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Review

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.

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-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

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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 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 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.

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 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 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.

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].