Corticosteroid-Sparing Effect of Intravenous Immunoglobulin Therapy in Patients With Pemphigus Vulgaris

Naveed Sami, MD; Ansa Qureshi, MD; Eleonora Ruocco, MD; A. Razzaque Ahmed, MD, DMSc

Background: Pemphigus vulgaris (PV) is a rare, potentially fatal autoimmune mucocutaneous blistering disease. The prolonged use of systemic corticosteroids, though clinically effective in high doses, can result in multiple debilitating adverse effects. Immunosuppressive agents, used as adjuvants and as corticosteroid-sparing agents, are not effective in all patients and are contraindicated in some. Therefore, alternative treatment modalities are needed to provide effective control of PV in such patients.

Objective: To demonstrate the corticosteroid-sparing effect of intravenous immunoglobulin (IVIg) therapy in patients with moderate to severe PV.

Design: A retrospective analysis in a cohort of 15 patients with moderate to severe PV who were treated with IVIg therapy. All 15 patients were corticosteroid dependent, and the use of other systemic conventional immunosuppressive agents was contraindicated. The patients were followed up over a mean period of 6.2 years.

Setting: Ambulatory tertiary medical care facility of a university-affiliated hospital.

Intervention: All 15 patients received an IVIg dose of 1 to 2 mg/kg per cycle.

Main Outcome Measures: The following information was documented in each of the 15 patients before and after the initiation of IVIg therapy: total dosage and total duration of prednisone therapy and number of relapses. Also, the highest dosage and adverse effects of prednisone therapy, as well as the total duration of observation, were recorded.

Results: All 15 patients had a satisfactory clinical response to IVIg therapy. The use of systemic prednisone was gradually discontinued over a mean period of 4.3 months. A statistically significant difference was noted in the total dose of prednisone ($P=.004$), total duration of prednisone therapy ($P=.003$), and number of relapses ($P<.001$) before and after the initiation of IVIg therapy.

Conclusions: Intravenous immunoglobulin therapy has a demonstrable corticosteroid-sparing effect. It is a safe and effective alternative treatment modality in patients with PV who are dependent on systemic corticosteroids or who develop significant adverse effects as a result of their use.

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PEMPHIGUS VULGARIS (PV) is a rare, potentially fatal autoimmune blistering disease. The lesions of PV can involve both cutaneous and mucosal tissues.[1-3] The diagnosis is confirmed by histological and immunopathological studies.[1-5] An intraepidermal vesicle with acantholysis is usually seen on routine histological examination of a biopsy specimen of the lesion.[1-3] Deposition of IgG on the surface of the keratinocyte cell surface is typically seen on direct immunofluorescence of perilesional tissue.[1-5] Indirect immunofluorescence, using monkey esophagus as a substrate, demonstrates the presence of antibodies to the keratinocyte cell surface antigen.[1-5] On an immunoblot assay, using human epidermis as lysate, patients' serum binds to a 130-kd protein identified as desmoglein 3.[6,7]

Systemic corticosteroids administered in high doses over prolonged periods of time can provide effective control of active disease and are often used for maintenance therapy.[1-8] As a consequence of the cumulative doses of systemic corticosteroids, patients often develop multiple serious adverse effects, sometimes resulting in a poor quality of life.[8,9] These adverse effects are occasionally fatal.[10,11] Several immunosuppressive agents, dapsone, and systemic antibiotics have been used with the explicit purpose of reducing the dosage of systemic corticosteroid therapy.[12-19] In many

From the Department of Oral Medicine, Harvard School of Dental Medicine (Drs Sami, Qureshi, Ruocco, and Ahmed), the Department of Dermatology, Harvard Medical School (Dr Ahmed), and the Center for Blistering Diseases, Department of Medicine, New England Baptist Hospital (Dr Ahmed), Boston, Mass.

treatment-resistant patients, alternative treatments such as plasmapheresis, extracorporeal photopheresis, and intravenous immunoglobulin (IVIg) have been recommended.[30-33]

We retrospectively studied the use of IVIg in 15 steroid-dependent patients with PV. The prolonged use of high-dose systemic corticosteroid therapy had resulted in multiple adverse effects. Continuation of such therapy was considered inadvisable because of the heightened risk of further adverse effects and possible mortality as a result of prolonged immunosuppression. In all 15 patients, the use of IVIg resulted in clinical control of disease, and a gradual reduction and an eventual discontinuation of the systemic corticosteroid therapy were possible.

A total of 15 patients with moderate to severe mucocutaneous PV were enrolled in the study. The following criteria had to be present before IVIg therapy was initiated: (1) moderate to severe mucocutaneous disease, defined as involvement of 30% or more of body surface and at least 2 mucosal surfaces; (2) an intraepidermal vesicle with acantholysis observed on routine hematoxylin-eosin staining; (3) deposits of IgG on the keratinocyte cell surface antigen of the epidermis demonstrated on direct immunofluorescence; (4) antibodies to the keratinocyte cell surface antigen at a titer of 1:160 or greater demonstrated by indirect immunofluorescence of serum samples using using monkey esophagus as a substrate; and (5) antibodies to a 130-kd protein on immunoblot analysis using human epidermis as a lysate.

PREDNISONE TREATMENT

In addition to sex and age at onset of disease, the following information was recorded for each patient before and during IVIg therapy (the dosage of systemic corticosteroid therapy was converted to an oral daily dose of prednisone):

1. The highest dose of prednisone, which was defined as the maximum dose per day a patient received to control PV during the course of the study and which was considered to be one of the indices to determine disease severity.
2. The total dose of prednisone.
3. The total duration of prednisone therapy.
4. The total number of relapses. Relapse was defined as a recurrence of lesions at previous and new sites. If patients had a relapse while taking only systemic corticosteroids, the dosage of prednisone therapy was increased to achieve clinical control.
5. Adverse effects. The adverse effects noted were a direct consequence of the prolonged use of high-dose corticosteroids. Those that required further medical intervention included hypertension, diabetes mellitus, gastrointestinal distress, peptic ulcer disease, psychological reactions (eg, depression, mood swings, and psychosis), myopathy, multiple infections (eg, urinary tract infection, pneumonia, and cellulitis), osteoporosis, and bone fractures. However, all patients developed other adverse effects, such as moon facies, buffalo hump, and redistribution of body adipose tissue, which are excluded from the discussion because they required no specific medical treatment.

INDICATIONS FOR IVIg TREATMENT

There were 3 indications for the use of IVIg therapy in the 15 patients with PV:

1. Dependence on high doses of systemic corticosteroids.[8] Patients required 30 mg/d or more of prednisone to keep diseases under control. Attempts to lower the dosage of prednisone therapy resulted in recurrence of lesions.
2. Multiple significant adverse effects from prolonged use of high-dose systemic corticosteroid therapy.[9]
3. Contraindications for the use of immunosuppressive agents,[34] including a strong family history of cancer, complex medical problems that required repeated adjustment of the dosage of other medications, and increased risk of infertility and teratogenicity in young patients.

All 15 patients refused other alternative treatment modalities, including plasmapheresis, photochemotherapy, and intravenous pulse doses of methylprednisone with cyclophosphamide.

IVIg TREATMENT

A recently described IVIg treatment protocol was used in every patient.[35,36] The dosage was 1 to 2 g/kg per cycle. The total dose for the cycle was divided into 3 equal doses, given on 3 consecutive days, as a slow 4- to 5-hour infusion. Initially, IVIg therapy was administered at a frequency of every 3 to 4 weeks, until an effective clinical response was achieved. Effective clinical response was defined as the complete healing of previous lesions and the absence of new lesions. Thereafter, the intervals between infusion cycles were slowly increased to 6, 8, 10, 12, 14, and 16 weeks. This gradual tapering of IVIg therapy was defined as the "maintenance therapy" period. The end point of therapy was defined as that point at which patients continued to remain free of lesions after 2 consecutive cycles of IVIg therapy at a 16-week interval.

In all 15 patients, relapses and adverse effects were closely monitored.[37] Also, all 15 patients were orally premedicated with 650 mg of acetaminophen and 50 mg of diphenhydramine hydrochloride to prevent headaches and hypersensitivity reactions, respectively.[35,36]

When IVIg therapy was instituted and control of disease was established, the dosage of oral prednisone was gradually reduced, and eventually the prednisone therapy was discontinued. Existing and new lesions were treated with sublesional triamcinolone injections and intensive topical therapy. When relapses occurred during IVIg therapy, the frequency of the infusions was temporarily increased until the disease was controlled. Systemic corticosteroids were not used during such relapses.

DURATION OF TOTAL OBSERVATION

The duration of total observation was defined as the interval between the initial diagnosis and the last documented visit of the patient.

STATISTICAL ANALYSIS

Wilcoxon signed rank tests were used to analyze pre- and post-IVIg data. The variables used in this analysis were total dose of prednisone treatment, total duration of prednisone treatment, and number of relapses.

The study included 8 male patients and 7 female patients (mean age at onset, 58 years; age range, 30-82 years). Before IVIg therapy was initiated, the dosage of prednisone therapy ranged from 80 to 160 mg/d (mean, 100 mg/d), the total dose ranged from 5200 to 90000 mg (mean, 21280 mg),
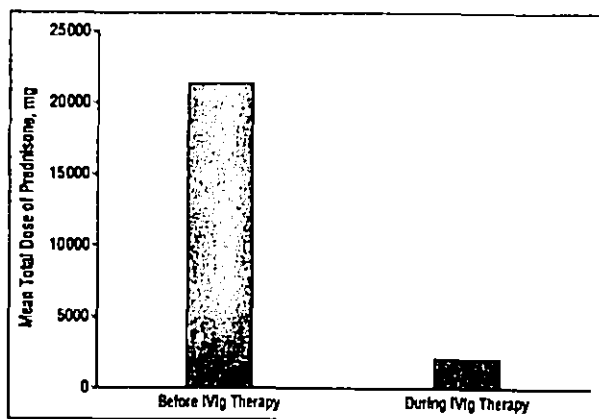
Figure 1. Comparison of the mean total dose of prednisone before and during intravenous immunoglobulin (IVIg) therapy.
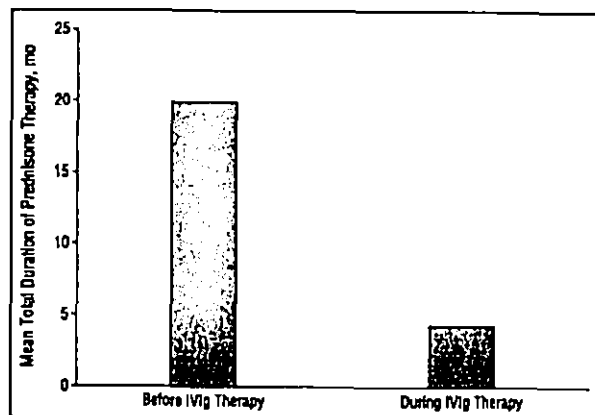

Figure 2. Comparison of the mean total duration of systemic prednisone therapy before and during intravenous immunoglobulin (IVIg) therapy. Note the significant decline in the total duration of prednisone therapy after the initiation of IVIg therapy.

and the duration ranged from 4 to 60 months (mean, 19.9 months). During IVIg therapy, the total dose of prednisone ranged from 300 to 9500 mg (mean, 1964 mg) (**Figure 1**), and the duration of prednisone therapy ranged from 2 to 18 months (mean, 4.3 months) (**Figure 2**).

Thirteen of the 15 patients had relapses after initial clinical response was achieved. The total number of relapses before IVIg treatment ranged from 3 to 7 (mean, 4.9 relapses). Only 5 patients had a relapse during IVIg therapy, and the number of relapses ranged from 0 to 3 (mean, 0.7 relapse). The total time of observation ranged from 2 to 17.25 years (mean, 6.2 years).

ADVERSE EFFECTS

During prednisone therapy, all 15 patients had psychological adverse effects that required medical treatment, including psychosis, depression, and mood swings. There were also several other systemic adverse effects, including multiple infections (10 patients [67%]), corticosteroid-induced myopathy (7 patients [46%]), hypertension (5 patients [33%]), osteoporosis (5 patients [33%]), cataracts (4 patients [27%]), diabetes mellitus (3 patients [20%]), and gastrointestinal distress and/or peptic ulcer disease (3 patients [20%]). Two patients also had vertebral fractures (13%), and 1 patient had a fracture of the neck of the femur (7%).

The most common adverse effects observed during IVIg therapy were headaches (5 patients) and nausea (2 patients), which were controlled with oral analgesics and antiemetics.[35-37]

RESPONSE TO IVIg THERAPY

All 15 patients responded to IVIg therapy. Effective clinical response was achieved in 3.2 to 5.4 months (mean, 4.6 months). Thereafter, the interval between the infusion cycles was increased. This maintenance period of IVIg therapy lasted 15 to 27 months (mean, 18.7 months). All patients achieved the end point of therapy.

STATISTICAL ANALYSIS

The Wilcoxon signed rank test showed highly statistically significant results before and during IVIg therapy

between the total doses of prednisone ($P = .004$), the duration of prednisone therapy ($P = .003$), and the number of relapses ($P < .001$).

COMMENT

Our study included 15 patients with PV who were treated with IVIg therapy. Before IVIg therapy was initiated, all 15 patients had received high daily doses and high total doses of oral prednisone. The majority of these patients had multiple relapses requiring frequent dose adjustment. All 15 patients had developed "corticosteroid dependency," in that it was not possible to reduce their daily oral prednisone dose without recurrence of disease and repeated increases in the dose were necessary. Consequently, these patients developed multiple debilitating adverse effects. Immunosuppressive agents, which are often used as corticosteroid-sparing agents in the treatment of PV, were contraindicated in all 15 patients, and the patients had refused other treatments such as plasmapheresis, photochemotherapy, and intravenous pulse corticosteroids with or without intravenous cyclophosphamide. Therefore, IVIg therapy was instituted. After the initiation of IVIg therapy, the oral corticosteroid therapy was gradually reduced in dosage and eventually discontinued. The patients were eventually treated with IVIg as monotherapy, with success. All 15 patients had a clinical remission and the IVIg therapy was discontinued.

The mortality of patients with PV has been significantly reduced since the advent of the use of systemic corticosteroids. Although most patients with PV do respond to prednisone therapy, such therapy can result in multiple adverse effects, requiring medical intervention, and can sometimes be fatal. There are many other systemic agents that have been reported to have proven clinical benefit in the treatment of PV and have been used as corticosteroid-sparing agents. However, in some patients, these agents are contraindicated because of their long-term, and often irreversible, adverse effects. Other alternative therapies, such as extracorporeal photopheresis and plasmapheresis, have been used as corticosteroid-sparing treatment modalities, but have required the simultaneous use of other systemic agents.

Intravenous immunoglobulin therapy has been used successfully to treat autoimmune blistering diseases, including PV, pemphigus foliaceus, cicatricial pemphigoid, bullous pemphigoid, linear IgA bullous disease, and epidermolysis bullosa acquisita, as well as many other chronic autoimmune inflammatory disorders, both as an adjuvant and a corticosteroid-sparing agent.[33,35-49] It has also been used as an adjuvant along with other therapies in patients who have failed to respond to treatment with multiple systemic agents.

In our group of 15 patients, IVIg therapy was a reasonable a choice, since there was a relative contraindication to the use of systemic immunosuppressive agents owing to their possible or potential serious adverse effects.[34] The incidence of long-term adverse effects requiring medical treatment has been reported to be relatively low with IVIg therapy compared with other alternative treatments.[37,43] The most common adverse effects of IVIg therapy, including headache, nausea, and hypersensitivity reactions, are usually short term.[35,43] Such adverse effects can be prevented by premedication with oral diphenhydramine and acetaminophen.[35,36] There are a few reports of patients developing acute renal failure and aseptic meningitis during IVIg therapy.[37,43]

Institution of IVIg therapy allowed the dosage of prednisone therapy to be slowly reduced over a mean period of 4.3 months, without any acute exacerbations. The differences in the total doses ($P=.004$) and duration ($P=.003$) of prednisone therapy before and during IVIg therapy were highly statistically significant, demonstrating that IVIg is an effective corticosteroid-sparing agent.

The number of patients who were having relapses declined while the patients were receiving IVIg therapy. The difference in the number of relapses that occurred between prednisone treatment and IVIg therapy was also statistically significant ($P<.001$). Only 5 patients had a relapse during IVIg therapy. The relapses occurred when patients did not receive their treatments at appropriate time intervals, owing to a shortage of the drug in the United States. Clinical control of disease was achieved when IVIg therapy was reinstituted, without additional systemic therapy. These relapses resulting from the abrupt involuntary interruption of IVIg therapy indicate that a slow withdrawal of IVIg therapy is necessary to maintain a sustained clinical remission. Most patients with PV and other chronic autoimmune diseases who are being treated with IVIg therapy have required multiple treatments over an extensive period and a gradual discontinuation of the therapy to maintain adequate control of their disease.[44-49]

During the course of therapy, antibody titers to the keratinocyte cell surface antigen were monitored and correlated with clinical disease. In all 15 patients, a decrease in antibody titers to the keratinocyte cell surface antigen was observed, corresponding directly to effective clinical control of their disease (data not shown). When patients achieved the end point of therapy and their disease was in clinical remission, antibody titers to the keratinocyte cell surface antigen were nondetectable (N.S. and A.R.A, unpublished data, 2002).

We recognize that the cost of IVIg is prohibitive. However, in these 15 patients, other alternatives were not available. The cost of treating present and future adverse effects of long-term therapy with high-dose systemic corticosteroids and immunosuppressive agents would also be high, and probably comparable.

There are 7 postulated mechanisms of action of IVIg therapy,[35,43] which is thought to work through antiidiotypic interactions in such chronic inflammatory autoimmune diseases as dermatomyositis.[35,43] A similar mechanism of immune modulation may be operative in PV.

This study demonstrates that IVIg therapy is an effective alternative for patients with PV whose disease cannot be controlled with long-term high-dose systemic corticosteroid therapy, which may also cause serious adverse effects. It is especially useful for patients in whom the use of immunosuppressive agents is contraindicated. Other benefits of IVIg therapy are that (1) it also has a corticosteroid-sparing effect; (2) it can be used as monotherapy; (3) it is relatively safe compared with systemic corticosteroid therapy; and (5) in addition to controlling PV, it can induce a sustained clinical remission. Further multicenter trials, with a larger group of patients, are needed to determine whether IVIg is an effective choice for the treatment of PV.

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