CASE REPORT

Complete remission in refractory relapsing polychondritis with intravenous immunoglobulins


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Introduction

Relapsing polychondritis (RP) is a rare inflammatory disease of the cartilaginous structures (ear, nose and tracheobronchial tree) and of other collagen-rich structures (eyes and blood vessels) (1). Pathogenic features suggest that RP is immune-mediated and involves an immunological reaction to collagen II (2). Treatment options include corticosteroids, dapsone, azathioprine or methotrexate, or cyclophosphamide in patients with severe forms (1). We report the successful treatment of a severe and refractory RP patient with intravenous immunoglobulins (IVIg).

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In July 2002, an 18-year-old woman was referred for a 2-year history of relapsing episodes of nasal chondritis with saddle nose deformity, arthralgias and scleritis. RP was diagnosed on the presence of clinical symptoms and negativity for all immunological tests including antinuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptides antibodies and anti-neutrophil cytoplasmic auto-antibodies (ANCA). Three intravenous (i.v.) pulses of methylprednisolone (500 mg) relayed by oral prednisone (1 mg/kg/d) resulted in temporary improvement of symptoms; after one month, relapse of RP occurred as bilateral hearing loss and scleritis. Treatment with 6 i.v. pulses of cyclophosphamide (0.6 g/m²) relayed by azathioprine (2 mg/kg/d) and prednisone (1 mg/kg/d) led to complete regression of symptoms. Relapse of chondritis occurred after tapering of prednisone to 8 mg/d, and was treated with increase of prednisone to 20 mg/d and azathioprine to 3 mg/kg/d. Relapse of auricular and nasal chondritis and scleritis recurred after tapering the prednisone dosage to 10 mg/d. An increase of prednisone dosage to 35 mg/d led to mild improvement. In September 2003, i.v. infliximab (3 mg/kg every 6 weeks) in addition to prednisone and azathioprine resulted in regression of chondritis and scleritis. After 5 i.v. infusions of infliximab and tapering of prednisone to 10 mg/d, episcleritis recurred. Increase dosage of prednisone to 35 mg/d and of infliximab to 5 mg/kg every 4 weeks resulted in improvement of episcleritis. In July 2004, azathioprine was replaced by mycophenolate mofetil (2g/d) because of its hepatotoxicity. Relapse of nasal chondritis and episcleritis occurred and oral methotrexate (10 mg/week) was introduced in September 2004. Relapses of episcleritis occurred in December 2004; infliximab was stopped, and an increased dosage of prednisone to 35 mg/d and methotrexate to 15 mg/week led to temporary improvement, but few relapses of episcleritis occurred. In October 2005, severe relapse of scleritis with onset of mild bilateral scleromalacia occurred. Methotrexate and mycophenolate mofetil were discontinued. Treatment with i.v. pulse of methylprednisolone (500 mg) and cyclophosphamide (0.6 g/m²), relayed with prednisone (1 mg/kg/d), led to mild improvement. In December 2005, bilateral scleritis relapsed after 3 i.v. pulses of cyclophosphamide; cyclophosphamide was stopped and IVIg every 3 then 4 weeks were introduced (2 g/kg on 2 days) in association with 25 mg/d of prednisone, allowing a dramatic improvement of scleritis after the first course of IVIg. Prednisone was tapered to 10 mg/d and no relapse occurred during 11 months of follow-up. In October 2006, IVIg were spaced every 6 weeks, but 5 weeks after the last infusion, a relapse of RP with unilateral perception hearing loss and episcleritis occurred. The courses of IVIg were brought back to every 4 weeks and led to rapid complete regression of episcleritis and hearing loss on audiometric tests 1 week later. The clinical and therapeutic time course is summarized in Figure 1.

As IVIg have been used effectively and safely in various autoimmune or inflammatory disorders, in particular, systemic vasculitides such as Kawasaki disease and ANCA-related vasculitides (3), and in the treatment of refractory bilateral uveitis (4), we initiated this treatment in our patient. Although the pathophysiology of RP is unknown, it was found that the disease is associated to immunoglobulin and complement deposits within chondritis lesions (5), autoantibodies against cartilage particularly collagen II (6) and increase of cytokines stimulating the monocyte-macrophage

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**Fig. 1.** Clinical and therapeutic time course of the relapsing polychondritis patient. The graph indicates the evolution of the prednisone dosage starting the date of diagnosis. In the upper section (treatment section), arrows indicate pulse of treatment. In the lower section (graph), arrows indicate relapses of relapsing polychondritis. Scl: scleritis; Ch: chondritis; Escl: episcleritis; MP: methylprednisolone; CYC: cyclophosphamide; AZA: azathioprine; MMF: mycophenolate mofetil; MTX: methotrexate; IVIg: intravenous immunoglobulins.

**References**

5. COURTNAY JS, DALLMAN MJ, DAYAN AD, MARTIN A, MOSEDALE B: Immunisation lineage (Macrophage Inflammatory Protein-1, Monocyte Chemoattractant Protein-1 and Interleukin-8) (7). These pathogenic features could explain the mechanisms of action of IVIg in RP. First, IVIg could exhibit their beneficial effects by interaction with complement proteins (8); Fc portions of IVIg link activated complement proteins such as C3b and C4b, reducing their level and their ability to settle in situ (9). Second, IVIg could neutralize circulating anti-collagen II antibodies, by the presence of anti-idiotypic antibodies (10). Third, IVIg down-regulated cytokine and chemokine synthesis and release, in particular by monocytes (10), but also the production of cytokines stimulating the monocytes-macrophage lineage such as MIP-1 (11). Finally, it was shown that IVIg exhibited a corticosteroid-sparing effect (10). However, rare cases reported the unsuccessful use of IVIg in RP (12-14).

In conclusion, IVIg might be an interesting and effective therapeutic option in patients with refractory RP. However, this beneficial effect appears to be only suspensive and needs to be evaluated in more patients.
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