Subcutaneous Immunoglobulin G in Idiopathic Inflammatory Myopathies: Therapeutic Implications

Chiara Gelardi MD, Luca Paolini MD and Maria G. Danieli MD

Department of Clinical and Molecular Sciences, Section of Clinical Medicine, Polytechnique University of Marche, Torrette di Ancona, Italy

KEY WORDS: polymyositis (PM), dermatomyositis (DM), subcutaneous immunoglobulin G (SCIg), intravenous immunoglobulin G (IVIg)

IMAJ 2014; 16: 646–647

Polymyositis (PM) and dermatomyositis (DM) are systemic autoimmune diseases of unknown etiology that primarily affect the skeletal muscle [1]. Despite the improvement achieved in recent years with new therapeutic options, the prognosis remains poor, with high rates of morbidity and mortality. Conventional first-line treatment is based on glucocorticoids. However, their use in many patients requires long-term administration, which increases the probability of side effects developing. Thus, there is often the need to add immunosuppressive or immunomodulatory agents to improve the disease's response to treatment and to reduce the long-term complications linked to glucocorticoids [2]. Among the treatment options, the use of immunoglobulin, by both the intravenous (IVIg) and the subcutaneous (SCIg) route, is still under debate [3].

IVIg as replacement therapy was first introduced in the middle of the 20th century for the treatment of immunodeficiencies, for which it is the treatment of choice [4]. Several mechanisms have been proposed to explain how IVIg acts by interaction with the humoral and cellular components of the immune system. However, its exact mechanism of action is not thoroughly understood [5,6]. In immune mediated disorders, IVIg is a therapeutic option considered as a steroid-sparing agent and for reducing side effects related to the use of immunosuppressants. In inflammatory myopathies (IIM), only IVIg has demonstrated statistically significant improvement in scores of muscle strength compared to placebo in high quality randomized controlled trials [2,7]. However, the use of IVIg is associated with several issues, namely, the need for an intravenous route of administration necessitates hospitalization, which leads to high costs and potentially severe systemic side effects (volume overload, anaphylactic reactions) [4].

SCIg is a blood product containing immunoglobulin G from healthy subjects, initially used in primary immunodeficiency diseases and more recently in immune mediated disorders or neurological conditions. In primary immunodeficiency SCIg has been demonstrated to reduce adverse reactions with reliable efficacy and improved quality of life [8]. We describe here our experience with the use of SCIg in patients with PM and DM.

METHODS

In our clinic, for each patient with a suspected IIM the biopsy-proven diagnosis was based on Bohan and Peter's criteria. Each patient was then followed with clinical evaluation (MRC muscle strength score and Rankin modified score) and laboratory and instrumental monitoring (creatine kinase serum levels and electromyography-electroneurography).

We administered SCIg according to two different treatment schedules:

- the "sequential IVIg-SCIg protocol" given to patients with severe disease (dysphagia, head drop, high levels of CK, severe weakness). It is based on a 6 month period of IVIg (1 g/kg/month given on 2 consecutive days each month) followed by maintenance treatment with SCIg (0.2–0.8 g/kg/month)
- the "direct SCIg protocol" for patients with moderately active PM/DM having either a new onset or recently relapsed disease, as add-on treatment to glucocorticoids [10].

In the last few years we used 20% SCIg (Hizentra®, CSL Behring GmbH, Marburg) infusions. The 20% SCIg has high purity (> 98% IgG), higher IgG content (20%) and lower viscosity. This permits low infusion volumes and high infusion rates, shorter length of infusion, and convenient product conservation compared to 16% SCIg.

At our Center of Clinical Medicine we observed the efficacy of the sequential IVIg-SCIg treatment in six patients (all females, mean age 48 years, three PM and three DM) who had clinical and laboratory remission after 12 months of follow-up. With sequential administration of IVIg, the maximum response to therapy in a short time was achieved, followed by a maintenance period with SCIg (0.2–0.8 g/kg/month). The first SCIg dose was administered 2 weeks after the last IVIg infusion [9,10].

Regarding the direct protocol, we documented its efficacy and safety using SCIg as add-on treatment to glucocorticoids in seven

Table 1. Recommendations for SCIg use as first-line treatment in idiopathic inflammatory myositis

Possible indications for SCIg as first-line therapy in patients with PM/DM
- Cancer-associated myositis, with recent cancer or with pre-neoplastic disease
- Contraindications to the use of immunosuppressants (hepatitis C virus, hepatitis B virus, human immunodeficiency virus, common variable immunodeficiency and/or other situation of immunodepression)
- Young women who wish to fall pregnant
- Contraindications to continued glucocorticoid treatment (i.e., poorly controlled diabetes, arterial hypertension, osteoporosis)

Possible indications for SCIg as preferred to IVIg in subjects with
- Difficulty of venous access
- Past thromboembolic events
- Selective IgA deficit
- Impaired renal function
- Heart involvement due to myositis or other causes

patients (five females and two males, mean age 55 years) with new-onset or recently relapsed PM/DM. SCIg infusions were given as previously described. In all patients we documented improvement in the MRC score and Rankin modified score, associated with a reduction in serum creatine kinase levels.

In both trials most of the patients were able to significantly reduce the dose of prednisone and, if applicable, of immunosuppressants as well.

CONCLUSIONS

Based on our experience, the use of SCIg may be a valid option alternative to IVIg in patients with refractory PM/DM or as first-line treatment when the use of glucocorticoids or immunosuppressants is contraindicated or if the patient is poorly compliant with these drugs and IVIg therapy [Table 1].

The sequential protocol with IVIg-SCIg in patients with new-onset myositis allows complete clinical and functional recovery with a long-term stable remission. The direct protocol should be considered in moderately active inflammatory myopathies as add-on treatment to glucocorticoids in patients with either new-onset or recently relapsed PM/DM or refractory disease.

Correspondence
Dr. C. Gelardi
Dept. of Clinical and Molecular Sciences, Section of Clinical Medicine, Polytechnique University of Marche, Torrette di Ancona, 60126, Italy
email: chiaragelardi@libero.it

References

1. Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975; 292: 344-7 and 403-7.
2. Gordon PA, Winer JB, Hoogendijk JE, et al. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis [Review]. *Cochrane Database Syst Rev* 2012; 8: CD003643.
3. Dalakas MC. Immunotherapy of myositis: issues, concerns and future prospects. *Nat Rev Rheumatol* 2010; 6: 129-37.
4. Berger M. Subcutaneous administration of IgG. *Immunol Allergy Clin North Am* 2008; 28: 779-802.
5. Blank M, Bashi T, Shoenfeld Y. Idiotype-specific intravenous immunoglobulin (IVIG) for therapy of autoimmune diseases. *Methods Mol Biol* 2014; 1060: 353-61.
6. Kessel A, Ammuri H, Peri R, et al. Intravenous immunoglobulin therapy affects T regulatory cells by increasing their suppressive function. *J Immunol* 2007; 179: 5571-5.
7. Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993; 329: 1993-2000.
8. Berger M. Subcutaneous IgG in neurologic diseases. *Immunotherapy* 2014; 6: 71-83.
9. Danieli MG, Gelardi C, Pedini V, Moretti R, Gabrielli A, Logullo F. Subcutaneous IgG in immune-mediate diseases: proposed mechanisms of action and literature review. *Autoimmun Rev* 2014; doi: 10.1016/j.autrev.2014.08.018. [Epub ahead of print].
10. Danieli MG, Pettinari L, Moretti R, Logullo F, Gabrielli A. Subcutaneous immunoglobulin in polymyositis and dermatomyositis: a novel application. *Autoimmun Rev* 2011; 10: 144-9.