

# Comparison Between Intravenous Immunoglobulin and Conventional Immunosuppressive Therapy Regimens in Patients With Severe Oral Pemphigoid

## *Effects on Disease Progression in Patients Nonresponsive to Dapsone Therapy*

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**Context:** Mucous membrane pemphigoid has a wide clinical spectrum. The clinical context was to determine whether pemphigoid disease that initiates in the oral cavity progresses to involve other mucosae and to determine the influence of systemic therapy on such progression.

**Objective:** To determine the clinical outcomes and disease progression in patients with oral pemphigoid for whom dapsone therapy was impossible.

**Design:** Retrospective analysis of a cohort of 20 patients with immunopathologic-proven oral pemphigoid studied between September 1, 1994, and October 31, 2000. Twelve patients received conventional therapy that consisted of a combination of oral prednisone with an immunosuppressive agent. Eight patients in whom such therapy was contraindicated received intravenous immunoglobulin therapy. Patients were followed up for 33 to 62 months (mean follow-up, 47.5 months).

**Setting:** Patients were treated in an ambulatory tertiary medical care facility of a university-affiliated hospital.

**Patients:** The 20 patients had pemphigoid disease lim-

ited to the oral cavity only at the initial clinical presentation and when enrolled in the study.

**Main Outcome Measures:** The following variables were compared between the 2 groups of patients: (1) duration of treatment, (2) frequency of relapses, (3) induction of remission, (4) adverse effects of therapy, (5) extra oral involvement, and (6) quality of life.

**Results:** Using the aforementioned factors, the group treated with intravenous immunoglobulin had statistically significant shorter treatment duration, fewer relapses, higher remission rate, fewer adverse effects, no extraoral involvement, and a better quality of life compared with the group who received conventional therapy.

**Conclusions:** Intravenous immunoglobulin is a safe and effective modality to treat mucous membrane pemphigoid. It seems to be a good option for patients who cannot be treated with dapsone and in whom conventional therapy is contraindicated or results in the development of serious adverse effects. In patients with progressive mucous membrane pemphigoid, intravenous immunoglobulin therapy may arrest disease progression.

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**T**HE PEMPHIGOID family of diseases is a group of autoimmune subepidermal-subepithelial bullous disorders. They are characterized by the *in vivo* linear deposits of immunoglobulins, complement, or both along the basement membrane zone.<sup>1</sup> The conditions have been subclassified into bullous pemphigoid that mainly affects the skin and cicatricial pemphigoid (mucous membrane pemphigoid) that mostly involves mucous membranes.<sup>2</sup> The oral and ocular mucosae are most frequently involved.<sup>3</sup> Many other subepithelial vesiculobullous disorders have been identified and the term *immune-mediated subepithe-*

*lial blistering disease* has been suggested to describe this group of disorders.<sup>4</sup> Each subset is probably associated with different target antigens, trigger mechanisms, and responses to therapeutic interventions. The clinical phenotype that is acquired consists of vesicles, bullae, and/or erosions affecting only the oral mucosa and is termed *oral pemphigoid* (OP).

Topical corticosteroids are the first choice of treatment for OP, especially for localized lesions.<sup>5-9</sup> If oral lesions extend, if new lesions develop, or if the disease progresses to involve the eye, larynx, or esophagus, then systemic therapy is indicated.<sup>10</sup> Dapsone, suggested as the first drug of choice, has several adverse effects that sometimes limit its use.<sup>11</sup>

## PATIENTS, MATERIALS, AND METHODS

### PATIENTS

#### Diagnostic and Inclusion Criteria

Only those patients who fulfilled the following criteria were enrolled. The presence of pemphigoid disease seen as vesicles, bullae, or erosions limited to the oral cavity and/or desquamative gingivitis. Patients with disease in any other mucous membrane or skin were excluded. Routine histological findings showing a submucosal vesicle with mixed inflammatory cell infiltrate in the submucosa. Direct immunofluorescence study of perilesional oral tissue showing deposition of IgG and/or C3 on the basement membrane zone. Severity of OP was determined by the scoring system of Ciarrocca and Greenberg<sup>11</sup> where 1 represents mild; 2, desquamative gingivitis; and 3, generalized severe disease in the oral cavity. All the patients in this study had severe disease in the oral cavity (grade 3).

All patients were treated with dapsone therapy to control OP since topical therapy and intralesional triamcinolone acetonide injections were ineffective. In all patients, dapsone treatment was discontinued because they developed significant adverse effects or it was ineffective despite prolonged use in adequate doses. We followed the Rogers and Mehregan<sup>24</sup> protocol for using dapsone. The dose was increased by increments of 25 mg when a satisfactory or appropriate clinical response was not observed. If lower doses were used to reduce toxic reactions, clinical benefit would not be obtained. These patients were then prescribed other therapies, since the disease remained active and progressive. The highest dose of dapsone used, total duration of dapsone therapy, response to dapsone, and the reasons to discontinue its use were noted for each patient.

#### Clinical Data

For each patient at each visit, a detailed history was taken and physical examination was performed, with special emphasis on ocular, nasal, pharyngeal, esophageal, laryngeal, and cutaneous regions. During follow-up, dose duration and adverse effects of drug used were documented. A complete blood cell count, serum chemistry study, and urine analysis were done frequently. Relevant data are given in **Table 1** and **Table 2**. The time during which topical

care with rinses, gels, and ointments was used until systemic therapy was initiated was termed duration of topical therapy.

#### Evaluation of Clinical Response to Systemic Therapy

Clinical response was described and categorized as follows.

**Remission.** The patient was free of lesions without systemic therapy for a minimum of 9 months. The duration of the remission was calculated after 9 months of disease and a drug-free interval.

**Control.** The patient is free of lesions but still receiving systemic therapy.

**Nonresponsive.** The presence of lesions despite systemic treatment for 3 months or longer. Three months' duration was considered an appropriate time of observation since OP is a chronic disease and a shorter observation may not provide sufficient time to determine the efficacy of the drug. Objective criteria included continued appearance of new lesions, new sites of involvement, and continued difficulty in eating, resulting in a loss of weight.

**Recurrence of Disease.** The reappearance of lesions in the oral cavity, which healed with topical therapy, supportive care, and occasionally by sublesional injections of triamcinolone acetonide. A change in systemic therapy was not required.

**Relapse.** A major widespread reappearance of lesions that could not be controlled by topical therapy or sublesional injections of triamcinolone acetonide. A change or readjustment in systemic therapy was needed to achieve clinical control.

#### Adverse Effects of Systemic Treatment

Only those adverse effects directly related to the drugs used to treat OP were noted. The profile of adverse effects of the drugs used is well known.<sup>11,17,20,28,29</sup> Adverse effects of long-term usage of systemic corticosteroids such as moon faces, buffalo humps, and redistribution of body adipose tissue were excluded from Table 2. The reason for this was that these adverse effects did not necessitate medical therapy, although bothersome to the patient. Serious adverse effects that required medical intervention and/or drug therapy

In such patients a short plasma half-life systemic corticosteroid (eg, prednisone or prednisolone) is used for brief periods.<sup>10,12,13</sup> Immunosuppressive agents such as azathioprine or cyclophosphamide are often used for their corticosteroid-sparing effects.<sup>11,14-16</sup> Combination therapies can have more adverse effects and mandate careful monitoring.<sup>17,18</sup> Intravenous (IV) immunoglobulin has been successfully used in the treatment of autoimmune and chronic inflammatory disorders, such as idiopathic thrombocytopenic purpura, Kawasaki disease, Guillain-Barré syndrome, and dermatomyositis.<sup>19</sup> Since the first report of its use in a few patients with bullous pemphigoid in 1985,<sup>20</sup> several investigators have reported on its

efficacy in the therapy of both bullous pemphigoid and pemphigus vulgaris.<sup>11,21-28</sup>

Our retrospective study describes 20 patients with involvement of the oral cavity who were observed between September 1, 1994, and October 31, 2000. Since topical therapy was ineffective, dapsone therapy was initiated. The patients were either nonresponsive or developed significant adverse effects necessitating discontinuation of dapsone therapy.

The disease remained progressive in these 20 patients. In 8 patients in group 1, treatment with systemic corticosteroids and other immunosuppressive agents was contraindicated, and they were treated with IV immu-

to control them and affected activities of daily living and the quality of life are listed in Table 2.

#### Extraoral Involvement

During the course of follow-up, patients underwent a detailed review of systems. They were specifically questioned to determine if other mucosae or skin were involved. If involvement was suspected, verification and documentation by endoscopy, evaluation by a specialist, and confirmation by routine biopsy and direct immunofluorescence, whenever possible, was done.

#### Clinical Outcome

The time to control the disease was recorded. Thereafter the patients received maintenance therapy. The clinical state of the patient at the last office visit with reference to the presence or absence of clinical disease and systemic therapy were recorded.

#### Quality of Life

Patients were asked to best describe the quality of life by a numeric score at the 2 stages of their diseases. First, at the initiation of systemic therapy, both IV immunoglobulin or conventional therapy and at the last recorded office visit. Patients were requested to consider the effects of both the disease and the adverse effects of therapy on their quality of life. The following numeric grading system was used: 1, poor; 2, unsatisfactory; 3, tolerant to reasonable; 4, reasonably good; and 5, excellent to high.

#### Duration of Follow-up

The duration of follow-up was defined as the interval between the enrollment of the patient into the study and the last recorded office visit.

### STUDY GROUPS

#### Group 1

Group 1 comprised 8 patients in whom use of systemic corticosteroids and ISAs was contraindicated. These contraindications were recorded in each patient. These patients were treated with IV immunoglobulin.

#### IV Immunoglobulin Therapy

The details of the protocol have been recently described.<sup>29-31</sup> Patients received 1 to 2 g/kg per cycle. The total dose of each cycle was divided into 3 equal doses given over 3 consecutive days by IV infusion over 4 to 5 hours. The frequency of IV immunoglobulin therapy initially was at 4-week intervals. Once previous lesions healed and no new lesions occurred, the interval between the infusion cycles was increased to 6, 8, 10, 12, 14, and 16 weeks. If no lesions occurred after a 16-week interval between infusion cycles, this was defined as the end point of therapy. The total number of cycles and duration of IV immunoglobulin therapy for each patient was recorded.

#### Group 2

Group 2 comprised 12 patients who were treated with systemic corticosteroids and ISAs. In these patients the highest dose of oral prednisone needed to control the disease was recorded. The dose was based on the extent and severity of disease and the patient's weight. Generally prednisone at 0.5 to 1 mg/kg per day was administered. The highest dose used and total duration of ISAs used were recorded. Once clinical resolution was obtained, the dosage of prednisone and ISAs was gradually reduced and whenever possible discontinued. The rate of decrease was partially determined by the patient's ability to remain disease free while decreasing the drugs. The dose of prednisone was first changed from daily to alternate-day therapy and then further reduced at approximately 5 g/d at weekly intervals. In 7 patients, a small dose was needed to control the disease because when prednisone therapy was totally discontinued, OP reappeared.

#### METHODS OF STATISTICAL ANALYSIS

Statistical analysis was performed using SAS NPARIWAY software (ie, the Wilcoxon and 1-way analysis of variance options) that correspond to the nonparametric 2-sample Wilcoxon and 2-sample *t* tests, respectively (version 6.12; SAS, Cary, NC). The 2 treatment groups were compared. The first set of variables, which were used to test the baseline comparability of the 2 treatment groups, consisted of age, duration of disease prior to treatment, duration of topical treatment, duration of dapsone treatment, maximum dapsone dose administered, and follow-up from enrollment in the study to the last office visit. The second set consisted of the following clinical outcome variables: duration of treatment, adverse effects, relapses, recurrences, remissions, quality of life, and extraoral involvement.

noglobulin. In group 2, 12 patients were treated with systemic corticosteroids and other immunosuppressive agents (ISAs). This study compared the response to therapy, its influence on clinical course and disease progression, and the adverse effects secondary to systemic therapy.

### RESULTS

The analysis of data on 20 patients in the 2 different groups regarding their treatment for OP provided the following information. All 20 patients were white. At the time of initiation of systemic therapy all patients had severe OP with multiple sites of involvement (grade 3), as de-

scribed by Ciarrocca and Greenberg.<sup>11</sup> Details of results are presented in Tables 1 and 2 and the **Figure**.

#### PATIENTS

Six of the 8 patients were female and 2 patients were male in group 1. In group 2, 8 of 12 patients were female and 4 patients were male. The age at onset was 43 to 67 years (mean age, 58 years) in group 1. In group 2, the age at onset was 44 to 66 years (mean age, 57 years). The duration of disease prior to diagnosis was 4 to 22 months (mean duration, 12.2 months) in group 1. In group 2, the duration was 7 to 20 months (mean duration, 13.1 months).

**Table 1. Group 1: Clinical Profile, Treatment, Adverse Effects, and Follow-up Data on Patients Treated With Intravenous (IV) Immunoglobulin**

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex/age at onset, y	F/43	F/57	F/62	M/61	M/65
Duration of disease prior to diagnosis, mo	9	16	22	4	9
Duration of topical therapy, mo	4	3	3.8	4.8	5.5
Dapsone therapy					
Dose, mg	175	125	200	125	150
Duration of treatment, mo	8.5	3.5	7.8	6	5.5
Response to treatment	Control	Nonresponsive	Control	Partial control	Partial control
Reasons for discontinuing treatment	Anemia	Intolerance	Anemia and tinnitus	Hepatitis	Anemia and myalgia
Contraindications to systemic corticosteroid treatment	Fertility drugs	Peptic ulcer disease and history of psychosis	Hypertension and diabetes mellitus	Diabetes mellitus	Uncontrolled hypertension
Contraindications to other immunosuppressive agents	Attempting pregnancy	Anemia	Anemia and thrombocytopenia	Family history of cancer	Anemia and thrombocytopenia
No. of cycles of IV immunoglobulin therapy	18	14	22	19	21
Duration of IV immunoglobulin therapy, mo	31	26	38	36	42
Adverse effects of IV immunoglobulin therapy	Headache	Nausea	None	None	None
Extraoral involvement	None	None	None	None	None
No. of recurrences	2	1	3	5	6
No. of relapses	0	0	1	0	0
Clinical outcome: duration of remission, mo	14.5	11	13	15	18
Quality of life*					
Before treatment	2	1	2	1	2
At the end of treatment	5	5	5	5	5
Total duration of follow-up, mo	55	53	73.8	56.8	71.5

\*The quality of life grading system was as follows: 1, poor; 2, unsatisfactory; 3, tolerant to reasonable; 4, good; and 5, excellent to high.

### Duration of Therapies

The duration of the topical therapy was 2.75 to 5.5 months (mean, 4.2 months) in group 1. In group 2, the duration was 3.0 to 5.2 4.1 months (mean, 4.1 months). The highest dose of dapsone used in group 1 was 125 to 200 mg (mean, 156.25 mg), with a duration of 3 to 8.5 months (mean, 5.91 months). In group 2, the highest dose was 100 to 225 mg (mean, 170.83 mg) with a duration of 2 to 14 months (mean, 6.47 months).

### Response to Dapsone Therapy

In group 1, 3 patients were nonresponsive to therapy, 2 patients had partial control of OP, and 3 patients' conditions were controlled. In group 2, 4 patients were nonresponsive to therapy, 4 patients had partial control of OP, and 4 patients' conditions were controlled.

### Reasons to Discontinue Dapsone Therapy

In group 1, 4 patients developed anemia. This was the most common reason for discontinuation of dapsone therapy, even though G6PD levels were normal. Two patients were unable to tolerate the drug. One patient each developed drug-related hepatitis and leukopenia. In group 2, 4 patients developed severe symptomatic anemia. Two patients developed drug-induced hepatitis and leukopenia. One patient was unable to tolerate the drug. The pres-

ence of tinnitus, drug-induced fever, myalgia, and severe headache was observed in one patient each.

### Contraindications to Systemic Corticosteroid Therapy

In group 1, diabetes mellitus in 3 patients, hypertension in 2 patients, and the presence of osteoporosis, glaucoma, peptic ulcer disease, and use of fertility drugs in 1 patient each did not allow the use of systemic corticosteroids.

### Contraindications to Other ISAs

The most common indication was anemia in 4 patients. An abnormal Papanicolaou smear, strong family history of cancer, leukopenia, and thrombocytopenia was present in 1 patient each. Impaired renal function and attempt for pregnancy did not allow ISA usage in 1 patient each.

## THERAPY

### Group 1: IV Immunoglobulin

The time required for initial control of disease ranged from 5.3 to 7.9 months (mean, 6.1 months). The number of cycles ranged from 14 to 22 cycles (mean, 18.4 cycles). The duration of therapy ranged from 26 to 42 months (mean, 32.9 months). The adverse effects of this therapy were as follows: 2 patients developed a mild headache;

## Therapy

Patient 6	Patient 7	Patient 8
F/67	F/50	F/59
16	15	7
5	4.6	2.75
150	125	200
4.5	3	8.5
Nonresponsive	Nonresponsive	Control
Nonresponsive	Intolerance	Anemia and leukopenia
Osteoporosis and multiple infections	Glaucoma and diabetes mellitus	Diabetes mellitus and personality disorders
Compromised renal function	Abnormal Papanicolaou smear	Anemia and leukopenia
19	16	18
26	30	34
None	Headache	None
None	None	None
2	1	2
0	0	0
15	12	14
2	1	1
4	5	4
59	58.6	54.7

1 had mild nausea. No adverse effects were observed in 5 patients.

### Group 2: Conventional Immunosuppressive Therapy

The time required for initial control of disease ranged from 6.5 to 11.6 months (mean, 8.5 months). The highest mean daily dose of prednisone ranged from 40 to 80 mg/d (mean, 59.58 mg/d). Methotrexate, azathioprine, and cyclosporine were used in 1 patient each. Three patients received cyclophosphamide only; 2 were treated with a combination of azathioprine, methotrexate, and cyclophosphamide; 1 received azathioprine and cyclophosphamide; and 3 were treated with azathioprine and methotrexate.

Adverse effects from corticosteroid use occurred in all 12 patients. These include cataract, hypertension, peptic ulcer, psychological abnormalities, clinical psychosis, diabetes mellitus, myopathies, osteoporosis, and multiple systemic infections.

Adverse effects of ISAs were documented in 10 patients. In 2, no adverse effects were observed. These include leukopenia, drug-induced hepatitis, multiple infections, and severe anemia. There is a statistically significant higher incidence of adverse effects in group 2 compared with group 1 ( $P < .001$ ).

The duration of therapy in the 12 patients ranged from 30 to 53 months (mean, 41.80 months). The duration of systemic therapy in group 2 is longer than in

group 1, and this difference is statistically significant ( $P < .02$ ).

## OUTCOME AND FOLLOW-UP

### Clinical Outcome

In group 1, a sustained clinical remission was induced in all patients. The duration of remission ranged from 11 to 18 months (mean, 14.1 months). In group 2, 5 patients (41.6%) achieved remission that ranged from 9 to 18 months (mean, 12.8 months). A higher rate of remission is observed in group 1 compared with group 2, and this difference is statistically significant ( $P < .005$ ).

### Recurrences and Relapses

In group 1, the mean recurrence rate was 1.8 episodes (range, 0-4 episodes). In group 2, mean recurrence was 3.4 episodes (range, 2-6 episodes). In group 1, only 1 patient had 1 relapse. In group 2, 10 patients had multiple relapses. In 2 patients no relapse was observed. The difference in the relapse rate between the 2 groups is highly statistically significant ( $P < .001$ ).

### Extraoral Involvement

In group 1, involvement of OP at extraoral sites was not observed in any of the patients during treatment and the follow-up period. In group 2, during the follow-up period 5 patients did not develop any extraoral involvement. Extraoral involvement with the pemphigoid disease process occurred in 7 (58%) of 12 patients during the follow-up period. The higher frequency of extraoral involvement in group 2 compared with group 1 is statistically significant ( $P < .01$ ).

### Quality of Life

The patients in groups 1 and 2 had a poor quality of life at the initiation of therapy. A statistically significant improvement occurred in the quality of life of patients in group 1 ( $P < .001$ ). A similar improvement did not occur in group 2.

At their final visit, all 8 patients in group 1 were in remission and had discontinued all systemic therapy. In group 2 systemic therapy had been discontinued in 5 patients. Seven patients were still receiving low-dose systemic therapy.

### Duration of Follow-up

In group 1, the duration of follow-up ranged from 37 to 60 months (mean, 46.94 months). In group 2, the duration ranged from 33 to 62 months (mean, 48.88 months). This difference was not statistically significant.

## SUMMARY OF STATISTICAL ANALYSES

For the following baseline variables, there were no statistically detectable differences between the 2 treatment groups: age, duration of disease prior to treatment, du-

**Table 2. Group 2: Clinical Profile, Treatment, Adverse Effects, and Follow-up Data on Patients Treated With Conventional Therapy**

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex/age at onset, y	F/49	F/62	F/59	F/66	F/63
Duration of disease prior to diagnosis, mo	7	14	10	18	15
Duration of topical therapy, mo	3	3.6	5	4	3.8
Dapsone therapy					
Dose, mg	100	150	200	150	200
Duration of treatment, mo	5	2	14	6	7.2
Response to treatment	Partial control	Nonresponsive	Nonresponsive	Partial control	Control
Reasons for discontinuing treatment	Drug-related hepatitis	Intolerance	Nonresponsive	Anemia and tinnitus	Drug-induced fever
Highest daily dose of oral prednisone, mg/d	40	80	60	80	75
Other immunosuppressive agents received	Methotrexate, 25 mg/wk	Azathioprine, 150 mg/d	Cyclophosphamide, 200 mg/d	Azathioprine, 150 mg/d; methotrexate, 20 mg/d; cyclophosphamide, 150 mg/d	Azathioprine, 150 mg/d; and cyclophosphamide, 150 mg/d
Adverse effects					
Of systemic steroids	Cataract and hypertension	Peptic ulcer disease and psychological changes	Psychosis and cataract	Diabetes mellitus and myopathy	Steroid myopathy and psychological changes
Of other immunosuppressive agents	None	None	Leukopenia	Hepatitis from zidovudine (Imuran)	Leukopenia
Duration of conventional therapy, mo	33	38.4	39	45	52
Extraoral involvement	None	None	Ocular and pharyngeal	None	Nasal and ocular
No. of recurrences	2	2	2	5	4
No. of relapses	1	0	2	4	3
Treatment at last visit	None	None	Cyclophosphamide (Cytoxan), 25 mg/d	Cyclophosphamide (Cytoxan), 25 mg/d	Cyclophosphamide (Cytoxan), 25 mg/d
Clinical outcome: duration of remission, mo	18	13	Control	Control	Control
Quality of life*					
Before treatment	1	1	1	2	1
At the end of treatment	2	3	2	3	1
Duration of total follow-up, mo	58	66	51	64	67.8

\*The quality of life grading system was as follows: 1, poor; 2, unsatisfactory; 3, tolerant to reasonable; 4, good; and 5, excellent to high.

ration of topical treatment, duration of dapsone treatment, and duration of follow-up. The IV immunoglobulin treatment group compared with the conventional therapy group had statistically significant fewer relapses, shorter treatment duration, more remission, less extraoral involvement, and better subjective assessment of improvement in the quality of life. The statistical analysis between the variables studied are given in **Table 3**.

#### COMMENT

In this study we present the clinical outcome in 20 patients with severe OP who could not be treated with dapsone because they were nonresponsive, intolerant, or developed serious adverse effects to it. We compared several objective factors between a group of 8 such patients who received IV immunoglobulin as monotherapy with a group of 12 patients treated with conventional therapy consisting of a combination of prednisone and immunosuppressive agents. The 2 groups were similar in age, sex, race, severity of disease, duration of disease prior to systemic therapy, duration of dapsone therapy, dose of dapsone, and

the duration of total follow-up. From the initiation of dapsone therapy to the time from enrollment in the study, the mean duration of follow-up in both groups exceeded 50 months. This extensive follow-up period was considered essential to determine the effect of treatment on a chronic disease with a protracted clinical course.

The clinical outcome in the patients receiving IV immunoglobulin was statistically significant and better. All the patients receiving IV immunoglobulin therapy went into remission. In contrast less than half of the patients receiving conventional therapy were in remission. The remaining patients required long-term use of low-dose immunosuppressive therapy to maintain clinical control of OP. The highest dose of systemic corticosteroids was modest. It is possible that the less than optimal response seen in patients treated with systemic corticosteroids and immunosuppressive drugs could be owing to their lack of aggressive therapy. We used optimal doses of immunosuppressive agents. The dose of systemic corticosteroids was not increased any higher because all 12 patients experienced significant adverse effects from them. Patients receiving IV immunoglobulin had fewer relapses and a

Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
F/65	M/44	M/58	M/61	M/57	F/53	F/55
8	13	18	20	7	16	11
4.4	3.2	4.5	5.2	3.1	5.2	4.6
175	175	200	225	175	150	150
6.3	8.5	3.6	4.2	6	8	6.8
Control Hepatitis	Control Anemia, leukopenia, and severe headache	Nonresponsive Nonresponsive	Nonresponsive Nonresponsive	Partial control Anemia and myalgia	Control Leukopenia	Partial control Anemia
50	60	50	80	40	40	60
Azathioprine, 175 mg/d; and methotrexate, 20 mg/d	Cyclosporine, 200 mg/d	Cyclophosphamide, 150 mg/d	Cyclophosphamide, 200 mg/d	Azathioprine, 150 mg/d; methotrexate, 25 mg/d	Azathioprine, 175 mg/d; and methotrexate 25 mg/d	Azathioprine 150 mg/d; cyclophosphamide, 200 mg/d; and methotrexate, 25 mg/d
Osteoporosis and hypertension	Psychosis, hypertension, and diabetes mellitus	Hypertension and peptic ulcer	Cataract and insomnia	Mood swings and oral <i>Candida</i> species	Diabetes mellitus, myopathy, and multiple infections	Multiple infections and decreased bone density
Infections	Leukopenia	Leukopenia	Leukopenia and anemia	Multiple infections and hepatitis from azathioprine (Imuran)	Multiple infections	Multiple infections
47.3	33	40	44	46.8	53	51
Skin and nasal	None	Ocular and skin	Ocular and nasal	Nasal, skin, and pharyngeal	Nasal and vaginal	None
5	4	2	3	3	3	6
3	2	0	1	2	4	3
None	Prednisone, 10 mg/d	Prednisone, 5 mg/d	Cyclophosphamide (Cytoxan), 25 mg/d	None	None	Methotrexate, 10 mg/wk
11	Control	Control	Control	13	9	Control
1	2	1	2	1	2	2
2	2	2	3	2	2	2
67.7	46.2	59.5	66.2	66.9	80.2	63.6

shorter period of treatment. The mean duration of IV immunoglobulin therapy was 32.6 months compared with 38.5 months for patients receiving conventional therapy ( $P < .02$ ). These data indicate that with continued use, IV immunoglobulin therapy does not lose its effectiveness. With time its effectiveness was enhanced because the intervals between infusions increased, yet remission was sustained. This study also suggests that IV immunoglobulin can be effective as monotherapy. Data in this study suggest that short-term use of IV immunoglobulin would be ineffective in achieving a long-term sustained remission. For such results, on effective control of acute disease, a gradual reduction in frequency of infusion is preferable. This is similar to mechanisms of gradual withdrawal of corticosteroid therapy. Despite the small sample size, these data demonstrate that conventional therapy produces significant adverse effects since 83.3% of patients developed such adverse effects.

Only 3 of 8 patients receiving IV immunoglobulin therapy developed mild adverse effects such as headaches or nausea. While IV immunoglobulin is a relatively safe drug, adverse effects can occur. Severe hypersensitivity-

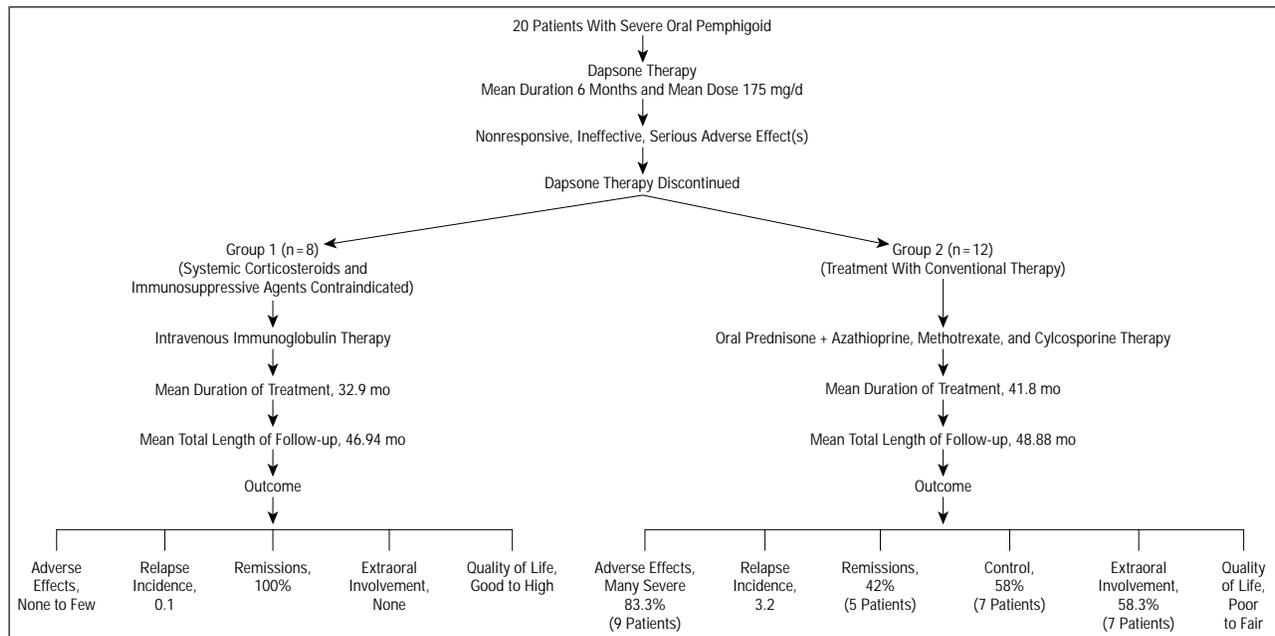
like reaction can occur in patients with selective IgA deficiency. Acute renal failure and aseptic meningitis have been reported.<sup>32</sup> The methods to evaluate quality of life were rather simple and subjective. The patients receiving IV immunoglobulin therapy had a higher quality of life than patients receiving conventional therapy. It is possible that the adverse effects such therapies produce add to the poor quality of life these patients claimed to have experienced.

#### IV IMMUNOGLOBULIN THERAPY IS EXPENSIVE

The cost is variable (\$3000 to \$5000/cycle) and often determined by availability. If the price of conventional therapy (prednisone and ISAs) was to include the cost of adverse effects, that results from their use, then the overall costs would be comparable.

#### OP IS A CHRONIC DISEASE

In a study of 29 patients with OP, Mobini et al<sup>1</sup> documented that the mean duration of the treatment period was 42 months (range, 24-78 months). Hence, they be-



Flowchart depicting clinical outcome in patients with mucous membrane pemphigoid, comparing 8 patients treated with intravenous immunoglobulin infusion (group 1) with 12 patients treated with conventional therapy (group 2).

**Table 3. Statistical Analysis of Variable Studied in the Treatment of Oral Pemphigoid With Intravenous (IV) Immunoglobulin and Conventional Therapy**

Clinical Outcome and Baseline Variables	Conventional Treatment (n = 12)			IV Immunoglobulin Treatment (n = 8)			Statistical Analysis	
	Average With Conventional Treatment	Minimum	Maximum	Average With IV Immunoglobulin Treatment	Minimum	Maximum	P Value, Wilcoxon 2-Sample Test	P Value, 2-Sample t Test
Age, y	57.7	44	66	58	43	67	.82	.92
Duration of disease prior to treatment, mo	13.1	7	20	12.2	4	22	.72	.76
Duration of topical treatment, mo	4.1	3.0	5.2	4.2	2.75	5.50	.94	.90
Dapsone therapy								
Dose, mg	170.8	100	225	156.3	125	200	.30	.34
Duration of treatment, mo	6.5	2.0	14	5.9	3.0	8.5	.79	.66
Follow-up from dapsone treatment to last office visit, mo	45.9	30	59	43.9	34	57	.54	.60
Duration of treatment (IV immunoglobulin or systemic), mo	41.8	30	53	32.9	26	42	.02	.008
No. of adverse effects	3.2	2	4	0.4	0	1	<.001	.00
No. of recurrences	3.4	2	6	1.8	0	4	.02	.03
No. of relapses	2.1	0	4	0.1	0	1	.001	.001
No. of remissions	0.4	0	1	1	1	1	.005	.005
Quality of life*	0.75	0	2	3.25	2	4	<.001	.00
Extraoral involvement	0.6	0	1	0	0	0	.01	.005
Duration of total follow-up, mo	48.88	33	62	46.94	37	60	.30	.62

\*The quality of life grading system was as follows: 1, poor; 2, unsatisfactory; 3, tolerant to reasonable; 4, good; and 5, excellent to high.

lieved that a long-term follow-up would be critical to determine the efficacy of the treatment and its effect on the clinical course of the disease. The patients were followed up for 30 to 60 months (mean, 45 months). This long-term follow-up would suggest that IV immunoglobulin therapy had the potential to influence the natural or clinical course of OP.

The most critical observation in this study is that none of the patients receiving IV immunoglobulin therapy developed OP in any other mucous membrane. In contrast, 58.3% of patients receiving conventional therapy developed OP at extraoral sites. It seems as if IV immunoglobulin therapy has the capacity to prevent progression of disease. In a study of similar patients with pem-

phigoid initially presenting in the oral cavity, Rogers et al<sup>27</sup> found that 50% of their patients developed extraoral disease at the end of a 3-year follow-up. We observe a slightly higher incidence because our mean follow-up period (47.91 months) is longer than that observed by Rogers et al.

It has been proposed that there are 7 potential mechanisms for the action of IV immunoglobulin therapy that may facilitate or enhance the achievement of its clinically beneficial effects.<sup>29-31</sup> These are (1) anti-idiotypic interactions, (2) Fc-receptor modulation, (3) cytokine inhibition, (4) neutralization of causative microbe or toxin, (5) superantigen neutralization, (6) effects on complement, and (7) acceleration of IgG catabolism. The precise mechanism of action of IV immunoglobulin in oral or mucous membrane pemphigoid is presently unknown.

While the sample size of the patient population studied is small, it must be recognized that this is a rare disease, and this is a subset within it. The observation in this study suggests that compared with conventional therapy, the remission rate was higher in the IV immunoglobulin-treated group, and that these patients maintained their remission.

We are not recommending that all patients with OP be treated with IV immunoglobulin. However, in patients with severe extensive symptomatic disease whose conditions cannot be satisfactorily controlled with dapsone therapy and in whom there is a high risk of developing adverse effects to conventional therapy or such adverse effects have developed, IV immunoglobulin may be an appropriate alternative or treatment option.

We recognize the small number of patients studied. However, the study demonstrates that OP it is not a trivial disease and warrants prompt attention and follow-up. If it progresses to involve other mucosa, the consequences are significant, catastrophic, and potentially fatal. The detailed information on each patient may provide guidelines to designing future studies. Intravenous immunoglobulin is effective and safe in treating OP. The promising results in this study would indicate that a multicenter trial, clearly identifying inclusion criteria, outcome factors, and appropriate control groups is warranted and needed.

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