Published in final edited form as:

Pediatr Dermatol. 2013 ; 30(2): 240–244. doi:10.1111/j.1525-1470.2012.01730.x.

Pediatric Pemphigus Vulgaris: Durable Treatment Responses Achieved with Prednisone and Mycophenolate Mofetil (MMF)

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Abstract

Pemphigus vulgaris (PV) is a chronic autoimmune blistering disease of the skin and mucous membranes. Most cases occur in adults; cases in children are rare. This report describes the clinical presentations and treatment responses of three children with PV, as confirmed according to histology and indirect immunofluorescence studies. In all three cases, oral prednisone used in conjunction with mycophenolate mofetil (MMF) resulted in complete clinical remission, during which all pharmacotherapy was successfully discontinued. Resolution of the skin and mucosal blistering tended to occur quickly with prednisone, and after initiation of treatment with MMF, discontinuation of all pharmacotherapy was achieved within a range of 10 to 30 months in the three patients. One patient experienced a recurrence of genital lesions 19 months after discontinuation of therapy, but the condition remitted within 2 weeks with topical corticosteroid therapy. At the time of this report, the duration of complete remission ranged from 6 to 19 months. In summary, combination therapy with prednisone and MMF for pediatric PV appears to be a safe and effective approach that is associated with durable remission.

CASE 1

A 15-year-old Caucasian girl initially presented with a 1-month history of pruritic and painful blisters that began on her trunk and subsequently spread to involve her oral mucosa; axillary, chest, abdominal, and genital skin; and associated mucosal areas (Fig. 1). The blisters were accompanied by bloody, purulent discharge. Her past medical history was significant for a recent history of a prolonged upper respiratory illness, recurrent aphthous oral ulcers refractory to treatment, and intermittent dysphonia. The patient's brother also had a history of frequent aphthous ulcers.

Viral and bacterial skin cultures were negative. Empiric treatment with trimethoprim-sulfamethoxazole, acyclovir, and topical silver sulfadiazine had produced no clinical improvement.

The results of two skin biopsies for histopathology and direct immunofluorescence (DIF) were consistent with pemphigus vulgaris (PV), and enzyme-linked immunosorbent assay (ELISA) confirmed the presence of antidesmoglein-1 and antidesmoglein-3 antibodies. Chest radiograph was normal and revealed no evidence of thymoma.

Initial treatment consisted of oral prednisone 60 mg daily (1.5 mg/kg per day), along with a topical mixture of triamcinolone and benzocaine for oral mucosal use. Oral ranitidine was given for gastric ulcer prophylaxis. The patient achieved clinical remission within 2 weeks of initiating therapy, but experienced recrudescence of disease upon steroid tapering. At this time, steroid-sparing therapy in the form of mycophenolate mofetil (MMF) was started at 500 mg twice daily (~20 mg/kg per day) and eventually increased to 600 mg twice daily (~25 mg/kg per day). Sixteen months later, she successfully tapered off of prednisone and MMF without residual activity on the skin or genital mucosal surfaces. She has remained in remission for the past 6 months and continues to have no residual disease activity.

CASE 2

An 11-year-old Caucasian girl presented with complaints of widespread blistering that began on the chest and scalp and later spread to the forehead and extremities (Fig. 2). Her past medical history was noncontributory. She was not taking any medications and had not travelled internationally. She was initially treated for presumed staphylococcal impetigo with clindamycin, with no clinical response.

The initial biopsy was consistent with pemphigus foliaceus, but she had only a partial response to treatment with topical corticosteroids. Three months later, the condition progressed to include hard palate and perineal erosions, with crusted erosions concurrently observed on the scalp, back, and upper extremities. The results of a second biopsy and DIF yielded a diagnosis of PV, while ELISA detected antibodies to desmoglein 1 and 3. A chest radiograph was normal, with no evidence of thymoma.

The patient was treated with oral prednisolone at 2 mg/kg per day given once daily and experienced rapid resolution of blistering within the first 4 weeks. Oral MMF was then added to her regimen at 500 mg twice daily (30 mg/kg). Because of gastrointestinal upset, her dose was reduced to 500 mg once daily (15 mg/kg). Within 8 weeks, her oral prednisolone was successfully discontinued with no significant recrudescence of blistering. She completed three additional months of MMF and then discontinued its use after 5 months of therapy. Nineteen months later, she relapsed with several small genital ulcerations and a positive ELISA, but her disease remitted with use of topical desonide ointment for 2 weeks. She has remained in ongoing clinical remission for 6 months.

CASE 3

A 14-year-old Caucasian boy presented with an 18-month history of scalp and mouth erosions that later involved the face, chest, and back. A skin punch biopsy was consistent with PV, with the indirect immunofluorescence revealing only antibodies to desmoglein 3. Chest radiograph was normal, with no evidence of thymoma. He responded well to oral prednisone at 40 mg once daily (0.6 mg/kg per day) in conjunction with topical corticosteroids as needed. He successfully tapered to 4 mg daily over the ensuing 3 months but at lower doses would develop new blisters. Six months after starting prednisone, he began MMF as a steroid-sparing agent at 500 mg twice daily (17 mg/kg per day), increasing

to 1,000 mg twice daily (35 mg/kg per day) because of ongoing mild blistering on the face. After 4 months of therapy with MMF, his PV remitted, although he required ongoing maintenance doses of 1 to 2 mg of prednisone every other day to maintain remission. Two years after disease onset, he was successfully tapered off of prednisone. Over the next 8 months, he was gradually tapered off MMF, slowed by occasional recurrences as the dose was decreased. Three years after disease onset, he achieved complete remission off systemic immunosuppressants. Sixteen months later, his condition remains in complete ongoing clinical remission.

DISCUSSION

Pemphigus refers to a group of chronic autoimmune blistering diseases of the skin and mucous membranes (1,2). Autoantibodies directed against the keratinocyte cell surface, specifically desmoglein 1 and 3, lead to loss of cell-to-cell adhesion, resulting in acantholysis (1). Several clinical forms of pemphigus have been described, all of which occur rarely in childhood and adolescence (2–6). The majority of pemphigus in childhood is the vulgaris type, with the mean age of onset being 12 years (7). Pemphigus vulgaris in children affects both sexes equally (4,7). The prognosis of pemphigus in childhood is better than that of adult pemphigus but is extremely variable (6).

Nearly all patients with PV develop painful oral erosions, and for some, this is the only clinical manifestation (1,8). Other mucous membranes reported to be involved include the larynx, esophagus, conjunctiva, nasal mucosa, vagina, penis, anus, and labia (1). The diagnosis of PV is often delayed when oral lesions are the only manifestation, and the index of suspicion may be even lower in a young patient because of the rare occurrence of PV in children (4,7,9). Children may initially be misdiagnosed with impetigo, staphylococcal ecthyma, or herpes simplex infection.

More than half of individuals with PV will develop cutaneous vesicles and bullae (1). The primary skin lesion in PV is a flaccid, easily ruptured blister (1), although blisters do not usually involve the palms and soles. Ruptured blisters become erosions that can be slow to heal, leaving residual hyperpigmented patches (1).

Treatment

Before the advent of systemic corticosteroids, PV was fatal (1,6,9,10). Use of systemic corticosteroids has reduced the mortality of PV to 30% from 70% to 100% (6,7,11). Although PV remains a potentially fatal disease, newer treatments have reduced mortality to <5% (10,12). There has been some controversy over optimal systemic management of pemphigus in the pediatric population (12). Treatment of juvenile PV with steroids alone can have significant consequences in children, from its effects on physical appearance, susceptibility to infection, and nutrition. The reported frequency of side effects of therapy in children with use of steroids and immunosuppressants is higher than in adults, with growth retardation, sepsis, and death being the most notable (7,12).

Treatment is aimed at reducing antibody production and suppressing local inflammation to induce remission. Reported remission rates in old and new studies of PV treatment are approximately 30% (10). Factors that may predict treatment response and remission include disease severity at time of diagnosis, early response to treatment, and levels of indirect immunofluorescence and ELISA titers (10), but because of the infrequency of pemphigus and the paucity of controlled trials in PV, there are currently no Food and Drug Administration–approved therapies for PV, and the treatment guidelines available lack strength of evidence (1,2,6,10,12).

Systemic corticosteroids are the mainstay of treatment, whereas immunosuppressive agents are used as adjuvant therapy for their corticosteroid-sparing effects (1,10). The primary goal is to control disease with the lowest possible dose of corticosteroids, keeping in mind that mucosal lesions are the most recalcitrant to therapy (1,4). Prednisone is used in doses of 1 to 2 mg/kg per day, with 40 to 60 mg/day being the typical starting dose (1,7). Control of disease activity is marked according to the time that new lesions cease to form and old lesions begin to heal (13). Once control is achieved, steroids can be tapered, and an adjunctive immunosuppressant may be added. We have initiated systemic steroid-sparing therapies early in an effort to reduce systemic steroid exposure and steroid-related toxic effects (14).

Osteoporosis, slow linear growth, and rebound exacerbation of disease upon tapering typically preclude long-term use of systemic steroids in children (15). A systemic medication with a favorable risk–benefit ratio would be a welcome addition to the therapeutic armamentarium for pediatric patients (15). It appears that MMF may be one such candidate.

Examples of immunosuppressant drugs used in the treatment of PV include MMF, azathioprine, cyclophosphamide, and cyclosporine (1). Of these, MMF seems to be the most promising, although evaluation of any adjuvant therapy is difficult because of small sample sizes and the lack of well-controlled studies (4,7,16). MMF is a fermentation product of *Penicillium stoloniferum* (16). Once ingested, it is hydrolyzed to mycophenolic acid, the active form of the drug, which inhibits eukaryotic inosine monophosphate dehydrogenase (14–18). The effects of this enzyme inhibition include preferential inhibition of proliferating B and T lymphocytes and prevention of the formation of antibodies and of cytotoxic T cells (1,14,16,17). MMF undergoes hepatic metabolism and renal excretion but has demonstrated no hepatotoxic or nephrotoxic effects (14). The rate of hepatic drug metabolism seems to be inversely proportional to age, so younger children will require higher relative doses of MMF than older children and adolescents (15). The most common reported side effect of MMF is gastrointestinal distress, occurring in 10% to 30% of patients (1,14–16). Less common side effects include hepatotoxicity, which can be severe; genitourinary symptoms; hematologic aberrations; and neurologic symptoms (1,14,16). Malignancies and lymphoproliferative disorders have not been reported in children receiving MMF alone (15). The adverse effects, if present, are usually observed at a dose of 3 g/day, and discontinuation is usually unnecessary (14). Latent viral infections can be activated in response to therapy with immunosuppressant therapy, including cases of progressive multifocal leukoencephalopathy as well as BK virus-associated nephropathy. Live vaccines should be avoided while patients are receiving MMF. MMF is also teratogenic and has a Pregnancy Category D rating (19).

For more than a decade, MMF has been successfully used as an immunosuppressant in adults and children undergoing solid organ transplantation (15,17). In addition, there are several reports in the literature demonstrating the safety, efficacy, and utility of MMF adults and children for various cutaneous diseases, including pemphigus, pemphigoid, severe atopic dermatitis, dermatomyositis, and psoriasis (14). Strowd et al achieved 89% complete remission when they used a therapeutic ladder consisting of MMF and prednisone in 18 patients with PV (10). Edge et al (14) described the use of MMF in 12 patients with dermatomyositis recalcitrant to traditional therapies. Ten of twelve patients displayed significant improvement within 8 weeks of initiating MMF, with few adverse effects (14). Rouster-Stevens et al (18) performed a retrospective review of 50 children with juvenile dermatomyositis who received MMF after failing to respond to conventional therapies. Disease activity scores for muscle and skin had significantly improved after 12 months. The drug was well tolerated, with the most common side effect being infection, but none of them were serious or required hospitalization (18). A retrospective analysis that Heller et al

performed examined 14 children with severe atopic dermatitis (AD) treated with MMF as monotherapy at New York University (NYU) between August 2003 and August 2006. Their analysis demonstrated that MMF at a dose of 30 to 50 mg/kg per day is safe, well tolerated, and effective for the treatment of severe pediatric AD, with more than half of the patients in their series achieving complete clearance within 3 months of starting therapy (15). In one of the larger randomized controlled trials using MMF in adults with PV, Beissert et al (11) compared responses to prednisone and MMF with those to prednisone and placebo. Although there were no significant differences between the proportions responding to treatment (69.0% vs 63.9%, respectively), those who received MMF had faster and more-durable responses at 3 and 6 months. In our series, all three patients were able to achieve durable clinical remission through the use of prednisone and MMF.

Although several reports have indicated a favorable role for MMF in pemphigus, there are reports that have not indicated as much benefit from using MMF. In a multicenter nonblinded study by Beissert et al (20) involving 33 patients with PV and nine with pemphigus foliaceus, patients were randomized to receive prednisone and azathioprine or prednisone and MMF. MMF was not found to be superior to azathioprine. In another report by Chams-Davatchi et al (22), prednisone in conjunction with several adjunct therapies was examined, and azathioprine was found to be superior to pulse cyclophosphamide and MMF.

CONCLUSION

It is important for clinicians to be aware of the existence of juvenile PV because early diagnosis may have prognostic implications (7,8). It is known from treating adults that earlier intervention is associated with greater rates of clinical remission (4). Pemphigus vulgaris should be a consideration in children with chronic erosive mucous membrane disease (9). Our experience with children with PV treated with combination therapy using prednisone and MMF indicates that children can tolerate these treatments well. Pharmacologic therapy was able to be discontinued within 5 months to 3 years in these three patients, and remission for this typically chronic disorder in our patients has lasted from 6 to 19 months. There is emerging evidence in support of MMF as a safe and effective treatment for juvenile PV and other chronic cutaneous diseases. Combination therapy with corticosteroid and MMF may be effective at achieving durable clinical remission in pediatric pemphigus.

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Figure 1.
Pemphigus vulgaris characterized by multiple erosions involving the back.

Figure 2.
Pemphigus vulgaris characterized by a crusted erosion on the lateral chest wall.