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CASE REPORTS

Intravenous immunoglobulin treatment of selected patients with primary antibody defects

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ABSTRACT

Objective: *The approach to primary immunodeficiencies was not standardized in our practice until the launching of the National Programme for Prophylaxis and Treatment of Humoral Immunodeficiencies. This allowed us to substantially improve the diagnosis and treatment of these rare, but extremely severe diseases. We were therefore prompted to review our experience with intravenous immunoglobulin in the long term treatment of six cases of antibody defects.*

Materials and methods: *In the last four years 41 cases with PID were admitted in our hospital: 33 with humoral immunity disorders, 4 with combined immunodeficiencies, 2 with cyclic neutropenia, 1 with chronic granulomatosis disease and 1 with Nijmegen syndrome.*

Results: *Six of these 41 cases of PID were periodically treated for replacement of their antibody deficiency. All the ten cases of transient hypogammaglobulinemia of infancy received IVIG only during life – threatening infections. The tolerance was a very good one, all the products being safe.*

Conclusions: *Intravenous immunoglobulin is indeed a life – sustaining blood product, our six patients are the living proof of their efficiency. The tolerance was a very good one, all the products being safe, except one ataxia – telangiectasia case with very severe adverse reactions to those products with a relative high content of IgA. Monthly administration of intravenous immunoglobulin may create discomfort and adverse reactions to some patients.*

Keywords: intravenous immunoglobulin, primary immunodeficiencies

INTRODUCTION

Intravenous immunoglobulins (IVIG) are a life sustaining blood product that has become standard replacement therapy for most people living with primary immunodeficiencies (PID). About 70% of PID patients receive immunoglobulin replacement therapy (1). The most common PID are antibody defects. IVIG infusion is believed to deliver missing immune antibodies against pathogens (i.e., immune factors), which are constituents of the humoral limb of the adaptative immune system. This treatment is largely evidence based and is aimed at substitution or passive immunization against

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multiple bacteria and viruses (2). The first documented use of IVIG was in the 19th century when humans were inoculated with various preparations of animal sera for the treatment of smallpox, rabies and diphtheria, but the true revolution begun in the mid 1980s when IVIG were used for replacement of primary antibody deficiencies (3). The annual worldwide consumption of IVIG has increased since 1984 from 7.4 to 55 metric tons (4). Approximately 25 to 30% of IVIG used in Unites States remain as replacement therapy for PID5. The goals of treatment in patients with antibody (IgG) deficiency are three:

1. treat the acute infection;
2. prophilaxy of repeated infections;
3. prevent or treat pulmonary disease secondary to repeated bouts of bronchitis and pneumonia (6). IVIG prevent end–organ damage (bronchiectasis) and reduce mortality from life–threatening invasive infections.

We like to emphasize the experience obtained in the treatment of PID cases during the past four years at our institution, according to the National Program for Prophylaxis and Treatment of humoral primary immunodeficiencies. ❑

MATERIALS AND METHODS

This is a retrospective review of the PID cases admitted and treated at our institution over the past 4 years. The study was conducted after the local Ethics Committee approved the research proposal. Cases were identified and charts were reviewed to record clinical data. There were 41 patients admitted in our hospital.

In order to help physicians formulate a diagnosis in patients with abnormalities of the immune system, the European Society for Immunodeficiencies (ESID) and the Pan American Group for Immunodeficiencies (PAGID) are dividing the diagnosis criteria in three categories: definitive, probable, possible. For definitive diagnosis patients have a greater than 98% probability that in 20 years would still be given the same diagnosis. The method is mutation detection. Some disorders demonstrate absence of specific mRNA or protein; others present only transiently expressed or produced at very low levels mRNA and/or protein (clinical methods failed). In cases of probable diagnosis patients have all of the clinical and laboratory characteristics of a particular disorder, but do not have a documented abnormality in the gene, mRNA or protein known to be abnormal in this disorder. Greater than 85% will be given the same diagnosis in 20 years. For possible diagnosis patients have some, but not all, of the characteristic clinical or laboratory findings of a particular disorder. These diagnosis tools establish simple, objective and clear guidelines using the same definitions for different physicians and scientists. The ESID/PAGID diagnosis criteria used for our PID cases are presented in Table 1. ❑

RESULTS

A total of 41 cases with PID were admitted in our hospital: 33 with humoral immunity disorders (17 with selective IgA deficiency; 10 with transient hypogammaglobulinemia of infancy with clinical manifestations; 3 with X–linked agammaglobulinemia; 1 with common variable immunodeficiency; 1 with hypogammaglobulinemia and 1 with hyper–IgM syndrome); 4 with combined immunodeficiencies (1 with PNP deficiency, 1 with ataxia-telangiectasia, 1 with Wiskott-Aldrich syndrome and 1 with DiGeorge syndrome); 2 with cyclic neutropenia, 1 with chronic granulomatous disease and 1 with Nijmegen syndrome.

Six (14.6%) of these 41 cases of PID were periodically treated for replacement of their antibody deficiency: 3 cases with X–linked agammaglobulinemia (XLA), 1 case with common variable immunodeficiency (CVID), 1 case with ataxia–telangiectasia (A-T) and 1 case with Wiskott–Aldrich syndrome. All the 10 cases of transient hypogammaglobulinemia of infancy received IVIG only during life–threatening infections. One exception to this was the case of moderate hypogammaglobulinemia in a 7-year-old boy with Haemophilus influenzae meningitis who constantly after recovery presented levels of IgG between 500 and 700 mg/dl without IVIG treatment.

None of the 6 treated patients had familial disease or consanguinity. The clinical and laboratory data about these patients, as well as the final diagnosis and outcomes of their disease are presented below.

Case No 1.

The patient is a 20-year-old male with *onset of symptoms* in October 1987. *Signs and symptoms*: recurrent pneumonias, bronchiectasis

Disease	Definitive	Possible	Probable
X–linked agamma-globuli-nemia	Male with CD19+ B cells< 2% and at least one of the following: 1. mutation in Btk 2. absent Btk mRNA or northern blot analysis of neutrophils or monocytes 3. absent Btk protein in monocytes, platelets 4. maternal cousins, uncles or nephews with less than 2% CD19+ B cells	Male with CD19+ B cells< 2% in whom other causes of hypogammaglobulinemia (HGG) have been excluded and at least one of the following is positive: 1. onset of recurrent bacterial infections in the first 5 years of life 2. serum IgG, IgA, and IgM*< 2 DS below normal 3. absent isohemaglutinins	Male with CD19+ B cells< 2% plus all of the following are positive: 1. onset of recurrent bacterial infections in the first 5 years of life 2. serum IgG, IgA, IgM*< 2 DS below normal; 3. absent isohemaglutinins and/or poor response to vaccines other causes of hypogammaglobulinemia (HGG) excluded.
Common variable immuno-deficiency	N/A	Male or female patient who has a marked decrease (at least 2 SD below the mean for age) in one of the major isotypes (IgM, IgG and IgA) and fulfills all of the following criteria: 1. onset of immuno-deficiency at greater than 2 years of age; 2. absent isohemaglutinins and/or poor response to vaccines; 3. defined causes of HGG have been excluded.	Male or female patient who has a marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and fulfills all of the following criteria: 1. onset of immunodeficiency at greater than 2 years of age 2. absent isohemaglutinins and/or poor response to vaccines 3. defined causes of HGG have been excluded.
Ataxia – Telangiectasia	Male or female with either increased radiation induced chromosomal breakage in cultured cells or progressive cerebellar ataxia plus disabling mutations of both alleles of ATM.	Male or female with progressive cerebellar ataxia and at least one of the following four findings: 1. ocular or facial telangiectasia; 2. serum IgA at least 2 SD below normal; 3. alpha fetoprotein more than 2 SD above normal; 4. increased chromosomal breakage after exposure to radiation	Male or female with progressive cerebellar ataxia and three of the following four findings: 1. ocular or facial telangiectasia; 2. serum IgA at least 2 SD below normal; 3. alpha fetoprotein more than 2 SD above normal; 4. increased chromosomal breakage after exposure to radiation.
Wiskott – Aldrich syndrome	Male patient with congenital thrombocytopenia (less than 70.000 platelets/mm^3), small platelets and at least one of the following: 1. mutation in WASP; 2. absent WASP mRNA on northern blot analysis of lymphocytes; 3. absent WASP protein in lymphocytes; 4. maternal cousins, uncles or nephews with small platelets and thrombocytopenia.	Male patient with congenital thrombocytopenia (less than 70.000 platelets/mm^3) and small platelets or a male patient splenectomized for thrombocytopenia that has at least one of the following: 1. eczema; 2. abnormal antibody response to polysaccharide antigens; 3. recurrent bacterial or viral infections; 4. autoimmune diseases; 5. lymphoma, leukemia or brain tumor.	Male patient with congenital thrombocytopenia (less than 70.000 platelets/mm^3), small platelets and at least one of the following: 1. eczema; 2. abnormal antibody response to polysaccharide antigens; 3. recurrent bacterial or viral infections; 4. autoimmune disease; 5. lymphoma, leukemia or brain tumor.

TABLE 1. ESID/PAGID diagnosis criteria used for our PID cases
*IgG < 200 mg/dl; IgA & IgM < 20mg/dl

(2001), lobectomy (right inferior lung lobe), septic arthritis (right hip 2001, right knee 2002). Date of PID diagnosis: 2001 (15 years old!). *Definitive diagnosis,* XLA: male patient with CD19+ B cells 0,22% (less than 2%) and mutation in Bruton tyrosine kinase (Btk)* (IVS 10-1 G>A sequence variant in the patient and heterozygosity for this mutation in the mother). Serum IgG was 348mg/dl. IgA and IgM were undetectable. Absent isohemaglutinins α and

β (blood group O, Rh O positive). *Therapy*: IVIG: 20 g/month, started 2001.

Outcome: no life threatening infections, bronchiectasis stabilization.

Case No 2.

The subject is a 10-year-old male, *with onset of symptoms* in 1998. *Signs and symptoms*: upper and lower respiratory infections; recurrent sinusitis and otitis; recurrent conjunctivitis, recurrent lobar pneumonias (4 times left inferior lobar, 2 times right inferior lobar) with pleurisis, urinary tract infections; septic arthritis (right knee). *Definitive diagnosis*, XLA: male patient with CD 19+ B cells O and mutation in Btk* (c.1921 C>G missense mutation in exon 19 of Btk gene which resulted a pR641G aminoacid substitution in the protein and heterozygosity for this mutation in the mother). Serum Ig: IgG = 248 mg/dl, IgA = 0, IgM = 14 mg/dl. Absent isohemaglutinins α and β (blood group O Rh positive). *Therapy*: IVIG 10 g/month, started 23.12.2003. *Outcome*: no invasive infections, good quality of life.

Case No 3.

The patient is a 3-year-old male, with *onset of symptoms* in May 2005 (2 years and 2 months of life). *Signs and symptoms*: chronic diarrhea (~1 year), episodic fever (7-10 days), weight loss (3 kg!), upper respiratory infections. *Laboratory findings*: persistent low levels of IgG (220mg/dl), IgA (16 mg/dl) and IgM (27 mg/dl), absent isohemaglutinins a (blood group B Rh positive); lymphocytic population with T cells predominance; CD 19+ B cells 5,75%. *Probable diagnosis*, XLA: male with CD 19+ 5,75%; onset of recurrent bacterial infections beyond 2 years of life, serum IgG, IgA and IgM <2 SD below normal, absent isohemaglutinins and other causes of hypogammaglobulinemia have been excluded. *Therapy*: IVIG (5 g/month, started April 2006). *Outcome*: improvement of diarrhea, remission of fever, partial recovery of body weight. After July 2006 the patient was lost to follow-up.

Case No 4.

The subject is an 11-year-old male, with *onset of symptoms* in February 1999. *Signs and symptoms*: recurrent lobar pneumonias with pleurisis; bronchiectasis; stomatitis; recurrent tonsillitis, cutaneous staphylococcal infections, recurrent herpes simplex infections, celiac disease, renal failure, dwarfism (IGF-1: 81.6 ng/dl; normal: 88-452 ng/dl). *Probable diagnosis*, CVID: male patient who has absent IgG (IgA and IgM also absent!) with onset of immunodeficiency after 2 years of age, absent isohemaglutinins (blood group A, absent natural β isohemaglutinins); excluded other causes of hypogammaglobulinemia (no Btk mutations!)*. Other *laboratory findings*: CD_{3+} T cells: 56,5%; CD_{4+}: 7%, CD_{19+} B cells: 2%. *Therapy*: IVIG 10 g/month, started 08.03.2003 (adverse reactions: chills, lombalgia, fever, abdominal pain). *Outcome*: bronchiectasis stabilization, no life-threatening infections, partially recovery of the nutritional status.

Case No 5.

This patient is a 15-year-old female, with onset *of symptoms* in May 1992 (~10 month old). *Signs and symptoms*: progressive cerebellar ataxia (1-2 years old); recurrent respiratory infections; pneumonias, sinusitis, bronchiectasis (7 years old); recurrent otitis, conjunctivitis, chronic diarrhea (celiac disease); ocular telangiectasia (noted at 13 years of life). *Probable diagnosis*, Ataxia – Telangiectasia: female patient with progressive ataxia and three from four diagnosis criteria: 1. ocular telangiectasia (fig.1); 2. serum IgA: traces; 3. alpha fetoprotein: 331,3 ng/ml (normal<13,9 ng/ml); we do not have the proof of chromosomal breakage induced by increased radiation in cultured cells and also mutations of ATM. Other *laboratory findings*: absent IgG and IgM ("traces"), decreased xylosemia (12 mg/dl). *Therapy*: IVIG 10 g/month, from the age of 5 years. Because the patient has "absence" of IgA she doesn't tolerate any product containing IgA (anaphylactic shock!). *Outcome*: progressive neurological degradation (wheel-chair!), disartria; stabilization of bronchiectasis and of celiac disease under IVIG treatment (7).

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FIGURE 1. 15-year-old female with ataxia-telangiectasia. Ocular telangiectasia

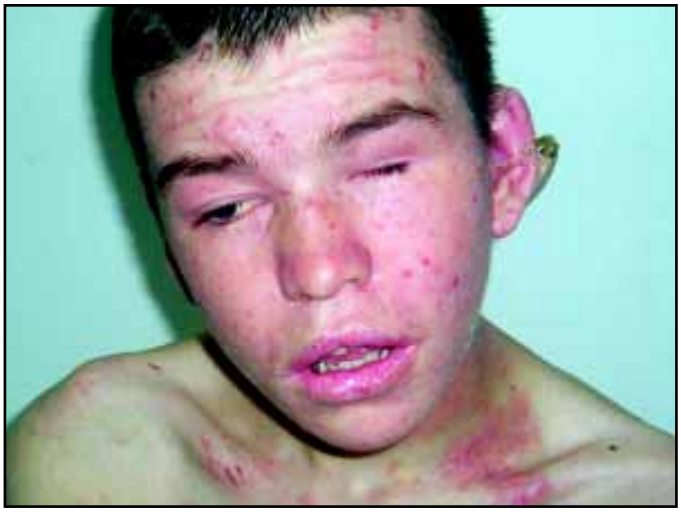

FIGURE 2. 16-year-old male with Wiskott–Aldrich syndrome. Generalized eczema, auditive prosthesis for deafness, enucleation of the left eye

Case No 6.

This subject is a 16-year-old male with *onset of symptoms* in 1993. *Signs and symptoms*: generalized eczema (atopic dermatitis) (Figure 2), recurrent staphylococcal skin infections, refractory scabies, left lobar pneumonia with pleurisy, chronic suppurative otitis, deafness, staphylococcal ophtalmia with enucleation of left eye, right glaucoma with amblyopia, mental retardation (IQ = 0,35), gait and equilibrium disturbance, disartria (in the last few months). *Laboratory findings*: moderate thrombocytopenia (70-90.000/mm^3), agammaglobulinemia (IgG 90 mg/dl, IgA 32 mg/dl, IgM 78 mg/dl), absence of natural isohemaglutinins, lymphocytic population with T cells predominance (95%), Th/Ts = 1,5/1, severe decreased B cells (0,5%) and NK (2,5%). *Probable diagnosis*, Wiskott – Aldrich syndrome: male patient with thrombocytopenia and at least two of the five criteria: eczema, recurrent bacterial infections. We can add antibody defects. Mutations of ATM are under study in a medical center from abroad*. *Therapy*: IVIG 15g/month, started November 2006. *Outcome*: improvement of eczema, no life-threatening infections, progressive neurological degradation. ❑

DISCUSSIONS

Among the six cases in our presentation, only 2 of them (XLA) have a definitive diagnosis documented, while the others have a possible diagnosis based on high clinical and laboratory degree of suspicion. These facts reflect the limitations of our study, in particular for the genetic diagnosis (8,9).

The purpose of the IVIG treatment is to maintain IgG levels in the low to normal range (IgG>700 mg/dl) or at least 500–700 mg/dl. The standard replacement dose used in our patients was 400–600 mg/kg (3,10) or 300 – 400 mg/kg/month (11) iv infusion, every 3–4 weeks. Higher doses were necessary only in ongoing suppurative infections (3). The loading dose of 1 g/kg in every newly diagnosed patient with antibody deficiency is recommended, especially if the patient is ill (3). Both the dose and dosing interval should be adjusted for each patient to provide adequate prophylaxis of symptoms. For some patients maintaining a constant IgG serum concentration of 400 mg/dl may be sufficient, but often they may require higher levels (11). The most important outcome is reduction/elimination of infections, regardless

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	Humaglobin	Octagam	Endobulin	Isiven
Lyophilized powder 5 – 10%	5%	5%	5%	5%
Sodium content	-	-	+	+
IgG	95%	>99%	>95%	95%
Method	Cold ethanol fractionation method. Low pH, 10h, 60^{0}C treatment	Cohn fractionation, SD – method, pH 4 treatment	SD – method. Viral double inactivation	Viral inactivation
Glycine (mg/ml)	15	-	Macrogol	-
Glucose (mg/ml)	15	Maltose, 100	+	+
pH	low	4	Not specified	Not specified
IgA (mcg/ml)	50	trace	50	50

TABEL 2. Comparison among the products of IVIG on the Romanian market

of the trough level achieved (5). The current IVIG preparations approved for use are finely purified IgG (90-100%) with traces of IgM. The main difference that is clinically significant in these products is the presence or absence of IgA. Many commercial products are now available in a variety of forms and concentrations. The ones present in Romania are presented in Table 2.

There are differences regarding the pH level (relevant for acid/base balance), stabilizers (i.e., maltose, sucrose, mannitol) affecting the osmolarity of mixed samples, the pharmaceutical form (liquid vs. lyophilized form reconstituted at the time of infusion) and the half lifes (21 – 33 days). The use of high osmolarity IVIG products has been associated with acute renal failure and thrombosis especially in patients with pre–existing renal disease or coagulation disorders, and in those receiving rapid infusions of high–dose IVIG (3,5,11). Because some patients are IgA deficient, it is important that their IgA levels are measured before receiving the first IVIG treatment. IgA deficient patients may develop immunity to IgA – and they are at increased risk of anaphylaxy if they receive a blood product that contains IgA (anti – IgA antibody titers should be obtained) (3,5,12). This phenomenon may be prevented using IgA – depleted immunoglobulin. Among our patients, 2 did not have IgA ("absent" or "traces"), resulting in low tolerance for IVIG preparations containing IgA (chills, fever, headache, lombalgia, abdominal pain in case No 4) or anaphylactic shock (case No 5). The only well tolerated preparation in case No 5 was Octagam, which is virtually IgA depleted. Excepting these two cases, IVIG administration was safe and well tolerated.

Side effects of IVIG infusion are generally present in approximately 5% of the patients. The most common side effects are headache (dose and rate dependent), flushing, chills, myalgia, low back pain, chest and abdominal pain, nausea, fatigue, wheezing, transient allergic rash, arterial hypo-/hypertension, tachycardia (3,6). These adverse reactions occur more frequently at the initiation of IVIG therapy, especially in the presence of an acute infection, most often early in an infusion. They usually disappear if the infusion rate is reduced. We attempted to prevent the side effects with premedication consisting of ibuprofen, antihistamine and corticosteroids therapy at every periodical administration of IVIG (5,10,12,13).

Rare side effects include anaphylactoid reactions (IgA deficiency), aseptic meningitis, acute renal failure (underlying kidney disease, diabetes) related to the products with sucrose, not sorbitol as stabilizer (5), pulmonary symptoms, mild hemolysis due to residual anti–A and anti–B antibodies in IVIG, thrombosis (disseminated intravascular coagulopathy) (14,15), transient neutropenia and transient arthritis and articular pain. Other side effects are life-threatening human Parvovirus B_{19} infection and hepatitis (3,11,12), severe cutaneous vasculitis (type II mixed cryoglobulinemia), post-infusion hyperproteinemia, increased viscosity and pseudohyponatremia, complement consumption, eczematous dermatitis and alopecia (3,12).

One theoretical risk of transfusing IVIG consists of the transmission of some previously unknown or emerging pathogens (currently undetectable) and novel pathogens. The risk of transmission of

infectious diseases derives from the large number of donors (from 3000 to 50000 donors for a given preparation), but all products are tested for HIV, hepatitis C and B, and HTLV (3,12). Solvent detergent treatment inactivates enveloped viruses (HIV), while other aggressive processing steps remove or inactivate pathogens (11,12,13). However, outbreaks of hepatitis C have been caused by contaminated lots of IVIG preparations (11). Thus, it is recommended to store a small amount of serum before each infusion for analysis (in the event of infectious diseases transmission).

To change the IVIG dose or frequency of administration, consideration should be given to the fact that it will take about 3-5 half lives (2-3 months) to reach a new study state of IgG level. The concentration of IgG should be measured each 3-6 months. In growing children regular dose adjustment is mandatory (3,11,12,16).

Regular clinical assessment includes efficacy of treatment, complications of treatment, complication of disease and, overall health (3). We determine seric IgG level every 3 months before and after IVIG, as well as blood count, acute reactants phase (ESR, CRP), liver enzymes and seric urea nitrogen. A clinical review of all our patients before and after IVIG is done monthly. Pulmonary status should be monitored by spirometry and/or high–resolution CT every 1-2 years, even in asymptomatic individuals (5,11). The rate of catabolism of intravascular IgG pool (48%), or fractional catabolic rate (FCR), the amount of protein broken down daily is 6,3% per day (3). Plasma proteins appear to distribute in the intravascular space and into one or more extravascular spaces. After iv administration, serum concentration of IVIG exhibits initial rapid decline for 1-2 days, followed by a more gradual rate of decline (4). The half life of IgG is approximately 21 days (4,12,16,17), but there are also products with 39 days half life (3,11). Table 3 shows the seric variations of the IgG levels in our patients before and after IVIG.

The protocol for administration is applied in conjunction with the product information: IVIG should reach room temperature before infusion, infusion device will be controlled (blood filter is not necessary). On first infusion in older children, to prevent rate related reactions, the rhythm of infusion will be progressively increased: 30 ml/hour for the first 15 minutes, 60 ml/hr for the following 15 minutes; 90 ml/hr for the following 15 minutes; 120 ml/hr for the following 30 minutes and than 250ml/hr (3). In small children the rate is calculated according to weight). Subsequent infusions: from 60 ml/hr to 250 ml/hr. Some patients (cases No 1 and No 2) tolerated rapid infusions (2 hours), but other patients presented rate-related reactions (cases No 4 and No 5 needed 6 hours for each infusion).

Temperature (at the beginning of IVIG and than as necessary), pulse and blood pressure must be monitored during infusion. Some authors recommend a reassessment of immune response to protein and polysaccharide antigens one year after initiation of IVIG therapy and every 2 years thereafter (3,5,6).

Vaccination is important in patients who don't have antibodies to the polysaccharides of Pneumococcus and H. influenzae, regardless of whether they have an absolute deficiency of IgG_2 (if appropriately diagnosed, PID is a lifelong disease, requiring lifelong treatment). If they don't respond to Pneumococcus and Haemophilus influenzae polysaccharide vaccine, revaccination with protein-conjugated vaccine is indicated after stopping therapy for 2-3 months. Such vaccination may result in the production of protective antibodies of IgG_1 or IgG_3 (5,6).

Case	BMC, 20 years XLA 20g/mo	PCF, 10 years, XLA, 7,5–10g/mo	GAG, 3 years, XLA, 5g/mo	MCL, 11 years, CVID, 7-10g/mo	BAI, 14 years, A-T 10g/mo	SF, 16 years, WAS, 15g/mo
Seric IgG before IVIG (mg/dl)	331-660	248-601	28-248	220	0-262	90
Seric IgG after IVIG (mg/dl)	768-1291	657-1160	493-1067	668	772-1068	790

TABLE 3. Variations of serum IgG levels before and after IVIG (minimal and maximal values).
XLA = X–linked agammaglobulinemia; CVID = Common variable immunodeficiency; A-T = ataxia-telangiectasia; WAS = Wiskott – Aldrich syndrome.

Over the last two years subcutaneous immunoglobulin replacement therapy emerged as a new treatment option to help patient with PID who do not tolerate IVIG, have poor venous access or serious side effects. This brings the freedom and convenience of safe home self–administration (dose: 158 mg/kg weekly) with a small portable pump (18,19).

Administration at home must be reserved for those PID patients who have been shown, under medically supervised conditions, to tolerate IgG replacement, without adverse events but, of course, with regular physicians follow-up (5).

Disease complications were bronchiectasis (cases No 1, 3 and 5) and celiac disease (cases No 1 and 5), representing chronic lung disease and autoimmune phenomena, respectively. Other possible disease complications include lymphoma, granulomatous disease, inflammatory bowel disease, malabsorption, hepatitis and other infectious diseases, and malignancy. (3,12) Progressive neurodegeneration of unknown etiology after a mean duration of 6.5 years of IVIG therapy (0.5 – 13.5 years) was described by Ziegner et al (20). Creutzfeldt – Jakob disease was also mentioned in the literature (21).

Conclusion

1. Our experience in the field of diagnosis and intravenous immunoglobulin therapy is limited to the past four years, after the start of the National Programme for Prophylaxis and Treatment of Humoral PID. We hope to improve the genetic diagnosis after increased funds will be allocated for this programme.
2. Intravenous immunoglobulins appear to be a life–sustaining blood product, with our six patients as living proof of their efficiency.
3. The tolerance was a very good one, all the products being safe, with the exception of the ataxia – telangiectasia case that had very severe adverse reactions to the products with a high content of IgA.
4. Monthly administration of intravenous immunoglobulin may create discomfort and adverse reactions to some patients so we are looking for subcutaneous immunoglobulins for these patients who refuse the hospital admission.

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