



Immunosuppressive therapy for autoimmune bullous diseases

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Abstract Adjuvant immunosuppressive drugs are widely used to minimize corticosteroid-related adverse effects in the short-term and long-term management of autoimmune bullous diseases. In bullous pemphigoid and pemphigus vulgaris, azathioprine and mycophenolate mofetil seem to be equally effective when used in combination with oral corticosteroids, but mycophenolate mofetil is less myelosuppressive and hepatotoxic. Due to a better safety profile, mycophenolate mofetil or enteric-coated mycophenolate sodium may gradually replace azathioprine as the first-line adjuvant of choice in the treatment of moderate to severe autoimmune bullous diseases, including epidermolysis bullosa acquisita and cicatricial pemphigoid. Cyclophosphamide still has a place in the treatment of severe relapsing autoimmune bullous diseases. Continuous oral cyclophosphamide provides optimal immunosuppression, but it also produces the highest cumulative dose. Several pulsed cyclophosphamide regimens have, therefore, been developed and are reported to be effective in severe forms of pemphigus. Randomized controlled studies are needed to compare the efficacy and safety of cyclophosphamide with newer treatment options, such as rituximab and immunoadsorption, and to define optimal dose ranges and duration of available immunosuppressive treatments in different stages of autoimmune bullous diseases. © 2012 Elsevier Inc. All rights reserved.

Introduction

Systemic corticosteroids are still the cornerstone of management in autoimmune bullous disorders. The use of corticosteroids has considerably reduced the mortality rate of pemphigus vulgaris (PV) from about 70% to less than 10%.¹ Long-term and high-dose treatment with systemic corticosteroids, however, carries the risk of significant adverse effects, including severe infections, gastric ulcers, hyperglycemia, hyperlipidemia, hypertension, steroid-induced myopathy, cognitive disturbances, osteoporosis, and thromboembolic complications. Steroid withdrawal is, therefore, frequently

necessary, especially in older patients with bullous pemphigoid (BP). A major goal in the management of patients with autoimmune bullous diseases has been the reduction of the patient's cumulative exposure to systemic corticosteroids.

Considerable variation exists in the corticosteroid regimen used, however. In mild cases of PV or BP, in children with immunoglobulin A linear disease, or in inflammatory epidermolysis bullosa acquisita (EBA), daily prednisolone equivalents of 0.5 to 0.75 mg/kg are often sufficient to suppress disease activity; in moderate-to-severe cases, daily prednisolone equivalents of 0.75 to 1.25 mg/kg are needed. Starting doses in BP greater than 0.75 mg/kg daily do not seem to give additional benefit, and lower doses may be sufficient to control disease activity and to reduce adverse steroid-related reactions.²

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A randomized controlled multicenter study in France that compared topical clobetasol propionate cream (0.05% daily) with systemic treatment with a prednisolone equivalent (1 mg/kg daily) in BP patients demonstrated superiority of topical steroid therapy in disease control and survival rate in highly active BP.³ This publication showed that very potent topical corticosteroids can be recommended as the first-choice therapy for BP, although the long-term use may be limited in extensive disease due to cutaneous side effects and tolerability.² When patients do not respond well to systemic prednisolone therapy even at higher doses, the change of prednisolone to other oral steroids (such as betamethasone, dexamethasone or methylprednisolone) may improve the patient's condition.⁴

Intravenous or oral pulsed steroid treatment regimens have been reported to be beneficial in the treatment of severe and recalcitrant PV,^{5,6} especially in patients with new-onset disease, whereas the role of pulsed corticosteroids has not been assessed in recalcitrant disease. The wide range of doses recommended and the poor standardization concerning duration and comedication make a retrospective evaluation of corticosteroid pulse therapy difficult.

Immunosuppressive agents

Adjuvant immunosuppressive medications are widely used in the treatment of BP, PV, cicatricial mucous membrane pemphigoid, linear IgA disease, and EBA, and include azathioprine, cyclophosphamide, methotrexate, ciclosporin, and mycophenolate mofetil. These adjuvant drugs not only have a corticosteroid-sparing effect but also affect B cells and T cells, resulting in a decreased production and action of pathogenic autoantibodies.

Adjuvant drugs with anti-inflammatory rather than immunosuppressive action are gold, dapsone, antimalarials, or tetracyclines combined with nicotinamide⁷; together with interventions such as pulsed high-dose intravenous immunoglobulins (IVIG), rituximab or immunoapheresis, mostly considered as third-line treatment options of severe recalcitrant forms of PV, cicatricial pemphigoid, or EBA, they will be covered in other contributions in this thematic issue. In most instances, however, these new treatments require a concomitant immunosuppressive therapy, as do corticosteroids.

Azathioprine

Metabolism

Azathioprine is nonenzymatically converted to 6-mercaptopurine after oral administration and absorption. Azathioprine and 6-mercaptopurine are both pro-drugs. 6-Mercaptopurine can be activated by several enzymatic steps to its active metabolites, the 6-thioguanine nucleotides (6TGNs), and can be inactivated by xanthine oxidase to 6-thiouric acid, or by thiopurine methyltransferase (TPMT)

to 6-methyl-mercaptopurine. The activity of TPMT is genetically determined. Approximately 10% of the population has a heterozygote genotype with intermediate enzyme activity and about 1 in 300 patients is homozygous for mutant alleles or is a compound heterozygote and has low enzyme activity.^{8,9}

Approximately 50% of myelosuppression diagnosed during the first 6 months of azathioprine therapy is due to low or intermediate TPMT enzyme activity.⁹ Determining TPMT genotype or enzyme activity phenotype before initiating azathioprine therapy therefore has the potential to reduce myelosuppression by 25% to 50%. Although TPMT genotyping tests are not routinely available (in Germany: Institut für klinische Molekularbiologie, Schittenhelmstr. 12, 24105 Kiel, Abt Sequenzierung), many specialized purine research laboratories offer TPMT enzymatic assays. Some patients will experience myelosuppression despite normal TPMT activity, and thus, all patients undergoing treatment with azathioprine and 6-mercaptopurine will need regular complete blood count monitoring during follow-up. An abrupt increase in serum transaminase levels observed soon after administration of azathioprine is a clue for deficient TPMT activity. Apart from genetic polymorphisms of TPMT, concurrent therapy with TPMT-inhibiting drugs, such as allopurinol or sulfasalazine, can also increase the risk of myelotoxicity.¹⁰ In patients with reduced TPMT activity, regardless of the cause, a substantial reduction in dosage is required. When very low or no TPMT activity is found, azathioprine should be avoided.

A meta-analysis of patients with Crohn disease treated with azathioprine showed that patients with therapeutic 6TGN concentrations were 3.27 times more likely to achieve remission than patients with subtherapeutic 6TGN concentrations.¹¹ Some patients appear to be "biochemically resistant" to azathioprine and cannot achieve therapeutic concentrations of 6TGN despite dose escalation.

Mechanism of action

Azathioprine antagonizes purine metabolism and inhibits synthesis of DNA, RNA, and proteins; it may also interfere with cellular metabolism and inhibit mitosis. In addition to its effects on nucleic acid synthesis, azathioprine also affects the immune system in a number of ways. It reversibly reduces the number of monocytes and Langerhans cells, impairs γ -globulin synthesis and T-cell lymphocyte function, and may effect the responses of B cells that depend on helper T cells and the function of suppressor B cells.^{10,11}

Adverse effects

Adverse drug reactions with azathioprine occur in 15% to 30% of patients and include leukopenia, thrombocytopenia, anemia, pancytopenia, and hepatotoxicity. Long-term immunosuppression increases the risk of infections and neoplasia. Azathioprine has also mutagenic potential in both men and women and possible hematologic toxicities. Skin disorders (alopecia, erythematous or maculopapular

rash), gastrointestinal problems (nausea, vomiting, anorexia, diarrhea, aphthous stomatitis, pancreatitis), and other rare adverse reactions can be observed.

Due to the evidence of risk to the fetus, azathioprine use in pregnancy is not recommended; the same applies for breastfeeding, because minimal concentrations of azathioprine and its metabolites have been found in breast milk.¹¹

Efficacy in autoimmune bullous diseases

Azathioprine is the best-characterized first-line immunosuppressive and steroid-sparing agent for the treatment of autoimmune blistering diseases.¹ The recommended dosage of azathioprine is 1 to 3 mg/kg daily. A daily dosage at the lower range is recommended for elderly patients. There might be a latent period of 3 to 6 weeks before azathioprine becomes effective.

Alone, azathioprine may control disease in a few patients with mild PV or BP. The combination of azathioprine with oral corticosteroids in low or medium-high doses is also standard in patients with moderate to severe relapsing BP that does not respond to corticosteroids.⁷ A small, randomized controlled trial (RCT) published in 1978 found a 45% reduction in the amount of prednisolone required for disease control in the group treated with corticosteroids plus azathioprine during a 3-year period vs the prednisolone-only group.¹² In PV, the corticosteroid-sparing effect of azathioprine was demonstrated in a more recent RCT.¹³

The available data on the efficacy of azathioprine in other autoimmune bullous diseases are less convincing. In cicatricial pemphigoid or EBA, dapsone has frequently replaced azathioprine as the first-line adjuvant drug. More potent immunosuppressive drugs, such as cyclophosphamide and mycophenolate mofetil, are preferred in severe cases of EBA or cicatricial BP.

Mycophenolate mofetil

Mechanism of action

Mycophenolate mofetil was originally developed for the treatment of psoriasis and tumors and shows potent immunosuppressive effects. Mycophenolate is rapidly absorbed after oral administration and is then hydrolyzed to its active metabolite mycophenolic acid (MPA), which selectively inhibits inosine monophosphate dehydrogenase and therefore inhibits the *de novo* pathway of purine synthesis in T and B cells. Unlike most other cells, lymphocytes rely on the *de novo* pathway more than the salvage pathway for purine biosynthesis. Because MPA specifically inhibits the *de novo* pathway, lymphocytes are the primary target of MPA action *in vivo*, thus minimizing unwanted effects on other cell types.^{14,15}

Adverse effects

Mycophenolate mofetil is generally well tolerated, and serious adverse effects are rarely observed. Several adverse

reactions include diarrhea, nausea, vomiting, infections, leukopenia, or anemia, or both. The IV administration of mycophenolate mofetil is commonly associated with thrombophlebitis and thrombosis. Infrequent adverse effects can include esophagitis, gastritis, gastrointestinal tract hemorrhage, or invasive cytomegalovirus infection. Studies of transplant recipients taking mycophenolate mofetil have shown it may increase the risk of some cancers, such as lymphomas and skin cancers. The use of mycophenolate mofetil during pregnancy is associated with increased risk of miscarriage and congenital malformations.¹⁰

Efficacy in autoimmune bullous diseases

Due to its safety profile, mycophenolate mofetil is gradually replacing azathioprine as the first-line adjuvant of choice in the treatment of moderate to severe autoimmune bullous diseases, including EBA and cicatricial BP. Several case reports have documented that adjuvant mycophenolate mofetil therapy showed a beneficial effect in recalcitrant PV patients^{16,17} and in patients with BP.^{18,19} In BP, mycophenolate mofetil has been used in some patients alone, with good results.²⁰

An RCT that compared the safety and efficacy of the standard combination of oral prednisolone with azathioprine vs oral prednisolone plus mycophenolate in 38 BP patients found both treatment arms showed similar efficacy and similar cumulative corticosteroid doses.²¹ A recently published RCT in patients with mild to moderate PV²² compared more than 52 weeks of mycophenolate mofetil plus oral prednisolone with placebo plus oral prednisolone and showed no clinical advantage of either treatment arm on clinical outcome. Mycophenolate mofetil, did however, seem to have a beneficial effect on secondary outcome measurements such as time to response and duration of response.

Mycophenolate mofetil (1000 mg, twice daily) is usually given in addition to systemic steroid therapy and is stopped when remission is achieved. Alternatively after remission, first a gradual reduction and then discontinuation of oral steroids can be tried while mycophenolate mofetil intake is prolonged for a variable time. Concerns about the tolerability of mycophenolate mofetil, particularly regarding gastrointestinal side effects, led to the development of enteric-coated mycophenolate sodium (EC-MPS), which is bioequivalent with MMF. The EC-MPS formulation of MPA leads to a decreased need for dose reductions caused, in particular, by gastrointestinal side effects and, therefore, provides potentially improved efficacy.²³ Side effects are usually mild and gastrointestinal symptoms, myalgia, neutropenia, lymphopenia, and various infections may occur; therefore, mycophenolate mofetil, in particular EC-MPS, seems to be promising as an immunosuppressive and steroid-sparing drug. Mycophenolic acid is also less myelosuppressive and hepatotoxic; therefore, use of EC-MPS in place of azathioprine may be preferable given the superior safety profile of EC-MPS.

Cyclophosphamide

Mechanism of action

Cyclophosphamide is a synthetic alkylating agent with antineoplastic and immunosuppressive activities that is chemically related to the nitrogen mustards. In the liver, cyclophosphamide is converted to the active metabolites aldophosphamide and phosphoramidate mustard, which bind to DNA and thereby inhibit DNA replication and initiate cell death.¹¹

Adverse effects

Adverse effects are frequent and significant, including chemotherapy-induced nausea and vomiting, stomach pain, diarrhea, darkening of the skin/nails, alopecia, changes in color and texture of the hair, and lethargy. Cyclophosphamide suppresses production of blood cells from the bone marrow, causing leucopenia, anemia, and thrombocytopenia, and accounts for hemorrhagic cystitis, which can be prevented by adequate fluid intake and sodium 2-mercaptoethane sulfonate (Mesna).

Cyclophosphamide is itself carcinogenic, potentially causing transitional cell carcinoma of the bladder as a long-term complication. It can cause temporary or, rarely, permanent gonadal problems. Gonadal toxic adverse effects are represented by amenorrhea, azoospermia, and infertility. These are dose-related, can be irreversible, and can occur after administration of as little as 6 grams of cyclophosphamide. Azathioprine therapy can lead to similar problems, but this event is much less common.

Use of cyclophosphamide during pregnancy may affect the fetus, causing missing fingers and toes and a poorly developed heart. Exposure in the second or third trimester may be less risky. Cyclophosphamide is excreted in breast milk and could cause serious problems in the breastfed infant.¹⁰

Whatever the additional benefit of cyclophosphamide therapy, it must be balanced against its significant toxic effects. Pulse cyclophosphamide is more effective than oral or IV pulse therapy with corticosteroid alone and may have fewer adverse effects than oral intake.²⁴

Efficacy in autoimmune bullous diseases

Adjuvant immunosuppressive treatment with cyclophosphamide is considered if patients with autoimmune bullous diseases (1) fail to achieve remission with combinations of corticosteroid and azathioprine or mycophenolate mofetil, (2) had clinically significant side effects with previous therapies, or (3) have rapidly progressive disease with extensive skin and mucosal lesions. Owing to its wide spectrum of adverse effects, it is rarely given to elderly patients with BP but has been used in the treatment of those forms of PV, EBA, and cicatricial pemphigoid that were refractory to standard treatment. The standard dosage of oral cyclophosphamide is 2 to 2.5 mg/kg daily,

followed by aggressive oral hydration, and IV cyclophosphamide must be combined with oral or IV Mesna to prevent bladder toxicity.

Although the continuous oral treatment with cyclophosphamide provides optimal immunosuppression, it also produces the highest cumulative dose. Therefore, several dosing schedules have been developed to minimize cumulative doses of cyclophosphamide (1) monthly IV, (2) monthly IV combined with low-dose daily oral cyclophosphamide, and (3) single-dose immunoablative therapy. Although the latter is not used in dermatology, several groups have reported other pulsed cyclophosphamide regimens are effective in severe PV, even though other studies showed no beneficial effects with this intervention.^{4,17} At present, the superiority between oral and pulsed cyclophosphamide is not known due to the lack of controls. Equally effective but possibly safer biologic therapies such as rituximab,²⁵ or interventions such as immunoapheresis,²⁶ will probably, in the near future, replace cyclophosphamide in the management of severe autoimmune disorders resistant to standard treatments.

Cyclosporine

Cyclosporine, in the dosage of 3 to 5 mg/kg daily, is infrequently used in addition to systemic corticosteroids as an adjuvant therapy in autoimmune blistering disease, mostly in PV. Two RCTs, including a comparison with corticosteroids alone, failed to demonstrate a conclusive effect of adjunct cyclosporine on various outcomes, including remission, disease control, safety, and cumulative corticosteroid doses.^{27,28} The efficacy of cyclosporine is probably less than that of azathioprine and mycophenolate mofetil; however, cyclosporine is considered the relatively safest immunosuppressive drug in pregnancy.^{4,10} The potential complications of a cyclosporine-based regimen, such as hypertension and renal dysfunction, further limit its use in older patients.

Methotrexate

Only a few studies have suggested that methotrexate may be useful as an immunosuppressive and steroid-sparing agent in autoimmune bullous diseases.^{4,29} The dosage of methotrexate used was 10 to 50 mg weekly. Despite the known profile of adverse effects, controlled trials—for example, in cicatricial BP or EBA—are needed to determine the efficacy and steroid-sparing effect of methotrexate in autoimmune blistering diseases.

Discussion

According to a survey published in 2009 among German dermatologists on current treatment standards for PV and BP, more than 69% of the participating hospitals reported

azathioprine as a first-line adjuvant drug given in BP, and 81% of hospitals used azathioprine as first-line adjuvant immunosuppression in patients with PV.³⁰ Immunosuppressive therapy for BP and PV was terminated by 58% and 46% of the hospitals 1 to 3 months after clinical remission, but the given cutoff times appeared to be quite variable. Dapsone and topical clobetasol propionate treatment were mentioned as alternative treatment options for BP, as well as mofetil mycophenolate or cyclophosphamide-dexamethasone pulse therapy for PV.

A review in 2009 of clinical data from 11 trials involving more than 400 patients with PV found that mycophenolate mofetil appeared to be more effective than azathioprine in controlling PV, although no differences were found in remission.³⁰ An excellent recent review on interventions in BP analyzed 10 RCT comprising more than 1000 patients.² The review concluded that lower doses of oral corticosteroids and potent steroid creams seem safe and effective, whereas more research is needed to evaluate the effectiveness of adding azathioprine or mycophenolate mofetil to corticosteroids in the treatment of BP. Owing to the very small number of patients with EBA or cicatricial pemphigoid, no RCT's exist for these entities.

The results and practical implications derived from RCTs involving patients with autoimmune blistering disease are often inconclusive, however,^{2,30} and do not give the answers expected, particularly in the context of an individual patient's clinical course, comorbidity, and drug intolerance. For staging and monitoring disease activity and course, immunologic parameters should be included, such as autoantibody titers measured by indirect immunofluorescence microscopy or enzyme-linked immunosorbent assay. These biomarkers correlate with disease activity in many patients with PV or BP, but a considerable discrepancy exists in others between antibody titers and clinical activity or remission, respectively. The optimal time for discontinuation of immunosuppressive treatments is therefore often difficult to determine. Also, there is little agreement whether oral corticosteroids alone at low doses or immunosuppressive drugs alone are more effective for maintenance or rebound prevention once clinical remission is achieved.

There is a need for further large RCTs addressing questions such as:

1. What is the optimal first-line corticosteroid dose regimen?
2. Which is the optimal adjuvant immunosuppressive agent in newly diagnosed vs long-term relapsing autoimmune bullous diseases?
3. Which is the optimal adjuvant for third-line interventions such as IVIG, rituximab, or immunoapheresis?
4. For how long should any therapy be continued?

In addition, there is a need for uniform outcome measurements, for clear definitions of disease control, remission, and relapse, as well as for the assessment of patient's quality of life in such trials.²⁸

Conclusions

The role of adjuvant immunosuppressive drugs in the short-term and long-term management of autoimmune bullous diseases has not been established. They are widely used to minimize corticosteroid-related adverse effects, but their potential to modify disease activity and course is not known. In BP and PV, azathioprine and mycophenolate mofetil, when used with oral corticosteroids, seem to be equally effective; however, mycophenolate mofetil has a better safety profile. Cyclophosphamide still has a place in the therapy of severe relapsing autoimmune bullous diseases, but newer treatment options, such as rituximab and immunoapheresis, may prove to be superior to cyclophosphamide and possibly safer. Further trials are needed to define optimal dose ranges, combinations, and duration of available immunosuppressive treatments in different stages of autoimmune bullous diseases and by using uniform primary and secondary outcomes for clinical activity, drug safety, and quality of life.

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