Successful Treatment of Mucous Membrane Pemphigoid With Infliximab

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

Our patient was diagnosed with cicatricial pemphigoid (CP) in 2001. She demonstrated classic clinical findings and underwent biopsies that supported this diagnosis. She unfortunately experienced severe CP involving both of her eyes, oral mucosa, pharyngeal mucosa, and esophagus. Her left eye was seriously affected early in the course of her disease. She experienced significant scarring of the cornea of her left eye as well as of both its upper and lower eyelids, resulting in symblepharon and complete blindness of this eye. She has also endured considerable disease in her right eye and has undergone multiple corneal transplants of this eye (in March 2001, September 2004, January 2005, and April 2005). The most recent corneal transplant in April 2005 was performed emergently for a ruptured corneal ulcer. Our dermatology team was consulted during the patient’s hospitalization for this event.

At our initial encounter with the patient, she had complete blindness of her left eye and had recently undergone emergent corneal transplant surgery on her right eye. The right eye was sutured closed and bandaged. On examination, we observed multiple erosions of her soft palate and buccal mucosa (Figure 1). She reported difficulty eating for the past several years. This difficulty had progressed to the point where she could tolerate only soft, bland foods, and her pain significantly affected her oral intake and nutrition.

Our patient had previously received multiple therapies to treat her CP, including prednisone, cyclophosphamide, and dapsone. She had received one 5-day course of intravenous immunoglobulin; however, she had no response to this treatment and was also felt to be a poor candidate for it given her risk of congestive heart failure. Her comorbid medical problems included diabetes mellitus, coronary artery disease requiring stent placement, and high blood pressure. None of the treatments for her CP resulted in substantial improvement, and her disease continued to progress.

THERAPEUTIC CHALLENGE

Our patient presented with extremely severe mucous membrane pemphigoid (MMP) requiring aggressive therapy. However, her disease had not responded to first-line therapies that included prednisone and cyclophosphamide as well as dapsone and intravenous immunoglobulin.

SOLUTION

There has been at least 1 report1 in the literature of MMP successfully treated with etanercept, an anti–tumor necrosis factor α (TNF-α) agent. We have also had success in treating 3 patients with MMP with etanercept at our institution. Therefore, we felt an anti–TNF-α agent would be a good therapeutic choice for our patient. Given the severity of her disease and our desire to achieve a rapid response, we elected to begin a therapeutic regimen of infliximab (Remicade; Centocor Inc, Malvern, Pa). She received a dose of 600 mg (approximately 5 mg/kg) during her hospital stay. She received additional infusions at 2 weeks and 6 weeks after her initial dose and then began a regimen of infusions every 8 weeks. Our patient experienced rapid improvement with treatment. Two weeks after her first infusion, her oral symptoms had improved significantly. Within 6 months of her first infusion, she reported no difficulty swallowing and no limitations in her selection of foods. Furthermore, no oral...
lesions were noted on examination (Figure 2). She sees an ophthalmologist regularly for follow-up and states that her ocular disease has stabilized. To date, she has not required additional corneal transplants of her right eye and has been able to maintain the minimal vision she has in that eye. Of note, our patient was initially referred to an otolaryngologist given her oral symptoms, and she was seen several weeks after starting the infliximab regimen. It was felt that she was effectively improving while receiving the infliximab and that no further workup or treatment was warranted.

**COMMENT**

Mucous membrane pemphigoid is described as a “group of putative autoimmune, chronic inflammatory, subepithelial blistering diseases predominantly affecting mucous membranes that is characterized by linear deposition of IgG, IgA, or C3 along the epithelial BMZ.”

Mucous membrane pemphigoid is the appropriate name for a group of heterogeneous diseases that includes CP, benign MMP, oral pemphigoid, desquamative gingivitis, and ocular CP. Mucous membrane pemphigoid affects the mucous membranes with or without skin involvement. The most commonly affected area is the oral cavity (90%), with the eyes (65%), nose, nasopharynx, anogenitals, skin (20%-30%), larynx, and esophagus involved less often.

Oral disease is characterized by erythematous patches, blisters, erosions, and ulcerations. The primary feature of ocular MMP is progressive, conjunctival fibrosis. Patients may develop conjunctival erosions, symblepharon, ankyloblepharon, shortening of the fornices, entropion, trichiasis, and scarring. Owing to exposure and repeated mechanical trauma of the cornea, these patients can develop recurrent corneal erosions, neovascularization, and scarring that eventually result in blindness. Corneal perforations and endophthalmitis may also follow.

Mucous membrane pemphigoid must be differentiated from other diseases involving the mucous membranes. An international consensus meeting in 1999 determined that diagnosis of MMP required consistent clinical and direct immunopathologic findings. Findings from other workup, including histologic findings and indirect immunofluorescence, can be used to support the diagnosis.

Treatment of MMP has not been evaluated using well-controlled clinical trials; therefore, most recommendations are based on published reports and the experience of treating physicians. The consensus meeting stressed the importance of a multidisciplinary approach often requiring the involvement of ophthalmologists, dentists, dermatologists, oral surgeons, primary care physicians, gynecologists, otolaryngologists, and gastroenterologists. The consensus meeting further recommended stratifying patients into high-risk and low-risk groups when determining appropriate therapy. Patients with disease involving ocular, genital, nasopharyngeal, esophageal, and laryngeal mucosa as well as patients with rapidly progressing disease should be treated using the high-risk algorithm. This consists of initial treatment with prednisone and cyclophosphamide. Alternative therapy recommended included dapsone, azathioprine, and intravenous immunoglobulin. Low-risk patients include those with disease occurring only in the oral mucosa or oral mucosa and skin. These patients have a much lower incidence of scarring; thus, they can be treated more conservatively.

Multiple therapies for MMP have been reported in the literature. Topical therapies include intralesional corticosteroids, topical corticosteroids, cyclosporine, and tacrolimus. Systemic therapies used have included oral corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, methotrexate, dapsone, tetracycline and nicotinamide, thalidomide, intravenous immunoglobulins, and plasma exchange. There has also been 1 report in the literature of a patient with recalcitrant CP successfully treated with etanercept.

The rational for using anti–TNF-α agents comes from recent scientific studies. Tumor necrosis factor α levels were found to be elevated in the serum samples of patients with MMP compared with controls in a study reported in 1993. Subsequent studies have supported the role of TNF-α in MMP. In addition, TNF-α was shown to induce the expression of migration inhibitory factor, a cytokine found to have elevated levels in conjunctival tissues in patients with ocular MMP. Macrophage colony-stimulating factor has also been demonstrated to have an increased expression in conjunctival tissue in patients with active ocular MMP. Macrophage colony-stimulating factor was further shown to be induced by TNF-α; TNF-α levels have also been demonstrated to be elevated in the blister fluid of patients with bullous pemphigoid, a similar autoimmune blistering disease.

Given that our patient had not received benefit from first-line therapies for her progressive MMP and that she needed aggressive, urgent treatment, we felt that an anti–TNF-α agent was a good option for her. The reported successful response in a patient with MMP treated with etanercept, as well as our personal success in treating a few patients in our institution with etanercept, supported our decision to begin a regimen of an anti–TNF-α agent in our patient. We chose infliximab because it was easy to initiate the infusions during her inpatient stay, and we were hoping to achieve a fast response to treatment.
The rapid, positive response of our patient to infliximab further supports the potential use in treating patients with MMP with the anti–TNF-α agents. We specifically note the encouraging results in this case obtained with infliximab, an anti–TNF-α agent, which, to our knowledge, has not previously been reported for use in patients with MMP. A more extensive study, preferably a randomized controlled trial, would be ideal in further evaluating this promising treatment.

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REFERENCES