Improvement of Intravenous Immunoglobulin Therapy for Bullous Pemphigoid by Adding Immunosuppressive Agents

Marked Improvement in Depletion of Circulating Autoantibodies

Annette Czernik, MS; Jean-Claude Bystryn, MD

Background: Various antibody-mediated autoimmune disorders are treated with intravenous immunoglobulin (IVIg). While the exact action of IVIg is unknown, it likely acts to rapidly and selectively lower the level of pathogenic antibodies. The most effective use of IVIg, an expensive and potentially toxic treatment of autoimmune disorders, remains undetermined. We propose that the addition of immunosuppressive agents to the IVIg regimen may increase the ability of IVIg to lower the level of pathogenic antibodies.

Observations: For 16 months, we observed a 78-year-old patient with autoantibody-mediated bullous pemphigoid who was treated with IVIg and an adjuvant therapy on 2 separate occasions as well as IVIg alone on 2 other occasions. We observed the greatest depression of bullous pemphigoid antibodies when IVIg was combined with an immunosuppressive agent.

Conclusion: These results support the hypothesis that agents that suppress antibody synthesis can offset the rebound in the level of individual antibody that follows their depletion and thus can improve the effectiveness of IVIg treatment while reducing the cost and the potential toxic effects of therapy.

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NTRAVENOUS IMMUNOGLOBULIN (IVIg) is an effective and increasingly used treatment for many autoimmune diseases,1,2 including autoantibody-mediated blistering diseases such as pemphigus vulgaris3,4 and bullous pemphigoid.2,5,6 However, the optimal way of using IVIg remains uncertain. This is a critical concern because IVIg is expensive and potentially toxic, with 1 cycle costing over $10 000 and repeated cycles usually being required.

The precise mechanism of action of IVIg in autoantibody-mediated blistering diseases is unknown. A variety of mechanisms have been proposed.7 but the most likely is that it rapidly and selectively lowers serum levels of the autoantibodies that mediate the disease.8 Our research group has found that 2 weeks after a single cycle of IVIg treatment, serum levels of the autoantibodies that mediate pemphigus vulgaris can decrease by over 60% compared with 16% after 3 weeks of conventional treatment with high doses of steroids and immunosuppressive drugs.9,10

However, a physiologic regulatory feedback mechanism maintains a constant level of individual antibodies in serum. It triggers new synthesis of any antibody when its level is lowered, with the resulting rebound in level sometimes exceeding that previously present.11 This feedback mechanism limits the effectiveness of any treatment, such as IVIg, that reduces serum levels of antibodies. The rebound can be suppressed in animals by the coadministration of a cytotoxic drug such as cyclophosphamide.11 This strategy has been applied to improve the effectiveness of the plasmapheresis treatment of pemphigus,12 a procedure that also rapidly lowers serum levels of pathogenic antibodies. We have speculated that the coadministration of an immunosuppressive agent will similarly improve the effectiveness of IVIg in pemphigus and other autoantibody-mediated blistering diseases.8

This hypothesis is supported by our observation herein of a patient with autoantibody-mediated bullous pemphigoid who was repeatedly treated with IVIg given with or without an immunosuppressive drug. This permitted the relative effectiveness of these 2 approaches of using IVIg to be compared in the same patient.

REPORT OF A CASE

A 78-year-old patient with bullous pemphigoid, based on clinical, histologic, and
immunofluorescence criteria, recalcitrant to conventional treatment with systemic steroids and various adjuvant therapies (mycophenolate mofetil, dapsone, minocycline, and high-potency topical steroids) was treated with 19 cycles of IVIg over the course of 16 months. The patient was given IVIg every 2 to 4 weeks with or without an immunosuppressant agent (mycophenolate mofetil or azathioprine) while receiving tapering doses of systemic steroids. In addition, during the course of treatment, the patient continually used topical steroids and prophylactic vitamin D, calcium, and H₂ blockers. Medical history included a seizure disorder for which the patient took phenytoin. The patient denied additional medications.

Serum level of IgG and IgG4 pemphigoid antibodies were measured by indirect immunofluorescence using monkey and guinea pig esophagus as the substrate and appropriate class-specific conjugates at each baseline and at least once 1 to 2 months later.

RESULTS

The patient was treated with IVIg with or without an immunosuppressive agent over a 20-month period (Figure 1) during which the systemic steroid dose was slowly tapered (Figure 2). The resulting changes in serum level of IgG and IgG4 pemphigoid antibodies are illustrated in Figure 1 and summarized in Figure 3. The most striking result is that serum pemphigoid autoantibody levels declined during the 2 treatment periods (periods 2 and 4) that IVIg was administered with an immunosuppressant agent (mycophenolate mofetil or azathioprine) while receiving tapering doses of systemic steroids. In addition, during the course of treatment, the patient continually used topical steroids and prophylactic vitamin D, calcium, and H₂ blockers. Medical history included a seizure disorder for which the patient took phenytoin. The patient denied additional medications.

Serum level of IgG and IgG4 pemphigoid antibodies were measured by indirect immunofluorescence using monkey and guinea pig esophagus as the substrate and appropriate class-specific conjugates at each baseline and at least once 1 to 2 months later.

TREATMENT PERIOD 1

In April 2005, the patient was treated with prednisone, 40 mg/d, and mycophenolate mofetil, 2 to 3 g/d. Serum titers of IgG and IgG4 pemphigoid antibodies were both 1280 at baseline and did not change during the ensuing 2 months. During this time the patient's existing lesions showed some improvement but continued to flare.

TREATMENT PERIOD 2

In September 2005, while taking prednisone, 20 mg/d, and mycophenolate mofetil, 3 g/d, the patient was treated

Figure 1. Timeline of changes in serum level of pemphigoid IgG and IgG4 antibodies during treatment with intravenous immunoglobulin (IVIg) given with or without an immunosuppressive agent. Note that when IVIg was given with mycophenolate mofetil (treatment period 2) or azathioprine (treatment period 4), the serum level of IgG and IgG4 autoantibodies declined. In contrast, when IVIg therapy was administered without an immunosuppressant (treatment periods 3 and 5), the level of pemphigoid autoantibodies increased. Pemphigoid antibody levels did not change when the patient was treated with high doses of steroids and mycophenolate mofetil without IVIg (treatment period 1).

Figure 2. Changes in prednisone dose while patient was receiving intravenous immunoglobulin therapy. Prednisone was slowly tapered over 20 months from 40 mg/d to 5 mg/d.
The most important observation is that the addition of an immunosuppressive agent to IVIg treatment resulted in a much greater decrease in serum levels of pemphigoid autoantibodies than IVIg used alone.

We had the unusual opportunity to observe the effects of IVIg given with or without an immunosuppressive agent on serum level of pemphigoid antibodies in the same patient with this disease. The disease was treated with multiple IVIg cycles given without an immunosuppressive agent on 2 occasions and with an immunosuppressive on 2 other occasions (azathioprine in one instance, mycophenolate mofetil in the other). On 1 occasion the disease was treated with mycophenolate mofetil without IVIg. In the 2 instances that IVIg was used without an immunosuppressive agent, there was either no change or an increase in serum levels of IgG and IgG4 pemphigoid antibodies after 3 to 4 cycles of therapy. By contrast, serum levels of IgG and IgG4 pemphigoid antibodies both decreased by an average of 70% after the same number of treatment cycles on the 2 occasions when IVIg was given with an immunosuppressive. This was not an effect of the immunosuppressive agent, as there was no change in serum level of pemphigoid antibodies when the patient was treated with the same doses of mycophenolate mofetil without IVIg. Furthermore, we have previously shown that there is little change in autoantibody levels in patients with pemphigus vulgaris treated with high-dose prednisone and an immunosuppressant drug. Also, these observations were made in the same patient; therefore, these differences could not have resulted from patient-to-patient variation in response to IVIg treatment. Nor are our observations the result of the tendency of pemphigoid to gradually improve over time; the course of treatment with or without an immunosuppressive agent was given on an alternating schedule.

These results support our hypothesis that agents that suppress antibody synthesis can offset the rebound in the level of individual antibody that follows its depletion and thus can improve the effectiveness of IVIg therapy. These findings are consistent with those of our group’s prior studies, which have shown that this rebound can be reduced in animals by using immunosuppressive agents that inhibit antibody synthesis. Our results are nearly identical to those reported previously that the rebound in antibody levels that follows pemphigus antibody depletion by plasmapheresis was suppressed by the concurrent administration of an immunosuppressive agent.

The implication of these observations is that the clinical effectiveness of IVIg may be improved by coupling it with the coadministration of an immunosuppressive agent.

**Figure 3.** Comparison of effects of intravenous immunoglobulin (IVIg) administered with and without an immunosuppressive drug on serum levels of pemphigoid IgG (A) and IgG4 (B) antibody levels. Note that there was a marked decrease in serum levels of IgG and IgG4 antibodies on the 2 occasions when IVIg was combined with an immunosuppressive agent. By contrast, on the 2 occasions when IVIg was used without an immunosuppressive agent, serum IgG and IgG4 levels remained stable or increased.

**TREATMENT PERIOD 3**

In February 2006, while taking a stable dose of prednisone, 5 mg/d, the patient was treated with 3 cycles of IVIg every 2 weeks administered without an immunosuppressive drug. Serum titer of pemphigoid IgG (320) did not change during the ensuing month, while that of IgG4 doubled (from 2560 to 5120). During this time, the patient had 1 flare with several new bullae.

**TREATMENT PERIOD 4**

In late March 2006, while taking prednisone, 5 mg/d, the patient was treated with IVIg every 2 weeks given together with azathioprine, 150 to 200 mg/d. The dose of prednisone was not changed. Two months later, after 4 cycles of IVIg treatment, serum titers of IgG and IgG4 had both decreased by 2-fold from 320 to 160 and from 2560 to 1280, respectively, and 3 months later, after 6 cycles, serum levels of IgG and IgG4 had both decreased 4-fold. Clinically, flares occurred during this time and several new bullae developed. No obvious correlation was noted between levels of bullous pemphigoid autoantibodies and disease activity.

**TREATMENT PERIOD 5**

In August 2006, the patient was taking prednisone, 5 mg/d, when treatment began with 4 cycles of IVIg every 3 to 4 weeks. In addition, the prednisone dose was increased to 10 mg/d. No immunosuppressive agents were given. Serum pemphigoid IgG titer doubled in 1 month (from 160 to 320), and IgG and IgG4 titers both quadrupled within 3 months, from 160 to 640 and from 640 to 2560, respectively. During this time, the patient continued to develop lesions at an average rate of 1 new bulla per week.

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This concept is supported by several case reports of IVIg being clinically effective for the treatment of blistering diseases when given with an immunosuppressive agent\(^{15,17}\) and ineffective when such an agent was not used.\(^{18,19}\) It is further supported by reports that months are required for IVIg to lower serum levels of pemphigus antibody when administered without an immunosuppressive agent,\(^{20}\) while the decline occurs in weeks if an immuno-suppressive drug is used.\(^{8}\)

In summary, the coadministration of agents interfering with antibody production may improve the IVIg treatment of pemphigoid and more generally of other auto-antibody-mediated diseases by reducing the amount of IVIg required to control disease activity and thus lessening the cost and potential toxic effects of this very expensive therapy.

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Correspondence: Jean-Claude Bystryn, MD, Department of Dermatology, New York University School of Medicine, 550 First Ave, Tisch Hospital, H313, New York, NY 10016 (bystryn@nyu.edu).

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