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Off-Label Dermatological Uses of Etanercept Treatment

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Abstract

Background: Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine that plays an immunomodulatory role in a variety of systemic and dermatologic disease. Its blockade can be achieved by using specific inhibitors like etanercept. At present, etanercept is approved for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and psoriasis treatment. However, it has been used with promising results in other inflammatory dermatoses. Etanercept treatment have been reported in the following dermatologic diseases: sarcoidosis, hidradenitis suppurativa, acne vulgaris, cicatricial pemphigoid, pemphigus vulgaris, Hailey-Hailey disease, Behçet's disease, oral aphthous stomatitis, pyoderma gangrenosum, multicentric reticulohistiocytosis, apthous stomatitis, Sneddon-Wilkinson disease, acrodermatitis continua of Hallopeau, SAPHO syndrome, pityriasis rubra pilaris, vitiligo, necrobiosis lipoidica, silicone granulomas, Sweet's syndrome, atopic dermatitis, dyshidrotic eczema, toxic epidermal necrolysis, alopecia areata, centrifugal annular erythema, primary amyloidosis, erythroderma-related pruritus in Sézary syndrome, cutaneous T-cell lymphoma, inflammatory linear verrucous epidermal nevus, excessive scarring, postherpetic neuralgia, dermatomyositis, vasculitis, lupus erythematosus, and scleroderma. The vast majority of these reports are in the form of individual case reports and small case series. A growing number of published reports suggest that etanercept treatment may be effective in the treatment of numerous inflammatory skin disease outside their currently approved indications.

Introduction

TNF-α is a cytokine with a central role in inflammation. Although mostly produced by monocytes and macrophages, TNF-α is also produced in the skin by keratinocytes, melanocytes, Langerhans cells, activated T cells, natural killer cells, and mast cells in response to infection or keratinocyte death. Soluble TNF-α monomers form a trimer, which binds to the TNF-α receptor 1 or TNF-α receptor 2, entities found in most cells of the body excluding erythrocytes and unstimulated lymphocytes. Cross-linked receptors induce signal transduction cascades that ultimately influence cell differentiation, mitogenesis, regulation of cytotoxic responses, inflammation, immunomodulation, and wound healing. Specifically, TNF-α receptor activation upregulates vascular cell leukocyte adhesion molecule 1, intercellular adhesion molecule 1 (ICAM-1), E-selectins, and metalloproteinases 1 and 3, all of which promote cellular infiltration. It also increases vascular endothelial growth factor, increases production of proinflammatory cytokines, increases keratinocyte production of transforming growth factor α causing epidermal proliferation, inhibits melanocyte activity, promotes growth of fibroblasts, and releases acute

phase reactants from hepatocytes. Most available data on the etanercept are related to studies of rheumatoid arthritis, but use for dermatologic conditions is increasingly common. Etanercept is a fusion protein of human IgG and the extracellular component of the TNF-α receptor. By binding unbound TNF-α, etanercept acts as a competitive inhibitor. Etanercept has Food and Drug Administration approval for treatment of rheumatoid arthritis, psoriasis and psoriatic arthritis, polyarticular juvenile idiopathic arthritis, and ankylosing spondylitis [**1, 2, 3**]. TNF-α, via its induction of proinflammatory cytokines and accretion of an inflammatory infiltrate, is necessary for granuloma development and maintenance. At present, etanercept is approved for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and psoriasis treatment. However, it has been used with promising results in other inflammatory dermatoses. We review the current literature on the offlabel uses of etanercept in dermatology (**Table 1**) [**2, 3**].

A.Neutrophilic Dermatoses

1.Pyoderma Gangrenosum

There have now been multiple reports describing successful treatment of PG with etanercept. There has been one report that suggests that etanercept may not be as effective as the other TNF antagonists for the treatment of PG. This case involved a patient with extensive skin ulcerations as well as abscesses in his spleen and psoas muscle that were also believed to be related to his PG. The patient responded rapidly to infliximab with the improvement of his skin lesions and the disappearance of the splenic and psoas muscle abscesses. Unfortunately, during his fourth infliximab infusion, he had an anaphylactoid reaction, which precluded further infusions. After infliximab was stopped, the patient's PG, including the splenic and psoas abscesses, again began to flare. Treatment was initiated with etanercept, 25 mg 3 times weekly. No benefit was seen after 3 weeks of treatment. At that time, etanercept was discontinued and treatment with adalimumab, 40 mg weekly, was initiated. The patient again experienced rapid improvement of both his skin and extracutaneous disease. Although etanercept was not effective for this patient, 3 other reports have been published of patients who achieved complete remission of PG with etanercept treatment. A case is presented of a 54-year-old man diagnosed with pyoderma gangrenosum. He completed treatment with oral prednisolone with favorable outcome, but with recurrence after glucocorticoid therapy withdrawal. Thalidomide was introduced, but after complaints of glove and sock paresthesia and hypoesthesia, the drug was discontinued. Taking into account the favorable outcome with thalidomide and the necessity of drug withdrawal, it was decided to introduce therapy acting on the same step in the inflammation cascade. In this regard, etanercept was initiated. The lesions were resolved and the authors suggested that etanercept was an alternative therapy for refractory pyoderma gangrenosum [**4, 5**].

2.Sweet's Syndrome

One report has been published of two patients with Sweet's syndrome and concurrent RA who achieved complete clearance with subcutaneously administered etanercept (50 mg twice weekly in the first patient and 25 mg twice weekly in the second patient). A previous report demonstrated elevated levels of TNF-α in the lesions of Sweet's syndrome, suggesting a possible mechanism for the improvement seen with etanercept. However, improvement in the underlying RA may also have been a contributing factor [**6, 7**].

3.Subcorneal Pustular Dermatosis (Sneddon-Wilkinson Disease)

Sneddon-Wilkinson disease (SWD), also known as subcorneal pustular dermatosis, is a rare, chronic eruption that is often difficult to treat, particularly in patients who do not respond to or cannot tolerate dapsone. Few case reports exist of patients with SWD treated with anti-TNF-α therapy. *Berk* et al reported two patients with SWD refractory to numerous treatments, who responded to etanercept. Sneddon–Wilkinson disease (SWD) is characterized by annular, superficial, sterile pustules typically involving the intertriginous

Table 1. Off-label Uses of Etanercept in Skin Diseases

A-Autoimmune Connective Tissue Disease
1-Lupus erythematosus
2-Dermatomyositis
3-Scleroderma
4-Graft-Versus-Host Disease
5-Behçet's disease
B-Autoimmune Blistering Diseases
1-Bullous pemphigoid
2-Cicatricial pemphigoid
3-Pemphigus vulgaris
4-Benign familial pemphigus (Hailey-Hailey disease)
C- Neutrophilic dermatoses
1-Pyoderma gangrenosum
2-Sweet's syndrome
3-Sneddon-Wilkinson syndrome
4-Vasculitis (Wegener granulomatosis and polyarteritis nodosa)
5-Acrodermatitis continua Hallopeau
D- Granulomatous Skin Diseases
1- Sarcoidosis
2-Granuloma annulare
3-Necrobiosis lipoidica
4-Silicone granulomas
5-Cutaneous granulomas in patients with common variable immunodeficiency
E-Other inflammatory dermatoses
1-Atopic dermatitis
2-Dyshidrotic eczema
3-Multicentric reticulohistiocytosis
4-Toxic epidermal necrolysis
5-Acne vulgaris
6-Hidradenitis
7-Oral aphthous stomatitis
8-Alopecia areata
9-Centrifugal annular erythema
10-Primary amyloidosis
11-Erythroderma-related pruritus in Sézary syndrome
12-Cutaneous T-cell lymphoma
13-Inflammatory linear verrucous epidermal nevus
14-SAPHO syndrome
15-Excessive scarring
16-Vitiligo
17-Postherpetic neuralgia
18-Pityriasis rubra pilaris
19-PAPA syndrome

areas, trunk and proximal limbs. SWD often affects middle-aged women, may be associated with autoimmune disorders and is often difficult to treat. There are four case reports of etanercept therapy for SWD. *Berk* et al reported two patients whose SWD was refractory to numerous treatments before responding to etanercept 50 mg twice weekly. Etanercept 50 mg twice weekly was started as systemic monotherapy, with topical steroids as needed. At follow-up 1 and 4 months after starting treatment, he was markedly improved. At the 7-month follow-up, the SWD was slightly flaring but remained well-controlled with < 5% BSA involvement, and at the 9-month follow-up, it was markedly improved. The patient noted that his SWD was better controlled on etanercept than any previous treatment. Many treatments for SWD have been reported, including dapsone, sulfapyridine, corticosteroids, retinoids, colchicine, ketoconazole, minocycline, ciclosporin, mebhydroline and phototherapy. Although dapsone is often considered to be the first-line treatment, some patients fail to respond or cannot tolerate the side-effects including haemolytic anaemia. The role of TNF-α in the pathogenesis of SWD is also supported by a case report that showed increases in blister fluid and serum TNF-α levels in SWD. TNF-α plays an important role in the pathogenesis of inflammatory bowel diseases, pyoderma gangrenosum and rheumatoid arthritis, which have all been associated with SWD. Finally, some authors believe that SWD may evolve into or even be a variant of pustular psoriasis, consistent with a therapeutic role for anti-TNF-α treatments. Etanercept could be useful in treating SWD, in combination with other agents or possibly as monotherapy, particularly in patients who are unable to tolerate or are refractory to dapsone. As proposed in the case of other neutrophilic dermatoses such as PG, TNF antagonists may act in SPD by disrupting leukocyte adhesion and migration and preventing the accumulation of the neutrophilic infiltrate. A role for TNF-α in the inflammatory process seen in SPD is also supported by an earlier report that found elevated TNF-α levels in the serum and blister fluid of a patient with SPD [**8, 9**].

4.Vasculitis

Several open-label trials demonstrating the efficacy of etanercept in Wegener's granulomatosis (WG) have now been conducted. However, numerous infections have occurred in these trials, raising some concern. Etanercept has been studied as a possible treatment for WG. However, results have not been as impressive. As in Crohn's disease and sarcoidosis, etanercept appears to be less effective than infliximab in treating WG. The mechanism of action of TNF antagonists in WG is likely similar to that in other granulomatous diseases. A recent study examining endothelial dysfunction in patients with antineutrophil cytoplasmic antibodyeassociated vasculitis found that forearm blood flow response to acetylcholine was reduced in patients with active disease as compared with normal control subjects, but improved after treatment with TNF antagonists, indicating that TNF antagonist therapy may act through effects on vasomotor dysfunction as well as inflammation. Several trials have studied the use of etanercept in patients with Wegener Granulomatosis. In a clinical trial, *Stone* et al compared etanercept 25 mg twice weekly and placebo in 20 patients also receiving conventional treatment. A significant decrease in vasculitis activity and a nonsignificant reduction in the mean prednisone dose were observed. The primary objective of this study was to evaluate the safety of prescribing etanercept to patients receiving conventional treatment, and the combination was found to be safe. In the Wegener's Granulomatosis Etanercept Trial patients were randomized to receive etanercept or placebo in addition to standard therapy for Wegener granulomatosis. As no differences were found between the 2 groups in either rates of remission or periods of reduced disease activity, the authors concluded that etanercept was not effective for the maintenance of remission in patients with Wegener granulomatosis. There are also a few anecdotal descriptions of patients who had a good response to etanercept, such as the case reported by Kleinert. A 5-year-old boy who presented with polyarteritis nodosa and palpable purpuric skin lesions was treated with a series of drug regimens, all of which included oral steroids given in different combinations with cyclophosphamide, intravenous immunoglobulin, azathioprine, and methotrexate. Nine years after onset of symptoms, etanercept was added to his treatment regimen, which at that time included prednisone 40 mg/d, azathioprine 2.5 mg/kg, and methotrexate 25 mg/wk. Over the next few years, it was possible to taper the doses of prednisone, methotrexate, and azathioprine without triggering a recurrence of the vasculitis. Although less well characterized than in WG, TNF-α may also have a role in other forms of vasculitis, and case studies have been published of the use of TNF antagonists in a variety of vasculitides, including giant cell arteritis, Churg-Strauss syndrome, Takayasu's arteritis, Kawasaki disease, tumor necrosis factor receptore associated periodic syndromee associated vasculitis, mixed cryoglobulinemiae associated vasculitis, RA-associated vasculitis, and leukocytoclastic vasculitis [**10,11**].

5.Acrodermatitis Continua of Hallopeau

Acrodermatitis continua of Hallopeau (ACH) is a rare acropustular eruption, characterized by sterile pustules, paronychia and atrophic skin changes, onychodystrophy and osteolysis of the distal phalanges of the fingers and toes. It is considered to be a variant of pustular psoriasis with a chronic relapsing course and frequent refractoriness to many therapeutic modalities, which can be amenable to successful treatment by tumor necrosis factor alpha antagonists. *Puig* et al reported a patient with pustular psoriasis and ACH whom he had been treated successfully with etanercept for 30 months. Blanching was initially achieved with etanercept 50 mg twice a week, but suppression of periungual inflammation then required combination therapy with etanercept 50 mg twice a week and methotrexate 10 mg weekly; lower doses of both drugs did not allow complete control of the disease. Eventually, adalimumab 40 mg every 2 weeks has provided the most cost-effective response in this patient, allowing maintenance of response with partial nail regrowth under monotherapy. *Bonish* et al also observed a case of etanercept responsive

acrodermatitis continua of Hallopeau [**12, 13**].

B.Autoimmune Blistering Diseases

1.Bullous Pemphigoid and Benign Mucous Membrane Pemphigoid

One report has been published of the successful use of etanercept for the treatment of mucous membrane pemphigoid (MMP), also known as cicatricial pemphigoid. The case involved a patient with MMP affecting the oral cavity, with disease resistant to multiple previous treatments. Etanercept, 25 mg twice weekly, was added to the existing regimen of prednisone 60 mg daily. The patient received 6 doses of etanercept. No new blister formation was observed after the third dose, and clinical remission persisted through 8 months of follow-up. During this time, the prednisone dosage was tapered to 1 mg daily [**2**]. There has also been one report of a patient with concurrent bullous pemphigoid (BP) and psoriasis who was successfully maintained on a regimen of etanercept after initial treatment with prednisone. Etanercept allowed for the safe and successful tapering of prednisone without a rebound of the patient's psoriasis or a flare of the BP. Patients with ocular MMP have elevated levels of serum TNF-α compared with normal controls. In BP, TNF levels are elevated in both serum and blister fluid and correlate with the severity of disease [**14**].

The treatment of cicatricial pemphigoid, also called benign mucous membrane pemphigoid (BMMP), poses a great challenge, because the condition often takes an intransigent course despite all therapeutic efforts. Because of its diverse clinical manifestations, patients with BMMP often have to be treated by a variety of specialists, including dermatologists, ophthalmologists, ear, nose, and throat specialists, and dentists. Since there are almost no randomized, controlled, double-blind studies comparing the use of various therapeutic agents in this condition, treatment decisions still rely heavily on individual clinicians' experience. Many different therapeutic regimens have been described in the literature, but only a few seem to hold up as valid alternatives. Systemic corticosteroids are still the agent of first choice, especially as rescue medication, for curtailing acute exacerbations. However, because of their well known long-term adverse effects, corticosteroids must be combined with immunosuppressive and/or anti-inflammatory agents. To determine which drug to choose, it is helpful to categorize patients in terms of high- and low-risk depending on the site and severity of their disease and on how rapidly it progresses. The recommended treatment for high-risk patients is a combination of prednisone and cyclophosphamide, or alternatively azathioprine. Once clinical improvement is evident, the corticosteroids should be slowly tapered. Dapsone is another alternative that may be used in high-risk patients, but patients who do not show any short-term improvement on this regimen should be switched to cyclophosphamide. Intravenous immunoglobulins are another effective, but expensive, treatment option in high-risk patients. Low-risk patients may well be managed with topical therapy alone, such as corticosteroids or cyclosporine. Other systemic options include dapsone, tetracycline, and nicotinamide as well as azathioprine in combination with low doses of corticosteroids. Various other systemic and topical agents, and recently biologics such as etanercept, have been reported to be effective in the treatment of MMP. However, most of the reported cases consisted of only small patient numbers and the true benefit of such agents in the condition is therefore not yet clear [**2**]. The use of etanercept to treat MMP has been reported in two case reports involving four patients. Its first use was in a 72-year-old woman with a 3-year history of MMP where the oral cavity was the only mucosal site involved, with marked erosive lesions of the buccal mucosa noted. The patient was unresponsive to systemic treatments which had included prednisone, azathioprine and mycophenolate mofetil. Treatment with etanercept was added to the existing daily regimen of 60 mg prednisone. No new blister formation was observed after the third dose, and in total the patient received six doses of etanercept, with complete healing of existing lesions. Clinical remission persisted through 8 months of follow-up. Significant steroid sparing was achieved during this time, with the prednisone dosage tapered to 7 mg daily after dose 3, and 1 mg daily at 8 months14.

More recently, three further cases of MMP refractory to conventional therapy where treatment with etanercept led to rapid resolution have been reported. In two cases, apart from having extensive oral mucosal and gingival lesions, significant ocular involvement was also a feature, and the condition was unresponsive to or the patient was medically intolerant of immunosuppression with azathioprine and dapsone. In both cases, etanercept was added to the existing treatment regimen, and after 1 month a rapid clearance of oral lesions, with stabilizing of the ocular disease was noted, allowing discontinuation or dose reduction in the systemic immunosuppressive therapies [**15**]. In the third case, where gingival erosions were the main feature of the disease, lesion clearance following use of etanercept for one month was also reported [**16**]. Tumour necrosis factor-α is thought to play a significant role in the TNF is thought to mediate the recruitment of neutrophils and eosinophils seen in the inflammatory infiltrate of BP and MMP lesions and stimulate the production of other inflammatory cytokines and chemokines pathogenesis of vesiculobullous disorders [**17**].

2.Hailey-Hailey Disease (Benign Familial Pemphigus)

One report has been published on the successful use of subcutaneous etanercept for the treatment of Hailey-Hailey disease. The dose was gradually increased from 25 mg weekly for 1 month, to 50 mg weekly for 6 months, and finally to 75 mg weekly to improve the response. Within 10 months of initiating treatment, the patient showed dramatic improvement, with only mild erythema in the groin and axillae remaining. Pruritus had markedly decreased as well. By 15 months, the patient had lost wieght and her Hailey-Hailey disease continued to abate. Although the weight loss may have contributed to this patient's improvement, the authors point out that the patient showed improvement while taking etanercept before any weight loss occurred. This suggests that TNF-α may have a role in the pathogenesis of Hailey-Hailey disease [**17, 18**].

3.Pemphigus Vulgaris

A 26-year-old woman with oral erosions and skin lesions diagnosed as pemphigus vulgaris was treated unsuccessfully with azathioprine, mycophenolate, systemic corticosteroids, cyclophosphamide, methotrexate, dapsone, and immunoglobulin therapy and continued to experience numerous severe flares. A regimen of prednisolone 30 mg/d, azathioprine 100 mg/d, and etanercept 25 mg twice weekly was started. After 3 weeks of this regimen, her lesions had improved considerably and the patient was able to taper prednisolone to 5 mg/d and azathioprine to 50 mg/d. While the blistering associated with pemphigus vulgaris was successfully controlled during the follow-up period, other lesions attributed to pemphigus vegetans required treatment with carbon dioxide laser. Another patient a 62 year-old-woman with pemphigus and rheumatoid arthritis, was prescribed a combination regimen of etanercept 25 mg twice weekly and prednisone 10 mg/d to treat her rheumatoid arthritis. After 3 doses of etanercept, the patient reported total remission of her pemphigus lesions and was able to discontinue treatment with prednisone. After 4 months of treatment she was free of disease. A 57-year-old patient with a 2-year history of pemphigus foliaceus lesions on the trunk had been treated with prednisolone at a dose of 30 mg/d without success. Treatment was then started with a regimen of prednisone 25 mg/d and etanercept 25 mg twice weekly. Improvement was observed after 15 days, with complete resolution of the lesions at 6 weeks. Prednisone treatment was discontinued, and she remained disease free after 4 months of monotherapy with etanercept [**17, 18**].

C.Autoimmune Connective Tissue Disease

1.Lupus Erythematosus

Tissue damage in lupus erythematosus is mediated by inflammation occurring after immune complex deposition and activation of the complement cascade; thus inhibition of TNF, an early proinflammatory cytokine, could theoretically interrupt the inflammatory cascade and decrease disease manifestations. One report described a patient with

rheumatoid arthritis and concurrent subacute cutaneous lupus erythematosus who had improvement in both conditions after treatment with etanercept. Autoantibody levels remained stable. *Napolitano* et al observed that toxic epidermal necrolysis-like acute cutaneous lupus erythematosus successfully treated with a single dose of etanercept in three cases. Another report described a patient with subacute cutaneous lupus erythematosus who improved with etanercept after an initial flare. There was no comment on autoantibody levels. Treatment of SLE with TNF antagonists remains controversial. These agents have been associated with the development of autoantibodies in a significant number of patients treated in clinical trials for rheumatoid arthritis and Crohn's disease. Although the vast majority of these patients do not experience any clinical manifestations, there are rare reported cases of drug-induced lupus with anti-TNF agents. Thus there has been concern that anti-TNF agents could exacerbate rather than alleviate disease in patients with lupus erythematosus. The limited findings presented herein seem to indicate that TNF antagonists may increase levels of autoantibodies in SLE patients, but this increase is not associated with worsening clinical disease. Further study will be necessary to determine the efficacy of TNF antagonists in cutaneous disease and to clarify the significance of treatment-associated autoantibody increases in SLE patients [**19, 20, 21**].

2.Scleroderma

Scleroderma or systemic sclerosis (SSc) is a connective tissue disease that affects various organ systems, including skin, gastrointestinal tract, lungs, kidney, and heart. The treatment of SSc is difficult and remains a great challenge to the clinician. Because the cause is unknown, therapies are directed to improve peripheral blood circulation with vasodilators and antiplatelet aggregation drugs, to prevent the synthesis and release of harmful cytokines with immunosuppressant drugs, and to inhibit or reduce fibrosis with agents that reduce collagen synthesis or enhance collagenase production. The purpose of this review is to critically analyze conventional and new treatments of systemic sclerosis and localized scleroderma. The therapeutic options discussed for the treatment of SSc include the use of vasodilators, angiotensin-converting enzyme inhibitors, and prostaglandins, immunosuppressant drugs and antifibrotic agents. The treatment options reviewed for localized scleroderma include the use of corticosteroids, vitamin D analogues, UV-A, and methotrexate. Preliminary reports on new therapies for systemic sclerosis are also considered. These include the use of minocycline, psoralen–UV-A, lung transplantation, autologous stem cell transplantation, etanercept, and thalidomide. The cause of SSc is unknown and is regarded as an autoimmune disease involving cellular and humoral immunity. Cellular infiltrates, perivascular or diffuse, have been demonstrated in skin, lungs, smooth muscle cells, esophagus, ileum and jejunum, synovium, and liver. These cells consist of T lymphocytes, B lymphocytes, and other nonspecific inflammatory cells, such as macrophages, mast cells, and eosinophils. The mechanism of fibrosis in SSc is not fully understood, although it is known that soluble mediators including transforming growth factor β, platelet-derived growth factor, interleukin IL-4, IL-6, TNF-α can affect the behavior of fibroblast growth, proliferation, collagen synthesis, and chemotaxis. The role of humoral immunity in SSc is unknown, although about 90% of patients with SSc show circulating antinuclear antibodies. Tumor necrosis factor α is a proinflammatory cytokine produced by activated T cells and macrophages. Tumor necrosis factor α stimulates the synthesis of other proinflammatory cytokines, promotes fibroblast proliferation, and enhances matrix metalloproteinase activity. Specific blocking agents against TNF-α have been developed. Etanercept has been shown to be effective in various forms of arthritis [**22**]. In a preliminary pilot study, 10 patients with diffuse SSc were treated with etanercept, 25 mg subcutaneously, twice weekly. After 6 months of therapy, there was improvement in skin score and healing in digital ulcers, while pulmonary function remained stable. The patients' sense of well-being improved, and tolerance was good. A trial of etanercept has been conducted in 10 patients with systemic sclerosis. Patients received etanercept, 25 mg administered subcutaneously twice weekly, for 6 months. Four patients had an improvement in their Rodnan skin score. Three of 4

patients with digital ulcers had clinical improvement of their lesions, while one had progressive disease. Pulmonary function tests, oral aperture, and hand extension measurements remained stable throughout the study [**23**]. There were no adverse events. Christopher-Stine and Wigley described two patients with scleroderma overlap/mixed connective tissue disease, one treated with etanercept and one treated with infliximab, who initially had alleviation of their symptoms but discontinued treatment after developing drug-induced lupus with autoantibodies and hypocomplementemia. Both patients had resolution of clinical symptoms and normalization of serologic markers after cessation of treatment. Several lines of evidence, beyond the scope of this article, suggest that TNF-α may play a complex, yet poorly elucidated, role in the pathogenesis of scleroderma. The clinical evidence indicates etanercept may be beneficial in scleroderma, but must be used with caution until further studies elucidate whether there is an increased risk of complications when treating this disease. More experimental evidence will be needed to understand how TNF-α interact to promote and inhibit the clinical manifestations of scleroderma [**24**].

3.Dermatomyositis

Several studies have indicated a prominent role for TNF-α in the pathogenesis of DM. There are reports of alleviation of both the skin and muscle symptoms of DM with the use of etanercept. The authors suggest using caution when prescribing TNF-α antagonists to patients with syndromes known to have a paraneoplastic association [**25, 26, 27**]. A randomized, pilot trial of etanercept in dermatomyositis were done by Muscle Study Group in 2011. The aims of this pilot study were to assess the safety and tolerability of etanercept in dermatomyositis (DM), the feasibility and safety of a forced prednisone taper and outcome measures, including those recommended by the International Myositis Assessment Clinical Study (IMACS) group. They conducted a randomized, double-blind, placebo-controlled trial of etanercept (50mg subcutaneously weekly) for 52 weeks in DM subjects. Subjects were tapered off prednisone in a standardized schedule as tolerated over the initial 24 weeks of the study. Principal outcomes included adverse events, time from randomization to treatment failure, and average prednisone dosage after week 24. Sixteen subjects were randomized, 11 to etanercept and 5 to placebo. There were no significant differences in adverse event rates between the treatment groups, although 5 etanercept-treated and 1 placebo-treated subjects developed worsening rash. All 5 subjects receiving placebo were treatment failures. In contrast, 5 of 11 subjects in the etanercept arm were successfully weaned off prednisone; the median time to treatment failure in this group was 358 days. The median of the average prednisone dosage after week 24 was 29.2mg/day in the placebo group and 1.2mg/day in the etanercept group. IMACS and other outcome measures demonstrated excellent test-retest reliability. There was no significant treatment effect on functional outcome. The findings of no major safety concerns and a steroid-sparing effect in our study suggest that further investigation of etanercept as a treatment for DM is warranted [**26**]. *Rouster* et al also evaluated the efficacy of etanercept in patients with juvenile dermatomyositis (JDM) refractory to standard treatment. Nine patients with JDM prospectively received etanercept 0.4 mg/kg subcutaneous twice weekly concurrently with baseline medications for 12 weeks. Patients were re-evaluated 12 weeks (week 24) after stopping etanercept. Outcome measures included a validated disease activity score (DAS), serum muscle enzymes, childhood myositis assessment scale (CMAS), and nailfold capillaroscopy. Six patients completed all visits; 2 patients completed through week 12; 1 patient stopped after the 5th etanercept dose due to marked worsening of rash. At week 12: 7 patients had mild decrease in DAS, 1 patient noted worsening of DAS. At week 24: 1 patient remained stable, 2 patients had worsening of DAS, 3 patients had improvement of DAS (1 patient with inactive disease), including the patient that worsened while on etanercept. This patient and patient that stopped (worsening rash) both had the TNF-α-308A allele. There was a trend of worsening NFC at week 12, while at week 24 improvement of NFC was noted. There was no appreciable change in serum muscle enzymes or CMAS throughout the study. In this trial of

patients with refractory JDM, etanercept did not demonstrate appreciable improvement and some patients noted worsening of disease. They suggested that caution should be taken when recommending TNF receptor inhibitors to patients with active symptoms of JDM; close follow-up is warranted. Further investigation of the interaction of the TNF-α-308A polymorphism and type 1 interferon is needed to define the mechanism of TNF blockade in JDM27.

4.Behçet's Disease

To date, the greatest experience in off-label use of biologicals relevant to oral medicine is that of the TNF-α antagonists like etanercept in the treatment of Behçet's disease (BD) [**28, 29, 30, 31, 32, 33**]. Etanercept has been shown to be effective in treating mucocutaneous BD, with data from a clinical study supporting that from a small number of uncontrolled case reports. A recent randomized controlled trial involving 40 patients with predominantly mucocutaneous BD compared etanercept (25 mg s.c. twice weekly) vs. placebo over 4 weeks, after an initial 4-week 'washout' of all other medications. Although in this study, etanercept had little effect upon genital ulceration, nor the pathergy reaction, a significant improvement in oral lesions, was seen as early as week one. After 4 weeks, 40% of patients treated with etanercept had complete remission of oral ulcers compared with 5% receiving placebo. Cutaneous lesions and arthritis also responded to etanercept therapy [**33**]. The value of etanercept in managing the oral aspects of BD is also illustrated in three case reports [**29, 32, 34**]. The first reported on two patients with recurrent apthous stomatitis (RAS) previously treated with thalidomide where this medication was discontinued due to adverse effects. In both cases, an association with BS was made, although the report was limited to discussion of the oral lesions. Treatment of both cases with etanercept (25 mg s.c. twice weekly) led to RAS lesion resolution in 3–5 weeks. This regimen was continued for 6 months, and following discontinuation recurrence rapidly developed, with further resolution following reintroduction of etanercept [**29, 32**]. Another case was reported by Sommer et al. who presented a 25-year-old patient with a long history of recurrent oral and genital ulcers, with a diagnosis of mucocutaneous BD based upon clinical history and features and HLA-B51 genotype. On presentation, extensive lingual, buccal, gingival and pharyngeal ulceration was noted. Treatment with etanercept led to rapid resolution of all ulcers with complete clearance after 3 weeks [**34**]. A further case report discussed a patient with BD refractory to her prior regimen of methotrexate and who achieved complete remission of her oral and genital ulcers, and also papulopustular skin lesions and erosive arthritis, after etanercept was added to her existing therapy. Case reports describe 3 patients with oral ulcers, one with probable and two with classic BD, treated with etanercept, 25 mg twice weekly, who achieved complete remission 3 to 5 weeks after starting treatment [**29, 32, 34**]. Another report describes a patient with refractory BD who achieved complete remission of her oral and genital ulcers, papulopustular skin lesions, and erosive arthritis after etanercept, 25 mg twice weekly, was added to her prior regimen of methotrexate and prednisolone. There is one double-blind placebo-controlled trial of etanercept in 40 male patients with mucocutaneous BD. Patients received either etanercept, 25 mg twice weekly, or placebo after a 4-week washout of all other medications. Significant improvement in oral ulcers, nodular and papulopustular skin lesions, and arthritis were seen after 1 week of treatment, with 45% of treated patients maintaining complete remission of oral ulcers throughout the course of treatment compared with 5% of patients receiving placebo. Etanercept had no significant effect on genital ulcers in this trial. Furthermore, etanercept was not effective in suppressing the pathergy or monosodium urate reactions [**33**]. *Cantarini* et al described the safety and efficacy of etanercept in children with juvenile-onset BD28. *Alty* et al reported a patient with neuro-Behçet's disease is successfully treated with etanercept: further evidence for the value of TNFalpha blockade [**31**]. The efficacy of TNF-blockade in treating BD may in part be explained by the underlying pathogenesis. Gamma delta (γδ) T cells are considered central to the mucosal immune dysfunction in BD. Increased numbers of γδ T cells have been reported in the peripheral blood of patients with BD, and these produce increased amounts of TNF-α, with

raised levels of soluble p75 TNF-α receptors also found in BD. The inflammatory cascade associated with TNF-α activity contributes to the lesional damage seen in BD. TNF antagonist treatment of BD has not been universally successful. One case of failure of etanercept treatment has been reported. The reported case of etanercept treatment failure was subsequently successfully treated with infliximab, suggesting that a differential effect between these two therapies, as seen in Crohn's disease, may also be a factor in the treatment of BD. The reports of successful treatment with TNF antagonists support a role for TNF-α in the pathogenesis of BD and identify another potential therapeutic approach for patients with disease resistant to traditional treatments [**35**].

5.Graft-Versus-Host Disease

In murine bone marrow transplant models, it has been demonstrated that both donor and hostderived TNF-α are integral to the development of GVHD and that treatment with anti-TNF antibodies decreases disease progression. Furthermore, in human studies higher TNF levels have been correlated to the development of acute GVHD. TNF has also been implicated in the pathogenesis of chronic GVHD and increased TNF-α levels have been reported in patients with chronic GVHD. Both experimental and clinical evidence now exists to support a role for TNF antagonists in the treatment of GVHD [**36, 37, 38, 39, 40, 41**].

a-Acute GVHD: Etanercept has also shown promise in the treatment of acute GVHD. One case report has been published of an 11-year-old girl who achieved complete remission of steroid-refractory acute GVHD with etanercept treatment [**40**]. In a phase II study of etanercept in combination with the IL-2 receptor antibody daclizumab for the treatment of steroid refractory acute GVHD in 21 patients, the overall response rate was 67%41. Similarly, in a pilot study on the use of etanercept in combination with tacrolimus and methylprednisolone as initial therapy for 20 patients with stage II or III acute GVHD, 75% of patients had a complete response within 4 weeks of initiating treatment [**37, 39**].

b-Chronic GVHD: Another study which describes 10 patients with steroid-dependent chronic GVHD treated with etanercept reported more than 50% alleviation of symptoms in 5 of 8 patients who were able to be evaluated and steroid dose reduction in 6 patients. Etanercept was administered at 25 mg twice weekly for 4 weeks and then once weekly for the subsequent 4 weeks; all patients were receiving concurrent steroids and 4 patients were started on a regimen of mycophenolate mofetil with etanercept. Two patients died before completion of the study and one patient died of infection after relapse of chronic GVHD that occurred after study completion [**38,40**].

Anti-TNF therapy seems to show promise for some patients with acute and chronic GVHD, though mortality rates for steroid-resistant disease remain high. On the basis of the reports presented herein, TNF antagonists appear to be most effective for skin and GI tract manifestations and less effective for liver involvement and high-grade acute disease [**39**].

D.Granulomatous Diseases

1.Sarcoidosis

Sarcoidosis is a multisystem disease of unknown etiology, characterized by the formation of noncaseating granulomas, especially in the lungs, lymphnodes, eyes and skin. Tumor necrosis factor antagonists may be used as treatment, however some cases of sarcoidosis secondary to these same drugs have been detected. Initial data for etanercept in the treatment of sarcoidosis were less encouraging. One small phase II trial of etanercept in the treatment of pulmonary sarcoidosis was initiated, but terminated early because of excessive treatment failures. However, 5 of 17 subjects were considered treatment successes [**42**]. Similar results were seen in a recent study involving 18 patients with ocular sarcoidosis. For most of the patients in this study, treatment with etanercept was not associated with a significant alleviation of ocular disease [**43**]. Another report describes a patient with lupus pernio and arthropathy who was started on a regimen of etanercept, 25 mg twice weekly, secondary to adverse effects and poor disease control with her baseline immunosuppressive regimen. Within 2 months her skin and joint disease had markedly improved

and prednisone and hydroxychloroquine were discontinued by 3 months. Complete remission has been maintained for 18 months of follow-up with a regimen of etanercept, 25 mg twice weekly, and methotrexate, 5 mg once weekly. This report may indicate some promise for etanercept in cutaneous manifestations of sarcoidosis despite the disappointing results of the other trials [**44**]. *Unterstell* et al reported the case of a female patient, with rheumatoid arthritis presenting with systemic sarcoidosis after 6 months of treatment with etanercept [**45**]. Recent studies demonstrated that TNF-α has a crucial role in forming the inflammatory granuloma, as well as in regulating adhesion molecules, recruiting cells and activating lymphocytes. The formation of the granuloma requires a cellular type (Th1) response pattern; involving macrophages and T CD4 activated lymphocytes. Interleukin-1b and gamma-interferon are important promoters during the initial phases of the granuloma development; TNF-α on the other hand, is critical during the latter phases of the granulomatous process. Tumor necrosis factor antagonists are used to treat sarcoidosis since; in theory, they would block this cytokine's action. However, paradoxically, some cases of sarcoidosis induced by these same medications have been reported [**46**]. This perplexing mechanism is not yet clear, but it is believed that these drugs do not inhibit all the signaling pathways of TNF-α, thus ensuing some "escape" routes. Thirtyfour cases of sarcoidosis induced by TNF-α antagonists had been described by *Catchcart* et al. Twenty-one of those occurred after the use of etanercept, 9 after infliximab and 4 after adalimumab. In this study, the mean time for the appearance of granulomas was 22 months after the start of medications. After a literature review, it was found 48 case reports of sarcoidosis induced by TNF-α antagonists. Thirty-one (64.58%) followed etanercept, 9 (18.75%) occurred after infliximab and 8 (16.66%) after adalimumab. Most patients had pulmonary and/or lymphnode involvement, 8 cases had cutaneous manifestations, mainly of erythema nodosum. Despite all the anti-TNF drugs having the ability to block pro-inflammatory cytokine TNF-α, they possess marked differences in their own structures, as well as their pharmacokinetics and pharmacodynamics' attributes, which explains, in part, the diversity that may be observed in clinical efficacy and adverse events, including the triggering of granulomatous lesions [**46**]. The inhibition of TNF-α by etanercept is not a complete one, since this drug connects only to the soluble TNF receptor and not to the transmembrane receptor. Partial neutralization of TNF-α by etanercept permits the redistribution of this cytokine in areas of lower concentration, such as the lungs. This may explain the stronger association of granulomatous reactions with the use of etanercept. The treatment of such cases has been the suspension of the anti-TNF agent and in some cases, as reported here, the introduction of corticoids. The mean time to recovery of symptoms after the interruption of the drug is 5.2 months. Considering that these drugs are increasingly used in dermatology, we must remain alert to the possibility of sarcoidosis, especially if respiratory symptoms, or erythema nodosum and/or granulomatous-cutaneous eruptions arise. Several lines of evidence support TNF antagonism as a therapeutic strategy in sarcoidosis. In multiple experimental models, TNF-α plays an essential role in the process of granuloma formation. Levels of TNF-α released from alveolar macrophages of patients with active sarcoidosis are significantly increased. Elevations in these TNF-α levels are predictive of poor long-term prognosis in patients without any current indication for steroid treatment. Studies show that lower levels of TNF-α bioactivity and higher levels of soluble TNF-α receptors are associated with milder pulmonary disease, suggesting that an innate mechanism of TNF blockade may play a role in limiting lung damage. Polymorphisms in the TNF-α promoter have been associated with distinct clinical forms of sarcoidosis, further implicating TNF in the pathogenesis of the disease. In addition, pentoxifylline and thalidomide, which both inhibit TNF-α among other effects, have been used successfully in the treatment of sarcoidosis [**45, 46**].

2.Granuloma Annulare

There is one report on the successful use of etanercept for the treatment of recalcitrant disseminated granuloma annulare (GA). The patient received etanercept, 50 mg biweekly, for 12 weeks. Most of the patient's lesions

cleared by week 7. By week 12, the remaining lesions had regressed as well, with only mild erythema remaining. The patient was still clear 12 weeks after treatment. The mechanism of action of TNF-α inhibitors in GA is likely similar to that of other granulomatous diseases [**47**].

3.Necrobiosis Lipoidica

Necrobiosis lipoidica (NL) is an idiopathic chronic granulomatous skin condition. There is currently no standardized effective treatment of NL. Ulceration occurs in up to 35% of cases. Treatment of ulcerative lesions is challenging and often unsuccessful. On the basis of the implication of the TNF-α on the formation of granulomas, since 2003 anti-TNF-α agents have been employed in cases of NL refractory to other therapeutic agents [**48, 49, 50**]. *Suárez-Amor* et al report a 50-year-old white woman with treatment-resistant chronic ulcerative NL of both shins successfully treated with subcutaneous etanercept [**50**]. There have been some other reports of NL treated with etanercept. A patient with multiple ulcerated lesions refractory to prednisone and dapsone was treated with surgical debridement and grafting followed by prednisone, 0.5 mg/kg per day, and etanercept, 25 mg twice weekly initiated 6 days after surgery. Prednisone was continued for 12 months and etanercept was continued for 16 months. All ulcerations healed and the patient remained in clinical remission throughout 2 years of follow-up. As previous surgical procedures had failed in this patient, it is likely that the addition of prednisone and etanercept contributed to the healing and maintenance of remission in this case [**48**]. Another report describes a patient with refractory NL who had a single plaque on her shin. She was treated with intralesional etanercept, 25 mg weekly, injected into the dermis at 1-cm intervals throughout the surface area of the lesion. Initial improvement was noted after 1 month of treatment, and the lesion continued to resolve over the next 8 months [**49**]. The mechanism of action of TNF antagonists for the treatment of NL is likely similar to that of other granulomatous diseases. Pentoxifylline and thalidomide, which inhibit TNF-α, have been effective in several cases of NL, which suggests that other TNF antagonists might also be beneficial in treatment of this condition. A review of the published literature suggests that etanercept should be considered as a therapeutic alternative mainly in ulcerative NL unresponsive to prior conventional regimens. The dose and duration of treatment with these agents is not defined, therefore it is required to report management of these patients in order to develop an optimal therapeutic strategy [**50**].

4.Silicone Granulomas and Cutaneous Granulomas In Patients with Common Variable Immunodeficiency

Several patients with granulomatous reactions to silicone implants or the adulterants these contain have been treated with etanercept. *Pasternack* et al71 reported the cases of 2 patients with foreign body silicone granulomas in the legs who had received silicone injections for cosmetic purposes years earlier. The 2 women received etanercept 25 mg twice weekly, and both showed improvement within 2 weeks of initiating treatment. One of the patients showed complete resolution at 2 months, while in the other case the lesions persisted but associated pain and erythema disappeared. A good response was also obtained in another reported case. By contrast, in an asymptomatic patient who had received silicone injections to treat acne scars, subsequent treatment with etanercept for arthritis 38 years later triggered the appearance of multiple granulomas at the sites where the silicone had been injected. The formation of granulomas in various organs is a relatively common complication in common variable immunodeficiency. In the case of an 18-year-old man with a 13-year history of chronic cutaneous granulomas on the left arm, the disease had proved refractory to multiple treatments including antibiotics, immunoglobulin therapy, systemic corticosteroids, interferon, cyclosporin, methotrexate, antimalarials, radiation therapy, and surgery. A year after starting treatment with etanercept 25 mg twice weekly, the patient showed significant improvement, a reduction in tumor mass size evaluated using magnetic resonance, and an improvement in the mobility of the affected arm [**18**].

E.Other Inflammatory Dermatoses

1.Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a common inflammatory skin disease. Medical treatment is often disappointing and in severe disease surgery remains the therapy of choice. Extensive surgery may be effective but also mutilating. Patients experience a significant reduction in quality of life and the need for new treatment modalities are urgent. In recent years patients with HS have been treated off-label with TNF-α inhibitors with a varying degrees of effect. Hidradenitis suppurativa is a recurrent and suppurative disease with an insidious onset. It is characterized by deep furuncles, abscesses, fistulas, sinus tracts, and scarring. Therapy varies based on the severity of disease, although there is considerable overlap between treatment groups. Mild HS consists of solitary nodules and abscesses, and treatment is generally conservative. Mainstays of treatment are nonsteroidal anti-inflammatory drugs for pain and inflammation, antiseptics, antibacterial soaps, warm compresses, hydrotherapy, and antibiotics. Antimicrobial treatment generally consists of topical clindamycin or oral antistaphylococcal agents for axillary disease, whereas more broad-spectrum coverage is called for in those with perineal disease. Oral contraceptive pills with a high estrogen: progesterone ratio as well as immunosuppressive drugs, such as cyclosporine, azathioprine, and prednisone, are occasionally successful. Single nodules may be injected with intralesional triamcinolone to decrease inflammation. Topical and oral retinoids inhibit keratinization and have been used with some success in mild to moderate HS. Acitretin and isotretinoin are more often used to decrease inflammation before surgery than as definitive treatments. Although there is no definitive evidence linking hyperandrogenism and HS, antiandrogens, such as cyproterone acetate and the 5α-reductase inhibitor, finasteride, also have been used with varying degrees of success. Weight loss and avoidance of heat and humidity can help reduce maceration and irritation of the affected sites. Other measures, such as avoidance of shaving affected areas, eliminating tight synthetic clothing, lowering stress, and smoking cessation, have only anecdotally been associated with amelioration of the disease. Carbon dioxide laser treatment is a less-invasive method of removing affected skin than traditional scalpel surgery. Disadvantages of carbon dioxide laser treatment and cryotherapy, another modality used to treat mild to severe HS, are substantial increases in healing time and pain. Radiotherapy has also been used for HS, but the long-term side effects make it less popular and probably less safe. Severe HS is comprised of multiple sites of draining abscesses and sinuses with associated scarring. In this case as well as some moderate cases of HS, local excision with wide margins has traditionally been the only effective therapy. Nevertheless, there is still a risk of recurrence adjacent to the excision site or even at a distant site. Screening for depression and psychological support is an important dimension of treatment, because patients with moderate to severe HS become progressively unable to interact socially or maintain employment due to pain, odor, and shame. It is important to stress to patients that HS is neither caused by poor hygiene nor contagious. Because surgical intervention can be disfiguring and not entirely curative, clinicians have pursued alternative treatment modalities [**50, 51**].

Etanercept, although not yet approved for treatment of HS, offer a potentially promising solution. Although HS is not primarily a granulomatous disease, granulomas have been observed in histologic examination of the skin surrounding HS sites. Inhibiting TNF-α is also thought to inhibit the keratinocyte activation cycle and to downregulate keratin 6, thereby preventing hyperkeratinization. High levels of TNF-α often go hand in hand with interleukin-1α, which has been shown to cause hypercornification of the follicular infundibulum and may be involved in the perpetuation of HS in its chronic state. Some of the current treatments of HS are also immunosuppressive or anti-inflammatory drugs, lending further credence to the hypothesis that immune dysregulation is at least partially responsible for the development of this disorder. Etanercept is administered subcutaneously as 25–50 mg weekly to twice weekly [**50, 51, 52**]. Via a literature search of etanercept and HS, the authors found 2 relevant case reports and 4 open-label clinical trials [**53, 54, 55, 56**]. The most common dosage regimen used was

50 mg weekly; only 1 study involved the use of the higher dose of 50 mg twice weekly, the currently approved induction dose for psoriasis in the United States. There is a recent open-label Phase II study of etanercept in 10 patients with severe hidradenitis. In the present study, patients were administered subcutaneous doses 50 mg once weekly for 12 weeks and then were followed up to 24 weeks using the Sartorius score and the visual analog scale (VAS). There was >50% score improvement in six patients at Week 12 and in seven patients at Week 24. The VAS was decreased compared to baseline in seven patients at Week 12 and in six patients at Week 24. Treatment was well tolerated by all patients with no reported adverse reactions, and all patients reported a decrease of local pain at the site of lesions after Week 4 [**55**]. Previously, Cusack and Buckley reported six patients with severe HS treated with etanercept. There was a reduction in the self-reported disease activity and in DLQI scores. At 24 weeks, the mean reduction for self-reported disease activity was 24% and DLQI was 64% [**57**]. There is another case report of the long-term efficacy of etanercept in HS. In this case report, a 32-year-old man with a 6-year history of severe hidradenitis was treated with 50 mg etanercept subcutaneously twice a week for 24 weeks, followed by a dose reduction to 25 mg twice weekly for 24 weeks. Treatment was well tolerated and a sustained improvement was noted after 4 weeks. Although these data are promising for efficacy in hidradenitis, a double-blind, placebo-controlled trial is required to fully understand the role etanercept may play in the long-term treatment of HS. In both case reports, improvement was seen within 1 month. Unfortunately, oral and topical antibiotics were also being given to the patient. A weakness of the case report by Zangrilli and colleagues is that although the baseline scores on the DLQI and VAS were given, no subsequent scores were reported, making it difficult to objectively assess the degree of improvement [**55**]. The first interventional study done on patients with HS treated with etanercept was in 2006 with 6 female patients [**53**]. The average decreases in disease activity and DLQI scores at 6 months of treatment were by 61% and 64%, respectively. All patients who finished the trial claimed it was their most effective treatment to date. In a subsequent prospective open-label clinical trial by Giamarellos-Bourboulis and colleagues, etanercept was given for 12 weeks in 10 patients with HS. Most patients relapsed within 4 to 8 weeks after discontinuation of treatment; nevertheless, 7 patients had a greater than 50% reduction in disease severity compared with baseline assessed by their Sartorius scale at week 24 [**53**]. Another single-armed, open-label, clinical trial published in 2008 was conducted on 4 patients who, after 6 months of treatment, had a 66.5% decrease in their DLQI scores and a 68.7% decrease in their Sartorius scale on average. Three months after ending treatment, 3 of the 4 patients had relapsed and had commenced a second course of etanercept. The only adverse events reported in these studies were mild injection site reactions [**51**]. The most recent study was published by Lee and colleagues. Response was defined as a greater than 50% decrease on the physician's global assessment (PGA) scale by week 12; only 3 of the 15 patients qualified as responders. No patient experienced complete remission, 29% had moderate improvement, and 57% had some improvement. Etanercept was generally well tolerated, although 2 patients discontinued treatment due to skin infections and 1 patient discontinued treatment due to worsening carpal tunnel syndrome. This last study demonstrated only minimal efficacy of etanercept for treatment of HS [**54**]. The cases and studies discussed in this article have no standardized dose or duration for treatment with etanercept. None of the studies had controls or a second arm of intervention, and none were blinded. The evidence is in support of etanercept for the treatment of HS with the notable exception of the last study discussed wherein only 20% of subjects responded. This study used a different scoring system for disease severity; perhaps the use of the PGA instead of the Sartorius scale played a role in the discrepancy between results. Also, there was an overall high relapse rate after discontinuation of treatment. Possibly, the strength of etanercept lies in the potential of reducing disease activity and not in ultimate eradication of HS. Based on the evidence, the authors give a grade C recommendation for use of etanercept for HS. Larger and more long-term studies are needed to fully elucidate the usefulness of this drug for HS and to help determine an op-

timal dosing regimen [**58**]. The side-effect profile of etanercept is similar to that of other TNF-α inhibitors. Most commonly reported side effects of etanercept are injection site reactions and infections. A few cases have been reported of an increase in antinuclear and anti–double-stranded DNA antibodies, drug-induced lupus, discoid lupus erythematosus, and necrotizing vasculitis due to cryglobulins. The authors also found a case report of a patient with an indwelling intravenous catheter taking etanercept and corticosteroids for HS who subsequently developed candidal septicemia and bilateral chorioretinitis. The use of etanercept for the treatment of HS has thus far proved to have variable long-term results and is laden with significant adverse effects. Nevertheless, enough evidence of efficacy has been provided to make further, detailed, and systematic investigation of these drugs for the treatment of HS advisable. At this point, an evidence-based decision on whether or not to use these agents for the treatment of HS lacks evidence of level 1 or 2 quality. The authors' recommendations are based on case reports and series, retrospective analyses, and small open-label clinical trials, stressing that a low-grade recommendation does not reflect low efficacy of the drug studied but rather the quality of available evidence. Because clinical trials are currently under way to evaluate biologics for treatment of HS, this grade is subject to change pending accumulation and publication of new evidence. Randomized, double-blinded, placebo-controlled trials are needed to better elucidate the future of these drugs for the treatment of HS. If conventional treatment options fail, the use of etanercept can be a useful supplement for the treatment of recurrent severe HS [**50, 51**].

2.Postherpetic Neuralgia

Recently, a study of patients with rheumatoid arthritis who developed herpes zoster while taking a TNF-α inhibitor reported a decreased incidence of postherpetic neuralgia. A retrospective review of herpes zoster patients on TNF-α inhibitors including infliximab, etanercept, or adalimumab was conducted in 12 dermatology clinics. Medical records of such patients were reviewed thoroughly to confirm herpes zoster and TNF-α inhibitors and any subsequent development of postherpetic neuralgia (pain score ≥ 3 out of 10 after 90 days of shingles onset) was noted. A total of 206 cases were reviewed, of which only 2 cases (<1%) developed postherpetic neuralgia, a considerably lower incidence rate than noted in the literature. Increasing age is a known risk factor in the development of postherpetic neuralgia. However, of the 58 (28.1%) cases ? 70 years of age, only 1 patient (1.7%) developed neuralgia compared to approximately 50% of patients who develop postherpetic neuralgia in this age group as reported in the literature. Treatment with etanercept may be associated with a lower incidence of postherpetic neuralgia but further prospective large-scale studies are needed to confirm this data [**59**].

3.Vitiligo

Experimental evidences have shown that TNF-α may play a role in the pathogenesis of nonsegmental vitiligo, and successful cases of vitiligo treated with TNF-α inhibitors have been recently reported. In the literature, 2 cases of refractory generalized vitiligo, which showed high tissue levels of TNF-α, were commenced anti-TNF-α antibody etanercept 50 mg weekly. A retrospective study, considering chart review and immunohistochemical staining for TNF-α, was then carried out on eight additional patients affected by untreated vitiligo. Etanercept achieved improvement of vitiligo in two patients at 6-month follow-up. Five out of eight specimens showed a strong cytoplasmic staining for TNF-α. Considering all 10 cases, patients with a strong TNF-α staining were characterized by a higher vitiligo disease activity score than patients with a weak staining. These findings, albeit limited in significance by the low number of cases and the retrospective nature of the study, confirm a probable role of TNF-α in the pathogenesis of vitiligo. The intensity of TNF-α staining in vitiligo lesions may be worth to be further studied as a biomarker for potentially successful anti-TNF-α treatment of nonsegmental vitiligo in cases refractory to conventional treatment [**60**].

4.Excessive Scarring

The potential of various biological agents to reduce or prevent excessive scar formation

has now been evaluated in numerous in-vitro studies, experimental animal models and preliminary clinical trials, in some cases with particularly promising results. Perhaps prominent among this group of biological agents, and, to some degree, possibly representing marketed compounds already being used 'off label' to manage excessive scarring, are the TNF-α antagonist like etanercept. Additional assessment of these novel agents is now justified with a view to reducing or preventing hypertrophic scars, keloid scars and the recurrence of post-excision keloid lesions [**61**].

5.Atopic Dermatitis

Atopic dermatitis (AD) is a common disease with worldwide prevalence, affecting up to 20% of children and 3% of adults. Recent evidence regarding pathogenesis has implicated epidermal barrier defects deriving from filagrin mutations with resulting secondary inflammation. Most cases of AD will benefit from emollients to enhance the barrier function of skin. Topical corticosteroids are first-line therapy for most cases of AD. Topical calcineurin inhibitors are considered second line therapy. Several novel barrier-enhancing prescription creams are also available. Moderate to severe cases inadequately controlled with topical therapy may require phototherapy or systemic therapy. The most commonly employed phototherapy modalites are narrow-band UVB, broadband UVB, and UVA1. Traditional systemic therapies include short-term corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, leflunamide and most recently biologic therapies. Atopic dermatitis is associated with the development of atopic respiratory disorders such as allergic rhinitis and asthma and persists beyond childhood in 40%–60% of cases. A preponderance of data indicates that AD is a genetic disease with variable expression that is highly influenced by immunologic and environmental factors. Originally, atopic dermatitis was thought to primarily be due to an abnormality in adaptive immunity due to dysregulation of Th1 and Th2 lymphocyte mediated immunity with inappropriate Th2-mediated inflammation leading to skin barrier dysfunction and pruritus. However, recent evidence points to atopic dermatitis being due to a primary barrier defect with resulting secondary inflammation. The barrier defect is due to null mutatons in the epidermal protein filagrin which is involved in normal cornification of the epidermis as well as acting as a natural moisturizing factor in the stratum corneum. On a population-based scale, 11%–15% of all cases of atopic dermatitis can be attributed to filaggrin null mutations. As TNF-α and TNF-dependent cytokines are involved in the immune-based inflammatory etiology of AD, blockade of this effector molecule is a plausible therapy target for chronic eczema. In a case report, two adults with chronic AD experienced complete resolution on etanercept (50 mg injected subcutaneously twice a week) for 8–11 months of therapy and remained in remission for 26–31 months after discontinuation. In contrast, etanercept was associated with no improvement in two pediatric patients with AD. Atopic eczema is a common inflammatory skin disease showing chronically relapsing eczema and high association with elevated serum IgE levels. A subgroup of atopic eczema patients requires systemic immunomodulatory treatment for long time periods. However, beyond cyclosporine A and azathioprine, only limited consent exists on systemic treatment options. Timely published systemic treatment modalities include etanercept with varying clinical results and with particular safety profiles. Although there is not yet a treatment modality reaching clinical efficacy of cyclosporine A as gold standard of systemic therapy, limitation in its application duration as in its side effect profile as well as the search for alternatives has set a focus on the new alternatives of which especially B-cell-directed therapies might be promising candidates [**62, 63**]. A 40-year-old woman with a 6-year history of recalcitrant dyshidrotic eczema had been treated with topical corticosteroids, psoralen-UV-A (PUVA), azathioprine, cyclosporin, acitretin, methotrexate, mycophenolate, sulfasalazine, minocycline, and repeated courses of prednisone [**51**]. After 6 weeks of treatment with etanercept 25 mg twice weekly, all her lesions healed. This improvement was maintained during the 4-month treatment period. However, once treatment was stopped, the patient suffered a renewed outbreak of lesions that was not controlled even when the dose of etanercept was doubled to 50 mg twice weekly [**18**].

6.Recurrent Apthous Stomatitis

The success of etanercept in the treatment of the oral ulceration component of BS has led to their off-label use in RAS. The use of etanercept to treat minor RAS was initially reported by Robinson and Guitart where a 50-year-old female presented with a 24 year history of a monthly cycle of nine to 12 new lesions which resolved in approximately 2 weeks. A variety of topical and systemic treatments had been previously employed including dapsone, colchicine and thalidomide, each of which was discontinued due to adverse side effects. Treatment with etanercept led to significant improvements within 1 month, with a reduction in frequency, duration and severity of RAS episodes. Another case report discussed the complete resolution of severe major aphthous stomatitis following treatment with adalimumab, in an 18-year-old man with a 7-year history of oral aphthae refractory to multiple standard therapies. Recently, the range of reported biologicals effective in the treatment of RAS has been extended to include efalizumab, which blocks T-cell activation and trafficking through its abrogation of LFA-1–ICAM-1 interaction. In this case report, the patient had a history of severe chronic plaque psoriasis as well as a long-standing history of near weekly episodes of minor RAS, the nature of which was unchanged despite the use of methotrexate for his skin disease. Following the use of efalizumab for 12 weeks, the patient reported no further episodes of apthous ulceration during this treatment course. On cessation of treatment, the pattern of RAS reverted to as before. Subsequent use of etanercept led to a good clinical response in psoriasis measures and, although the aphthae persisted, they were less numerous and of reduced frequency and severity. Like BD, the immune mechanisms involved in RAS are considered to be mediated by TH1. Increased numbers of γδ T cells are also found in RAS as are raised levels of TH1 cytokines including TNF-α. Thus, by reducing lymphocyte trafficking and blocking TNF-α activity, these agents act directly upon the underlying immune processes seen in RAS [**64**].

7.Pityriasis Rubra Pilaris

Adult pityriasis rubra pilaris type 1 is a rare chronic papulosquamous disorder with clinical and histological parallels with psoriasis. Pityriasis rubra pilaris (PRP) is an uncommon dermatosis of unknown etiology. The familial subtype is rare and usually presents as type 5 PRP. It is generally inherited in an autosomal dominant fashion with variable expression. Other forms of inheritance, such as autosomal recessive and X-linked, have also been reported. Treatment is challenging and recent case reports suggest a potential role for etanercept. Etanercept treatment may be of value in treating adult type 1 PRP refractory to other systemic agents but selective reporting bias, together with the lack of standard diagnostic criteria. The use of etanercept in treating resistant forms of PRP is promising given reports of its success in a few cases. *Vasher* et al report two cases of PRP arising in a mother and son and review the rare familial subtype of this disease. In addition, a successful therapeutic trial of etanercept was initiated in the mother based on case reports of its efficacy in other patients with PRP. The etiology of PRP is unclear. The condition shares several clinical and histologic features with psoriasis. This, along with the excellent responses in the above-described patients to treatment with the TNF antagonist, suggests that TNF-α may be an important mediator in the pathophysiology of this condition [**65, 66**].

8.SAPHO Syndrome

SAPHO syndrome is a syndrome of unknown origin characterized by synovitis, acne, pustulosis, hyperostosis, and osteitis. There have been 4 patients with SAPHO syndrome successfully treated with TNF antagonists reported in the literature. *Wagner* et al described two patients with treatment-refractory skeletal disease. One patient with diffuse sclerosing osteomyelitis of the mandible had significant alleviation of her symptoms, allowing a reduction of her prednisolone dose from 20 to 7.5 mg daily after 8 weeks of etanercept, 25 mg twice weekly. The second patient initially received 4 infusions of infliximab, which led to complete remission of her bone pain and swelling. Because of dyspnea experienced after infusions, the patient was switched to etanercept, 25 mg twice weekly. Both patients remained in remission through 9 months of follow-up while continuing etanercept treatment [**67, 68, 69, 70**].

9.Multicentric Reticulohistiocytosis

TNF-α has also been implicated in the pathogenesis of multicentric reticulohistiocytosis. There have been several reports on the use of TNF-α antagonists for the treatment of this disorder, including 3 reports on the use of etanercept. Most of these cases involved patients who had been refractory to several prior immunosuppressive medications. In these cases, TNF-α antagonist therapy was added to a regimen of other immunosuppressive disease-modifying agents. In two of the cases involving the use of etanercept, patients experienced significant alleviation of both skin and joint symptoms within 4 to 6 weeks, allowing for tapering of the more toxic immunosuppressive drugs. There was one report on the use of etanercept as initial therapy in conjunction with intramuscular steroids alone. The patient in this case failed to have a satisfactory response, suggesting that combination with disease-modifying agents may be required. Several authors have documented the use of etanercept in the treatment of this rare systemic illness that causes severe arthritis and cutaneous nodules. *Kovach* et al reported the case of a 46-year-old man who had been treated with methotrexate, antimalarials, chlorambucil, prednisone, and cyclophosphamide in combination with methotrexate, and prednisone. The disease had proved refractory to some treatments and the patient was unable to tolerate others. After etanercept at a dose of 25 mg twice weekly was added to the combination of prednisone 20 mg/d and methotrexate, gradual improvement was observed for 7 months. After this initial period, the patient experienced a relapse and methotrexate was replaced with leflunomide. This new combination resulted in renewed improvement and made possible a reduction in the doses of both prednisone and leflunomide. Another reported case involved a 22-year old woman who had been unsuccessfully treated with a number of drug regimens and surgery. In this patient, combination etanercept 25 mg twice weekly and hydroxychloroquine halted disease progression. In contrast to these successful outcomes, another case in the literature describes a 42-year-old man whose condition failed to respond to oral corticosteroids in combination with etanercept 25 mg or 50 mg twice weekly [**71, 72, 73**].

10.Erythema Annulare Centrifugum

One report has been published of the successful use of etanercept for the treatment of refractory erythema annulare centrifugum (EAC). Within 4 weeks of starting treatment with etanercept, 50 mg once weekly, the patient experienced significant improvement in his condition, with 95% clearance. One hundred percent clearance was achieved after 3 months. After 6 months of treatment, etanercept was stopped and the patient had a relapse of disease within 2 months. The etanercept was subsequently reintroduced and the patient experienced improvement after a similar clinical course to the previous treatment. The authors propose that the responsiveness of EAC to TNF-α antagonist therapy may suggest that EAC is a T hepler cell type 1 mediated disease associated with elevated levels of TNF-α and other proinflammatory cytokines [**74**].

11.Toxic Epidermal Necrolysis

TNF-induced apoptosis is partly responsible for the erosion of mucosal surfaces and epidermal shedding associated with toxic epidermal necrolysis. *Famularo* et al reported the case of a 59-yearold patient who presented with symptoms of toxic epidermal necrolysis secondary to ciprofloxacin treatment and was treated with prednisone 1 mg/kg and etanercept on days 4 and 8. A few hours after the first dose of etanercept was administered, improvement was observed in the cutaneous and mucosal lesions [**75, 76**].

12.Acne Vulgaris

A 22-year-old man with an 8-year history of refractory acne who had received many different treatments including oral antibiotics and isotretinoin and had reported thoughts of suicide was started on a regimen of etanercept for 24 weeks at a dose of 25 mg twice weekly. New lesions stopped appearing 2 weeks after this treatment was started, and all lesions had healed within 24 weeks. Another male patient aged 22 years from a family with pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome (PAPA) was treated with etanercept 25 mg twice weekly for 30 months.89 Both the acne and the episodes of

arthritis disappeared during this period [**77, 78**].

13.Alopecia Areata

No improvement was observed in a series of 17 patients with moderate-to-severe alopecia areata treated with etanercept 50 mg twice weekly. In another reported case, a 44-year-old patient with universal alopecia areata did not respond to treatment with etanercept. Moreover, a patient with a history of alopecia areata whose last episode had been years earlier experienced a recurrence of his condition after starting treatment with etanercept for rheumatoid arthritis [**79, 80, 81**].

14.Primary Amyloidosis

No effective treatment for primary amyloidosis has been found. One study reported the cases of 16 patients treated with etanercept at a dose of 25 mg twice weekly with promising results. In 1 of these patients, skin lesions showed marked improvement after 3 months of treatment [**82**].

15.Erythroderma-Associated Pruritus

Two patients with intense pruritus associated with erythroderma in the context of Sézary syndrome were started on etanercept 25 mg twice weekly. One showed substantial and the other moderate improvement of the pruritus, but neither experienced any improvement of the erythroderma. The authors commented that they have begun a clinical trial to evaluate the efficacy of etanercept in the treatment of treatment-resistant pruritus in patients with Sézary syndrome [**83**].

16.Cutaneous T-cell lymphoma

Tsimberidou et al studied 13 patients with cutaneous T-cell lymphoma refractory to at least 2 previous therapies (stages I-IIA) or to 1 treatment modality (stages IIB to IV). Twelve out of the 13 patients could be evaluated. Of these, 1 experienced partial remission and 1 had a minor response. Both these patients had early stage disease (IB) [**84**].

17.Inflammatory Linear Verrucous Epidermal Nevus (ILVEN)

A 55-year-old patient with a 6-month history of widespread and extremely pruritic ILVEN affecting the face, trunk, and limbs along the Blaschko lines had been treated with topical and systemic corticosteroids, pimecrolimus, and isotretinoin with little improvement. In light of the similarities between ILVEN and psoriasis, she was then treated with etanercept. Pruritus resolved after treatment, and the erythema improved over the 6-month follow-up period [**85**].

Adverse Effects of Etanercept

Side effects of TNF-α inhibitors include injection site reactions, reactivation of latent tuberculosis (TB), increased risk of sundry bacterial and fungal infections, demyelinating disease, worsening of congestive heart failure, hepatotoxicity, reactivation of hepatitis B virus, hypersensitivity reactions, pancytopenia and aplastic anemia, and autoimmune diseases. Although the most common infections associated with biologic treatment are upper respiratory tract infections, bronchitis, and urinary tract infections, deep fungal infections and TB are also documented. As a class, TNF therapy is associated with increased risks of infection and malignancy. Of 12 patients with AD treated with TNF inhibitors, one developed an infliximab-infusion reaction, one developed an urticarial reaction to etanercept, and one developed a methicillin-resistant Staphylococcus aureus infection while on etanercept. TNF-inhibitors are also associated with triggering an eczema-like drug eruption. In a prospective study of 92 patients treated for indications other than skin disease/psoriasis, 15 (16%) developed eczema during treatment with infliximab. A personal history of atopy was predictive of this medication-response.

Contraindications

Contraindications to treatment are active TB, known active and serious infections, hepatitis B, and heart failure classified as New York Heart Association (NYHA) level III or level IV. Caution is advised for patients with latent TB,

malignancy, heart failure classified as NYHA level I or II, or a hematologic disorder.

Etanercept and hepatitis C: In 2004, *Magliocco* and *Gottlieb* reported three cases of patients with worsening psoriasis while on antiviral therapy for hepatitis C who tolerated etanercept therapy without any worsening of their viral titres. Since that time, two other cases have been reported of patients with both psoriasis and hepatitis C where long-term etanercept therapy was administered without worsening of viral titres during the treatment course.

Summary

Although the majority of the data presented is limited to uncontrolled case reports, the clinical benefits described do suggest that, in selected patients, the use of etanercept may be of some value. In many patients, their skin disease was associated with significant morbidity and reduced quality of life and was refractory to conventional systemic immunosuppressive agents or the use of such was not tolerated. Etanercept may offer a real alternative in this patient group. In certain conditions, e.g. BD, and BMMP, etanercept therapy should be integrated with other clinical specialities involved in the individual's management. While the use of these agents in suitably selected patients may be increasingly reported, data from controlled studies are welcome and indeed required to provide an adequate evidence base, which is currently lacking, for their routine use in skin disease. Etanercept has demonstrated efficacy in the treatment of several dermatologic diseases. When choosing a biologic therapy, it is important to consider the mechanism of action of the drug in the context of the pathophysiology of the disease as well as the medical history of the patient. Cost is another important factor, with etanercept costing between 10,000 and 20,000 Turkish Liras annually. Because the safety profile of these medications appears to be much more favorable than many traditional immunosuppressive drugs, biologic immunomodulators are important alternatives for many patients. It is very likely that the role of biologic immunomodulators in dermatology will expand considerably in the coming years.

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