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Immunoglobulin replacement therapy in antibody deficiency syndromes: are we really doing enough?

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Immunoglobulin (Ig) replacement therapy has substantially changed the life of patients with primary antibody deficiency (PAD). In the majority of cases, patients with common variable immunodeficiency (CVID) or X-linked agammaglobulinaemia (XLA) now live to lead a near-normal life. Modern production facilities, a series of safety measures and a choice of several ways of administration make Ig replacement a safe and relatively easy therapy to use. The well-known presentations of PAD, such as pneumonia, septicaemia and other invasive bacterial infections [1], would continue to occur in PAD patients without regular replacement therapy. In this paper, we comment on the success and limitations of our present Ig replacement therapy in PAD. We also speculate how further improvement can be achieved in the treatment of complications from which PAD patients continue to suffer.

IgG replacement effectively prevents pneumonia and invasive bacterial infections, as shown in several large cohorts. For instance, in a large Italian cohort of CVID patients, the prevalence of pneumonia was reduced from 49·0 to 20·5% upon initiation of Ig therapy [2]. Prevention of pneumonia by Ig replacement therapy appears to be possible in a dose-dependent fashion. In a meta-analysis on IgG trough levels of 676 patients, the risk of pneumonia declined by 27% with each 0·1 g/kg body weight increment in the monthly IgG dose [3], although other factors, such as individual IgA levels, may determine the risk of pneumonia even more strongly [4].

However, the effect of IgG replacement therapy on bacterial bronchitis and sinusitis in PAD patients is less clear. In the Italian CVID cohort, prevalence of chronic bacterial airway infections rose markedly from time at diagnosis through an observation period of a mean of 11 years of performed IgG replacement therapy. Frequency of both chronic bronchitis and sinusitis increased from 33·9 to 46·4% and from 36·6 to 54·0%, respectively [2]. The increase of these conditions during Ig therapy was described similarly in XLA patients [1,4].

Chronic bronchitis and sinusitis in PAD is due almost exclusively to chronic bacterial infection. The fierce, but ineffective inflammatory response, which inevitably follows the presence of bacteria in the sinus and lower airways, leads to repeated cycles of damage and repair of the airway epithelium. This process leads eventually to the formation of polyps and obstruction of the ostia of the paranasal sinuses, and to irreversible scarring and bronchiectasis. In bronchiectasis, airway clearance is permanently impaired, perpetuating the vicious cycle of infection and inflammation [5].

Why is Ig replacement effective in preventing pneumonia, while markedly less so in preventing bacterial airway infection in PAD patients? The underlying reason may be that Ig replacement cannot fully substitute for an important part of the physiological airway defence. At the airway surface, the dominant isotype IgG is restricted to the alveolar space where it arrives after passive diffusion from the systemic circulation. Hence, inflammation in the alveolar space, i.e. pneumonia, is effectively prevented by systemic IgG replacement therapy. At the bronchial airway site, as well as in the nasal airways, however, IgA and IgM are the dominant isotypes in the immunocompetent individual. Both isotypes reach the airway lumen by active transport through the epithelium which is initiated by antibody-secreting cells located in the lamina propria of the airways [6]. Patients with primary immunodeficiency (PID) frequently lack both these Ig isotypes and the related antibody-secreting cells. This renders them susceptible to bacterial and also viral airway infections. Viral infections in turn may predispose to bacterial infection by impairing mucociliary clearance [7], inducing phagocytic dysfunction [8] and/or promote bacterial adhesion [9].

Table 1. Outstanding questions for preventing airway infection in primary antibody deficiency.

Outstanding questions for preventing airway infection in primary antibody deficiency
1. Which immunoglobulin (Ig) isotype would be the most feasible therapy for the management of airway disease?
2. How to transport Ig effectively to the site which includes difficult-to-reach areas, such as the paranasal sinuses and the terminal bronchioli?
3. Would IgG or monomeric IgA therapy result in a more fierce inflammatory response at the airway epithelium once it binds to pathogens?

IgA at the luminal site is predominantly polymeric, which leads to differing immune functions in comparison to monomeric IgA. Monomeric IgA largely resembles IgG in triggering a proinflammatory response. Polymeric IgA more effectively immobilizes pathogens, prevents their adhesion or binds toxins [10]. These mechanisms allow the removal of pathogens that are inhaled physiologically into the lower airways without causing inflammation, also referred to as immune exclusion [6].

Why is IgA supposed to be an important part of the antibacterial airway defence in PAD patients, while apparently the vast majority of individuals with a selected IgA deficiency are not susceptible to prolonged bacterial or viral airway infection? The main reason is probably that, in CVID and XLA, patients also lack both IgA and IgM. IgM shares much of the immunological properties of polymeric IgA and may substitute for the lack of IgA in patients with selective IgA deficiency. IgA deficiency was the strongest independent risk factor for bronchiectasis in a prospective study with CVID and XLA patients [4].

While it is widely accepted that Ig replacement therapy is not sufficiently effective in preventing airway disease, it is less clear which measures would ameliorate the disease course in the patients. The true prevalence of chronic sinusitis and bronchiectasis is still unknown. Currently, there is no consensus on the frequency on which these pathologies should be tested in routine care, how they should be tested or at what intervals. While chest CT and conventional chest X-ray are generally used to assess bronchiectasis, these techniques fail to detect a large proportion of bronchial pathologies. To date, there are no studies that demonstrate effective preventive or therapeutic measures against bronchiectasis in PAD patients. One of the major underlying reasons for the lack of studies is the difficulty to agree on a consensus protocol to reliably create quantitative data on bronchial pathology in a multi-centre setting. The international Chest CT in Antibody Deficiency Group (http://www.Chest-CT-Group.eu) aims to establish and validate a score for bronchiectasis and other structural lung disease for documenting the natural course of lung disease in PAD patients and potential effects in interventional studies. Preliminary data of the group show a steady increase of the prevalence of bronchiectasis with age from approximately 40% in patients aged less than 20 years to almost 80% in patients above 60 years in a large multinational cohort of CVID patients.

Assessing the prevalence and course of airway disease is only a prerequisite for improving the health of the patients. Which intervention is the most promising to improve efficacy over the present management? The role of antibiotic therapy has not been assessed thoroughly to date, and present practices range from no therapy to preventive antibiotic maintenance therapy. Different antibiotics may have differing effects which are not purely anti-bacterial, such as improvement of sputum rheology properties or anti-inflammatory effects, as shown for azithromycin in patients with cystic fibrosis [11]. Hypertonic saline, which proved effective in improving sputum clearance in cystic fibrosis patients, may also be beneficial in PAD patients. Other measures, such as dornase alpha, nasal irrigation and physiotherapy, could also be effective, but have not yet been assessed formally.

Most challenging, however, would be an effort to develop an Ig replacement strategy which is more physiological than the present practice. Is it feasible to replace serum IgA and IgM together with IgG systemically? In antibody-deficient patients, systemic replacement with serum IgA could lead potentially to the delivery of secretory IgA in the airway lumen, which is a natural process in healthy people. Indeed, these patients do not lack the expression of polymeric immunoglobulin receptor (pIgR), which is involved in the transepithelial transport of polymeric IgA and IgM (J-chain-positive IgA and IgM) on mucosal surfaces. However, this approach might not be as effective as desired for PAD patients, as serum IgA is mainly monomeric. It may eventually be more effective to apply Ig directly to the luminal site of the airways. Again, a number of challenges have to be met and are summarized in Table 1.

In summary, there is still a long way to go until all issues of the care of PAD patients are resolved satisfactorily.

Disclosures

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