Annals of Clinical Case Reports

Case Report
Published: 14 Apr, 2017

Safe Subcutaneous Immunoglobulin Replacement Therapy in the Treatment of X-Linked Agammaglobulinemia Patient: A Case Report

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Abstract

Bruton's agammaglobulinemia is a rare X-linked humoral immunodeficiency (XLA) characterized by recurrent bacterial infections. The usual treatment of this primary immunodeficiency consists of life-long immunoglobulins (Igs) replacement, administered intravenously or subcutaneously. We report the case of an18-year-oldpatient affected by XLA, diagnosed during childhood. Over time, his subcutaneous Igs dose had been progressively reduced and the intervals between administrations prolonged. After three years of subcutaneous Igs administration, he was able to maintain an IgG level higher than 700 mg/dl, by taking 10.000 mg of subcutaneous Igs every 20 days. This dose regimen provided a continuous protection against infections, while no significant adverse event was observed. Patient adherence was guaranty by a home-based therapy; a regular follow-up and serum IgG level monitoring were also assured. Given the shortage of Ig available for the treatment of different primary immunodeficiencies, a therapy that, with a low Ig amount together with a reduced number of administrations, is able tosustaining a safe IgG level, is essential to preserve patient adherence.

Keywords: X-linked agammaglobulinemia; Bruton's tyrosine kinase (Btk); Subcutaneous immunoglobulin (SCIG); Local tolerability; Serum IgG trough level

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Received Date: *02 Feb 2017*

Accepted Date: *12 Apr 2017*

Published Date: *14 Apr 2017*

Citation:

Giuseppe P, Elisa T, Antonio P, Claudio L. Safe Subcutaneous Immunoglobulin Replacement Therapy in the Treatment of X-Linked Agammaglobulinemia Patient: A Case Report. Ann Clin Case Rep. 2017; 2: 1333.

ISSN: 2474-1655

Introduction

X-linked agammaglobulinemia (XLA) or Bruton's disease is a rare inherited disorder of the immune system: XLA is a primary immunodeficiency, occurring in 1 of 190,000 male births in the United States [1,2]. XLA represents nearly 85% of agammaglobulinemia cases, and is caused by a defect in gene, located on the X chromosome, coding for Bruton's tyrosine kinase (BTK). BTK gene mutation causes a failure in B-lymphocytes maturation, associated with a failure of Ig heavy chain rearrangement, leading to a decrease in antibody production [2]. XLA patients may present recurrent bacterial infections as well as non-infectious complications, or exhibit heterogeneous clinical phenotypes [3]. This complex clinical outline and the variable severity of symptoms entail an early correct diagnosis to properly manage patients, with appropriate treatment [4]. Symptoms appear during the first year of life, in half of patients, and, within the age of 5 years in in more than 90% of the subjects affected [5]. XLA is diagnosed in approximately 60% of individuals who develop a severe, life-threatening infection [6].

The majority of the diagnosed patients show low level in serum Igs. IgG levels < 200 mg/dl, IgA levels < 15 mg/dl, and IgM levels < 40 mg/dl [2], or serum IgG, IgM and IgA more than 2 SD below the normal level for age [5], and a reduced B-cell number, i.e. < 2% of CD19- or CD20-positive blood lymphocytes [2] are found. Therefore, early diagnosis and development of immunoglobulines formulations, ensuring normal serum IgG concentrations, were the key factors in improving prognosis of patients with XLA, during the last 25 years [2,5].

Case Presentation

An 18-year-old Caucasian man, who was the second-born child, had apparently normal growth and development until he was 4-year-old. At this age, after he started kindergarten, the patient suffered for frequent episodes of upper airway infections, high fever, cough and, in general, sickness. Moreover, retrocardiac bronchopneumonia was diagnosed. After a second episode of

bronchopneumonia, he was admitted to the hospital and severe hypogammaglobulinemia was detected (IgG, 41 mg/dl; undetectable IgA and IgM- Normal range, as measured in our laboratory, IgG 700-1600 mg/dl; IgA 70-400 mg/dl; IgM 40-230 mg/dl). Flow cytometric evaluation of peripheral blood lymphocytes showed, at that time, a considerably decreased number of CD19+ cells (4 cells/µl, 0.1% of lymphocyte count. Normal range, in our hand, B lynphocites, 110-393 cells/µl), while the other lymphocyte subsets were normal. No remarkable signs were reported upon physical examination.

Given the hypogammaglobulinemia and the low B-cell count, the diagnostic approach included a suspected primary immunodeficiency; hence, a broad spectrum of clinical and laboratory investigations were performed. BTK gene mutation (T592G in the exon 6) was detected in the patient as in the mother, and diagnosis of XLA was made according to diagnostic criteria [5]. A written informed consent was obtained; the study was approved by the Local Ethics Committee. At 4 years of age, the patient initiated intravenous immunoglobulin substitution (IVIG) (0.4 g/kg every 4 weeks) with prompt positive clinical response in terms of serum IgG level, reacting 750 mg/dl. Lymphocyte typing highlighted a complete absence of B-cells, whereas all other parameters were normal. After diagnosis, the patient did not have any other severe infective episodes requiring hospitalization. When the patient was 15-year-old, he started a weakly subcutaneous immunoglobulin administration (SCIG)once a week, with the benefit of a more comfortable home therapy. As per international guidelines, the dosage of 0.4 g/kg/month was continued. Total monthly amount of Igs was slightly increased, based on the patient's growth and when the patient was 17 to 18-year-old, the monthly dosage of 30 g (50 ml contains 10 g of Ig) was divided in three administrations (10 g every 10 days). During this time, clinical and laboratory benefits were retained. Then, since the patient refused to come to the University Hospital Day Service, the intervals between administrations was progressively delayed from 10 to 20 days in order to keep the adherence to the therapy.

The frequency of SCIG administrations was reduced and the current schedule is 15 g/month of SCIG (Hizentra®, IgPro 20, CSL Behring GmbH, Berne, Switzerland) divided in two boluses, 10 g each, one every 20 days, in order to maintain target serum IgG level higher than 700 mg/dl, necessarily to maintain clinical benefits. Every three months, serum Igs levels were monitored by blood test; follow-up visits, including physical examination, were planned during the intervals between administrations, based on clinical conditions (in particular, lack of infections) and patient preference. Table 1 summarizes the patient's main characteristics and immunological parameters at diagnosis, after IVIG treatment and SCIG treatment. Figure 1 shows dosages of Igs replacement, number of infusions per month administered, and corresponding serum IgG levels over the years.

The patient regularly undergoes hematological examinations (full blood count), and instrumental examinations (abdominal ultrasound, chest X-ray or high resolution TC; pulmonary functional tests). Regarding safety features, neoplasia or autoimmune diseases have not been observed during the follow-up. In the last 3 years, no relevant infective episodes have been occurred, except for some colds in the wintertime and one upper airway infection, rapidly resolved.

Discussion

Timely started, lifelong Igs replacement therapy demonstrated a significant reduction in mortality, prevention from morbidities, improved quality of life of XLA patients [2,3], and is the gold standard in the management of primary antibody deficiency [2,6]. The replacement therapy with IgG can be administered to patients intravenously or subcutaneously. The intravenous route is the most common, since it allows a larger and faster amount of Igs infused; however, it may have side effects related to increased blood viscosity. Thus, SCIG administration has become increasingly wide spread, leading to a more stable serum IgG level, due to the use of lower and more frequent doses and opening to the possibility of home-based self-administration, improving life quality [6,7]. Currently, numerous SCIG products are available; they differ mainly in IgG concentration (16%, 16.5%, and 20%), and all of them are administered once a week or more frequently according to the serum IgG level obtained to minimize peak/trough variations [8]. The case reported describes the experience of switching from IVIG to SCIG administration in a 15-year-old XLA patient. Administration route change had a positive impact, improving the adherence of the patient to the therapy, sustaining clinical benefits.

Between the ages of 15 and 17, the once-a-week SCIG was able to guarantee clinical and serological benefits. The initial monthly amount of SCIG, 30 g, was the same as previously given intravenously, while the serum level of IgG was stable at nearly800 mg/dl. Serum IgG level was identified as the more important parameter, instead the infusion timing, given the optimal response to the SCIG t therapy, at this dose. Dosage reduction and infusion schedule, SCIG from 30 g to 10 g, every 20 days (15 g/month), was carried out strictly along with monitoring of plasmatic IgG levels. This infusion plan assured that the serum IgG level was higher than 700 mg/dl; not relevant local or systemic infections were observed. The benefits of Igs therapy in primary immunodeficiencies are not only related to antibody replacement but also to immune response modulation [9,10]. These hallmarks have been observed when Igs is administered intravenous; however, we can hypothesize that a similar outcome may also be found after subcutaneous administration. Such observations may lead to a therapy with reduced amount of monthly Igs, achieving positive effects on infections prevention.

Pharmacokinetic studies have highlighted the equivalent bio-available features of IVIG and SCIG administrations [7]. The SC administration is featured by a progressive release of IgG into the circulation, with a stable serum IgG level achieved. As described by in the results of a multicenter European study, SCIgs increase serum IgG levels of 17.7% compared to IV Igs, when equivalent doses of Ig were used, in patients who switched from the IV to the SC route [11]. Moreover, retrospective and prospective cohort studies have demonstrated that SCIG reach similar levels and efficacy to IVIG administration, with a lower incidence of side effects and improved quality of life [12]. Home-based SCIG has been shown to be safe and effective both for pediatric [13] and elderly patients [14].

Among the different commercially availableSCIG preparations, Hizentra® hasthe highest concentration of Ig (20% human Ig), and it has been shown to achieve sustained IgG level sat equivalent doses of IVIG [15,16]. The high concentration of Ig of Hizentra® allow time infusion and number administrations reduction [6,17]. The choice, among various SGIG formulations, should be perform to minimize number of infusions and to keep the steady state target of IgG levels [17]. With the view to a treat-to-target strategy of replacement therapy, reduction in the risk of infections is the primary goal. Each

patient has his own "biological IgG level" that needs to be identified [18]. In our clinical case, the "biological IgG level" was maintained with a 20-day interval regimen, and the patient stayed substantially infection-free.

Different administration intervals of SCIG that maintain serum IgG levels with flexible dose regimens, may further address the patients' adherence needs and quality of life [19]. Given the shortage of Ig supply and the wide spectrum of diseases in which Ig are used, the possibility of reducing the amount of Igs infused and the number of injections is important to obtain better adherence to XLA replacement therapy. The objective of Igs replacement therapy management in XLA patients, which is to maintain appropriate protection against infections, is based on regular follow-ups and monitoring of serum IgG levels. The availability of manageable Igs replacement therapies may offer a tailored dose regimen and personalized treatment for each single patient. Moreover, an effective home-based SCIG therapy may facilitate patients' adherence to the replacement therapy.

Acknowledgement

Editorial assistance for the editing the manuscript was provided by Content Ed Net with the helpful assistance of Dr Rossella Ferrari, and funded by CSL Behring Sp A, Milano Italy.

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