Efficacy of IVIg Therapy in Inflammatory Myositis

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Abstract—The aim of this retrospective study is to evaluate the efficacy and safety of intravenous immune globulin (IVIg) as immunomodulatory treatment in patients with inflammatory myopathies. We analyzed six patients, observed in a single-center from 2004 to 2012, affected by polymyositis (PM), dermatomyositis (DM) or inclusion body myositis (IBM) and treated with IVIg. IVIg has been successfully used as rescue therapy in all patients with a periodical dose of 1-2 g/Kg administered in 5 days. The mean follow-up was 37 months. Beneficial effects of IVIg were evaluated utilizing clinical notes, muscle enzyme levels and clinimetric score. All patients showed an improvement of muscle strength and a significant reduction of muscle enzyme levels (p<0.01 and p<0.05, respectively). Adverse events were mild and tolerable. Although IVIg has been demonstrated to be effective as steroid-sparing agent when other immunosuppressive drugs had failed, in all patients, however, a progressive reduction of clinical response after a variable number of IVIg cycles was observed. IVIg may safely be used and represents an effective rescue therapy in autoimmune myositis. Larger controlled studies are however needed to establish the IVIg actual efficacy in inflammatory myopathies, define standard therapeutic guidelines and detect predictive factors of response.

Index Terms—Inflammatory Myopathies, Dermatomyositis, Polymyositis, Inclusion Body Myositis, IVIg.

I. INTRODUCTION

INFLAMMATORY myopathies are a heterogeneous group of diseases characterized by muscle weakness and inflammation. They could be classified into 3 main subtypes: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM). Every subtype has different pathogenesis, clinical features and histological findings. Actually, treatment of inflammatory myopathies is based on glucocorticoids and immunosuppressive drugs, often associated to obtain remission through a synergistic effect. In case of resistance to standard therapy intravenous immune globulin (IVIg) is generally used [1], even though its efficacy may vary in different subtypes. Despite the large part of literature is based on case reports [2-8], often regarding clinical situations which represent either a contraindication to immunosuppressive therapy, such as pregnancy [9-11] and active severe infections [12], or a particular organ involvement, such as lung [13, 14] and esophagus [15, 16], also randomized controlled trials have been developed. In DM, in fact, IVIg efficacy was evaluated in two randomized controlled trials (RCT), which have shown a significant improvement in patients unresponsive to common treatment [17, 18]. In PM IVIg could be used in patients with first-line therapy failure either in relapses or in life-threatening disease [19]. Other open prospective and retrospective studies [20] in PM and DM patients showed IVIg efficacy in most cases, although it seems to be ineffective as first-line therapy [21]. Despite two randomized controlled trials report a variable and modest response in IBM [22, 23], IVIg may however be employed for lack of alternative therapies. In 9 children with refractory juvenile dermatomyositis, IVIg induced clinical improvement and allowed to reduce corticosteroids dose [24]. Despite the need of more studies, in order to better define IVIg efficacy in autoimmune myopathies, lack of controlled trials is dependent on the difficulty to collect a meaningful patient number and the limited IVIg availability.

II. PATIENTS AND METHODS

A. Patients and Methods

In 6 patients (mean age±SD 59.43±7.91 years; M/F:2/4) affected by inflammatory myopathies and refractory to standard therapy, IVIg was administered as an add-on treatment. According to Bohan and Peter criteria [25], diagnosis was of DM in 2 patients (N°1-2), both in overlap with Systemic Lupus Erythematosus (SLE), PM in 3 patients (N°3-4-5), one associated with Systemic Sclerosis (SSc), and IBM in the last patient (N°6). At the start of IVIg infusions all patients showed an important muscle involvement characterized by progressive muscle weakness, limiting daily life activities; furthermore the 2 DM patients presented a severe cutaneous involvement (heliotrope rash and Gottron's papules). Creatine Kinase (CK, normal value <174 U/l), Lactic Dehydrogenase (LDH, normal value <193 U/l) and Myoglobin (normal value <85 U/l) serum levels were higher than normal values before IVIg therapy. An electromyography and a diagnostic muscle biopsy were performed in all patients.

IVIg therapy was justified by failure of treatment with
glucocorticoids and other immunosuppressants (Methotrexate, Azathioprine and Cyclosporin A). In only one patient (N°1) IVIg courses started a few weeks after disease onset, as a consequence of a contemporaneous active *M. tuberculosis* infection with necrotizing mediastinic lymphadenitis [12], which represented a contraindication to immunosuppressive treatment. The time between disease onset and IVIg infusions was on average 54.85 months.

All patients received IVIg (Endobulin, Baxter; Flebogamma, Grifols; Intratect, Biotest Pharma GmbH; Privigen, CSL Behring; Sandoglobulin, CSL Behring) at the dose of 1-2 g/Kg, administered in 5 days with an infusion rate of 40-320 ml/h and they were periodically treated for a mean period of 37 months, with a range of 3-14 courses/patient. Oral glucocorticoids have been generally maintained during IVIg cycles, at the dose already established before IVIg introduction (mean dose of prednisone in all patients: 6.7 mg/day) in patients N° 1 and 4, whereas in the other 4 patients (N°2,3,5-6) they were slowly tapered at the lower possible dose according to clinical conditions.

The efficacy was established by evaluating clinical notes, laboratory tests and muscle function with Functional Index-2 (FI-2) [26] performed before and after every IVIg course. In case of elevated serum levels before IVIg cycles, muscle enzymes were compared with the post-treatment level. FI-2 was performed during one cycle for 3 patients (N°2-3-4), during 2 cycles for 2 patients (N°1 and N°5) and the patient with IBM (N°6) was evaluated for 3 IVIg cycles. In only one DM patient (N°1), histological changes were studied in muscle biopsy performed after four infusion cycles.

Lastly, severe and mild adverse events to IVIg infusions were recorded.

**B. Statistical analysis**

Data were analyzed using Epi-info statistical program. The Student's t-test was employed for normal distributions and Wilcoxon's signed-ranks test for non-normal distributed data.

**III. RESULTS**

All patients reported a clinical improvement characterized by an increase of muscle strength and less difficulty in accomplishing daily life activities (i.e. climb the stairs); moreover, the two DM patients showed a resolution of cutaneous involvement.

Before IVIg infusions CK serum levels were increased in 5 out of 6 patients, only 3 had a high level of plasmatic myoglobin and all patients, at least in one occasion, showed LDH increase. In all the tested samples, excepting one, a significant decrease of LDH (p<0.01), CK (p<0.01) and Myoglobin (p<0.05) was recorded (Fig.1-2-3).

An improvement of muscle function (FI-2) was observed in all patients. Comparing the number of repetitions of all exercises performed before and after IVIg course an improvement was observed (Fig. 4). An increase of muscle function, mostly in lower limbs (Fig. 5), with the exception of one patient (N°2), was recorded.

In only one patient histological findings, in muscle biopsy obtained after IVIg therapy, showed the net reduction of perimisial lymphocytic inflammatory infiltrate associated with residual fiber hypertrophy. However, in 4 patients, as inferred from clinical notes, a reduction of clinical response was observed after 3, 3, 5 and 15 infusion cycles respectively; the patient N°1 who received 15 cycles had started IVIg infusions at an early stage of disease. The fifth patient (N°5) interrupted therapy for refusal of intravenous administration and the other one (N°6) is still receiving IVIg infusions.

No serious adverse events were observed; only 3 patients presented mild reactions characterized by headache, hypertension and transient febrile episodes (39°C), however promptly resolved with paracetamol.
IV. DISCUSSION

Overall IVIg have led to a clinical and laboratory improvement in the cases examined. The safety has been witnessed by the mild and manageable adverse events, thus confirming the possibility of IVIg use either in cases of poor response or intolerance to other immunosuppressive drugs. Unlike other immunosuppressants, in fact, active infections are not a contraindication to IVIg treatment, representing instead an additional indication (patient N°1). The improvement of muscle function is differently distributed in the inflammatory myopathy subtypes, in decreasing rank order being better for DM, PM and IBM. The patient with IBM showed a satisfactory clinical response and maintenance of a benefit during the infusions, reaching a level of muscle function greater than that at treatment start. This observation is relevant because of the general poor response of IBM to standard immunosuppressive therapy and IVIg. In all treated cases, with the exception of the patient with minor response (N°2), regardless of the level of improvement, it was possible to observe a greater benefit in the muscle groups of the lower limbs.

In 4 patients, a progressive efficacy reduction after variable number of IVIg courses has been observed, whereas in the patient N°1 the efficacy was long-lasting (14 courses), probably for the early IVIg start, at a disease stage characterized by more active inflammation and less fibrosis (damage already anatomically established).

IVIg may influence the immunopathogenesis [27] of inflammatory myopathies through multiple mechanisms of action [28]. The inhibitory effect on complement activation has particular importance in DM, in which complement is responsible for muscle and skin damage [29]. The inhibition of cytokine production and the expression of adhesion molecules could also contribute to the efficacy of IVIg therapy [30]. Furthermore, IVIg is able to modify gene expression in patients with inflammatory myopathies [31]. In PM and IBM IVIg may modulate T lymphocyte activation, either directly or through interaction with the dendritic cells (DC) and macrophages, by interfering with the IgG Fc-Receptors (FcγR). Although the cytotoxic damage and cell death, often observed in PM, are mediated by CD8+ cells, probably also the Fas pathway is involved [32]. The modulation of apoptosis mediated by IVIg could positively influence its effect on PM [33]. Moreover, IVIg may revert the proinflammatory cytokine-dependent glucocorticoid resistant state [34], by improving glucocorticoid-receptor binding, through a still poorly defined mechanism, which may include suppression of pro-inflammatory cytokine production [35, 36].

In one patient (N°5) IVIg was suspended for refusal of intravenous administration. In analogous cases subcutaneous immune globulin (SC Ig) may be used, considering its higher safety profile and similar immunomodulatory activity in inflammatory myopathies compared to IVIg [37, 38].

V. CONCLUSION

IVIg is safely used and represents an effective rescue therapy in inflammatory myopathies, in particular when immunosuppressive drugs are contraindicated. Moreover it has a role as steroid-sparing agent.

It could be interesting to understand the mechanism at the basis of observed loss of efficacy. An early IVIg treatment is associated with a better clinical response, thus suggesting that they could modify the disease progression. More data is needed in order to establish the IVIg/SC Ig actual efficacy in inflammatory myopathies, define standard therapeutic guidelines and detect predictive factors of response.

REFERENCES


