Epidermolysis bullosa acquisita (EBA) is a rare, chronic, subepidermal, mucocutaneous blistering disease characterized by skin fragility and spontaneous as well as trauma-induced blisters that heal with scar formation and milia. Treatment is often frustrating because conventional therapy with corticosteroids and immunosuppressive agents frequently does not result in significant clinical improvement. We review the conventional treatment of EBA and critically analyze the literature on various adjuvants and therapeutic modalities that have recently been used. These include cyclosporine, colchicine, plasmapheresis, extracorporeal photochemotherapy, and intravenous gammaglobulins. Although the data are preliminary, they suggest that intravenous immunoglobulins may be a promising treatment modality for resistant, nonresponsive, or refractory EBA. The use of intravenous immunoglobulins results in significant improvement of skin and mucosal lesions, and it is quite safe, with minimal side effects. (J Am Acad Dermatol 2001;44:818-28.)
reveals subepidermal blister formation, with a variable inflammatory infiltrate within the dermis. Direct immunofluorescence of perilesional skin reveals linear deposition of IgG at the dermoepidermal junction. Indirect immunofluorescence (IIF) of patient’s serum may reveal the presence of circulating anti-BMZ antibodies. Their staining pattern may be indistinguishable from that seen in other subepidermal blistering diseases such as bullous pemphigoid.

Immunoelectron microscopy reveals the immune deposits in patients with EBA to be located beneath the lamina densa of the cutaneous BMZ. IIF demonstrating linear deposits of IgG exclusively on the dermal side of the artificial dermoepidermal separation is considered to be diagnostic of EBA. However, these studies are not always specific; other blistering diseases such as bullous SLE, cicatricial pemphigoid, and linear IgA bullous dermatosis may also produce similar findings. A more accurate diagnosis of EBA can be made by means of a Western immunoblotting procedure. This technique detects circulating autoantibodies in patients’ sera against a 290-kd protein that represents the alpha chain of type VII collagen. A second, 145-kd epitope may also be identified in the sera of some patients with EBA. This 145-kd band represents a globular domain of the alpha chain.

EBA is a frustrating and frequently difficult disease to treat. Severely affected patients tend to experience repeated cycles of relapses with enormous difficulty in healing. Because lesions are often located on the hands and feet, patients experience significant pain and restriction of activities of daily living. Walking becomes difficult, and patients are often unable to work. Several authors advocate use of high doses of systemic corticosteroids either alone or in combination with immunosuppressive agents such as azathioprine, methotrexate, and cyclophosphamide as adjuvants, as in the case of other mucocutaneous autoimmune diseases. Such therapies are nonspecific in nature and in pharmacologic basis. Dapsone, an anti-inflammatory drug, has also been used as an adjuvant agent. Adjuvants are used both for their corticosteroid-sparing effect and in an attempt to induce remission in patients whose disease is refractory to corticosteroids alone. No controlled studies have been performed to evaluate efficacy of therapy with steroids accompanied by an immunosuppressive adjuvant versus treatment with corticosteroids alone. Most patients with EBA, particularly those with the classic, noninflammatory, mechanobullous form of the disease, are refractory to such conventional or usual treatment with corticosteroids and/or adjuvants. Even when remission is induced, it is usually incomplete and of short duration. Relapse occurs while patients are still receiving therapy. In addition, the side effects of long-term use of high-dose corticosteroid therapy are severe, hazardous, crippling, and potentially fatal. These include hypertension, diabetes/glucose tolerance, aseptic necrosis of bone, osteoporosis, psychiatric disorders, immune suppression, recurrent systemic infections, poor wound healing, adrenal suppression, and peptic ulcer disease, among others. For these reasons, there is a need for the identification of safe and effective alternatives for the treatment of EBA.

Whatever the systemic agents used, nonspecific, supportive measures are extremely important in the care of patients with EBA. Use of proper emollients to prevent fissuring from xerosis and of topical or systemic antibiotics to control secondary infection of the chronic lesions is vital. Patients should be taught strategies for proper wound care and specifically instructed to avoid trauma.

Recently, several new therapeutic agents and modalities have been reported and show promise in the treatment of patients with EBA. These include cyclosporine, colchicine, plasmapheresis, extracorporeal photochemotherapy (ECP), and in particular, intravenous immunoglobulin (IVIg).

**MATERIAL AND METHODS**

The peer-reviewed, English-language literature cited on MEDLINE between 1970 and 2000 was retrospectively reviewed for reports on the use of the following 5 agents or modalities in the treatment of EBA: cyclosporine, colchicine, plasmapheresis, ECP, and IVIg. Information on patients’ sex, age at presentation, extent, severity, and total duration of disease, previous therapies, dose or method of use of the drug or modality being studied, and objective response to therapy was collected when available. The data provided in these reports were analyzed to determine whether trends were emerging and whether any preliminary conclusions could be made that would facilitate providing guidelines for therapy of EBA.

**RESULTS**

**Cyclosporine**

Analysis of the data is presented in Table I. The first use of cyclosporine, a potent T-cell suppressor, in EBA was reported in 1987. A total of 9 reports on 9 patients exist in the literature. One patient initially described by Connolly and Sander was subsequently re-treated with cyclosporine by another group 3 years later and presented in a different report.
Sex and age distribution. Five of the 9 patients were male, and 4 were female. The average age of the patients was 50 years, with a range of 28 to 67 years.

Duration/severity. Duration of disease ranged from 6 months to 11 years. On the basis of clinical history, duration, course of disease, and therapies used, it is apparent that these patients had severe and recalcitrant disease that was resistant to previous therapy with corticosteroids and a variety of adjuvants and immunosuppressive agents.

Previous therapy. Eight of the 9 patients had received previous therapy with oral corticosteroids at varying doses. Most of these patients were also treated with adjuvant agents including methotrexate, azathioprine, gold, dapsone, and cyclophosphamide. Despite the use of these agents, signifi-
cant clinical remission and corticosteroid-sparing effect were not observed. In the last patient, this information was not provided, but it appears likely that this patient also had failed previous therapy, because duration of disease was 7 years at the time of initiation of cyclosporine therapy.

**Use of cyclosporine.** Daily doses in the range of 5 to 9 mg/kg were used, with a mean daily dose of 7 mg/kg. Duration of treatment ranged from 1 to 12 months. In 4 of the patients, cyclosporine was used alone, without any other concomitant systemic therapy. In the rest of the patients, it was given along with oral corticosteroids, typically prednisone at a daily dose ranging from 30 to 100 mg/day (mean, 48 mg/day).

**Response to cyclosporine.** All patients experienced significant clinical improvement after cyclo-

<table>
<thead>
<tr>
<th>Duration of treatment</th>
<th>Side effects</th>
<th>Response to therapy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>Possible pancreatitis</td>
<td>Marked decrease in blister formation. Prednisone tapered to 60 mg/d.</td>
<td>CS discontinued because of side effects. No relapse 2 mo after discontinuing CS. Total follow-up of 3 mo since initiation of CS.</td>
</tr>
<tr>
<td>2.5 mo</td>
<td>Urticaria, diarrhea, ascites, elevated serum creatinine</td>
<td>Decrease in blister formation.</td>
<td>Partial remission maintained 2 mo after discontinuing CS because of side effects. Total follow-up of 4.5 mo since initiation of CS.</td>
</tr>
<tr>
<td>3 mo</td>
<td>None</td>
<td>Dramatic and rapid healing of lesions; marked decrease in new lesion formation. Prednisone tapered to 7.5 mg every other day.</td>
<td>No relapse in total follow-up period of 3 mo since initiation of IVlg.</td>
</tr>
<tr>
<td>Not stated</td>
<td>None</td>
<td>Dramatic reduction in blister formation. Prednisolone tapered to 15 mg/d.</td>
<td>No relapse since initiation of CS (follow-up period not stated).</td>
</tr>
<tr>
<td>12 mo</td>
<td>None</td>
<td>Improvement noted by end of 2nd mo. Complete cessation of blistering after 6 mo. Prednisone tapered to 10 mg/d.</td>
<td>In remission 18 mo after discontinuation of CS. Total follow-up period of 30 mo since initiation of CS.</td>
</tr>
<tr>
<td>2 mo</td>
<td>Same as above.</td>
<td>Moderate decrease in new blister formation by wk 2-4.</td>
<td>Total follow-up period 2 mo after initiation of treatment.</td>
</tr>
<tr>
<td>4 mo</td>
<td>Clear-cell carcinoma of lung?</td>
<td>Marked reduction in blister formation. Prednisone tapered and discontinued.</td>
<td>In remission for 8 mo follow-up after initiation of CS. Disease recurred at this time.</td>
</tr>
<tr>
<td>Approximately 4 mo total. One mo initial therapy, wit 2 mo cessation followed by 3 mo further treatment.</td>
<td>None</td>
<td>Dramatic improvement few weeks after initiation of therapy.</td>
<td>Total follow-up period of 6 mo since initiation of CS therapy. In remission for 3 continuous mo.</td>
</tr>
<tr>
<td>12 mo</td>
<td>Renal impairment on higher dose; reversible on dose reduction.</td>
<td>Marked reduction in blister formation within 3 wk of initiation of therapy.</td>
<td>In remission for total follow-up period of 12 mo since initiation of CS.</td>
</tr>
</tbody>
</table>
sporine therapy. There was a marked decrease in blister formation with healing of pre-existing blisters. In addition, there was a significant corticosteroid-sparing effect. Oral corticosteroid dose was tapered to a mean of 17 mg/day, with a range of 0 to 60 mg/day.

Follow-up period. The follow-up period ranged from 3 to 30 months after initiation of cyclosporine therapy.

Side effects. In 2 cases, cyclosporine had to be discontinued because of intolerable side effects including possible pancreatitis, urticaria, diarrhea, ascites, and elevated serum creatinine. One patient was diagnosed with clear cell carcinoma of the lung after treatment with cyclosporine. Two other patients had mild side effects that disappeared during the course of therapy or upon reducing the dose of cyclosporine. The remaining 5 patients experienced no significant side effects from their cyclosporine therapy.

Colchicine

Analysis of the literature is presented in Table II. The successful use of colchicine in the treatment of refractory EBA was first reported in the French-language literature in 1989. There have been 2 subsequent reports in the English-language literature of its use in EBA. A total of 6 patients have been described.

Sex and age distribution. Three of the 6 patients were male, and 3 were female. The average age of the patients was 67 years, with a range of 35 to 75 years.

Severity/extent/duration. On the basis of the therapy used and the duration and course of disease, it is apparent that these patients had severe and extensive disease that was refractory to conventional therapy. Duration of disease ranged from 2 months to 6 years.

Previous therapy. Four of the patients had received previous therapy with oral corticosteroids at varying doses. Two of these were also treated with adjuvant agents, including dapsone and azathioprine. Despite use of these agents, significant clinical remission was not observed. Only 1 patient had received no other therapy before trial of colchicine. In the sixth case, this information was not provided.
Use of colchicine. The drug was administered at a daily dose ranging from 1 to 2 mg. In 4 of the 6 cases, it was given as monotherapy. In the remaining 2 cases, oral prednisone was given concomitantly. Azathioprine and sulfapyridine were used as additional adjuvants in one case.

Response to colchicine. All 6 patients demonstrated rapid and marked clinical improvement in response to colchicine. Healing of old lesions and significant reduction in rate of new blister formation were observed. In several cases, dramatic improvement was noted as early as 2 weeks after initiation of therapy. A corticosteroid-sparing effect was observed in both cases in which they were used concomitantly with colchicine. In both cases, it was possible to taper and eventually discontinue the corticosteroids.

Follow-up period. The follow-up period ranged from 12 to 48 months after initiation of colchicine therapy.

Side effects. In 5 of the 6 patients, there were no significant side effects as a result of colchicine therapy. In the sixth case, the patient had diarrhea when attempts were made to increase the dose beyond 1.2 mg/day.

Plasmapheresis

There is only one report in the literature of plasmapheresis as an effective adjunct to conventional treatments for patients with EBA. In 1986, Furue et al.²⁷ described its use in a 60-year-old male EBA patient with a 4-year history of severe disease refractory to therapy with steroids and a variety of adjuncts including azathioprine, dapsone, intramuscular gold, and vitamin E. The patient was unable to tolerate high-dose cyclophosphamide. Thirteen plasma exchanges were performed over 4 months. The patient continued to receive oral betamethasone at 3 mg/day during this period. After the sixth plasma exchange, 50 mg/day of cyclophosphamide was added. This regimen of plasma exchange in combination with oral corticosteroids and low-dose cyclophosphamide resulted in marked clinical improvement and a sharp decrease in anti-BMZ antibody titers from 1:640 to 1:40. Unfortunately, this
patient died from infection caused by severe iatrogenic immunosuppression.

**Extracorporeal photochemotherapy**

A total of 4 patients have been described in 2 reports. Two were male, and 2 were female, with an average age of 55 years (range, 31-71 years). All suffered from severe, debilitating disease refractory to therapy with oral corticosteroids and adjuvants including methotrexate, azathioprine, colchicine, dapsone, cyclosporine, and plasmapheresis. Three patients who were prospectively studied by Gordon, Chan, and Woodley received 6 to 7 cycles each consisting of 2 consecutive days of treatment at regular 3-week intervals. One of these patients was also treated with cyclosporine 3 mg/kg daily for 4 weeks after completing the photopheresis treatment. The fourth patient, described by Miller et al., received a total of 3 cycles each consisting of 2 consecutive days of treatment over a 5-week period. Three of the 4 patients showed significant clinical improvement. In two cases, healing of old lesions with a reduction in the rate of new blister formation was demonstrated. In these patients, improvement continued during the 6-month follow-up period after completion of the last cycle. The third patient experienced rapid and dramatic reduction in blister formation after the first treatment cycle and remained in remission for 2 years after the last ECP treatment with no new blister formation. Only one patient experienced no clinical improvement either during or after the trial. There was a fall in circulating levels of anti-BMZ antibodies as measured by IIF in all 4 patients. Antibody titers fell to undetectable levels in all patients either during the course of the therapy or several months after administration of the last cycle. There were no significant side effects to ECP necessitating discontinuation of therapy. Most patients experienced some degree of nausea, requiring antiemetic medication in some cases.
### IVIg

Analysis of the literature is presented in Table III. A total of 7 patients with EBA treated with IVIg have been described.30-36

**Sex and age distribution.** All patients described in these 7 studies were male. The average age of the patients was 36 years, with a range of 16 to 60 years.

**Duration/severity/extent.** Duration of disease ranged from 6 months to 9 years. The exact severity and extent of disease could not be accurately quantified on a described scale because different authors were involved in the 7 reports. However, on the basis of clinical history, duration, course of disease, and therapy used, it appears evident that these patients had severe, widespread, recalcitrant EBA that had failed to respond to previous therapy with steroids and numerous adjuvant agents.

**Previous therapy.** Previous therapies had been used in all except one patient. Five of the remaining 6 patients had all received systemic corticosteroid therapy at varying doses and durations, which did not result in significant sustained clinical remission. In addition, adjuvant drugs such as azathioprine, dapsone, cyclosporine, and methotrexate were used in all 6 patients without satisfactory clinical remission or steroid-sparing effect. Thus most of the patients described may be considered to have failed adequate trials of conventional therapy.

**Use of IVIg.** High-dose IVIg, at a typical dose of 400 mg/kg daily given over 5 days at 4- to 6-week intervals, was used in 6 of the 7 patients. In the remaining patient, low-dose IVIg (40 mg/kg daily over 5 days at 3- to 4-week intervals) was used. IVIg was given as monotherapy in 3 cases. In one case, in which disease was triggered by UV radiation, it was given with systemic (beta-carotene) and external (topical sun-blocker) UV protection. In the remaining cases, it was administered with oral corticosteroids alone or with other adjuvant agents such as cyclosporine and azathioprine.

<table>
<thead>
<tr>
<th>Concomitant therapy</th>
<th>Response to IVIg</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine, oral prednisolone continued.</td>
<td>Marked reduction in new blister formation; healing of pre-existing blisters. ↓ in prednisolone and cyclosporine doses.</td>
<td>Total duration of follow-up not stated.</td>
</tr>
<tr>
<td>None</td>
<td>No objective clinical improvement.</td>
<td>Total follow-up period of 6 mo since initiation of IVIg therapy.</td>
</tr>
<tr>
<td>Oral prednisolone, dapsone, azathioprine, colchicine continued.</td>
<td>Marked reduction in new blister formation after 3 cycles; enhanced healing of old lesions. Tapering and eventual discontinuation of dapsone facilitated.</td>
<td>In clinical remission for 5 mo. Total follow-up period of 9 mo after initiation of IVIg.</td>
</tr>
<tr>
<td>Low-dose prednisolone.</td>
<td>Cessation of new blister formation and healing of pre-existing blisters after 4 mo. Prednisolone discontinued after 1 y.</td>
<td>Total follow-up period of &gt;16 mo since initiation of IVIg. Disease free for 10 continuous mo.</td>
</tr>
<tr>
<td>None</td>
<td>Slow but steady improvement in skin condition. Occasional trauma-induced blistering and continued skin fragility.</td>
<td>Total follow-up period of &gt;2 y since initiation of IVIg therapy, with no significant relapse in this period.</td>
</tr>
<tr>
<td>None</td>
<td>Marked improvement. Reduced blistering, with partial relapse between courses.</td>
<td>4 mo</td>
</tr>
<tr>
<td>None</td>
<td>See Harman et al, 1998.</td>
<td>&gt;2 y. Maintenance IVIg q 3 mo.</td>
</tr>
<tr>
<td>Systemic and external UV protection.</td>
<td>Cessation of blister formation with marked healing of pre-existing lesions.</td>
<td>9 mo</td>
</tr>
</tbody>
</table>
Response to IVIg. Six of the 7 patients, including the one on low-dose IVIg and 2 of the patients on IVIg monotherapy, experienced marked improvement in their skin condition. There was a sharp decrease in new blister formation, accompanied by healing of pre-existing lesions. Tapering of adjuvants was possible in all cases in which they were used. Only one patient, who received IVIg as monotherapy, showed no response to therapy.

Follow-up period. The follow-up period ranged from 3 months to more than 2 years after initiation of IVIg therapy. Although the follow-up is variable in both detail provided and duration, and the data have been collected from multiple studies, the periods were adequate for drawing certain preliminary conclusions.

Side effects. No significant side effects were observed in any of the 7 patients for the duration of follow-up. Thus IVIg therapy appears to be relatively safe.

DISCUSSION

Although the reports in this analysis are few and contain preliminary data, they do reveal some emerging trends and provide preliminary but interesting conclusions. The therapies discussed appear to be promising in the treatment of EBA.

Cyclosporine, a potent immunosuppressive agent primarily used in organ transplantation, demonstrated significant beneficial response in some patients with EBA. It appears that in some cases, remission persists even after the discontinuation of cyclosporine therapy. The mechanism of action of cyclosporine in EBA is unknown. A reduction in the titer of circulating anti-BMZ antibodies paralleling clinical improvement has been reported in some cases.\(^{15,17,23}\) It is thus possible that cyclosporine may exert its therapeutic effects via inhibition of T cells involved in stimulation of autoantibody production by B cells.

However, cyclosporine has serious side effects. These are potentiated by multiple drug interactions. The risks of its use must therefore be carefully weighed against any potential benefits. Nephrotoxicity is the most severe potential complication. Irreversible interstitial fibrosis of the kidney may occur with long-term use.\(^ {27}\) Other side effects such as hypertension, hypertrichosis, hepatotoxicity, paresthesia, and immunosuppression can occur. Cyclosporine has also been associated with the occurrence of lymphoproliferative malignancies\(^ {38}\) and clear-cell lung cancer.\(^ {21}\) In many cases in which cyclosporine has proved successful in ameliorating the disease, it had to be discontinued because of its side effects. Not all patients with EBA respond to cyclosporine. There are no known clinical or pathologic features that distinguish responders from nonresponders. It is thus considered to be a drug of last resort used only in patients refractory to other treatments and whose daily activities are significantly impaired by the disease.

Colchicine has been effective in few patients with EBA. It has a low incidence of serious side effects. It can commonly cause nausea, vomiting, diarrhea, and abdominal pain, and rarely cytopenia, alopecia, and rash.\(^ {25}\) The specific mechanism of action of colchicine in EBA is not known. However, the drug is known to bind to microtubular proteins, thereby interfering with numerous cellular functions including polymorphonuclear leukocyte chemotaxis and mitosis\(^ {39}\) and inhibition of leukocyte function by enhancing release of prostaglandin E.\(^ {40}\) This may account for its efficacy in EBA patients. The limited number of case reports makes it difficult to evaluate its efficacy. Because long-term follow-up was not provided, it is unclear whether colchicine induced a prolonged clinical remission or whether patients subsequently became nonresponsive and the drug had to be discontinued or an additional drug was added.

Although there are several reports on the use of plasmapheresis in the therapy of other autoimmune bullous diseases such as pemphigus vulgaris, this modality has rarely been used to treat EBA.\(^ {41,42}\) In one case it resulted in a marked decrease of anti-BMZ antibody titers. It may be a useful adjunct to concomitant systemic therapy.

ECP is a novel immunomodulatory technique first used in the treatment of cutaneous T-cell lymphoma.\(^ {45}\) One patient with pemphigus vulgaris has been reported to respond to ECP.\(^ {44}\) This technique may be useful in patients with refractory EBA. The mechanism of action of ECP in immune-mediated diseases is unclear. However, the decline in anti-BMZ antibodies suggests that the T-cell–directed B cell response to type VII collagen may be reduced by it. Selective activation of 8-methoxypsoralen in irradiated leukocytes is believed to result in damage to pathogenic T cells by cross-linking nuclear and cell membrane molecules.\(^ {28}\)

ECP has not been associated with the significant immune suppression that accompanies many other therapies used in the treatment of EBA. It is unclear at this time whether it is needed for only a limited time, or whether it is required for several years or lifelong to maintain a remission. It is also unclear whether efficacy would be the same or would decline with protracted use.

The preliminary data contained in the 7 reports on the use of IVIg in EBA suggest that IVIg may be of tremendous benefit in the therapy of EBA. Its benefit may be maximal in patients with longstanding, severe disease that is unresponsive to conventional therapy with systemic corticosteroids and/or adju-
vant agents. It is a relatively safe drug and appears to be most effective when given in conjunction with other drugs. However, clinical improvement was also seen in 2 of the 3 patients receiving IVIg as monotherapy. A corticosteroid-sparing effect was seen in 2 of the 3 patients. Complete discontinuation of systemic corticosteroid therapy was facilitated in one case. The high cost of IVIg therapy is a major factor limiting its use. However, the medical, social, and opportunity costs arising from complications of long-term corticosteroid therapy have not been taken into account.

On the basis of the analysis of available literature, certain preliminary conclusions can be drawn. The conventional therapy using high-dose, long-term, systemic corticosteroid therapy with immunosuppressive agents is unwarranted and very unlikely to produce a prolonged clinical remission. On the contrary, it is likely to produce significant and catastrophic side effects. In patients with very limited or mild disease a trial of colchicine for 4 to 6 months to determine clinical benefit may be useful. If no significant improvement is seen, colchicine should be abandoned. Use of cyclosporine should be limited to patients with few or no concurrent medical problems and no evidence of renal disease. If cyclosporine induces a clinical remission, its further use requires careful monitoring and realization that silent renal disease may occur. Its long-term use should be discouraged. ECP is an invasive technique, and concerns for serious infection and possible long-term side effects presently make it an undesirable treatment option. Although its ability to control the disease is evident, its potential to maintain the remission is yet to be conclusively demonstrated. In patients with widespread disease, especially with mucosal involvement, it may be the agent of choice. Evidence to support such a recommendation comes from recent studies that demonstrate its long-term benefit in patients with mucous membrane pemphigoid (OCP). If it is truly capable of not only inducing but maintaining a satisfactory clinical remission, then the cost could be outweighed by its long-term benefit.

The most significant observation this data analysis provides is that it is necessary to create an EBA study group in which multiple investigators conduct controlled studies to determine the benefit of various therapeutic options using defined criteria for inclusion, diagnosis, response, and outcome. Because EBA is a rare disease, in the absence of such a study group it will not be possible to arrive at reasonable and accurate treatment algorithms, to develop strategies for management of EBA, or to assess the capabilities of present or future drugs to produce effective clinical control of EBA.

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