SUBCUTANEOUS REPLACEMENT IN SYSTEMIC IMMUNOGLOBULIN ADVERSE REACTIONS

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Introduction
Replacement of immunoglobulin IgG is a standard therapy for patients with primary immunodeficiency disease (PIDD) characterized by primary antibody deficiency (PAd). Administering IVIG reduces the incidence and severity of infection, improves health-related quality of life, and significantly reduces mortality and morbidity in patients with PIDD. Since IVIG is a biological product derived from blood products, there are some adverse reactions associated with its regular administration. The reported incidence of adverse reactions varies widely, from 1% to 40% depending on the study and the immunoglobulin used. The most common adverse events are immediate-type reactions, occurring within 48-72 hours after initiation of the infusion. These reactions are classified as mild, moderate, and severe (Breman et al.), and were defined as follows:

<table>
<thead>
<tr>
<th>Mild / Moderate</th>
<th>Severe</th>
<th>Rare</th>
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</thead>
<tbody>
<tr>
<td>Headache, fatigue</td>
<td>Acute meningeitis</td>
<td>Serum sickness</td>
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<tr>
<td>Nausea, vomiting</td>
<td>Acute renal failure</td>
<td>Hemolytic anemia</td>
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<tr>
<td>Myalgia, arthralgia</td>
<td>Stroke</td>
<td>Pulmonary edema</td>
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<tr>
<td>Urticaria, rash, itching</td>
<td>Myocardial infarction</td>
<td>Leukopenia</td>
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<tr>
<td>Low-grade fever, chills</td>
<td>Severe wheezing</td>
<td>Neutropenia</td>
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<tr>
<td>Wheezing, chest pain</td>
<td>Bronchospasm</td>
<td>Multi-organ failure</td>
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<tr>
<td>Low back pain</td>
<td>Collapse</td>
<td></td>
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<tr>
<td>Abdominal pain, cramps</td>
<td>Anaphylactic reactions</td>
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<tr>
<td>Flushing, malaise</td>
<td></td>
<td></td>
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<tr>
<td>Nostril irritation</td>
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<td></td>
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<tr>
<td>Muscle cramps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
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<tr>
<td>Blood pressure changes</td>
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</tbody>
</table>

Mild reactions require the infusion to be slowed and antihistamines and non-steroidal anti-inflammatory drugs (NSAIDs) to be administered.

Moderate reactions include mild reactions worsening and require the infusion to be discontinued and antihistamines and NSAIDs to be administered.

Severe reactions include moderate reaction persisting or becoming worse; and serious and potentially fatal side-effects requiring the administration of epinephrine and further medical attention (Table 1).

Associated factors with adverse reactions caused by IVIG
- First administration
- Infection
- Rate of infusion
- Change in preparations
- Delay after the last infusion
- Anti-IgA antibodies

Case report
Following the case report of the first experiences of initiation of home-based treatment with subcutaneous immunoglobulin (SCIg) with the patient diagnosed with primary valvular immunodeficiency (CVID). While treating this patient mild, moderate, but also severe adverse events occurred after previous administration of different intravenous and even intramuscular preparations, in the past personal history.

Medical history
- Grandfather died at age of 60 of lung cancer
- Father died at age of 55 of myocardial infarction
- Mother and brother are healthy
- Son attended at the age of 5
- On an appointment at the age of 16

The patient was treated by pediatric allergist/immunologist for recurrent respiratory infections from 2008-2004. Laboratory tests confirmed antibody deficiency (IgG, IgA, IgM), parameters innate and adaptive cellular immunity were in the physiologic range. The treatment was initiated by intravenous immunoglobulin therapy (IVIG) – Norga® (manufactured by Grifols). The patient is satisfied with the current treatment (SCIg), except for mild local side effects – pain, swelling and redness at the infusion sites lasting for the period of first two months (Table 3).

Adverse reactions to previous immunoglobulin therapy
- The patient treated at immunology-immunology outpatient clinic since 2005 with the diagnosis of hypogammaglobulinemia (IgG, IgA, IgM) with normal B cell count, using IVIG (CVID confirmed primary immunodeficiency). With the repeated administration of intramuscular and intravenous immunoglobulins (IVIG, IMIG) repeatedly occurred slightly minor or moderate side-effects as well as serious adverse reactions, which resulted in discontinuation of the replacement therapy (see the following information below).

Year 2006
Pasturised Human Immunoglobulin Grifols® 16% solution (Instituto Grifols, S.A., Barcelona, Spain) – IMIG – malaise occurred in the evening, followed by fatigue, fever, back pain, lasting 2 to 3 days after administration.

Years 2006-2008
Flebogamma®85% (Instituto Grifols, S.A., Barcelona, Spain): IVIG – right at the initiation of infusion, at a dose of 5.5 gram, occurred chills, abdominal pain, diarrhea, headache, back pain, muscle pain, low-grade fever, malaise. Followed by the administration at a dose of 5 grams occurred chills, tachycardia, facial flushing, wheezing. In the evening, the patient was examined in the emergency room for repeated complications – chills, facial flushing, swelling of the lips, arm pain. Despite predemedication and reduction of the prescribed rate of infusion, adverse reactions occurred repeatedly with increasing doses over 5 grams, therefore the treatment was irregular and later discontinued.

Years 2009-2010
Kogvær® (Baker's Art, Volkstof, Switzerland) – IVIG – at a dose of 5 grams fever and dizziness occurred in the evening hours. With the increasing of dose to 6.5 grams occurred sudden chills, chest tightness, headache, nausea, hypotension, tachycardia, low back pain, myalgias, muscle cramps, peripheral oedema and syncope, thyroid pulse, anxiety, anaphylactoid reaction with the necessity of administration of epinephrine, hydrocortisone and antihistamines (emergency transport).

Years 2010-2011
Octagam® (Octapharma, Vienna, Austria) – IVIG – during the administration of IVIG, the patient felt severe pain in the right arm, followed by redness, swelling of the hand, fever, pruritus of the skin, urticaria, fever, chills, nausea, vomiting, facial flushing, wheezing, cough, malaise, and muscle cramps occurred.

Discussion
Despite initial concerns about possible adverse reactions at home, either by the patient or physician, we evaluate the first months of treatment to be highly positive. There are several advantages of SCIG over IVIG. The patient is satisfied with the current treatment (SCIg), as an advantage she considers reducing the number of doctor’s office visits, less frequent contact with the patients in healthcare facilities, reducing the frequency and rate of infusions, diversified range of antibiotics, fewer absences from work, and limitations in daily activities (Table 2).

Adverse reactions to previous immunoglobulin therapy
- The patient treated at our immunology-immunology outpatient clinic since 2005 with the diagnosis of hypogammaglobulinemia (IgG, IgA, IgM) with normal B cell count, using IVIG (CVID confirmed primary immunodeficiency). With the repeated administration of intramuscular and intravenous immunoglobulins (IVIG, IMIG) repeatedly occurred slightly minor or moderate side-effects as well as serious adverse reactions, which resulted in discontinuation of the replacement therapy (see the following information below).

Conclusion
In summary, systemic reactions rates with SCIG are low and reportedly occur less frequently than with IVIG infusions. SCIG systemic reactions rates are reported as 0% to 5%, generally occurring in less than 1% infusions. SCIG provides greater ease, flexibility and convenience than IVIG because it can be administered according to the patient’s schedule and can be infused at home, without requiring venous access. Studies have suggested similar efficacy with SCIG compared with IVIG in preventing infections in patients with PIDD. Compared with IM or IV formulations and administration, for selected patients, SCIG is better tolerated, clinically efficacious, safe, less costly, and appreciated by the patients. Our initial clinical experience also shows that patients with serious side effects to previous immunoglobulin therapy can be safely treated with subcutaneous replacement therapy.

References

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