Subcutaneous Administration of Immunoglobulins
What Are the Advantages?

Ann Gardulf and Lennart Hammarström

Division of Clinical Immunology, Department of Immunology, Microbiology, Pathology and Infectious Diseases, The Karolinska Institute at Huddinge University Hospital, Stockholm, Sweden

Contents

Summary ........................................... 108
1. Primary and Secondary Immunodeficiencies ........................................... 109
2. Immunoglobulin Replacement Therapy .................................................... 109
3. Adverse Effects of Immunoglobulin Replacement Therapy .......................... 110
4. History of Subcutaneous Infusions of Immunoglobulins ............................ 110
5. Home Therapy with Immunoglobulins ...................................................... 110
6. Costs of Immunoglobulin Replacement Therapy ....................................... 111
7. Method of Subcutaneous Administration of Immunoglobulin ..................... 112
8. Advantages of Subcutaneous Administration of Immunoglobulin ............... 112
  8.1 Low Risk of Virus Transmission .......................................................... 112
  8.2 Low Frequency of Adverse Systemic Reactions ..................................... 113
  8.3 Ability to Obtain High Serum Immunoglobulin Levels ............................. 114
  8.4 Increased Health-Related Quality of Life ............................................. 115
  8.5 Reduced Costs for the Healthcare Sector and for the Patient ................ 115
9. Conclusions ......................................................................................... 115

Summary

Immunoglobulin (IgG) therapy has hitherto mainly been given as intramuscular injections or intravenous infusions. However, due to disadvantages using these methods, we have developed a method for rapid subcutaneous infusion of IgG which is well tolerated (no virus transmission and no severe adverse reactions), improves the health-related quality of life, is highly appreciated by patients and leads to reduced costs for the healthcare sector and the patients. Altogether, more than 60 000 subcutaneous IgG infusions have now been given to patients with primary and secondary antibody deficiencies. Our experience suggests that this form of therapy constitutes the current treatment of choice both for the clinician and the patient.

The immune system comprises several different cell types which have the ability to recognise infectious microbial agents such as viruses, bacteria, fungi and parasites. In addition to lymphocytes, monocytes and granulocytes, different soluble factors, such as immunoglobulins, complement and cytokines, participate in the combat against infectious agents. The immunoglobulins, which are produced by B lymphocytes, are divided into 5 main classes: IgG, IgA, IgM, IgD and IgE. IgG is furthermore sub-
divided into the subclasses IgG1, IgG2, IgG3 and IgG4.

The most common primary immunodeficiency in man is a lack of or low levels of immunoglobulins, which leads to an increased susceptibility to respiratory and gastrointestinal infections. Individuals with these conditions are often in need of lifelong, prophylactic, replacement therapy with human immunoglobulin (IgG) to prevent or reduce the severity of their infections. This replacement therapy has hitherto mainly been given in the form of intramuscular injections or intravenous infusions. The major drawbacks with intramuscular therapy are the risk of severe, or even anaphylactoid, adverse systemic reactions and the problem of giving sufficient amounts of IgG via the injections. The major disadvantages of intravenous therapy are the risk of virus transmission and the higher prices of the intravenous immunoglobulin products. It is therefore important to find a safe, efficient and low-cost replacement therapy that could serve as an alternative. Likewise, the method of administration should be easy for patients to handle and have a minimal negative impact on their daily lives.

We therefore initiated a method of high-dose IgG replacement given by rapid subcutaneous infusions, both as hospital-based therapy and as home therapy. The subcutaneous method and the home therapy regimen have been found to:

- be well tolerated (no virus transmission and no severe adverse reactions)[1,2]
- improve health-related quality of life[3]
- be highly appreciated by patients[4]
- result in serum IgG levels within the normal range of healthy individuals[5]
- reduce costs, both for the healthcare sector and the patients.[2, 6]

1. Primary and Secondary Immunodeficiencies

The primary immunodeficiency diseases are naturally occurring defects of the immune system which remain for life, whereas the secondary immunodeficiency diseases result from conditions such as malignancies, metabolic diseases, malnutrition, drugs, burns and infections.[7]

X-linked agammaglobulinaemia (XLA) and common variable immunodeficiency disease (CVID) are both characterised by low levels of serum IgG and IgA, and often also IgM. Individuals with XLA or CVID are prone to recurrent bacterial infections in both the upper and the lower respiratory tracts. An increased frequency of gastrointestinal infections, septic arthritis, encephalitis and malignancies has also been reported in this group of patients. The prevalence of CVID has been estimated to be 1.2 to 5.0 per 100 000 individuals.

Selective IgA deficiency is the most common antibody deficiency, with an estimated prevalence of 1 per 500 Caucasian individuals. It is associated with an increased rate of infections in the upper respiratory tract and the gastrointestinal tract in approximately 30 to 50% of cases.

Low levels of serum IgG1 and/or IgG2 immunoglobulins are related to an ineffective defence against bacteria, causing recurrent respiratory tract infections. The clinical features of selective IgG3 deficiency have been described differently, with repeated attacks of fever for 3 to 6 days with sore throat and muscle pain suggestive of recurrent viral infection.

2. Immunoglobulin Replacement Therapy

Bruton published a case report in 1952 that not only described the first known case of antibody deficiency in man, but also introduced IgG replacement therapy.[8] Today, individuals with CVID or XLA should receive replacement therapy with IgG. Also patients with IgA and/or IgG1 and IgG2 subclass deficiencies are known to benefit from replacement treatment. The protective effect of the administration of IgG in individuals with selective IgG3 or IgG4 subclass deficiencies is not yet well established. Nevertheless, substitution is in practice often initiated in infection-prone patients with a selective IgG3 deficiency.

In 1969, the Medical Research Council in England recommended that individuals with primary