

# High-Dose Facilitated Subcutaneous Immunoglobulin in a Patient with Refractory Polymyositis and Severe Interstitial Lung Disease

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**P**olymyositis is a rare immune-mediated disease. Therapeutic options comprise glucocorticoids, immunosuppressants and immunoglobulin, administered intravenously (IVIg) or subcutaneously (SCIg). Recently a new modality of immunoglobulin administration, the facilitated SCIg (fSCIg, 10% immunoglobulin plus recombinant human hyaluronidase), has been used.

Idiopathic inflammatory myopathies (IIM) consist of a group of chronic autoimmune diseases mainly affecting musculoskeletal systems and the skin in the form of dermatomyositis. Patients usually present with progressive proximal muscle weakness, muscle enzyme elevation, or a typical inflammatory pattern on muscular biopsy. Nevertheless, IIM can affect extra-muscular areas such as the lungs, heart, joints, and gastrointestinal tract.

A first-line treatment is represented by high-dose oral or intravenous glucocorticoids. Second-line therapy consists in immunosuppressive drugs like azathioprine, methotrexate, mycophenolate mofetil, or cyclosporine A. If response to glucocorticoids is unsatisfactory, IVIg at immunomodulatory doses and/or ritux-

imab can be useful in inducing remission. Weekly infusions of 20% subcutaneous immunoglobulin (20% SCIg) may help in controlling disease activity [1]. A new therapeutic modality can be represented by 10% facilitated subcutaneous immunoglobulin (10% fSCIg), with the possibility to infuse large drug volumes without resorting to intravenous administration.

## PATIENT DESCRIPTION

A 61-year-old Caucasian man came to our attention in February 2018 due to worsening hyposthenia and dyspnoea. His past medical history included mellitus diabetes type 2, systemic arterial hypertension, severe mitral insufficiency. The patient smoked until the age of 30 years.

Muscle weakness started in 2017 with involvement in the girdles regions, increased serum levels of creatine kinase (CK), and myopathic changes at electromyography. Findings during muscular biopsies were consistent with the diagnosis of polymyositis. The patient was initially treated by glucocorticoids with partial improvement, and subsequently, with immunosuppressants, including azathioprine, methotrexate, mycophenolate mofetil, and cyclosporine A, with poor response.

When he was referred to our medical facility, physical examination confirmed the four-limb proximal hyposthenia, with a manual muscle test score (MMT8) of 70/80 points. Cardiovascular examination was significant for a 2/6 systolic murmur in the absence of signs of cardiac failure.

Lung auscultation revealed bilateral basal crackles with 94% oxygen saturation. During hospitalization, the patient's condition rapidly deteriorated, with a decline in muscular strength, aggravation of dyspnoea, and reduction of oxygen saturation.

Blood tests showed a significant increase in serum CK levels (1246 U/L, normal values < 170 U/L). At the autoantibodies screening, we found antinuclear antibodies (ANA 1:320, granular pattern). Myositis specific antibodies and myositis-associated antibodies results were negative. A magnetic resonance imaging (MRI) of the proximal inferior limbs documented edema of the thigh muscles, with particular involvement of the left femoral biceps.

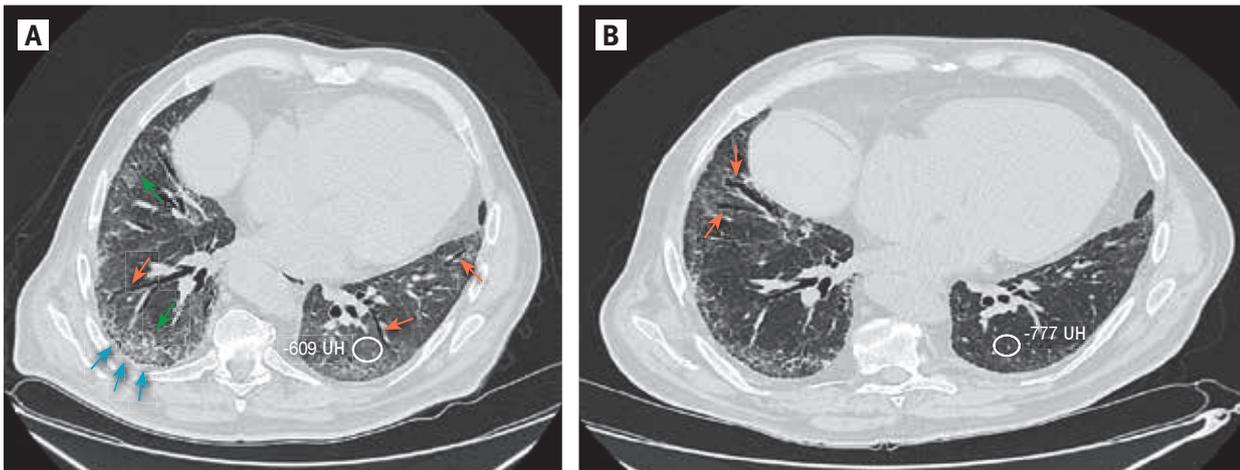
The diagnosis of polymyositis was confirmed according to Bohan and Peter's criteria and to the new diagnostic criteria of the European League Against Rheumatism/American College of Rheumatology.

Pulmonary function tests revealed a restrictive pattern with a marked DLCO reduction. A chest computed tomography showed a severe interstitial lung disease with non-specific interstitial pneumonia (NSIP) radiological pattern [Figure 1A]. An echocardiography and a cardiac MRI confirmed the already known severe mitral insufficiency, evidenced a cardiac hypertensive hypertrophy and excluded both pericarditis and myocarditis. We definitively ascribed dyspnoea to ILD in course of rapidly progressive IIM in phase of severe activity.

To control the rapid disease progression, we firstly administered intravenous

**Figure 1.** High-resolution computed tomography findings

**[A]** Before rituximab and fSCIg treatment (February 2018) showing parenchymal increased density (ground-glass opacities), traction bronchiectasis (orange arrows), bilateral pulmonary interstitial thickening with reticular opacities (green arrows), and small honey-combing subpleural areas (blue arrows), especially in pulmonary lower lobes. **[B]** After treatment (January 2019) showing reduction in bilateral ground-glass areas and improvement of pulmonary interstitial thickening. Traction bronchiectasis (orange arrows)



fSCIg = facilitated subcutaneous immunoglobulin, HU = hounsfield unit

methylprednisolone at the rate of 1 g/day on 3 consecutive days, followed by oral prednisone 1 mg/kg/day with subsequent tapering. Rituximab (1 g/day for two infusions, 2 weeks apart) was added to the schedule. Subsequently, to definitively induce and maintain remission, the patient began treatment with IVIg 1 g/kg/day on two consecutive days each month (140 g/month).

After 3 months, we obtained disease remission. To offer the patient the possibility of a home self-administered therapy, we decided to maintain a schedule with fSCIg. Considering the severity of clinical conditions at the diagnosis, we chose a schedule with high-dose fSCIg at the previously IVIg dose (fSCIg 35 g/week = 140 g/month). We adopted this dose for 3 months and then we reduced it to 35 grams every 2 weeks.

At 9 months follow-up, the patient reported complete normalization of CK serum levels, significant improvement of muscular strength (MMT8 78/80), and reduction of dyspnoea (oxygen saturation 96%) with concomitant reduction of a daily dose of prednisone, without relapses. Even the radiologic pattern showed an improvement, as shown in Figure 1B.

**COMMENT**

IIM can sometimes result in life-threatening conditions, requiring a massive immunosuppressive therapy [2]. Lung and heart involvements are usually connected to the most unfavorable outcomes, potentially developing into acute heart and respiratory failure. However, immunosuppressive drugs can be linked to severe side effects such as new-onset infections or latent infections reactivation. Moreover, neoplasms and other co-morbidities can contraindicate their use. Immunoglobulin can thus represent a safe and effective therapy not just in cases of severe and refractory IIM, but also in presence of contraindications to conventional medications. Nevertheless, immunoglobulin may be necessary for acquired hypogammaglobulinemia, which can often arise following the administration of rituximab.

The immunomodulatory role of IVIg is widely accepted and its use is approved in selected immune-mediated diseases (i.e., idiopathic thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy). Several mechanisms have been proposed to explain this action. Many

are linked to the blood peak following the high-dose IVIg administration. Even 20% SCIg can have an immunomodulatory role, as reported in myositis and in other autoimmune conditions, probably linked to different mechanisms than IVIg. Our group already demonstrated the effectiveness and safety of SCIg in patients affected by IIM [1].

Recently, a new combination of 10% SCIg and recombinant human hyaluronidase PH20 (fSCIg) has become available as replacement therapy in primary immunodeficiencies. Hyaluronidase, breaking the hyaluronan chemical bonds, creates a pocket in the subcutaneous tissue, facilitating immunoglobulin passage in the lymphatic vessels and enabling the administration of large volumes of medicament. This may permit to employ immunomodulatory doses in patients with immune-mediated diseases. This aspect can also be reinforced by the pharmacokinetic properties of fSCIg, whose administration leads to a blood IgG peak similar to the one of IVIg, even if lower and later. The use of high-dose fSCIg has already been tested not only in immune-mediated cytopenias related to common variable immunodeficiency, but

also in juvenile dermatomyositis, with satisfactory results [3-4].

In our case, the rapid progression of lung disease and the partial response to other immunosuppressants made necessary the use of rituximab. To strengthen its action, but also to reduce the potential risk of infection, we decided to associate the administration of IVIg, shifting to fSCIg after 3 months. The high-dose fSCIg therapy was well tolerated, with no side effects. After 6 months, the patient completely recovered muscle strength and reported a relevant improvement of dyspnoea. Moreover, it was possible to reduce prednisone daily dose without relapses, as documented for IVIg [5]. The patient did not report serious infectious episodes during the 9-month follow-up period.

Considering the severity of clinical and radiological lung involvement, a notable aspect is represented by the great reduction of NSIP-pattern of pulmonary interstitial disease after rituximab and fSCIg therapy. While the effectiveness of IVIg in inducing remission in IIM is recognised, its use in ILD is rarely described in literature. Some case reports and case-series showed the

impact of IVIg in ILD-IIM, in particular in association with immunosuppressive drugs in case of refractory or rapidly progressive ILD, or as first-line therapy in case of contraindications to immunosuppressants. To the best of our knowledge, nobody has investigated the potential role of SCIg on ILD, even in case of IIM. This case report can thus represent the first proof of fSCIg effectiveness and safety in maintaining remission of severe ILD in course of IIM.

#### CONCLUSIONS

Our preliminary data documented that immunomodulatory high-dose fSCIg was a feasible and safe maintenance treatment in a patient with refractory IIM associated with ILD requiring a high immunosuppressive therapy. fSCIg was not only effective in maintaining remission, but also in avoiding infections and as steroid-sparing agent. The subcutaneous infusion of immunoglobulin is associated to several advantages, such as the possibility of home self-administration, with a higher quality of life; better adverse reactions profile with lower incidence of systemic events; absence of hemodynamic overload and more stable serum IgG levels.

However, further studies are necessary to investigate the potential immunomodulatory role of fSCIg in immune-mediated disorders.

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#### Capsule

##### Inheriting microbiome variation

In mice, the bacterial species in the gut microbiome are maternally inherited. **Yardeni** and colleagues found reduced gut microbiome species diversity in mice with variations in mitochondrial DNA (mtDNA) that were associated with increased reactive oxygen species (ROS) production. When pups were cross-fostered, the gut microbiome species after

weaning reflected not the microbiota community of the nursing mother but rather the inherited mtDNA variation. Pharmacological or genetic reductions in mitochondrial ROS levels increased microbiome diversity.

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#### Capsule

##### A shocking contributor in anaphylaxis

Classic anaphylaxis is thought to depend on immunoglobulin E (IgE) engagement of Fc receptors on granulocytes, but allergen-specific IgE is not always present. To resolve this conundrum, **Jönsson** and colleagues studied samples from people who experienced anaphylaxis after anesthesia. Drug-specific IgG complexes could trigger neutrophils ex vivo, and anaphylactic subjects had increased neutrophil extracellular

traps. Not all of the subjects had detectable antidrug IgE. Thus, alternative pathways may be at play, and knowledge of these pathways could aid the development of tests to reduce risks in anesthesia.

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