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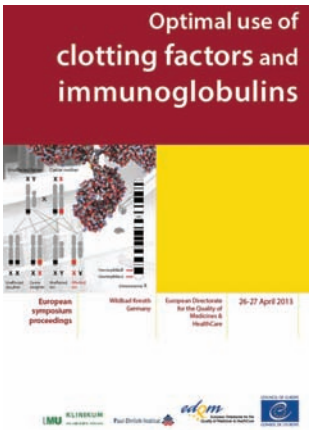
European consensus proposal for immunoglobulin therapies

The use of immunoglobulin (Ig) preparations (intravenous, IVIg, subcutaneous, SCIg) for replacement and immunomodulation therapy worldwide has tripled in the past 20 years and represents an ever-increasing cost factor for healthcare organizations. The limited access to the starting material of this essential medicinal product is currently the driving force for human plasma collection. Increasing awareness and improved diagnosis of human primary immunodeficiencies and a broadening of immunomodulatory indications are responsible for this development, and on a longer run might lead to plasma supply shortages. Consensus recommendations for the optimal use of Ig in clinical practice, including priority rankings for the most urgent indications, are therefore urgently needed. During a recent meeting in Kreuth, Germany, expert nominees from 36 Council of Europe states, together with colleagues from observer countries and regulatory agencies came up with this consensus statement.



Introduction

Meetings of plasma product experts from across Europe have traditionally been held at Wildbad Kreuth as part of an attempt to produce consensus statements about the regulation, use, and research into clotting factors for therapeutic use. The Kreuth consensus statements have had a significant influence on the use of the latter products [1]. At the third Wildbad Kreuth meeting (Kreuth III), held in April 2013 under the aegis of the Blood Transfusion Steering Committee (Comité Directeur (accord partiel) sur la transfusion sanguine [CD-P-TS]) of the Council of Europe, Ig therapies were also addressed. The representatives of the CD-P-TS and the members of the Scientific Programme Committee nominated experts of Ig therapies to participate in the conference. This was an opportunity for nominees from all Council of Europe member and observer states, along with colleagues from regulatory agencies (e.g. European Medicines Agency [EMA] and the United States Food and Drug Administration), to review trends in Ig use. Participants attended a series of presentations on "state-of-the-art" production, licensing, and clinical use of Ig preparations, then met in workshops to discuss and reach consensus by majority voting on recommendations regarding research and regulation policies for Ig therapies in Europe (for details see ref. [2]; http://www.edqm.eu/medias/fichiers/full_proceedings_kreuth_iii.pdf). Thirty-two representatives from 25 different states took part in the Ig workshop (see Supporting Information Table 1 with the list of the participants at the Ig workshop), at the conclusion of which 14 experts volunteered to participate in the "Kreuth Ig Working Group" (WG) in order to draft a publication and take forward the agreed recommendations for further approval through the CD-P-TS. There were no significant areas of disagreement and throughout the publication drafting process all participants of the Kreuth Ig WG were involved and consented to the changes proposed.

Access to, and demand for Ig preparations — A brief history and future perspectives

Plasma fractionation for the preparation of albumin, clotting factors, and subcutaneous/intramuscular Ig began in the 1940s; industrial scale plasma fractionation started in 1943. Intravenous Ig (IVIg) was introduced in the early 1970s and became the driving market force in the 1990s when plasma-derived Factor VIII and Factor IX were increasingly replaced by recombinant products [3, 4]. Worldwide, the demand for plasma products has continuously increased in the past 20 years; however, the consumption per capita varies greatly from country to country [4]. Currently, the largest markets are North America and Europe, accounting for ~73% of the global consumption (http://www.ipopi.org/uploads/Patrick%20Robert.pdf; Accessed May 14, 2013).

In Europe in the last 15 years, the demand for IVIg and subcutaneous Ig (SCIg) preparations multiplied 2.5-fold

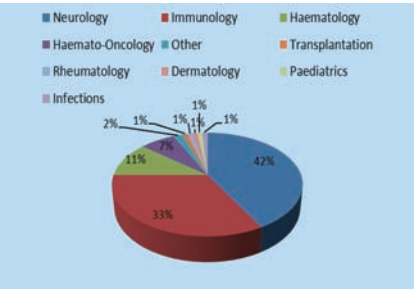


Figure 1. Diversity of IVIg/SCIg use in clinical practice in the UK (adapted from 'Third National Ig Database Report' 2010–2012, NHS).

from ~11 to 28 metric tons, and globally from 35.5 metric tons to an estimated >100 metric tons [4, 5]. Simultaneously, the Factor VIII demand in Europe increased threefold to ~3.9 million IUs, increasing the demand for recombinant Factor VIII (~60% of all Factor VIII consumption) more than that for plasma-derived Factor VIII [4]. Currently, the global total market (plasma-derived and recombinant products) is estimated to be worth ~7.4 billion US dollars per year [4].

It is assumed that the demand for Ig will continue increasing mainly due to new indications and emerging markets [4]. This will, in part, be due to increased awareness and diagnosis of human primary immunodeficiencies (PIDs) and to new indications in the immunomodulatory setting [2, 6–9]. Recently, the 3rd Nat. Ig Database Report of the British NHS highlighted that neurologic indications are currently leading the world IVIg consumption by 42%, followed by PID with 33% global consumption, and hemato-oncology with 18% global consumption (Fig. 1).

At the time of the Kreuth III conference in 2013, a Phase III trial on the use of therapeutic Ig in Alzheimer's disease was nearing completion and held both the possibility of a positive outcome and the threat of ensuing shortages for patients with other disorders. Although the trial's negative results put these imminent concerns to rest, Ig is being used off-label in a wide array of conditions (Supporting Information Table 2).

The "widening of indications" we referred to in the previous paragraph might best be substantiated by mentioning some trials being performed presently in areas such as dermatomyositis/polymyositis, MS, chronic idiopathic, and complex regional pain syndrome, diabetic painful polyneuropathy, glioblastoma, neuroblastoma, autoimmune autonomic ganglionopathy, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, HIV-associated myelopathy, parvovirus B19-mediated anemia and/or cardiomyopathy, spinocerebellar ataxia type 3, acute ischemic stroke, sickle cell pain crises, mysathenia gravis (MG), Lambert-Eaton syndrome (LEMS), toxic epidermal necrolysis (Lyell syndrome), systemic lupus erythematoses (SLE) and lupus nephritis, idiopathic severe and refractory solar urticaria, septic shock, pregnant women with primary cytomegalovirus infection, recurrent spontaneous abortion, removal of HLA alloantibodies in organ-transplant recipients (an approved indication in the United States), and treatment of antibody-mediated acute rejection in organ transplantation (this list is not exhaustive).

It is currently difficult to estimate for how many of these conditions the Ig therapy trials will actually come to fruition, as the underlying mechanism of action of Ig in any given immunomodulatory disorder is still poorly understood.

Issues associated with Ig therapy

Ig preparations are administered to patients either to compensate significant deficiencies (replacement therapy) and/or to induce immunomodulation in a vast range of disorders where immunological homeostasis has gone awry. Within the latter group, some indications are licensed (on-label) while others are not (off-label). The discussion on which indications are on- and which are off-label appears to vary across Europe. There are still significant regulatory issues regarding licensing of individual products for each disease. The regulatory status of each product is particularly significant in those countries with an insurance-based healthcare system, as funding for Ig therapy then depends on insurers rather than on government mandate.

Ig for replacement therapy

In the field of PID, awareness and diagnosis of new patients have greatly increased. Instrumental in this process were public awareness campaigns of national and international patient organizations such as IPOPI, JMF, the inauguration of a European online-PID registry in 2004 (20 000 cases registered by January 2014, www.esid.com) [10], and the establishment of new PID referral centers throughout Europe. As ~75% of PID patients suffer from hypogammaglobulinaemia and require long-term Ig substitution, the demand for therapeutic Ig preparations is steadily increasing from this group. The availability of 5 and 10% IVIg preparations, 16 and 20% SCIg preparations, and recently a 10% SCIg combined with hyaluronidase, has introduced greater flexibility in the replacement procedure. It is expected that not only greater awareness and better diagnosis of PID but also the current good availability of IVIg and SCIg and improvement in the reimbursements by health insurance organizations will further increase the demand for Ig concentrates [4, 5, 7–9].

Ig for immunomodulation

Besides substitution of the antibody repertoire, immunomodulatory effects occur both through mechanisms mediated by the Fab and the Fc-portion of antibodies (Table 1). The relevant mechanisms depend on the dose used, as well as the disease being treated [11, 12]. Increasing interest is developing in the status of the various Ig glycoforms, particularly the terminal sialylation of IgG [13], which may play a role in the immunosuppressive and anti-inflammatory actions of Ig [14]. While this seems to hold true for some animal models [13], the translation into humans is still controversial [15–17]. Based on various clinical trials, some former off-label indications have become either product-registered-specific indications or generally "established indications," i.e. accepted as treatable by all IVIg products that are authorized within the EU on the basis of the EMA Guideline for the Core summary of product characteristics (SPC). In other cases, former off-label indications have been granted to individual companies based on studies with their product. Further work is required to address how much clinical evidence is needed for other off-label uses to become "established indications" and for Ig products to be licensed beyond the "class effect" indications. Efficacy aspects of five IVIg products, including an Fc-modified IVIg product, are highlighted in Figure 2, emphasizing differences in immunomodulatory capacity among IVIg products, all of which received marketing authorization for immune thrombocytopenia (ITP).

Safety aspects of Ig therapy

The main side effects of Ig therapy encompass chills, headache, dizziness, fever,

Table 1. Potential immunomodulatory mechanisms of IgG [13].

Potential mechanisms of IVIg action	Fab[a)]-mediated	Fc[b)]-mediated	References
Neutralization of auto-antibodies (anti-idiotypes) and binding to variable regions of T and B cells (V-connected network)	x		[62–64]
Binding to MHC class I antigens	x		[65]
Downregulation of T-cell and B-cell function, upregulation of Treg-cell function	x	x	[66–69]
Inhibition of dendritic cells	x		[70, 71]
Suppression/neutralization of proinflammatory cytokines; induction of anti-inflammatory cytokines	x		[72, 73]
Blockade of CD95 (interference with Fas–FasLigand interaction)	x		[74]
Inhibitory effects of IVIg-mediated via FcγRIIb binding; Fc sialylation effects		x	[14, 51, 52, 75]
Enhanced clearance of pathogenic autoantibodies via saturation of the FcRn with normal IVIg		x	[31, 76]
Immunomodulation via IgG4		x	[77, 78]

[a)] Mechanism mediated by Fab portion of the Ig molecule.
[b)] Mechanism mediated preferentially via the Fc portion of Ig molecule.

vomiting, allergic reactions, nausea, arthralgia, low blood pressure, and moderate low back pain. Anaphylactic shock, aseptic meningitis, hemolytic anemia, acute renal failure, and thromboembolic reactions can occur in isolated cases.

Considering the source of Ig, they have, in general, had a good safety record. After various outbreaks of hepatitis B virus in the mid-1970s and hepatitis C virus in the 1980s (following anti-D and IVIg therapies) and in 1994, the threat of viral transmission has been greatly reduced through adequate laws and recommendations by authorities, e.g. strict adherence to current good manufacturing practice, regulation and batch control, the screening of donors, inventory hold and multiple viral inactivation/filtration steps introduced in the manufacturing process [18, 19].

For variant Creutzfeld–Jacob disease, so far no prion transmission through Ig preparations has been observed. To contain any possible threat, time and geographic restrictions have been imposed on plasma donations. Recently, a blood-based test that could be widely used for diagnosis and screening of prion contamination has yielded encouraging results [20].

Various sugars used as excipients have given rise to concern and have led to the introduction of product-specific warning statements in the product information, e.g.

(i) patients with rare hereditary problems of fructose intolerance should not take sorbitol- or fructose-containing products (in babies and young children hereditary fructose intolerance may not yet be diagnosed and sorbitol or fructose may be fatal);

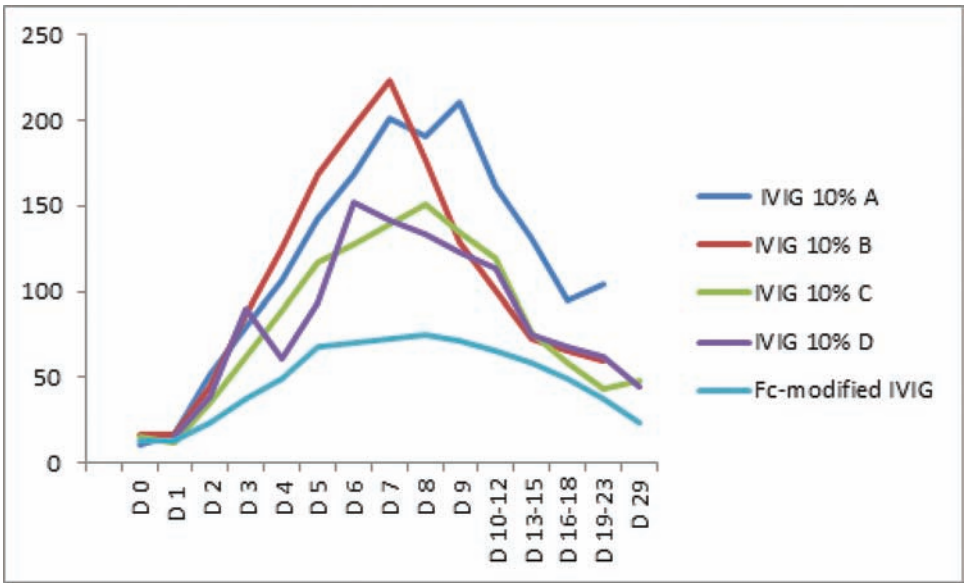


Figure 2. Clinical trial data submitted to the Paul-Ehrlich Institute from 5 IVIg products were assessed within the immunomodulatory setting of ITP, where increases of platelet counts above the critical level of 50 × 109/L are seen for all products. Interestingly, only the four unmodified products but not the chemically Fc-modified product induced normal platelet levels (≥ 150 × 10E9/L).

(ii) maltose may interfere with blood glucose assays and thus result in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia;
(iii) sucrose can lead to renal dysfunction through osmotic nephrosis and acute renal failure in patients at risk.

Recently, thromboembolic events (TEEs) and hemolysis have become the focus of concern and attention.

TEEs are a known side effect of IVIg with a frequency of <1:10.000 patients. Age, underlying co-morbidities (immobilization, previous TEE, cardiovascular disease) and administration-related factors (high and rapid protein influx) play the main role in TEE development. However, in 2010, due to a cluster of TEEs with a single IVIg product, another cause of TEE was uncovered: activated Factor XI [21]. This led to a temporary suspension of this product from the market and after implementation of corrective measures (leading to removal of Factor XIa) the product was re-introduced. Procoagulant activity was also found to be increased in an SCIg product. As a consequence, both the *Eur. Pharm. Monographs* for IVIg (Ref. Nr. 0338) and for SCIg (Ref. Nr. 2788) were changed to request proof that procoagulant activity is removed through specific steps and that tests for procoagulant activity reveal satisfactory results in the final products.

Hemolysis, due to the presence of IgG hemagglutinins, has been considered as a usually harmless adverse event of IVIg treatment, occurring at a rate of <1:10.000. It was mainly observed in patients with non-O blood groups, who had an underlying inflammatory state and were receiving high doses of IVIg. As anti-A and anti-B IgG hemagglutinins are co-purified with other IgGs, the final concentration of IgG hemagglutinins is influenced by the blood group distribution of donors and their anti-A and anti-B titers. Since 2003, an increase in the IVIg-associated hemolysis rate was seen with certain products, which had high anti-A and anti-B titers [22, 23]. Changes in the manufacturing process were implemented to minimize the risk of IVIg-associated hemolysis by excluding donors with high titers of IgG anti-A/B hemolysins. As other products are also affected, discussions are currently on-going with regard to acceptable cut-off titers determined with direct hemagglutination tests [24] (see also European Pharmacopoeia: direct method for testing anti-A/B hemagglutinins [monograph 2.6.20], threshold level: 1:64).

Optimal dosing and specialized products

The currently recommended dosing according to the "Guideline on Core SPC for human normal immunoglobulin for intravenous administration (IVIg)" (EMA/CHMP/BPWP/94038/2007 Rev. 4) is shown in Table 2.

The WG agreed that dosing schedules in replacement therapy should no longer be based on body weight or body mass index [25]. Optimal use of Ig replacement therapy in PID should be adjusted on an individual basis until effective IgG trough levels, which significantly reduce infections, are reached [28]. This "effective level" for IVIg usually corresponds to trough levels above 5–6 g/L IgG. However, additional factors such as residual serum IgA concentration, mannose-binding lectin levels [29, 30] or polymorphism of the neonatal FcRn receptor [31] might govern susceptibility to infection even at "effective" IgG levels. An unresolved problem of dosing in PID is those cases with infections and concomitant noninfectious complications, e.g. in common variable immunodeficiency and X-linked agammaglobulinemia up to 30% of the cases may present with noninfectious complications such as granulomas, autoimmune cytopenias, or lymphoproliferation [30, 32]. In these cases, joint aspects of replacement and immunomodulatory therapy may have to be considered.

Similar dosage guidelines are lacking for immunomodulatory indications, where "custom and practice" has largely resulted in single doses of 0.8 g/kg in childhood acute ITP [33] and 2 g/kg in Kawasaki disease (KD) [34, 35] given initially and repeated upon failure of disease resolution. While IVIg and SCIg have been shown to be effective in chronic inflammatory demyelinating polyneuropathy [12, 36–39] recently alternative treatment options such as immune adsorption, rituximab, and pulsed dose dexamethasone are emerging [40] and effectiveness and cost-utility aspects are being examined [41]. Clearly, further disease-specific dosing studies will be needed to better define optimal doses and relative efficacy of different Ig products for a given disease; in addition, these findings have to be compared to emerging novel treatment options.

Demand, access, and priority ranking

Several national authorities have published priority rankings and guidelines for IVIg/SCIg use in clinical practice, notably the Canadian Blood Services [42, 43] the National Blood Authority of Australian [44], the Belgian Superior Health Council [11], and the British National Health Service [45]. The German and French guidelines were not considered by the WG as they date from 2003 and 2007, respectively. Interestingly, the cited literature differs considerably in the Australian and British guidelines (for comparison, see the Kreuth III proceedings 2013: http://www.edqm.eu/medias/fichiers/full_proceedings_kreuth_iii.pdf).

Particularly the demand management plan/Demand Management Programme (DMP 2012) implemented in England is an outstanding example of effective regulation and optimal Ig use in daily practice [45, 46]. It takes into consideration a ranking of conditions, with contingency plans for possible supply shortages. Use is recorded in a national registry, which is used to forecast bulk purchase of Ig in accordance with a National Commissioning Plan. Products are selected by a scoring system based on a range of quality and financial measures. In England, there are now 12 highest priority conditions (evidence grade 1A, B), 16 medium priority conditions (evidence grade 1C-2A), 24 low priority conditions (evidence grade 2B-C) and a large number of "not recommended" indications. Not all listed conditions are within the product license, but for many of them some evidence of efficacy exists. Interestingly, when comparing the priority rankings in the Australian, Canadian, and British guidelines, there are considerable differences in the ranking of conditions recommended for IVIg/SCIg therapy. A comparison of the three guidelines reveals 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 (for details, see Supporting Information Table 2). These discrepancies clearly underline the continued need for an international harmonization of guidelines for the optimal use of Ig in clinical practice.

Table 2. Current IVIG core summary of product characteristics (EMA/CHMP/BPWP/94038/2007 Rev. 4).

Indication	Dose	Frequency of injections
A) Replacement therapy for		
Primary immunodeficiency	• Starting dose: 0.4–0.8 g/kg • Thereafter: 0.2–0.8 g/kg	Every 3–4 weeks to obtain IgG trough level of at least 5–6 g/L Every 3–4 weeks to obtain IgG trough level of at least 5–6 g/L
Secondary immunodeficiency	0.2–0.4 g/kg	Every 3–4 weeks
Pediatric HIV/AIDS	0.2–0.4 g/kg	Every 3–4 weeks to obtain IgG trough level above 5 g/L
Hypogammaglobulinaemia (<4 g/L) in patients after allogeneic hematopoietic stem cell transplantation	0.2–0.4 g/kg	
B) Immunomodulatory therapy for		
Primary immune thrombocytopenia	0.8–1 g/kg or 0.4 g/kg/day	On day 1, possibly repeated once within 3 days for 2–5 days
Guillain–Barré syndrome	0.4 g/kg/day	for 5 days
Kawasaki disease	1.6–2 g/kg or 2 g/kg	In divided doses for 2–5 days in association with acetylsalicylic acid In one dose in association with acetylsalicylic acid

With regard to newly emerging indications beyond immunodeficiencies and neurology [8], promising results have been reported in solid organ transplantation [47] and autoimmune blistering disease [48] by giving either IVIg alone or in combination with rituximab to reduce the respective allo- or autoantibodies [8, 47, 48].

Resolutions of the Kreuth III meeting

During the Kreuth III meeting, a WG of experts encompassing 36 EU nations (see Kreuth proceedings, http://www.edqm.eu/medias/fichiers/full_proceedings_kreuth_iii.pdf) agreed on the following recommendations for optimal use of IVIg and SCIg.

Recommendation 1: A process for Ig demand management across Europe should be adopted to ensure adequate supplies for all patients who need Ig treatment

There was widespread approval that the British DMP 2012, presented during the meeting, is an appropriate model to emulate [39, 40]. Some countries have a similar system in place, and it was agreed that these could be harmonized, using England's as a model. The aim of the DMP would be to ensure continuity of supply to all patients who need Ig, particularly in times of product shortage (whether because of plasma collection or manufacturing issues, contamination incidents, or other reasons).

The process recognizes that different diseases have different priorities of treatments; with some conditions having absolute priority, as there are no effective alternatives, and for others there will be a range of relative priorities. Conditions that need absolute priority in times of Ig shortage include: PID, KD, Guillain–Barré syndrome, childhood ITP, and other life-threatening diseases that failed to be improved by other medications [49]. As clinical evidence of efficacy changes over time, it is important that the DMP is reviewed regularly, and there is merit in linking this process to rare disease registries. For off-label indications, local committees can usefully be involved in making decisions basing them on expert knowledge, evidence-based guidelines, and knowledge of product supply status. The WG recommended that a European WG be established to make priority recommendations.

Recommendation 2: All European countries should acknowledge that Ig is a "WHO Essential Medicine" and should ensure that all patients who need this drug have access to sufficient quantities of Ig to be clinically effective

The WG was concerned to see evidence from both IPOPI and the European Society for Immunodeficiency Registry of PID that the availability of Ig therapies (and in some cases adequate doses of Ig) is not equitable across Europe, and that some patients are experiencing significant harm and reduced life expectancy because of this. The WG discussed the appropriate doses of Ig and acknowledged that the Core SPC suggests a starting dose in PID of 0.4 g/kg/month — but emphasized that current evidence suggests that the "clinically effective dose" for each patient should be titrated to efficacy [25–28]. There was recognition that every patient is different, and that catabolic rate [31] and co-morbidities such as bronchiectasis, enteropathy, chronic disease, and others, can affect the effective dose [26, 29, 30, 32]. There was an understanding that "dose per kilogram" may be irrelevant, as evidence indicates that body mass index does not affect serum IgG levels for a given dose of Ig [25, 26], and that initial prescribing according to "ideal body weight" may be valid. Challenging noninfectious complications of common variable immunodeficiency or X-linked agammaglobulinemia such as autoimmune cytopenias and lymphoproliferation may benefit from the immunomodulatory action of IVIg/SCIg [31, 32].

In immunomodulatory indications, it was recognized that the traditional single dose of 2 g/kg being most effective in acute KD [29] can be lower in childhood ITP [33]. Similarly, in acute myasthenia gravis, 2 g/kg IVIg did not show a better efficacy than 1 g/kg [50], underlining the urgent need of more studies addressing the

dosing issue. In the future, better target values supported by biomarkers of IVIg resistance [51, 52] could also contribute to significant savings. The WG agreed that there is little point in prescribing Ig if the amount given is not sufficient to produce a sustained clinical benefit.

Recommendation 3: All recognized routes of Ig administration should be made available to patients

The WG agreed that SCIg therapy is well established now for PID [27]. It was agreed that SCIg and IVIg doses per time interval can be similar and there was complete acceptance that patient choice is paramount in deciding whether Ig replacement therapy should be intravenous or subcutaneous. At this occasion, the WG did not deal with "facilitated" or "rapid push" SCIg therapy [53, 54]. The WG recognized accumulating evidence that SCIg therapy may work as well for some immunomodulatory indications, especially some neurological diseases [38, 39] but is not suitable for all patients and in particular not for acute conditions [12, 36, 37]. The WG noted that the dose equivalence between SCIg and IVIg for immunomodulatory indications is not known; the sharp IgG serum peak after IVIg application, which is not seen after SCIg, may be of importance for immunomodulatory efficacy in some diseases.

Recommendation 4: Agreement that Ig products differ from one another

The WG agreed that Igs are not generic products, and had extensive discussion about when they are similar and when they are different. There was agreement that the beneficial clinical effects of differing brands are likely to be similar. However, as shown in Figure 2, the efficacy and side effects (see *Safety considerations of Ig therapy*) may differ from product to product, and even from batch to batch (e.g. TEE and hemolysis). Understanding the underlying mechanisms for these differences may change this view, particularly in replacement therapy for PID, and should be subject to more research. Issues such as difference in specific antibody titers, IgG glycosylation, the patient's Fc-γ-receptor polymorphisms, and copy number variation may be involved [11, 43–46, 51, 52]. In terms of product choice, so far no benefit can be drawn from the very few, usually small scale, head-to-head studies comparing products.

Recommendation 5: Recognition that better mechanisms for Health Technology Assessment of Ig therapies are required

The WG noted that assessment of risk/benefit and price/benefit are currently separated topics. However, during clinical trial development of other products, companies are increasingly asking for "combined" advice at the EMA, i.e. scientific advice and Health Technology Assessment advice. It is not clear what implications this may have for Ig, as apparently no company has sought this path as yet. However, as all Ig preparations follow the European Monographs for quality control and the Core SPC for labeling and they all have to adhere to the European Guideline for clinical trials, the products may easily be compared.

Ideally, companies should cooperate in undertaking joint studies in order to cost-effectively produce more robust data (as in many successful HIV trials); particularly in indications for rare diseases. Making maximum use of pharmacovigilance registries and postmarketing surveillance is also recommended.

Recommendation 6: More research is needed on the use of Ig in treatment of secondary immunodeficiencies

The use of IVIg in the treatment of secondary immunodeficiency is increasing [9, 55–57]. Ig therapy can be used in selected patients with recurrent infections, hypogammaglobulinemia, and specific antibody deficiency, secondary to lymphoma, chronic lymphocytic leukemia [58, 59], hematopoietic stem cell transplantation [60], and following chronic immunosuppressive treatment. A useful approach for patient selection is to determine serum Ig concentrations and the levels of specific serum antibody titers in response to vaccination with protein (e.g. tetanus, diphtheria) and polysaccharide (e.g. pneumococcal, meningococcal) vaccine antigens [61].

The WG recommended that more studies are needed to assess patient suitability for Ig therapy in these conditions. The original study data should be re-examined to determine if low specific antibody levels are sufficient for patient selection. For the time being, the WG recommends decisions only regarding individual cases.

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Abbreviations: **CD-P-TS**: Comité Directeur (accord partiel) sur la transfusion sanguine · **DMP**: demand management plan/Demand Management Programme · **EMA**: European Medicines Agency · **ITP**: immune thrombocytopenia · **IVIg**: intravenous Ig · **KD**: Kawasaki disease · **PID**: primary immunodeficiency · **SCIg**: subcutaneous Ig · **SPC**: summary of product characteristics · **TEE**: thromboembolic events · **WG**: working group

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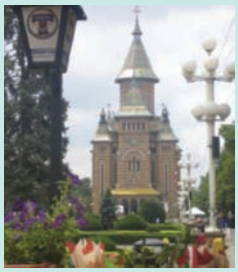

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