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Secondary hypogammaglobulinemia in Waldmann's disease treated with subcutaneous immunoglobulins

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KEY WORDS

primary intestinal lymphangiectasia; Waldmann's disease; secondary immunodeficiencies; subcutaneous immunoglobulins; protein-losing enteropathy

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Summary

Primary intestinal lymphangiectasia (PIL) is rare disorder characterized by congenital malformation or obstruction of intestinal lymphatic drainage; it is responsible for protein losing enteropathy leading to lymphopenia, hypoalbuminemia and hypogammaglobulinemia. A low-fat diet associated with medium-chain triglyceride supplementation is the cornerstone of PIL management. The administration of intravenous immunoglobulins does not always lead to satisfactory plasma levels and therefore the replacement therapy with immunoglobulins is controversial. We describe here the case of a patient with PIL and severe hypogammaglobulinemia treated with immunoglobulins. The striking aspect of this case is the clinical and serological benefit obtained with the subcutaneous compared to the intravenous immunoglobulins administration.

Introduction

Primary intestinal lymphangiectasia (PIL), also known as Waldmann's disease, is a rare disorder characterized by dilated intestinal lymph vessels resulting in lymph leakage into small bowel lumen that leads to protein-losing enteropathy and ultimately to lymphopenia, hypoalbuminemia and hypogammaglobulinemia (1). The last one is not only due to protein loss, but also to B cells defect characterised by a decreased number of B lymphocytes, a defective production of immunoglobulins and a poor antibody response (2,3). Therefore, in patients with PIL, the risk of pyogenic bacterial infections and the occurrence of malignancy, especially lymphomas, is increased. Even if low fat diet associated with supplementary medium chain tryglicerides (MCT) remains the cornerstone of PIL medical management (4), other medications have recently been taken into consider-

ation (i.e. antiplasmin and octreotide) whose efficacy is variable and insufficiently evaluated (1). Among the therapeutic options, the replacement therapy with immunoglobulins is controversial but needs to be considered in patients with severe hypogammaglobulinemia and recurrent infections. Indeed, in these patients the administration of Intravenous Immunoglobulins (IVIg) does not always guarantee the achievement of satisfactory plasma levels because of both pharmacodynamics of IVIg and loss of the immunoglobulins from the gastrointestinal tract. We describe here the case of a young man with PIL, who developed secondary immunological abnormalities, treated with the specific diet and Subcutaneous Immunoglobulins (SCIg) obtaining clinical and immunological improvement. According to our knowledge this is the first report of a case of PIL treated with SCIg.

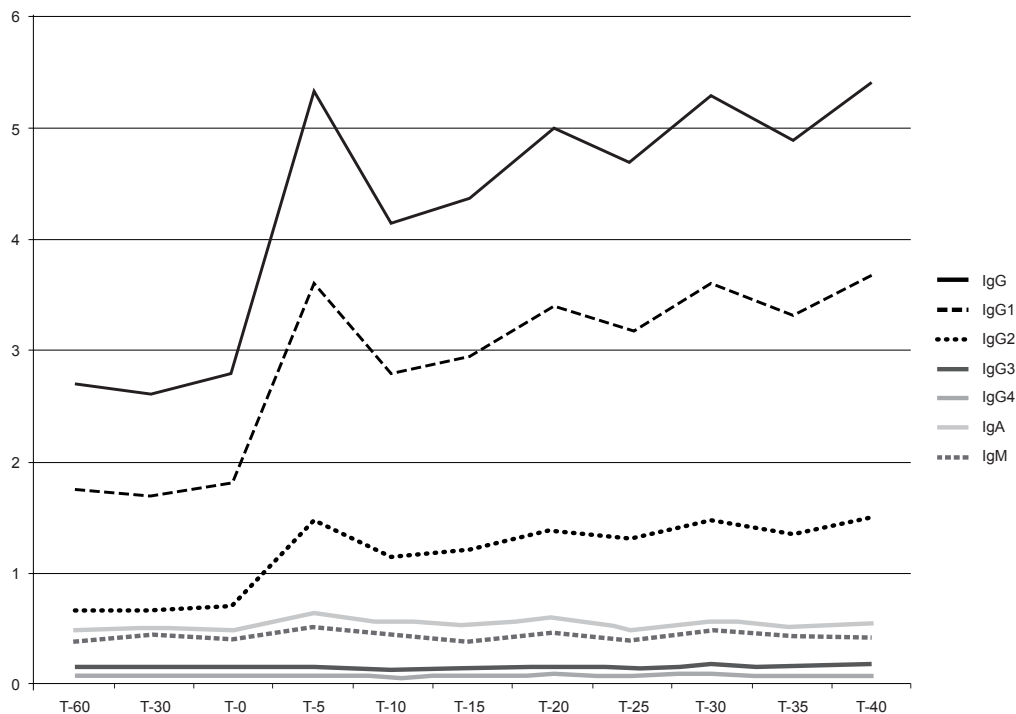
Case report

MA, a 26 years old Caucasian man, was diagnosed to have PIL with secondary immunological defect and congenital peripheral oedema at the age of 3. At birth he presented with right arm and leg pitting oedema and, at 7 months of age, he underwent a derivate lymphatic microsurgery in the upper arm. The second surgery was not performed because of immunological defects: decreased number of T and B cells and severe hypogammaglobulinemia. At the age of 3 years, the patient presented clinical signs of malabsorption such as abdominal pain, nausea, vomiting, loss and inability to gain weight, growth retardation and fatigue. Therefore, the patient underwent gastroduodenoscopy and duodenum biopsies which revealed diffuse dilated mucosal and submucosal lymph vessels, confirming the diagnosis of PIL. The patient started a specific diet with medium chain tryglicerides obtaining clinical improvement. A new laboratory evaluation was also performed and confirmed the previous findings of immunological abnormalities such as hypogammaglobulinemia, with an increase number of NK cells and decreased number of B and T cells. Moreover, a nearly absent response to "in vitro" stimulation and to vaccines was observed.

The patient experienced good health till the age of 23 years, when suddenly he started to complain of recurrent upper and lower airways infections. The patient was treated with several antibiotics without clinical benefit. He performed a chest and paranasal sinuses CT scan that showed several bronchiectasis and nasal turbinates' mucosal hyperplasia. A new evaluation of the immunological defects confirmed severe hypogammaglobulinemia (IgG 2.28 g/L, IgG1 1.82 g/L, IgG2 0.70 g/L, IgG3 0.17 g/L, IgG4 0.11 g/L, IgA < 0.06 g/L, IgM < 0.05 g/L) and a lymphocytopenia with B and T cell depletion (WBC 4160/mmc, lymphocytes 420/mmc). Therefore, we decided to start the administration of IVIg as replacement therapy (0,4 g/kg per month). Even if this treatment obtained a slight improvement in the recurrence of infections, the serum IgG levels remained unsatisfactory (**figure 1**). In order to gain higher titres of IgG and a better quality of life we switched to SCIg (10 g every 10 days) with very good results on the persistence of acceptable levels of IgG (**figure 1**).

The striking aspect of this case is the clinical and serological benefit on immunodeficiency obtained with the SCIg compared to the IVIg administration (**figure 1**).

Figure 1 - Plasma levels of Immunoglobulins before and after the administration of SCIg. *The beginning of SCIg administration is indicated as T0. Before T0 the plasma levels of Ig was evaluated monthly. From T0 the dosage of plasma Immunoglobulins was performed every 5 days (T5; T10; T15...)*



Discussion

Intravenous Immunoglobulins are a therapeutic compound obtained from the serum IgG fraction pooled by several thousands of healthy donors. It has been used for years as a replacement therapy in a wide range of primary and secondary immunodeficiencies, and represents the first therapeutic option for antibody deficiencies (5). Immunoglobulins can be administered via SC or IV route; SCIg preparations were introduced in the 1980s in US and Europe. However, slow infusion technique and low concentration of available preparations at that time, made SCIg less attractive than IVIg to patients and healthcare professionals. Therefore, IVIg, which allowed infusions of higher monthly doses, became the best route of administration. Pure and highly concentrated SCIg preparations with relatively low viscosity that allow a relatively rapid administration have recently been developed. Whereas IVIg is infused every 3-4 weeks, SCIg is administered once a week or biweekly, with the total IVIg monthly dose divided in smaller doses. The SC administration is characterised by a progressive release of IgG into the circulation obtaining a more stable serum IgG levels. Moreover, a multicentre European study showed that SCIg increases serum IgG levels of 17.7% compared to IVIg using equivalent doses of Ig, in patients who switched from the IV to the SC route (6). Subcutaneous Immunoglobulins are easy to use and to self-administer, providing patients with flexibility and improved quality of life. Furthermore, patients require less assistance from healthcare professionals, reducing the cost associated with Ig replacement therapy, and take a greater control over their treatment.

For all these reasons and since the patient had not lymphangectasia on the abdominal wall, we chose to shift from IVIg to SCIg replacement therapy.

Among all the SCIg preparations available, we used Hizentra[®], a 20% (200 g/L) ready-to-use liquid preparation of polyvalent human IgG for subcutaneous administration. Currently, it is the only 20% SCIg therapy approved by the US Food and Drug Administration and European Medicines Agency for treatment of primary and secondary immunodeficiencies.

The choice of Hizentra[®] lead us to perform the administration of SCIg once every 10 days, for a total amount of 30 g of Ig per

month (the same monthly dosage previously used by the patient via IV route). As shown in **figure 1**, using the new therapeutic regimen we have observed a progressive increase in plasma levels of IgG, which slowly edged up and stabilized around 6 g/L (IgG1 3.67 g/L, IgG2 1.51 g/L, IgG3 0.19 g/L, IgG4 0.11 g/L), result never observed before using the IVIg route.

We now want to evaluate whether SCIg administration leads not only to a more stable levels of circulating Ig, but also to modulation of immune response as shown for IVIg (7-9).

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