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Review

Immunoglobulin replacement therapy in primary and secondary antibody deficiency: The correct clinical approach

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ABSTRACT

Immunoglobulin therapy is the administration of human polyvalent IgG and represents the most effective treatment to prevent recurrent infections in antibody deficiency patients. Primary antibody deficiency represents the main indication of immunoglobulin replacement therapy and includes a wide range of disorders characterized by impaired antibody production in response to pathogens and recurrent infections. However, not all primary antibody deficiency patients require immunoglobulin replacement. Indeed, immunoglobulin preparations are expensive and, once prescribed, usually result in lifelong therapy. Moreover, many patients significantly benefit from a long-term antibiotic prophylaxis and a prompt begin of antibiotic therapy in case of infectious events. Even more controversial is the decision to initiate immunoglobulin replacement therapy in secondary antibody deficiency, a heterogeneous and expanding group including B-cell lymphoproliferative syndromes, protein losing states and therapeutic agents. This review seeks to define the indication to immunoglobulin replacement in primary and secondary antibody deficiency disorders, distinguishing those in which the beginning of immunoglobulin therapy is always indicated at the same time as the diagnosis has been made, from those lacking of defined indication to replacement therapy. In addition, we propose a clinical approach, mainly based on the evaluation of infectious history, vaccine response and bronchiectasis finding, to support the decision to initiate immunoglobulin therapy in an individual patient.

1. Introduction

Immunoglobulin therapy is the administration of human polyvalent IgG derived from large pools of plasma from healthy donors [1]. Bruton, who successfully treated a boy with agammaglobulinemia and recurrent pneumococcal infections, first described it in 1952 [2]. In the 1950s, immunoglobulin was administered via the intramuscular route, which implied pain, poor bioavailability and risk of nerve injury [3]. Since the 1970s, intravenous immunoglobulin (IVIG) formulations have been developed thanks to the advancement of immunoglobulin purification and stabilization systems, thus allowing the infusion of higher volumes [4,5]. Finally, in the last two decades, immunoglobulin therapy has evolved to include the subcutaneous route. Subcutaneous immunoglobulin (SCIG) can be self-administered at home and is associated with fewer systemic adverse events [6]. The progressive improvement of the viral inactivation methods of the plasma-derived products has made immunoglobulin formulations increasingly safe. Therefore, various immunoglobulin preparations are now included among the World Health Organization's model lists of essential medicines for adults and children [7]. Although immunoglobulin therapy is also used at higher dosage in a wide range of autoimmune and inflammatory conditions for its immunomodulatory effects [8,9], the main indication of this treatment is the lifelong replacement therapy of primary and secondary immunodeficiency to prevent and treat recurrent infections [10]. Primary immunodeficiencies (PIDs) include more than 200 genetic diseases characterized by various degrees of immune response impairment and recurrent or unusually severe infections [11]. Among PIDs, primary antibody deficiency (PAD) represents the main clinical indication of immunoglobulin replacement therapy (IgRT) [12]. However, not all PAD patients require IgRT. This issue is crucial, given that immunoglobulin preparations are expensive and, once prescribed, usually result in lifelong therapy. Moreover, beyond the economic aspects, as all plasma derived products, they are subjected to a limited availability. On the other hand, a delay in the beginning of IgRT may implicate a significant worsening of the prognostic outcome in some PAD patients [13]. Even more challenging is

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Table 1
Antibody deficiency diseases with and without defined indication to immunoglobulin replacement therapy. IgRT: immunoglobulin replacement therapy.

Antibody deficiency diseases (AD)	
AD with defined indication to IgRT	AD without defined indication to IgRT
Common variable immunodeficiency (CVID)	Unspecified antibody deficiency (UAD)
X-linked agammaglobulinemia (XLA or Bruton disease)	Selective polysaccharide antibody deficiency (SPAD)
Autosomal recessive agammaglobulinemia (ARA)	IgG subclass deficiency
Hyper-IgM syndromes (HIGM)	Secondary antibody deficiency (SAD)

the establishment of the indication to replacement therapy in secondary antibody deficiency (SAD), a heterogeneous group of diseases including B-cell lymphoproliferative syndromes, protein losing states (notably enteropathies and nephropathies), disorders of lymphatic circulation, increased immunoglobulin catabolism and a growing number of therapeutic agents [14]. In this perspective, the development of practical guidelines supporting the decision to initiate immunoglobulin therapy is a much-debated issue. In this review, we discuss the indication to IgRT in various primary and secondary antibody deficiency disorders, distinguishing those in which the beginning of IgRT is always indicated at the same time as the diagnosis has been made, from those lacking of defined indication to replacement therapy (Table 1). In addition, we seek to pinpoint the clinical and laboratory criteria that have to be assessed before deciding whether and when to initiate IgRT in an individual patient.

2. Antibody deficiency with defined indication to immunoglobulin replacement therapy

This group includes common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), autosomal recessive agammaglobulinemia (ARA) and Hyper-IgM syndromes (HIGM). CVID is the most frequent of these, with a prevalence of 0.07 to 0.98 patients per 100,000 inhabitants (selective IgA deficiency occurs with higher frequency overall but is often asymptomatic) [15,16]. CVID is characterized by reduced serum levels of IgG, IgA and/or IgM, lack of antibody production in response to pathogens and a wide spectrum of clinical manifestations including infections, inflammatory and autoimmune diseases, and malignancies [17]. Over the past four decades, IgRT has proven to reduce significantly the burden of infections in CVID, thus improving the prognostic outcome. In a large Italian cohort, the beginning of replacement therapy resulted in a decrease of CVID patients presenting acute pneumonia from 13.1% to 7.1% [18]. Similarly, in another multicentric Italian study from the Ipinet Group investigators, the pre-infusion IgG level (trough level) was the most relevant risk factor associated with severe infections in CVID patients receiving IgRT. In particular, patients with IgG trough level lower than 400 mg/dL had a four times higher rate of acute bacterial pneumonia [19]. According to these findings, several studies report that delay in CVID diagnosis, and consequently in IgRT beginning, is associated with a poor prognostic outcome [13,20,21]. In particular, our group has recently demonstrated that this association is more significant in CVID patients with a marked reduction of IgA serum levels [22]. As consequence, fulfilling the diagnostic criteria for CVID defined by the European Society for Immunodeficiency (ESID) in 2014 generally implies the initiation of IgRT [23]. However, IgRT has not proven efficacy on the non-infectious manifestations of CVID. Among these, malignancies (notably gastrointestinal cancers and lymphoproliferative syndromes), chronic liver disease and chronic lung disease, have progressively become the major cause of mortality in CVID [24]. Similar considerations can be made for agammaglobulinemic diseases (XLA and ARA), which are the result of a B cell maturation block and represent the prototype of PAD. Indeed, agammaglobulinemia is the first-described and the clearest indication to immunoglobulin therapy [25,26]. In retrospective analyses, the occurrence of severe infections in agammaglobulinemic patients, notably bacterial pneumonia and viral meningo-encephalitis, was inversely correlated with both the dose of Ig administered and the IgG trough level [27,28]. Analogously, IgRT is considered definitely beneficial in HIGM syndromes, a heterogeneous group of genetic disorders resulting in defects of immunoglobulin class switch recombination, with or without defects of somatic hypermutation. In the two largest studies assessing the efficacy of IgRT in HIGM patients, a decrease of the incidence of all infectious events was observed. The most significant result was the decrease of prevalence of acute pneumonia from 7.6% to 1.4% after the beginning of immunoglobulin therapy [29,30]. However, even in HIGM syndromes IgRT is only able to prevent infectious events whereas do not exert any protective effect on the non-infectious complications (i.e. hepatopathy and lymphoproliferation).

3. Antibody deficiency without defined indication to immunoglobulin replacement therapy

This group includes various primary and secondary disorders that exhibit a broad spectrum of impairment of the humoral immune response leading to a wide range of severity of clinical manifestations. Among the PAD defined by the ESID, unclassified antibody deficiency, specific antibody deficiency and IgG subclass deficiency fall within this category. Unclassified antibody deficiency (UAD) is characterized by a reduction of less than two standard deviation of one or more class of immunoglobulin (mainly IgG) associated with one or more clinical manifestations proper of antibody deficiency (recurrent or severe bacterial infections, autoimmune phenomena, polyclonal lymphoproliferation) and a poor IgG antibody response to vaccines [23]. The decision to begin a lifelong expansive IgRT in UAD patients is very controversial. Some of these subjects suffer with complications not responding to IgRT as enteropathy, lymphoproliferation or cytopenias and do not develop recurrent or severe respiratory infections [31,32]. Moreover, UAD patients suffering with recurrent infections may significantly benefit from a long-term antibiotic prophylaxis and a prompt begin of wide-spectrum antibiotic therapy in case of infectious events. These patients are generally excluded by large multicentric studies, as they do not fit the diagnostic criteria for the immunodeficiencies the studies are designed for. As consequence, there is a lack of evidence regarding the prognostic stratification of UAD patients not allowing the draft of therapeutic algorithms. Anyway, a close clinical and immunological follow-up is required, since some of these patients gradually progress, over months or years, towards a better-defined immunodeficiency disease, as CVID [33].

An inadequate antibody response to *Streptococcus pneumoniae*, either after documented invasive infection or after 23-valent pneumococcal polysaccharide vaccine (PPV23), associated with normal serum IgG, IgA, IgM and IgG subclass levels, characterizes specific antibody deficiency, also known as selective polysaccharide antibody deficiency (SPAD) [34]. The signs and symptoms of SPAD are similar to those of other antibody deficiency syndromes and include chronic and recurrent otitis media, sinusitis, bronchitis, pneumonia and sepsis. However, SPAD encompasses multiple phenotypes (mild, moderate, severe, and poor immunologic memory) based on the degree of pneumococcal polysaccharide nonresponsiveness [35]. This immunological heterogeneity accounts for the wide range of clinical severity and prognostic outcome observed. IgRT should be considered in SPAD patients with recurrent infections if a long-term prophylactic antibiotic therapy is not able to significantly reduce the burden of infectious events. In these cases, a possible approach is the suspension of immunoglobulin therapy after a 6–12 month period and the re-evaluation of the immune