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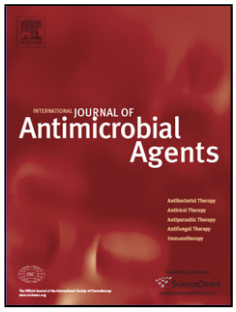

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Immunoglobulin treatment in primary antibody deficiency

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ABSTRACT

The primary antibody deficiency syndromes are characterised by recurrent respiratory tract infections and the inability to produce effective immunoglobulin (Ig) responses. The best known primary antibody deficiencies are common variable immunodeficiency (CVID), X-linked agammaglobulinaemia (XLA), immunoglobulin G (IgG) subclass deficiency, and selective antibody deficiency with normal immunoglobulins (SADNI). Therapy in these patients consists of prophylactic antibiotics and/or Ig replacement therapy. Diagnostic delay remains common owing to limited awareness of the presenting features and may result in increased morbidity and mortality. Replacement therapy with immunoglobulins increases life expectancy and reduces the frequency and severity of infections, but the effect on end-organ damage is still unknown. Both intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (SCIg) treatment appear to be safe, with comparable efficacy. A starting dose of 300–400 mg/kg/month in IVIg and 100 mg/week for SCIg is recommended. IgG 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 foremost in choosing the dose and trough level. Infusion-related adverse reactions are generally mild owing to improved manufacturing processes. In this paper, aspects of Ig replacement therapy in primary antibody-deficient patients will be addressed.

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1. Introduction

The primary antibody deficiency syndromes represent the largest group of primary immunodeficiencies. Multiple molecular defects have been identified in the pathways involved in B-cell development; in a US study, B-cell defects comprised 78% of primary immunodeficiencies [1].

Primary antibody deficiencies share the feature of recurrent upper and lower respiratory tract infections (RTIs) with encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, but other infections may also be associated with particular syndromes.

Common variable immunodeficiency (CVID) is the most common primary antibody deficiency. It is defined as the triad of recurrent respiratory (and/or gastrointestinal) infections, a reduction in immunoglobulin G (IgG) levels (total IgG >2 standard deviations below the mean for age), IgA and/or IgM levels, and a reduced antibody response to vaccination. CVID represents a heterogeneous disease spectrum that may also involve autoimmune phenomena, chronic granulomatous and inflammatory organ disease, and an increased risk of cancer. Diagnostic delay is very common, with a mean of 6–8 years after the onset of symptoms [2,3], but it can take as long as a decade before the appropriate diagnosis is made. The principal defect in CVID is a failure in B-cell differentiation leading to reduced serum immunoglobulin (Ig) levels and an abnormal antibody response [4]. Although some associated gene defects have been recognised to cause a disruption in B-cell differentiation and B-cell function (ICOS, TACI, CD19, BAFF-

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R, MSH5, CD20 and CD81) [5–7], in the majority of patients no genetic defect has yet been established. Approximately one-half of CVID patients also show abnormalities in the T-cell compartment [3,8].

X-linked agammaglobulinaemia (XLA) is a hereditary immunodeficiency [9] caused by mutations in the *BTK* gene, representing a tyrosine kinase that is important for B-cell development [10,11]. Patients present with recurrent bacterial infections at a very young age and a profound deficiency of all Ig isotypes resulting from an arrest in B-lymphocyte development in the bone marrow. Other features are chronic and unremitting systemic infections with enteroviruses [12,13], mycoplasma and ureaplasma as well as chronic gastroenteritis caused by rotaviruses and *Giardia lamblia* [10,14,15]. Furthermore, a variety of malignancies have been reported, including lymphoreticular malignancies [15,16] and gastric and colorectal carcinoma [17–19]. In a few families, other gene mutations have been recognised involved in B-cell development that cause autosomal recessive congenital agammaglobulinaemia.

Other, more frequent, antibody deficiencies are IgG subclass deficiency and selective antibody deficiency with normal immunoglobulins (SADNI). A clinically significant subclass deficiency is defined as reduced levels of one or more IgG subclasses (IgG1–4) in a patient with normal total IgG concentrations [20] and is characterised by recurrent sinopulmonary infections and inadequate response to vaccination. Subclass deficiency might merely be a laboratory finding in the absence of a clinical disorder; up to 20% of

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the population may have subnormal levels of one or more subclasses [21]. In adults, the most common deficiency is IgG3, whereas in children it is IgG2 [22].

SADNI is classified as recurrent sinopulmonary infections and an abnormal response to polysaccharide vaccination in the presence of normal antibody levels [23,24]. The prevalence of SADNI in two studies was 5–10% in children over 4 years of age who were referred with recurrent infections [25,26] and it was 8% in adult patients with recurrent pneumonia [27].

Other less frequent primary antibody deficiencies are the hyper-IgM syndromes, IgA deficiency and selective IgM deficiency.

The mainstay of therapy for patients with primary antibody deficiency is the use of prophylactic antibiotics and/or Ig replacement therapy in order to reduce the infection rate and end-organ damage. The most important complication of recurrent respiratory infections in antibody deficiency is the development of bronchiectasis, which may lead to chronic pulmonary disease (CPD). Diagnostic and treatment delay has been related to higher morbidity and subsequent reduced pulmonary function [14,28–31]. It is therefore important to establish the diagnosis early in order to initiate appropriate treatment and to prevent irreversible end-organ damage.

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2. Immunoglobulin replacement therapy

2.1. Historical perspective

Human Ig therapy for antibody deficiency was initiated by Bruton following his description of the first case of XLA in 1952 [9]. The initial route of Ig administration was intramuscular (IMIg). In the USA, human intravenous immunoglobulin (IVIg) was first licensed for primary antibody deficiencies in 1981. This product was a less painful alternative and allowed administration of much larger volumes with fewer side effects [32,33]. Since that time, more purified and better tolerated IgG preparations have become available [32]. At the same time, subcutaneous IgG (SCIg) therapy became available [34,35]. Initially, SCIg infusion was limited by the (slow) infusion rate, although this has improved over the years [36–39]. However, IVIg still remains the dominant form of Ig replacement therapy in the USA and Europe.

2.2. Production and content of immunoglobulins

Multiple safety steps are undertaken to provide a safe, pure and efficient product that contains antibodies against a wide range of pathogens. Many blood-borne pathogens, such as human immunodeficiency virus (HIV), hepatitis C virus, parvovirus B19, West Nile virus and prions, have been recognised to constitute a danger for patients treated with immunoglobulins. In the mid 1990s an outbreak of hepatitis C occurred in Europe and was associated with Ig therapy [40–43]. Specific methods have been developed to assure maximal removal of pathogens [44], including donor screening for HIV and hepatitis B and C virus, detergent and solvent treatment, virus inactivation, destruction

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and removal steps such as pasteurisation at 60 °C, treatment with low pH/alcohol, and nanofiltration. However, a small risk of transmission of blood-borne diseases remains.

All available Ig products contain >95% IgG with all IgG subclasses represented. Most products contain no IgM and very small amounts of IgA. IgM is removed because it can rapidly form large complexes leading to a variety of adverse reactions. CVID patients frequently develop anti-IgA antibodies that may provoke anaphylactic reactions to IgA-containing blood products. Various strategies are used to remove all traces of donor IgA molecules [45,46], and minor differences in IgA levels exist between the current products.

IgG1 and IgG2 make up 85% of the total amount of IVIg, whereas IgG3 and IgG4 are minor components (5–8% and 1–5%, respectively). The repertoire of immune antibodies is thought to reflect the infectiological experience of the donor population. To best cover the needs of patients, it is believed that Ig therapy is optimal when the recipient belongs to the same population as the donors [45,46].

2.3. Effect of IgG replacement therapy on infections and end-organ damage

2.3.1. Morbidity and mortality

The life expectancy of patients with XLA and CVID was very poor before the era of Ig replacement therapy. In 1971, the 10-year survival rate was 37% in 201 CVID patients treated with IMIg [47]. Few, if any, XLA patients survived past early childhood before

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antibiotic and Ig therapy became available [48]. In one study, ca. 75% of 170 XLA patients diagnosed before the introduction of IVIg had developed chronic lung disease at the age of 20 years, 5–10% had developed a cor pulmonale and 18% had died, mostly due to infectious complications [49]. Owing to early diagnosis, more effective treatment with Ig and more liberal use of antibiotics, survival of patients with an antibody deficiency has significantly improved over the last decade [47,50]. A study of 248 CVID patients receiving IVIg therapy reported a 10-year survival of 78% compared with 97% in the general population [3].

However, despite IgG therapy, patients with complications due to inflammatory autoimmune diseases and neoplasms still have a shorter life expectancy [50]. Diagnostic delay is a major concern and the main cause of the development of organ damage. In a 2005 review of 89 patients with a primary antibody deficiency, the median diagnostic delay was 2 years (mean 4.4 years), resulting in substantial morbidity [29]. A moderate improvement had been achieved compared with an earlier 1980s study that showed a median delay of 5.5 years in adults and 2.5 years in children [48].

2.3.2. Benefit in acute respiratory infections

A strong body of evidence has demonstrated the efficacy of Ig therapy in CVID and XLA patients. The studies are listed in Table 1. Although sample sizes are small and most of the studies are retrospective case series, it is clear that Ig therapy reduces the incidence and severity of infections, the rate of hospitalisation and the use of antibiotics, albeit at variable doses and variable follow-up periods in these studies.

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Scarce evidence supports Ig replacement in IgG subclass deficiency or SADNI patients. Ig replacement may be appropriate if prophylactic antibiotics do not result in fewer infections. In a retrospective study, patients with a selective or combined IgG subclass deficiency with four or more episodes of bacterial RTIs per year were treated with IVIg 0.4 mg/kg/month, which led to a 50% reduction in antibiotic-demanding (i.e. presumably bacterial) infections in 70% of patients ($P < 0.001$) [66].

In an open-label study [67], 10 adult patients with symptomatic IgG subclass deficiency were treated with monthly IVIg for 1 year followed by 3 months of observation off IVIg therapy. All patients showed a significant reduction in the number of infections, days of antibiotic usage and hospitalisations during the 12 months of IVIg. The benefit of IgG replacement in patients with SADNI has not been evaluated in randomised, placebo-controlled trials, however uncontrolled series of paediatric SADNI patients have consistently reported significant decreases in the number of infections [68].

2.3.3. Benefit in chronic respiratory disease and end-organ damage

Few studies have evaluated the effect of Ig treatment on the evolution of chronic sinopulmonary disease and pulmonary damage such as bronchiectasis. In a prospective study [61] of 24 previously untreated adult CVID patients, the effect of IVIg on the evolution of lung damage was evaluated 2 years after stable trough levels of IgG > 6 g/L were achieved. To achieve the desired trough levels, patients with CPD needed higher doses of IVIg than those without CPD (285 ± 53 mg/kg/21 days vs. 222 ± 23 mg/kg/21

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days; *P* = 0.002). Some pulmonary improvement was demonstrated in patients with CPD, as the forced expiratory volume in 1 s (FEV_1) as a percentage of the predicted value rose from 54 ± 13% (range 26–67%) to 61 ± 13% (range 35–76%) (*P* = 0.004) and overall high-resolution computed tomography scores improved in patients with CPD, which was attributable to the reduction in bronchiectasis and signs of inflammation. The median IgG trough level in the CPD group was 7.2 ± 1.4 g/L (range 5.7–9.8 g/L) and in the group without CPD it was 8.5 ± 1.6 g/L (range 6.0–11.6 g/L). A recent study [69] confirmed that CVID patients with bronchiectasis need higher replacement doses to achieve similar IgG trough levels (0.70 ± 0.29 g/kg/month vs. 0.53 ± 0.20 g/kg/month).

In contrast, a prospective study in 22 patients receiving IVIg treatment showed progression of pulmonary changes in one-half of the patients after a 3-year follow-up [30]. In another multicentre prospective study [70] of 224 CVID patients, the number of patients with CPD and chronic sinusitis also increased over 11.5 years despite IVIg treatment and despite the significant reduction in the percentage of patients who were affected by acute respiratory infections.

In conclusion, the beneficial effect of Ig replacement therapy on short-term respiratory complications (acute respiratory infection rate and antibiotic usage) is undisputable, but conflicting evidence exists on the beneficial effect on long-term complications.

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2.3.4. Benefit in gastrointestinal disease

Non-infectious inflammatory disease of the gut is common in patients with primary antibody deficiencies. Many of the inflammatory disorders mimic the classic forms of the disease (in the absence of immunodeficiency) such as coeliac disease, inflammatory bowel disease and pernicious anaemia [3,48,71–74], but differ in the pathogenesis and are unresponsive to Ig treatment. Different explanations may justify the occurrence of these conditions in patients with antibody deficiencies despite appropriate Ig replacement therapy. First, IVIg therapy only substitutes IgG, whilst IgA (the major secretory antibody at mucosal surfaces) is not replaced. Other possible explanations could be ongoing inflammation after treated infections [75] and concurrent T-cell defects [3,75].

At this time, treatment for gastrointestinal disease associated with antibody deficiencies is based on treatment modalities used for similar disorders in immunocompetent patients [76–78].

2.4. Indications for IgG replacement therapy

The most obvious justification for Ig therapy is the absence of functionally mature B-cells, as in XLA patients. Another clear ground for IgG replacement is reduced levels of serum Ig in patients with recurrent bacterial infections.

In general, Ig replacement therapy is indicated in (i) patients with IgG levels <2 g/L, (ii) patients with documented frequent infections and a specific antibody deficiency with IgG

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levels between 2 g/L and 5 g/L or (iii) patients with IgG levels >5 g/L but severe and recurrent infections and a specific antibody deficiency [79].

In asymptomatic individuals with subclass deficiencies, Ig replacement therapy is not warranted. It is advisable to follow these patients, as some might evolve into CVID [80]. Patients with an IgG subclass deficiency or SADNI who suffer from severe or recurrent RTIs despite prophylactic antibiotics are candidates for Ig therapy [66,67].

Although scarce evidence exists, treatment of patients with an IgG subclass deficiency and/or poor response to polysaccharide vaccines might include vaccination with pneumococcal conjugate vaccine [81]. IgG replacement might be appropriate for selected SADNI patients with recurrent infections despite immunisation with conjugate vaccines and appropriate antibiotic treatment. Additional grounds for IgG replacement might be uncontrollable recurrent otitis media with risk for permanent hearing loss, the presence of bronchiectasis, and patients with hypersensitivity to multiple antibiotics.

Lastly, management of other conditions predisposing to recurrent sinopulmonary infections such as asthma and allergic rhinitis is warranted.

2.5. Choice of product and administration route

The efficacy and safety of IVIg [79,82,83] and SCIg [36,84,85] has been well established. Both treatment options appear to be safe, with comparative efficacy and costs. Two small comparative studies showed no significant difference in the rate of

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infections, adverse events [86] or IgG steady-state levels [36] between the two treatment modalities.

The benefits of weekly SCIg infusions over 3-weekly IVIg therapy include stable IgG levels, less frequent and less severe systemic side effects [34,37–39,85], no necessity for venous access and more flexibility in the patient's social life. A disadvantage of SCIg is the limitation in volume that can be administered, prompting weekly infusions.

Many centres provide training in SCIg and IVIg home therapy, which has clear benefits for patients, such as increased lifestyle flexibility and taking control of the management of their disease [87–89].

The choice of product must be individualised for each patient and will be based on the clinical condition of the patient, the patient's wishes and the side effects. Patient-related factors that influence this choice are age, cardiovascular impairment, renal dysfunction, thromboembolic risk, and the presence of (pre) diabetes mellitus and anti-IgA antibodies. The product features that affect clinical tolerability are listed in Table 2.

The difference in tolerance to the various Ig products in individual patients is striking and unpredictable and is probably caused by the spectrum and concentration of antibodies and other plasma proteins. For elderly patients and patients with congestive heart failure, concentrated IgG products (10%) and products with a lower sodium content might be more suitable [91]. Sodium content has also been associated with a higher

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incidence of thromboembolic complications and could thus be a further restricting factor [92]. Various sugars have been added to the different IgG products (sorbitol, glucose, sucrose or maltose) to minimise IgG aggregate formation. Although concentrations are not particularly high, they may lead to deregulation of glucose levels in diabetic patients. Sucrose has also been associated with renal failure due to osmotic nephritis [93]. Risk factors associated with renal adverse events include pre-existing renal disease, diabetes, hypovolaemia, sepsis, age (≥65 years) and concomitant nephrotoxic therapy [92].

The therapeutic strategy of IgG replacement in patients with anti-IgA antibodies is a critical issue. It has been demonstrated that patients with IgA antibodies can be treated more safely with SCIg [94,95]. SCIg might induce tolerance by gradual exposure to IgA owing to the slow resorption of the subcutaneous deposit of Ig [96].

2.6. Dosing regimen and trough levels

The major goal of Ig replacement therapy in patients with primary antibody deficiency is to reduce and prevent morbidity, such as infection rate and end-organ damage, and mortality.

The appropriate dose of Ig for antibody-deficient patients is determined by the IgG trough level, the median half-life of IgG and the intrinsic metabolism of the patient. However, the pharmacokinetics of IVIg shows considerable intrapersonal and

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interpersonal variability, and the patient's intrinsic IgG production will interfere with measurements of half-life and clearance.

It has been demonstrated that serum IgG levels initially decline rapidly following intravenous infusion and by Day 7 a substantial part of the infused Ig has disappeared [97,98], followed by a period of more gradual decline to baseline depending on the metabolic rate of the patient and the half-life of the preparation. Using radiolabelled IgG it has been shown that the catabolism of IgG follows multicompartmental first-order kinetics. After an initial period of equilibrium between intravascular and extravascular compartments, the concentration of IgG in the serum is eliminated at a rate independent of the remaining concentration [99].

The mean half-life of IgG is 25–32 days in patients with a primary immunodeficiency, however in patients with extremely low baseline levels of IgG the variations in half-life are greater [97,100].

In contrast to IVIg, weekly subcutaneous infusions of IgG will generate a local depot resulting in slow absorption and a nearly constant serum level of IgG.

Ig dosing is more complex in patients in whom IgG production is deficient but not completely absent such as in CVID, subclass deficiency or SADNI. In patients with high baseline serum IgG concentrations (>5 g/L), the half life of IgG tends to be the longest,

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suggesting that intrinsic IgG production might prolong the calculated half-life of IgG, leading to an incorrect estimate of the half-life [99].

Another important parameter in determining the dose of replacement therapy is the clinical condition of the patient in relation to the IgG trough level.

Several studies have compared the effect of dosage and IgG trough levels in patients with a primary humoral immunodeficiency (see Table 3). These studies are difficult to compare as they are heterogeneous with regard to methodology, routes of administration (IMIg, SCIg and IVIg) and study populations. Furthermore, the studies are limited by sample size and follow-up. None the less, the majority of these studies show that higher Ig dosage and IgG trough levels result in fewer infections and a reduced duration of the remaining disease episode [52,53,56–58,62,64,101,102]. The exact IgG trough level that will protect antibody-deficient patients against recurrent bacterial infection and progression to chronic lung damage remains uncertain. Long-term outcome parameters such as structural organ damage are difficult to follow; IgG trough levels are thus used as surrogate parameters. The majority of studies show a significant reduction in infection rates with a higher IgG trough level, especially >8 g/L [58]. A recent meta-analysis showed that the incidence of pneumonia declined by 27% with each 1 g/L increment in IgG trough level. The incidence of pneumonia with a trough level of 5 g/L was 0.113 cases/patient-year versus 0.023 cases/patient-year with a trough level of 10 g/L [103].

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Furthermore, a recent study supports the idea of individualising the replacement dose. In this prospective cohort study, 107 CVID and XLA patients showed a wide range of IgG trough levels preventive of breakthrough bacterial infections (5–17 g/L) with a replacement dose ranging from 0.2 g/kg/month to 1.2 g/kg/month [69].

Based on various studies, a 2006 review by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology [104] recommends that IgG 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. Furthermore, an IgG trough level of >5 g/L reduces the infection rate, and IgG trough levels >8 g/L might improve chronic pulmonary outcome [52,53,56–58,62,64,101,102].

IVIg is administered every 3–4 weeks with a usual starting dose of 0.4 g/kg for patients without chronic lung disease and 0.6 g/kg for patients with bronchiectasis. SCIg dosing is the same but divided over 4 weeks. Given the costs involved, leading factors in choosing the dosing regimen are the clinical parameters of an individual patient in combination with trough levels.

Dosage adjustments are required in exceptional situations such as acute illness, before/after surgery and pregnancy [105]. No specific protocols for pregnant women have been published. Replacement therapy is not only necessary for the mother but also for the foetus. The foetus and the newborn synthesise little Ig and rely on active placental transport of IgG from the maternal circulation [105–110]. During pregnancy,

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the increase in blood volume can cause inadequate IgG trough levels, which may lead to an increased infection rate. IgG trough levels should be checked more often during pregnancy and breastfeeding to make sure that they remain adequate, and the patient must be informed about the importance of these measures. A study from 2001 showed that normal maternal IgG and IgG subclass concentrations can also be achieved by the SCIg route [111].

2.7. Risks and adverse reactions of immunoglobulin therapy

2.7.1. Intravenous immunoglobulin

Although in general IVIg is well tolerated by patients with an antibody deficiency, side effects can occur at any point during treatment and are mostly related to the infusion rate. Patients who are naïve to IgG replacement or who have active infections have an increased risk of infusion-related adverse effects. These effects may be related, in part, to the formation of antigen–antibody complexes [79]. Factors that potentially affect the risk and intensity of adverse events include age and underlying conditions, such as migraine and cardiovascular or renal disease.

Infusion-related adverse events can be immediate (during the infusion), delayed (hours to days after the infusion) or late reactions. Immediate reactions can be either true IgE-mediated anaphylaxis or ‘anaphylactic’ reactions. The difference is that the latter is associated with hypertension rather than hypotension. True anaphylaxis may occur in patients who are deficient in IgA but still have the capacity to produce IgE [112].

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The most common reaction is an immediate adverse event related to the infusion rate. Mild reactions include headache, flushing, chills, fever, nausea, anxiety and muscle aches. Moderate reactions consist of chest pain, wheezing and vomiting, and severe reactions are severe headaches, chest pain and wheezing. Slowing or temporarily stopping the infusion may allow the symptoms to subside. Infusion can then be continued at the previously tolerated rate. If this fails to prevent symptoms, pre-medication with antipyretics, antihistamines and/or corticosteroids may help to treat the symptoms. When symptoms persist or rapidly worsen, immediate discontinuation of the infusion and administration of adrenaline may be warranted [79].

Overall, the risk of infusion-related events has been reduced owing to improved manufacturing processes. In a large prospective study of 459 antibody-deficient patients with 13 508 infusions, the reaction rate was 0.8% over 2 years (111 events, comprising 91 mild and 20 moderate); no severe reactions occurred (0.1% were moderate and 0.6% were mild). The most important symptoms were headaches, chills and fever and most of the reactions occurred during higher infusion rates. Most reactions occurred in patients with an active infection (5.1%) [113].

In another retrospective study (71 patients, 1231 infusions), 152 adverse events (12.3%) occurred in 35 patients, of which 131 events were mild (86.2%) and no severe reactions occurred. Again, most adverse events were related to the infusion rate and active infections [114].

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The most common immediate side effect of IVIg therapy is a headache that may last for several days. The reported incidence was as high as 56% in one study [115]. Often, patients who experience headaches during infusion have a history of migraine or hypertension. In the latter it may be prevented by taking an extra dose of blood pressure medication before the infusion. Non-steroidal anti-inflammatory drugs (NSAIDs) may also be effective in case of minor headaches. It is proposed that headaches can be prevented by slowing the infusion rate [116] or reducing the total dose of IVIg [117]. In general, many patients develop headaches only during the first few cycles of IVIg therapy [117].

Urticarial reactions are common during IVIg and might be minimised by pre-medication with antihistamine or low-dose corticosteroids. A low-grade fever often occurs during infusion, which can be prevented by antipyretics.

Delayed symptoms consist of nausea, malaise and myalgia and typically occur 1–3 days after administration of IVIg.

Late adverse events are rare but can be severe and unpredictable as they can occur after months or years of uneventful therapy. They have mainly been reported with the higher dosing regimens used for treatment of autoimmune and haematological disorders. The most important late side effects are acute renal failure and thromboembolic events [118]. Other late adverse events include aseptic meningitis, stroke [119], progressive neurodegeneration [120], neutropenia, autoimmune haemolytic

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anaemia, skin reactions and (rarely) arthritis and pseudohyponatremia. A thorough and complete medical evaluation of each patient is warranted before initiation of therapy to identify risk factors associated with severe side effects. Less than 5% of the reported cases of IVIg-associated renal insufficiency occurred in patients with primary immune deficiency [121]. Acute renal failure is usually oliguric and reversible and has been related to osmotic injury secondary to sucrose. The majority of cases of renal dysfunction occurred in the first 10 days after the first cycle of IVIg therapy [122–124]. Patient risk factors associated with renal adverse events include pre-existing renal disease, diabetes mellitus, hypovolaemia, sepsis, age (≥65 years) and concomitant nephrotoxic therapy [92].

2.7.2. Subcutaneous immunoglobulin

Serious systemic adverse events are rare in subcutaneous therapy. Common reactions due to SCIg therapy are local swelling, redness and an itching or burning sensation, occurring in 8–49% of infusions. These effects are rarely serious and disappear after several hours and are more common at initiation of treatment [36,85,86]. The safety of SCIg has been established in a study with 165 primary antibody-deficient patients [39]: 106 adverse systemic reactions were recorded during 33 168 subcutaneous infusions in 28 patients, of which 100 were mild and 6 were moderate. No severe or anaphylactic reactions occurred. In a randomised crossover trial of IVIg and SCIg treatment, the systemic reaction rate of IVIg therapy was 5% compared with a SCIg reaction rate of 3.3% [86]. However, most studies have reported <1% systemic events in SCIg therapy [125].

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3. Additional therapies

Infections in IgG-treated patients might indicate inadequate dosing and IgG trough levels. Patients who continue to have respiratory infections and develop CPD despite adequate IgG trough levels should be treated more aggressively by a strategy directed against the ongoing process of inflammation and infection, such as prophylactic antibiotics [126,127], macrolides (also as anti-inflammatory agents) [128], corticosteroid inhalation therapy [129], bronchodilators, mucolytic agents, and physical or mechanical aids for airway clearance. Serial sputum testing, including antibiotic sensitivity testing of the cultured organism, should direct prophylactic antibiotic therapy.

4. Conclusion

The primary antibody deficiency syndromes are characterised by an inability to produce clinically effective Ig responses. Patients most commonly present with recurrent respiratory infections. Diagnostic delay remains common owing to limited awareness of the presenting features. Diagnostic delay and subsequent delay in initiation of Ig replacement therapy can result in increased morbidity and mortality. Replacement therapy with Ig increases life expectancy and reduces the frequency and severity of infections. However, the effect on end-organ damage remains disputable.

Clear indications for IVIg replacement are the absence of functionally mature B-cells such as in patients with XLA, and, secondly, reduced levels of serum Ig in patients with

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recurrent bacterial infections such as CVID patients. In general, IgG replacement is indicated in (i) all patients with IgG levels <2 g/L, (ii) patients with documented frequent infections and a specific antibody deficiency with IgG levels between 2 g/L and 5 g/L and (iii) patients with IgG levels >5 g/L but severe and recurrent infections combined with a specific antibody deficiency [79].

Both IVIg and SCIg treatment appear to be safe, with comparable efficacy. Infusion-related adverse reactions have been reduced considerably in recent years owing to improved manufacturing processes. The advantages of SCIg are more stable IgG levels, the absence of serious systemic adverse events and more flexibility in the patient's social life.

The overall consensus is that (i) the starting dose of IVIg and SCIg should be 400 mg/kg/month and 100 mg/week, respectively, (ii) IgG 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 and, finally, (iii) the clinical response should be foremost in choosing the right dose and trough level.

Key areas for further research would be: to determine the optimal dose of Ig therapy required to improve overall health outcome; to develop infusion methods leading to improved and less frequent SCIg dosing (e.g. once in 2 or 3 weeks); and identification of prognostic markers to allow specific intervention and optimal therapy for subgroups of patients.

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Table 1

Efficacy of immunoglobulin therapy

Year	Patients	Type of study	*N*	Treatment regimen	Outcome
1979 [51]	Adults, children; CVID, XLA	RCT	20	IMIg 3.3 g/month vs. IVIg 150 mg/kg/month	0.3 vs. 0.1 infections/month
1984 [52]	Adults, children; CVID, XLA	PC	21	IVIg 300 mg/kg/3 weeks vs. previous IMIg	Less days of illness/antibiotic use ($P < 0.1$) for 18 of 21 patients, less sick days (total 834 days to 258 days), less days on antibiotics (total 3249 days to 1820 days)
1985 [53]	Adults; CVID, XLA	PC	7	IVIg 600 mg/kg/month vs. previous IMIg	Reduction in infection rate (25 vs. 4 per year)
1987 [54]	Children; antibody deficiency	CO	12	IVIg 150 mg/kg/month vs. 500 mg/kg/month crossover	Significant reductions in days with infections
1990 [55]	Children; antibody deficiency	RCS	23	IVIg 150–300 mg/kg/3 weeks vs. prior IMIg	75% less days of fever/antibiotics, 91% less hospital days, 50% less absence from school, 65% less days with infection ($P < 0.01$)

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1992 [56]	Adults, children; XLA	RCS	20	No treatment (1)	Reduction in hospitalisation ($P < 0.01$) and pneumonia ($P < 0.04$) in (4) vs. (1) and (2)
			14	IMIg <100 mg/kg/3 weeks (2)	
			3	IVIg up to 200 mg/kg/3 weeks (3)	
			15	IVIg 350–600 mg/kg/3 weeks (4)	
1999 [57]	Children; XLA	RCS	31	Mean dose 390 mg/kg/3 weeks	Reduction in annual bacterial infections during therapy (0.06 vs. 0.4) ($P < 0.01$)
2001 [58]	Adults, children; CVID, XLA	RCT CO	43	IVIg: adults, 300 mg/kg/month vs. 600 mg/kg/month	Mean infection rate: low-dose 3.5 ± 2.6/patient vs. high-dose 2.5 ± 2.4/patient ($P = 0.004$)
				Children, 400 mg/kg/month vs. 800 mg/kg/month	Mean duration of infections: low-dose 33 days vs. high-dose 21 days ($P = 0.015$)
2001 [59]	Adults, children; CVID	RCS	19	IVIg 300–600 mg/kg/3 weeks, trough IgG >4 g/L	0.28 vs. 0.16 RTIs/patient/year (before vs. after therapy) ($P < 0.01$)
2002 [60]	Adults, children; CVID	RCS	50	IVIg 300–400 mg/kg/3–4 weeks	Reduction in number of patients with pneumonia from 42 to 11 after treatment ($P < 0.01$)

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2004 [61]	Newly diagnosed adults; CVID	PC	24	IVIg 200–300 mg/kg/3–4 weeks	Serious infections [a] 1.3 ± 1.2/year to 0.2 ± 0.5/year (P < 0.01); mild infections [b] 4.9 ± 4.1/year to 2.2 ± 2.0/year (P < 0.01) during treatment
2004 [62]	Adults, children; XLA	RCS	23	IVIg 300–400 mg/kg/3–4 weeks	Pneumonia/year 0.8 to 0.1 (P < 0.01), reduction in hospitalisation (P = 0.02) during treatment
2005 [63]	Adults; CVID	RCS	7	No treatment, then 200 mg/kg/3 weeks, then 400 mg/kg/3 weeks	Infections/patient-year 5.0 to 2.8 (P < 0.01) to 1.5 (P = 0.02) during therapy
2005 [64]	Children; CVID, XLA, HIM	RCS	46	Median dose 370 mg/kg/2–4 weeks	Infection rate 12.4 to 3.2/patient/year; hospitalisation rate 1.2 to 0.2/patient/year after treatment
2006 [65]	Adults, children; CVID, XLA	RCS	26	IVIg 400 mg/kg/3–4 weeks	Pneumonia in 80% to 35% of patients (P < 0.01), hospitalisation rate 88% to 46% (P < 0.0025) after starting treatment

CVID, common variable immunodeficiency; XLA, X-linked agammaglobulinaemia; HIM, hyperimmunoglobulin M; RCT, randomised controlled trial; PC, prospective cohort; CO, crossover; RCS, retrospective case series; IMIg, intramuscular immunoglobulin; IVIg, intravenous immunoglobulin; RTI, respiratory tract infection.

[a] Serious infections include pneumonia, sepsis, meningitis and/or pulmonary abscess.

[b] Mild infections includes episodes of bronchitis, otitis, sinusitis or fever.

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Table 2

Product features affecting clinical tolerability [90]

Volume load (rate of infusion)
Osmolality
Sodium content
Sugar content
IgA content

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Table 3

Effect of treatment regimen on immunoglobulin G (IgG) trough level and outcome of infections

Year (ref)	Patients	Type of study	*N*	Treatment regimen	Outcome
1984 [52]	Adults, children; CVID, XLA	PC	21	IVIg 300 mg/kg/3 weeks vs. previous IMIg	Average IgG levels increased 2.4 g/L
1984 [101]	Adults, children; CVID, XLA	RCT	16	IVIg 100 mg/kg/month	Trough levels increases with higher dose
			19	IVIg 400 mg/kg/month	
1985 [53]	Adults, children; CVID, XLA	PCS	7	IVIg 600 mg/kg/month vs. previous IMIg 100 mg/kg/2–4 weeks	IgG trough levels 5–7.5 g/L: 4 vs. 25 hospital admissions, improvement sinusitis/bronchiectasis
1987 [102]	Adults, children; CVID, XLA	RCT CO	12	IVIg 600 mg/kg/month vs. 200 mg/kg/month	Trough levels >5 g/L with fewer minor (12 vs. 31) and major (3 vs. 16) infections
1992 [56]	Adults, children; XLA	RCS	20	No treatment	IgG trough levels 0.9 ± 0.8 g/L vs. 2.2 ± 0.8 g/L vs. 2.8 ± 0.7 g/L vs. 6.5 ± 1.2 g/L, respectively

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			14	IMIg <100 mg/kg/3 weeks	
			3	IVIg up to 200 mg/kg/3 weeks	
			15	IVIg 350–600 mg/kg/3 weeks	
1999 [57]	Children; XLA	RCS	31	Mean dose 390 mg/kg/3 weeks	Annual incidence of bacterial infections by trough level: 0 when >8 g/L, 0.05 when 5–8 g/L and 0.16 when <5 g/L
2001 [58]	Adults, children; CVID, XLA	RCT CO	43	IVIg: adults, 300 mg/kg/month vs. 600 mg/kg/month Children, 400 mg/kg/month vs. 800 mg/kg/month	Trough level 6.4 g/L vs. 9.4 g/L; mean infection rate, low-dose 3.5 ± 2.6/patient vs. high-dose 2.5 ± 2.4/patient (P = 0.004); mean duration of infections, low-dose 33 days vs. high-dose 21 days (P = 0.015)

CVID, common variable immunodeficiency; XLA, X-linked agammaglobulinaemia; HIM, hyper immunoglobulin M; PC, prospective cohort; RCT, randomised controlled trial; PCS, prospective case series; CO, crossover; RCS, retrospective case series; IVIg, intravenous immunoglobulin; IMIg, intramuscular immunoglobulin.