Long-term Clinical Outcome of Antibody Replacement Therapy in Humoral Immunodeficient Adults With Respiratory Tract Infections

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ABSTRACT

In severe humoral immunodeficiency the indication for antibody replacement therapy (ART) is clear, and supported by several large studies. However, for milder forms of humoral immunodeficiency, the indication for ART is less clear. This is a retrospective cohort study of 87 adults with recurrent respiratory tract infections who received ART. The patients had severe or mild humoral immunodeficiency, and were followed up for a median of 62 months. Infection frequency, pharmacy-registered antibiotics use and hospital admissions significantly decreased under ART compared to the year prior to starting ART (median 5.50 (anamnestically) – 0.82 (physician-confirmed) infections/year, p < 0.001; median 4.00 – 2.05 antibiotics courses/year, p < 0.001; mean 0.75 – 0.44 hospital admissions/year, p = 0.009). These beneficial effects of ART were seen in both severe and mild immunodeficiency. Bronchiectasis was present in 27 patients when ART was started, but was not associated with clinical outcomes. An increase in hospital admissions under ART, observed in some patients, was significantly associated with pulmonary emphysema and current smoking. In conclusion, this study shows that ART is a long-term effective therapy in adults with recurrent respiratory tract infections with severe as well as with milder forms of humoral immunodeficiency.

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common variable immunodeficiency (CVID) or X-linked agammaglobulinemia (XLA).

In milder forms of humoral immunodeficiencies e.g. IgG subclass deficiency (IgGSD) or specific antibody deficiency (SAD) there is less evidence supporting ART. There are few studies that thoroughly compare clinical and immunological characteristics before and during ART in these patients. The most extensive study is a retrospective study of 132 adult patients with IgGSD and ≥ 4 RTI per year (Ollendorf-Nielsen et al., 2007). Treatment with ART in the form of subcutaneous immunoglobulins (SCIG) resulted in a significant reduction of antibiotic-treated RTI in the most recent year of ART. Other studies have much smaller patient populations or were unable to obtain objective measures of infection frequency or baseline measurement with which to compare infection frequency under ART (Bjorkander et al., 1986; Abdou et al., 2009; Abrahamian et al., 2010). There have been no studies of ART with long-term follow up and robust outcome parameters in patients with mild immunodeficiency. As ART is an expensive therapy (20,000–30,000 euros per patient per year) it is important to establish clinical efficacy in patients with mild immunodeficiency.

The outpatient clinic of the Department of Pulmonology at the St. Antonius Hospital is a referral center for adult patients with recurrent RTI. Clinical and immunological characteristics of the patients are systematically evaluated, and then a multidisciplinary decision is made whether or not to initiate ART. This patient group comprises both severe adult-onset immunodeficiency such as CVID and mild adult-onset immunodeficiency such as SAD. Here we present the clinical and immunological data from adult patients with recurrent RTI who were treated with ART at our center. The objective of this study was to determine the efficacy of ART in this population. Clinical outcome parameters were compared between the period prior to ART and long-term follow-up.

2. Patients and Methods

In this retrospective cohort study we included 87 patients referred for analysis of recurrent RTI in the period 1992 until 2014. The clinical and immunological screening before starting ART comprised infection history and immune status investigation according to the immune status protocol of that time (the Dutch National Working Group for Immunodeficiencies (WID) and European Society for Immunodeficiencies (ESID) protocols) (Vossen and Zegers, 1988, de Vries et al., 2000, de Vries, 2006). Data were retrieved from patient records. For every patient, the history and laboratory results, including response to pneumococcal vaccination, at time of immunological screening were collected, as well as clinical and laboratory follow up data after that time. Data were collected up until July 2014, or until a patient was lost to follow up or died. Thus, there was no fixed length of the follow-up period. If patients gave written consent their home pharmacy was contacted with a request for providing the patient’s antibiotics use. Antibiotics use was only available for patients who started with ART after 2002. The local medical ethics committee approved of the study and allowed contacting the pharmacies of patients that had passed away. The study was conducted in accordance with the principles of the Declaration of Helsinki (2013 version).

2.1. Antibody Replacement Therapy

ART was started in patients with a diagnosed immune deficiency and recurrent infections. Intravenous immunoglobulins (IVIG) were given monthly at the outpatient department of the hospital or at home, whereas SCIG was given (self-)administered daily or weekly at home. The choice between these two administration routes was made on an individual basis. The preferred administration route for ART was IVIG in case of CVID. The starting dose depended on serum IgG levels. In patients with IgG levels ≤ 5 g/l the dose was 400 mg/kg/week. In case of IgGSD the preferred route was SCIG with a starting dose of 2 ml (160 mg/ml) daily or 15 ml (160 mg/ml) every week by a subcutaneous infusion pump, depending on patient preference. Dose adjustments and changes in administration route were made based on IgG trough levels and infection frequency. The target IgG trough level was 7 g/l. ART with SCIG was usually discontinued after six months to evaluate infection frequency. ART was restarted if infection frequency and/or antibiotics use increased.

2.2. Immune Status Investigations

Standard laboratory investigations included blood leucocyte count with differentiation, complement status, serum immunoglobulins and IgG subclass-level measurement and pneumococcal antibody response after vaccination. All patients were vaccinated intramuscularly with a single dose of 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23; Merck, Rahway, N.J, USA). Blood samples were routinely drawn before and 3–6 weeks after vaccination. Serum samples were stored at −80 °C until use. Until 2008 total antibodies against capsular polysaccharides of two or three Streptococcus pneumoniae serotypes (3, 4 and 9) were measured by ELISA as previously described (van Kessel et al., 1999). After 2008 IgG antibodies against 8, 13 or 14 different pneumococcal polysaccharides were measured as described previously (Meerveld-Eggink et al., 2009; Elberse et al., 2010; van Kessel et al., 2014). For categorization of the antibody response to pneumococcal polysaccharide vaccination, the 2005 AAAAI/AACAI classification criteria were used (Bonilla et al., 2005).

2.3. Diagnostic Classification of Immunodeficiencies

Patients were classified in different categories of primary immunodeficiency according to recent definitions. A patient was classified as CVID when fulfilling the following criteria: (1) IgG level < 7 g/l; (2) IgM level < 0.4 g/l and/or IgA level < 0.7 g/l; (3) onset of immunodeficiency at > 2 years of age; (4) absent isohemagglutinins and/or poor response to vaccinations; and (5) exclusion of other defined causes of hypogammaglobulinemia (Conley et al., 1999). When patients fulfilled criteria 1, 3 and 5, but not criteria 2 and/or 4, they were classified as Idiopathic Primary Hypogammaglobulinemia (IgM) (Driessen et al., 2013). Patients with IgA levels < 0.07 g/l and normal serum IgG and IgM levels in whom other causes of low IgA levels had been excluded, were categorized as IgA deficiency (Bonilla et al., 2015). Patients with normal levels of IgG, but IgG subclass levels below cut-off value they were classified as IgGSD (Bonilla et al., 2015). Patients with normal levels of immunoglobulins and IgG subclasses, but an impaired response to pneumococcal polysaccharide vaccination, were classified as SAD (Bonilla et al., 2015). Patients with a serum monoclonal protein were classified as MGUS when: (1) serum M-protein < 30 g/l; (2) bone marrow clonal plasma cells < 10%; (3) no evidence of other B-cell proliferative disorders; and (4) no related organ or tissue impairment (International Myeloma Working Group, 2003). For the purpose of this study, we refer to CVID and IPH as severe immunodeficiency, and to IgGSD and SAD as mild immunodeficiency.

2.4. Clinical Outcome Parameters

Recurrent RTI were defined as having three or more infectious periods per year. Infection frequency prior to starting ART was based on patient reporting. Infection frequency after ART was based on confirmation of infectious episodes by a physician. Infectious episodes were categorized as sinusitis, bronchitis or pneumonia. Data on antibiotics use was provided by patient’s home pharmacies. In the Netherlands antibiotics are only available with a prescription from a physician and all antibiotics use is registered. Hospital admissions were scored in case of infection and/or exacerbation of underlying pulmonary disease.
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