The treatment of pemphigus vulgaris (PV) is generally regarded as challenging. Patients with the disease require long-term systemic therapy, creating concern for the toxicities of these treatments. Corticosteroids, as drugs of first choice, often must be combined with steroid-sparing agents to prevent hazardous long-term side effects. We describe a 62-year-old woman with long-standing PV whose cutaneous disease responded to therapy with the tumor necrosis factor α (TNF-α) antagonist etanercept, which was started for treatment of her inflammatory seronegative arthritis. To our knowledge, this is the first report of its efficacy in the treatment of PV.

Case Report
A 62-year-old woman presented to the rheumatology clinic for treatment of inflammatory seronegative arthritis involving both ankles and knees that had been diagnosed in 1983. She had been diagnosed with PV during a hospitalization in 1989 and had been treated for the disease since that time. The patient initially presented with painful oral blisters that had spread into her throat. Her medical history included a diagnosis of osteoporosis, possibly a result of her prednisone regimen, and a family history of arthritis and breast cancer.

After the initial diagnosis of PV, the patient was given intravenous corticosteroids for 3 weeks as an inpatient. Subsequently, outpatient treatment included a prednisone dose ranging as high as 120 mg daily, tapering down to 5 mg every other day, with wide fluctuations as the disease flared and improved. During the course of the disease, trials of methotrexate and oral gold were discontinued because of lack of efficacy. In 2002, mycophenolate mofetil was started at 1500 mg twice daily in conjunction with prednisone 5 mg every other day. This was initially followed by a dramatic improvement in the PV, which flared as the mycophenolate mofetil was tapered. The patient tolerated this treatment well, but reported a worsening of her arthritis with tapering of prednisone.

To treat her arthritis, the patient was placed on a therapeutic regimen in May 2003 with etanercept 25 mg subcutaneously twice weekly in combination with prednisone 10 mg daily. The patient discontinued mycophenolate mofetil. After the third dose of etanercept, the patient reported a cessation of
blistering and a subsequent remission of her PV. The patient then discontinued prednisone usage for the first time in 11 years and remained disease free for 4 months. At that point, she developed a few oral and cutaneous erosions. Mycophenolate mofetil was restarted at 2000 mg twice daily, and the patient was prescribed prednisone 20 mg daily. Etanercept was discontinued. The patient subsequently developed an increase in her arthritic symptoms and further erosions. After several weeks, the mycophenolate mofetil was discontinued and etanercept 25 mg subcutaneously twice weekly was restarted. The patient is currently on this dose of etanercept in addition to prednisone 10 mg every other day and has no cutaneous or oral erosions.

Comment

Evidence has pointed to a possible role of TNF-α associated with PV. In 1994, Ujihara et al. first noted elevated TNF-α levels in association with PV. A 76-year-old woman with many bullae and erythema on her trunk and extremities was diagnosed with PV using a biopsy specimen and direct immunofluorescence. Examination of her blood revealed that she also had autoimmune hemolytic anemia. TNF-α was detected at significant levels in the blister fluid of this patient. The authors argued that further investigations were needed to clarify the role of TNF-α in PV.

To elucidate the role of complement (C) in PV and to define which cytokines play a role in C₃ messenger RNA (mRNA) expression, Feliciani et al. performed an in vitro study in human keratinocytes. Normal human epidermal keratinocytes were incubated with PV serum and C₃ mRNA was measured. An early C₃ mRNA expression was seen after 30 minutes with a peak level after 1 hour. Blocking studies using antibodies against human interleukin 1α (IL-1α) and TNF-α in normal human epidermal keratinocytes, together with PV-IgG, showed reduction of in vitro–induced acantholysis and inhibition of C₃ mRNA expression. The results of this study supported the hypotheses that complement C₃ is important in PV acantholysis and complement activation is increased by IL-1α and TNF-α.

To further study the role of IL-1α and TNF-α in the pathogenesis of PV, Feliciani et al. performed both in vitro and in vivo studies. The results of the in vitro study demonstrated that PV IgG induced IL-1α and TNF-α mRNA in the skin. The potential pathogenic role of these mediators was demonstrated by a blocking study using antibodies against human IL-1α and TNF-α in keratinocyte culture specimens. A combination of these antibodies inhibited in vitro PV IgG–induced acantholysis.

To confirm the role of these 2 cytokines in PV, the authors conducted passive transfer studies using IL-1–deficient mice (ICE/-, IL-1β/-) and TNF-α receptor–deficient mice (TNFR-1R2/-). Both groups demonstrated a decreased susceptibility to the passive transfer of PV. The authors concluded that their data supported the role of cytokines IL-1 and TNF-α in the pathogenesis of PV.

Lopez-Robles et al. obtained 16 biopsy specimens from patients with various types of pemphigus. The specimens were studied by in situ hybridization using DNA fluorescent probes for IL-6 and TNF-α mRNA. Fifty-six percent of lesional biopsy results exhibited cytokine gene expression, which was poorly expressed in noninvolved skin. Deposits of TNF-α and IL-6 were products of in situ transcription at the epidermal level. The authors concluded that inflammatory cytokine expression around the blister could play a mediator role in pemphigus lesions by increasing epithelial damage.

Etanercept is a 100% human TNF receptor made from the fusion of 2 naturally occurring TNF receptors. It binds to TNF with greater affinity than natural receptors, which are monomeric. The binding of etanercept to TNF renders the bound TNF biologically inactive, resulting in significant reduction in inflammatory activity. Etanercept is currently approved for the treatment of rheumatoid arthritis and psoriatic arthritis but has been used successfully in the treatment of psoriasis.

Sacher et al. recently reported successful treatment of recalcitrant cicatrical pemphigoid with etanercept. They described a 72-year-old woman with long-standing cicatrical pemphigoid recalcitrant to established treatment regimens who responded rapidly and lastingly to therapy with etanercept. The patient was initially treated with varying amounts of prednisone, azathioprine (discontinued because of elevated liver enzymes), and mycophenolate mofetil (discontinued because of adverse side effects). After being lost to follow-up for one year, the patient re-presented on a solely prednisone regimen (10 mg/d). She was admitted to a clinic, and the prednisone was increased to 70 mg daily. In addition, topical cyclosporine and anesthetizing oral irrigation was administered. However, response to this treatment was limited. Due to the patient’s age, concomitant internal and neurologic diseases, and merely fair general condition, the authors were disinclined to resort to more toxic systemic agents such as dapsone, methotrexate, cyclosporine, or cyclophosphamide. Because of recent publications reporting elevated levels of TNF-α in serum and
Recalcitrant Pemphigus Vulgaris

blister fluid in patients with bullous autoimmune disorders, they treated their patient with etanercept (25 mg subcutaneously twice weekly) in combination with prednisone (initially 60 mg/d). After the third dose, cessation of oral blistering with subsequent healing occurred, and the prednisone was rapidly reduced below 7 mg daily. Six injections were administered in total, and the patient has remained virtually disease free for more than 8 months on just 1 mg of prednisone daily.6

Our patient with PV showed a similar fortuitous response, with tapering off of prednisone after initiation of etanercept for her arthritis and a subsequent period free of disease. The patient experienced a minor flare after 4 months, and the etanercept was discontinued, resulting in further worsening of the PV. Upon reinstitution of etanercept, the patient’s blisters once again cleared. This rechallenge is a positive indication of a true clinical effect of etanercept in this case. Based on our case, etanercept may be a potential maintenance and steroid-sparing therapy in PV without the organ toxicity of current therapeutic options. Further studies are needed to better evaluate the efficacy of etanercept in PV; however, our report and that of Sacher et al6 both suggest a possible important future role in the treatment of autoimmune blistering diseases.

REFERENCES