Medical costs from administrative data. Non medical costs from experts	€8 897 IVIg vs SCIg
Lazzaro 2014	2013	1 year	IVIg/SCIg	Patients with CIDP	IG, drugs and management of AEs, staff time, pump, disposables. Transport, losses of working and leisure time (patients and caregivers)	Public sources and expert opinion	€1 361 IVIg vs SCIg
Martin 2013	2011	3 years	IVIg/SCIg (via rapid push)	Adult patients with PID	Supplies and personnel costs. Ig costs were not considered since thought to be equivalent for IVIg and SCIg	Hospital's SCIg home infusion program	CAN$ 5 736 (≈€3 920) IVIg vs SCIg
Beaute 2010	2008	1 year	SCIg/IVIg	PID patients	Out-patient treatment, hospitalisation, transportation; nursing costs and costs of supplies (eg pumps)	Reimbursement costs for medication and services, national statistics for productivity costs and surveys	€797/year IVIg vs SCIg; €6 099 hospital-based vs home IVIg

Author	Costing yr	Time horizon	Test/Comparator	Population	Costs included	Cost source	Mean incremental cost*
Maroto Hernando 2009	2006-2008	1 year	IVIg/SCIg	Paediatric patients with common variable immunodeficiency (CVID) receiving SCIg	Medication, pumps, infusion kit, other medical costs, training and infusion times/visits (patients and family carers), transportation	Data captured for every patient during the study	€1 921 (1st year); €4 030 (following years) IV vs SCIg
Comparisons between different brands of IVIg							
Connolly 2011	2009	1 infusion	Kiovig/Multigam/Sandoglobulin	Adults suffering from PID	Ig costs, pharmacy administration, nursing costs, hospital infusion costs, costs of AEs, and productivity costs	Belgian public sources and administration costs	Multigam: €56 and Sandoglobulin: €101 vs Kiovig

AEs: Adverse Events; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; GB: Guillain-Barre; Ig: Immunoglobulins; IVIg: Intravenous Immunoglobulins; ITP: Immune thrombocytopenia purpura; LoS: Length of Stay; MG: Myasthenia Gravis; PE: Plasma Exchange; PID: Primary Immunodeficiency; QoL: Quality of Life; RCT: Randomised controlled trial: SCIg: Subcutaneous Immunoglobulins; SID: Secondary immunodeficiency.

3.3.8.2 Incremental outcomes

Table 10 shows the outcomes reported in the studies included in this review. As already mentioned, more than half of the studies consisted of CMAs and therefore, they did not report or focus on outcomes, although they all provided references of studies showing equivalence or non-significant differences in the efficacy of the therapies compared. These CMAs referred mostly to evaluations comparing different formulations of Ig (ie IV versus SC), or studies comparing IVIg with plasma exchange, which appears not to differ significantly from IVIg in terms of effectiveness. Although the efficacy of IV and SCIg appears to be equivalent, it is important to note that the different types of administration may not suit the same patients, and that a direct comparison purely based on costs may offer just a partial view on the appropriateness of one administration versus the other, which should be assessed by specialists taking into consideration patient preferences and circumstances (clinical and personal).

Regarding the comparisons of plasma exchange versus IVIg, although the studies carried out so far have not shown significant differences, it is important to note that in order to offer a complete view on costs linked to the different therapeutic alternatives, further information on AEs would be necessary. Although the frequency of AEs appears to be similar (based on short-term studies), their nature may differ, and the cost of managing these different types of AEs could have an impact on the overall costs of these therapies.

From the studies that assessed outcomes, one CCA,[309] showed similar efficacy with IVIg and SCIg, reporting 21 episodes of infections (in 7/11 patients at a rate of 2,74 infections per patient per year) for IVIg, versus 17 episodes (in 8/10 patients at a rate of 2.22 infections per patient per year) with SCIg. It is important to note that this was based on a very small sample (n=11) and that thus, their results should be considered purely exploratory.

The seven CUAs carried out, did not report in any case LYGs and focused on QALYs instead. All studies comparing IVIg versus other active treatments, reported incremental gains in QALYs when using IVIg, although these gains varied greatly from a low of 0,0044[297] to a high of 0,4.[294] All of these studies but one, based their effectiveness data on the published literature, relying mostly on SRs of RCTs. The available evidence on utilities appear to be limited to small, single studies. One of the CUAs consisted of a RCT and based their effectiveness on the results of their study, which had a very low sample size (n=25).[296]

The only CUA comparing the two different formulations of Ig (IV versus SCIg), reported incremental gains in QALYs of 0,44, in favour of SCIg. However, these results were based on a very small sample of patients (n=13) and are therefore, subject to great uncertainly.[304]

3.3.8.3 Incremental cost-effectiveness ratios (ICERs)

Table 11 gives an overview of the ICERs reported in those evaluations included in this review, which performed a CE or CU analysis. Two of these seven studies showed ICERs that were considered positive for IVIg, with Blackhouse et al. reporting an ICER of CAN$53 846/QALY[297] (≈€36,837/QALY) for their study on children suffering from acute ITP, and Soares et al. showing an ICER of GBP20 850/QALY (≈€24,410/QALY) for patients with severe sepsis.[294] All other analyses reported high ICERs. Two with a focus on CIDP, gave ICERs of CAN$687,287/QALY[293] (≈€470,200/QALY) and €268 000/QALY.[296]

A further study on adults with chronic ITP gave an ICER of CAN$1.13 mil/QALY (≈773,095€)/ QALY).[301]

One study on acute Childhood ITP showed for IVIg to be dominated by anti-D.[302]

Nevertheless, as we will see later, great uncertainty appears to surround all these results, which should thus, be interpreted with caution. The only CUA which focused on comparing IV to SC Ig, found SCIg to be dominant.[304]

Table 10 – Outcomes of economic evaluations on Immunoglobulins (Ig)

Author	Test/Comparator	Population	Outcomes	Incremental QALYS**	Other outcomes	Data source for outcomes
Comparisons Ig versus other active treatments or standard care						
Blackhouse 2012	IVIg/Anti-D/ prednisone/ IV methylpred/observation	Hospitalised children with ITP	QALYs	0.0044	NA	RCTs (mainly from a SR: Chen et al. 2008)
Soares 2012	IVIg + standard care/standard care	Patients with severe sepsis	QALYs	0,45	NA	Literature (RCTs and MAs); Ut. from Drabinski et al (study on ut. after severe sepsis)
Blackhouse 2010	IVIg/corticosteroid	CIDP	QALYs	0.177	NA	Response rates from MA of 6 RCTs; relapse rates from 1 study. Ut. from literature
Xie 2009	IVIg/oral prednisolone	Adults with persistent, chronic ITP	QALYs	0.0071	NA	Published literature
O' Brien 2007	IVIg/anti-D; methylpred/prednisone	Acute Childhood ITP	QALYs	NA	NA	Published literature
McCrone 2003	IVIg/Prednisolone	CIDP	QALYs	0.014	NA	RCT (n=25)
Comparisons IV versus SC Ig						
Windegger 2019	IVIg/SCIg	Adult patients with SID	QALYs	0,44 SCIg vs IVIg	NA	N. of infections, ED visits and hospitalisations from patient's charts (n=13).
Maroto Hernando 2009	IVIg/SCIg	Children with common variable immunodeficiency (CVID) receiving SCIg	N., type and severity of infections; AEs	NA	IV: 21 infec. episodes (7/11 patients at 2,74 infections/patient/yr); SCIg: 17 episodes (8/11 patients at 2,22/infections/patient/yr)	Data captured during the study (n=11)

AEs: Adverse Events; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; ED: Emergency Department; Ig: Immunoglobulins; IVIg: Intravenous Immunoglobulins; ITP: Immune thrombocytopenia purpura; MA: Meta-Analysis; QoL: QALYs: Quality-Adjusted Life Years; RCT: Randomised controlled trial: SCIg: Subcutaneous Immunoglobulins; SID: Secondary immunodeficiency; SR: Systematic Review

Table 11 – ICERs for Economic evaluations on Immunoglobulins (Ig)

Indication	Author	Intervention/Comparator	ICER	Prob. Of test being cost-effective
Acute ITP in children	Blackhouse 2012	IVIg/Anti-D/ prednisone/ IV methylpred/observation	CAN$53,846 (≈36,837€)/QALY	Highest prob. of being CE: Prednisone at WTP<CAN$112,000 (≈76,625€)/QALY; IVIg at WTP>CAN$112,000
	O' Brien 2007	IVIg/anti-D; methylpred/prednisone	IVIg dominated by anti-D	NA
Chronic ITP in adults	Xie 2009	IVIg/oral prednisolone	CAN$1.13 million (≈773,095€)/ QALY	20%, at WTP =CAN$100,000 (≈68,410€)
Severe sepsis	Soares 2012	IVIg + standard care/standard care	GBP20,850 (≈24,410€/QALY)	50,5% at WTP=GBP20,000 (≈23,417€); 78,9% at WTP=GBP30,000 (≈35,130€)
CIDP	Blackhouse 2010	IVIg/corticosteroids	CAN$687,287 (≈470,200€/QALY)	< 1% for IVIg at WTP of CAN$50,000 (≈34,210€)
	McCrone 2003	IVIg/Prednisolone	€268 000/QALY	50% at WTP>€250 000/QALY
SID in adults	Windegger 2019	IVIg/SCIg	SCIg dominant	88,3% at a WTP A$50 000 (≈58,549€)/QALY

CE: Cost Effectiveness; IVIg: Intravenous Immunoglobulins; QALYs: Quality-Adjusted Life Years; SCIg: Subcutaneous Immunoglobulins; WTP: Willingness to Pay

3.3.9 Sensitivity analysis

Uncertainty is intrinsic to any economic evaluations and should therefore always be accounted for. All evaluations with the exception of two[303, 309] performed some kind of sensitivity analysis to assess the robustness of their results, although eight of them limited their tests to one-way (or two way) sensitivity analyses[296, 298-300, 302, 305, 307, 308] and a further presented results of a one way sensitivity analysis together with scenario analyses.[306]

The remaining studies undertook probabilistic sensitivity analyses, with some of them offering both probabilistic and deterministic analyses.[294, 297, 301, 304] Overall, none of the studies who assessed uncertainty found robust results and all presented important uncertainties.

In *comparisons between IVIg and other active therapies or standard treatment*, results appeared to be primarily sensitive to patient's weight/body mass,[297,298,302,307] and the cost of therapies.[296, 300, 302, 307] Other factors appear to have important weights on the results of individual studies. These included: the choice of clinical effectiveness model,[294] the number of plasma exchanges and ICU and hospital length of stay;[307] frequency of dosing and maintenance IVIg,[293] and time horizons, utility weights and discounts.[301]

In evaluations *comparing different Ig formulations (IV versus SCIg),* results appear to be most sensitive to the cost per gram of Ig.[304-306] Other study specific factors that appear to have some weight on results included: cost of equipment and number of infusions required;[305] number of visits and time required per visit,[299] and number of pumps and doses.[308]

The only study looking at *different brands of IVIg,* showed results sensitive to the treatment of AEs and nursing and family time linked to the care of these patients.[295]

3.3.10 Conflict of interest

All 17 studies included in their manuscripts a declaration of conflict of interest for their authors and/or funding declaration. Only four studies reported no conflict of interest and no direct funding from the industry.[294, 297, 307, 308] The existence of conflicts of interest may introduce a bias which could affect the validity of the study results, although there is, up to date, no hard evidence on this.

3.4 Discussion and conclusions

Despite relatively consistent results found in the economic evaluations published up to date, showing that Ig is unlikely to be cost effective at commonly quoted WTP thresholds, it is important to highlight a number of limitations of these analyses which should be borne in mind.

Sources of clinical data

The clinical data on which the cost utility analyses here included are based are limited, of mixed quality and coming mostly from small size trials.

In particular, sources for utility gains appear to be very scarce and assumptions on this regard tend to be derived from single studies.

More specifically, as we already saw in our review of the clinical literature, the *evidence supporting IV use versus other active therapies*, is often limited to very small studies, in some cases with a cross over design, and with short follow up and limited reporting of AEs. The management of AEs can also have an important weight, especially in those cases when long term treatment is needed. Rare AEs may be unlikely to come up in RCTs but could be more frequent in clinical practice. Some studies justified not including AEs on the fact that AEs appear to be infrequent with Ig and the comparator (eg plasma exchange). However, similar frequency does not mean the same AEs are present with one therapy or the other, and the management of different AEs could in turn, lead to different overall costs.

The *comparisons between IVIg and SCIg* are common and show a cost benefit favouring SC versus IVIg. However, although these are expected given the fact that SCIg can be administrated at the patient's home avoiding

monthly hospital visits, these different formulations may be appropriate for different types of patients or indications and thus, may only be interchangeable in some cases. Although a switch for some patients/indications may be appropriate, this should be left to the specialists to carefully evaluate the clinical and personal situation of the patient.

An important number of assumptions was made in these evaluations (mostly CMAs), which often were based on very few patient cases.

Type of economic evaluation

Although using CMA may be justified in comparisons between SC and IVIg, we already mentioned previously that different formulations may be suitable for different patients.

On the other hand, evaluations comparing Ig with other active therapies, CEAs or CCAs may have been more appropriate. Comparisons with plasma exchange appear common and the equivalence in terms of effectiveness is based on evidence of non-significant differences. Nevertheless, the existing evidence is not exempt form uncertainties and very simple cost comparisons with short time frames, may offer just a partial view on the value of these therapies.

Modelling/assumptions

Most of the studies included important assumptions not well backed-up with literature. These were made explicit, but posed questions regarding the validity of the results of some of these studies, which appear more exploratory than conclusive.

Conclusions

- **More than half of the models consisted of simple CMAs, assuming equal outcomes (most often IV versus SCIg and IVIg versus Plasma Exchange).**
  - **Those comparing SC to IV Ig consistently show that SCIg offers a cheaper option when compared to IVIg.**

  Regarding comparisons with other active therapies:
  - **The two studies for MG comparing IVIg and plasma exchange show conflicting results one concluding that IVIg is cheaper and the other showing it to be more expensive.**
  - **For all other indications, IVIg appears to be more expensive than other active therapies, with large variations due to different populations, time horizons, assumptions and approaches used.**
  - **Focusing purely on CUAs, all studies show high ICERs due to the high costs linked to Ig, despite Ig offering incremental gains in QALYs.**
- **Important limitations exist regarding the clinical evidence on which the evaluations are based, which explains the great uncertainties that surround the resulst of all studies included in this review.**

4 HOW DO THE INDICATIONS REIMBURSED IN BELGIUM COMPARE TO INDICATIONS REIMBURSED IN OTHER COUNTRIES?

The limited supply of Ig in the international market have encouraged countries to implement a combination of clinical practice guidelines and procedures to monitor the use of this expensive product. Thus, the year 2018 was characterised by several national initiatives and publications of national recommendations on Ig use in different countries. This chapter focuses on these recent initiatives in Australia, France, England and Canada.

4.1 Methods

We retrieved information on the different countries through grey literature (including websites, and official documents), and through personal contact with national experts[y].

4.2 Belgium

In Belgium, Ig are reimbursed in 8 indications (see Table 1). For reimbursement purposes, medicines in Belgium are classified in a number of categories (A, B, C, Cs, Cx, D, Fa, Fb) and chapters (I, II, III, IV, IVbis, VII). Ig are placed in chapter IV, which means that their reimbursement is subject to conditions and limited in terms of indications, target group, age, dosages, prescribers, etc. For Chapter IV medicines, the law foresees a special application form, needed to be completed by prescribers, most often specialists. In the case of IVIg, this application form is not registered centrally, but must be kept at the hospital pharmacy, and made available to the national health insurance (via the advisory physician of the sickness fund) upon request. For SCIg the application form must be sent a priori to the advisory physician of the sickness fund, for obtaining an approval.

For Ig, only licenced indications (authorized by the European Medicine Agency or the national agency FAMHP) are considered for reimbursement. A recent harmonisation, based on the EMA guidelines for Ig market approval, foresees that most Ig on the Belgian market are reimbursed for the 8 established indications. Exceptions and off-label use are possible via an Unmet-Medical Need program or the Special Solidarity Funds. In both programs, a commission decides on possible reimbursement on an individual basis.[z]

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y Belgium: Joel Daems, Marc Van De Casteele, Martine De Witte from RIZIV-INAMI, Laure Geslin division Post-authorisation / Proper Use at the FAMHP, Margaretha Haelterman, Quality cel of FPS Public Health

Australia: Jo Cameron - Director, Immunoglobulin Governance National Blood Authority

France: Gaelle Guyader - Deputy Director of the Drugs Directorate in Oncology, Hematology, Transplantation, Nephrology, Cell Therapy, Blood Products and Radiopharmaceuticals of the National Agency for the Safety of Medicines and Health Products (ANSM)

Canada: Brian O´Rourke director at the CADTH , Brent Fraser from CADTH and Sylvain Grenier-Director, Plasma Protein Products Formulary Program with the Canadian Blood Services

England: Rob Coster - National Programme of Care Manager-Blood and Infection, NHS England

z https://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/onderzoek_ontwikkeling/gebruik_in_schrijnende_gevallen_medische_noodprogrammas[aa] Calculation based on the cost of Sandoglobulin® (IV) and Hizentra® (SC) in 2019 for a 70 kg person. The price for one administration of Ig would therefore, be lower when used in pediatric indications.

The Special Solidarity Funds receive applications for reimbursement outside the licenced indications. The following criteria must be met to be eligible: rare disease, threatening vital functions, no therapeutic alternative, and scientific effectiveness/value.[311] An upward trend can be observed: in 2016, there were 9 individual applications, in 2017 16, and in 2018 there were 18.

Another possibility for off-label use is when there is a Medical Need program of a company, authorised by the FAMPH. At the moment Privigen® is registered in a medical need program for treatment of bleeding in patients with acquired von Willebrand syndrome, which means that a treating physicians can ask the company to supply Privigen® for a specific patient at no cost. Patients must fulfil inclusion criteria and give an informed consent. In return the company receives information on safety aspects (pharmacolvigilance), which can be used in future possible licencing applications.

However, when an off-label application becomes prescribed and there is no unmet-medical need program, nor an approved application of the Solidarity Fund, the patient pays the cost of the Ig. In that case, the hospital must inform the national health insurance that the reimbursement conditions were not met. The price of one administration of IVIg (for an average weight of 70Kg), ranges between €1100 and €5800, depending on whether it is used as a replacement therapy (0.4g/kg) or an immunomodulatory dose (2g/kg). Often, multiple administrations are necessary (mainly on a monthly basis). For SCIg the price is similar with a range between €1300 and €6700 (but subdivided into more frequent administrations of smaller doses).[aa]

At the moment there is no national data capturing of the indication specific use, neither for the reimbursed indication, nor for non-reimbursed, off-label use of Ig. A study published in 2011 described Ig use in Belgium, using data from 47 Belgian hospitals in the year 2007.[17] The study reported an off-label use in 4,437 patients, representing 46% of all patients receiving IVIg. The majority of off label use of IVIg occurred in unspecified conditions, but was linked to the domains of surgery (e.g. digestive, vascular and obstetrical surgery, and surgery aftercare), orthopedics (e.g. dorsopathies and other fractures), and oncology (e.g. lung, breast, colorectal, prostate, and other solid cancers). There was limited use of IVIgs in myasthenia gravis.

The use of Ig is rising (as shown in figure 1). Due to its high costs, a regular follow up of the financial impact on the national insurance budget is performed in the MORSE report (only reimbursed products). Monitoring of Ig use in Belgium is done via a monthly follow-up of the tender procedure, which reflects around 50% of the reimbursed market of IVIg. Following the supply problems faced since 2018, the three companies selling Ig in the Belgian market were requested to provide data to FAGG, to facilitate monitoring product sales. No information on indications is currently captured via these systems.

4.3 Australia

In Australia, Ig is provided at no direct cost to patients for a range of medical conditions for which the Australian federal, state and territory governments have decided to provide funding (details on reimbursed indications also called ‘Criteria’ can be found in Supplement 6.2.1).

The high cost and demand for use in Australia means that eligibility for access to Ig must be achieved through strict governance arrangements. These arrangements are managed by the National Blood Authority (NBA) through the Immunoglobulin Governance Program and the Criteria for the clinical use of Ig in Australia (the Criteria). The Criteria describe the diagnostic and eligibility requirements to access government-funded Ig. National Criteria were first published in 2007 after an expert systematic review of the literature and clinical consensus and underwent a partial review and updated in 2012. On 22 October 2018, the NBA released version

[aa] Calculation based on the cost of Sandoglobulin® (IV) and Hizentra® (SC) in 2019 for a 70 kg person. The price for one administration of Ig would therefore, be lower when used in pediatric indications.

3 of the Criteria, after four years of indication reviewing by specialist working groups.[312]

The Criteria are publicly available online (at https://www.criteria.blood.gov.au/). Fifty-two medical conditions are supported for funding in Version 3 of the Criteria. Indications are categorised into '*established therapeutic role'*, '*emerging therapeutic role*', '*exceptional circumstances only.* A fourth category lists conditions that are '*not supported*' for funding.[9]. The four categories are based on a review of the literature and expert opinion (See Supplement 6.2.2).

- *Established therapeutic use* indicates that for these conditions, Ig product use is supported by reasonable-quality evidence and expert opinion. For a number of these conditions Ig products are considered a first-line therapy in selected patients and may be the only established treatment option.
- *Emerging therapeutic use* indicates that there is clinical support for Ig product use in selected patients, although the quality of the available evidence is variable. For many of these conditions, Ig products are considered a second or third-line therapy only, and are only allowed under the Criteria when standard therapies have proven to be ineffective, become intolerable, or are contraindicated.
- *Exceptional use* indicate that these conditions rarely, if ever, require Ig product use, either because there are safe and effective alternative therapies, or because the evidence of benefit does not justify use in most cases. Ig products are considered to have a therapeutic role only in exceptional circumstances, such as in emergencies or life-threatening circumstances.
- *For non-supported indications*, there is either evidence of no benefit, insufficient evidence of benefit, or some evidence of benefit but preferred alternative therapies are available.

Most indications mentioned in the Criteria are for IV administration of Ig. There are five indications for which SC use is also a possibility when treated by a clinical specialist within a hospital based SCIg program (primary immunodeficiency, specific antibody deficiency, acquired hypogammaglobulinaemia related to haematological malignancy or post HSCT, secondary hypogammaglobulinaemia unrelated to haematological malignancy or post HSCT and chronic inflammatory demyelinating polyneuropathy (CIDP).

Together with the revised Criteria, access to government-funded Ig products in Australia is more controlled, and fall under a national distribution system. Prescribing physicians must make an application through the online system BloodSTAR (Blood System for Tracking Authorisations and Reviews), where they must specify/justify how the diagnostic and eligibility requirements (the Criteria) are met.[312]

For conditions not funded under the national blood arrangements, a medical officer may be able to seek access for Ig products through a jurisdictional direct order (JDO) or access Ig privately. The JDO arrangements allow hospitals to purchase the product directly from the supplier. However, only imported Ig products are available under JDO arrangements. Domestic Ig products made from Australian plasma are restricted to treating indications listed within the Criteria under the national blood arrangements.

A performance improvement program was also set up to identify trends and variations in usage and prescribing practice. Data collected will inform the development of national benchmarking and performance indicators and will inform future policy improvements including revisions to the Criteria.

4.4 France

In France only licenced/ authorised indications are covered under the national health insurance. The Minister of Health decides the list of reimbursed medication based on evaluations and recommendations made by the French National Authority for Health (HAS). Ig are licenced for 12 indications in France (see supplement 6.3.1). A report of the OMEDIT IDF showed that in 2016, 66% of the Ig are used for authorised indications and consequently more than 30% is used off-label[30]. When therapeutic alternatives are lacking, exceptional, off-label prescribing is allowed for innovative and costly medicines in the hospital setting (registration on an "additional list") for which full reimbursement is applicable. Prescribers must justify their choice, including available scientific evidence in the patient's

medical file, and must also consider the prioritization framework established by the ANSM. In this way, certain off-label indications for Ig use are financed in the hospital setting.

In France, there is no official database registering the consumption of Ig. However, a database of pharmaceutical companies, covering 99% of all sold medications in France (i.e. GERS) is closely followed by the ANSM (Agence National de sécurité du medicaments et des produits de santé). Since 2018 an increase in SC use is seen, possibly caused by a shortage of IVIg. A study performed in 2016 in Ile-de-France showed a yearly increase of 6.5% of Ig use, mostly in non-authorised indications. The same study identified Ig as one of the top 3 most expensive pharmaceuticals in Ile-de-France. A more detailed qualitative and quantitative report is planned to be published in 2020 by ANSM.

The threat of possible shortages have encouraged the French authorities to take measures. In 2008, a national steering committee for monitoring supplies and managing shortages was set up. Monitoring use is foreseen, via a monthly update on the stock and needs. Based on consumption information and data received from the laboratories that produce Ig, the ANSM publishes a monthly update on their website.[13] A colour code indicates whether there is a risk for a shortage within 15 days, 30 days or if there is no real threat expected for the following month. In case of possible shortages, there is a priority list of indications called "*Hiérarchisation des indications des immunoglobulines humaines en situation de forte tension d'approvisionnement"* (see Supplement 6.3.2). It was produced by the AFSSAPS in 2008 (now called the ANSM), and has been updated in 2011, 2013, and 2018, on the basis of recommendations by a temporary, specialised scientific committee. The last update dates from April 2019.[313] Established indications as well as new emerging indications were analysed based on experts' discussions and a decision algorithm which took into account the following elements: rarity and severity of disease, alternative therapeutic options, estimations on required consumption and the feasibility of a request for specialized advice by a reference network for rare diseases.

The objective was to limit the priority list or install prerequisites such as clinical and biological thresholds, the need for prior validation of the prescription by a specialist or a reference network for rare diseases (CRMR, FSMR)[314] and a regular evaluation (after 3 to 6 months, depending on the pathology) of the tolerance and effectiveness of the treatment carried out by a specialist.

A new version of the list was published in April 2019 (see Supplement 6.3.2). The indications were classified into:

- Indications considered a priority,
- Indications reserved for emergencies likely to be life-threatening and/or for which no therapeutic alternatives exist,
- Indications not considered a priority,
- Indications considered unacceptable or unjustified, in the absence of any new evidence.

4.5 Canada

In Canada health care is regulated per province or territory, leading to differences in delivering and funding of healthcare, (f. ex each providing its own prescription drug benefit plan). However, the Canada Health Act mandates that every province and territory in Canada provide universal health coverage for hospital care, including hospital-dispensed medication.

In 1997, after a tainted blood scandal (known as the Krever Inquiry) a National Blood Authority was established. This National Blood Authority is the Canadian Blood Services (CBS). It covers all provinces and territories, except for Québec which has its own Blood Authority (i.e. Héma-Québec). As Ig are blood products, they are centrally purchased via a national tendering procedure, and distributed to all Canadian hospitals free of charge by CBS (except the ones in Québec, which are supplied by Héma-Québec). In hospitals, Ig are dispensed through hospital blood banks, which are required to screen orders to ensure requests are appropriate. However, there is a small volume available via a private pay model, which does not involve the CBS and is not (or only partly) covered, depending on private pay drug plans.

Canada is among the top three highest users of Ig per capita in the world. In 2019, 5 million grams of IVIg and 1.5 million grams of SCIg were deemed necessary. Less than 20 percent of the necessary Ig is manufactured from CBS plasma. The remainder is procured directly from fractionators that collect their plasma in the US from paid donors. From 2017 to 2018, a yearly growth rate of 7.9% was observed (see Figure 4). There is a lack of formal oversight of Ig use in Canada, which makes it difficult to determine if the growth of Ig use is due to appropriate vs inappropriate use. This has led to concerns about ensuring a sustainable supply. A report of an expert panel "protecting access to immune globulins for Canadians" was released in May 2018, providing information which could inform policy decisions. The report found that all provinces and territories have either implemented an Ig utilisation program, have one under development, or are actively monitoring Ig use. Utilisation management programs are specific to each province but generally, offer guidelines, dosage calculators and other decision support tools, as well as requiring the clinician to complete an Ig request form [315]. Within the hospital, blood banks are generally required to screen orders for Ig, to ensure requests are appropriate. At the CBS they are working in increasing the capability to capture clinical information about the use of all plasma-derived products.

In Canada, Ig is licensed for six indications: primary and secondary immune deficiency diseases, immune thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, and multifocal motor neuropathy. Ig is publicly funded independently of whether it concerns registered or off label use.

Clinical guidelines or recommendations were developed to advice physicians on correct use in off label indications. However, there are no formal restrictions for publicly funding Ig for off-label indications. A national analysis in Canada reported that physicians approving the release of Ig find it very difficult to refuse the product to colleague-clinicians.[315]

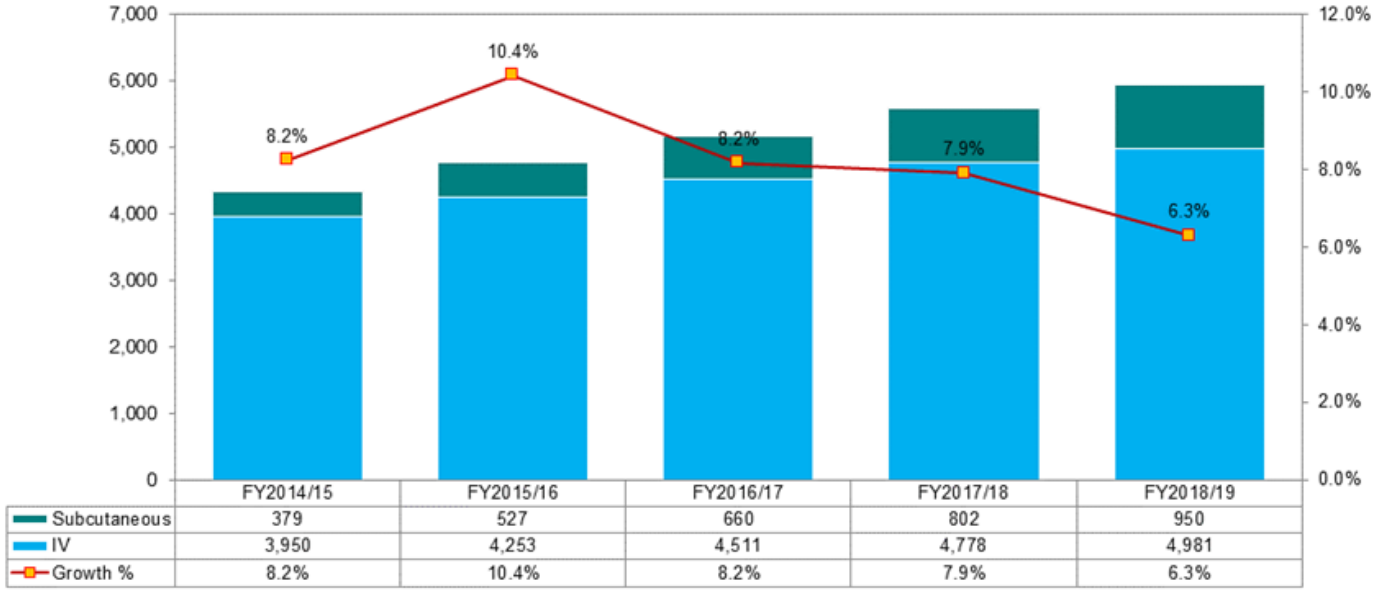
The first guidelines supported by the National Advisory Committee on Blood and Blood Products (NAC) were developed between 2007 and 2010 (Neurological and Hematological indications, Solid Organ Transplant and Primary Immune Deficiencies).[316-319] Further publications for other indications will follow.

Provinces and territories developed recommendations and guidelines in recent years (see supplement 6.4.1).[8,320-322] The development was approached differently in the different provinces, ranging from a literature review, validated with clinical expertise, to only a literature review or only expert opinion.

The Canadian Agency of Drugs and Technologies in Health (CADTH) is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence. The CADTH is often involved when provinces have to make decisions on reimbursement. The CADTH foresees often a health economic analysis. In 2017 and 2018 the CADTH published a bundle of rapid reviews on Ig off label indications: in transplantation,[235] autoimmune diseases,[215] dermatology,[214] in neurology,[196] haematology,[323] non-neurological diseases,[324] and recurrent spontaneous abortion.[325]

An analysis of the different recommendations between the different provinces, revealed a consensus in 13 indications (see supplement 6.4.2). For almost all, conditions prerequisites were formulated (e.g. specific diagnosis and request by specialist, clinical biology parameters, failure of other therapies, and regular reassessment). The number of indications for which recommendations exist differ between the different guidelines (see supplement 6.4.3).

Figure 4 – Canadian Ig use: 5 year trend by grams



	FY2014/15	FY2015/16	FY2016/17	FY2017/18	FY2018/19
Subcutaneous	379	527	660	802	950
IV	3,950	4,253	4,511	4,778	4,981
Growth %	8.2%	10.4%	8.2%	7.9%	6.3%

Source: provided via personal contact with the Canadian Blood Services in 2019

4.6 England

Health care in the United Kingdom is a devolved matter, with England, Northern Ireland, Scotland and Wales each having their own systems of publicly funded healthcare, called National Health Service (NHS). In England a prescription fee per medicine is generally charged. However, Ig are entirely funded by NHS England, which means they are free from any prescription charges, as any other blood product. Ig are always prescribed in the first instance via a hospital, although in the particular case of SCIg, home services exist, which can then offer the provision of SCIg at home. These home services do have sometimes charges but they are general charges, not linked specifically to the Ig. Some hospitals have their own home services, while others need to contract them via private companies, which could have an impact on charges. SCIg are mostly used at the patient's home and rarely administered at hospital (with the exception of the first infusion, always offered at a hospital for training/educational purposes).

Ig fall within the top 10 drugs for expenditure within the NHS England, with GBP150 million (approximately €180 million) spent in 2016-2017 and a growth of around 10% per year.[7]

UK Ig have been sourced from plasma donated outside the UK since the bovine spongiform encephalopathy (BSE) outbreak due to the potential risk of Creutzfeldt–Jakob disease transmission. Plasma used to fractionate Ig is sourced from countries that have not had BSE outbreaks and have only background (sporadic) Creutzfeldt–Jakob case numbers. The UK is therefore, fully reliant on a global market for the supply of plasma products.

In 2006, the Department of Health produced a review which led to the creation of two complementary programmes; one based on securing supply under "normal" circumstances, and the second, the Demand Management Programme for Ig, overseeing the meeting of demand within the UK in particular when there are supply problems (e.g. stock ruptures or withdrawals of certain products from the market). Setting up the Demand Management Programme required the creation of the National Immunoglobulin Database (http://igd.mdsas.com). Launched in 2008, the database captures prospectively all Ig use in England, where data entering is mandatory and incentives were put in place to ensure coverage in its early phases. Other UK countries such as Northern Ireland and Scotland also make use of the database, although coverage in these countries may not be as broad as it is in England. Wales appears to be the only country in the UK which does not use the database at present. The database provides the basis of detailed reports on Ig use. The latest covers the period 2017-2018.[7] Although access to the database is restricted, all reports are publicly available (at http://igd.mdsas.com/reports/).

Regarding the current reimbursement/coverage system in England for Ig, this is based on a "colour coding" national demand management system. Under such system, indications are colour-coded to reflect prioritisation and approval for IVIg treatment (see Supplement 6.5.1).

Under normal circumstances, red and blue indications (see Appendix 5.4.1 for details) receive an automatic approval. The red category includes indications for which treatment is well established with Ig. Blue indicates a disease for which there is a reasonable evidence base, but where other treatment options are available. 'Grey' indications are split into two separate groups: the first of these, lists indications for which there is little evidence of efficacy, and the second, indications for which there is no evidence of efficacy. For indications that fall in the first of these grey categories, Ig assessment panels, in each large hospital and available via networks for smaller hospitals, will assess if use is justified, and if it is, outcomes will be captured (mandatory). If outcomes are not captured, Ig treatment will be stopped. The second "grey" category, requires an Individual Funding Request (IFR) to NHS England before treatment can be started. Use will only be authorised if the patient case is considered exceptional. Under the black category, use is not allowed.

The current Demand management Plan, foresees that in situations of shortages, Ig should not be used for the grey categories. However, these appear to count for a small proportion of overall use. If demand cannot yet be met, then usage on the blue category will need to be revised. However, the proportion of blue indications account for an important proportion of the total use and make it difficult to refuse use in all of these indications. Alternative strategies, such as considering to lower doses whenever possible, or controlling that treatment is stopped or changed as soon as

there is no response, have and are continuing to be explored. In order to facilitate such strategies, periodic, frequent medical revisions are recommended.

NHS England plan to move away from commissioning by 'colour coding' to an evidence-based policy approach, supporting either routinely or not routinely commissioned position. In order to facilitate such a change, clinical experts, royal colleges and specialist societies have been asked to perform a rapid clinical review of the existing guidelines that could highlight those indications for which there is a need for updating the current list, on the basis of new evidence.

The first change to the current system which has already been completed, and for which results will soon be published, consisted in moving indications under the original red or blue categories, for which no new evidence was identified by the experts to a "routinely commissioned" category. Indications initially listed under the black category will be moved to the "not routinely commissioned" category.

The current grey categories would also need to be reviewed and the indications split between the new "routinely commissioned" and the "not routinely commissioned" categories. Originally, a Cochrane review was hoped to be completed for these less established, unclear "grey" categories. However, the funds and resources as well as the time that would need to be invested in order to complete such an exercise, coupled with the fact that a lot of these indications are rare and thus, the existing clinical evidence surrounding them remains weak, made it for a comprehensive approach involving working with experts, to appear more appropriate. Experts are divided in four Policy Working Groups (Immunology, Neurology, Haematology and others) and would aim at reaching a clinical consensus, regarding the eligibility criterion for all indications as well as the appropriate doses and length of treatment; identifying where indications are no longer valid. This step would cover 27 indications (see Appendix 5.4.1 for details) and is likely to take a considerable time. Therefore, in the meantime, it is foreseen that the grey indications will continue to be commissioned via the original system (i.e. approval via Immunoglobulin Assessment Panels (IAP) and/or Individual Funding Request process). As part of this project, work is being undertaken to improve the scrutiny of Ig usage within Trusts.

4.7 Interpretation international:

Differences between countries

Table 12 shows whether the selected indications considered in our clinical literature review are recognised in the countries included in this international comparison (i.e. Australia, Canada, France and England), and if so, under what circumstances (e.g. emergency use only). The table already shows how these countries appear to be more inclusive than Belgium, even if the table only offers a partial view on their full lists of recognised indications (see appendix for full lists).

Overall, 52 indications are recognised in Australia, 29 are on the priority list in France, 30 are prioritised in the England and finally, in Canada, there are 13 indications for which there is a consensus between provinces, while inconsistencies in the recommendations exist between the provinces for a large list of other indications (see appendix for full list). In comparison, 8 indications are currently reimbursed in Belgium.

The discrepancies, may be partly explained by the reimbursement/coverage of off-label indications in countries such as Australia, Canada and England. In Belgium recommendations on off-label indications are not available, since only licenced indications can be on the reimbursement list. In France a general rule is that reimbursement is also limited to licenced indications. However, French prescribers are able to prescribe Ig off-label, as long as they justify their use on a per patient basis. Moreover, there is some guidance via a list of indications (including off-label indications) considered a priority for Ig use, which was recently established. This priority list is regularly updated by the national authorities (last update in April 2019).

In Belgium there is also the option to use Ig in the context of an unmet medical need program for specific cases or via a request to the Special Solidarity Fund (e.g. diseases affecting vital signs). However, only 18 applications to the Fund were made for Ig use in 2018, and although the

applications are slowly increasing each year, the volume of publicly funded off-label use in Belgium appears to remain low.

While in Belgium no recent detailed data on off label use exist, a French study reported that more than 30% of their Ig use is on off label indications.[30] Similarly, in Canada audits reveal that a significant proportion of Ig use falls outside of the established criteria and guidelines.[315]

A similarity found between the countries analysed is that indications are not reimbursable without prerequisites. The most common is the need for a specialist physician considered an expert in the field of the disease, often working at a specific reference centre to diagnose the patient. In addition to this, Ig appear to be recommended as first line treatment only in a limited number of indications, (e.g. PID Guillain Barre, CIPD, ITP). For other indications it is only considered as second line therapy, in case of failure or contraindication of other therapies (most of the time corticosteroids). Documenting the prerequisites, the date of follow-up visits for individual patients is a must in countries were a central supply system is in place (Australia, England). In Canada there is a central supply system, but no systematic data capturing on indications is yet in place. In France and Belgium there is no central supply system in place that captures all the requests for Ig. However, monitoring of sales data is carried out. Finally, in all countries eligibility for reimbursement must be documented in the medical patient file.

Contrary to Belgium, some countries have a system of prioritisation, put in place to respond to potential future stock ruptures or for shortages in Ig supply due to other causes. However, with the exceptions of the indications in which the use of Ig is well established and those for which RCT evidence is available, rankings appear to differ from one country to another. This is due to the fact that in those cases in which limited evidence is available (not uncommon, given the rare nature of some of these diseases), experts were consulted and involved in drafting priority lists.

A European consensus paper compared priority rankings in the Australian, Canadian, and English guidelines, and found considerable differences in the conditions recommended for IVIg/SCIg therapy. A comparison of the three guidelines revealed 88% concordant recommendation in the high priority group, 84% in medium priority group, 48% in the low priority group, and 32% in the group of “not recommended” indications. These discrepancies highlight a need for an international harmonization of guidelines to ensure optimal use of Ig in clinical practice.[326]

In terms of volume of use, Australia and Canada have the highest per capita use of Ig (together with the US), in comparison to the UK, which has a significantly lower per capita utilisation rates.[315] In the UK, Ig use is more aligned with national guidelines, whereas in Canada there is less scrutiny over Ig use. In addition to a more general increase in the use of Ig, due to the expansion of indications, the growing incidence of obesity worldwide also appears to have an impact on Ig volumes, given that dosing is mainly weigh-based.

Internationally, there have been significant efforts to create effective utilisations programs to manage the appropriate use of Ig. The UK is seen to have perhaps the most robust and successful national monitoring system. Some speculate that UK clinicians and the health care system developed a culture of judicious use following the UK variant Creutzfeldt Jaob disease crisis in which all domestic plasma collection stopped and the UK became entirely dependent on imports.

In Australia the National Blood Authority put in place a monitoring system in October 2018, by which clinicians need to specify how their patient meet the relevant criteria before Ig will be allowed. At the moment it is too early in its implementation to measure its impact.

In France there is no official separate database monitoring the consumption of Ig use. However the database of the pharmaceutical companies that covers 99% of all sold medications in France (GERS) is closely followed by the ANSM.

In Canada, there is a lack of formal oversight of Ig utilization, but efforts for increasing the capability to capture clinical information are currently a priority for the Canadian Blood Services.

Table 12 – Summary of recognition in the different included countries for the "selected indications"

Indications	Belgium	Australia	Canada	England	France
Primary Immunodeficiency Disease (PID)	Y	Y	Y	Y (priority)	Y (priority)
Secondary hypogammaglobulinemia (SID)	Y	Y	Y	Y	Y (emergency)
Post-hematopoietic stem cell transplantation (HSCT)	Y	Y	Y (only under some circumstances)	Y (priority in PID patients)	Y (emergency)
Chronic Inflammatory demyelinating polyradiculoneuropathy (CIDP)	Y	Y	Y	Y (priority)	Y (emergency)
Toxic shock-invasive streptococcal group A infection (streptococcal toxic shock syndrome)	Y	Y (emerging therap. Role)	Y	Y	N
Kawasaki disease (KD)	Y	Y	Y	Y (priority)	Y (priority)
Multifocal Motor Neuropathy	Y	Y	Y	Y	Y (emergency)
Idiopathic/immune thrombocytopenic purpura (ITP)	Y	Y (for adults, (for children, emerging therap. Role)	Y	Y (priority for acute and persistent, excluding chronic)	Y (priority for severe cases)
Guillain-Barre Syndrome (GB)	Y	Y	Y	Y (priority)	Y (priority for child; for adults if PE not possible)
Myasthenia Gravis (MG)	N	Y	Y	Y	Y (emergency)
Dermatomyositis and Polymyositis	N	Y	Y (juvenile)	Y (inflammatory myopathies)	Y (emergency in cortico-resistant patients)
Solid organ transplant (antibody mediated rejection)	N	Y (emerging therap. Role)	Y *	Y	Y (priority when other treatments failed)
FetoNeonatal Thrombocytopenia	N	Y	Y	Y (priority)	Y (priority if proven antecedent)

Pure red cell aplasia	N	Exceptional circumstances only	Y * (linked to parvovirus)	Y	Y (priority for immunocompromised patients after parvovirus infection)
Post transfusion purpura/Thrombocytopenia	N	Y (emerging therap. role)	Y *	Y	N
Pemphigus Vulgaris, Foliculae	N	Y (emerging therap. role)	Y *	Information not available	Y (emergency in cortico-resistant patients)

The indications are not reimbursed as such, mostly various conditions/prerequisites must be met.
Belgium based on the reimbursement criteria from the NIHDI.
Australia based on the national recommendations (Ig Criteria 2019) categorising indications into established use, emerging role, exceptional and not recommended.
*Canada based on recommendations in Provincial guidelines (British Colombia, Ontario, Atlantic Provinces, and the joint guideline of Alberta, Manitoba and Saskatchewan). The guideline of Quebec was only on neurological conditions. * Indicates that it is recommended in at least 3 provincial guidelines.*
England based on the priority list (updated in 2018) categorising indications into high priority, medium, low and not recommended.
France based on the priority list (updated in 2019) categorising indications into priority, only in case of emergency, non-priority, and not recommended.

Conclusions

- **The countries here analysed appear to be more inclusive than Belgium in their recognition and coverage of Ig use for different indications for which evidence is limited.**
- **Prerequisites (such as and or diagnosing rights restricted to specialists, mandatory data registration or need to justify failure with other therapies prior use of Ig) are common.**
- **Prioritisation system and regular updates of their recommendations have been recently put in place in all countries in order to respond to potential future supply shortages.**

5 DISCUSSION AND CONCLUSIONS

5.1 Discussion

The therapeutic use of polyvalent Ig has grown worldwide in the last decades and continues to evolve at present, with new indications being studied and added to the already long list of (often rare) diseases treated with these products, derived from human plasma. Given this growth and continued evolution of target indications, the constraints their production is subject to (dependant on the number of donors), and their high cost, ensuring an appropriate use by focusing in those indications for which Ig are clinically more beneficial is of great interest to health authorities worldwide. This rapid review aimed at offering an overview of the evidence available, and an assessment of its quality, as well as a description of the reimbursement systems and indications prioritised in countries where Ig have been reviewed in the last years. This work will be complemented with a data analysis on current use in Belgium and estimations on future provision needs, which will be captured in a second report to be published in 2020.

Established indications for Ig treatment.

For indications already reimbursed in Belgium, which appear to also be recognised in the other 4 countries analysed in our international comparison, the evidence identified via our review (based on SR and RCTs) shows a clinical benefit linked to the use of Ig in all cases, with the exception of post-haemopoietic stem cell transplantation, where no significant benefits have been identified when Ig are used prophylactically, in the absence of infections. This indication is not recommended for routine used in the analysed countries (see international comparison chapter), although it is still accepted in emergencies or exceptional cases. The current Belgian reimbursement criteria for HSCT patients allows Ig use only when there are proven recurrent infections which require antibiotic use.

In some of these indications, the use of Ig is well established as the preferred first line treatment option. This is most often the case in indications for which no other (therapeutically effective) options appear to be available: PID, in which use was originally based on positive clinical outcomes from observational studies; SID (linked to haematological cancer), Kawasaki disease, and MMN. In these well-established indications, recent research has focused more on studying the equivalence of different Ig formulations (SC versus IV), different doses, different ways of administrations (aiming to have less frequent or time-consuming infusions), different Ig brands, or in the case of Kawasaki disease, on Ig refractory patients, a population in which effective treatment remains to this date a challenge.

In most other reimbursed indications, treatment alternatives similarly effective when compared to Ig exist (for example plasma exchange, or corticosteroids). These indications include: CIDP and GBS. However, some uncertainties remain regarding the safety of these alternatives. Although our review described the AEs found in the body of evidence identified via our searches, no safety-specific search was undertaken and thus, significant differences between treatment alternatives on that regard cannot be excluded. A thorough analysis on safety would have required the inclusion of non-randomised studies with longer time horizons, and higher patient numbers, more appropriate to identify possible long-term, or very rare (but potentially severe) AEs. Such analysis was considered unfeasible given our time and resources constraints. Furthermore, alternatives like plasma exchange are considered more invasive, which may explain why most countries reimburse and recognised both Ig and plasma exchange, despite the fact that in general, plasma exchange is thought to be a less costly treatment option.

For ITP, treatment alternatives exist but Ig appear to be more effective, and are therefore often chosen as the preferred treatment option. However, the existing body of evidence appears to focus on paediatric children with acute ITP, while no clear conclusions can be drawn for children with chronic ITP or adult patients.

Finally, highly limited evidence coming from a SR including observation studies only (4 studies, n=144) on streptococcal toxic shock in a subgroup of patients treated with antibiotics, appears to show a significant effect on all-cause mortality compared to standard care. Despite the limitations of the

evidence, the severity of streptococcal toxic shock has resulted in wide recognition of this specific indication across different countries.

Non-reimbursed, commonly recognised indications.

A number of indications not currently reimbursed in Belgium appear to be frequently recognised and accepted in the other countries and were therefore, analysed in some detail.

From this analysis, it became apparent that Ig could be clinically beneficial for patients suffering from severe or worsening myasthenia gravis (as adjuvant therapy), and feto/neonatal thrombocytopenia. These being indications for which other treatment options exist. On the other hand, pemphigus vulgaris, or foliculae appear to be indications for which steroids remain the first line option and Ig are only saved for steroid-resistant patients, for which they appear to be effective, compared to placebo.

In dermatomyositis and polymyositis, two very rare indications, only two very small RCTs were identified, which displayed conflicting evidence with one US study reporting significant improvements with IVIg in terms of muscle strength in dermatomyositis patients, and the other showing improvements both the in the IVIg and the control group, concluding that no significantly different improvements occurred between the two groups. This second study differed from the previous one in its patient population (Japanese patients with either dermatomyositis or polymyositis), as well as in their wash out period which was shorter than that of the US study. These factors may explain the difference in their results. Two ongoing studies in dermatomyositis were identified via our search in registries (see section on ongoing studies for more detail). These appeared to aim at recruiting relatively large patient's numbers. Their results will be of great value to fill in a current evidence gap and reach clearer conclusions regarding the clinical value of Ig in these patients.

For two commonly recognised very rare indications (pure red aplasia and port transfusion purpura/ thrombocytopenia) no RCTs were identified since only retrospective case series have been carried out, so clear conclusions could not be drawn.

Finally on AMR in solid organ transplantation, evidence from a small trial showed significant increases in graft survival, (kidney re-transplantation), but no studies reported significant differences in overall patient survival.

Limitations of the evidence

The available evidence in the "selected" indications, presents some limitations, first, it comes mainly (with the only exception of post-haemopoietic stem cell transplantation), from trials with very small sample sizes, which appear to reflect the "rare" nature of (most of) these diseases. Cross-over designs are not uncommon and an important number of studies are subject to unclear risk of bias, mainly due to a lack of clarity regarding allocation concealment. Some studies are not blinded, and although this is in some cases justified due to an impossibility of blinding patients to the different treatment alternatives, it may have resulted in the introduction of certain bias, specifically in those cases where no hard outcomes such as mortality, or objective measures such as platelet count are considered. Overall, the quality of the evidence was low to moderate, although this was indication, and study-dependent.

International comparison

Our international comparison highlighted a number of important factors.

All countries analysed offer more inclusive reimbursement of Ig when compared to Belgium, allowing off-label use. However, they also appear to already have in place or planned, careful monitoring systems via indication specific data registration, allowing frequent updates, which in turn, enable them to better understand changes in use and evolutions, while also responding quickly to potential supply shortages. The country most referred to as having a good monitoring system is the UK. Some speculate that UK clinicians and the health care system developed a culture of judicious use following the UK variant Creutzfeldt-Jakob disease (vCJD) crisis in which all domestic plasma collection stopped and the UK became entirely dependent on imports. Australia has had an intensive 4-year process reviewing the indication list and eligibility for which Ig products derived from domestic plasma can be allowed, alongside with setting up a monitoring system that

can help identify usage trends and identify variations in usage and prescribing practice. In Belgium some indication-specific data on use for reimbursed indications is already captured via the existing (reimbursement) application forms, though not centralised. No general overview nor registry exists (neither on currently reimbursed indications, nor on off-label indications).

All reviewed countries have systems in place with recommendations, either via specific recommendations linked to evidence and/or priority lists. Priority lists give recommendations regarding the indications which should be covered in case of shortages. The priority lists are regularly re-assessed, in France the last version dates from 2019, while in England they are in the process of being reviewed (eg. England for the “grey” indications, for which reimbursement is either conditional to an approval by a hospital committee, or limited to case by case exceptional authorisations).

The analysis of recently published evidence from our searches and discussions with international experts also highlighted a growing interest, not only in the identification of those indications which appear to be most relevant from an evidence base perspective, but also to study (via clinical studies but also data registries) optimization of doses prescribed. Some recent RCTs have compared different dosses of Ig in the hope to identify the lowest “effective” dose at either an indication level or at a patient level. Our search in the clinical literature identified 11 studies looking at different doses in PID, CIDP, ITP, pemphigus vulgaris or foliaceus, HSCT. Ongoing studies on dosing were also identified, mainly in CIPD and PID. This dose optimization research line is of particular interest in immunomodulatory indications, where the mechanisms are not yet fully elucidated. Bearing in mind that Ig are currently dosed according to body weight, and that a heavy weight population can have a significant impact on quantities used, this new line of research offers an interesting field.

A further area that should also be explored is the possibility to limit treatment duration whenever possible, without negatively affecting clinical outcomes in those areas where there is not yet consensus on treatment duration/cessation. Stopping treatment as soon as Ig proves not to be effective should be a priority, in order to avoid wasting the limited resources, especially in those indications for which chronic use is often envisaged. Limits in the treatment period are common in all countries including Belgium and these should be monitored closely and updated when new relevant evidence becomes available.

Limitations of this review

Our review is not exempt from limitations.

As already described in our methods section, a conscious decision was made to pursue a rapid review in view of the large list of indications for which Ig have been studied. Thus, a number of steps were pursued, aimed at answering our research question.

1st SRs were used as the starting point of our analysis. In order to re-use already validated research and avoid the duplication of efforts this was thought to be a time efficient approach.

Although such process may bring in some inconsistencies to our review, in particular with regards to the assessment performed on the quality of the included studies, it should be stated that the majority of SRs identified via our searches appeared to be of high or moderate quality (according to the AMSTAR tool), offering a rigorous explanation of their methods, including detailed systematic literature searches, critical appraisals linked to the evidence base and clear conclusions. Cochrane reviews were available for most of the selected indications.

2nd No automatic updating of MAs for the selected indications was made and instead, this was performed only when the more recent evidence appeared to contradict the overall results found in the SRs, which was not the case for any of the studied diseases. Nevertheless, the research team decided to provide a detailed description of the more recent studies found via our search for completeness.

An important 3rd limitation linked to the rapid nature of our review, was that such an update (search of recent primary studies) was limited to RCTs. Although RCTs continue to be the gold standard of clinical research, the majority of the indications here studied are rare or very rare, and as a consequence, challenges linked to identifying a large enough pool of

patients to carry out this type of studies is a reality that should be recognised and may have limited our findings. Moreover, the centralised EMA procedure allows single arm open label clinical trials for obtaining a licence/registration for Ig. Linked to this, the importance of including observational studies may be more relevant in those cases where chronic treatment is necessary. Also, as already recognised the assessment of safety presented in this review offers only a partial view, describing only the AEs reported in the SRs and RCTs studies identified via our searches, while we believe serious AEs are probably poorly reported in those studies because of their low frequency, short duration of follow-up, and small sample size. Instead, a better assessment of Ig safety could have been made via the analysis of non-randomised literature as well as the inclusion of indication-specific registries covering larger patient pools treated for longer time periods.

Nevertheless, (small) RCTs were identified for almost all indications, and in an attempt to ensure no important studies had been missed (RCTs or observational studies), a group of experts was contacted and queried on that regard. The answers to our query appear to confirm that no key studies have been missed from our review.

Other limitations

The strength of evidence identified would have ideally been assessed on an outcome basis by means of GRADE. However, this was not thought to be a realistic option given the heterogeneity of the study outcomes, populations and comparators coupled with the constraints on time and resources. Instead the quality of the RCTs was based on RoB and description highlighting the number of studies identified for each indication, and their sample sizes in order to inform the reader.

Finally, study selection was done individually, although any doubts were discussed between two authors.

5.2 Conclusions

The area of Ig appears to be expanding in a context of limited supply. Evidence appears to show that this therapy offers clinical benefits in a number of (often rare) indications. However, given the rarity of these diseases, the evidence and in particular the number and size of RCTs appears to be limited and presents methodological limitations worth considering.

Countries facing similar challenges (have or) are putting in place frequently updated data registrations systems which allow a continuous evaluation of this complicated and rapidly evolving area. Efforts are currently being placed on the development of international registries (e.g. the European PID registry), which could help future research and evidence generation on larger patient pools.

Important questions remain regarding usage in Belgium, which will be the subject of a second KCE report on this topic, to be published next year.

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