Treatment of pemphigus with intravenous immunoglobulin

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Background: Intravenous immunoglobulin (IVIg) has recently been advocated as a treatment for pemphigus, but the results of published studies are in conflict. This study was conducted to re-examine the effectiveness of IVIg for the immediate control of active disease and to study the mechanisms of its action.

Methods: Six patients with active pemphigus vulgaris unresponsive to conventional therapy with high doses of corticosteroids were treated with IVIg (400 mg/kg per day for 5 days) and concurrently given cyclophosphamide (100-150 mg/d). The primary end points were healing of skin lesions and changes in the level of intercellular antibodies and steroid dose.

Results: New lesions ceased to form within 1 week of initiating IVIg therapy, and within 2 weeks the extent of existing skin lesions was reduced by 80% or more in all but one patient. Within 3 weeks, steroid doses were reduced by an average of 41%. The improvement was more rapid than that in patients previously treated with similar doses of steroids and cytotoxic agents at the same institution. Clinical improvement was associated with a rapid decline in pemphigus antibodies whose levels decreased by 72% within 1 week of initiation of IVIg therapy. The rapidity and extent of this decline were similar to those achieved with intensive plasmapheresis. The decline was not due to blocking the synthesis or the immunologic activity of intercellular antibodies by IVIg, suggesting that it resulted from increased immunoglobulin catabolism.

Conclusions: These results indicate that IVIg can effectively and rapidly control active pemphigus unresponsive to conventional therapy and suggest that the mechanism of its action is decreasing serum levels of intercellular antibodies. (J Am Acad Dermatol 2002;47:358-63.)

Systemic corticosteroids are the mainstay of treatment for pemphigus vulgaris.[1] Alternative or adjuvant therapies for patients who do not respond to or who experience complications from corticosteroids include immunosuppressants such as cyclophosphamide, azathioprine, cyclosporine, methotrexate, and mycophenolic acid and immunomodulatory drugs and procedures such as dapsone, gold, and plasmapheresis.[1] Unfortunately, some patients do not respond to these agents, the response to most of these treatments is delayed by a number of weeks, and all are associated with their own adverse effects, which include immunosuppression, myelosuppression, hepatotoxicity, sepsis, and other complications.[1] Thus, there is a need for alternate approaches that can rapidly control active pemphigus unresponsive to large doses of systemic corticosteroids.

Intravenous immunoglobulin (IVIg) is increasingly used to treat a variety of antibody-mediated autoimmune diseases including Guillain-Barré syndrome, chronic inflammatory demyelinating neuropathies, myasthenia gravis, immune thrombocytopenia, and Kawasaki syndrome.[2-4] Recently, it has also been applied to treat pemphigus.[5-12] However, the effectiveness of IVIg in the treatment of pemphigus remains unclear, because some report it is effective[7,9,10] and others report that it is not.[6,8]

This study was conducted to examine the effectiveness of IVIg for the immediate treatment of active pemphigus vulgaris unresponsive to intensive conventional therapy and the impact of this procedure on the level of intercellular (IC) antibodies associated with this disease.

METHODS

Patients

The study group consisted of 6 patients with pemphigus vulgaris as determined by clinical, histo-

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Table I. Clinical characteristics of patients

Patient No.	Age (y)/Sex	Disease duration	Therapy at baseline*	IC antibody at baseline*	No. of IVIg courses
1	59/M	2.5 y	P: 60 mg	640	1
2	67/M	2 mo	P: 120 mg; C: 100 mg	640	3
3	65/M	2 y	P: 280 mg; C: 100 mg	160	1
4	78/F	1.8 y	P: 60 mg; C: 100 mg	320	1
5	57/M	5 y	P: 160 mg; C: 150 mg	160	1
6	70/M	1.5 y	P: 80 mg OD; C: 150 mg; M: 2.5 mg/wk	320	2

C, Cyclophosphamide; *M*, methotrexate; *OD*, once a day; *P*, prednisolone.
*Daily dose of medication at baseline before initiation of IVIg therapy.

logic, and immunofluorescence criteria who were unresponsive to at least 2 months of conventional therapy. The clinical characteristics of the patients are summarized in Table I. All but one patient had long-standing disease, and all had been receiving continuous therapy with systemic steroids for at least 2 months. The disease was active in all patients at the time IVIg therapy was initiated as evidenced by the development of new bullae and the failure of older lesions to heal. In all cases the disease was unresponsive to conventional therapy with prednisone in doses ranging from 60 to 280 mg/d, which had been administered at that level for at least 2 weeks before initiation of IVIg therapy. At baseline before IVIg therapy, all patients had circulating IC antibodies in titers of 160 to 640.

IVIg therapy

IVIg therapy was administered as a standard protocol. Human immunoglobulin, 5% solution (Venoglobulin S; Alpha Therapeutics Co, Los Angeles, Calif) was infused intravenously at a rate of 75 mL/h. Total dose was 400 mg/kg daily for 5 days. In all cases, the patients were also treated with cyclophosphamide at a dose of 50 mg twice a day or three times a day, beginning with the initiation of IVIg therapy. Other therapy remained unchanged.

Evaluation of clinical response

Patients had complete skin examinations at baseline and 1 and 2 weeks after initiation of therapy. Response to therapy was evaluated on the basis of decreased pruritus, absence of new lesion formation, and healing of existing lesions and quantitated on the basis of the percentage of existing lesions that were completely healed.

Assay of circulating IC IgG antibodies

The effect of each IVIg procedure on the level of IC antibodies was measured by indirect immunofluorescence, by using a standard procedure as previously described.[13] The substrate used for assay was monkey esophagus, and the conjugate was goat anti-human IgG (Tago, Camarillo, Calif). Antibody levels were measured at baseline, 1 week after initiation of therapy, and in most cases at 2 weeks after initiation and 2 to 4 months later.

Assay for blocking factors in IVIg

A 1.0-mL aliquot of sera collected at baseline from 3 patients was incubated with an equal volume of the 5% immunoglobulin preparation used to treat the patients or as control with an equal volume of a 5% unrelated protein preparation (bovine serum albumin) or normal saline solution for 30 minutes at 27°C. The level of immunoreactive IC antibodies was determined before and after the procedure by indirect immunofluorescence as described previously.

RESULTS

Effect of IVIg on the activity of pemphigus vulgaris

Nine courses of IVIg were administered to 6 patients with pemphigus vulgaris unresponsive to conventional therapy with high doses of prednisone. The characteristics of the patients are summarized in Table I. All but one of the patients had pemphigus for more than 1.5 years. All had active disease at the time they were began receiving IVIg, evidenced by the continued appearance of new skin lesions and the presence of multiple nonhealing skin erosions despite therapy with high doses of systemic steroids (60-280 mg/d). All patients had circulating IC antibodies in titers ranging from 160 to 640.

Each course of IVIg consisted of intravenous infusion of immunoglobulin at a dose of 400 mg/kg daily for 5 days. Four patients were treated with a single course; one patient received two courses 3 weeks apart; and one patient received two courses 2 weeks apart and a third course 7 months later. All patients were concurrently treated with prednisone at a level that did not change for at least 2 weeks before initiation of IVIg therapy and began receiving cyclophosphamide, 100 to 150 mg/d, at the begin-

Table II. Clinical response of pemphigus vulgaris to IVIg

Patient No.	No. of IVIg procedures	Clinical response to IVIg		Decline in prednisone dose at 3 wk (%)
		1 wk after initiation of IVIg	2 wk after initiation of IVIg	
1	1	NA	Oral 50% healed	83
2	2	Skin lesions 90% healed	Skin 95% healed	0
2	3	Oral lesions 40% healed Skin lesions 100% healed	Oral 50% healed Oral 100% healed	75
2	4	Oral lesions 50% healed NA	Oral 80% healed Oral 40% healed	17
3	5	Skin lesions 90% healed	Skin 100% healed	64
4	6	Skin lesions 80% healed	Skin > 80% healed	33
5	7	Skin lesions 80% healed	Skin 90% healed	50
6	8	No improvement	No improvement	0
6	9	Oral lesions 50% healed	Oral > 50% healed	50
Average				41

NA, Not available.
*Percentage decrease from baseline level immediately before initiation of procedure.

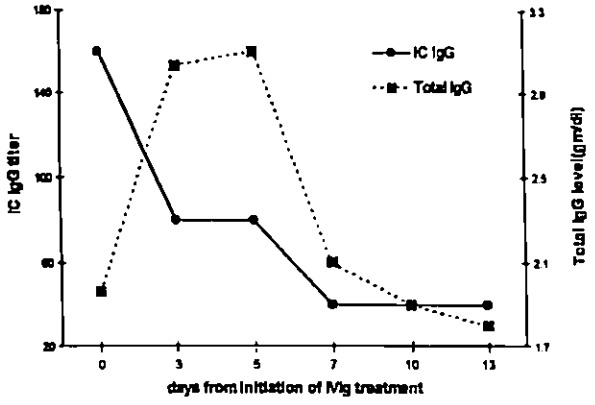

Fig 1. Changes in serum levels of total IgG antibodies and of pemphigus IC IgG autoantibodies associated with IVIg therapy in a representative patient. Note that administration of IVIg is associated with a rapid decline in serum levels of IC antibodies and that the decrease is selective because it occurs concurrently with a striking increase in total IgG antibody levels.

ning of the procedure if they were not already receiving it.

Clinical responses were evaluated 1 and 2 weeks after initiation of treatment, and each course of IVIg was analyzed independently. Disease activity improved within several days of initiation of all but one of the IVIg courses (see Table II), as evidenced by decreased pruritus, cessation of new lesion formation, and healing of older lesions. Two weeks after initiation of IVIg therapy, none of the patients had new lesions; established lesions were healed by an average of 80% or more, and oral lesions, by 40% to 100%. Improvement was sufficient to begin reduction of steroid doses a median of 16 days after initiation of IVIg. Three weeks after initiation of treatment, steroid doses had been reduced by an average of 41% of baseline levels. The one patient who did not respond to the initial course of IVIg responded with improvement of both skin and oral lesions within 1 week of initiation of a second course 3 weeks later. One patient had a mild stroke while receiving IVIg. This was thought to be secondary to long-standing hypertension. The patient recovered completely. There were no other adverse effects.

Effect of IVIg on the circulating levels of IC antibodies

IVIg treatment was associated with a rapid decline in circulating levels of IC antibodies, as shown in Fig 1 for a representative patient. The data for all 9 courses of IVIg are summarized in Table III. One week after initiation of IVIg, the level of IC IgG antibodies had decreased by an average of 72% (range, 50%-100%). Follow-up titers were available 2 weeks and 2 to 4 months after initiation of IVIg therapy for 7 of the treatment courses. At 2 weeks, there was no further changes in titer after 5 of the treatment courses and a slight increase in titer (by 1 doubling dilution) after the 2 other courses. Overall, the titer of IC antibodies 1 week, 2 weeks, and 2 to 4 months after initiation of IVIg therapy was on average 72%, 66%, and 75% lower than at baseline immediately before the procedure.

Correlation between serum levels of total and IC antibodies

There was an inverse correlation between changes in serum levels of total IgG antibodies and

Table III. Effect of IVIG on circulating levels of intercellular antibody

IVIg procedure	Baseline Titer	IC IgG antibody titer					
		1 wk*		2 wk*		2-4 mo*	
		Titer	% Decrease†	Titer	% Decrease†	Titer	% Decrease†
1	640	160	−75	NA†	NA	320	−50
2	640	80	−87	80	−87	NA	NA
3	80	40	−50	80	0	0	−100
4	160	0	−100	0	−100	0	100
5	160	40	−75	40	−75	40	−75
6	320	160	−50	NA	NA	160	−50
7	160	80	−50	80	−50	80	−50
8	320	40	−87	80	−75	NA	NA
9	80	20	−75	20	−75	0	−100
Average			−72		−66		−75

NA, Not available.
*Postinfection IVIg therapy.
†Percentage decrease in titer from baseline level in same patient.

Table IV. Effect of IVIg on serum level of total IgG

IVIg procedure	Baseline level	Serum IgG level (g/dL)			
		1 wk		2 wk	
		Level	% Change*	Level	% Change*
1	1.8	2.9	+61	NA	NA
2	3.0	5.3	+77	4.3	+43
3	4.3	3.9	−10	3.3	−23
4	3.4	NA	NA	2.5	−26
5	1.9	3.1	+61	1.8	−9
6	1.5	3.5	+121	NA	NA
7	3.0	NA	NA	2.7	−10
8	2.5	3.9	+56	3.0	+20
9	3.0	NA	NA	2.8	−7
Average			+61		−1.7

NA, Not available.
*From baseline level.

of IC IgG antibodies, as shown in Fig 1 and summarized in Table IV. Serum levels of total and of IC IgG antibodies at baseline and 1 week after initiation of therapy were available for 6 of the IVIg treatment courses. As expected, total IgG antibody levels were markedly higher 1 week after initiation of therapy—by an average of 61% over baseline. In contrast, the level of IC IgG antibodies was 72% lower than the level at baseline. Two weeks after initiation of IVIg therapy, total IgG antibodies had declined to normal levels and were, on average, 1.7% below the baseline level; whereas there were no further changes in IC IgG antibodies, whose levels were still 66% below baseline.

Presence of "blocking" factors in IVIg

Because there is a possibility that the decrease in IC antibodies after IVIg administration was due to blocking factors in the IVIg preparation that inactivated or interfered with the assay for IC antibodies, we examined the effects of the immunoglobulin preparation used to treat the patients on the immunologic activity of IC IgG antibodies present at baseline before therapy. This was done by incubating patient's serum obtained at baseline with the IVIg preparation or as control with normal saline solution or a similar concentration of an unrelated protein (bovine serum albumin). The results obtained in 3 patients are listed in Table V. There was no difference in the level of IC IgG antibodies between sera incubated with saline solution, the IVIg preparation, or a similar amount of an unrelated protein.

DISCUSSION

The major findings of this study are that IVIg can rapidly and effectively control the activity of pem-

phigus vulgaris unresponsive to conventional therapy and that the treatment is associated with a rapid and selective decline in circulating pathogenic IC antibodies.

In this study of 6 patients with severe pemphigus unresponsive to conventional therapy with high doses of systemic corticosteroids, IVIg was rapidly and highly effective in controlling disease activity after most but not all procedures. Improvement, evidenced by cessation of new lesion formation and healing of established lesions, usually occurred within a few days of initiating therapy. Within 1 to 2 weeks of initiating therapy, skin lesions were healed by 80% or more, and oral lesions, by 40% or more in all but one patient. Clinical improvement was sufficient to permit steroid doses to be reduced by an average of 41% of baseline level within 3 weeks of initiating IVIg. The improvement appeared to be a result of IVIg administration because of its very rapid onset within days and the lack of response to prior therapy. The improvement was unlikely to have resulted from the concurrent administration of cyclophosphamide with IVIg, because the benefits of this drug normally take approximately 6 weeks to become evident.[1] The treatment was generally safe. However, one patient had a mild stroke, though it is unclear whether it was related to the IVIg treatment because the patient had long-standing hypertension.

The clinical response to IVIg was more rapid than that observed in 2 historical control groups of patients with severe pemphigus treated in the same institution by the same investigator (J.C.B.) with similar doses of prednisone and cytotoxic drugs and with or without plasmapheresis.[13] One group (n = 11 patients) was treated with high doses of prednisone (average level of 103 mg/d) and with azathioprine or cyclophosphamide (in doses of 100-150 mg/d); the other group (n = 11 patients) was treated with intensive plasmapheresis in addition to high doses of prednisone (average level, 127 mg/d) and with azathioprine or cyclophosphamide. After 3 weeks, prednisone doses had been reduced by an average of only 11% and 26% of baseline levels in the 2 groups, respectively, compared with 41% for IVIg treatment.

Another major finding was that IVIg treatment is associated with a very rapid decline in the level of the IgG IC antibodies associated with pemphigus. These declined by an average of 72% (range, 50%-100%) within 1 week of initiating IVIg therapy. The decrease was maintained for at least 2 to 4 months. This decline was markedly faster than that achieved by means of conventional therapy with high doses of steroids and cytotoxic agents; in a group of 11 patients with pemphigus, treated in the same institution with similar dose levels of prednisone and cytotoxic drugs, IC antibodies were reduced by an average of only 16% in 3 weeks.[13] The decrease in IC antibodies was as rapid and profound as that induced by intensive plasmapheresis, which in another historical group of 11 patients with pemphigus treated in the same institution decreased antibody levels by an average of 71% in 3 weeks. It is of note that the decrease in IC antibodies occurred at the same time that the level of other antibodies, reflected by the total serum IgG level, was markedly increased. This observation suggests that the mechanism of action of IVIg in pemphigus is rapid lowering of the IC antibody levels.

Table V. Effect of IVIg on immunoreactivity of IC antibodies in patients' sera

Patient No.	IC Antibody titer (g/dL) after incubation with*		
	5% IVIg	5% Albumin	Saline solution
4	320	320	320
5	160	160	160
6	320	320	320

*IC antibody titer by indirect immunofluorescence.

How IVIg causes a rapid decrease in serum levels of IC antibodies is not known. Several possible explanations appear unlikely. These include suppression of IgG synthesis, because the half-life of IgG in the circulation is approximately 3 weeks. Thus, even if IVIg had immediately and totally suppressed all IgG synthesis, the level of IC IgG antibodies could not have decreased by more than 15% to 20% during the first week of therapy, compared with the 72% that actually occurred. For the same reason, the decrease cannot be ascribed to suppression of antibody synthesis by the cyclophosphamide. Nor can the decrease be explained by blocking factors in the IVIg, such as anti-idiotype antibodies or immune complexes that might inactivate IC antibodies, because incubation of the IVIg preparation with sera obtained from patients before treatment did not reduce the levels of IC antibodies. Nor can the decrease be explained by dilution of circulating IC antibodies in the extravascular department whose volume was expanded by the immunoglobulin that was administered, because the level of antibody should then have increased again as serum immunoglobulin levels declined to normal. In addition, the 75% or greater reduction in IgG antibody titer that occurred in a majority of patients would have required intravascular volume to have increased by several folds, which is highly unlikely.

We believe a more likely explanation for the rapid decline in IC antibodies is that IVIg increases

the catabolism of all IgG molecules as a result of the large increase in the serum levels of IgG caused by the treatment. Serum IgG levels were, on average, 61% above their baseline levels 1 week after initiation of IVIg therapy. This hypothesis is based on the existence of a physiologic mechanism that regulates serum levels of immunoglobulins and results in the catabolism of IgG increasing in direct proportion to its total concentration in serum.[14] Even though the catabolic process degrades all antibodies regardless of their specificity, only the level of IC antibodies would actually be reduced because the level of normal IgG antibodies is restored by those present in the IgG preparation. This hypothesis is supported by our observation that the changes in IC IgG levels were inversely related to serum levels of total IgG. The decrease in IC IgG antibodies peaked when the total serum IgG level was highest and no longer changed once the total IgG level returned to normal.

In summary, IVIg is effective for the rapid control of active pemphigus unresponsive to conventional therapy. Our hypothesis is that the procedure works by causing a rapid decrease in the level of IC antibodies.

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