

CLINICAL STUDY

An intravenous immunoglobulin therapy of serious autoimmune rheumatic diseases

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Abstract: Intravenous immunoglobulins (IVIg) have been widely used in clinical practice for more than 35 years. Their efficacy has been established in many clinical trials for the treatment of autoimmune rheumatic diseases including systemic lupus erythematosus, ANCA positive vasculitis and dermatomyositis, but these indications are classified as the „off label“ treatment. For the diseases mentioned above there are no generally accepted therapeutic guidelines.

The case reports (one patient with lupus erythematosus chorea, two patients with dermatomyositis and one with the Wegener's granulomatosis) present a treatment of systemic connective tissue diseases with IVIg following the failure of standard therapeutic regimens. A successful therapy has been realized using different doses of IVIg, which raises a question on an appropriate dose.

Based on our experience, we conclude that intravenous immunoglobulins are effective in the treatment of many „off label“ indications in rheumatology, particularly in cases when standard immunosuppressive therapy could be harmful. Despite the evidence of efficacy, the dosage and timing of IVIg therapy, and questions of costs/benefits ratio still remain insufficiently documented and multicentric controlled clinical trials with consecutive development of guidelines are necessary (*Ref. 27*). Full Text (Free, PDF) www.bmj.sk.

Key words: intravenous immunoglobulin, autoimmune rheumatic diseases, failure of standard regime, IVIg dosage.

Intravenous immunoglobulins (IVIg) have been widely used in clinical practice for more than 35 years. The first therapeutic use of immunoglobulins was in 1952 by C. O. Bruton in a case of a primary antibody deficiency (1). This historical event initiated the use of IVIg in the treatment of primary and secondary antibody deficiency. Later, IVIg were demonstrated to be effective also in an autoimmune disorder – idiopathic thrombocytopenic purpura. Since then, IVIg in high dose have been established in controlled clinical trials to be efficacious in the treatment of many autoimmune/inflammatory diseases (Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, multifocal motor neuropathy, multiple sclerosis, dermato/polymyositis, Kawasaki's syndrome, ANCA positive vasculitis) and in the prevention of graft-versus-host reaction (2–6). Benefits have been reported also in other autoimmune conditions, but controlled trials are lacking (7), e.g. systemic lupus erythematosus (SLE) and proliferative lupus nephritis have also responded to IVIg in open labeled studies and case

reports (8, 9). Recent study revealed a rapid expansion of intravenous immunoglobulins for a growing number of conditions including systemic inflammatory disorders such as asthma and sepsis (10, 11).

The purpose of our case reports is to present four cases of autoimmune inflammatory connective tissue diseases, which were treated with IVIg due to the failure of standard therapeutic regimens. A successful treatment has been performed with different doses of IVIg, what leads to a question on the appropriate dose of IVIg.

Case reports

Case 1

A 33-year-old Caucasian female was admitted due to generalized choreiform movements. Eleven years ago (1996) she had been diagnosed with SLE and had been treated with corticosteroids and azathioprine for four years. In 2005 she developed the Libman-Sachs endocarditis with the involvement of the mitral valve, which was replaced by a bioprosthesis later in the same year.

On admission, the patient manifested involuntary choreatic movements of the right extremities spreading to left side of the body and face accompanied by severe cognitive impairment. Hematological evaluation revealed a mild leukopenia and thrombocytopenia. Blood and CSF biochemical routine tests were in the normal range. Immunological essays revealed highly positive an-

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tibodies: ANA, ENA, ds-DNA, RNP, aCL with positive lupus anticoagulans (LA) and high levels of antineuronal antibodies.

There were no signs of cerebral vasculitis on MRI – angiography. Microbiological analysis of the cerebrospinal fluid did not detect bacterial or fungal infection.

Treatment started on the 3rd hospitalization day and included methylprednisolone 500 mg i.v. daily and a low molecular weight heparin 2x0.6 ml subcutaneously per day. This therapy led to a mild and transient improvement of the choreiform symptoms so the treatment with intravenous immunoglobulins (IVIg) was suggested. IVIg were administrated at a dose of 20 g i.v. for five days. This treatment led to a prompt improvement of the neurological and mental status and the patient recovered completely within 7 days.

Case 2

A 66-year old Caucasian female was admitted due to fever, severe muscle weakness, diffuse joint pain and dysphagia. Laboratory evaluation revealed a mild anemia, leucocytosis and thrombocytosis with normal coagulation parameters. Liver enzymes were increased and hyperazotemia with an impaired glomerular filtration rate and a mild proteinuria were documented. Inflammatory markers (sedimentation rate, CRP) were increased. An elevated serum myoglobin indicated the muscle damage. Antibodies (ANA, ENA, anti JO-1) were negative and only anti-RO was slightly positive. Electromyography detected acute myogenic lesions supporting the diagnosis of polymyositis, which was definitely confirmed by the histology.

Treatment started on the 8th day of hospitalization with a pulsating dose of 500 mg methylprednisolone i.v. On the next day a progression of muscle weakness, hypotension, and respiratory failure were present and patient was admitted to the intensive care unit for artificial ventilation after a tracheotomy.

Later in the clinical course, the methylprednisolone therapy in combination with cyclophosphamide was not successful and respiratory failure together with progressive dysphagia was observed. The therapy with the IVIg, 20 g given i.v. for 5 days, started. The clinical status of the patient rapidly improved with a mild remission of dysphagia and gain of muscle strength. On the 7th day after starting the IVIg therapy, oral feeding was possible again. The tracheotomy cannula was removed after 3 weeks. Therapy continued with an oral administration of corticosteroids and cyclophosphamide.

Case 3

A 57-year-old woman was hospitalized due to weakness, swelling of joints, dry cough, dyspnea or loss of appetite, haemoptysis, haematuria and oliguria. There was no history of fever and loss of weight in previous weeks. On admission, only a mild swelling of maleolar joints was present.

Hematological evaluation revealed a mild anaemia and leucocytosis. Biochemical analysis showed high levels of urea and creatinine. A reduction of renal functions (glomerular filtration rate, tubular reabsorption) and massive proteinuria were present. Inflammatory markers (sedimentation rate, CRP) were elevated. An im-

munological evaluation revealed highly positive cANCA antibodies, and unspecifically mildly positive SS-B and Sm antibodies.

A high resolution CT of the lungs detected signs of interstitial and alveolar pulmonary edema with a small amount of fluidothorax. Pulmonary function testing revealed a combined obstructive and restrictive respiratory impairment.

According to the clinical and laboratory findings (cANCA), the diagnosis of an acute severe pulmo-renal syndrome with suspected Wegener's granulomatosis was established. The patient refused any other invasive diagnostic procedures (VATS, renal biopsy) to specify the condition.

Treatment started with high doses of corticosteroids and cyclophosphamide. This therapeutic regimen led to a clinical improvement of the pulmonary symptoms, however renal functions worsened and an acute renal insufficiency developed. Due to an acute clinical status, plasmapheresis and haemodialysis started immediately. After two weeks, septic status developed. Corticosteroid dose was reduced and immunosuppressives were withdrawn. Therapy with IVIg in the dose of 10 g in 5 consecutive days was applied. Patient was discharged with only a mild residual renal dysfunction.

Case 4

A 54-year-old Caucasian woman was admitted due to weakness, skin erythema, pain in the proximal muscles of upper and lower extremities, oedema of eyelids, xerostomia and dysphagia. On admission, the patient was without any significant physical symptoms, except of a mild swelling of eyelids and skin erythema.

Hematological evaluation revealed normal values except of a slight neutrophilia and thrombocytopenia. A moderate elevation of the sedimentation rate was present. Biochemical analysis showed elevated values of CK, uric acid, myoglobin and circulating immunocomplexes. The antibodies against smooth muscle were highly positive. Electromyographic evaluation showed signs of muscle damage typical for the dermatomyositis. Additionally, biopsy of the right m. quadriceps femoris supported the diagnosis.

The treatment started with corticosteroids and immunosuppressives. This therapy led only to a mild improvement of symptoms but caused serious side effects. Despite the treatment, the myoglobin level increased and the signs of secondary (post-therapeutic) immunodeficiency status (loss of CD8, decreased IgG) with a massive clinical manifestation (aphtosis, rhinosinusitis, stomatitis) appeared. Because of the disease progression, the treatment with IVIg – in the dose 30 g/daily during five consecutive days started. After the IVIg therapy, the clinical status improved and a significant decrease of creatinine kinase activity and myoglobin level was observed. Patient was discharged on a low dose of oral corticosteroids. After two months, the maintenance dose of 30 g of IVIg was administered.

Discussion

Mechanisms of action of intravenous immunoglobulins are complex. Jolles et al (12) summarized multiple immunomodulatory actions of IVIg in four separate components: 1) actions

mediated by the variable regions Fab, 2) actions of the Fc region on a range of Fc receptors, 3) actions mediated by complement binding within the Fc fragment and 4) immunomodulatory substances other than antibody in the IVIg preparations (cytokine network, cytokine receptors, etc). It seems also necessary to emphasize two new hypotheses on mechanisms of action of IVIg. The IVIg treatment may result in the saturation of FcRn receptors, and through a competition may prevent pathogenic autoantibodies from binding, with the resulting accelerated degradation (13, 14). The second hypothesis postulates the IVIg capability of reversing the steroid resistant state by reducing the binding affinity of corticosteroid receptor-beta to corticosteroids (15, 16).

In the present case reports of four patients with the rheumatologic autoimmune diseases (one patient with lupus erythematosus chorea, two patients with dermatomyositis and one patient with Wegener's granulomatosis) we present our approach for using the intravenous immunoglobulins. For the diseases mentioned above there are no generally accepted therapeutic guidelines (17). In the United states, there are currently 6 clinical indications for which the IVIg has been licensed by FDA as follows: (1) treatment of the primary immunodeficiencies, (2) prevention of bacterial infections in patients with hypo-gammaglobulinaemia and recurrent bacterial infection caused by the B-cell chronic lymphocytic leukemia, (3) prevention of coronary aneurysms in the Kawasaki's disease, (4) prevention of infections, pneumonitis, and acute graft-versus-host disease after a bone marrow transplantation, (5) reduction of serious bacterial infection in children with HIV and (6) increase of platelets counts in the idiopathic thrombocytopenic purpura to prevent bleeding. All other conditions are classified as the "off label" treatment (18, 19, 20). In the clinical course of our patients we must emphasize three common points: an acute severe manifestation of the disease (1), failure of the standard therapeutic regimen (corticosteroids, immunosuppressives) and worsening of the disease (2) complicated in three cases with infection and in one case with respiratory failure and admission to the intensive care unit and subsequent IVIg treatment resulting in rapid and long lasting improvement (3). In the autoimmune/inflammatory diseases, an immunomodulatory effect is expected. The IVIg in the case of a bacterial infection presumably improve the plasma bacterial activity caused by neutralizing and opsonizing IgG and IgM antibodies, as well as stimulate the phagocytosis and neutralization of bacterial toxins (21). In our cases, this adjunct effect can also be classified as an adjuvant/replacement treatment, where the loss of natural immunoglobulins in plasma is supplemented by the IVIg.

According to many papers the "high dose" immunomodulatory therapy represent the application of 2 g/kg/course infused in five daily doses of 0.4 gram/kg each. However, some studies found a superior effect of IVIg when given in a single full dose rather than divided doses (2, 7, 22). In our group of patients, the amount of IVIGs varied from 1gram/kg up to 3 gram/kg pro course. Beside the dose, all our treatment regimens were successful. A question on the appropriate dose appears in the relation of the cost/benefits ratio of such "off label" treatment. We

have observed an adequate response in the case of Wegener's granulomatosis after a lower "high dose" regimen (1 gram/kg), which lasts by now (one year after treatment). Genevay et al (23) published an effective use of IVIg in lower doses (0.8 g/kg) but only for the maintenance treatment in polymyositis and concluded a considerable reduction in treatment costs without a negative influence on patient's health conditions. We observe an effective short-term treatment at various levels of IVIg doses in the cases of dermatomyositis following the failure of the standard therapy (corticosteroids+immunosuppressive drugs). In one case (case 4), the success of the IVIg therapy could be caused by the adjunct anti-infective defense. The lack of validated and generally accepted outcome measures makes it difficult to compare the effect of interventions in different cases (14).

An especially important question relates to the decision when to start IVIg therapy (2). We have started our IVIg therapy only following the failure of standard regimes. IVIg is shown to be a useful adjunctive therapy in ANCA-positive systemic vasculitis, refractory to the standard immunosuppressive therapy (24, 25) and can be used as the single drug in cases without involvement of vital organs (26). In the case of the Wegener's granulomatosis (case report 3), we have observed the failure of vital organ (an acute renal insufficiency) and consecutive septic status following the standard therapy, but after the admission of IVIg, a massive clinical improvement appeared. Question still remains about the sole or first line therapy. In literature, there is a note on using IVIg for cases of childhood and juvenile pemphigus, where this therapy can delay the need for the administration of immunosuppressive drugs with the potential of serious adverse effects (27).

Conclusion

Intravenous immunoglobulins are considered to be an effective treatment in many "off label" indications in rheumatology, particularly in cases when the standard immunosuppressive therapy could be harmful. Besides the evidence of efficacy, dosage and timing IVIg therapy, and questions of the costs/benefits ratio still remain insufficiently documented and multicentric controlled clinical trials with consecutive development of guidelines are necessary.

References

1. Bruton CO. Agammaglobulinaemia. *Pediatrics* 1952; 9: 722—728.
2. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *J Amer Med Ass* 2004; 291: 2367—2375.
3. Gold R, Stangel M, Dalakas MC. Drug Insight: the use of intravenous immunoglobulin in neurology-therapeutic considerations and practical issues. *Nat Clin Pract Neurol* 2007; 3: 36—44.
4. Levy J. New aspects in the management of ANCA-positive vasculitis. *Nephrol Dial Transplant* 2001; 16: 1314—1317.
5. Rowley AH, Shulman ST. Kawasaki syndrome. *Clin Microbiol Rev* 1998; 11: 405—414.

6. **Siadak MF, Kopecky K, Sullivan KM.** Reduction in transplant-related complications in patients given intravenous immunoglobulin after allogeneic marrow transplantation. *Clin Exp Immunol* 1994; 97: 53–57.
7. **Kazatchkine MD, Kaveri SV.** Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *New Engl J Med.* 2001; 345: 747–755.
8. **El-Shanawany T, Sewell WAC, Misbah SA, Jolles S.** Current clinical uses of intravenous immunoglobulin. *Clin Med* 2006; 6: 356–359.
9. **Toubi E, Kessel A, Shoenfeld Y.** High-dose intravenous immunoglobulins: an option in the treatment of systemic lupus erythematosus. *Hum Immunol* 2005; 66: 395–402.
10. **Alejandria MM, Lansang MA, Dans LF, Mantaring JB.** Intravenous immunoglobulin for treating sepsis and septic shock. *Cochrane Database Syst Rev* 2002; 1: CD001090.
11. **Niven AS, Argyros G.** Alternative treatments in asthma. *Chest* 2003; 123: 1254–1265.
12. **Jolles S, Sewell WAC, Misbah SA.** Clinical uses of intravenous immunoglobulin. *Clin Exp Immunol* 2005; 142: 1–11.
13. **Hansen RJ, Balthasar JP.** Intravenous immunoglobulin mediates an increase in anti-platelet antibody clearance via the FcRn receptor. *Thromb Haemost* 2002; 88: 898–899.
14. **Yu Z, Lennon VA.** Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases. *New Engl J Med* 1999; 340: 227–228.
15. **Landwehr LP, Jeppson JD, Katlan MG, Esterl B, McCormick D, Hamilos DL, Gelfand EW.** Benefits of high-dose i.v. immunoglobulin in patients with severe steroid-dependent asthma. *Chest* 1998; 114: 1349–1356.
16. **Levy Y, Sherer Y, George J, Rovinsky J, Lukac J, Rauova L, Poprac P, Langevitz P, Fabbri F, Shoenfeld Y.** Intravenous immunoglobulin treatment of lupus nephritis. *Semin Arthritis Rheum* 2000; 29: 321–327.
17. **Hundt M, Manger K, Dörner T, Grimbacher B, Kalden P, Rascu A, Weber D, Burmester GR, Peter HH, Kalden JR, Schmidt RE.** Treatment of acute exacerbation of systemic lupus erythematosus with high-dose intravenous immunoglobulin. *Rheumatology (Oxford)* 2000; 39: 1301–1302.
18. **Nimmerjahn F, Ravetch JV.** The antiinflammatory activity of IgG: the intravenous IgG paradox. *J Exp Med* 2007; 204: 11–15.
19. **Orange JS et al.** Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006; 117 (Suppl): S525–S553.
20. **Provan D, Nokes TJC, Agrawal S, Winer JB, Wood P.** Clinical guidelines for the use of intravenous immunoglobulin. Department of Health, London; 2007.
21. **Christensen RD, Brown MS, Hall DC, Lassiter HA, Hill HR.** Effect on neutrophil kinetics and serum opsonic capacity of intravenous administration of immune globulin to neonates with clinical signs of early-onset sepsis. *J Pediatr* 1991; 118: 606–614.
22. **Jolles S.** High dose intravenous immunoglobulin (hdIVIg) in the treatment of autoimmune blistering disorders. *Clin Exp Immunol* 2002; 129: 385–389.
23. **Genevay S, Saudan-Kister A, Guerne PA.** Intravenous gammaglobulins in refractory polymyositis: lower dose for maintenance treatment is effective. *Ann Rheum Dis* 2001; 60: 635–636.
24. **Jayne DR, Chapel H, Adu D, Misbah S, O'Donoghue D, Scott D, Lockwood CM.** Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *Q J Med* 2000; 93: 433–439.
25. **Negi VS, Elluru S, Sibérel S, Graff-Dubois S, Mouthon L, Kazatchkine MD, Lacroix-Desmazes S, Bayry J, Kaveri SV.** Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. *J Clin Immunol* 2007; 27: 233–245.
26. **Jayne DR, Lockwood CM.** Intravenous immunoglobulin as sole therapy for systemic vasculitis. *Br J Rheumatol* 1996; 35: 1150–1153.
27. **Szep Z, Danilla T, Buchvald D.** Treatment of juvenile pemphigus vulgaris with intravenous immunoglobulins. *Cas Lek Ces* 2005; 144: 700–703.

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