

Current Therapy of Pemphigus Vulgaris

MICHAEL J. FELLNER, M.D., AND ALLEN N. SAPADIN, M.D.

Abstract

Pemphigus vulgaris (PV) is a potentially fatal autoimmune blistering disease of the skin and mucous membranes, characterized by flaccid bullae that rupture and leave erosions. Its treatment is challenging. Although the use of systemic corticosteroids remains the cornerstone of effective therapeutic regimens for PV, their prolonged administration may lead to serious side effects. It is therefore necessary, for many patients, to add immunosuppressive agents or use immunomodulatory procedures to achieve remission. This paper will summarize the treatments available for PV, while focusing on the most recently available therapeutic options.

Key Words: Pemphigus vulgaris, therapy.

Introduction

THE PEMPHIGUS GROUP OF DISEASES is characterized by potentially life-threatening blistering of the skin and mucous membranes. An autoimmune process, directed against keratinocyte desmosomal cadherins, interferes with the adhesive function of these molecules. This results in separation between keratinocytes, which in turn leads to the clinical manifestation of blistering.

There are three major types of pemphigus: pemphigus foliaceus (PF), pemphigus vulgaris (PV), and paraneoplastic pemphigus (PNP). In PF, scaly crusted erosions evolve from flaccid blisters. The lesions may be localized and have a seborrheic distribution, or may become generalized. Mucous membrane involvement is rare. Patients with pemphigus erythematosus, a variant of PF, have some serologic findings suggestive of systemic lupus erythematosus, in particular, antinuclear antibodies.

In PNP, a severe mucocutaneous blistering eruption develops in the context of an underlying neoplasm. Approximately 70% of the patients will have underlying non-Hodgkin's lymphoma or chronic lymphocytic leukemia, although other lymphoproliferative disorders have been described. Erosions of the lips with hemorrhagic crusting are the most constant clinical

finding, and may resemble Stevens-Johnson syndrome. The disease is usually refractory to treatment and the prognosis is grave. Combination therapy with prednisone and cyclosporine may prolong survival for some patients.

PV is the most common form of pemphigus. Its incidence is 0.1–0.5 per 100,000 in the U.S. population, but higher among Jewish people (1). Men and women are equally affected, and the mean age of onset is 50–60 years. Clinically, PV is characterized by flaccid bullae that subsequently rupture and leave erosions. The blisters may occur anywhere on the skin surface, but intact blisters may be sparse. Involvement of the oral mucosa is common; it is the site of onset in more than 50% of patients. Intact bullae are uncommon in the mouth, and the painful erosions of PV are often misdiagnosed as herpes simplex virus infection. Pemphigus vegetans is a variant of PV, in which vegetating lesions are seen, often in intertriginous areas.

Routine histopathologic examination reveals a suprabasilar blister, acantholysis (separation between keratinocytes), and a mild, superficial, dermal inflammatory infiltrate. Direct immunofluorescence (using the patient's perilesional skin as a substrate) reveals antibody (IgG) deposition in the intercellular spaces of the keratinocytes. Indirect immunofluorescence (using the patient's serum on monkey esophagus substrate) is positive in more than 90% of patients with active disease (2). Desmoglein 3, a 130 kDa component of the desmosome, is the target antigen in this disease. Deletion of the desmoglein-3 gene in mice re-

From the Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

Address correspondence to Michael J. Fellner, M.D., Department of Dermatology, Box 1047, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

sults in a phenotype consistent with PV, including oral mucosal and skin erosions (3).

The severity and natural history of PV are variable. Many published reports group PV and PF patients together. This makes it difficult to analyze the specific data on PV. In the era before corticosteroid therapy, the vast majority of patients with the pemphigus group of disorders died from their disease. Changes in therapy over the past century have reduced the mortality from this disease to less than 10% and many of these deaths are now iatrogenic in nature. This dramatic decline in mortality is due primarily to the marked improvement in therapeutic options, but also to earlier diagnosis and initiation of therapy.

The current treatment options for PV are listed in Table 1. This paper will review these conventional and new treatments, with an emphasis on the most recent literature.

Corticosteroid Treatment

Before the 1950s the majority of patients with pemphigus died, usually from overwhelming sepsis, within one year of the onset of their disease. A clear and rapid fall in the mortality rate occurred after the introduction of corticosteroids in the 1950s (4).

Topical and Intralesional Corticosteroids

Both topical and intralesional corticosteroids have been used in the treatment of PV,

but they are more effective in the treatment of PF and bullous pemphigoid. Dumas et al. (5) described 7 pemphigus patients, 3 of whom were treated with clobetasol propionate 0.05% cream as monotherapy for their mild PV. PV was defined as "mild" if fewer than 10 new bullae appeared per week and if the circulating pemphigus antibody titer was $\leq 1:320$. The cream was applied twice a day for at least 15 days, then tapered. Lesions were controlled in only 1 of the 3 PV patients.

Triamcinolone acetonide, diluted to 5–10 mg/mL, may be used for intralesional injections of cutaneous lesions. A higher concentration, 10–20 mg/mL, is recommended for intraoral lesions (6). Multiple injections may be necessary for large lesions. The injections should be administered at weekly or biweekly intervals until complete resolution of the lesions is achieved. The injections are useful for the treatment of PV of mild severity, for the treatment of resistant lesions, for vaginal lesions (7) and to treat new lesions in patients whose systemic medication is being tapered.

Systemic Corticosteroids

Systemic corticosteroids are the most useful drugs in the treatment of pemphigus vulgaris and continue to be the mainstay of therapy for this disease. Their use rapidly induces remission in the majority of patients (8–10).

Oral corticosteroids. The oral route of administration of corticosteroids is the one most preferred, and prednisone is the medication most frequently used. Various treatment strategies have been reviewed in detail (6, 11), but there are no controlled studies to evaluate their relative efficacy or safety profiles. For severe disease, the Bystryn regimen (6) recommends 80 mg of prednisone administered daily. If necessary, the dose is increased by 50% every 4–7 days until control is achieved, as demonstrated by the absence of new lesions and the disappearance of itching. This dose is maintained until there is 80–90% clearance of lesions. Reduction of the dose by 50% is recommended at two-week intervals.

Moderately severe pemphigus is managed with 60–80 mg/day of prednisone. Mild disease is treated with a trial of topical corticosteroids, followed by low-dose (20 mg/day) oral steroids (11). When the daily dose of prednisone exceeds 120 mg, it is given in 2 divided doses. If the total daily dose exceeds 240 mg, alternative options are considered. About 50%

TABLE 1

Treatment of Pemphigus Vulgaris.

1. Corticosteroids

Topical and intralesional corticosteroids
Oral corticosteroids
Pulse therapy

2. Immunosuppressive Drugs

Azathioprine
Cyclophosphamide
Cyclosporine
Mycophenolate mofetil
Chlorambucil
Methotrexate

3. Anti-inflammatory Drugs

Gold
Dapsone
Nicotinamide and tetracycline

4. Immunomodulatory Procedures

Plasmapheresis
Extracorporeal photopheresis
Intravenous immunoglobulin

of the patients receiving this treatment regimen are ultimately able to discontinue all therapy (12). An additional one third of the patients require daily maintenance therapy with a prednisone requirement of less than 10 mg or with an additional medication listed in Table 1. Larger maintenance doses will be required by 10–20% of the patients.

Pulse corticosteroid therapy. "Pulse corticosteroid treatment" refers to the intravenous administration of 1 gram/day of methylprednisolone, or its equivalent, over a period of 1–3 hours, for several consecutive days. The goal of this approach is to quickly achieve the immunosuppressive effects of glucocorticoids, while avoiding the long-term side effects associated with the oral route of administration. It is well tolerated in young and otherwise healthy patients, but may result in serious complications in those suffering from chronic disease. These include severe electrolyte imbalances, hypertension, pancreatitis, seizures, and cardiac arrhythmias (13).

A retrospective review of outcomes in a group of PV patients treated with (n=9) and without (n=6) pulse glucocorticoids indicates long-lasting benefits for the patients treated with pulse therapy (14). All patients in both groups received treatment with azathioprine, cyclophosphamide, or methotrexate. Some of the patients also received dapsone or gold. The difference in initial disease severity was not statistically significant in the two groups.

Six of the 9 patients treated with pulse therapy were classified as responders, patients whose lesions improved during pulse therapy and continued to improve afterward. Four of these patients discontinued all therapy and achieved remission. None of the 6 control patients achieved long-term remission. Based on this study, pulse corticosteroid therapy appears to be a promising option for those patients with severe PV who do not rapidly respond to conventional therapy.

Combination Therapy

Therapy which combines corticosteroids and additional medications to control severe PV is utilized to minimize the adverse effects of prolonged steroid use. Combination therapy is currently gaining popularity even as the initial treatment of PV. Bystryn (6) advocates the use of adjuvants only if serious adverse effects of corticosteroids appear, relative contraindications to their use exist, or they cannot be ta-

pered because of repeated exacerbations of disease activity.

Immunosuppressive Drugs

Azathioprine

In 1973 Roenigk and Deodhar (15) described the successful use of azathioprine (50–250 mg/day) for the treatment of early PV in ten patients. Seven of these patients had never received corticosteroids or had had them completely withdrawn. Since the onset of action of azathioprine is 3–5 weeks, the authors cautioned that monotherapy with this agent was not the treatment of choice for the severe, generalized form of PV.

A 1987 study involving 29 patients with severe PV concluded that the combination of corticosteroid and azathioprine was successful (16). In that report 45% of the patients achieved remission. (Two patients died.) The use of azathioprine allowed for a significant reduction in the dosage and side effects of corticosteroids.

Reohr and associates treated two sisters who had PV with a combined schedule of azathioprine and steroid (17). One patient began with combination therapy of prednisone 80 mg daily plus azathioprine 150 mg daily. The second patient had a complete remission while on prednisolone (150 mg daily) monotherapy. Azathioprine (100 mg daily) was then added in order to facilitate tapering of the steroid. Both patients achieved a good result. Ouahes et al. (7) treated three PV patients with initial combination therapy of prednisone (80–180 mg daily) and azathioprine (100 mg daily). The steroids were subsequently tapered with good responses.

Cyclophosphamide

Cyclophosphamide is an alkylating agent with cytotoxic and immunosuppressive activities. Adverse effects include myelosuppression, alopecia, hemorrhagic cystitis, and gonadal damage (18). Carcinogenic effects include the development of bladder carcinoma, non-Hodgkin's lymphoma and squamous cell carcinoma of the skin. The indications for the use of cyclophosphamide in the treatment of PV include: (1) patients who do not tolerate large maintenance doses of corticosteroids because of the development of steroid-related complications; and (2) patients in whom steroids alone fail to control the disease.

Although use of cyclophosphamide as monotherapy was found to be ineffective (19), the addition of cyclophosphamide to prednisone often results in satisfactory control of the disease and/or permits a reduction in the prednisone dose. In 1978 Fellner et al. (20) described the use of cyclophosphamide in combination with prednisone as the initial treatment of 5 patients with PV. During a one-to-four-year follow-up period, all 5 patients remained free of lesions. Four of these 5 patients required no further medication.

The use of pulse intravenous cyclophosphamide may decrease adverse effects and risk of malignancy associated with the oral administration of this drug (21), while maintaining or improving efficacy. In 1988 Pasricha et al. (22) reported remission in 60 of 79 patients treated with intermittent, intravenous, high-dose dexamethasone and cyclophosphamide coupled with 50 mg/day of oral cyclophosphamide administered between the pulses. Intravenous dexamethasone and cyclophosphamide were given on day 1 of the pulse, while intravenous dexamethasone without cyclophosphamide was administered on days 2 and 3. The pulses were repeated every 2–4 weeks. Mortality was 3%. Complete remission was observed in 25 of 67 (37%) patients who were available for follow-up study. Partial remission was seen in an additional 52% of the patients. Of these, 25 received maintenance therapy with oral cyclophosphamide and 10 were still receiving intravenous pulse therapy. The authors later reported that, without further treatment, the disease in 5 of these patients did not recur during the subsequent 2–7 years (23).

More recently, Fleischli et al. (24) reported an uncontrolled study in which nine patients with severe or previously recalcitrant pemphigus were treated with pulse intravenous cyclophosphamide. The monthly pulses were initially administered at a dose of 0.5–1.0 g/m² of body surface area. The cyclophosphamide was increased by 100–250 mg per dose if the white blood cell count did not fall by more than $20 \times 10^9/L$ at the 2-week nadir. All patients were treated concurrently with oral administration of prednisone (dosage adjusted for disease severity) and a daily dose of 50 mg of cyclophosphamide.

Seven of the nine patients had PV. Four of these seven patients had an “excellent” response to therapy, after which their prednisone requirement decreased to the range of 10–20 mg/day or was discontinued entirely (one pa-

tient). The duration of the follow-up period for these four patients ranged from 2–7 years.

Most recently Hayag et al. (25) described the successful use of immunoablative, high-dose cyclophosphamide without stem cell rescue in a patient with severe PV refractory to multiple therapies. This procedure, previously described for refractory cases of aplastic anemia, systemic lupus erythematosus, and paraneoplastic pemphigus, involves the intravenous administration of 50 mg/kg of cyclophosphamide for 4 days. Four months after the treatment, the patient's skin and oral lesions had completely healed and his pemphigus titers had decreased to zero. He is presently on no medications and his skin remains clear of lesions.

Cyclosporine

The mechanisms of action, adverse effects and monitoring recommendations for cyclosporine (CSP) have been reviewed (26). Barthelemy et al. (27) treated 9 PV patients with 6–8 mg/kg of CSP, including 4 patients in whom it was used as monotherapy. Of those 4, only 1 had a remission which lasted only 2 months after CSP had been discontinued. After failing CSP monotherapy, the remaining 3 patients in this group received combination therapy with prednisone. In 2 of these patients, the lesions cleared with the addition of 10 mg per day of prednisone.

Four of the 9 patients who were studied had not responded to steroid treatment. Within 3 weeks of the addition of cyclosporine to their regimen, the lesions had resolved. However, only 1 of these 4 patients remained clear after discontinuation of CSP.

Lapidoth et al. (28) studied 16 hospitalized patients with PV who were treated with prednisone and CSP. A historical control group consisted of 15 patients who received prednisone at an initial dose of 120 mg/day. This was decreased according to clinical response. There was a decreased time to new blister formation in the group treated with combination therapy (mean 11.1 vs. 20.5 days). Hospital stay in the treatment group was shorter (mean 32.6 vs. 50.7 days in the control group). The mean total cumulative prednisone dosage during hospitalization and follow-up was about one third less for the treatment group.

CSP was successfully administered as monotherapy in two siblings with severe PV (29). A good response was seen in both without

any major side effects. The patients had been in remission for more than 20 months after discontinuation of the CSP.

More recently, Mobini et al. (30) described six patients with severe PV, including skin and oral disease, who were unresponsive to prolonged high-dose systemic corticosteroids. Subsequent therapies included azathioprine, cyclophosphamide, dapsone, gold, and methotrexate. Three patients had a major recurrence when their dosage of azathioprine was reduced. They were then treated with cyclophosphamide. Its discontinuation was necessary because of severe side effects. Dapsone, gold and methotrexate were used without success.

CSP starting doses were 1–3 mg/kg daily. The oral dose was adjusted over a 4-week period to obtain a serum level of 100–125 mg/mL. Existing lesions improved and no new lesions appeared within 8–10 weeks. By 16–20 weeks, most lesions were healed. The total duration of treatment with CSP ranged from 13–20 months. Patients received no systemic therapy during the 3.5–5-year follow-up period. There were no recurrences during this period.

While CSP is of limited benefit as monotherapy for PV, it appears more useful when used in combination with prednisone. However, better-controlled prospective studies are necessary in order to clarify its true efficacy as a steroid-sparing agent.

Mycophenolate Mofetil

Mycophenolate mofetil is an ester prodrug of mycophenolic acid, an active immunosuppressant that is a potent inhibitor of inosine monophosphate dehydrogenase. This enzyme is crucial for the *de novo* synthesis of the guanosine nucleotides necessary for DNA synthesis. B and T lymphocytes which rely on this *de novo* pathway more than on the salvage pathway, are subject to the inhibition of their proliferation and production of antibodies (31). The major side effects of mycophenolate mofetil are bone marrow suppression, diarrhea, nausea, vomiting and increased susceptibility to infection.

First approved for use in 1995 by the Food and Drug Administration, this drug is primarily used to prevent rejection in patients who have received renal and/or other organ allografts (32). Recent reports describe its use in several skin diseases, including psoriasis (33, 34) and relapsing idiopathic nodular panniculitis (35). Mycophenolate mofetil has also been used recently in the treatment of other immunobullous

diseases, including bullous pemphigoid (36, 37) and pemphigus foliaceus (38).

Enk and Knop reported its use in PV, first in 1997 (39) and later, with a larger series of patients, in 1999 (40). In the latter study 12 patients with PV who had failed combination therapy with prednisolone and azathioprine received prednisolone and mycophenolate mofetil (2 g/day). Eleven of the 12 patients improved and did not relapse during the 9–12 month follow-up period, even after tapering of the steroid. The mycophenolate mofetil, 2 g/day, was continued during this period. One patient did not respond. Nousari and Anhalt (41) advocate dosages in the range of 2.5–3.0 g/day to induce remission in patients with pemphigus (both PF and PV).

The effective use of mycophenolate mofetil as monotherapy for PV was recently reported (42, 43). Bredlich et al. (42) described the cessation of new blisters in a patient with PV two weeks after the initiation of therapy with mycophenolate mofetil, 1 gram administered twice daily. Complete clearing of lesions occurred after 6 weeks of treatment. Grundmann-Kollmann et al. (43) described an additional patient who experienced complete remission after initiation of mycophenolate mofetil monotherapy. The period of remission was not specified in either of these case reports.

Use of this drug is not associated with nephrotoxicity or hepatic damage. In view of the fact that cyclosporine and methotrexate are contraindicated in certain clinical contexts, clinical trials investigating the use of mycophenolate mofetil monotherapy compared to combination therapy with prednisone and other immunosuppressive treatments appear warranted.

Chlorambucil

Chlorambucil, an alkylating agent similar to cyclophosphamide, inhibits DNA synthesis through the alkylation of nucleic acids. It preferentially affects B cells over T cells. However, bladder toxicity, observed with daily administration of cyclophosphamide, is not caused by chlorambucil. Its successful use has been reported for other diseases, including rheumatoid arthritis, systemic lupus erythematosus, juvenile rheumatoid arthritis, Wegener's granulomatosis, pyoderma gangrenosum, Behçet's disease, dermatomyositis, and bullous pemphigoid.

Its use in combination with prednisone for the treatment of pemphigus has recently been reported by Shah et al. (44). This was an uncontrolled retrospective study in which the records of 9 pemphigus patients were reviewed. Patients

were started on 4 mg of chlorambucil once daily. This dosage was increased to a maximum dose of 10 mg daily, based on clinical response and toxicity. Seven of the 9 patients studied had PV. Four of these 7 patients improved and experienced remission. One patient improved while on combination therapy that also included dapsone. The two PV patients who did not improve had isolated mucosal disease without skin involvement.

It is difficult to draw conclusions from this retrospective and uncontrolled study. The authors noted a decrease in corticosteroid requirements during treatment with chlorambucil, but did not quantify the decrease for individual patients. The periods of remission were also not specified. While patients must be monitored carefully for the development of bone marrow suppression, induction of malignancy (particularly acute myeloblastic leukemia) is the most feared complication of therapy. For these reasons, a trial of chlorambucil should be reserved for those patients that have failed treatment with other immunosuppressive regimens.

Methotrexate

Smith and Bystryn (45) recently revisited the use of methotrexate as an adjuvant treatment for PV. Nine patients with PV, for whom steroid therapy could not be tapered without an exacerbation, were additionally treated with 2.5 mg of methotrexate given every 12 hours for 3 doses each week. This dose was increased by 2.5–5.0 mg every 2 weeks, if necessary. The maximum dose was 17.5 mg per week.

For 6 of the 9 patients (67%) systemic corticosteroid therapy was discontinued without a flare within 6 months of initiation of methotrexate therapy. The disease was quiescent until discontinuation of the methotrexate, at which time all 6 patients experienced a flare (mean 23 days) of disease. The authors noted that low-dose methotrexate may be a useful adjunct in PV patients for whom steroid therapy cannot be tapered without an exacerbation of disease activity. It is obvious that, at some point, adjuncts in addition to methotrexate must also be used in these patients, since no patient in the study group experienced a complete remission on this regimen.

Anti-inflammatory Drugs

Gold

In 1973 Penneys et al. (46) first reported the use of gold for the treatment of pemphigus. Au-

rothiomalate and aurothioglucose, the two major parenteral gold medications in the United States, are approximately 50% gold by weight (47). Auranofin, an orally absorbed compound, contains 29% gold. Parenteral gold is administered intramuscularly in a manner similar to that recommended for the treatment of rheumatoid arthritis. The initial test dose of 10 mg is followed by a 25 mg injection one week later. Subsequent weekly injections of 50 mg are administered until the patient responds clinically. Maintenance therapy consists of 50 mg injections administered at longer intervals or a lowered dose of gold continued at weekly intervals. After a cumulative dose of 1 gram has been administered, the medication is discontinued if there has been no clinical response.

Use of gold therapy is attractive for patients in their reproductive years, because carcinogenesis and infertility are not a major concern, as they are in treatment with immunosuppressive medications. However, one third of patients will experience an adverse effect during treatment (48). Fifty percent (50%) of these side effects are mucocutaneous in nature, either skin eruptions or oral ulcers. Gastrointestinal, renal and hematologic effects may be severe. Ocular, pulmonary and neurologic effects are more infrequent. Patients should be carefully monitored while on gold therapy. The results of complete blood counts with platelet counts and urinalysis should be checked prior to each injection. A complete biochemical profile should be checked before the initiation of therapy.

PV patients with mild disease may benefit from gold as monotherapy (49), but it is unclear if the use of gold induces remission in these patients or if these remissions would have occurred spontaneously. Penneys et al. (50) reported the use of gold in 18 patients with pemphigus. Three patients received gold as monotherapy, while the remaining 15 patients received combination therapy with gold and corticosteroids/immunosuppressive drugs. Seventy-two percent (72%) of the patients improved, while 44% experienced complete remission. No deaths were reported.

In 1984 Poulin et al. (51) reported the Mayo Clinic experience with gold treatment in a series of 13 patients with PV. The study involved a relatively long follow-up period, averaging 41.2 months. All patients received combination therapy with varying doses of prednisone and gold (50 mg/week). Seven patients experienced complete remission (54%) and required no further treatment. One death occurred. The aver-

age dose of gold was 2.374 g for a mean treatment period of 18.3 months. Two of these 7 patients had recurrence of the disease, 5 months and 3 months after cessation of gold therapy. The duration of the remission for the remaining 5 patients was 32 months (mean).

Gold therapy in this study was discontinued, temporarily or permanently, because of toxicity in 5 patients (38%). Proteinuria (2 patients), eosinophilia, mild leukopenia, and urticaria were reported and rapidly cleared after discontinuation of the drug.

More recently, Pandya and Dyke (52) reviewed the efficacy of gold in 26 pemphigus patients, 21 of whom had PV. In this 1998 study, 85% of the patients responded to gold therapy. A positive response was defined as an improvement in blistering, and ability to decrease prednisone dosage to less than 20 mg/day or to completely discontinue it. Only 4 patients (15%) were in complete remission at the end of the study. This is significantly lower than the complete remission rate reported in prior studies discussed above (38–54%) (34–36). Only 1 of these 4 patients had a recurrence. Seven patients discontinued prednisone and were free of disease, but they were still receiving gold. Five patients responded to gold therapy but were still receiving prednisone and gold therapy and had some degree of blistering at the end of the study. Complications from therapy developed in 42% of the patients, but these all resolved with discontinuation the gold.

Dapsone

Dapsone may be useful in the treatment of both PF and PV, although there is greater support in the literature for its efficacy in PF (53). Three of 6 pemphigus patients treated with daily doses of 100–300 mg of dapsone and prednisone improved within 2–3 weeks after initiation of dapsone therapy (11). Within 1–3 months their corticosteroid requirements were drastically reduced or eliminated. These patients included those with PV and PF, but the numbers of each were not specified.

Although the concept of using dapsone in PV to minimize the long-term adverse reactions of corticosteroids is appealing, there are only occasional reports that support its use in this disease. The addition of 100 mg of dapsone daily was followed by a full remission in a few patients that had been treated with high doses of corticosteroids in combination with methotrex-

ate (54). One PV patient with gingival and vaginal lesions, but no skin lesions, responded well to 150 mg daily of dapsone (7). The patient also received intralesional and topical vaginal corticosteroids.

Nicotinamide and Tetracycline

The primary advantage of tetracycline and nicotinamide therapy in PV is a lower toxicity and a broader safety profile. Alpsy et al. (55) studied 15 patients with pemphigus to determine if this combination alone was effective. Ten of the 15 patients had PV. For 2 months, 2 g of tetracycline and 1.5 g of nicotinamide were administered on a daily basis. Any concurrent therapies were discontinued. A “complete response” indicated clearing of all lesions. A “partial response” indicated clearing of 50% or more of the lesions. “No response” indicated clearing of less than 50% of the lesions. Lesions were generalized in all but one patient, who had disease localized to the oral mucosa. Of the 10 patients with PV, 2 had a complete response, 3 had a partial response, and 5 had no response. The authors concluded that this combination was not an effective alternative to the first line therapeutic options.

In a 1993 study 6 patients with PV were treated with nicotinamide, 1.5 g/day, and tetracycline, 2 g/day, with or without corticosteroids (56). Three achieved a complete response (total clearing of lesions), 2 experienced a partial response (clearing of more than 50% of lesions) and the remaining patient did not respond (clearing of less than 50% of lesions). Only 2 of the 5 patients that responded received nicotinamide and tetracycline as the only oral agents. The 3 others required a daily dose of oral prednisone ranging from 2.5–30.0 mg/day. One of these 3 patients was treated additionally with azathioprine. The follow-up period for these 6 patients ranged from 6–13 months. These results are difficult to interpret, in view of the fact that this was an uncontrolled study and because the degree of disease severity was not specified for the patients.

The efficacy of tetracycline in combination with corticosteroids, but without nicotinamide, was evaluated recently by Calebotta et al. (57). Thirteen hospitalized patients with PV receiving prednisone were administered tetracycline 2 g/day for the first month, followed by 1 g/day for the second month. Prednisone was then gradually tapered. A control group consisted of 7 patients treated with prednisone and azathio-

prine. In the study group, 6 patients (46%) were classified as severe, while only 2 of the 7 patients (29%) in the control group were categorized as severe.

Cessation of new blister formation occurred within 5.4 days (average) in the study group, compared to 23.7 days (average) in the control group. Reduction of prednisone could begin at 16.5 days (average) in the study group, compared to 31.2 days (average) in the control group. The authors claim that the clinical response was not associated with the location of the lesions or with the severity of the disease.

The average starting dose of prednisone was only 76.5 mg/day in the study group and 118.5 in the control group. The average remission time in the control group was more than double that of the treatment group (11.95 months versus 5.84 months). In short, it seems that the treatment group responded faster, but the control group remitted longer. This fact attenuates the significance of the lower short-term prednisone requirements in the treatment group.

Immunomodulatory Procedures

Plasmapheresis

Plasmapheresis is a procedure in which pathogenic autoantibodies are removed from the patient's blood by filtration of the plasma. Although this procedure temporarily lowers the level of circulating autoantibodies, a reactive burst of antibody production from pathogenic B cells results in a rebound effect that replaces and even overshoots the initial decrease. Therefore, to retain the decrease in circulating autoantibody levels, it is imperative to couple intensive plasmapheresis with the administration of immunosuppressive medication (6). Tan-Lim and Bystry (58) reported 22 patients with PV who were treated with similar doses of prednisone and immunosuppressive medications, 11 of whom additionally received thrice-weekly plasmapheresis. The average level of pemphigus antibodies decreased by 83% in the patients receiving plasmapheresis, while it decreased by only 18% in the control group. More recently, 7 patients with severe PV uncontrolled by high-dose corticosteroids were treated with plasmapheresis, after which immunosuppression therapy was administered for an average of 2 months (59). High doses of corticosteroids were then administered and tapered approximately 3 months after the last plasmapheresis. Four patients achieved com-

plete remission. Two patients experienced a partial remission, and their disease was then controllable with corticosteroids which were being tapered at the time of the report. One patient showed only short-term improvement. Although pulse intravenous cyclophosphamide was the favored immunosuppressant, pulsed corticosteroid and azathioprine resulted in remission in 2 patients.

These studies demonstrate that plasmapheresis immediately followed by immunosuppressive therapy offers a valuable treatment option for patients with PV unresponsive to conventional therapies. Plasmapheresis in combination with corticosteroids, even without additional immunosuppression, has been advocated as an effective option in pregnant patients who experience a severe exacerbation of their disease (60).

Extracorporeal Photopheresis

During extracorporeal photopheresis (ECP), a leucocyte/lymphocyte-enriched cell fraction is separated from the peripheral blood, washed in 8 methoxypsoralen and irradiated with ultraviolet A light. Treated lymphocytes are then reinfused into the patient. ECP is normally performed for 4 hours per day on 2 consecutive days every 4 weeks. The treatment is well tolerated and causes few side effects. The procedure was designed for the management of diseases mediated by malignant lymphocytes, such as cutaneous T cell lymphoma, and for other diseases mediated by aberrant lymphocyte function, e.g., autoimmune diseases. In the treatment of PV it is reserved for patients who fail to improve with conventional treatment modalities. The aim in this context is to inhibit the B-cells that produce pathogenic pemphigus antibodies.

In 1989 Rook et al. (61) treated 4 PV patients with ECP; the patients were concomitantly receiving corticosteroid and immunosuppressive therapy. All patients improved. In 1992 Liang et al. described a patient who had 70% of his skin affected by PV (62). The patient's disease resisted control with high doses of prednisone, even when used in combination with gold, cyclosporine, methotrexate, azathioprine, pulse steroids, and pulse cyclophosphamide. At the time ECP was started, the patient was receiving methotrexate (20 mg weekly), azathioprine (100 mg daily) and prednisone (240 mg daily). After seven cycles of ECP, cessation of new blister formation oc-

curred. Prednisone was tapered and methotrexate was discontinued. Skin lesions healed.

More recently, Wollina et al. (63) reported on the use of ECP as an adjuvant in 7 patients with bullous pemphigoid or pemphigus who failed therapy with immunosuppressive medications. Three patients had PV and all three showed a complete remission of disease during 24, 34, and 10 month follow-up periods. Although these results seem promising, prospective controlled trials are necessary in order to better evaluate the efficacy of ECP.

Intravenous Immunoglobulin

Although intravenous immunoglobulin (IVIG) has been used successfully in the treatment of other autoimmune and inflammatory diseases (64), its use in the treatment of patients with PV is relatively recent. Tappeiner and Steiner (65), the first to report its use in PV in 1989, found no clinical change in 2 patients and progression of disease in a third patient, after receiving one cycle of IVIG therapy.

Subsequent studies analyzing the use of IVIG in PV reported greater success and were recently reviewed by Engineer et al. (66), who summarized the use of IVIG for PV in 8 papers which appeared since the initial report by Tappeiner and Steiner (65). IVIG was effective in 17 of the 18 patients described. It appeared to be effective if administered for 2 or more monthly cycles, each of which consisted of 5 consecutive days of treatment. For optimum results it is recommended that a minimum dosage of 400 mg/kg be administered each day of the cycle.

IVIG has a rapid onset of action and results in improvement within days of its initiation. However, the benefit appears to be short lived and disappears after only a few weeks. IVIG appears most effective when used as an adjunct to conventional therapy, and may be helpful in the treatment of patients unable to tolerate other agents. It is effective as a corticosteroid-sparing agent and achieved this effect in almost all the patients studied. Although its safety is not a significant issue (no side-effects from IVIG therapy were reported during the follow-up periods of the patients studied), its high cost is often a major deterrent to more widespread use. When it is available, it should be tried early in patients with severe PV that is recalcitrant to conventional therapies, or in patients at risk for developing serious side effects from prolonged corticosteroid therapy.

Preliminary Observations — Cigarette Smoking

A case of PV improved by cigarette smoking was recently reported (67). The patient had a 3-year history of PV and was not improving on combination therapy with prednisone, cyclophosphamide and dapsone. He noted that his disease flared coincident with the cessation of cigarette smoking. One week after the patient began smoking cigarettes again (15 cigarettes per day), lesions rapidly started to clear. The dapsone was discontinued. The prednisone and cyclophosphamide were tapered and discontinued over a 2-month period. The lesions were still clear 5 months after he started to smoke again.

An inverse relationship between cigarette smoking and/or nicotine and the activity level of certain diseases has been reported for ulcerative colitis, pyoderma gangrenosum, and aphthous stomatitis (68–70). Several immunomodulatory effects of smoking have been reported (71), although the exact mechanism responsible for these findings is presently unknown. Because the deleterious effects of cigarette smoking are well known and may outweigh the potential “benefits” of such a habit, research leading to more specific therapeutic interventions tailored to the exact mechanism of action may be warranted in the future.

Survey of Mount Sinai Dermatologists Regarding Therapy for Pemphigus Vulgaris

Table 2 is a summary of some treatment preferences of Mount Sinai Dermatology faculty. Of ten physicians who responded to the survey, nine indicated they treat patients with PV. All nine use prednisone or another corticosteroid as the first choice of therapy. Six of nine start therapy with prednisone and another agent such as cyclophosphamide. This survey indicates the preference among Mount Sinai dermatologists for choosing combination therapy as the initial treatment for patients with PV.

Summary and Conclusions

Inconsistencies in the responses to therapy of patients with PV may be explained in part by their heterogeneous autoantibody production in response to epidermal antigens. Patients with PV may display antibodies to the major PV antigen, the cadherin known as desmoglein 3, as expected, as well as to desmoglein 1, in a manner which is not predictable so far.

TABLE 2

A Summary of Therapy Preferences of 10 Mount Sinai Dermatologists for Patients with Pemphigus Vulgaris.

1. Do you treat patients with pemphigus vulgaris? Yes: 9, No: 1.
2. Do you use prednisone or other corticosteroid as your first choice of therapy? Yes: 9, No: 0.
3. Do you start with prednisone and an adjuvant such as cyclophosphamide? Yes: 6, No: 3.
4. What other medications have you used?
 - Gold: 7
 - Imuran: 5
 - Methotrexate: 3
 - Dapsone: 1
 - Tetracycline: 1
 - Nicotinamide: 1
5. How many pemphigus vulgaris patients have you treated in your career so far?
 - 0–15: 6
 - 16–30: 2
 - 31–45: 0
 - 46 or more: 1
6. How many years have you been in practice?
 - 0–15: 3
 - 16–30: 3
 - 31–45: 3

To date, the avidity of antibodies in PV has not been adequately studied. Avidity studies showing different binding energies of these antibodies might help explain why patients with limited disease are sometimes more difficult to bring into good control than patients with widespread disease. Research into and development of chemical molecules that can specifically turn off or down-regulate the pemphigus-specific antibody responses will no doubt offer more promise for future effective therapy in curing this potentially lethal disease.

References

1. Becker BA, Gaspari AA. Pemphigus vulgaris and vegetans. *Dermatol Clin* 1993; 11:429–452.
2. Krasny SA, Beutner EH, Chorzelski TP. Specificity and sensitivity of indirect and direct immunofluorescence findings in the diagnosis of pemphigus. In: Krasney SA, Beutner EH, Chorzelski TP, editors. *Immunopathology of the skin*, 3rd ed. New York: John Wiley; 1987. pp. 207–247.
3. Koch PJ, Mahoney MG, Ishikawa H, et al. Targeted disruption of the pemphigus vulgaris antigen (desmoglein-3) gene in mice causes loss of keratinocyte cell adhesion with a phenotype similar to pemphigus vulgaris. *J Cell Biol* 1997; 137:1091–1102.
4. Savin JA. The events leading to death of patients with pemphigus and pemphigoid. *Br J Dermatol* 1979; 101:521–534.
5. Dumas V, Roujeau JC, Wolkenstein P, et al. The treatment of mild pemphigus vulgaris and pemphigus foliaceus with a topical corticosteroid. *Br J Dermatol* 1999; 140:1127–1129.
6. Bystryń J-C, Steinman NM. The adjuvant therapy of pemphigus. *Arch Dermatol* 1996; 132:203–212.
7. Ouahes N, Qureshi TA, Ahmed AR. Infertility in women with pemphigus vulgaris and other autoimmune diseases. *J Am Acad Dermatol* 1997; 36:383–387.
8. Rosenberg FR, Sanders S, Nelson CT. Pemphigus. A 20-year review of 107 patients treated with corticosteroids. *Arch Dermatol* 1976; 112:962–970.
9. Lever WF, Schaumberg-Lever G. Treatment of pemphigus vulgaris: Results obtained in 84 patients between 1961 and 1982. *Arch Dermatol* 1984; 120:44–47.
10. Lever WF, White H. Treatment of pemphigus with corticosteroids: Results obtained in 46 patients over a period of 11 years. *Arch Dermatol* 1963; 87:52–66.
11. Bystryń J-C. Adjuvant therapy of pemphigus. *Arch Dermatol* 1984; 120:941–951.
12. Huilgol SC, Black MM. Management of immunobullous disorders. II. Pemphigus. *Clin Exp Dermatol* 1995; 20:283–293.
13. Chrousos GA, Kattah JC, Beck RW, Cleary PA. Side effects of glucocorticoid treatment: Experience of the optic neuritis treatment trial. *JAMA* 1993; 269:2110–2112.
14. Werth VP. Treatment of pemphigus vulgaris with brief, high-dose intravenous glucocorticoids. *Arch Dermatol* 1996; 132:1435–1439.
15. Roenigk HH, Deodhar S. Pemphigus treatment with azathioprine. Clinical and immunologic correlation. *Arch Dermatol* 1973; 107:353–357.
16. Aberer W, Wolff-Schreiner EC, Stingl G, Wolff K. Azathioprine in the treatment of pemphigus vulgaris. *J Am Acad Dermatol* 1987; 16:527–533.
17. Reohr PB, Manglabruks A, Janiga AM, et al. Pemphigus vulgaris in siblings: HLA-DR4 and HLA-DQw3 and susceptibility to pemphigus. *J Am Acad Dermatol* 1992; 27:189–193.
18. Ahmed AR, Hombal SM. Cyclophosphamide (Cytosan). A review on relevant pharmacology and clinical uses. *J Am Acad Dermatol* 1984; 11:1115–1126.
19. Pasricha JS, Sood VD, Minocha Y. Treatment of pemphigus with cyclophosphamide. *Br J Dermatol* 1975; 93:573–576.
20. Fellner MJ, Katz JM, McCabe JB. Successful use of cyclophosphamide and prednisone for initial treatment of pemphigus vulgaris. *Arch Dermatol* 1978; 114:889–894.
21. Boumpas DT, Austin HA, Fessler BJ, et al. Systemic lupus erythematosus: Emerging concepts, 1: Renal, neuropsychiatric, cardiovascular, pulmonary, and hematologic disease. *Ann Intern Med* 1995; 122:940–950.
22. Pasricha J, Thanzama J, Khan U. Intermittent high-dose dexamethasone cyclophosphamide therapy for pemphigus. *Br J Dermatol* 1988; 119:73–77.
23. Pasricha J, Das S. Curative effect of dexamethasone-cyclophosphamide pulse therapy for the treatment of pemphigus vulgaris. *Int J Dermatol* 1992; 31:875–877.
24. Fleischli ME, Valek RH, Pandya AG. Pulse intravenous cyclophosphamide therapy in pemphigus. *Arch Dermatol* 1999; 135:57–61.
25. Hayag MV, Cohen JA, Kerdel FA. Immunoablative high-dose cyclophosphamide without stem cell rescue in a patient with pemphigus vulgaris. *J Am Acad Dermatol* 2000; 43:1065–1069.
26. Groisser DS, Griffiths CE, Ellis CN, Voorhees JJ. A review and update of the clinical uses of cyclosporine in dermatology. *Dermatol Clin* 1991; 9:805–817.

27. Barthelemy H, Frappaz A, Cambazard F, et al. Treatment of nine cases of pemphigus vulgaris with cyclosporine. *J Am Acad Dermatol* 1988; 18:1262–1266.
28. Lapidoth M, David M, Ben Amitai D, et al. The efficacy of combined treatment with prednisone and cyclosporine in patients with pemphigus: Preliminary study. *J Am Acad Dermatol* 1994; 30:752–757.
29. Alijotas J, Pedragosa R, Bosch J, Vilardell M. Prolonged remission after cyclosporine therapy in pemphigus vulgaris: Report of two young siblings. *J Am Acad Dermatol* 1990; 23:701–703.
30. Mobini N, Padilla T, Ahmed AR. Long-term remission in selected patients with pemphigus vulgaris treated with cyclosporine. *J Am Acad Dermatol* 1997; 36:264–266.
31. Fulton B, Markham A. Mycophenolate mofetil. *Drugs* 1996; 51:278–298.
32. Silverman Kitchin JE, Pomeranz MK, Pak G, et al. Rediscovering mycophenolic acid: A review of its mechanism, side effects, and potential uses. *J Am Acad Dermatol* 1997; 37:445–449.
33. Haufs MG, Beissert S, Grabbe S, et al. Psoriasis vulgaris treated successfully with mycophenolate mofetil. *Br J Dermatol* 1998; 138:179–181.
34. Geilen CC, Tebbe B, Bartels CG, et al. Successful treatment of erythrodermic psoriasis with mycophenolate mofetil. *Br J Dermatol* 1998; 138:1091–1104.
35. Enk AH, Knop J. Treatment of relapsing idiopathic nodular panniculitis (Pfeifer-Weber-Christian disease) with mycophenolate mofetil. *J Am Acad Dermatol* 1998; 39:508–509.
36. Bohm M, Beissert S, Schwartz T, et al. Bullous pemphigoid treated with mycophenolate mofetil [letter]. *Lancet* 1997; 349:541.
37. Nousari HC, Griffin WA, Anhalt GJ. Successful therapy for bullous pemphigoid with mycophenolate mofetil. *J Am Acad Dermatol* 1998; 39:497–498.
38. Katz KH, Marks JG, Helm KF. Pemphigus foliaceus successfully treated with mycophenolate mofetil as a steroid-sparing agent. *J Am Acad Dermatol* 2000; 42:514–515.
39. Enk AH, Knop J. Treatment of pemphigus vulgaris with mycophenolate mofetil [letter]. *Lancet* 1997; 349:541.
40. Enk AH, Knop J. Mycophenolate is effective in the treatment of pemphigus vulgaris. *Arch Dermatol* 1999; 135:54–56.
41. Nousari HC, Anhalt GJ. The role of mycophenolate mofetil in the management of pemphigus [letter]. *Arch Dermatol* 1999; 135:853–854.
42. Bredlich R-O, Grundmann-Kollman M, Behrens S, et al. Mycophenolate mofetil monotherapy for pemphigus vulgaris [letter]. *Br J Dermatol* 1999; 141:934.
43. Grundmann-Kollman M, Kaskel P, Leiter U, et al. Treatment of pemphigus vulgaris and bullous pemphigoid with mycophenolate mofetil monotherapy. *Arch Dermatol* 1999; 135:724–725.
44. Shah N, Green AR, Elgart GW, Kerdel F. The use of chlorambucil with prednisone in the treatment of pemphigus. *J Am Acad Dermatol* 2000; 42:85–88.
45. Smith TJ, Bystry J-C. Methotrexate as an adjuvant treatment for pemphigus vulgaris. *Arch Dermatol* 1999; 135:1275–1276.
46. Penneys NS, Eaglstein WH, Indgin S, Frost P. Gold sodium thiomalate treatment of pemphigus. *Arch Dermatol* 1973; 108:56–60.
47. Thomas I. Gold therapy and its indications in dermatology. *J Am Acad Dermatol* 1987; 16:845–854.
48. Zvaifler NJ. Gold and antimalarial therapy. In: McCarty DJ, editor. *Arthritis and allied conditions: A textbook of rheumatology*. 9th ed. Philadelphia (PA): Lea & Febiger; 1979. pp. 355–364.
49. Rotstein H. Gold therapy for pemphigus vulgaris. *Australas J Dermatol* 1977; 18:119–122.
50. Penneys NS, Eaglstein WH, Frost P. Management of pemphigus with gold compounds. *Arch Dermatol* 1976; 112:185–187.
51. Poulin Y, Perry HO, Muller SA. Pemphigus vulgaris: Results of treatment with gold as a steroid-sparing agent in a series of thirteen patients. *J Am Acad Dermatol* 1984; 11:851–857.
52. Pandya AG, Dyke C. Treatment of pemphigus with gold. *Arch Dermatol* 1998; 134:1104–1107.
53. Basset N, Guillot B, Meynadier J, Guilhou JJ. Dapsone as initial treatment in superficial pemphigus. *Arch Dermatol* 1987; 123:783–785.
54. Jablonska S, Chorzelski T. When and how to use sulfones in bullous diseases. *Int J Dermatol* 1981; 20:103–105.
55. Alpsoy E, Yilmaz E, Basaran E, et al. Is the combination of tetracycline and nicotinamide therapy alone effective in pemphigus? *Arch Dermatol* 1995; 131:1339–1340.
56. Chaffins ML, Collison D, Fivenson DP. Treatment of pemphigus and linear IgA dermatosis with nicotinamide and tetracycline: A review of 13 cases. *J Am Acad Dermatol* 1993; 28:998–1000.
57. Calebotta A, Saenz AM, Gonzalez F, et al. Pemphigus vulgaris: Benefits of tetracycline as adjuvant therapy in a series of thirteen patients. *Int J Dermatol* 1999; 38:217–221.
58. Tan-Lim R, Bystry J-C. Effect of plasmapheresis therapy on circulating levels of pemphigus antibodies. *J Am Acad Dermatol* 1990; 22:35–39.
59. Turner MS, Sutton D, Sauder DN. The use of plasmapheresis and immunosuppression in the treatment of pemphigus vulgaris. *J Am Acad Dermatol* 2000; 43:1058–1064.
60. Piontek J-O, Borberg H, Sollberg S, et al. Severe exacerbation of pemphigus vulgaris in pregnancy: Successful treatment with plasma exchange [letter]. *Br J Dermatol* 2000; 143:455–456.
61. Rook AH, Jegasothy BV, Heald P, et al. Extracorporeal phototherapy for drug-resistant pemphigus vulgaris. *Ann Intern Med* 1990; 112:303–305.
62. Liang G, Nahass G, Kerdel A. Pemphigus vulgaris treated with photopheresis. *J Am Acad Dermatol* 1992; 26:779–780.
63. Wollina U, Lange D, Looks A. Short-time extracorporeal phototherapy in the treatment of drug-resistant autoimmune bullous disease. *Dermatology* 1999; 198:140–144.
64. Jolles S, Hughes J, Whittaker S. Dermatological uses of high-dose intravenous immunoglobulin. *Arch Dermatol* 1998; 134:80–86.
65. Tappeiner G, Steiner A. High-dosage intravenous gammaglobulin: Therapeutic failure in pemphigus and pemphigoid. *J Am Acad Dermatol* 1989; 20:684–685.
66. Engineer L, Bhol KC, Ahmed AR. Analysis of current data on the use of intravenous immunoglobulins in the management of pemphigus vulgaris. *J Am Acad Dermatol* 2000; 43:1049–1057.
67. Mehta JN, Martin AG. A case of pemphigus vulgaris improved by cigarette smoking. *Arch Dermatol* 2000; 136:15–17.
68. Pullan RD, Rhodes J, Gnes S, et al. Transdermal nicotine for active ulcerative colitis. *N Engl J Med* 1994; 330:811–815.
69. Wolf R, Ruocco V. Nicotine for pyoderma gangrenosum. *Arch Dermatol* 1998; 134:1071–1072.
70. Axell T, Henricsson V. Association between recurrent aphthous ulcers and tobacco habits. *Scand J Dent Res* 1985; 93:239–242.
71. Meliska CJ, Stunkard ME, Gilbert DG, et al. Immune function in cigarette smokers who quit smoking for 31 days. *J Allergy Clin Immunol* 1995; 95:901–910.