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Immunoglobulin Treatment in Polymyositis and Dermatomyositis

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1. Introduction

Polymyositis (PM) and dermatomyositis (DM) are systemic autoimmune diseases of unknown aetiology in which the skeletal muscles are the main targets (Bohan & Peter, 1975). Despite the improvement obtained in recent years with new therapeutic options, their prognosis remains poor, with higher rates of morbidity and mortality (Dalakas, 1991, 2001). Due to the rarity of the disease, few well-designed studies have been published and, to the best of our knowledge, only five randomised controlled trials have been carried out (Choy, 2002). A low incidence of the disease, a characteristic relapsing/remitting or chronic and persistently active course, a lack of agreed standardised criteria for diagnosis and for assessment of disease activity makes it difficult to carry out and to compare studies. Conventional first line therapy is based on glucocorticoids and their use in many patients requires long-term use to control disease. Many patients suffer from the side effects of glucocorticoids while others can be refractory to first-line therapy. Thus, there is often the need to add immunosuppressive or immunomodulatory agents both to improve the disease's response and to reduce the risk of long-term complications linked to glucocorticoids (Choy, 2009).

Among the treatment options, the use of intravenous immunoglobulin is still matter of debate.

In this chapter we describe the use of intravenous immunoglobulin in inflammatory myopathies, revising the literature and reporting our experience. Most of the patients with polymyositis or dermatomyositis receive an immunosuppressant such as azathioprine, methotrexate, cyclosporine A or mycophenolate mofetil. We decided to verify if the use of intravenous immunoglobulin as add-on treatment with cyclosporine A or mycophenolate mofetil could improve the outcome or reduce the rate of side effects that are usually linked to the immunosuppressant. The subcutaneous administration of immunoglobulin could be considered as an alternative to intravenous immunoglobulin. In primary immunodeficiency, subcutaneous immunoglobulin has been demonstrated to be linked to a lower incidence of adverse reactions, with reliable efficacy and improvement in the quality of life of treated subjects. We have been the first to publish a series of seven patients with immune-mediated myopathies treated with subcutaneous immunoglobulin. Here we present data relating to a larger series. Finally, our intention is to review the data related to the mechanisms of action

of immunoglobulin in immune-mediated diseases, in particular underlining the different proposed mechanism of intravenous and subcutaneous immunoglobulin.

2. Intravenous immunoglobulin in inflammatory myopathies

2.1 Background

Intravenous immunoglobulin is a therapeutic preparation of pooled polyspecific IgG obtained from the plasma of a large number of healthy individuals. The preparations were commercialized in the early 1980s to replace intramuscular preparations of polyspecific IgG, which were the only available substitutive therapy at that time for patients with primary or secondary immunodeficiencies. For patients with primary immunodeficiencies, intravenous immunoglobulin (or subcutaneous immunoglobulin) remains the treatment option of choice.

Despite the large number of autoimmune diseases treated with intravenous immunoglobulin, guidance on the clinical usage is limited to only three conditions: idiopathic thrombocytopenic purpura, Guillian-Barrè syndrome and Kawasaki disease (rev. in Elovaaraa et al., 2008). In other neurological conditions, such as chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, and in acute exacerbations and short-term treatment of severe myasthenia gravis, their use is codified (Elovaaraa et al., 2008).

Because of the costs, finite supply and time required for the patient receiving intravenous therapy, there is a need to rationalize and prioritize the disorders for which, based on currently available evidence, intravenous immunoglobulin is adopted. In France, the Comité d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT) -Intravenous Immunoglobulin Expert Group, aims to identify scientifically validated uses and issue recommendations regarding the usage of intravenous immunoglobulin (Mouthon, 2006). Guidelines for the use of immunoglobulin have also been developed in the United Kingdom (UK Department of Health, 2009), Canada (Mydlarski, 2006; Feasby et al., 2007), Australia (Australian Health Minister, 2009) and elsewhere.

For most of the diseases, intravenous immunoglobulin is not always used as a first-line therapy. It may be administered as a steroid-sparing agent and in certain conditions may represent an alternative to other available therapeutic approaches, such as immunosuppressants, plasma exchange or monoclonal antibodies. Intravenous immunoglobulin is also often employed to treat diseases that are refractory to other treatments or where conventional therapies result in unacceptable side effects. Combination therapy of intravenous immunoglobulin with immunosuppressants has been applied successfully in several conditions, including autoimmune vasculitis, and chronic inflammatory myopathies (Hartung et al., 2009; Harvey, 2005).

In 1987, Roifman et al. described the first patient with refractory polymyositis successfully treated using intravenous immunoglobulin, whereas in 1991 Lang et al. were the first to highlight the beneficial use of intravenous immunoglobulin in the treatment of dermatomyositis. Several additional papers have since been published. However, a review of the available literature about the use of intravenous immunoglobulin in inflammatory myopathies shows the lack of randomised controlled trials due to the difficulty of conducting high quality randomised controlled trials in rare diseases. Despite the different significance and rationale regarding the use of intravenous immunoglobulin treatment in polymyositis and dermatomyositis, the majority of studies reported the use in mixed

populations of patients with both diseases. Moreover, in most studies, intravenous immunoglobulin has been used in association with other drugs, such as immunosuppressants. It is thus difficult to evaluate optimal strategies and efficacy: safety ratio in inflammatory myopathies. Here we present a brief revision of the most relevant studies on the use of intravenous immunoglobulin in inflammatory myopathies. The application in combined treatment with immunosuppressant is analysed in Paragraphs 3 and 4.

2.2 Mechanisms of action of intravenous immunoglobulin

Intravenous immunoglobulin was first introduced in the middle of the twentieth century for the treatment of primary immunodeficiencies. In 1981, Paul Imbach noticed an improvement of immune-mediated thrombocytopenia in patients receiving intravenous immunoglobulin for immunodeficiencies (Imbach et al., 1981). This opened a new era for the treatment of autoimmune conditions with intravenous immunoglobulin. Since then, intravenous immunoglobulin has become an important treatment option in an ever-increasing number of autoimmune diseases (Arson et al., 2009; Kivity et al., 2010; Mimouni et al., 2011) and, more recently, for the treatment of tumor metastases (Damianovich et al., 2009). Immune dysregulation and loss of self-tolerance are the keystones of autoimmunity (Agmon-Levin et al., 2011). There is a large body of evidence that intravenous immunoglobulin has the ability to modulate immune reaction at several cellular levels (T and B cells, macrophages), interfere with antibody production and degradation, modulate the complement cascade, and effect the cytokine network. Despite success in clinical application, the precise mechanism of action is not yet clear, but several non-mutually exclusive mechanisms have been proposed to explain the beneficial effects of intravenous immunoglobulin.

To understand how intravenous immunoglobulin reverses inflammation in autoimmune disease, it is helpful to consider how immunoglobulin G (IgG) auto-antibodies cause inflammation. IgG molecules are the most abundant antibody class in the sera of humans; they are a family of molecules consisting of four subclasses which vary in their serum prevalence and capacity to trigger effector functions, such as binding to cellular Fc-receptors for IgG or activating the complement pathway. They seem to have the unique feature of initiating pro- and anti-inflammatory reactions: they are the primary mediators of protective humoral immunity against pathogens, but they can also be pathogenic. Acting as cytotoxic molecules or as immune complexes, IgG auto-antibodies are the principal mediators of autoimmune diseases. This pro-inflammatory activity mainly depends on the presence of cellular Fc-receptors for IgG.

Aschermann et al. (2010) proposed a possible explanation based on the interaction interference of cellular Fc-receptors on IgG (FCγR), and the complement components of the Fc-fragment which could prevent the auto-antibodies-mediated FCγR activation by blocking FCγ and FCγR interaction. Anthony et al. (2008) describe a model wherein sialylated IgG Fc protein interacts with a currently unidentified sialic acid-specific receptor on specific regulatory macrophages in the marginal zone of spleen. This consequently enhances the expression of the Fcγ receptor IIB on effector macrophages, highlighting that Fcγ receptor has a critical role in mediating the therapeutic effects of intravenous immunoglobulin. The mechanisms by which high doses of pooled, monomeric IgG provide anti-inflammatory activity have been the subject of much speculation, stemming from the fact that IgG can form many different binding interactions through both their antigen binding and Fc

domains. In some cases, antigen binding alone might be sufficient to mediate the anti-inflammatory effects attributed to intravenous immunoglobulin, for example, by blocking interactions between a pro-inflammatory ligand and its receptor or by neutralizing its ability to elicit an inflammatory response.

Moreover, due to their presence in natural auto-antibodies against the receptors sialic acid binding immunoglobulin (Ig)-like lectin (Siglec)-8 and Siglec-9 that mediate cell death, anti-proliferative effects and inhibition of cellular activities, intravenous immunoglobulin may exert anti-inflammatory properties by increasing the concentration of natural anti-Siglec autoantibodies in blood and tissues (Von Gunten et al., 2008). Due to the content of anti-Siglec-8, the usefulness of intravenous immunoglobulin can be hypothesised in hypereosinophilic syndrome or in Churg-Strauss syndrome, because of the documented death's induction by natural antibodies against Siglec-8 and Siglec-9 present in intravenous immunoglobulin in both eosinophils and neutrophils in a concentration-dependent manner. In a controlled trial regarding Churg-Strauss syndrome it was documented that all patients in the intravenous immunoglobulin group were in remission with a significantly favourable outcome, compared to controls, which remained after three years. (Danieli et al., 2004).

It is possible that not all IgG in intravenous immunoglobulin is effective and in all probability the involved mechanisms vary from one disease to another. The different molecular and cellular pathways involved could explain the wide spectrum of diseases in which intravenous immunoglobulin could exert its immunomodulatory and anti-inflammatory properties. Particular intravenous immunoglobulin activities are also believed to be related to the sialylation of IgG through which they become functional in restricted subset of diseases such as inflammatory-ones (Seite et al., 2008).

Due to the method of preparation, the content of immunoglobulin product is variable, including natural antibodies and natural auto-antibodies that play a major role in its activity (Seite et al., 2008; Vani et al., 2008; Schwartz-Albiez et al., 2009). Other relevant supposed mechanisms of action take account of modulation of idiotype-anti-idiotype dimers network by binding idiotypic determinants of auto-antibodies; activation, differentiation and effector functions of T and of antigen-presenting cells; modulation of B cells via the antigen receptor; and interferences with activation of complement and the cytokine network (Seite et al., 2008).

In regard to inflammatory muscle diseases, which have different clinical, histological, and immunopathological features, the mechanism of action may be different according to the properties of individual diseases. The cause of polymyositis and dermatomyositis is unknown, but an immune-mediated pathogenesis is strongly implicated.

As illustrated by Dalakas (2006) intravenous immunoglobulin is thought to work by inhibiting complement consumption and intercepting membrane attack complexes, suppressing cytokines, adhesion molecules and fibrogenetic factors, and altering biologically relevant immunoregulatory or tissues remodelling genes. Resolution of the aberrant immunopathological parameters, including interception of complement activation products and down-regulation of T cells, intercellular adhesion molecule-1 (ICAM-I), vascular cell adhesion molecule (VCAM), transforming growth factor (TGF)-b and major histocompatibility complex (MHC)-I molecules, was also noted.

Dermatomyositis is histologically characterised by complement-mediated microangiopathy beginning with complement activation in the periphery that eventually leads to the formation of membrane attack complexes, which are deposited on the capillaries causing destruction of endomysial capillaries. A number of cytokines and chemokines are thought to

be in involved in the process. These molecules may also be responsible for the up-regulation of the major histocompatibility complex (MHC) class I antigen and signal trasducer and activator of transcription (STAT) 1 expression on the perifascicular's muscle fibre. The actual effectiveness of intravenous immunoglobulin was demonstrated by Dalakas (2006) in a double-blind placebo-controlled study. His results demonstrated the improvement in muscle cytoarchitecture, down-regulation of cytokine and adhesion molecules, effect on complement activation and MAC formation and the improvement of the muscle microvasculature. Down-regulation of intercellular adhesion molecule-1 (ICAM-I) more than likely has an effect on the exit of activated T cells from the capillaries toward the muscle fibres, reducing inflammatory cells infiltrate. Another possible effect is the down-regulation of TGF-β and TGF-β mRNA, which induces chronic inflammation and fibrosis if in excess, as seen in the tissue of patients with dermatomyositis, where it is in generally up-regulated. Consequently, intravenous immunoglobulin facilitated neovascularisation and normalisation of the capillaries and muscle fibres.

In polymyositis the muscle injury appears to be T-cells mediated and directed against unknown antigens expressed on the sarcolemma of the muscle fibres. A severe perturbation of peripheral blood T cell TCR repertories was displayed, characterized by the presence of antigen specific T-cell with killer/effector phenotype (Mizuno et al., 2004). Thus, CD8+ cytotoxic T cells clonally expand and lead to muscle fibres necrosis via perforin pathway, according to the observed rearrangement of T-cell-receptor genes among autoinvasive T cells and expression of co-stimulatory molecules, adhesion molecules and cytokines (Dalakas, 2010).

With intravenous immunoglobulin it is thus possible to restore immunoregulation and normal immune homeostasis (Gurcan et al., 2010; Seite et al., 2008).

2.3 Intravenous immunoglobulin in dermatomyositis

With regard to dermatomyositis, a Cochrane review article looking at randomised controlled studies (Choy, 2009) identified only the pioneering trial of Dalakas (1993) in 15 patients with treatment-resistant disease which compared monthly infusions of 2 g/kg of immunoglobulin for three months in association with pre-existing low-dose glucocorticoids to placebo. The study demonstrated a statistically significant improvement in muscle strength measured by mean scores on the neuromuscular symptom scale (P = .035) and the modified Medical Research Council scale (from 76.6 to 84.6; P = .018; with a mean difference of 9.50 (95% confidence interval (CI) 4.33 to 14.67) in the treated group. Even though the trial measured muscle strength after only three months, the improvements, even in cutaneous manifestations, lasted for several weeks. This trial remains the fundamental work demonstrating that intravenous immunoglobulin is a beneficial strategy in dermatomyositis.

The successful use of intravenous immunoglobulin has also been highlighted in other studies that show the improvement of 75% to 92% of adults using this treatment modality for refractory disease (Gelfand, 1989; Mastaglia, 1998; Marie, 2001). A recent work by Gottfried et al. (2000) indicated that remission was documented in particular in patients with predominant cutaneous symptoms, absence of autoantibodies, without accompanying neoplasia.

Based on expert consensus, Feasby et al. (2007) conclude that intravenous immunoglobulin is recommended, in combination with prednisone, for patients with dermatomyositis who have not satisfactorily responded to glucocorticoids. Intravenous immunoglobulin is recommended, in association with immunosuppressants, as a steroid-sparing option or as

the first-line treatment in life-threatening disease (Feasby et al., 2007). With regards to treatment dose and duration, the reported dose is usually 2g/kg, given for two/five days in adult patients. In a single treatment course the maximum dose should be 2g/kg. In patients responding to this treatment, every attempt should be made to determine the minimum effective dose and the use of intravenous immunoglobulin should be continued only if there are objective measures of sustained effectiveness.

2.4 Intravenous immunoglobulin in polymyositis

The application of intravenous immunoglobulin in polymyositis has not yet been assessed with a randomised trial. Their efficacy was highlighted by Cherin et al. in 1991 with a study of 20 patients with chronic and refractory polymyositis or dermatomyositis showing clinical improvement of fifteen patients (75%) and biochemical improvement in all of them (Cherin, 1991). The subsequent follow-up, with an increased series including 35 patients with refractory dermatomyositis or polymyositis, presented pooled data confirming the improvement of patients treated with this regime (Cherin & Herson, 1994). The authors documented a significant improvement in mean muscle power ($P = 0.01$) with a reduction in mean steroid dose ($P = 0.05$) and a decrease in creatine kinase levels ($P = 0.01$). The same group presented data on the only published non-randomised controlled trial specifically addressed to polymyositis (Cherin et al., 2002). This study reported clinical improvement in 71% of patients with significant improvement in muscle power, muscle disability scores, and creatinine kinase levels ($P < 0.01$). All of the 22 patients who received intravenous immunoglobulin were able to significantly reduce the dose of glucocorticoids ($P < 0.05$). In conclusion, in polymyositis, intravenous immunoglobulin can be considered as an alternative therapeutic option in patients who do not respond to conventional first-line treatment (glucocorticoids). Dose and duration of the treatment are as recommended for dermatomyositis (Feasby et al., 2007; Elovaara et al., 2008).

Despite intravenous immunoglobulin demonstrating adequate efficacy and rapid onset of beneficial effects, there are no indications for its use as first-line therapy. The use of intravenous immunoglobulin, in an attempt to replace glucocorticoids as first-choice treatment to avoid steroid-related myopathy in six adult patients with dermatomyositis and in five with polymyositis, did not lead to a significant increase in muscle strength, although creatine kinase levels significantly decreased (Cherin et al., 1994). Only three patients showed significant clinical improvement. The low success rate obtained by intravenous immunoglobulin as first-choice in inflammatory myopathies, compared to their usual efficacy in association with glucocorticoids in chronic refractory diseases, suggests a synergistic action on both cellular and humoral systems (Cherin et al., 1994). More recent studies, in accordance with previous literature, confirm indication of the value of intravenous immunoglobulin as a second-line agent in patients with dermatomyositis and polymyositis (Cherin, 2008; Dalakas, 2010).

2.5 Other indications of intravenous immunoglobulin

Besides the cutaneous and muscle involvement, intravenous immunoglobulin has been evaluated in other clinical manifestations of inflammatory myopathies. A rapid onset of therapeutical effects was substantiated by Marie et al. (2010) in a recent retrospective multicentre study reviewing 73 patients with oesophageal involvement in which intravenous immunoglobulin (1 g/kg daily for two consecutive days each month for at least seven months) produced improvement within two weeks after the first infusion with a

clinical resolution or a marked improvement of oesophageal clinical involvement in 65 patients (89%), thus suggesting their use as first-line therapy in life-threatening oesophageal manifestations. This data confirms previous studies in smaller series (Marie et al., 1999; Cherin et al., 2001). Contrasting results have been documented in interstitial lung disease associated with polymyositis and dermatomyositis, in which only a small number cases show benefits from intravenous immunoglobulin (Suzuki et al., 2009).

Intravenous immunoglobulin may also be an alternative option when other drugs are not recommended, especially during pregnancy and in breast-feeding mothers. Pregnancy in association with an inflammatory myopathy is a rare event, therefore any published data is primarily based on case reports or very small groups of patients (Silva et al., 2003; Mosca et al., 2005; Williams et al., 2007). Even in this context, intravenous immunoglobulin has been shown to be very effective in the treatment of inflammatory myopathies, in particular in dermatomyositis (Cherin et al., 2002), and is widely used for various autoimmune conditions during pregnancy. It is also used in the treatment of other pregnancy complications, such as idiopathic thrombocytopenic purpura and recurrent miscarriages, and appears to be safe and well tolerated by pregnant patients (Branch et al., 2001).

2.6 Our experience with intravenous immunoglobulin in polymyositis and dermatomyositis

We report our experience on the use of intravenous immunoglobulin only associated with glucocorticoids in polymyositis and dermatomyositis diagnosed according to the Bohan and Peter criteria (1975). Despite alternative classifications being previously proposed and the fact that this classification presents some limitations it is the most widely used set of criteria in the literature.

	Definition
Diagnosis of polymyositis and dermatomyositis	Bohan and Peter's criteria (1975): Symmetrical weakness, usually progressive, of the limb-girdle muscles Muscle biopsy evidence of myositis Elevation in serum of creatine kinase levels Electromyographic triad of myopathy Characteristic dermatologic features of dermatomyositis
Active disease	Decreased skeletal muscle strength assessed using the Medical Research Council scale (Miller et al., 1992); Elevation of creatine kinase for at least 2 months; Typical electromyographic features (Kimura, 1989; Wilbourn, 1993)
Refractory disease	Inadequate response to steroid and/or at least 2 immunosuppressants given for at least two months; OR Steroid-dependency: flare-up when the steroid dose was reduced to less than 0.25 mg/kg/day; OR Steroid-resistance: non-responsiveness to high-dose steroid treatment (at least 1 mg/kg/day for six weeks)
Relapse	Disease reactivation after a remission lasting six months or more

Table 1. Working definitions used in this chapter.

The data of the ten patients in which we used intravenous immunoglobulin were extrapolated from our series of 74 patients with polymyositis and dermatomyositis, prospectively followed up in our Department.
There were five cases each of polymyositis and dermatomyositis in one male and nine females (all Caucasian) with a median age of onset at 49 years (range 28-63 years). In six patients the disease was particularly aggressive with severe muscle involvement and dysphagia. Associated clinical features were arthritis (four patients), Raynaud's phenomenon (other four), interstitial lung disease (two patients) and cardiovascular involvement (one case). Before treatment serum creatine kinase values were 2326.5 U/l (range 637-5500). ANA and anti-ENA positivity were detected in two cases each. Disease duration prior to treatment was 17 months (range 4-131), and the median follow-up period was 82 months (range 30-170 months). Intravenous immunoglobulin was given on occurrence of refractory (7 patients) or relapsed disease (3 patients), definitions of which are illustrated in Table 1.
Initial therapy was based on oral steroids (prednisone 1mg/kg/daily) for one month and then slowly tapered to 5-10 mg every other week. Intravenous immunoglobulin was infused at 1 g/kg (5g/hour) on two consecutive days each month for six months, followed by three further cycles given every other month. The response to treatment was evaluated as outlined in Table 2.

Complete remission	an increase in strength of at least one Medical Research Council grade and normalisation of the serum creatine kinase levels.
Partial remission	when only one of the above criteria was fulfilled
Relapse	recurrence of active disease after a remission lasting six months or more

Table 2. Parameters employed to evaluate the response to treatment.

After one month of therapy we documented a partial improvement of muscle strength associated with a decrease in creatine kinase levels. At one year follow-up this result was confirmed, with six patients in complete remission and three in partial remission (Figure 1). The last patient dropped out from the study for meningism related to the intravenous immunoglobulin infusion. At long-term follow-up (mean 82 months), we could observe three relapses, two of which in patients with previous relapsing-remitting recurrences (respectively after 31 and 61 months from the beginning of the treatment).
The treatment was well tolerated with a low incidence of mild adverse events (nausea and vomiting) which could be successfully managed by reducing the speed of infusion. All patients reported a good tolerance profile of the intravenous administration of immunoglobulin. In Dalakas' study (1993) of dermatomyositis no adverse events were reported. In the study of Cherin and Herson (1994) no patients stopped infusions because of side effects. Accordingly to the literature, the treatment with intravenous immunoglobulin is generally a safe procedure, when given in a slow infusion rate in well-hydrated patients, and avoiding patients with known risk factors (Katz et al., 2007). Our data, in accordance with the literature, confirms our previous findings (Danieli et al., 2009b) that intravenous immunoglobulin is an effective and safe option as second-line therapy in patients with

refractoriness to steroids or with relapsing-disease. Subjects treated with intravenous immunoglobulin achieve a clinical and functional remission in a high percentage of cases which is maintained at long follow-up period.

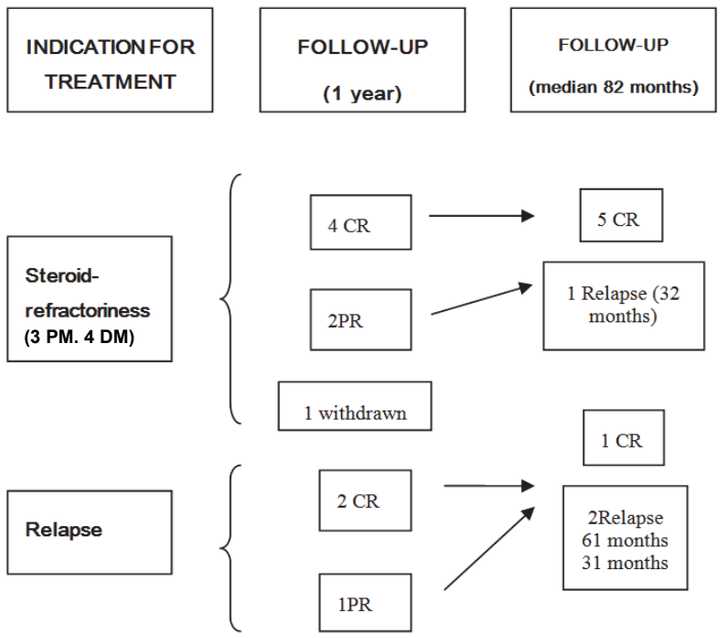

Fig. 1. Outcome and treatment response in 10 patients treated with glucocorticoids and intravenous immunoglobulin.

3. Cyclosporine A and intravenous immunoglobulin in inflammatory myopathies

3.1 Introduction

The use of cyclosporine is widely accepted in organ rejection, other studies emphasizes its importance in the therapy of systemic lupus erythematosus (Moroni et al., 2009) and other immune-mediated disease such as inflammatory myopathies. The following presents our experience with this drug in a large series of patients with polymyositis and dermatomyositis, testing the hypothesis if the add-on of intravenous immunoglobulin could improve the outcome or reduce the rate of side effects usually linked to the immunosuppressant's use. Finally, we report the revision of the literature related to the use of cyclosporine A in polymyositis and dermatomyositis.

Cyclosporine is a pro-drug in which its immune effects are secondary to a relative selective inhibition of T cell activation. In the cytoplasm, cyclosporine A, after binding to its specific cytoplasmic receptor cyclophillin, interferes with calcineurin, a complex of phosphatases crucial for the progression of the events that ultimately lead to the lymphocyte proliferation. During the physiological immune response, the contact between antigen-presenting cells and lymphocytes triggers a strong influx of calcium ions into lymphocytes, with calcineurin activation and subsequent dephosphorylation of a family of proteins called nuclear factor activating T cells (NFAT). The dephosphorylation mediated by calcineurin leads nuclear factor activating T cells (NFAT) to enter the nucleus and promote the synthesis of interleukin-2 that, in turn, activates the lymphocyte proliferation. By interfering in this

cascade, cyclosporine may alter the production of the pro-inflammatory cytokines that interplay at different levels among the cellular, immunological and biochemical mediators of inflammation. Cyclosporine A may hamper the pro-inflammatory cytokines that promote the activation, the maintenance of the immune inflammation, and the migration of the lymphocytes to target organs. The main role of cyclosporine A resides thus in the interference with T autoreactive cells, while it has little impact on humoral immunity.

3.2 Our experience with cyclosporine A and intravenous immunoglobulin in inflammatory myopathies

Since 1992, we used three different cyclosporine A-based regimens to treat 24 patients with definite myositis according to the Bohan and Peter criteria (1975). The 24 patients had either dermatomyositis (12 cases) or polymyositis (12 cases); subjects with connective tissue-associated, cancer-associated or inclusion body and those with juvenile myositis were excluded. The disease was newly diagnosed in seven patients, three of them had glucocorticoid refractoriness (Group I). The other 17 patients presented with refractory disease, as indicated by non-responsiveness to high-dose steroid treatment or to methotrexate and/or azathioprine (nine cases, Group II) or the recurrence of a previously quiescent disease (eight cases, Group III). All of the patients had active disease, as confirmed by the parameters of increased median values of creatine kinase levels (in all cases), Medical Research Council grade (in all cases), the electromyographic myogenic changes (in all cases) and the histological characteristics (in 75% of the 18 patients who underwent muscle biopsy). The baseline characteristics of the three groups of patients were homogenous, as shown in the following table.

	Group I Control group (PDN-CsA)	Group II Refractory disease (PDN-IVIg-CsA)	Group III Relapsed disease (PDN-IVIg-CsA)
PM/DM	3/4	4/5	5/3
Men /women	2/5	3/6	1/7
Age of onset (years)	34	48	35
Baseline serum CK levels (U/l)	706	2584	2468
Baseline MRC scale	74.4	73.4	68.8
Disease duration * (months)	14	24	35
Duration of follow-up (months)	40	57	59

* Before the start of indicated treatment.

Table 3. Baseline characteristics of the three groups of patients treated with different cyclosporine A-based regimens. Data are expressed as median. Abbreviation: AZA, azathioprine; CsA, cyclosporine A; CK, creatine kinase; DM, dermatomyositis; IVIg, intravenous immunoglobulin; MRC, Medical Research Council; MTX, methotrexate; PDN, prednisone; PM, polymyositis.

As customary, the treatment was based on oral prednisone, which was started at 1 mg/kg/day and then slowly tapered to an average of 0.25 mg/kg every other day. Initially,

oral cyclosporine A was given as 3 mg/kg/day for six months, and then reduced to a maintenance dose of 2 mg/kg/day. Patients were given microemulsion (Sandimmun Neoral ®, Novartis) which has a better bioavailability and more predictable pharmacokinetic properties. In the 17 patients with refractory disease (Group II and III), intravenous immunoglobulin were infused at 1 g/kg (5g/hour) on two consecutive days each month for six months, followed by three further cycles given every other month. In all of the patients, the first treatment period lasted one year during which the patients were re-evaluated every three months. The parameters used to evaluate the response to treatment are outlined in Table 2. The mean follow-up of the entire series as a whole is five years. The responses in the three groups are shown in Figure 2.

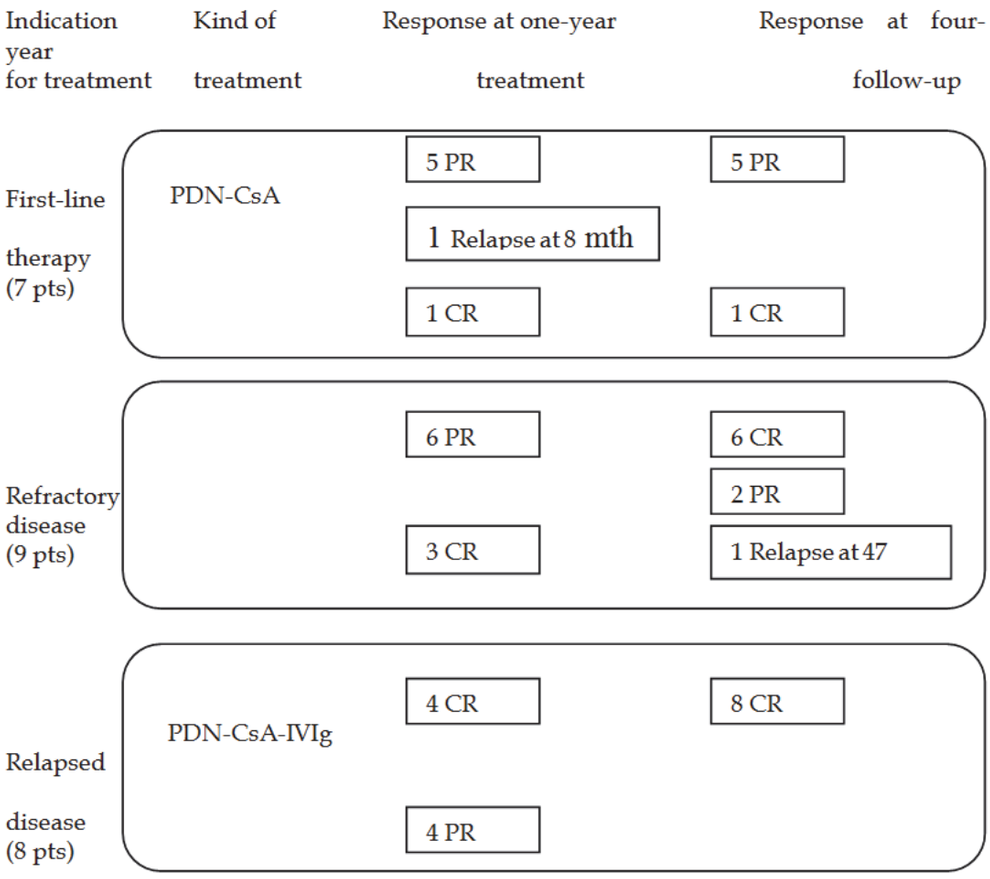

Fig. 2. Response to cyclosporine A associated or not with intravenous immunoglobulin in 24 patients with Polymyositis and dermatomyositis.

At the end of the one-year treatment period, we did not document any significant difference among the three treatment groups. Indeed, five of the patients in group I had a partial response, one was in complete remission and one relapsed eight months after the start of treatment. All of the patients in group II and III had improved. In the following period, positive results were documented almost exclusively in patients treated with cyclosporine A associated with intravenous immunoglobulin (Groups II and III). In group I, one patient was in clinical and functional remission 19 months after the start of treatment; the other five

cases were still in partial remission. In Group II, all of the patients improved with a complete remission in six out of nine patients, and one patient was able to maintain a complete remission without any further treatment; only one patient relapsed. In group III all of the patients were in persistent remission after having discontinued all treatment. Globally 82% (14/17) maintain a complete remission at the end of the follow-up period.

The statistical analyses revealed a significant difference at the end of the follow-up period between patients in remission with intravenous immunoglobulin and those treated only with cyclosporine A and prednisone ($P < 0.001$, chi-square analysis). We could not detect any other correlation between the response to treatment in the three groups and other variables such as the kind of myositis (polymyositis or dermatomyositis), the duration of the disease prior to the treatment with intravenous immunoglobulin and cyclosporine A, or the kind of organ involvement.

No new or major side effects leading to the interruption of treatment were recorded during the trial. In 30% of the patients treated with cyclosporine A we documented minor adverse effects consisting of hypertrichosis (three cases) minor gastrointestinal disturbance (nausea or vomiting in two cases), gingival hyperplasia (one case), transient increase in serum creatinine levels (one case).

3.3 Literature review on the use of cyclosporine A in inflammatory myopathies

We revised the English language literature related to the use of cyclosporine A in myositis. Since 1976, reports have been published of more than 100 patients with polymyositis and dermatomyositis treated with cyclosporine A. In early trials, cyclosporine A was given at high doses, ranging from 7.5 to 10 mg/kg/day, in patients with disease unresponsive to glucocorticoids or immunosuppressants. As reported, the disease improved, but unacceptable side effects were documented in the majority of patients. In more recent years, improved knowledge of the drug made it possible to lessen the dosage of cyclosporine A, with a proportional decrease of side effects. Cyclosporine A, usually between 2 and 5 mg/kg/day, allowed for a complete remission in 70% of cases, even in those with refractory disease (Danieli et al., 2002; Dankò & Szegedi, 1991; Qushmaq et al., 2000; Vencovsky et al., 2000). Two retrospective studies of respectively ten (Dankò & Szegedi, 1991) and twelve (Sanchez Román et al., 1995) patients have suggested the efficacy of cyclosporine A as a valid second-line therapy in refractory dermatomyositis. The only randomized controlled trial that has evaluated the impact of cyclosporine A in the treatment of polymyositis and dermatomyositis was carried by Vencovsky et al. (2000). The authors could not document any significant difference between cyclosporine A and methotrexate in terms of efficacy and toxicity evaluated at 6-month. In the majority of the cited reports, a good clinical response was documented within the first weeks of treatment.

The efficacy of cyclosporine A was principally evaluated in the treatment of interstitial lung disease associated with myositis. The two first reports of respectively eight (Maeda et al., 1997) and five (Nawata et al., 1999) patients confirmed its effectiveness, in particularly when used early. Other later reports confirm these data, with a complete or partial remission in more than 50% of the patients (Kameda et al., 2005; Kotani et al., 2008). It is important to remember that most patients typically died of respiratory failure related to interstitial pneumonia.

The usefulness of cyclosporine A in myositis seems to be improved by the association with intravenous immunoglobulin. Saadeh et al. (1995) were the first to describe a patient with dermatomyositis who improved after being treated with cyclosporine A and intravenous

immunoglobulin. This preliminary report is in line with our experience, in which 82% of treated patients reached a complete remission. The patients had a particularly severe disease, due to the presence of non-responsiveness to high-dose steroid treatment or a previous relapse. Our data at long-term follow-up reinforces these results, with a highly statistically significant difference detected at the end of the follow-up period when compared to patients treated with prednisone and intravenous immunoglobulin. The association of intravenous immunoglobulin and low-dose cyclosporine A produces improved control of disease activity and keeps the least amount of glucocorticoids.

In literature, no serious side effects are generally described, but 8-15% of patients treated with cyclosporine A develop arterial hypertension, hypertrichosis, tremor and transient renal dysfunction (Qushmaq et al., 2000). Other adverse events linked to the use of cyclosporine A are hyperlipaemia and diabetes. All these events are usually dose related. It is extremely important to keep the dose of cyclosporine A at 3 mg/kg/day to avoid untoward side effects. It is also recommended to avoid cyclosporine A in patients with renal impairment (creatinine clearance <60 ml/min) and/or uncontrolled arterial hypertension, and to carefully monitor the serum creatinine and potassium levels. Revising the literature, we documented that 20% of the patients with inflammatory myopathies treated with cyclosporine A experienced a major side effect such as renal toxicity and arterial hypertension. These percentages are lower in subjects treated with cyclosporine A and intravenous immunoglobulin, with 5% of patients reporting renal dysfunction and none arterial hypertension. Despite these statistics, the conceivable value of intravenous immunoglobulin is that its use makes it possible to reduce the doses of glucocorticoids and cyclosporine A in most patients, thus lowering the rate of side effects linked to use of these drugs.

While treating patients with cyclosporine A it is important to slowly taper the drug to avoid the risk of hyperacute relapse of the disease, as it has been reported in patients with systemic lupus erythematosus (Radhakrishnan et al., 1995). To improve the tolerance to the drug, some authors advocate the single daily administration, that has been demonstrated to be as effective than the bis in die administration but with fewer side effects in patients with organ transplant (Tarantino et al., 2004) and in those with idiopathic nephrotic syndrome (Rasche et al., 2007). Another important issue is how long to treat patients safely with cyclosporine A. We did not document nephrotoxicity even in long term treated patients, perhaps because we used lower doses of the drug (<2- 3mg/kg/day) than usually reported. However, the optimal duration of the treatment is unknown.

In our series cyclosporine A associated with intravenous immunoglobulin was successfully used both to control the disease activity and to keep the doses of glucocorticoids to a minimum. With this combined treatment we documented the best and statistically significant results as compared to steroid-cyclosporine A based treatment. This treatment was beneficial even in subjects with refractory disease and major organ involvement. We did not find any increase in the number or type of side effects. Further randomized trials may confirm the true benefits of various treatments in different subset of polymyositis and dermatomyositis.

4. Mycophenolate mofetil and intravenous immunoglobulin in inflammatory myopathies

4.1 Introduction

Mycophenolate mofetil is an immunosuppressive drug mainly used in the prevention of allograft rejection in renal, cardiac or liver transplantation and in immune-mediated

diseases, such as systemic lupus erythematosus, with or without renal involvement (Bomback & Appel, 2010; Mok, 2007), systemic vasculitis (Hoffman, 2010), autoimmune rheumatic diseases (Iaccarino et al., 2007) and myasthenia gravis (Hehir et al., 2010). Mycophenolate mofetil is a prodrug of mycophenolic acid that was developed to enhance its bioavailability. Following oral administration, mycophenolate mofetil is entirely metabolized to mycophenolic acid. With regards to its action, mycophenolate mofetil is a potent selective inhibitor of inosina-5′-monophosphate dehydrogenase. Mycophenolate mofetil blocks the de novo synthesis of guanosine nucleotides, a critical pathway for the DNA synthesis in lymphocytes, acting on T- and B- cell proliferation and interfering on expression of adhesion molecules and on antibody production (reviewed in Ritter & Pirofski, 2009). Thus, mycophenolate mofetil could influence the course of cell- and antibody-mediated diseases.

Despite its use in myositis since 2000, literature supporting the efficacy of mycophenolate mofetil is scarce with only case reports and a few small series. The following describes our experience with patients with polymyositis and dermatomyositis and compares our results with those of previous reports.

4.2 Our experience with mycophenolate mofetil and intravenous immunoglobulin in inflammatory myopathies

In an open study we prospectively followed up nine patients with polymyositis and dermatomyositis, the baseline characteristics are shown in the following table. Our previous positive experiences with intravenous immunoglobulin prompted us to treat them with a combined therapy based on intravenous immunoglobulin serial infusions and oral daily mycophenolate mofetil administration.

In this series, polymyositis and dermatomyositis were diagnosed according to the Bohan and Peter's criteria and the diagnosis was further confirmed by a muscle biopsy in all patients, except one case who declined. Indications for treatment were refractoriness to steroid (three cases) or two immunosuppressants given for at least two months (four cases) and glucocorticoids dependency (two cases). Overall patients received a median of two immunosuppressants (range from one to five) including methotrexate, cyclosporine A, cyclophosphamide, azathioprine and rituximab. The disease had a particularly aggressive course with myogenic damage predominating in the axial muscles in one case (F/49 with dermatomyositis) and cardiopulmonary involvement with cardiac arrhythmias and progressive decrease of lung function in another patient (FM/35 with dermatomyositis). At study entry, all of the patients had active myositis (see Table 1 for definition) with severe muscle involvement with difficult walking and dysphagia and/or dyspnoea. In subjects with dermatomyositis, the skin involvement was characterised by diffuse erythematosus and heliotrope rash. Median serum creatine kinase levels were above the normal range (Median ±SD = 1909±714; normal values < 170 IU/l). The initial oral mycophenolate mofetil dose of 500 mg/day was gradually increased to the definite dosage of 30 mg/kg/day in all of the patients with a subsequent median treatment duration of three years. As previously reported, intravenous immunoglobulin was infused at 1 g/kg (5g/hour) on two consecutive days each month for six months, followed by three further cycles given every other month. Prednisone was used according to our standard regimen. Previous immunosuppressants were withdrawn at the start of the study. Within two months of the start of the treatment an improvement in muscle strength with attenuation of cutaneous findings was observed.

Sex/ Age at the diagnosis (years)	DM/PM (date of diagnosis)	Disease duration prior to IVIg-MMF (months)	Previous ineffective therapies	Indications for IVIg-MMF treatment	Outcome
F/51	PM	204	PDN, IVM, MTX, CSA, CYC, Rituximab	Refractory to immunosuppressants	Partial remission Withdrawn MMF
F/50	DM	120	PDN, IVM, MTX, CSA, AZA	Refractory to immunosuppressants	Complete remission
F/38	PM	16	PDN, IVM, MTX, CSA	Refractory to immunosuppressants	Complete remission Withdrawn MMF
F/65	PM	14	PDN, MTX	Refractory to immunosuppressants	Complete remission
F/49	DM	45	PDN, IVM, MTX, CSA	Glucocorticoid-dependency	Complete remission Withdrawn MMF
F/57	PM	16	PDN, CYC	Glucocorticoid-dependency	Complete remission Withdrawn MMF
F/47	DM	42	PDN, IVM	Refractory to glucocorticoids	Complete remission
M/52	DM	16	PDN, IVM	Refractory to glucocorticoids	Partial remission
F/35	DM	13	PDN, IVM	Refractory to glucocorticoids	Partial remission Withdrawn MMF

Abbreviations: AZA, azathioprine; CSA, Cyclosporine A; CYC, cyclophosphamide; DM, dermatomyositis; IVM, intravenous methyl-prednisolone; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MTX, methotrexate; PDN, prednisone; PM, polymyositis.

Table 4. Baseline characteristics of nine patients with polymyositis or dermatomyositis treated with intravenous immunoglobulin associated with mycophenolate mofetil.

During the subsequent follow-up period, the treatment with intravenous immunoglobulin and mycophenolate mofetil enabled a significant improvement in the clinical (cutaneous and muscle strength) parameters, with a concomitant reduction of serum muscle enzymes and a progressive decrease and then disappearance of spontaneous pathological activity in

the sampled muscles at electromyographic studies performed at month 8 from the start of the treatment. In addition, we documented a significant improvement of Medical Research Council scale and modified Rankin score, the two main parameters employed to evaluate the muscle strength and the degree of disability, respectively. Another important result of this combined treatment was the statistically significant reduction of the daily prednisone dose. At the end of the follow-up period of nearly four years (49 ± 16 months), three of the patients (Table 4) showed a partial response, six were in complete remission. These successful results allowed us to withdraw mycophenolate mofetil in four patients who are now in remission with a low-dose prednisone.

The treatment was well tolerated in all of the patients. The most prevalent complaint was represented by abdominal discomfort at the beginning of the mycophenolate mofetil treatment with a spontaneous resolution over time. In another patient, the administration of intravenous immunoglobulin was associated with mild headache which was subsequently resolved by reducing the infusion rate. Considering our complete series of patients with inflammatory myopathies treated with intravenous immunoglobulin, we detected a relative low prevalence of side effects (Table 5).

Meningism	Withdrawn	1/36 (2%)
Nausea e/o vomiting	Resolution after infusion speed slowing down	7/36 (19%)
Headache	Resolution after paracetamol administration and/or infusion speed slowing down	3/36 (8%)

Table 5. Adverse events observed in our complete series of patients with polymyositis and dermatomyositis treated with intravenous immunoglobulin. Ten patients have been treated only with intravenous immunoglobulin, the other 26 with intravenous immunoglobulin associated with cyclosporine A (17) or mycophenolate mofetil (9).

4.3 Literature review on the use of mycophenolate mofetil in inflammatory myopathies

With regards to the literature on/relating to mycophenolate mofetil in inflammatory myopathies, the experience is still limited, since only case reports or predominantly retrospective small case series have been published. We performed a Medline search of English language from 2000 to 2011 related to the use of mycophenolate mofetil in dermatomyositis and polymyositis in adult patients. We analysed in particular the role of mycophenolate mofetil on muscle involvement. The literature search revealed that 62 subjects (23 polymyositis and 39 dermatomyositis), including ours, have been reported to date. Indications for treatment were mainly refractoriness to glucocorticoids or to immunosuppressants and prior intolerance to previous drugs employed to control the myositis (Danieli et al., 2009a). In two series (Chaudhry et al., 2001; Majithia & Harisdangkul, 2005) mycophenolate mofetil was used as initial immunosuppressive agent. The administration of mycophenolate mofetil, orally at 2 g daily, is linked to clinical improvement and decrease in serum creatine kinase levels in 73% of the subjects with polymyositis and in 77% of those with dermatomyositis. Mycophenolate mofetil is active even in cutaneous manifestations, initially documented by Gelber et al. (2000) in four patients with dermatomyositis refractory to glucocorticoids, hydroxychloroquine and methotrexate. Analysis of these reports appears to confirm our data that the association of intravenous immunoglobulin to mycophenolate mofetil may improve the proportion of

patients in remission and reduce the rate of side effects. Indeed, in approximately 30% of the responding patients (6/17 for polymyositis and 7/30 for dermatomyositis) remission was reached by a treatment based on intravenous immunoglobulin and mycophenolate mofetil even in refractory or particularly severe cases. The synergism in the action of intravenous immunoglobulin associated with mycophenolate mofetil is probably linked to the suppression of early stages of the activation and proliferation of lymphocytes. This synergism could even explain the relatively fast response (within one month in our experience) of the disease to the treatment, as it has been known that the onset of action of mycophenolate mofetil is usually delayed. In the literature, serum levels of mycophenolic acid, the active metabolite of mycophenolate mofetil, were not reported, probably as they are not usually performed in clinical practice. However, a recent paper on mycophenolate mofetil in kidney transplantation documented that patients exhibiting a lower rejection rate were those in whom the mycophenolate mofetil dose was not fixed but in accordance to serum mycophenolic acid levels (Le Meur et al., 2007). We cannot exclude that patients who did not respond to mycophenolate mofetil received a lower dose than necessary.

Among the advantages linked to this combined therapy, there is the issue of drug-associated side effects. With regards to glucocorticoids, the majority of patients is able to taper or discontinue the dose of prednisone, thus significantly reducing the rate of side effects linked to its use.

Concerning infective complications, the reported papers show a higher frequency and a greater severity of major side effects in dermatomyositis when compared to polymyositis. In their series of ten patients with dermatomyositis, Rowin et al. (2006) reported an exceedingly high rate of opportunistic infections (30%) that were, however, associated with contributing factors such as interstitial lung disease in two patients and previous treatment with cyclophosphamide in one patient. The same subject received a high mycophenolate mofetil dose (3 g daily). The third patient with opportunistic infection had open skin lesions predisposing her to *Mycobacterium xenopi* abscess of the left thigh. In those patients described in the literature in which mycophenolate mofetil was associated to intravenous immunoglobulin, no infectious complications were documented. It is conceivable that intravenous immunoglobulin enables a reduction in the infective risk in subjects treated with an immunosuppressant. This point is of particular interest since immunodeficiency states are increasingly recognised in patients with immune-mediated diseases and they are due to intrinsic defects linked to the disease itself and/or to the immunosuppressive drugs employed throughout the disease management. Diagnostic strategies have been recently addressed for rheumatic diseases (Samson et al., 2010).

4.4 Other indications for mycophenolate mofetil

A paper of Morath et al. (2006) suggests a cardioprotective role in vivo for mycophenolate mofetil due to its inhibitory effect on the proliferation of fibroblasts and vascular smooth muscle cells. This effect, if documented in larger series of patients, is of great importance, given the high rate of cardiovascular disease associated with inflammatory myopathies. In systemic lupus erythematosus, the data indicating a cardioprotective role of mycophenolate mofetil are, unfortunately, uncertain (Davies et al., 2009). In cardiology, anti-inflammatory effects of intravenous immunoglobulin has been studied in some patients with heart failure, dilated cardiomyopathy, myocarditis, pericardial diseases, neonatal lupus (Nussinovitch & Shoenfeld, 2008).

The choice of the immunosuppressant should be adjusted to the patient's characteristics. For example, mycophenolate mofetil has no, theoretically, mutagenic potential but is teratogenic

in rats, rabbits and, probably, in humans. Atypical malformations (microtia or anotia in twelve newborns, external auditory canal atresia in nine and cardiovascular malformations in other six) in fourteen offspring of women exposed to mycophenolate mofetil in early pregnancy have been recently reported (Anderka et al., 2009). The underlying maternal conditions were different, ranging from kidney, liver or heart transplantation (nine patients), lupus nephritis (four cases), and recurrent erythema multiforme (one patient). No correlation between dose of mycophenolate mofetil and severity was noted. Hence when long-term immunosuppression is planned in a woman in child-bearing age, it is important to choose the immunosuppressant accordingly. Azathioprine and cyclosporine A can be safely used during pregnancy whereas mycophenolate mofetil and methotrexate are absolutely contraindicated.

Another relevant issue, especially during economically restrained times, is that of cost. With regards to intravenous immunoglobulin, this point will be addressed in Paragraph 6. As for mycophenolate mofetil, the cost is generally ten times higher than that of other, older, immunosuppressants, such as azathioprine and cyclosporine A. However cost should be balanced against the effectiveness of the drug and its relative safety.

5. Subcutaneous immunoglobulin

5.1 Introduction

The subcutaneous administration of immunoglobulin could be considered as an alternative to the more common intravenous route. Subcutaneous immunoglobulin is a blood product containing immunoglobulin G from normal subjects, initially used in primary immunodeficiency diseases and, more recently, in immune-mediated diseases or neurological conditions. In primary immunodeficiency, subcutaneous immunoglobulin used at replacement dosage, has been demonstrated to be linked to a lower incidence of adverse reactions, with reliable efficacy and improvement of the quality of life of treated subjects. Subcutaneous immunoglobulin has become increasingly popular in recent years, and now, the attention focuses on their possible use as a treatment of immune-mediated disease: we have been the first to publish on a series of seven patients with inflammatory myopathies successfully treated with subcutaneous immunoglobulin (Danieli et al., 2011).

5.2 Proposed mechanism of subcutaneous immunoglobulin in inflammatory myopathies

Like intravenous immunoglobulin, subcutaneous immunoglobulin could have multiple mechanisms, relevant to the pathogenesis of polymyositis and dermatomyositis (Vani et al., 2008; Seite et al., 2008). Subcutaneous immunoglobulin treatment leads to more stable immunoglobulin levels, without peaks which are frequently responsible for side effects. However, since their kinetics is different from that of intravenous immunoglobulin, it is possible that subcutaneous immunoglobulin could act at different levels. Recent studies brought attention to the role of T-regulatory cells in autoimmune diseases, due to their role in suppressing the activation, the proliferation and the cytokine production of self-reactive T cells, thus contributing to the prevention of autoimmune phenomena and to the regulation of the immune homeostasis. Kessell et al. (2007), from the group of Professor Shoenfeld, were the first to demonstrate the direct influence of intravenous immunoglobulin on peripheral CD4+ CD25+ T-regulatory cells by increasing their suppressive function. Moreover, in the mouse model of experimental autoimmune myositis, which resembles

human polymyositis in several aspects, the depletion of T-regulatory cells aggravated the disease, whereas the injection of polyclonal T-regulatory cells reduced both the incidence and the severity of the disease (Allenbach et al., 2009). Intravenous immunoglobulin treatment has also been shown to be effective in a mouse model for experimental allergic encephalomyelitis (Ephrem et al., 2008) increasing numbers and function of peripheral CD4+ CD25+ T-regulatory cells. Recent studies have demonstrated that intravenous immunoglobulin induces the expansion of T-regulatory cells and enhances their suppressive functions (Maddur et al., 2010). Even though no data is available on the action of subcutaneous immunoglobulin on T-regulatory cells, it can be hypothesised that in chronic autoimmune disease, such as inflammatory myopathies, the effects on T-regulatory cells exerted by subcutaneous immunoglobulin (von Gunten et al., 2008) could be more relevant due to the accelerated catabolism of pathogenic IgG, than intravenous immunoglobulin (Vani et al., 2008; Seite et al., 2008).

5.3 Our experience with in subcutaneous immunoglobulin inflammatory myopathies

Since 2009, January, we offered the option of subcutaneous immunoglobulin to our patients with idiopathic inflammatory myopathies (polymyositis or dermatomyositis) diagnosed according to the Bohan and Peter's criteria. The disease was considered refractory, resistant or recurrent as shown in Table 1. Patients unable to follow instructions, with known allergic reaction to intravenous immunoglobulin, cancer-associated disease, inclusion body myositis or juvenile myositis, were excluded.

At the start of our study, eight subjects agreed to perform the treatment with subcutaneous immunoglobulin: all the patients were Caucasian females; in all of them, the diagnosis was confirmed by a muscle biopsy, and the histological samples collected were examined by means of light and electron microscopy. Major findings were the changes in fibre size and the myofibers degeneration and regeneration with diffuse or focal inflammatory infiltrates, sometimes confined to the peri- and endomysium but usually interspersed between the individual muscle fibres as well. Perifascicular and perivascular inflammatory infiltrates were the typical findings in dermatomyositis. In all of the patients we performed nerve conduction and concentric needle electromyographic studies according to standard techniques that were repeated when clinically indicated. Fibrillation potentials and recruitment abnormalities were rated using commonly described methods (Wilbourn, 1993) and motor unit potentials were evaluated on the basis of their duration, configuration and amplitude by means of a trigger and delay line using a Nicolet Viking IV. At the start of subcutaneous immunoglobulin treatment, all the patients had active disease, confirmed by increased serum creatine kinase levels and the electromyographic findings. Clinically, they presented diffuse and persistent weakness due to severe muscle involvement with dysphagia in two cases and diffuse skin rash in four further cases.

5.3.1 Treatment regimen

At the beginning of treatment all the patients were taking oral prednisone at the previously assumed dose, maintained for at least one month. After this first period, prednisone was slowly tapered to an average of 0.25 mg/kg every other day. Two patients were treated only with prednisone, whereas the remaining patients were using it in addition to several other immunosuppressants. In particular, one patient was treated with oral cyclosporine A (3 mg/kg/day in two refracted doses), two patients with oral mycophenolate mofetil (at 30 mg/kg/day) and the last three patients with methotrexate (15 mg/week i.m.). During the

first three months of treatment with subcutaneous immunoglobulin, previous immunosuppressants were continued at the initial dose, and then, according to the patient's clinical condition, these were slowly tapered.
Prior to starting treatment with subcutaneous immunoglobulin all patients, apart from one case, were given immunoglobulin by the intravenous route at the dose of 2 g/kg, generally infused at 1 g/kg (5g/hour) on two consecutive days each month for at least six months. Four of them were successfully treated with intravenous immunoglobulin several years earlier. The three cases already in intravenous immunoglobulin treatment switched to the subcutaneous treatment one week after the last intravenous infusion, whereas the other patient directly began subcutaneous weekly infusion.

5.3.2 Treatment with subcutaneous immunoglobulin

At the beginning of the study, when we decided to treat our patients with inflammatory myopathies with subcutaneous immunoglobulin, one problem we encountered was dosage. We consequently decided to give patients the usual intravenous bimonthly dose (2g/kg) fractioned into equal doses given subcutaneously at weekly intervals: so, subcutaneous immunoglobulin (Vivaglobin ® CSL Behring) was infused weekly at the dose of 0.2 g/kg/week, nearly double the dose infused in subjects with primary immunodeficiency diseases (Berger, 2008).
Subcutaneous immunoglobulin administration needs a programmable pump (CRONO super PID), with a syringe capacity of 10, 20, 30 or 50 ml, depending on the producer. The site of administration must change for every infusion, choosing among arms, abdomen or thigh, allowing the administration of no more than 15 ml of the product (2.4 g of subcutaneous immunoglobulin) in the same subcutaneous area, at the infusion rate of 10 ml/h into each site and, accordingly to the patient's tolerance, it could be progressively increased up to 20-22 ml/h, according to the literature (Berger, 2008) and to what is currently advised in Italy. No premedication is required.

5.3.3 Training of the patients

A very important step for enhancing adherence to this kind of home regimen is training which can improve patient's home-infusion experience and increase their acceptance of subcutaneous immunoglobulin. Therefore, all patients received an explicative brochure and were trained to perform home self-administration. Patients were even alerted about the potential problems linked to infusion and consequent management. In particular it is important to explain to them what might occur during infusion and how to minimise their own discomfort. It is essential to provide telephone support, so, a telephone emergency number was supplied to all patients. Best practice is reached by obtaining feedback on the process and its relative possible problems: a telephone follow-up should be conduced to evaluate the infusion experience and verify proper infusion techniques. The first two initial infusions were usually given in Day Hospital regimen with the aid of a physician and a nurse who instructed patients about performing subcutaneous infusion and explained the procedure to them: only when patients and a relative feel confident with the treatment, can further self-infusions be carried out at home.

5.3.4 Results

At 3-month evaluation, almost all patients showed a good response to the treatment, documented by creatine kinase serum levels normalisation, improvement in the Medical

research Council scale (a mean of 8 point) and in Rankin modified scores. Only two patients showed a partial response to the subcutaneous immunoglobulin treatment.

Table 6 shows long-term follow-up analyses (a mean of 16.8 months). A marked beneficial clinical and laboratory response was documented in six patients in this series; they were all able to reduce the glucocorticoid dose and three of them were able to suspend the immunosuppressive agent. Even patients with relapsed disease showed a good response to subcutaneous immunoglobulin. Among these patients, the following briefly reports the history of a 69-year-old woman with a 2-year history of polymyositis, previously treated only with prednisone and methotrexate. She had never previously been treated with intravenous immunoglobulin. In her case, indication for the treatment with subcutaneous immunoglobulin was the appearance, after six months of treatment with methotrexate, of an elevated lymphocyte count (lymphocytes=4130 /mmc) with a small clonal NK/T CD3+ CD4+ CD8+ CD56+ cell population (10% of the total circulating lymphocytes) bearing monoclonally the V/β17 chain of TCR (90% of these CD4+ CD8+ cells). Due to the risk of progression to lymphoma linked to the use of methotrexate, we decided to discontinue this drug and to start the subcutaneous immunoglobulin treatment. After six months, with the patient's muscle disease in remission, we documented the lymphocyte count normalisation and the clonal population reduction (70% of the CD4+ CD8+ cells).

Among the partially responding patients is the case of a 39-year-old woman, presenting with long-term dermatomyositis (more than 20 years). From the onset, she showed a very aggressive form of the disease, with diffuse erythematosus and heliotrope rash, severe muscle involvement, characterised by weakness of the proximal and paraspinal muscles with a hanging head and an inability to execute any upward movement, rendering her dependent in performing daily activities. Over the years, she tried different types of therapeutic approaches; including methotrexate, cyclosporine A, high-dose glucocorticoids. The disease was eventually controlled only with serial infusion of intravenous immunoglobulin, which was maintained with increasing intervals for some years. In January 2009, she returned to our attention with a new relapse of the disease. She was immediately treated with high-dose prednisone, subsequently tapered, and intravenous immunoglobulin (2 g/kg) in monthly infusion for six months and then switched onto subcutaneous administration. After an initial positive response, at month 6, she had a flare-up with persistent weakness and elevated serum creatine kinase levels requiring an intravenous immunoglobulin infusion (at the dose of 2 g/kg in two consecutive days) that brought the disease's activity under control. The intravenous immunoglobulin was repeated three months later. In the subsequent follow-up period, while continuing the subcutaneous immunoglobulin, she was able to reduce the prednisone dose and despite this recurrence of disease, she showed a high level of satisfaction with treatment.

One patient, a 74-year-old woman with polymyositis diagnosed on July 2006, had no response to subcutaneous treatment. She was initially treated with methyl-prednisolone (1 g per day for 3 days) followed by a decreasing dose of oral prednisone associated with methotrexate (10 mg/weekly i.m.) with a poor response. In 2008, she presented a recurrence of the disease with reduction in muscle strength and a marked increase in serum creatine kinase levels; we thus decided to start intravenous immunoglobulin at monthly cycles (2 g/kg for each month), obtaining a good response. She subsequently switched to subcutaneous self-administration with clinical stabilisation, but without any laboratory improvement. At the first follow up visit, after one month, we noticed a slight increase of serum creatine kinase levels, despite stability in clinical assessment, tested by the Medical

Sex/ Age at the diagnosis (years)	DM/PM (date of diagnosis)	Disease duration prior to SCIg (months)	Previous ineffective therapies	Indications for SCIg treatment	Outcome
F/54	DM	72	PDN, IVIg, MTX, PP, CSA	Refractory to immunosuppressant	Partial remission. Reduction of immunosuppressant
F/53	DM	223	PDN, MTX, Anti-TNF, MMF, IVIg	Refractory to immunosuppressant	Complete remission. Withdrawn MMF
F/39	DM	167	PDN, MTX, CSA, IVIg	Refractory to immunosuppressant and steroid-dependency	Initial remission, but new flare-up after six months controlled by IVIg
F/47	PM	151	PDN, CYC, IVIg	Recurrence of a previously quiescent disease	Complete remission. Significant reduction of PDN and MMF dosage
F/71	PM	52	PDN, MTX, CSA, MMF, PP, IVIg	Recurrence of a previously quiescent disease	Complete remission. Withdrawn MTX
F/43	DM	10	PDN, MTX, IVIg	Recurrence of a previously quiescent disease	Complete remission. Significative reduction of PDN dosage
F/69	PM	24	PDN, MTX	Contraindication to immunosuppressant	Complete remission. No immunosuppressant consumption
F/74	PM	43	PDN, MTX, IVIg	Recurrence of a previously quiescent disease	Poor response with slight improvement in muscular power and persistant elevation of CPK levels
M/22	OM	144	PDN, MTX, CSA	Refractory to immunosuppressant and steroid-dependency	Complete remission. Withdrawn CSA and significant reduction of PDN dosage

Abbreviations: anti-TNF□, etanercept; CSA, Cyclosporine A; CYC, cyclophosphamide; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MTX, methotrexate; OM, ocular myositis; PDN, prednisone; PP, plasmapheresis.

Table 6. Baseline characteristics and treatment response in 8 patients treated with glucocorticoids and subcutaneous immunoglobulin.

Research Council scale. Moreover, laboratory tests showed an elevation on liver enzymes that induced a discontinuation of methotrexate and to introduce mycophenolate mofetil, by continuing the subcutaneous immunoglobulin infusion.
In this series, we encountered the case of a 22-year-old-boy affected from infancy by an ocular form of myositis, previously refractory to different immunosuppressive therapies (cyclosporine A and methotrexate) and steroid-dependent. After starting the treatment with subcutaneous immunoglobulin, he was able to discontinue the immunosuppressants and to gradually reduce the prednisone (used for 15 years of his life).
In all of the responding patients, the subcutaneous administration of immunoglobulin was continued one year after remission, associated in most cases with a low-dose prednisone.

5.3.5 Patient satisfaction with subcutaneous immunoglobulin

Satisfaction with the subcutaneous immunoglobulin treatment was high in all patients. At the end of the follow-up period we documented an improvement in our patient's quality of life, the highest scores being for global mental health, measured using the validated Italian version of the Medical Outcome Study Short Form 36 (SF-36) questionnaire, which has two major domains – physical health and mental health indexes – and measures physical activity and restrictions, physical pain, global health status, vitality, social and occupational activities, restrictions and mental health (Apolone & Mosconi, 1998). We investigated patient interest in and satisfaction with the treatment, and the quality of communication provided by the staff, testing the level of agreement with a statement. The most significant items suggested by the patients were the reduction in problems while receiving treatment and the increased freedom in organizing daily activities. Considerable satisfaction was felt with the quality of disease-related information, its usefulness in treatment management and the high level of communication with health professionals.

5.3.6 Side effects with subcutaneous immunoglobulin

In our series, no major side effects were documented. In literature, systemic adverse effects have been reported in less than 1% of subcutaneous infusions, as opposed to 5% of intravenous infusion (Berger, 2008). These only include mild local reactions, including swelling, redness and "burning" sensation in the infusion site that usually resolve spontaneously within 24-48 hours, as reported in literature (Wasserman, 2008). These effects were transient and declined over time, specifically after 8 to 10 weeks. The recording of side effects is subjective and it is possible that very weak reactions were not mentioned by the patients, due to their acceptance of the treatment and to their gradual adaptation to the local phenomena.
The different pharmacokinetic properties between intravenous and subcutaneous immunoglobulin regimens reflect the differences in their adverse effects. Despite not checking the serum IgG levels in our patients, it is conceivable that fractioning the usual monthly intravenous dose into subcutaneous weekly doses facilitated near stable IgG levels. It is likely that the metabolised IgG are constantly being replaced by IgG freshly absorbed from the subcutaneous injection site. Taking this into account, the subcutaneous route administration and the reduced dose given in weekly subcutaneous infusion could lead to a reduction in the risk of systemic reactions and of thromboembolic events. It is noteworthy that various reports described the safe use of subcutaneous immunoglobulin in patients with previous serious systemic adverse reactions to intravenous immunoglobulin (Quinti et al., 2008).

Finally, the global costs of subcutaneous immunoglobulin treatment, are usually 15-25% less than those of intravenous immunoglobulin treatment as later reported (Paragraph 6). Furthermore, the ability to use subcutaneous immunoglobulin in patients with difficult venous access or in those with associated selective IgA deficiency, of course after a tolerability check given the variable individual response of the IgA deficient patients, will in future make subcutaneous immunoglobulin as the first choice.

5.4 Subcutaneous immunoglobulin in other immune-mediated diseases

Although subcutaneous self-infusion of immunoglobulin is currently labelled and increasingly used for replacement therapy in primary immune deficiencies, with documented effectiveness and safety, only a few cases report the use of subcutaneous immunoglobulin for its immunomodulatory and anti-inflammatory properties in chronic inflammatory disease.

In a case report, subcutaneous immunoglobulin was successfully used as an adjuvant treatment in a subject with dermatomyositis (Schleinitz et al., 2008) after 1-year follow-up.

Other experiences with subcutaneous immunoglobulin as a treatment of chronic inflammatory disease were carried out in particular for immune-mediated neurological disorder, as multifocal motor neuropathy or chronic inflammatory demyelinating polyneuropathy.

A preliminary experience was reported by Koller at al. (2006) in three subjects with chronic inflammatory demyelinating polyradiculoneuropathy with relapses, in which the use of subcutaneous immunoglobulin (at the dose of 0.1 g/kg of body weight given once weekly for 6 months), in concomitance with mycophenolate mofetil, lead to a stable disease during the 6-month follow-up period. Subsequently, Harbo et al. (2009) performed a randomized single-blind cross-over study on nine intravenous immunoglobulin responsive patients suffering from multifocal motor neuropathy, directly comparing the subcutaneous and the intravenous route, given in sequence, showing that using equivalent doses, the effectiveness of two treatments is similar in regard to muscular strength. No significant differences between treatments on health-related quality of life occurred, but as suggested by the authors and by Dimberg (2009), who discussed this data the relatively short treatment period may have played down subcutaneous immunoglobulin. In this regard, he performed another study, showing that long-term subcutaneous immunoglobulin therapy is an alternative approach to intravenous immunoglobulin that is desirable for some patients (Dimberg, 2009) in a small case series of six intravenous immunoglobulin responsive patients with multifocal motor neuropathy on long-term subcutaneous immunoglobulin maintenance therapy with dose equivalent to their previous intravenous regimen, followed for two years. Five of them preferred to continue the subcutaneous administration after the trial and another patient chose to apply for this kind of treatment. A case report on a patient with multifocal motor neuropathy positively treated for six months and in maintenance therapy with subcutaneous immunoglobulin was described by an Italian group (Dacci et al., 2010). Similar results were reported by Eftimov et al. (2009); in his single-centre open-label pilot intervention study, ten patients affected by multifocal motor neuropathy treated with intravenous immunoglobulin were included and then they were switched to weekly subcutaneous immunoglobulin. The first group (five patients) started with a subcutaneous dose equivalent to 50% of the intravenous dose, and then, in case of deterioration they received a loading dose of intravenous immunoglobulin and doubling of subcutaneous dose. The second group (five patients) started with a dose equivalent to the intravenous

maintenance dose. They demonstrated that in four patients, the subcutaneous immunoglobulin therapy was feasible and safe and maintained strength as well as the intravenous route, while in the latter case a higher dose was needed; he brought attention to the subcutaneous dose as a maintenance treatment, monitoring serum immunoglobulin concentrations. Whereas patients in intravenous treatment show a swinging trend of immunoglobulin levels, with spikes corresponding to the therapy and deep valleys in the interim periods, during subcutaneous immunoglobulin treatment, immunoglobulin levels appeared stable and slightly higher than normal, preventing end- of-dose weaving observed in intravenous treatment. In previous experiences in primary immunodeficiency patients treated with subcutaneous immunoglobulin, it was documented that the mean serum IgG levels are usually higher than those obtained by the intravenous route when using the same total monthly dose (Berger, 2008).

6. Cost of the immunoglobulin treatment

The use of intravenous immunoglobulin is linked to the well known problems of supply and costs. First of all, the decision to use intravenous immunoglobulin for the treatment of myositis should be made in consultation with an expert in neuromuscular disease. Before treatment, it is essential to have a pathologic confirmation by means of a skeletal muscle biopsy for the diagnosis of polymyositis or dermatomyositis. As recommended by Feasby et al. (2007), the muscle specimen must be procured, processed, and interpreted in a specialised laboratory and the final diagnosis must be made by an expert in neuromuscular pathology. Once a diagnosis is obtained, immunoglobulin should be used in accordance with the main international guidelines (Feasby et al., 2007; Elovaara et al., 2008) and local directives.

The preparation of immunoglobulin is a multi-step process that leads to different products as supplied by manufacturers (Gurcan, 2010). In order to discover the real benefits of (intravenous or subcutaneous) immunoglobulin therapy in health-economical terms, analyses must be performed in each country, since economic systems for the provision of healthcare, including pharmacy handling, vary substantially (Gardulf, 2007). Most of these data, unfortunately, are inadequate and the majority of the reports published in the literature are related to the pharmacoeconomic evaluation on the use of intravenous or subcutaneous immunoglobulin in patients with antibody deficiency.

The first ever health-economic evaluation of immunoglobulin therapy has been performed in Sweden (Gardulf, 1995). It showed that the change from in-hospital intravenous immunoglobulin therapy to home-based subcutaneous immunoglobulin treatment saved $US10.100 per patient per year (1993 annual costs). All factors being equal, the use of subcutaneous immunoglobulin self-infusions at home for 80% of the 1300 Swedish patients known to be using immunoglobulin replacement therapy today would lead to a cost reduction of $US 10.504.000 per year for Swedish society. A recent cost analysis in Germany showed that a switch of 60% of the patients on intravenous to subcutaneous immunoglobulin therapy would lead to the German health insurance system saving between €17 million and €77 million each year (Hogy et al., 2005).

In the US, it has also been calculated that the cost of subcutaneous immunoglobulin self-infusions at home is $US 48, compared with $US 164–314 for using intravenous immunoglobulin at home administered by nurses (Radinsky & Bonagura, 2003) and that "it may be expected that cost savings of $US2000–5000 per patient per year" will be the result of home instead of hospital therapy (Berger, 2003).

In Italy the only cost-minimisation analysis has been performed by Matucci et al. (2008) using data from the Tuscany Health Service. It compares the annual direct medical costs (immunoglobulin, premedication, infusion pump, infusion materials, medical staff, ambulatory) of subcutaneous and intravenous immunoglobulin in patients with antibody deficiency observing a difference of € 2,212.98 in favour of subcutaneous immunoglobulin due to lower costs for both medical staff and ambulatory. The Italian experience, in accordance with the literature, substantiates the cost-sparing effect of subcutaneous immunoglobulin home treatment from both patient and medical point of view. It is important to note that the production of intravenous immunoglobulin is more complex than that of subcutaneous immunoglobulin, thus largely rendering the latter a more viable option in regards to overall yield. Moreover, home management lead to a reduction in the costs linked to hospitalisation, substantially reducing the time and the workload necessary for the department to handle the intravenous therapy of patients. Indirect costs that favour the use of subcutaneous immunoglobulin are transportation to hospital and time lost from work (Gaspar et al., 1998).

Another concern regarding the costs of intravenous immunoglobulin therapy is the frequent need of their use as maintenance therapy after the initial remission. Dalakas (2006) documented that the benefits appear lasting an average of six weeks and that for long-term benefits, continued infusions may be required. Genevay et al. documented that low-dose (0,8 g/kg/monthly) treatment with intravenous immunoglobulin can be helpful in maintaining clinical remission after high-dose initial infusions (2g/kg/monthly) in patients with refractory polymyositis (Genevay, 2001).

However, the problem of cost should be balanced with proven effectiveness in otherwise life-threatening situations or as short-term treatment in patients with severe refractory disease.

7. Conclusions

In this chapter we examined the role of immunoglobulin therapy in polymyositis and dermatomyositis. The revision of the literature evidenced the lack of randomised controlled trial, basically due to the rarity of the diseases. Another major problem in evaluating the published reports in polymyositis and dermatomyositis is the lack of international consensus on diagnostic criteria and outcome measures. A consensus on this will significantly improve the analyses of published data. Despite these biases, most of the papers report the efficacy and the safety of intravenous immunoglobulin, when standard therapeutic regimens fail, even in refractory or relapsing cases. Indication for the use of intravenous immunoglobulin is in particular the oesophageal involvement. In other reports intravenous immunoglobulin is used in association with immunosuppressants. In relation to cyclosporine A and mycophenolate mofetil, the add-on of intravenous immunoglobulin enables an increase in the rate of responding patients, with a short- and long-term stable remission and a reduced rate of infective complications. Recently, subcutaneous immunoglobulin has been used in selected autoimmune diseases. We documented the feasibility and the high tolerability of subcutaneous immunoglobulin, with relevant improvement in the clinical and laboratory features. Moreover, subcutaneous immunoglobulin increases patient quality of life giving them the possibility to receive treatment at home. This “self-management” is generally appreciated by most patients, in particular as it renders them independent from healthcare providers and hospitalisation,

with a significant improvement in treatment satisfaction. This improvement is mostly associated with flexibility, reduced infusion-related issues and enhanced freedom in organising daily activities. The low rate of side effects which improves quality of life, the possibility to withdraw the immunosuppressants and the steroid sparing effect, make the subcutaneous immunoglobulin a viable option in selected patients with myositis when standard therapeutic regimens fail or when immunosuppressants are contra-indicated.

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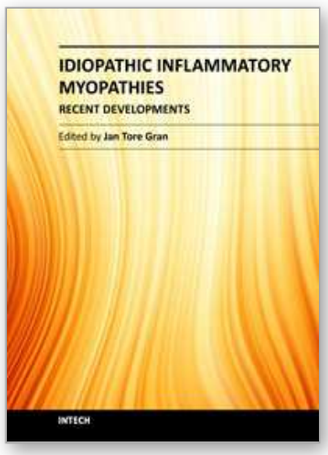

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The term "myositis" covers a variety of disorders often designated "idiopathic inflammatory myopathies". Although they are rather rare compared to other rheumatic diseases, they often cause severe disability and not infrequently increased mortality. The additional involvement of important internal organs such as the heart and lungs, is not uncommon. Thus, there is a great need for a better understanding of the etiopathogenesis of myositis, which may lead to improved treatment and care for these patients. Major advances regarding research and medical treatment have been made during recent years. Of particular importance is the discovery of the Myositis specific autoantibodies, linking immunological and pathological profiles to distinct clinical disease entities. A wide range of aspects of myopathies is covered in the book presented by highly qualified authors, all internationally known for their expertice on inflammatory muscle diseases. The book covers diagnostic, pathological, immunological and therapeutic aspects of myositis.

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