Successful Treatment of Mucous Membrane Pemphigoid With Etanercept in 3 Patients

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Background: Mucous membrane pemphigoid (MMP), also known as cicatricial pemphigoid, is a serious, autoimmune, blistering disorder that can result in blindness and other complications as a result of scarring of the mucous membranes. Effective treatment modalities are often toxic. Herein, we describe a novel therapeutic approach that is based on 2 reports in the literature of the successful use of etanercept to treat MMP.

Observations: Three patients with MMP were treated with subcutaneous injections of 25 mg of etanercept twice weekly. All 3 patients had oral mucosal involvement, and 1 had severe, recalcitrant, ocular disease. Oral mucosal disease improved in all 3 patients. The patient with ocular involvement experienced stabilization of progression.

Conclusions: Effective treatment modalities for MMP are often toxic. Etanercept may be an effective treatment option for MMP of the oral and ocular mucous membranes. This therapy should be considered as an alternative treatment option for patients who would require other aggressive systemic treatments, such as cyclophosphamide, corticosteroids, azathioprine sodium, and intravenous immunoglobulin.

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Mucous membrane pemphigoid (MMP), also known as cicatricial pemphigoid, is a heterogeneous group of autoimmune, subepithelial blistering diseases, with a propensity to affect the mucous membranes more often than the skin. Ultimately, scarring of the mucous membranes occurs, which can result in blindness as well as stenosis of the nasopharynx, trachea, esophagus, vagina, urethra, and rectal mucosa.

There is no gold standard therapy for MMP. Treatment for mild disease includes topical or intralesional corticosteroids,1 tetracycline hydrochloride along with niacinamide,2,3 topical tacrolimus,4 and topical cyclosporine.1 For more severe cases, including those with ocular, laryngeal, pharyngeal, or esophageal involvement; those with more widespread involvement; or for those recalcitrant to previous therapies, systemic anti-inflammatory or immunosuppressive medications have been used.1 Some of these systemic medications include corticosteroids,5 dapsone,6,7 cyclophosphamide,8 mycophenolate mofetil hydrochloride,9 intravenous immunoglobulin,10,11 azathioprine sodium, mitomycin C,9 interferon alfa-2b,12 and methotrexate.13 The response of MMP to these treatment modalities has been variable. Moreover, many of them are associated with toxic effects.

Tumor necrosis factor (TNF)α has been implicated in the pathogenesis of MMP.5,14-17 Moreover, there have been 2 case reports18,19 in the literature describing the successful treatment of 2 patients with MMP with the anti-TNF-α agent etanercept. Based on these reports, we treated 3 patients with MMP with subcutaneous injections of 25 mg of etanercept (Enbrel; Amgen, Thousand Oaks, Calif) twice weekly. All 3 patients had oral mucosal involvement, and 1 had severe, recalcitrant, ocular disease.

REPORT OF CASES

CASE 1

A 60-year-old woman with a medical history of osteoarthritis, diet-controlled diabetes mellitus, breast cancer, and cervical cancer presented with a history of painful, oral erosions that began in 1996. She was initially diagnosed as having infectious gingivitis. In 2000, she began to experience painful eyelids and had mucous discharge from her eyes. She was referred to an ophthalmologist, who diagnosed her as having trichiasis with associated dry eye syndrome. She was referred to a surgeon, who subsequently per-
formed a gingival mucosal biopsy, the findings of which were consistent with a diagnosis of MMP. She was treated for several years with 75 mg of dapsone 3 times daily, 50 mg of prednisone once daily, and 100 mg of azathioprine sodium twice daily.

By August 2002, she was not much better and continued to have significant oral pain. She was referred to the Washington University (St Louis, Mo) medical dermatology clinic. On examination, she had multiple erosions along the upper and lower gingiva. Nystatin swish and swallow and clobetasol propionate ointment were added to her regimen, and the prednisone was tapered off. This led to good control of symptoms until February 2004. At that time, the patient developed anemia and fatigue. Consequently, the dose of dapsone was reduced to 75 mg once daily and the dosage of azathioprine sodium to 150 mg once daily. This led to an immediate flare with erosions developing on her gingiva, hard palate, and lateral tongue (Figure 1A).

The dosage of azathioprine sodium was increased back up to 100 mg twice daily; the dosage of dapsone was kept at 75 mg once daily. In addition, treatment with etanercept, 25 mg subcutaneously twice weekly, was initiated. Within 1 month, the erosions on her hard palate and tongue had healed (Figure 1B), and the gingival erosions were improved. She reported being able to eat solid foods for the first time in years. At this time, treatment with dapsone was discontinued. One month later, she continued to do well clinically. Therefore, the dosage of azathioprine sodium was decreased to 150 mg once daily, and the etanercept treatment was continued at the same dose.

After 3 months of therapy with etanercept, the patient developed myalgias and stopped taking the etanercept on her own accord. Eighteen days later, she returned to the clinic emergently with multiple painful oral erosions. Treatment with etanercept was resumed at 25 mg subcutaneously twice weekly. Approximately 1 month after the etanercept was resumed, she was clear of all oral erosions except for 1 recalcitrant upper gingival erosion. Her symptoms remained well controlled for nearly a year. Unfortunately, owing to loss of her health insurance, the patient was forced to discontinue etanercept. Within 1 month she again developed numerous gingival erosions. She continues to have problems with recurrent trichiasis, for which she receives frequent epilation.

CASE 2

A 47-year-old woman, with a medical history of osteoarthritis and hypertension, presented with a 4-year history of painful, gingival erosions. A gingival mucosal biopsy performed 2 years prior to presentation demonstrated desquamated strips of squamous epithelium with a marked chronic inflammatory infiltrate, along with areas of focal acute inflammation. These findings were most consistent with a diagnosis of lichen planus or MMP. She was treated with dexamethasone elixir and topical fluocinonide gel, 0.05%.

In July 2003, the gingival erosions worsened, and she developed a new painful lesion on her scalp. She was seen at our clinic, and a physical examination revealed erosions on the lower gingiva and an ulceration on her scalp (Figure 2A). A biopsy of the scalp ulceration was performed, which demonstrated a subepidermal blister that extended down along the hair follicle. There was also a band of scarring in the papillary dermis, along with a lymphocytic, plasma cell, and eosinophilic infiltrate. Direct immunofluorescence demonstrated immunoglobulin G, immunoglobulin M, and complement 3 along the basement membrane zone. These findings were consistent with a diagnosis of MMP.

The patient’s disease progressed to involve her eyes. She was referred to the ophthalmology department, where she was found to have bilateral symblephara, a left conjunctival and corneal ulceration with subepithelial erythema and early fibrosis, and bilateral keratopathy. Owing to progressive ocular disease, aggressive therapy with intravenous immunoglobulin 2 g/kg given over 5 days every 3 weeks, 60 mg/d of prednisone, 100 mg of dapsone once daily, clobetasol propionate ointment topically twice daily, and nystatin swish and swallow twice daily was ini-
tiated in September 2003. After 3 cycles of intravenous immunoglobulin, she developed hypertension and headaches. She was treated with 25 mg of hydrochlorothiazide daily, and the dosage of prednisone was reduced to 40 mg/d. Although her oral lesions improved somewhat on this regimen, her ocular disease continued to worsen.

The addition of cyclophosphamide was considered. However, in October 2003, she began having increased pain and the sensation of a foreign body in her eyes. Ophthalmologic evaluation revealed herpetic conjunctival ulcerations, for which she received 1 mg of valacyclovir hydrochloride orally 3 times daily and acyclovir ointment to both eyes 4 times daily. Because of the herpetic ulcerations, treatment with cyclophosphamide was not initiated.

In November 2003, a complete blood cell count revealed pancytopenia (white blood cell count, 2.0 × 10^9/L; hemoglobin, 10.7 g/dL; hematocrit, 32.7%; and platelet count, 158 × 10^9/L). Findings from a bone marrow biopsy showed changes that were most consistent with drug-induced pancytopenia. Therefore, treatment with prednisone and dapsone were discontinued. The intravenous immunoglobulin, nystatin, and topical clobetasol were continued, and she received treatment with topical cyclosporine, 0.05%, eye drops. Therapy with mycophenolate mofetil was initiated but was discontinued owing to development of elevated liver enzymes.

By May 2004, the patient’s ocular disease continued to progress despite 10 cycles of intravenous immunoglobulin. The course of her illness was further complicated by repeated herpetic ulcerations despite treatment with 1 g of valacyclovir hydrochloride 3 times daily for 7 months. Owing to persistent pancytopenia, therapy with cyclophosphamide was not considered a safe option. Given our success in the use of etanercept with patient 1 and the low risk of bone marrow suppression with etanercept, therapy with subcutaneous injections of 25 mg of etanercept twice weekly was initiated in June 2004.

Within 4 weeks, she had only 1 remaining gingival erosion, which healed 3 months later, and she felt a notable improvement in her ocular symptoms. The interval between intravenous immunoglobulin cycles was lengthened by 2 weeks after each cycle. Her ocular disease gradually became inactive. Nearly 2 years later, she remains free from oral, scalp, or active ocular involvement, and her symblephara remain stable (Figure 2B). She has had no further herpetic complications since she began treatment with etanercept. She has been tapered off intravenous immunoglobulin, and her dose of etanercept has been changed to 50 mg subcutaneously once weekly for greater convenience. Her blood cell counts have normalized except for persistent lymphopenia.

**CASE 3**

A 49-year-old woman, with a medical history of hypertension and diabetes mellitus, presented with a 3-year history of painful erosions on her gingiva. In July 2004, a gingival biopsy was performed, which demonstrated a focal area of subepithelial separation, dermal sclerosis with a chronic inflammatory infiltrate composed primarily of plasma cells, and a focal interface mucositis with exocytosis of lymphocytes in the basal layer of the epidermis. Direct immunofluorescence showed IgG, IgM, and complement 3 at the basement membrane zone. These findings are consistent with a diagnosis of MMP. Ophthalmologic examination of her eyes revealed only minimal nuclear sclerosis without symblepharon. Treatment with clobetasol propionate ointment applied twice daily to the gums and daily nystatin swish and swallow was initiated early in September 2004. However, no improvement was noted, so etanercept, 25 mg twice weekly, was added in November 2004. Within 1 month, her gingival erosions healed.

**COMMENT**

Mucous membrane pemphigoid is a rare, chronic, autoimmune disorder that typically affects the mucous membranes more often than the skin. It ultimately results in erosions, ulcerations, and scarring and has a significantly increased morbidity and mortality associated with it. Typically, MMP affects older individuals (those aged 60-80 years), but it has also been reported in young children.

Any mucous membrane can be involved, but the most commonly involved sites in decreasing frequency in-
clude the oral mucosa (85%), conjunctiva (64%), skin (24%), pharynx (19%), external genitalia (17%), nasal mucosa (15%), larynx (8%), anus (4%), and esophagus (4%). Oral MMP most commonly presents as desquamative or erosive gingivitis, but severe involvement can lead to ulcerations, erosions, and fibrosis of the oral mucosa. Ocular MMP is characterized by conjunctival inflammation, which is followed sequentially by conjunctival shrinking and fibrosis, leading to trichiasis, entropion, symblepharon, surface keratinization, and ankyloblepharon. Nasopharyngeal involvement can lead to ulcerations of the septum, stenosis, and obstruction necessitating a tracheostomy. Esophageal disease may manifest with ulcerations, dysphagia, odynophagia, strictures, and stenosis. Urethral stenosis, vaginal orifice stenosis, and rectal stenosis have also resulted from chronic inflammation and scarring attributable to MMP.

Although the exact pathogenesis of MMP has not been elucidated, support for an autoimmune etiology comes from several studies. Several auto-antibodies against epithelial basement membrane antigens have been discovered in patients with MMP, including bullous pemphigoid antigens 1 and 2, laminin 5 and 6, type 7 collagen, integrin β4 subunit, and as-yet unidentified antigens (a 45-kDa protein, uncein, a 168-kDa protein, and a 120-kDa protein). It is hypothesized that a genetic predisposition, as demonstrated by the association of human leukocyte antigen—DQB1*0301 with MMP along with an environmental trigger, results in the production of auto-antibodies against these antigens, resulting in deposition of IgG, IgA, and complement 3 at the epithelial basement membrane.

Cellular immunity and cytokines also play a role in the pathogenesis of MMP, particularly in regard to inducing a fibroblastic proliferation, with the end result being excessive collagen production and fibrosis. The cytokine TNF-α is thought to play a prominent role in the pathogenesis of MMP. Tumor necrosis factor α is a proinflammatory cytokine released by macrophages, mastocytes, keratinocytes, and fibroblasts in response to environmental injury or microbial invasion. It induces other chemokines, which attract neutrophils, macrophages, and memory T cells to the site of injury. Tumor necrosis factor α is also one of the major fibrotic cytokines along with interleukin 1, platelet-derived growth factor, fibroblast growth factor, and transforming growth factor β, and it has been shown to stimulate the growth of fibroblasts.

Chronic overproduction of TNF-α has been recently implicated in the pathogenesis of MMP and other autoimmune blistering disorders. Lee et al demonstrated the presence of significantly increased levels of TNF-α in the serum of people with ocular MMP compared with serum from control groups. Razzaque et al have demonstrated increased expression of the proinflammatory cytokines, macrophage migration inhibitory factor, and macrophage-colony stimulating factor in conjunctival fibroblasts of patients with ocular MMP compared with controls. Tumor necrosis factor α has been shown to induce the expression of these cytokines.

Similarly, increased levels of TNF-α have been found in the sera and blister fluid of patients with other autoimmune blistering disorders, such as pemphigus vulgaris and bullous pemphigoid. Satci et al showed significantly elevated tear TNF-α levels in patients with scarring trachoma, which were increased in concordance with the severity of scarring noted. This study re-emphasizes the involvement of TNF-α in the ocular cicatrizizing processes.

Currently, there are 3 anti–TNF-α agents available: infliximab, adalimumab, and etanercept. These anti-TNF-α therapeutics have been used to treat psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn disease, and ankylosing spondylitis. Further trials are currently being undertaken to determine their efficacy for many other inflammatory and autoimmune diseases.

Etanercept is a recombinant human dimeric fusion protein consisting of the extracellular ligand binding domain of the TNF-α receptor fused to the Fc portion of human IgG1. It acts as a competitive inhibitor of TNF-α by binding to both soluble and receptor-bound molecules of TNF-α.

To our knowledge, the use of etanercept for the treatment of MMP has been documented only twice in the literature. Sacher et al reported the use of etanercept in a 72-year-old woman with a 3-year history of oral MMP that was recalcitrant to prednisone (up to 1 mg/kg per day), azathioprine sodium (100 mg/d), mycophenolate mofetil hydrochloride (1 g/d), and topical cyclosporine. They initiated treatment with 25 mg of subcutaneous etanercept twice weekly, in combination with 60 mg of prednisone daily. After only the third dose, cessation of the oral blistering with subsequent healing occurred. After a total of 6 injections, the patient reportedly remained virtually disease free for more than 8 months when receiving only 1 mg/d of prednisone. Labrecque and Null described a 68-year-old woman with oral CP that progressed to scarring and ocular MMP despite aggressive oral corticosteroids and dapsone. Etanercept at a dose of 25 mg twice weekly with concomitant systemic corticosteroids resulted in decreased ocular inflammation within 10 days. The dose of etanercept was increased to 50 mg twice weekly, which enabled the patient to discontinue systemic steroids. The patient still requires systemic corticosteroids on an as-needed basis.

Mucous membrane pemphigoid is a serious disorder with potentially devastating consequences, including stricture formation of the mucosal surfaces and blindness. It can be difficult to treat, and without treatment, progression of the disease is likely. There is no gold standard therapy for MMP. The improvement in MMP after treatment with etanercept in 2 patients previously reported in the literature, as well as in the cases of 3 patients reported herein, supports the hypothesis that TNF-α plays an important role in the pathogenesis of MMP. Given the notable efficacy of etanercept in these 5 patients and the low adverse effect profile of etanercept and the other anti–TNF-α agents compared with other more nonspecific immunosuppressants, anti–TNF-α agents should be considered as an alternative treatment option for patients who would require aggressive systemic treatments, such as cyclophosphamide, corticosteroids, azathioprine, and intravenous immunoglobulin. A randomized, controlled clinical trial is warranted to further investigate the safety and efficacy of anti–TNF-α agents in the treatment of MMP.
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