We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Immunoglobulin Treatment of Immunodeficient Patients

Yıldız Camcıoğlu

Additional information is available at the end of the chapter

1. Introduction

There is a large number of immunodeficient patients requiring lifelong IgG replacement. This review is focused on currently available Intravenous Immunoglobulin (IVIG) preparations, manufacturing procedures, dose arrangements, mechanisms of actions, benefits of antibody replacement treatment and careful administration of IVIG considering, numerous side effects. Subcutaneous IgG (SCIG) treatment has gained ground in recent years as an alternative to IVIG. Data show that the efficacy of SCIG in preventing infections is proportional to the steady-state levels achieved and similar to that of IVIG.

Intravenous immunoglobulin (IVIG) is mainly indicated as replacement therapy for patients with primary and selected secondary immunodeficiency diseases characterized by absent or deficient antibody production. Antibody deficiencies are a heterogeneous group of diseases mainly consisting of primary immunodeficiency diseases (PID) [1-4]. Primary antibody deficiencies (PAD) can be divided into four main subgroups: X-linked agammaglobulinaemia, class-switch recombination defects (hyper-IgM syndromes (HIGM), hypogammaglobulinaemia (particularly common variable immunodeficiency (CIVD) and selective immunoglobulin deficiencies (selective IgA deficiency). Over the past 20 years, 18 genetic defects have been defined as leading causes of PAD, but no gene defects were identified in patients with hypogammaglobulinaemia and selective immunoglobulin deficiencies, because of the variability of the affected stages of B cell differentiation and maturation, and the onset time of clinical symptoms like childhood or adulthood with increased susceptibility to mainly bacterial infections [5,6].

Substitution of immunoglobulin G (IgG) is the efficient and standard treatment for many years [7-11]. Immunoglobulins pooled from thousands of healthy donors contain a wide range of antibody specificities. These immunoglobulin preparations also have anti-inflammatory and immunomodulatory effects in addition to their use as replacement

therapy [12,13]. The benefits in diseases such as childhood thrombocytopenia and Kawasaki disease refractory to or intolerant of conventional treatment have been well established [14,15]. It has been 30 years since therapeutic contribution of intravenous immunoglobulin (IVIG) administration has been proven by scientists, an increasing number of immune-mediated diseases have been treated with intravenous immunoglobulin rather than corticosteroids and cytoxic drugs. IVIG has become the therapy of choice in autoimmune diseases, severe asthma, neurological diseases, transplantation, sepsis, septic shock, toxic shock syndromes and dermatologic disorders [15,16]. The recommendation of IVIG treatment in other diseases than those approved by FDA is based on limited data or some of these diseases do not have any alternative treatment regimen to compare with [16]. However, IVIG administration in the treatment of many diseases is raising the possibility of product shortages and increasing costs. Thus, concerning the shortages of products, cost and adverse reactions, definite indications for IVIG treatment are essential [12,13,16,17]. The aim of immunoglobulin therapy should be to protect the patients from frequent and severe infections finally resulting in organ damage. Advances in human immunology, has led to identify responsible genes for PID, thereby particular groups of defects are associated with susceptibility to specific types of infection [18]. Improved diagnostic precision is likely to increase more specialized management strategies of patients with PID, some of which are only supported by expert consultation. However, there are no sufficient number of studies in PID, to optimize the quality and uniformity of management of PID.

2. History and recent development (IVIG)

Cohn et al produced the first human immunoglobulin IgG product in1946 and it was referred as immune serum globulin (ISG)[19]. This first commercial human ISG solution tended to form aggregates during storage, therefore it was delivered via the intramuscular or subcutaneous route. After diagnosing his first patient with agammaglobulinemia in 1952, Bruton began to treat his patients by subcutaneous replacement therapy with ISG [20]. After a short time, intramuscular ISG treatment became available for all patients, but the amount of Ig used for treatment was limited and not effective enough to reduce recurrent infections and the adverse effects were also high due to IgG aggregates [21]. These disadvantages were abolished by Cohn fraction II that had been developed in 1960's by Barandum and his colleagues in collaboration with Swiss Red Cross [9,21]. The first IVIG was produced by pepsin digestion (enzymatic method: pepsin or trypsin) to reduce anticomplement activity, but this process cleaved the immunoglobulin molecule into two parts, resulting in fragments of the fc portion and Fab. Several manifacturers produced chemically modified IVIGs containing minimal anti-complement activity and no IgG fragments. Reduced bacterial opsonic activities and shortened circulating half-lives were demonstated in some antibodies of enzyme-digested or chemically modified IVIG preparations. Non-denaturating processes such as precipitation with polyethylene glycol (PEG), ion exchange chromatography, diafiltration and stabilisation of IgG at low pH, do not modify the IgG molecule and the half-life of IgG is generally 22-25 days [21].

Intravenous immunoglobulin (IVIG) preparations contain 16% human serum immunoglobulin and more than 95% IgG, scanty amount of IgA, IgM and other serum proteins. IgA and IgM do not have any therapeutic effects due to their short half-life and small amount [22,23]. Prognosis of patients with deficient IgG production has thoroughly improved after replacement therapy with IVIG [24]. Since 1980, it has been the most striking therapeutic agent due to its unproposed anti-inflammatory and immunomodulatory effects and used to treat a wide variety of pathologies including vasculitis, HIV infection, autoimmune diseases and immune-mediated neurological diseases [12,14,15, 25-28]. Currently, subcutaneous immunoglobulin infusions administered by a special pump has become an alternative to IVIG treatment. It has been demonstrated that this product is safe and has some clinical advantages over intravenous preparations. It has been recommended especially for selected patients with primary immunodeficiencies [29,30].

3. IVIG production

IVIG preparations are derived from plasma of a huge number of human blood donors or paid plasmapheresis donors. Since IVIG preparations are blood-derived products having the risk of transmission of infectious transfusional diseases, viral safety needs to be considered [13,21,23]. The safety of IVIG products depends on donors, validated manufacturing processes and various virus clearance steps as listed below:

a. recruitment of the donor
b. donation screening
c. use of validated manufacturing processes
d. effective viral inactivation/removal procedures

To produce a single product lot, sufficient number of donor recruitment and screening of viral markers (HBs-Ag, HIV-p24 antigen, antibodies to syphilis, HIV-1,HIV-2, HCV, HAV) are necessary to prevent the transmission of viruses [21].

FDA (Center for Biologics Evaluations and Research) and Plasma Protein Therapeutics Association recommended the number of donors to be minimum 15.000, but not more than 60.000. Manifacturing processes implemented in commercial IVIG preparations are the classical Cohn fractionations treated with solvent detergent, caprylate, acid or pepsin to inactivate pathogens [31-33].

Immunoglobulin, produced by cold ethanol fractionation method may contain trace amounts of contaminants such as prekallikrein activator, prekallikrein, activated coagulation factors, complement proteins, IgM, IgA, plasmin and plasminogen. Currently many manufacturers began to use purification with anion exchange (DEAE) chromatography adjusted to cold ethanol fractionations in order to obtain safe products.

Treatment at pH4 with trace amounts of pepsin is also validated by some manifacturers. Both, alcohol fractionation and acid treatment procedures eliminate other proteins and inactivate dangerous live viruses such as HIV, Hepatitis B, HCV.

Improved quality standards for plasma products and new blood borne pathogens such as SARS forced the scientists to develop and integrate new specific viral inactivation methods. RNA virus with lipid envelope, DNA virus with lipid envelope and non-lipid enveloped virusus must all removed by viral inactivation procedures. The heat and chemical treatment processes are able to remove and/or inactive blood-borne pathogens:

a. Pasteurisation: Based on heating to 60°C in an aqueous solution for 10 hours in the presence of stabilizers.
b. Solvent/Detergent: The solvent/detergent consists of an organic solvent (ether, 0.3% tri-n-butylphosphate (TNBT) and 0.2% detergent (Tween 80, sodium cholate or triton-100). The process lasts for 6 hours and destroys infectivity of lipid-enveloped viruses.
c. Nanofiltration: This procedure is effective to remove small non-enveloped (B19V, HAV) viruses.
d. Low pH-incubation: This incubation at elevated temperatures completely removes lipid-enveloped viruses like HIV, HBV/HCV).

Transmission of Prion diseases such as Creutzfeldt–Jakob disease (CJD) or variant CJD by administration of blood products is also possible, since the incubation period of the disease is too long leading to difficulties in risk determination. Because of this possibility, donors who have spent more than 6 months in the United Kingdom from 1986 to the present are not allowed to donate blood or plasma in the United States and Europe [21]. Some researchers demonstrated that depth filtration step that is common in all IVIG production procedures and nanofiltration removed hamster scrapie protein reactivity. The Finish Red Cross Blood Transfusion Service (FRC BTS' Helsinki, Finland) had developed a liquid 5% IVIG product (IVIG-L) in which a nanofiltration step was incorporated into the production process [34]. Van der Meer JWM et al. evaluated efficacy and safety of that nanofiltered liquid IVIG product and showed that IVIG-L was efficacious and pharmacokinetic properties were comparable to other IVIG preparations. In addition relatively low level of adverse reactions and the absence of seroconversion were observed. Thus, this liquid form product is considered to be safe and well tolerable. Over the past years, improved manifacturing processes and integrated specific viral inactivation steps have increased the safety and quality of IVIG products (Table 1). Commercially available products represent recent advancements in IVIG product formulation, but potential transmission of emerging pathogens can still not be ruled out completely.

Currently licensed IVIG preparations are supplied either in lyophilized powder or premixed solution, contains 95% IgG at a concentration of 16.5% (165 mg/ml), all the IgG subclasses, multiple IgG allotypes (Gm and Km), minimal anti-complement activity, broad spectrum of antibodies against viruses and bacteria, and no difference in therapeutic efficacy. Half-life of immunoglobulins is approximately 21-25 days. The osmolarity varies between 253 mOsm/L for a 5% IgG product to1250 mOsm/L for a 10% product. The final sterile product contains varying amounts of sodium, glycine, polyethylene glycol, D-mannitol, D-sorbitol, sucrose, glucose or maltose, glycerol as the stabilizer, and thiomersal as the preservative and has a pH of 6.8 (Table 2).

Virus inactivation/removal procedure	Product
Solvent-detergent inactivation	Gammagard S/D Gammagard liquid Flebogamma 5% DIF Octagam
Heat inactivation(10h at 60 C)	Vivaglobulin Flebogamma 5% Flebogamma 5% DIF
Removal by nanofiltration	Gammagard liquid Carimune NF Privigen
pH4 incubation (in process)	Flebogamma 5% DIF Octagam Privigen
Low pH incubation in final container(21 day)	Gamunex
Low pH incubation at elevated temperature in final container	Gammagard liquid
Pepsin treatment	Carimune NF
Caprylic acid virus inactivation	Gamunex

Table 1. Dedicated virus inactivation procedures used in IVIG production [22]

Product	Manufactu-rer	Dosage form	Sodium Content mEq/mL	Stabilizing agent /PH	Antimicrobial processes	IgA µg/mL	Osmolarity mOsm/kg
Octagam	Octapharma	5 %Liquid	0.03	Maltose PH 5.1-6	Cold ethanol fractionation Solvent-detergent	100	310-380
Gamimune N	Bayer	10%Liquid	Trace	Glycine pH4.25	Dialfiltration, Ultrafiltration Solvent-detergent	Trace	274
Carimune NF liquid	CSL Behring AG	3, 6 ,9,12% lyophilized	<20	sucrose 1.67 per gram protein PH 5.3	Kistler&Nitchman Fractiotion, trace Pepsin, pH 4.0 Nanofiltration	720	192-1074
Gammagard 5% S/D	Baxter	5% lyophilized powder	0.145	2% glucose PH 6.8	Ultrasantrifuge, Ion exchange chromatography, Solvent-detergent	<2.2.	636
Gammagard 10% S/D	Baxter	10% lyophilized powder	0.145	4% glucose PH 6.8	Ultrasantrifuge, Ion exchange, chromotography, Solvent-detergent	270	1250
Gammagard S/D10% (KIOVIG)	Baxter	10% liquid	none	glycine PH 4.85	Cohn-Oncley fractionation, Ion exchange chromotography, Nanofiltration, Solvent-detergent, pH 4 filtration	37	240-300

Product	Manufactu-rer	Dosage form	Sodium Content mEq/mL	Stabilizing agent /PH	Antimicrobial processes	IgA µg/mL	Osmolarity mOsm/kg
Flebogamma DIF	Grifols	5% , 10% Liquid	<0.032	D-sorbitol PH 5.0-6.0	Cold alcohol fractionation, PEG, Ion exchange, chromotography, PH4 treatment, Solvent-detergent, double sequential nanofiltration	5%: < 50 10%: < 100	240-370
Venoglobulin S	Alpha	5 % 10% Liquid		Albumin (human) D-sorbitol	PEG, Ion exchange Chromotography, Solvent-detergent,	24	
Gammar-PIV	Centeon, L.L.C., Kankakee	lyophilized	0.085	Albumin (human) Sucrose PH 6.8	Cold ethanol fractionation, heat10 hours 60°C	25	258
Iveegam	Immuno US	lyophilized 5%	0.05	Glucose, NaCl	Polyetilene glycol/trypsin	5	>240
Endobulın	Baxter Immuno France	lyophilized	3mg	Glucose, Polyetylene glycol(PEG),	Solvent-detergent		
IgVena	Sclavo	Liquid		Maltose	Solvent-detergent pH 4 filtration	100	
Privigen	CSL Behring AG	Liquid	Trace amount	None	Octanoic acid fractionation, CH9 filtration, pH 4.0 incubation, Depth filtration, Chromotography, Nanofiltration ,	≤25	Isotonic (320)
Gamunex- C	Talecris Biotherape-utics	Liquid	Trace amount	None	Cohn-Oncley fractionation, caprylate precipitation, Sepharose chromatography, Cloth and depth filtration Final container pH 4.25 ±0.25incubation	46	258
Omr-IgG-am	Omrix Biopharmaceuticals Ltd	Liquid		50 mg/mL; 100 mg/mL maltose	Cold ethanol fractionation, S/D, 24 h @ pH 4, pH 5.5 ± 0.4,		

Table 2. Commercial IVIG Products and properties (Data from Immune Deficiency Foundation, October 2011 and reference [17, 22])

All the available IVIG preparations approved by FDA and EMEA should at least have the following features:

- Sterile >4000[5000-10000]donors

- >20 days of half life
- >90 % monomeric IgG
- Effective IgG subclasses, a profile similar to that of human plasma
- Complete Fc functions, complement fixation, opsonophagocytosis
- No pyrogenic and vasoactive agents (kinin or plasmin), protein aggregates
- Low adverse effects
- Trace IgA concentration
- Stabile in solution
- Low price

4. Mechanism of action

Human immunoglobulin is obtained from a large number of donors and exceeding 2.000 donors is preferred. IVIG contains large spectrum of antibody specificities such as antibodies to foreign (non-self) antigens, to self-antigens (natural autoantibodies) and to other antibodies (idiotypic antibodies which represents antibody repertoire of each donor [35]. That is the reason of the differences between immunoglobulin batches [13,21,35]. The mechanism of activity of the substituted IgG is easily understood for immunodeficiency disorders considering common pathogen-specific IgG antibodies are replaced by those from the donor pool [35]. Thereby, regular intravenous immunoglobulin therapy reduces the incidence of infection in these patients compared to their infection rates before IVIG treatment [7-13]. Immunomodulatory effect of IVIG therapy depends on several mechanisms. Proposed early immunomodulatory effects of IVIG infusion are shown below [35-37]:

- Modulation of production and release of proinflammatory cytokines and cytokine antagonists
- Functional blockade of Fc receptor on splenic macrophages
- Neutralization of circulating autoantibodies
- Neutralization of superantigens
- Inhibition of complement-mediated damage
- Changes in solubility and rate of clearance of immune complexes

On the other hand, IVIG infusion downregulates IVIG-reactive B cell clones in long-term. Serum IL-6, IL-8, IL-1Ra and TNFalpha concentrations were increased in patients with primary immunodeficiencies following IVIG infusion, without any difference in serum IL-beta, IFNgamma or IL-2 levels. Understanding these immunomodulatory effects of IVIG is essential to define IVIG indications in autoimmune disorders [35-37]. In severe infections regarding increased catabolism of IgG, IVIG can be added to antibiotic treatments [16, 17].

The concentration of IgG is very important for its pro-inflammatory or anti-inflammatory properties. Low-dose IVIG has proinflammatory properties, but high dose IVIG has anti-inflammatory effects. The proinflammatory properties are dependent on complement activation or binding of the Fc fragment of IgG to IgGspecific (FcγR) on effector cells of the innate immunity leading to receptor clustering, activation of intracellular signaling pathways and finally to cell activation. The anti-inflammatory effect of IgG is still not clear, but IgG is known to inhibit the differentiation and maturation of human dendritic cells (DCs), expression

of co-stimulatory molecules like CD80 and CD86, both leading to lower self antigen processing and presentation [8]. Fc and F(ab')$_2$ fragments of IgG molecule are both able to suppress of DCs. Antibodies with the intrinsic capacity to recognize foreign antigens or common pathogen-specific IgG antibodies are replaced by those from the donor pool [35].

At a lower dose, administered generally to patients with immunodeficiencies, however, IVIG exerts a contrasting effect. DCs of patients with common variable immune deficiency (CVID) differentiated in the presence of IVIG and presented with an up-regulated expression of CD1a and the co-stimulatory molecules CD80, CD86 and CD40 [38,39]. Defective functions of DCs have been associated with predisposition to several pathological conditions. CVID patients display high susceptibility to recurrent infections and autoimmune diseases that could be due in part to impaired DC functions [38,39].

Advantages of IVIG administration are the following:

- Painless administration
- Absence of proteolysis of the product
- No sterile abscess
- Rapid onset of action
- Easy administration of large doses

Unfortunately, there are also some disadvantages of IVIG administrations:

- High cost
- Requirement for a venous access
- Long duration of the infusion
- 5-15% adverse events
- Severe adverse reactions such as anaphlaxis

5. IVIG preparations

In recent years, manufactures aim to develop products that provide a high-yield, safe, well tolerated and stable concentrates of polyclonal IgG. Each new intravenous immunoglobulin product has to be tested for its biochemical characterization done by standart methods focusing on purity, integrity and functionality. Efficacy must be shown by opsonization, protein A affinity chromatography and mouse protection tests. Pharmacokinetics of the product, the influence of product on vital functions, acute toxicity, anaphylactoid potential, thrombogenicity should be evaluated in rats, dogs or a rabbit models. Development of new methods for fractionation, combining processes and integrating three dedicated virus clearance steps provided fulfilling the clinical requirements for intravenous administration of second-generation intravenous immunoglobulins products (Table 2) [21].

The US Food and Drug Administration (FDA) standardized clinical trials with IVIG in patients with primary immunodeficiencies. FDA has proposed to measure the rate of serious bacterial infections during regular infusions of investigational IVIG for 12 months to avoid seasonal variations. Serious bacterial infection term has to be well defined, thus bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess were defined as serious infections [8].

The guidelines for clinical Investigation of human normal Immunoglobulin for Intravenous administration of the European Medicines Agency (EMA/CHMP/BPWP/94033/2007 rev.2) and FDA recommended that an immunoglobulin product is effective if treated patients experience less than 1.0 serious infection per year [21,34]. A new IVIG product must have 'intact IgG' which means pharmacokinetic properties of Immunoglobulin G is similar to endogeneous IgG and available other immunoglobulin preparations.

6. Indications of IVIG treatment

IVIG, has been licensed by FDA for only 6 clinical indications [8,22,23]:

1. Treatment of primary immunodeficiencies
2. Prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent bacterial infections caused by B-cell chronic lymphocytic leukemia
3. Prevention of coronary artery aneurysms in Kawasaki disease
4. Prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) after bone marrow transplantation
5. Reduction of serious and minor bacterial infections, to decrease the frequency of hospitalisation in children with HIV
6. Increase of platelet counts in idiopathic thrombocytopenic purpura to prevent or control bleeding

IVIG therapy has been evaluated in a number of clinical conditions mentioned above and categorization of evidence, basis of recommendation and strength of recommendation have been established (Table 3 and Table 4) [16].

Categorization of evidence and basis of recommendation
Ia From meta-analysis of randomized controlled studies
Ib From at least one randomized controlled study
IIa From at least one controlled study without randomization
IIb From at least one one other type of quasiexperimental study
III From nonexperimental descriptive studies such as comparative, correlation or case control studies
IV From expert committee reports or opinions or clinical experience of respected authorities or both
Strenght of recommendation
A Based on category I evidence
B Based on category II evidence or extrapolated from category I evidence
C Based on category III evidence or extrapolated from category I or II evidence
D Based on category IV evidence or extrapolated from category I, II or III evidence

Table 3. Categorization of evidence and basis of recommendation and strength of recommendation [17]

Benefits	Diseases	Evidence	Strenght of

		category	recommendation
Definitely beneficial	Primary immune defects with absent B cells	IIb	B
	Primary immune defects with hypogammaglobulinemia and impaired specific antibody production	IIb	B
Probably beneficial	Chronic lymhpocytic leukemia with reduced IgG and history of infection	Ib	A
	Prevention of bacterial infection in HIV infected children	Ib	A
	Primary immune defects with normogammaglobulinemia and impaired specific antibody production	III	C
Might provide benefit	Prevention of neonatal sepsis	Ia	A
Unlikely to be beneficial	Isolated IgA deficiency	IV	D
	Isolated IgG4 deficiency	IV	D

Table 4. Recommendation of IVIG in primary and secondary immunodeficiencies [17]

7. Treatment of primary immunodeficiencies

Primary antibody deficiencies [25], account for approximately 65-50% of primary immunodeficiencies (PID) [3,40]. Due to defects in critical stages of B cell development, B cells areabsent/reduced and B cell functions are impaired in patients with PAD [41]. B cell defects are a heterogeneous group of disorders consisting of patients presenting a wide variety of clinical conditions ranging from asymptomatic to severe and recurrent infections. Patients with selective IgA and IgG subclass deficiencies are often asymptomatic, while children with agammaglobulinemia present encapsulated bacterial infections initiating at 6 months of age. Reduced immunoglobulin concentrations and lack of antibody response against protein antigens (diphtheria, tetanus toxoids) or polysaccharide antigens (pneumococcal polysaccharide) are well defined in patients with agammaglobulinemia or hypogammaglobulinemia [40-42]. Although these patients have frequent or recurrent bacterial infections, they could not mount IgG antibody responses against antigens and this condition is a clear indication for immunoglobulin replacement therapy (Table 5) [21, 42].

Therefore, the aim of replacement therapy is to avoid acute infections, respiratory complications such as bronchiectasis, gastrointestinal complications, to improve quality of life and to increase life expectancy of patients [17, 22]. The delay in diagnosis of primary immunodeficiencies remains a significant problem, as a consequence of delay recurrent pneumonias results in structural lung damage such as bronchiectasis, pulmonary hypertension and finally cor pulmonale [10].

1. Antibody deficiencies
X -linked Agammaglobulinemia(XLA)
Common variable immunodeficiency(CVID)
Hyper IgM syndrome
Transient hypogammaglobulinemia of infancy(selected cases)
IgG subclass deficiency± Selected IgA deficiency (selected cases)
Impaired specific sntibody production with normal plasma immunoglobulin evel
2. Combined immunodeficiencies
All type of severe combined immunodeficiencies(SCID)
3. Other well-defined immunodeficiency syndromes
Wiskott –Aldrich syndrome
DNA repair defects; Ataxia-telangiectasia, Nijmegen breakage syndrome
Di George Anomaly
Primary CD4 deficiency
ICF syndrome
4. Diseases of immune dysregulation
X-linked lymphoproliferative syndrome (XLP)

Table 5. Primary Immunodeficiencies benefit IVIG treatment

Evaluation of IVIG use in patients lacking immunoglobulin has demonstrated reduction of acute and chronic bacterial infections frequency, pneumonia, days of antibiotic usage, days of fever and hospital admission [16]. Retrospective studies in patients with XLA revealed that severity and number of infections are decreased depending on IVIG dose. Serious bacterial illnesses and enteroviral meningoancephalitis were prevented when maintained IgG levels were above 800mg/dL [16,21,42,43].

Barıs S et al. evaluated the efficacy of IVIG treatment (500 mg/kg every 3 weeks) in 29 children diagnosed with CVID. During therapy, median serum IgG levels increased from 410 to 900 mg/dL. The mean number of respiratory infections per patient per year decreased significantly from 10.2 to 2.5. The annual number and length of hospital stays decreased significantly from 1.36 to 0.21 and 16.35 to 6.33 days per patient, respectively. The mean annual number of antibiotics used decreased significantly from 8.27 to 2.50 per patient. Twelve patients had developed bronchiectasis before initiation of IVIG [44].

Intravenous immunoglobulin therapy has to be started without any delay in patients with CVID predisposed to chronic lung diseases. Appropriate replacement therapy in these patients, reduced the incidence of pneumonia and prevent progression of lung involvement [17, 42-47].

A 5-year multicenter prospective study on 201 patients with CVID and 101 patients with XLA was conducted to identify the effects of long-term immunoglobulin treatment and the IgG trough level to be maintained over time required to minimise infection risk. Overall, 21% of the patients with CVID and 24% of patients with XLA remained infection free during the study. Pneumonia episodes had been reduced. Patients with pneumonia did not have

significant lower IgG trough levels than patients without pneumonia, with the exception of patients whose IgG trough levels were persistently <400 mg/dL. In addition, in XLA co-morbidity risk factor identified for pneumonia was the presence of bronchiectasis [10,23].

Studies have shown that 10 years survival of CVID patients receiving IVIG treatment was 78%; while expected survival in the general population at ten year was 97% [28].

Patients with severe combined immunodeficiency(SCID) syndromes are also agammaglobulinemic and have significant inability to produce antibody against antigens. Hematopoietic stem cell transplantation is choise of therapy for these patients, but functional B-cell reconstitution often fail following marrow engraftment and these patients could not produce antibodies. Regular replacement therapy with IVIG is indicated for these patients.

Hyper IgM syndromes are usually defined with reduced levels of IgG and IgA, but high or normal IgM. These patients have normal B cell counts, but defective class switching do not allow to generate specific antibodies, thus these children experience frequent infections like agammaglobulinemic individuals. Adequate replacement of IVIG has been shown to reduce the incidence of pneumonia from 7.6% to 1.4% per year and patients did not have meningitis [10, 25, 48].

Selective antibody deficiencies or normogammaglobulinemia with impaired specific antibody production are group of disorders characterized by impaired production of specific antibody with normal serum IgG levels. Evidence of recurrent infection and absent or reduced specific antibody production against polysaccharide antigens after vaccination, are requirements for IVIG therapy. Therapy can be stopped after clinical improvement and the immune response of patient should be re-evaluated at least 5 months later. Usually antibody response to antigens, improve in growing children, but in conditions of unresponsiveness to antigens, restart to IVIG treatment is appropriate due to recurrence of infections.

Immunoglobulin treatment is not commonly recommended to patients with selective IgA deficiency unless poor specific antibody or IgG2 subclass deficiency exists [21].

Replacement therapy is also recommended in patients with combined immune deficiencies, other well-defined immunodeficiency syndromes and X-linked lymphoproliferative syndrome (XLP)(Table 5).

8. Choosing a commercial brand for IVIG therapy

There are several factors required for selection of an IVIG brand:

1. To obtain enough information about the IVIG product: lyophilized powder or premixed solution, amount of sodium, IgG and IgA, stabilizing sugar, preservative, viral inactivation methods, concentration, osmolarity
2. Safety and tolerability
3. Price

Regarding lyophilized or liquid forms, sugar content, amount of IgA (varies between <0.4 μg/mL and 720 μg/mL), used antimicrobial processes and stabilizing agent, an appropriate commercial immunoglobulin preparation should be selected for treatment of immunodeficient patients(Table 1). The patients with diabetes may have high blood glucose levels due to maltose-containing products therefore they have to adjust doses of insulin [5, 8, 21, 23, 49].

Patients with selective IgA deficiency carry the risk of anaphylaxis due to production of anti-IgA antibodies. Selective IgA deficient patients having high anti-IgA (>1/1000) titers should not be treated with IVIG or a IgA-free immunoglobulin product should be chosen for the treatment [8, 21, 50, 51]. Since IVIG administration is a life-saving therapy, the treatment should be supported by scientific clinical evidence regardless the economic impact of therapy [52]. Therefore considering scarcity of resource for IVIG, its judicious use must be promoted for the diseases FDA approved.

9. Dose

The common recommended dose of IVIG treatment for antibody replacement is between 0.3 and 0.6 g/kg, administered every 2 to 4 weeks via the intravenous route. The first dose of IVIG infusion usually results more frequently in adverse reactions compared to the following second or third doses. Thus, the first IVIG infusion to a patient with antibody deficiency must be given slowly as a 5% solution, starting with a rate of 0.5 to 1.0 mg/kg per minute. Patient should be monitored closely for any adverse reactions during infusion. If the patient tolerates well, the infusion rate may be increased to 1.5 to 2.5 mg/kg per minute after 15 to 30 minutes. The maximal infusion rate is 4 mg/kg per minute. Infusion of an IVIG product should last 2 to 4 hours. For subsequent infusions IVIG concentrations of 10% and 12% can be used, with rates 4 mg/kg per minute. The aim of IVIG therapy in patients with PID is to maintain serum IgG levels between 350 mg/dl and 500 mg/dl [7,10,16,17,25,42,43,45,48,51].

Since, there is large variation in individual IgG elimination rates, periodic measurement of serum IgG concentration is critical to monitor the adequacy of replacement during therapy.

10. Adverse effects of IVIG

There are two main risks of immunoglobulin treatment: Infusion related adverse effects and transmission of blood–borne viruses [5,7,22,23]. Incidence of adverse reactions, have been found 44% in more than 1.000 patients with PID, in a study done by Immune Deficiency Foundation (IDF) [16]. This rate was surprisingly higher than those observed in licensing studies (Table 6). The IDF survey showed that 34% of patients experienced adverse reactions during the first administration of IVIG and who has had a recent bacterial infection. Reactions may develop 1 to 15% in the first 30 minutes of IVIG infusions. After second or third doses of the same IVIG product additionial infusion dependent reactions become less

likely. Most IVIG reactions are mild, however anaphylaxis may occur occasionally. Adverse reactions are characterized by chills, headache, low grade fever, back or abdominal pain, nausea, vomiting, myalgias, rhinitis, asthma, flushing on face, vertigo, anxiety, conjunctival congestion, occasional rash and drop of arterial pressure. Varying rates of adverse events have been reported (Table 6) [53-56]. Thus, close monitoring of a patient during infusion is essential to identify and manage reactions [8,24,53]. Recently, manufacturing processes of immunoglobulins have been improved and new IVIG products have been developed. Several trials with these products demonstrated that the infusion related adverse reactions were reduced [24,53]. IVIG infusions have to be done at hospital or home by professionally educated staff if possible. Local anesthetic cream (EMLA Cream) could be applied on skin prior infusion to reduce pain in small children. Administration IVIG via indewelling venous catheter is not encouraged because of additional adverse events such as thrombotic and infectious complications.

Product	Study Duration Months	Patients Treated	Dose	Acute Serious Bacterial Infect/subj/y	Other Bacterial Infect/subj/y	Related, Temporally Associated AEs (%of Infusions	Drug-Related SAEs
CarimuneNF Liquid (12%)	6	42	200-800 mg/Kg/21–28 d	0	3.65	21.7% a	0
Flebogamma 5%	12	51	300–600 mg/Kg/21–28 d	0	061. NR	8.2% c	2
Flebogamma 5% DIF	12	46	300–600 mg/Kg/21–28 d	0.021	1. 96	11.8% c	0
Gammagard liquid 10%	12	61	300–600 mg/Kg/21–28 d	0	0.07	31.2% c	2 (1 patient)
Gamunex 10%	9	73	100–600 mg/Kg/21–28 d	0.07	0.18	5.7% a	0
Octagam 5%	12	46	300–600 mg/Kg/21–28d.	0.1	0	5.5% b	0
Privigen 10%	12	80	200–888 mg/Kg/21–28 d	0.08	3.55	18.5% b	5 (1 subject)
Vivaglobin 16%	15	51	34–352 mg/Kg/wk	0.04	4.4	Local, 49%; Systemic 5.4%	0

AE:Adverse event, infect/subj/y: infections per subject per year, NF:nanofiltration, SAE:serios adverse event a) 0-48 h postinfusion, b) 0-430 min postinfusion, c) 0-72 h postinfusion

Table 6. Clinical trials in patients with primary immunodeficiency disorders [22]

11. Late-onset side effects of IVIG

A variety of side effects due to IVIG therapy have been reported in different tissues [7-11,21-25,27,28,57]:

Central nervous system: rarely aseptic menengitis

Hematologic: hemolytic anemia, leukopenia, neutropenia, monocytopenia, disseminated intravascular coagulation and changes in blood rheology

Cardiovascular system: rarely heart attack, most commonly, drop in arterial blood pressure

Urogenital system: During the period between June 1985 and November 1998, 88 cases of kidney injuries had been reported to FDA. Acute renal failure occured with IVIG preparations stabilized with sucrose, where as those stabilized with D-sorbitol did not cause such an effect. Patients whose urinary output decreases, who suddenly gain weight with edeme on feet and ankles and those who experience dyspnea should be monitored very closely.

Liver Disease: The risk of Hepatitis C, Hepatitis B, HIV infection, prion disease disappeared after the initiation of viral inactivation (solvent-detergent or pasteurization) methods and PCR studies which took place after CDC's confirmation of 88 infections among 137 suspected hepatitis C cases (occuring after IVIG) in 1994. Therefore they are reliable preparations.

Skin: severe cutaneus vasculitis, dermatitis (egzema) and hair loss

Other: Life threatening parvovirus B19 has occured due to IVIG, hyperproteinemia, increased serum viscosity, pseudo-hyponatremia during infusions, transient serum sickness.

12. How to manage adverse reactions?

An expert monitoring is necessary for prompt diagnosis and treatment of adverse reactions. Most side effects resolve by themselves and are usually due to the speed of infusion. Infusion should temporarily be stopped 15 to 30 minutes if the symptoms appear or should be continued with slower rate once the symptoms disappear. Since the side effects are usually non-IgE dependent, the use of antihistamines is controversial, but diphenhydramine, acetaminophen or ibuprofen may be helpful. More severe reactions can be treated with 50 to 100 mg of hydrocortisone in adults and intravenous hydration is helpful.

Those who are reactive to IVIG should receive premedication. Thirty minutes prior to IVIG administration, oral nonsteroid anti-inflamatory agent (acetaminophen 15 mg/kg), antihistaminic agent (Benadryl 1mg/kg) or one hour prior to infusion intravenous hydrocortisone (6 mg/kg) should be administered [8,24].

13. Subcutaneos immunoglobulin

As an alternative to intravenous immunoglobulin treatment, immunoglobulins can be administered subcutaneously to patients with primary immunodeficiencies, Subcutaneous infusion of IgG was introduced more than 20 years ago but has gained ground in recent

years [29,30,58-64]. Three ready-to-use liquid preparations of human IgG specifically formulated for subcutaneous infusions have been lisenced in US (Table 7). It can be stored at a temperature up to 25°C.

Product	Manufacturer	Dosage form	Sodium Content	Stabilizing agent /PH	Antimicrobial processes	IgA µg/mL	Osmolarity mOsm/kg
Gammagard S/D10%	Baxter Corporation	10% liquid <40 kg:20 mL/hr/site >40 kg:30 mL/hr/site	none	glycine PH 4.85	Cohn-Oncley fractionation, Ion exchange chromotography, 35 nmNanofiltration, Solvent-detergen, pH 4, elevated temperature incubation	37	240-300
Hizentra	BayerC CSL Behring CSL Behring	20% Liquid	Trace <10mmol/L	pH4.6-5.2	Cold alcohol fractionation, Octonic acid fractionation Anion exchange chromatography,Depth filtration Nanofiltration, pH4.0incubation TSE reduction steps include; Octonic acid fractionation, Depth filtration and virus filtration	<50	380
Vivaglobulin	CSL Behring	16% liquid	3mg/mL	none	Cold alcohol fractionation, Ethanol-fatty alcohol/pH precipitation, pasteurization, Diafiltered and ultrafiltered	<1700 µg/mL	445

Table 7. Commercial subcutaneous IG Products(Immune deficiency Foundation, October 2011)

The infusion can be applied through fine butterfly needles under the skin into the abdomen or thighs. Infusion pumps are used to administer the infusions and usually take 45 to 90 minutes. The amount of fluid given weekly to babies and children is 10 mls per site and 30 mls per site for older children. Subcutaneous infusion of 10-20% immunoglobulin, with the rate of 0.05-0.20 ml/kg/hour is advised. The recommended maintenance dose is 100 mg/kg/week. Immunoglobulin trough levels should be >5 g/L for patients with agammaglobulinaemia and 3 g/L greater than the initial IgG level for patients with CVID; however, the clinical response should be consider in choosing the dose and trough level [24]. Parents and patients can be educated on how to infuse the preparation at home. These infusions are better tolerated compared to IVIG and time sparing (home administration). Subcutaneous infusions are recommended to patients who are small children or reactive to IVIG or have poor veins.

Bioavailability and pharmacokinetics properties of subcutaneous IgG (SCIG) differs from intravenous IgG (IVIG). There are still debates about how the dose should be adjusted when

switching from IVIG to SCIG. Berger M et al reported that the doses that will yield desired serum levels for IVIG and SCIG may be estimated with the help of pharmacokinetic studies [8]. Area under the curve (AUC) of serum IgG versus time and trough level ratios (TLRs) on SCIG/IVIG were evaluated as guides for adjusting the dose. The mean dose adjustments required for non-inferior AUCs with 2 different SCIG preparations were 137% (± 12%) and 153% (± 16%). However, there were wide variations between adjustments required by different subjects, and in the resulting TLRs. Recent studies allow estimation of the ratio of IgG levels with different dose adjustments, and of the steady state serum levels with different SCIG doses [8]. When switching a patient from IVIG to SCIG, practising immunologist can tailor the dosage based on measured serum IgG levels and the clinical response Skoda-Smith S et al recommended a sample calculation process for converting from IVIG to subcutaneous IG, thus weekly dose for subcutaneous Ig should calculate as 1.37 X IVIg dose [65].

Safety and therapeutic efficacy of subcutaneous immunoglobulin products has been demonstrated in children and pregnant women. Therapeutic efficacy of intravenous or subcutaneous immunoglobulin treatment in reducing infections was equal [5,28,57,65,66]. In an international study performed by Chapel et al. the efficacy of immunoglobulin replacement therapy given via intravenously or subcutaneously in patients with PAD was compared [60]. Forty patients received subcutaneous or intravenous immunoglobulin for the first year and switched to the alternative treatment in the second year, and the study showed that there was no difference in efficacy and adverse reactions between both routes. In another study, Fasth A et al. used a 16%, ready-to-use human normal immunoglobulin solution subcutaneously in children with PID previously receiving regular IVIG treatment, and the study showed that mild injection reactions were the adverse effects of the treatment, and the rate of bacterial infections was not different between both IVIG treatments. In the at home treatment there were fewer missed school days, low healthcare expenses [62].

The cost effectiveness of the use of subcutaneous IG compared to IVIG therapy had been investigated in several studies [67,68]. The mean cost of both immunoglobulins was evaluated in the study performed by Beaute J et al. and they showed that monthly doses were equal for both routes of administration. In addition SCIG and IVIG (hospital-based) costs were also similar, but the costs may differ from one country to another [52]. Although this theoretical model showed little difference between the costs, SCIG seems to be expensive compared to IVIG due to the doses of immunoglobulin, but further studies are needed. Overall costs may be higher in CVID, because these patients need higher doses of immunoglobulin [21,52].

The SCIG home therapy was reported to give better health and improved school/social functioning for the children, reduced emotional distress and limitations on personal time for the parents and fewer limitations on family activities [58-64]. Pharmacokinetic studies reveal a more physiologic profile, in peak and trough levels of serum IgG [62,66]. Local tissue

reactions are more frequent but the systemic side effect profile is low. Local tissue reactions are often mild and tend to improve over time. Adults switching therapy reported improved vitality, mental health, and social functioning. Treatment satisfaction (TS) scores and health-related quality of life (HRQOL) was improved in adults and children with immunodeficiency [69].

According to ESID registry (http://www.esid.org), 4462 of 10,039 patients with PID receive IgG replacement (74% intravenous, 26% subcutaneous, <0.5% intramuscular). There is a wide variety of frequency of subcutaneous IgG replacement therapy in European countries. Sweden was the first country to deliver IgG via the SC route, therefore more than 80% of all patients with antibody deficiencies receive SCIg [3].

14. Conclusion

Replacement therapy with immunoglobulin either via intravenous or via subcutaneous is in patients with immunodeficiencies are associated with reduced infection frequency and organ damage and increased life expectancy. IVIG has been widely used in US and Europe for many years. Monthly IVIG treatment offered steady-state IgG level throughout the dosing cycle, dedicated viral inactivation steps improved safety concerns, pooled analyses confirmed the efficacy and safety, benefits of therapy and adverse events has been welll established.

Recent advances in the basic science of immunoglobulins and meta-analyses of patient data have provided new approaches in using polyclonal IgG to treat patients with primary immunodeficiencies. The old fashion subcutaneuos IG infusion reintroduced to treat patients with immunodeficiencies. The subcutaneous-IG therapy was reported to be effective, safe and well tolerated in children and adults. In addition, the SCIG home therapy high treatment satisfaction (TS) scores and health-related quality of life (HRQOL) was advantages of SCIG. Subcutaneous infusions are recommended to patients who are small children or reactive to IVIG or have problem with vascular access. Practicing immunologists can use new concepts in tailoring their approach to treat patients with primary immunodeficiencies.

Author details

Yıldız Camcıoğlu*
Istanbul University Cerrahpasa Medical School, Department of Pediatrics
Infectious Diseases, Clinical Immunology and Allergy Division, Cerrahpasa, Istanbul

15. References

[1]   Stiehm ER, Vaerman JP, Fudenberg HH. Plasma infusions in immunologic deficiency states: metabolic and therapeutic studies. *Blood*, 1966. 28(6): p. 918-937.

---

* Corresponding Author

[2]   Fischer A. Primary immune deficiencies of B-lymphocytes. *Rev Prat*, 1991. 41(9): p. 790-794.

[3]   Gathmann B, Binder N, Ehl S, Kindle G. The European internet-based patient and research database for primary immunodeficiencies: update 2011. *Clin Exp Immunol*. 167(3): p. 479-491.

[4]   Notarangelo LD. Primary immunodeficiencies. *J Allergy Clin Immunol*. 2010.125(2 Suppl 2): p. S182-194.

[5]   van der Burg M, van Zelm MC, Driessen GJ, van Dongen JJ. New frontiers of primary antibody deficiencies. *Cell Mol Life Sci*. 2012. 69(1): p. 59-73.

[6]   Driessen G, van der Burg M. Educational paper: primary antibody deficiencies. *Eur J Pediatr*. 2011.170(6): p. 693-702.

[7]   Cunningham-Rundles C, Intravenous immune serum globulin in immunodeficiency. *Vox Sang*, 1985. 49 Suppl 1: p. 8-14.

[8]   Berger M. Principles of and advances in immunoglobulin replacement therapy for primary immunodeficiency. *Immunol Allergy Clin North Am*, 2008. 28(2): p. 413-437.

[9]   Thampakkul S. Replacement intravenous immune serum immunoglobulin therapy in patients with antibody immune deficiency. *Immunol Allergy Clin North America*, 2001. 21(1): p. 165-184.

[10] Wood P, Stanworth S, Burton J, Jones A, Peckham DG, Green T, Hyde C, Chapel H. Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review. *Clin Exp Immunol*, 2007. 149(3): p. 410-423.

[11] Lee ML, Gale RP, Yap PL. Use of intravenous immunoglobulin to prevent or treat infections in persons with immune deficiency. *Annu Rev Med*, 1997. 48: p. 93-102.

[12] Fontan G, Garcia MC, Pascual-Salcedo D, Lopez Trascasa M, Alvarez-Doforno R, Ferreira A. (New indications for gamma globulins). *An Esp Pediatr*, 1992. 36 Suppl 48: p. 135-138.

[13] Lemieux R, Bazin RNeron S. Therapeutic intravenous immunoglobulins. *Mol Immunol*, 2005. 42(7): p. 839-848.

[14] Imbach P, *Morell A*. Idiopathic thrombocytopenic purpura (ITP): immunomodulation by intravenous immunoglobulin (IVIg). *Int Rev Immunol*. 1989; 5(2):181-8.

[15] Abe TKawasugi K, Use of intravenous immunoglobulin in various medical conditions. A Japanese experience. *Cancer*, 1991. 68(6 Suppl): p. 1454-1459.

[16] Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, Buckley R, Chinen J, El-Gamal Y, Mazer BD, Nelson RP, Jr., Patel DD, Secord E, Sorensen RU. Wasserman RLCunningham-Rundles C, Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol*, 2006. 117(4 Suppl): p. S525-553.

[17] Yong PL, Boyle J, Ballow M, Boyle M, Berger M, Bleesing J, Bonilla FA, Chinen J, Cunninghamm-Rundles C, Fuleihan R, Nelson L, Wasserman RL, Williams KC, Orange JS. Use of intravenous immunoglobulin and adjunctive therapies in the

treatment of primary immunodeficiencies: A working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology. *Clin Immunol*.2010. 135(2): p. 255-263.

[18] Casanova JL. (Genetic predisposition to infectious diseases: identification of new genetic immunodeficiencies). *Bull Mem Acad R Med Belg*, 2004. 159(1-2): p. 132-136.

[19] Cohn EJ, Strong LE et al. Preparation and properties of serum and plasma proteins; a system for the separation into fractions of the protein and lipoprotein components of biological tissues and fluids. *J Am Chem Soc*, 1946. 68: p. 459-475.

[20] Bruton OC. Agammaglobulinemia. *Pediatrics*, 1952. 9(6): p. 722-728.

[21] Hooper JA. Intravenous immunoglobulins: evolution of commercial IVIG preparations. *Immunol Allergy Clin North Am*, 2008. 28(4): p. 765-778.

[22] Schwartz SA. Intravenous immunoglobulin treatment of immunodeficiency disorders. *Pediatr Clin North Am*, 2000. 47(6): p. 1355-1369.

[23] Maarschalk-Ellerbroek LJ, Hoepelman IM, Ellerbroek PM. Immunoglobulin treatment in primary antibody deficiency. *Int J Antimicrob Agents*. 2011. 37(5): p. 396-404.

[24] Hoernes M, Seger R, Reichenbach J. Modern management of primary B-cell immunodeficiencies. *Pediatr Allergy Immunol*.2011. 22(8): p. 758-769.

[25] Quinti I, Soresina A, Guerra A, Rondelli R, Spadaro G, Agostini C, Milito C, Trombetta AC, Visentini M, Martini H, Plebani A, Fiorilli M. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. *J Clin Immunol*.2011. 31(3): p. 315-322.

[26] Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med*, 2001. 345(10): p. 747-755.

[27] Berkman SA, Lee ML, Gale RP, Clinical uses of intravenous immunoglobulins. *Ann Intern Med*, 1990. 112(4): p. 278-292.

[28] Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol*, 1999. 92(1): p. 34-48.

[29] Gardulf A, Hammarstrom L, Smith CI. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. *Lancet*, 1991. 338(8760): p. 162-166.

[30] Stiehm ER, Casillas AM, Finkelstein JZ, Gallagher KT, Groncy PM, Kobayashi RH, Oleske JM, Roberts RL, Sandberg ET, Wakim ME. Slow subcutaneous human intravenous immunoglobulin in the treatment of antibody immunodeficiency: use of an old method with a new product. *J Allergy Clin Immunol*, 1998. 101(6 Pt 1): p. 848-849.

[31] Teschner W, Butterweck HA, Auer W. Muchitsch EM, Weber A, Liu SL, Wah PS, Schwarz HP, A new liquid, intravenous immunoglobulin product (IGIV 10%) highly purified by a state-of-the-art process. *Vox Sang*, 2007. 92(1): p. 42-55.

[32] Roifman CM, Schroeder H, Berger M, Sorensen R, Ballow M, Buckley RH, Gewurz A, Korenblat P, Sussman G, Lemm G. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary

immune deficiency. A randomized double-blind trial. *Int Immunopharmacol*, 2003. 3(9): p. 1325-1333.

[33] Ochs HD, Pinciaro PJ. Octagam 5%, an intravenous IgG product, is efficacious and well tolerated in subjects with primary immunodeficiency diseases. *J Clin Immunol*, 2004. 24(3): p. 309-314.

[34] van der Meer JW, van Beem RT, Robak T, Deptala A, Strengers PF. Efficacy and safety of a nanofiltered liquid intravenous immunoglobulin product in patients with primary immunodeficiency and idiopathic thrombocytopenic purpura. *Vox Sang*. 2011. 101(2): p. 138-146.

[35] Durandy A, Kaveri SV, Kuijpers TW, Basta M, Miescher S, Ravetch JV, Rieben R. Intravenous immunoglobulins-understanding properties and mechanisms. *Clin Exp Immunol*, 2009. 158 Suppl 1: p. 2-13.

[36] Ibanez C, Sune P, Fierro A, Rodriguez S, Lopez M, Alvarez A, De Gracia J, Montoro JB. Modulating effects of intravenous immunoglobulins on serum cytokine levels in patients with primary hypogammaglobulinemia. *BioDrugs*, 2005. 19(1): p. 59-65.

[37] Aschermann S, Lux A, Baerenwaldt A, Biburger M, Nimmerjahn F. The other side of immunoglobulin G: suppressor of inflammation. *Clin Exp Immunol*. 2010. 160(2): p. 161-167.

[38] Bayry J, Lacroix-Desmazes S, Carbonneil C, Misra N, Donkova V, Pashov A, Chevailler A, Mouthon L, Weill B, Bruneval P, Kazatchkine MDKaveri SV, Inhibition of maturation and function of dendritic cells by intravenous immunoglobulin. *Blood*, 2003. 101(2): p. 758-765.

[39] Scott-Taylor TH, Green MR, Eren E, Webster AD. Monocyte derived dendritic cell responses in common variable immunodeficiency. *Clin Exp Immunol*, 2004. 138(3): p. 484-490.

[40] Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A. Hammarstrom L, Nonoyama S, Ochs HD, Puck JM, Roifman C, Seger R, Wedgwood J. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. *J Allergy Clin Immunol*, 2007. 120(4): p. 776-794.

[41] Ballow M, Notarangelo L, Grimbacher B, Cunningham-Rundles C, Stein M, Helbert M, Gathmann B, Kindle G, Knight AK, Ochs HD, Sullivan KFranco JL, Immunodeficiencies. *Clin Exp Immunol*, 2009. 158 Suppl 1: p. 14-22.

[42] Chapel HCunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. *Br J Haematol*, 2009. 145(6): p. 709-727.

[43] Bayrakci B, Ersoy F, Sanal O, Kilic S, Metin A, Tezcan I. The efficacy of immunoglobulin replacement therapy in the long-term follow-up of the B-cell deficiencies (XLA, HIM, CVID). *Turk J Pediatr*, 2005. 47(3): p. 239-246.

[44] Baris S, Ercan H, Cagan HH, Ozen A, Karakoc-Aydiner E, Ozdemir C, Bahceciler NN. Efficacy of intravenous immunoglobulin treatment in children with common variable immunodeficiency. *J Investig Allergol Clin Immunol*. 2011. 21(7): p. 514-521.

[45] Plebani A, Soresina A, Rondelli R, Amato GM, Azzari C, Cardinale F, Cazzola G, Consolini R, De Mattia D, Dell'Erba G, Duse M, Fiorini M, Martino S, Martire B, Masi M, Monafo V, Moschese V, Notarangelo LD, Orlandi P, Panei P, Pession A, Pietrogrande MC, Pignata C, Quinti I, Ragno V, Rossi P, Sciotto A, Stabile A. Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicenter study. *Clin Immunol*, 2002. 104(3): p. 221-230.

[46] Quartier P, Debre M, De Blic J, de Sauverzac R, Sayegh N, Jabado N, Haddad E, Blanche S, Casanova JL, Smith CI, Le Deist F, de Saint Basile G, Fischer A. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr*, 1999. 134(5): p. 589-596.

[47] Kaveri SV, Maddur MS, Hegde P, Lacroix-Desmazes S, Bayry J. Intravenous immunoglobulins in immunodeficiencies: more than mere replacement therapy. *Clin Exp Immunol*.2011. 164 Suppl 2: p. 2-5.

[48] Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J Allergy Clin Immunol*, 2002. 109(6): p. 1001-1004.

[49] Misbah S, Kuijpers T, van der Heijden J, Grimbacher B, Guzman D, Orange J. Bringing immunoglobulin knowledge up to date: how should we treat today? *Clin Exp Immunol*. 2011. 166(1): p. 16-25.

[50] Bjorkander J, Hammarstrom L, Smith CI, Buckley RH, Cunningham-Rundles C, Hanson LA. Immunoglobulin prophylaxis in patients with antibody deficiency syndromes and anti-IgA antibodies. *J Clin Immunol*, 1987. 7(1): p. 8-15.

[51] Cunningham-Rundles C. Lung disease, antibodies and other unresolved issues in immune globulin therapy for antibody deficiency. *Clin Exp Immunol*, 2009. 157 Suppl 1: p. 12-16.

[52] Beaute J, Levy P, Millet V, Debre M, Dudoit Y, Le Mignot L, Tajahmady A, Thomas C, Suarez F, Pellier I, Hermine O, Aladjidi N, Mahlaoui N, Fischer A. Economic evaluation of immunoglobulin replacement in patients with primary antibody deficiencies. *Clin Exp Immunol*. 2011.160(2): p. 240-245.

[53] Ballow M. Safety of IGIV therapy and infusion-related adverse events. *Immunol Res*, 2007. 38(1-3): p. 122-132.

[54] Baxley A, Akhtari M. Hematologic toxicities associated with intravenous immunoglobulin therapy. *Int Immunopharmacol*. 2011. 11(11): p. 1663-1667.

[55] Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev*, 2003. 17(4): p. 241-251.

[56] Ochs HD, Fischer SH, Wedgwood RJ, Wara DW, Cowan MJ, Ammann AJ, Saxon A, Budinger MD, Allred RU, Rousell RH. Comparison of high-dose and low-dose

intravenous immunoglobulin therapy in patients with primary immunodeficiency diseases. *Am J Med*, 1984. 76(3A): p. 78-82.

[57] Pautard B, Hachulla E, Bagot d'Arc M, Chantreuil L. (Intravenous immunoglobulin (Endobulin) clinical tolerance: prospective therapeutic follow-up of 142 adults and children). *Rev Med Interne*, 2003. 24(8): p. 505-513.

[58] Bhole MV, Burton J, Chapel HM. Self-infusion programmes for immunoglobulin replacement at home: feasibility, safety and efficacy. *Immunol Allergy Clin North Am*, 2008. 28(4): p. 821-832.

[59] Jolles S, Sleasman JW. Subcutaneous immunoglobulin replacement therapy with Hizentra, the first 20% SCIG preparation: a practical approach. *Adv Ther*. 2011.28(7): p. 521-533.

[60] Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. *J Clin Immunol*, 2000. 20(2): p. 94-100.

[61] Ochs HD, Gupta S, Kiessling P, Nicolay U, Berger M. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol*, 2006. 26(3): p. 265-273.

[62] Fasth A, Nystrom J. Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency. *Acta Paediatr*, 2007. 96(10): p. 1474-1478.

[63] Gustafson R, Gardulf A, Hansen S, Leibl H, Engl W, Linden M, Muller A, Hammarstrom L, Rapid subcutaneous immunoglobulin administration every second week results in high and stable serum immunoglobulin G levels in patients with primary antibody deficiencies. *Clin Exp Immunol*, 2008. 152(2): p. 274-279.

[64] Gardulf A, Nicolay U, Asensio O, Bernatowska E, Bock A, Carvalho BC, Granert C, Haag S, Hernandez D, Kiessling P, Kus J, Pons J, Niehues T, Schmidt S, Schulze I, Borte M. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies--a prospective, multi-national study. *J Clin Immunol*, 2006. 26(2): p. 177-185.

[65] Skoda-Smith S, Torgerson TR, Ochs HD, Subcutaneous immunoglobulin replacement therapy in the treatment of patients with primary immunodeficiency disease. *Ther Clin Risk Manag*. 2010. 6: p. 1-10.

[66] Berger M, Rojavin M, Kiessling P, Zenker O. Pharmacokinetics of subcutaneous immunoglobulin and their use in dosing of replacement therapy in patients with primary immunodeficiencies. *Clin Immunol*.2011. 139(2): p. 133-141.

[67] Haddad E, Berger M, Wang EC, Jones CA, Bexon M, Baggish JS. Higher doses of subcutaneous IgG reduce resource utilization in patients with primary immunodeficiency. *J Clin Immunol*.2012. 32(2): p. 281-289.

[68] Membe SK, Ho C, Cimon K, Morrison A, Kanani A, Roifman CM. Economic assessment of different modalities of immunoglobulin replacement therapy. *Immunol Allergy Clin North Am*, 2008. 28(4): p. 861-874, x.

[69] Gardulf A, Borte M, Ochs HD, Nicolay U. Prognostic factors for health-related quality of life in adults and children with primary antibody deficiencies receiving SCIG home therapy. *Clin Immunol*, 2008. 126(1): p. 81-88.