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Treatment of Subepidermal Immunobullous Diseases

FENELLA WOJNAROWSKA, DM
GUDULA KIRTSCHIG, MD
NONHLANHLA KHUMALO, MD

The subepidermal autoimmune bullous diseases are, with the exception of dermatitis herpetiformis, characterized by autoantibodies directed against components of the hemidesmosomal adhesion complex whose function is adhesion of stratified squamous epithelium to dermis or mesenchyme. The mechanisms by which the antibody-antigen interaction results in blistering is still being elucidated: however, the evidence is accumulating that the autoantibodies are pathogenic.

The treatments used have different mechanisms. Some are aimed at suppression of the inflammatory process, by the use of drugs such as corticosteroids (local and topical), dapsone, and sulfonamides, anti-inflammatory antibiotics, and other anti-inflammatory drugs. Other treatments are aimed at suppression of production of the pathogenic antibodies by the use of immunosuppressive drugs e.g., corticosteroids, azathioprine, ciclosporin, cyclophosphamide, methotrexate, and other drugs. Plasmapheresis/plasma exchange is used for removal of the pathogenic antibodies and inflammatory mediators. Immune modifying treatments include intravenous immunoglobulins and extracorporeal photochemotherapy. Many of these treatments are common to several diseases. Dermatitis herpetiformis is the only disease with a specific treatment, namely a gluten free diet that by removing gluten reverses the underlying gluten sensitive enteropathy and in time results in remission of the skin disease.

The aim of treatment is to suppress disease activity with the minimum dose of drugs necessary. Bullous disease patients are often elderly, commonly on many drugs, and very susceptible to adverse drug reactions and side effects, some of which are life threatening. During prolonged treatment, it is advisable to aim for the presence of a blister once every few weeks. The treatment should be reduced whenever the disease has been well controlled for a month or more. In this way it is possible to ensure that the patient is not being over treated.

From the Department of Dermatology, Oxford Radcliffe Hospital, Oxford, England, United Kingdom.

Address correspondence to Fenella Wojnarowska, DM, Department of Dermatology, Oxford Radcliffe Hospital, Old Road Headington, Oxford, England, OX3 7LJ, UK.

Bullous Pemphigoid

Bullous pemphigoid (BP) is the most common autoimmune blistering disease in the West with an estimated incidence of six to seven cases per million population per year in France and Germany.[1,2]

The natural history of both treated and untreated BP is for persistent disease with eventual remission occurring within five years in the majority of cases, within which time relapses and exacerbations may occur. The aim of treatment is to suppress disease activity with the minimum treatment. The majority of BP patients are over 70 years old, commonly on many drugs, and susceptible to adverse drug reactions.

A systematic review of treatments for BP has so far identified only six randomized controlled trials with a total of 293 patients. Two trials, one comparing prednisolone 0.75 with 1.25 mg/kg and another of methyl prednisolone versus prednisolone, did not find any statistical difference in the groups compared for effectiveness.[3,4] Two trials (one of prednisolone versus prednisolone and azathioprine, and another of prednisolone versus prednisolone and plasma exchange) suggested that the combination treatments maybe better than prednisolone alone.[5,6] A fifth trial, however included all three treatment groups, and no difference was found between combination treatment and prednisolone alone.[7] The sixth trial comparing prednisolone with tetracycline and nicotinamide suggested that there was no statistically significant difference in response parameters in the two groups, but that the prednisolone group had more serious adverse effects.[8]

Therefore, in spite of the fact that BP is the commonest of the immunobullous diseases of the skin, the evidence for the effectiveness of treatment is limited largely to case reports and the clinical experience of experts in the field.

Topical and systemic steroids are the mainstay of treatment. Localized or mild disease may respond satisfactorily to potent topical steroids alone.[9,10] Oral corticosteroids are indicated for more severe or unrespon-

655 Avenue of the Americas, New York, NY 10010

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sive disease, although steroid-induced problems are common. Those patients with more disseminated disease need oral prednisolone in a dose of 20–40 mg daily. Higher doses of prednisolone (up to 100 mg daily) or pulse steroid therapy are occasionally required in patients with very severe and active disease. Steroid dosage can often be reduced quite quickly over the course of a few weeks to a dose of 15–20 mg daily. The majority of patients can be maintained on doses of less than 10 mg prednisolone daily, which can be slowly withdrawn; we use a reducing regime of 1 mg per month reduction once the dose is below 10 mg daily. There may be occasional flares that will require temporary increases in therapy. Corticosteroid therapy has lowered the morbidity from the disease considerably. Most patients achieve remission off all therapy, and the side effects can be limited by the use of lower doses.

The role of azathioprine is controversial. Originally azathioprine was shown to reduce steroid requirements significantly.[5] Recently, however, this has been refuted,[7] and it does seem to increase mortality as well as having significant morbidity in the elderly.[7,11] Even though this evidence is based on small and often uncontrolled studies, the addition of azathioprine to steroids should no longer be routine.

There is currently much interest in the combination of tetracycline and nicotinamide for bullous pemphigoid, and it has been used successfully as first line treatment by a number of authors.[12,13] The doses of tetracycline up to 2000 mg (or minocycline/doxycycline 200 mg) and nicotinamide 2500 mg daily are used. The already mentioned small, double-blind study found the combination to be effective and to have significantly fewer side effects than oral steroids.[8]

A minority of patients with BP appears to be responsive to dapsone, sulfamethoxypyridazine, or sulfapyridine,[14,15] but such significant adverse effects as hemolysis and methemoglobinemia limit their usefulness (see linear IgA disease and Table 1).

Plasmapheresis/plasma exchange, usually with corticosteroids and immunosuppression, has been used in a number of patients with bullous pemphigoid with benefit,[6,16,17] although this was not confirmed in a subsequent published double blind study.[7] Intravenous immunoglobulins have not been demonstrated to be of major benefit,[18] and ciclosporin has had anecdotal success in some patients.[19,20] Methotrexate is sometimes useful in the elderly and in patients with BP and psoriasis.[21,22] There have been small uncontrolled studies demonstrating the efficacy of cyclophosphamide and chlorambucil; however, these treatments are not recommended for routine use.[23–26]

The mortality rate in the initial 30 cases reported by Lever in 1953 was 24%; this was prior to the use of oral steroids. In spite of medical advances the mortality rate is still about 15–20% in treated patients and is usually related to treatment especially in the elderly and debilitated.[11] It is therefore essential to use the least toxic treatment at the lowest possible dose that will control the disease to limit side effects.

Table 1. Monitoring Dapsone/Sulfonamide Therapy

Adverse events
hemolytic anemia
methemoglobinemia
hepatitis
neuropathy
drug eruption
Clinical signs/symptoms
anemia
cyanosis
angina
jaundice
fever/septicemia/systemic illness
weakness
rash
Prior to treatment
full blood count
renal function
hepatic function
G6PD level
During treatment
full blood count
reticulocyte count
renal function
hepatic function
methemoglobinemia
motor neuropathy (walk on tiptoes, grip)

Pemphigoid Gestationis (Herpes Gestationis)

Treatment of pemphigoid gestationis is based on clinical experience; there have been no randomized controlled trials of treatment.[27,28] There are additional aspects to the treatment: the drugs used must be suitable for use in pregnancy and breastfeeding, and, in rare cases, the neonate may also require treatment. The disease is almost always self-limiting, but there may be a post-partum flare. In some cases delivery has been induced because of severe disease.[27,29–31]

In mild cases of pemphigoid gestationis (about 20% of cases) potent topical steroids (e.g., betamethasone esters or equivalent) or very potent steroids (e.g., clobetasol propionate) often combined with a systemic antihistamine suitable for use in pregnancy, (for example, chlorpheniramine, which is, however, sedating) are usually adequate treatment.[27,28] The sedating antihistamine chlorpheniramine seems to be helpful in alleviating the pruritus in many patients.[28] Topical steroids can be used in combination with systemic treatments to lower the doses of systemic treatments required.

Once blisters appear it is usually necessary to use systemic corticosteroids, and these are used in the majority of patients. The range used is prednisolone 5–180 mg daily.[27,28] All but the most severe cases respond to

20–40 mg daily of prednisolone, and this can usually be reduced fairly rapidly to a much lower maintenance dose. Plasmapheresis/plasma exchange can be considered in the most severe cases, as it helps temporarily with pruritus and the eruption, but may need repeating at intervals.[28,30,32]

Other drugs that have been used with variable success include dapsone and sulfonamides, which are contra-indicated peripartum and postpartum if breastfeeding.[28,33] Pyridoxine is unhelpful in most cases.[28,34] There is a report of ritodrine, used to suppress uterine contractions in premature labor, being helpful; however, this drug has many potentially serious side effects and is not recommended for use for more than 48 hours; it is thus unsuitable for treatment of pemphigold gestationis.[35]

A postpartum exacerbation is frequent, and postpartum treatment can be a problem if the mother wishes to breastfeed, as the drugs pass into the breast milk. Antihistamines can cause drowsiness in the baby. It is worth increasing the corticosteroid dose temporarily at the first sign of a flare; however, corticosteroids (topical and systemic) may cause adrenal suppression. The recommendation in the UK is that breastfeeding should be avoided if the mother is taking more than 40 mg of prednisolone daily; the pediatricians should therefore be consulted in this situation. Dapsone and sulfonamides cause hemolysis in the neonate. Although most cases remit within 6 months of delivery,[28] some are persistent. Some cases may be severe or continue for years postpartum, and treatments used in these cases include azathioprine, goserelin, ciclosporin, intravenous immunoglobulins, and pulsed dose cyclophosphamide.[27,28,36–38] We have successfully used minocycline postpartum for persistent disease in a single case.

The oral contraceptive can produce an exacerbation or recurrence of the disease in perhaps 50% of patients.[30,34] The oral contraceptive, although causing flares, may be used in some cases when the pemphigoid gestationis is in remission without a problem.

The rare cases of neonatal blistering because of pemphigoid gestationis usually resolve within a few days and do not require treatment.

Linear IgA disease (Chronic Bullous Disease of Childhood, Linear IgA Bullous Dermatosis)

The treatment of linear IgA disease evolved because of the initial failure to distinguish it from dermatitis herpetiformis, and its response to dapsone contributed to the confusion. Dapsone (diaminodiphenylsulfone, DDS) and sulfonamides are the mainstay of treatment but have never been the subject of randomized controlled trials.[39–41]

The treatment of children and adults is essentially the same with the necessary extra precautions for children. The treatment of the children can be more difficult, because side effects limit the dosage of drugs used.[39] In young women the possibility of pregnancy must be borne in mind and appropriate precautions taken; however, pregnancy is not contraindicated, and often there is a remission of the disease in the last two trimesters with a postpartum flare often at around 3 months.[42]

A few patients have mild disease and can be controlled with topical steroids alone. This has been our experience particularly with some children.

Dapsone is used in doses starting at less than 0.5 mg/kg daily, which often means giving it as 25 mg alternate daily or less in young children, and 25–50 mg daily in an adult. The dose may be slowly increased over weeks and months if required to a dose of 1 mg/kg daily or a little more in a child, and 100–150 mg daily in an adult to keep the patient comfortable without significant side effects. Too rapid an increase in the dose often results in a severe hemolytic anemia, which does not reach its maximum for a month. A fall in hemoglobin with a low MCV indicates iron deficiency (because of intravascular hemolysis) rather than pure hemolytic anemia. Patients (males > females) from the Mediterranean, Africa, Middle East, Southeast Asia, and Oceania are at risk of glucose 6-phosphate dehydrogenase (G6PD) deficiency. Such patients should be screened prior to treatment, and dapsone and sulfonamides avoided if they are G6PD deficient. Dapsone has been used successfully in African and Asian children.[43–46] Methemoglobinemia is common, reaching a steady state after about 2 weeks, and may cause cyanosis, breathlessness, and angina. There is potentiation of this with local anaesthetic. Headache is a common side effect. Hepatitis, the dapsone syndrome (lymphadenopathy, eosinophilia, hepatitis, and rash), and agranulocytosis are serious, usually early, complications. Motor neuropathy may occur. Severe drug eruptions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, are reported. Most complications occur in the first 3 months. There are reviews summarizing the use and problems of dapsone and sulfonamides, and a summary is given in Table 1.[47–49]

Sulfonamides are alternatives if dapsone is not tolerated. Sulfapyridine 250 mg–3 g daily usually controls the eruption rapidly, but the dose may need frequent adjustment, and the drug is often poorly tolerated. Sulfamethoxypyridazine (adult dose 250 mg–1.5 g daily) is an alternative, which is often better tolerated. Sulfonamides have a similar side effect profile to dapsone, but cutaneous allergic reactions (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis) hepatitis, or agranulocytosis are more common. An obliterative bronchiolitis may occur with sulfonamides, and breathlessness must always be investigated.[49,50] Dapsone and sulfonamides can be combined to lessen the dose of

Table 2. Approved/Non-proprietary/Generic Drug Names and U.S. Proprietary/Trade Names of Drugs

Approved/non-proprietary/ generic drug names	*U.S. proprietary/trade drug names**
azathioprine	Immuran
chlorambucil	Leukeran
ciclosporin	Sandimmune
colchicine	Colsalide Improved
cyclophosphamide	Ifosfamide
dapsone	Dapsone
dicloxacillin	Pathocil, Dynapen, Dycill
doxycycline	Doxy, Doxycycline
immunoglobulins	Immuneglobulin, Gamma globulin
mesalazine	
methotrexate	Abitrexate, Folex
methylprednisolone	Medrol, Metrocort
minocycline	Minocin, Dynacin
niacinamide	Nicotinamide
prednisolone	Cortalone
sulfamethoxypyridazine	
sulfapyridine	
tetracycline	

** Based on search in MD. Consult.*

both drugs and improve patient tolerance. The patients must be intensively monitored both as regards clinical and laboratory parameters, initially weekly and, after 3 months, monthly and, later, every 3 months (see Table 1). Patients wishing to conceive should be given folic acid in combination with dapsone, and sulfonamides should be avoided. Often the drugs can be reduced or stopped in the second trimester.[42] Dapsone and sulfonamides cause neonatal hemolysis and should be stopped prior to delivery and not restarted whilst the mother breastfeeds.[33]

Some patients do not respond completely to dapsone or sulfonamides, and corticosteroids may need to be added. They are rarely effective on their own at doses less than 30 mg daily. Dapsone has been used in this way with corticosteroids in African children.[43,44]

Success has been reported in 3 adult cases with tetracyclines (2 g daily) and nicotinamide (1.5–2 g daily) and a single report of other antibiotics.[51–53] In children the penicillins dicloxacillin (40 mg/kg 3 times daily) and oxacillin (50 mg/kg daily) have been reported to suppress the disease.[44,54,55]

Colchicine has been used in children and adults. There is a single adult case report of a good response to 0.5 mg three times daily.[56] Colchicine suppressed the disease in G6PD deficient children in Israel and Oman. The dose was 0.5 mg twice daily as higher doses caused diarrhea. Initially, it was introduced with corticosteroids, but in most children it was effective as a sole agent and could be reduced from 0.5 mg twice daily to once daily.[57–59] It does have potentially very severe side effects, including blood dyscrasias, hepatic, and renal damage, but is often well tolerated.

A few patients are very difficult to control and may need additional azathioprine, ciclosporin, or methotrexate.[60] There is a single case report of the successful use of intravenous immunoglobulins; however, the infusions were required at regular intervals to suppress the disease.[53]

A gluten free diet is ineffective.[61]

The cutaneous lesions are always much more responsive than the mucosal lesions, which can be treated with topical steroids (see Mucous Membrane/Cicatricial Pemphigoid).

In view of the ultimate spontaneous recovery, in the majority of patients attempts should be made to avoid overtreatment and the production of side effects with systemic corticosteroids and other drugs. Regular attempts should be made to reduce and withdraw treatment.

Mucous Membrane Pemphigoid/Cicatricial Pemphigoid

Treatment of mucous membrane pemphigoid/cicatricial pemphigoid (MMP) is difficult. The disease often cannot be completely suppressed and unfortunately patients may develop severe scarring despite immunosuppressive therapy.[62,63]

It is important to examine the patient's skin and all mucous membranes carefully because this will influence the decision about which treatment may be suitable for an individual patient. MMP may only involve the oral mucosa, for example, presenting as a desquamative gingivitis without major morbidity. Involvement of the ocular, nasopharyngeal, oesophageal, and laryngeal mucosa, however, lead to blindness or life threatening complications in severe cases. Therefore at each patient visit, assess which mucous membranes are involved, how severely the site is involved, and how progressive the process is.

There are only two randomized controlled trials in ocular MMP comparing cyclophosphamide, prednisolone, and dapsone.[64] There are no randomized controlled trials for all other patients with MMP therefore treatment recommendations can only relay on case series, case reports and personal experience.

Patients with Mild Disease (Mainly Oral Mucosa and Skin Lesions)

As mentioned above, there are no controlled trials to support the superior effectiveness of any treatment. Therefore, it is advisable to choose the treatment that puts an individual at least risk of side effects.

Potent (betamethasone valerate 0.1% ointment, 5mg betamethasone soluble tablets, triamcinolone acetonide 0.1–0.5%) to very potent (clobetasol propionate 0.05% ointment) topical corticosteroids are applied twice per day. Mouthwashes may initially be necessary more fre-

quently. Topical treatment with corticosteroids is helpful in some patients with localised oral and skin disease, including the genitals.[65,66]

High dose oral prednisone (over 1 mg/kg daily) is effective in controlling MMP, but long term treatment is associated with too many side effects. Therefore systemic steroids are only used in high doses short term or in very low doses (<0.5 mg/kg daily) for longer periods of time if needed.[64,67]

Sulfones or sulfonamides are indicated if topical treatment fails in localised oral and skin MMP and in ocular MMP with marked to moderate inflammation. The current drug of choice is dapsone. Dapsone (25–200mg daily) is contraindicated in patients with G6PD deficiency and must be used with caution in the elderly (for side effects, see Linear IgA disease and Table 1). Dapsone is beneficial in 30 to 70% of MMP patients, and a response can be expected within 2 to 12 weeks. Low dose treatment should be started and the blood monitored weekly for 3 months and after any dose increase and then monthly (full blood count, methemoglobin, and liver function). The daily dose may be increased by 25–50 mg after 4 weeks, hemolysis is observed mainly during the first weeks of treatment and is dose dependent. Dapsone may be combined with topical and systemic corticosteroids, sulfonamides, and immunosuppressants (e.g., azathioprine).[66,68]

Sulfamethoxypyridazine used at a dose of 500 to 1500 mg daily causes less hemolysis and seems as effective as dapsone. Side effects include a toxic reaction with pyrexia, arthralgia, and albuminuria, an erythematous maculopapular rash, hemolytic anemia, fixed drug reaction, photosensitivity, alveolitis, and obliterative bronchiolitis.[49]

Sulfapyridine (500–3000 mg daily) is an alternative to dapsone. It is reported to be effective in 50% of patients with mild to moderate ocular MMP. Side effects include nausea, headache, arthralgia, drug fever, allergic skin rash, and mild leukopenia; rarely, neurotoxicity, hepatotoxicity, polyarteritis, agranulocytosis, blood eosinophilia with pneumonitis, lupus-like syndrome, and hemorrhagic colitis.[68,69]

The beneficial effect of tetracyclines in MMP is supported by a few case series (minocycline 100–200 mg, doxycycline 100–200 mg, or oxytetracycline 500–2000 mg daily). Although they have never been compared to other treatment regimes in controlled trials, tetracyclines seem effective, may be as effective as dapsone, and are associated with fewer side effects. If long-term minocycline/tetracycline is required, liver function tests should be performed every 6 months. Minocycline is known to cause a pneumonitis accompanied by blood eosinophilia, this requires immediate withdrawal of the drug and treatment with systemic corticosteroids.[70–72]

Nicotinamide at doses of 500 to 2500 mg daily is usually used in combination with tetracylcines in MMP. There seems to be an additional effect.[70] We start with 500 mg daily and increase the dose by 500 mg to 2000 mg daily at 2-week intervals. Side effects include gastrointestinal up-set and hepatotoxicity in very high doses. Tetracyclines and nicotinamide should be introduced consecutively.

Always start with the lowest dose possible and increase according to clinical measures. Antibiotics and nicotinamide may be combined; this may be more effective. Low dose systemic corticosteroids (<0.5 mg/kg body weight prednisolone equivalent) may be added if needed to all above mentioned regimes.

Patients with Severe Disease (Progressive Ocular, Nasopharyngeal, Esophageal, Laryngeal)

A combination of medications and additional topical corticosteroids may be required to suppress severe disease and to minimize drug side effects. Antibiotics plus nicotinamide or dapsone may be tried in severe cases of MMP; however, one controlled trial favors cyclophosphamide in combination with prednisolone over dapsone for the treatment of severe ocular MMP.[64] Systemic immunosuppressive therapy should be offered to patients with severe progressive disease, but not to patients with quiescent or end stage disease.

Cyclophosphamide (1–2 mg/kg daily) intravenously or orally is used in addition to prednisone (0.5–1.5 mg/kg daily). In a randomized trial cyclophosphamide (2 mg/kg daily) was given in conjunction with prednisone (1 mg/kg daily) and prednisone tapered by 0.25 mg/kg daily after week 1, week 3, and week 7, and then monthly until completely discontinued. All 12 patients responded to that regime within 8 weeks, active conjunctival inflammation subsided completely. Initially, weekly, then monthly, full blood count with differential white count and urine analysis is required. Side effects include alopecia, leukopenia, anaemia, hemorrhagic cystitis, infections (candida), bladder cancer, and infertility.[62,64,73]

Azathioprine (1–2 mg/kg daily) may substitute for cyclophosphamide; its action may be slower than that of cyclophosphamide. Regular full blood count is required, and in renal and hepatic impairment a reduced dose should be administered. Measuring the serum level of thiopurine methyltransferase activity is important because a low level is associated with increased risk of leukopenia, and these patients also may have a poor clinical response to azathioprine because of inadequate empiric dosing. Side effects include bone marrow suppression, hypersensitivity reactions, infections, hepatotoxicity, and development of malignancies.[62,74–76]

Methotrexate seems ineffective in controlling MMP.[77]

Oral ciclosporin seems ineffective in MMP,[64,67,78]; however, topical ciclosporin is reported to be beneficial

in oral MMP, but the medication is not widely available.[19,79]

Local interferon alfa-2b has been reported to be beneficial for ocular MMP.[80]

Subconjunctival 5-fluoruracil and mitomycin C 0.1 mg are currently being tested for reduction of mucosal fibrosis.[81]

Intravenous immunoglobulins seem effective in severe ocular MMP. They have been used as a last resort in some patients in whom conventional immunosuppressive treatment has failed to control the disease; however, they are costly. There are different preparations available and their efficacy seems to vary; later reports are more optimistic than earlier ones. Side effects are minimal (alopecia, urticaria); however, there may be a risk of other side effects including the transmission of infections.[77,82,83]

Surgery may be necessary in organ failure because of scarring (e.g., airway obstruction, blindness), and patients then have to be referred to the relevant specialist.

Epidermolysis Bullosa Acquisita

Treatment of epidermolysis bullosa acquisita (EBA) is difficult. Clinical features in EBA are heterogeneous; classical EBA resembles the inherited forms of dystrophic epidermolysis bullosa with major skin fragility and a distribution of lesions over trauma-exposed sites. A second group of EBA patients shows clinical features resembling bullous pemphigoid, including widespread blisters often on an inflammatory base; then there are patients with major mucous membrane involvement resembling MMP.[84–86] It seems that patients with the classical form are the ones most resistant to treatment; the others may better respond to the usual immunosuppressive/antiinflammatory regimes as described for the other subepidermal bullous diseases. We could not identify any randomized controlled treatment trials for EBA; most publications are case reports. Topical treatment with corticosteroids, antibiotics, and emollients are effective in reducing friction and controlling secondary infections but do not influence the general course of the disease. Any measure that decreases friction and trauma to the skin is helpful.

Systemic corticosteroids (1–2.5 mg prednisone equivalent/kg daily) seem helpful in patients with inflammatory disease and disease localized to face, genitalia, and mucous membranes; however, patients will develop limiting side effects.[84,87,88]

In addition to systemic steroids, azathioprine (1–2 mg/kg daily) is helpful in some patients with inflammatory EBA; other investigators do not see a steroid sparing effect.[84,87,89,90]

Cyclophosphamide (pulse therapy 1500 mg single dose once per month for 6 months) and chlorambucil (up to 15 mg daily) were tried in single cases, but it is difficult to judge their efficacy.[84,91,92]

Methotrexate (10–25 mg/week) is described as beneficial in single cases of inflammatory EBA in conjunction with high dose systemic steroids.[87,90,93]

Ciclosporin (4–10 mg/kg daily) usually combined with steroids gave a satisfactory response in some patients who failed to respond to other immunosuppressants. Improvement was sometimes seen within one month, and in some patients ciclosporin was stopped without relapse.[94]

Dapsone (50–200 mg daily) in conjunction with systemic corticosteroids is only helpful in single cases; it seems more beneficial in children with EBA (see below).[95]

Mesalazine (3 × 800 mg daily) is reported to have dramatically improved inflammatory EBA when administered because of inflammatory bowel disease.[96]

Colchicine (0.5–2 mg daily) has been used in a few patients, and some responded within weeks. It has to be introduced at a low dose and may then be increased by 0.5 mg daily each week to a maximum dose until diarrhea develops. It is sometimes combined with systemic steroids or dapsone and seems to reduce blister formation in patients who did not respond well to other immunosuppressants. It is usually avoided in patients who have inflammatory bowel disease. Side effects include diarrhea, and renal and hepatic damage.[91,97]

Plasmapheresis/plasma exchange in addition to prednisolone and cyclophosphamide has been used in one patient who did not respond to several other immunosuppressants.[98]

Extracorporeal photochemotherapy is reported to be helpful in patients resistant to conventional treatment.[99–101]

Intravenous immunoglobulins (2 g/kg daily once a week at 2-week intervals or 400 mg/kg daily 4–5 days per week at 2–6 week intervals) are controversial. There are encouraging and disappointing reports. In most patients it was combined with immunosuppressants, and these patients responded better to the intravenous immunoglobulins. The response may also depend on the preparation used and on the type of EBA. It is an expensive treatment and therefore not used in routine practice.[91,102–104]

Surgery may be necessary in organ failure because of scarring (e.g., airway obstruction, blindness), and patients then have to be referred to the relevant specialist.

EBA in childhood is very rare, and the disease in children may be self-limiting. Many are in remission after 2 to 3 years disease duration; however, the course may be protracted and lead to blindness.[86,105,106] Emollients and topical corticosteroids are helpful in some cases. In more severe disease, dapsone (1–2 mg/kg daily; 50–200 mg daily) and/or systemic corticosteroids (1–2 mg/kg daily) should be used.[105,106] Chloroquine

(25 mg daily) in addition to prednisolone was successfully used in one 3.5-year-old girl; the child suffered from gastrointestinal upset after dapsone.[107]

Dermatitis Herpetiformis

Treatment of dermatitis herpetiformis has two components. Initially, there is a need for suppressive treatment with dapsone or alternative to rapidly eliminate the skin lesions; in the longer term the treatment of choice is the removal of gluten from the diet and healing of both the gluten sensitive enteropathy and skin.[48]

There have been no randomized controlled trials of treatment in dermatitis herpetiformis; however, the effect of dapsone in switching off the disease is so dramatic that it has been used by some clinicians as a diagnostic test. There is considerable evidence supporting the beneficial effects of a gluten-free diet. Dapsone is the most widely used treatment for dermatitis herpetiformis, and usually has a rapid and dramatic effect in suppressing the disease within a few days. The problems and precautions required are outlined above (see Linear IgA Disease and Table 1). It is wise to start at 25 to 50 mg daily in an adult and slowly increase to a dose that keeps the patient comfortable without significant side effects; too rapid an increase in the dose often results in symptomatic hemolytic anemia and methemoglobinemia with cyanosis, breathlessness, and angina. The dose needed for the average case is 100 to 200 mg daily, but a few may require and tolerate higher doses.[108]

Sulfonamides are alternatives for patients who cannot tolerate dapsone, and their main side effects and problems are outlined above (see Linear IgA Disease and Table 1). Sulfapyridine (1.5 g daily) can be substituted; however, a few patients may need higher doses. The long-acting sulfonamide sulfamethoxypyridazine is an alternative treatment and usually 0.5 to 1.5 g daily is sufficient to control dermatitis herpetiformis; the incidence of side-effects increases with doses above 1 g daily.[49]

Heparin has been used successfully in the past, and recently, tetracycline and nicotinamide have been used with variable success.[108]

A gluten free diet is the treatment of choice in the long term. There are several reasons for this. A gluten-free diet reverses the gut changes of gluten-sensitive enteropathy, resulting in the disappearance of gastrointestinal symptoms, which may have been severe or have been considered by the patient to be normal. The malabsorption is cured and there is an increase in weight, energy, and wellbeing in most patients. The diet in the long term permits discontinuation of drug therapy for the rash and avoidance of all the potential problems of drug therapy. The risk of lymphoma associated with dermatitis herpetiformis is decreased or abolished after 5 to 10 years of a gluten free diet.[109] For all these reasons, whenever possible patients should be encouraged to follow a gluten free diet. To obtain strict adherence to the diet the patient needs to be highly motivated, intelligent, and leading a regular life; sometimes it may be wise to postpone starting the diet until a more settled period. Unlike patients with celiac disease, ingestion of small quantities of gluten does not always precipitate symptoms. Wheat must be avoided, but oats are not damaging.[110,111] The help of a dietician and the Celiac Society are essential. The patients put on weight, lose their abdominal symptoms, and often feel generally much better. It is usually many months and sometimes years before patients are able to reduce their dapsone requirements. Often dapsone can be discontinued altogether after 2 to 3 years on a strict gluten-free diet, but some patients take much longer.[112] Re-introduction of gluten in selected patients produced a relapse in skin lesions.[113] Although systemic corticosteroids are in the main ineffective and not indicated, topical steroids may be helpful in lessening symptoms.[108]

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