Treatment of Linear IgA Bullous Dermatosis of Childhood With Mycophenolate Mofetil

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REPORT OF A CASE

A 27-month-old girl presented with a 5-week history of blistering that was initially localized to the popliteal fossae and face but subsequently progressed to involve the majority of her extremities, her genitals, and portions of her trunk. Treatments initiated prior to dermatologic evaluation included amoxicillin and betamethasone dipropionate and resulted in no improvement. Her medical history was significant for asthma, α thalassemia trait, and neonatal ocular chlamydia infection. She was taking no oral medications and had no known history of drug allergies.

Examination revealed a quiet girl in obvious discomfort. There were numerous tense bullae on an inflammatory base, many with an annular configuration and central crusting, distributed on her extremities (Figure 1), labia majora, ears, and face. There were fewer lesions on her trunk. Involved areas also revealed multiple crusted erosions, and she had hypopigmented annular patches on her upper inner thighs. The oral and ocular mucosae were uninvolved.

The patient was clinically diagnosed with linear IgA bullous dermatosis (LABD) of childhood. Treatment was begun with prednisolone at a dose of 12 mg/d (1 mg/kg per day) while a baseline laboratory evaluation was initiated. Hydroxyzine and cephalexin were also prescribed for pruritis and secondary superinfection, respectively.

A 4-mm punch biopsy specimen of a skin lesion revealed a subepidermal bulla containing neutrophils, supporting the clinical diagnosis of LABD of childhood. Direct immunofluorescence confirmed the diagnosis, revealing linear immunoglobulin deposition, primarily IgA, at the dermoepidermal junction. A baseline laboratory evaluation at this time included a glucose-6-phosphate dehydrogenase (G6PD) level, hepatic panel, renal panel, and complete blood cell and reticulocyte counts. The results were notable for a hemoglobin level of 10.7 g/dL, hematocrit of 32.6%, mean corpuscular volume of 73 fl, and a reticulocyte count of 0.4%. The G6PD level and findings of the renal panel were within normal limits. The hepatic panel results were also normal except for a mildly elevated aspartate aminotransferase level of 45 IU/L and an alkaline phosphatase value of 204 IU/L.

THERAPEUTIC CHALLENGE

Treatment with dapsone was begun at an initial dose of 6.25 mg/d (0.5 mg/kg per day). At the same time, a prednisolone taper was begun. The patient was closely monitored with weekly, biweekly, and eventually monthly blood examinations including a complete blood count, reticulocyte count, and hepatic and renal panels. Over the course of the next 6 months, the dapsone dose was gradually increased to 25 mg/d (2 mg/kg per day) in an attempt to gain better control of her disease. Her laboratory parameters remained stable, with an expected drop in her hemoglobin to as low as 9.2 g/dL and a corresponding increase in the reticulocyte count (maximum of 1.8%). The patient tolerated the treatment well and experienced some improvement in her condition, but she never experienced a complete remission and required numerous bursts of oral prednisolone (1 mg/kg of Prelone syrup; Muro Pharmaceuticals, Tewksbury, Mass) with a 3-week taper for flares. These episodes were only partially controlled with the combined dapsone and corticosteroid-burst therapy. Her energy level was consistently low, her affect depressed, and her disease a source of much emotional and financial distress (due to lost work time) for her family. The patient also began to exhibit signs of developmental delay.

SOLUTION

After 8 months of treatment with dapsone and intermittent pulsed corticosteroids, the patient began treatment with mycophenolate mofetil (CellCept; Roche Pharmaceuticals, Nutley, NJ) at 310 mg/m² per day (100 mg twice daily) and continued dapsone therapy at 25 mg/d. After 10 days of treatment, she experienced some lethargy with decreased oral intake and mild fevers. At this time, out of concern for possible mycophenolate mofetil toxic effects or a superimposed viral illness, the dose was de-
Linear IgA bullous dermatosis of childhood, also known as chronic bullous dermatosis of childhood, is a rare, acquired, self-limited autoimmune subepidermal bullous disease. Skin manifestations include large tense bullae as seen in bullous pemphigoid and/or vesicular lesions characteristic of dermatitis herpetiformis. The lesions are typically most prominent on the abdomen and perineum but may also involve the trunk, extremities, face, and mucous membranes. It is also common to see new lesions at the periphery of older blisters forming a configuration known as a “cluster of jewels.” The target antigen of the IgA autoantibodies in LABD is a 120-kd secreted antigen known as a “cluster of jewels.” The target antigen of the IgA antibody deposits in a linear fashion at the basement membrane zone—specific IgA antibody deposited in a linear pattern in the absence of other immunoglobulins under direct immunofluorescence examination of perilesional skin. Although these criteria are required to meet the strict definition of LABD, in the research setting there have been several cases of LABD with IgG antibody deposits in a linear fashion at the basement membrane zone in addition to the IgA antibodies. Pathologically, these cases represent an overlap of LABD and bullous pemphigoid. Clinically, however, the patient is usually treated in accordance with which antibody response predominates.

The most well-recognized treatment for LABD is dapsone or, if that fails, sulfapyridine. Other corticosteroid-sparing agents that may be beneficial include azathioprine, cyclosporine, and colchicine, but the risk-benefit profile for some of these therapies may not justify their use. Dapsone is an antimicrobial agent indicated for the treatment of all forms of leprosy as well as for dermatitis herpetiformis and Pneumocystis carinii pneumonia prophylaxis. It has traditionally proven very beneficial and well tolerated in the treatment of LABD in children. The main adverse effects of treatment with dapsone include hemolysis, methemoglobinemia, agranulocytosis, and peripheral neuropathy. It is therefore recommended that a complete blood count with differential and a reticulocyte count be done every 2 weeks for the first 3 months of therapy and then every subsequent 3 months. Due to the risk of hemolysis, extremely close monitoring is indicated if the drug is used in G6PD-deficient patients. In patients who do not tolerate dapsone, sulfapyridine is an alternative, with the addition of low-dose prednisone bursitis traditionally being the next step for those whose disease remains uncontrolled with monotherapy. Dicloxacillin has also been advocated as a possible therapy, which if effective, might be a safe and inexpensive alternative for some patients.

Recently, the newly developed immunosuppressive agent mycophenolate mofetil has been found to be a corticosteroid-sparing agent that is useful in the treatment of some blistering conditions. Mycophenolate mofetil is a new formulation of an old drug, mycophenolic acid, which was investigated in the 1970s as an oral agent for psoriasis. The drug was subsequently rediscovered in its new form, the prodrug of mycophenolic acid, and approved by the Food and Drug Administration in 1997 for the prevention of renal allograft
rejection. Once mycophenolate mofetil is absorbed, it is rapidly converted to mycophenolic acid, which acts by noncompetitively binding to inosine monophosphate dehydrogenase and thus blocking steps critical for de novo purine biosynthesis.23 Furthermore, it is relatively specific for lymphocytes, since they rely on the de novo pathway of purine synthesis rather than the salvage pathway. When the proliferative response of T and B lymphocytes is blocked, there is a reduction in antibody formation and the generation of cytotoxic T cells. It is likely that this decrease in antibody production is the mechanism of action for mycophenolate mofetil in the autoimmune blistering diseases. Mycophenolate mofetil is available in 250- or 500-mg capsules and a 200-mg/mL suspension.

Although mycophenolate mofetil is generally well tolerated, adverse effects of gastrointestinal disturbance (diarrhea, nausea, vomiting, and abdominal cramping) occur in up to 50% of patients. Other observed effects include reversible dose-dependent anemia, neutropenia, leukopenia, and an increased risk of infections including herpes zoster, herpes simplex, and flulike viral syndromes.24 Neurologic adverse effects include weakness, headache, tinnitus, and sleep disturbances.25 These hematologic, infectious, and neurologic complications of treatment are most often seen in patients concurrently receiving other immunosuppressant therapies and taking adult doses of mycophenolate mofetil greater than 2 g/d.26

The recommended dosage, monitoring regimen, and exact role of mycophenolate mofetil in the treatment of autoimmune and inflammatory cutaneous diseases remain anecdotal. Reports of mycophenolate mofetil being used in the treatment of skin disease have been published for psoriasis,18,27,28 bullous pemphigoid,26-31 pemphigus vulgaris,28,29,32 dyshidrotic eczema,33 arthritis,34 atopic dermatitis,35-38 and pyoderma gangrenosum39,40 in adults. These patients typically received doses between 2 and 3 g/d. This dose is comparable with that of adult organ-transplant recipients who receive 2 g/d for kidney and 3 g/d for heart transplants, in combination with other immunosuppressive therapy. To date, there are no published reports of children treated for blistering diseases with mycophenolate mofetil.

Our patient began treatment with mycophenolate mofetil at a dose of 310 mg/m² per day (100 mg twice daily), which is approximately one quarter of the 1.2 g/m² per day maximum dose recommended in pediatric renal transplantation patients.41,42 The dose was subsequently reduced to 155 mg/m²/day (30 mg twice daily) when the patient developed potential symptoms of toxic effects or a viral infection. The choice and initial dosing regimen of mycophenolate mofetil was based on the recommendation of a dermatologist (Grant J. Anhalt, MD) very experienced in the care of patients with autoimmune blistering diseases.

Cost analysis for treatment of a 15-kg child reveals that 2 daily doses of 100 mg of mycophenolate mofetil (CellCept suspension) costs $12.60 per month, while each monthly prednisolone burst (Preleone syrup) of 1 mg/kg/day with a taper over 3 weeks costs $17.40. These costs are fairly cost competitive, although other factors would influence this calculation, including the cost of necessary laboratory monitoring.

Our patient responded rapidly and quite well to the regimen of mycophenolate mofetil in combination with dapsone, experiencing only 1 episode of mild blistering over the course of 8 months. Prior to this, the patient required on average 1 steroid burst per month for disease control. Under our treatment, her laboratory parameters were consistently stable, and her overall status improved with gains in her energy level and catch-up in development.

Mycophenolate mofetil may be a useful adjunct in the treatment of LABD in childhood when monotherapy with dapsone fails, and it may hold promise for other autoimmune blistering diseases of childhood as well. Further clinical observations will clarify the potential roles of this steroid-sparing immunosuppressive agent.

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