Off-Label Use of Biologic Agents in the Treatment of Dermatosis, Part 2: Etanercept, Efalizumab, Alefacept, Rituximab, Daclizumab, Basiliximab, Omalizumab, and Cetuximab

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Abstract. In recent years, a series of new drugs have been developed through the application of molecular biology. These drugs act by blocking specific molecules of the immune system and have been developed to act on specific targets that play an important role in the pathophysiology of the diseases in which their therapeutic use has now been approved. Over time, experience has been accumulated in the use of these drugs in the treatment of skin diseases for which they have not been approved but in which the pathophysiology suggests that they could also be effective. The use of these drugs is increasing in difficult-to-treat cases of skin diseases for which the drugs are not approved. The second part of this review of off-label use of biologic agents in dermatology considers the use of etanercept, efalizumab, alefacept, rituximab, basiliximab, omalizumab, and cetuximab.

Key words: biologic agents, dermatosis, off-label use.

Introduction

In recent years, a number of biologic agents have come onto the market. These drugs are proteins derived from living organisms (animals, microorganisms, and humans) used to prevent, treat, and cure disease. The first part of this review article dealt with 2 monoclonal antibodies that block the action of tumor necrosis factor (TNF). This second part deals with a second agent that reduces the effect of TNF (etanercept), a lymphocyte function antigen (LFA) 1 inhibitor (efalizumab), an LFA-3 inhibitor (alefacept), an anti-CD20 receptor antibody (rituximab), an anti-immunoglobulin (Ig) E antibody (omalizumab), 2 antibodies that block the interleukin (IL) 2 receptor (daclizumab and basiliximab), and an antireceptor antibody that targets the epidermal growth factor receptor (EGFR) (cetuximab).

These drugs have all been used off-label to treat different skin diseases on the basis of the pathophysiology of each
one, and several reviews have been published on this subject.1-7 These new biologic agents are often used to treat patients with skin disease that has failed to respond well to conventional treatment, and sometimes prove extremely useful in such cases. The successful experiments have in turn given rise to other articles describing the effectiveness of these agents in other hard-to-control diseases. The present review is based on publications in the current literature, although new articles may have been published in the interval between its writing and its publication.

### Etanercept

Etanercept is a fully human fusion protein consisting of the extracellular domain of the TNF receptor-2 fused to the constant portion of IgG1.8 It binds exclusively to soluble TNF-α thereby preventing this cytokine from binding to its receptors. Unlike infliximab, etanercept does not fix complement. It was the first biologic agent to be approved for use in psoriasis and psoriatic arthritis (moderate-to-severe plaque psoriasis in patients in whom conventional systemic therapy is contraindicated or when response to such treatment is poor). It is also approved for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis.9-12

### Posology

The standard dose regimen is 50 mg administered subcutaneously twice weekly; this can subsequently be reduced to 25 mg twice weekly.

The formation of antietanercept antibodies occurs in under 10% of the patients and does not reduce the treatment efficacy.

### Side Effects

This agent is generally well tolerated. Skin reactions at the injection site are the most commonly reported side effects, appearing in 40% of the patients treated.

As is the case with other molecules that block the action of TNF, treatment with etanercept has been associated with the development of infectious complications, especially those in which the body’s main defense is the development of granulomas. A higher rate of tuberculosis has been reported among patients receiving this drug than that found in the general population.13 Cases have also been reported of lymphomas associated with etanercept treatment, and the possible relationship between these lymphomas and treatment with etanercept or the immunosuppressed state that often characterizes the etanercept-treated patients is still unclear.14

### Contraindications

Allergy to etanercept or any of its components. The presence of any active infection.

### Off-label Uses in Skin Diseases (Table 1)

**Collagen Disease**

**Lupus erythematosus.** Although the possibility of a relationship between etanercept treatment and drug-induced lupus erythematosus is well known,15-26 2 cases have also been reported of patients with subacute lupus erythematosus who have responded to treatment with etanercept.27,28 Norman et al27 reported the case of a 42-year-old woman with polymyositis and an eruption clinically and histologically consistent with a diagnosis of localized subacute lupus erythematosus in photoexposed areas. The lesions were not controlled by treatment with methotrexate, hydroxychloroquine, and prednisone. When etanercept was added to the regimen at a dose of 25 mg twice weekly, the lupus lesions slowly disappeared, allowing discontinuation of the antimalarial agent and tapering of corticosteroid therapy. Fautrel et al28 reported the case of a 65-year-old woman with rheumatoid arthritis and subacute lupus erythematosus who was prescribed etanercept for her rheumatoid arthritis. This treatment produced an improvement in the rheumatoid arthritis, and the patient also reported complete disappearance of the lupus erythematosus lesions.

**Dermatomyositis.** Several authors have described the possible therapeutic effect of etanercept in patients with dermatomyositis.27,29,30 Improvement was reported in 6 out of a series of 8 cases of patients with dermatomyositis or polymyositis treated with etanercept (6), infliximab (1), or both (1).30 In another case, a 42-year-old patient with dermatomyositis refractory to treatment with methotrexate, hydroxychloroquine, and mycophenolate who tolerated oral corticosteroids very poorly was started on a regimen of methotrexate and etanercept at a dose of 25 mg twice weekly and showed an excellent response after 24 weeks of treatment, with improvement in both cutaneous and muscular symptoms.27

By contrast, Iannone et al31 described a series of 5 patients treated with etanercept in whom disease worsened in all cases.
Scleroderma. In a preliminary pilot study, 10 patients with systemic scleroderma were treated with etanercept 25 mg twice weekly. After 6 months of treatment, digital ulcers healed in 4 patients. The same patients also reported subjective improvement and showed an improvement in skin score but no changes in lung function.

Neutrophilic Skin Diseases

Sweet syndrome. Yamauchi et al33 reported good results in 2 women with Sweet Syndrome and concurrent rheumatoid arthritis. One was a 42-year-old woman with a 10-year history of Sweet syndrome who had multiple facial lesions that had recurred after treatment with systemic corticosteroids and azathioprine. She was diagnosed with rheumatoid arthritis and started treatment with etanercept 50 mg/wk. After 2 weeks of treatment, the patient’s condition had improved progressively and all her lesions healed within 6 weeks. The lesions recurred when treatment with etanercept was interrupted and once again resolved when this was resumed. The other was a patient who presented recurrent flares of Sweet syndrome lesions refractory to dapsone that had resolved with corticosteroid therapy only to recur with etanercept therapy. The lesions resolved gradually after the introduction of etanercept at a dose of 25 mg twice weekly, and the patient remained asymptomatic during the 6-month follow-up period.

Pyoderma gangrenosum. Less information is available about the use of etanercept than infliximab in patients with pyoderma gangrenosum because, unlike infliximab, etanercept is not approved for the treatment of inflammatory bowel disease, the most common cause of pyoderma gangrenosum. There are, however, several articles in the literature that indicate its possible usefulness. Hubbard et al34 described the case of a patient who presented extensive skin ulcerations associated with abscesses in the psoas muscle and spleen who responded very well to infliximab. When that treatment had to be discontinued because of an anaphylactic reaction, the patient was switched to a regimen of etanercept at a dose of 25 mg 3 times a week for 3 weeks without success.

Roy et al35 obtained excellent results in 3 patients with pyoderma gangrenosum treated with etanercept 50 mg/wk. Complete resolution of the lesions was observed in 2 of these patients within 2 months, while a smaller lesion persisted in the other patient. All 3 patients received etanercept as monotherapy with no concomitant corticosteroid or immunosuppressive therapy.

McGowan et al36 published the case of a 30-year-old patient with pyoderma gangrenosum whose condition improved with a regimen of etanercept and prednisone. In this case, a dose of 100 mg/wk proved necessary to control the disease.

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

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Goldenberg et al17 reported the case of a 30-year-old patient with a 2-year history of pyoderma gangrenosum associated with autoimmune hepatitis. Treatment with etanercept 25 mg twice weekly and prednisone resulted in gradual improvement of the lesions and allowed withdrawal of prednisone after 3 months. During the 5-month follow-up, the patient had no dermatological symptoms.

An 80-year-old patient with a refractory foot ulcer that had been diagnosed as pyoderma gangrenosum did not respond to treatment with prednisone and cyclosporin.38
When treatment was started with a combined regimen of etanercept 25 mg twice weekly and cyclosporin, improvement was rapid and the ulcer disappeared within 8 weeks. Treatment was discontinued after the patient had been asymptomatic for 1 year.

Finally, Disla et al.19 obtained a good response with complete resolution of all ulcers after 4 week’s treatment in a 40-year-old patient with pyoderma gangrenosum and comorbid rheumatoid arthritis.

Graft-Versus-Host Disease

The rationale for the use of anti-TNF therapy in the treatment of graft-versus-host disease is based on the importance of the pathophysiologic role played by TNF in the development of this entity.40-44

Acute graft-versus-host disease. In one documented case, an 11-year-old girl with acute corticosteroid-refractory graft-versus-host disease achieved complete remission after treatment with a course of etanercept 0.4 mg/kg twice weekly.45 Wolff et al.46 published the results of a phase II study of 21 patients with acute graft-versus-host disease refractory to oral corticosteroids who were treated with a regimen of etanercept 16 mg/m² on days 1, 5, 9, 13, and 17 and daclizumab (an IL-2 receptor antibody) on days 1, 4, 8, 15, and 22. In that study, 8 patients achieved complete remission, 6 partial remission, and 7 did not respond to treatment. During treatment, 11 patients presented infectious complications. Of the 21 patients, 12 subsequently developed chronic graft-versus-host-disease.

Kennedy et al.47 used a combination of etanercept and antithymocyte gamma globulin with or without mycophenolate mofetil to treat patients with acute graft-versus-host-disease. They found that the addition of etanercept increased survival as compared to conventional treatment alone, with no increase in infectious complications.

In a study of 20 patients with biopsy-proven acute graft-versus-host-disease, a combination of etanercept (25 mg twice weekly), methylprednisolone (2 mg/kg/d), and tacrolimus obtained complete resolution in 75% of the patients after 4 weeks of treatment.48

Busca et al.49 recently reported a case series of 21 patients with acute (13 patients) and chronic (8 patients) graft-versus-host-disease who were treated with etanercept 25 mg twice weekly. Complete remission was achieved in 55% of patients and partial remission in 9%. Infectious complications were frequent and included reactivation of cytomegalovirus in 48% of the patients treated.

Chronic graft-versus-host disease. In another study, 10 patients with chronic graft-versus-host-disease were treated with etanercept and oral corticosteroids with the addition of mycophenolate mofetil in 4 cases. Seven of these patients showed some improvement during the 2-month follow-up period and there were no adverse effects.50

In the study carried out by Busca et al.49 described above, 62% of the 8 patients with chronic disease had some degree of response, although only 1 experienced a complete response.

Spongiotic Dermatitis

Dyshidrotic eczema. 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.

Atopic dermatitis. Buka et al.52 reported the cases of 2 children with atopic eczema who were treated with etanercept and did not improve. Moreover, both these patients suffered complications (in 1 case a methicillin-resistant Staphylococcus aureus infection and in the other a viral exanthema) although it was not possible to establish a relationship between these complications and the treatment.

Blistering Diseases

Bullous pemphigoid. A 64-year-old man with a long history of psoriasis who developed bullous pemphigoid experienced considerable improvement in the symptoms of both disorders after starting treatment with prednisone.53 Etanercept 25 mg twice weekly was added to this regimen and subsequently, because of a recurrence of the pemphigoid when the dose of prednisone was tapered, this was increased to 50 mg twice weekly, resulting in complete resolution of the blisters.

Cicatricial pemphigoid. A 72-year-old woman with oral and ocular cicatricial pemphigoid had been unsuccessfully treated with prednisone, azathioprine, and mycophenolate mofetil. She was then prescribed etanercept 25 mg twice weekly.54 Three weeks after the start of this regimen, it was possible to reduce the prednisone to 1 mg/d. After 8 months of follow-up and only 6 injections of etanercept, the patient was completely free of disease.

An 82-year-old patient with ocular cicatricial pemphigoid who had been treated with dapson, cyclophosphamide, cyclosporin, and corticosteroids began combination
treatment with dapsone 100 mg and etanercept 25 mg twice weekly.55 Her condition began to improve a month after starting this regimen, and after 6 month's treatment the conjunctival hyperemia had disappeared resulting in improved vision. No relapse occurred during the 1-year treatment period.

Cañizares et al56 reported a series of 3 women with cicatricial pemphigoid, 2 with oral mucosal involvement and 1 with both oral and conjunctival disease. All 3 patients were treated with etanercept at a dose of 25 mg twice weekly. Oral mucosal disease improved in all 3 patients, and ocular disease progression stabilized in the patient with conjunctival involvement. In the first patient, treatment with etanercept in combination with azathioprine 100 mg/d and dapsone 75 mg/d achieved good control of the disease. Disease recurred when etanercept was discontinued because the patient lost her health insurance. The second patient was treated with intravenous immunoglobulin and etanercept with good results. The third patient, who was treated with etanercept 25 mg twice weekly as monotherapy, experienced complete cure of her oral erosions within 1 month.

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.57 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.58 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.

Pemphigus foliaceus. 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.59 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.

Hailey-Hailey disease. A 47-year-old woman was diagnosed with Hailey-Hailey disease refractory to multiple treatments (ciprofloxacin, tetracyclines, mupirocin, levofloxacin, fluconazole, trimcinolone acetonide, ketoconazole, diphenhydramine, cyclosporin, pimecrolimus, isotretinoin, cryotherapy, and laser treatment).27 She was then treated with etanercept 25 mg/wk for 1 month followed by 50 mg/wk for 6 months and subsequently 75 mg/wk. During the first 10 months her condition improved substantially.

Granulomatous Diseases

Sarcoidosis. A study of etanercept in the treatment of pulmonary sarcoidosis was terminated because no improvement was observed.60 The results of etanercept treatment in patients with ocular sarcoidosis have also been poor.61 In cutaneous sarcoidosis, a patient with lupus pernio resistant to prednisone, hydroxychloroquine, and methotrexate was treated with etanercept 25 mg twice weekly.62 After 2 months of this treatment, he showed substantial improvement and was able to gradually withdraw prednisone and hydroxychloroquine treatment and reduce the dose of methotrexate. No signs of active disease were observed in this patient during an 18-month follow-up period. Another patient with progressive cutaneous sarcoidosis resistant to systemic corticosteroids and immunosuppressive agents responded significantly to monotherapy with etanercept.63 Somewhat paradoxically in the light of these good results in cutaneous sarcoidosis, a case has been published of a 70-year-old woman receiving treatment with etanercept for ankylosing spondylitis who developed facial lesions after 21 months of treatment. The clinical and histological findings were consistent with a diagnosis of sarcoidosis and pulmonary lymphadenopathy.64

The skin lesions disappeared 2 months after treatment with etanercept was discontinued. Another patient receiving treatment with etanercept for rheumatoid arthritis developed granulomatous lesions in both parotid glands but she did not fulfill the criteria for sarcoidosis.53 Another article reported the case of 2 women who developed sarcoidosis during treatment with etanercept for rheumatoid arthritis.66

Granuloma annulare. Data on the efficacy of etanercept in the treatment of granuloma annulare are inconsistent. Shupack et al67 reported the case of a patient with disseminated granuloma annulare who was treated with etanercept 50 mg twice weekly and showed improvement after 7 weeks that was sustained during the 12-week follow-up period. However Kreuter et al,68 who used etanercept to treat 4 patients with refractory granuloma annulare, reported that 2 patients failed to improve and the condition of the other 2 deteriorated.
Necrobiosis lipoidica. The case has been published of a patient with necrobiosis lipoidica and multiple ulcerated lesions refractory to corticosteroids and dapsone who was treated with surgical debridement and grafts followed by prednisone 0.5 mg/kg/d and etanercept at a dose of 25 mg twice weekly.69 Corticosteroid therapy was continued for a year and etanercept for 16 months; he remained asymptomatic during the 2-year follow-up period. Another patient with refractory disease and a single localized lesion on 1 leg, who was treated with intralesional etanercept at a dose of 25 mg/wk, showed progressive improvement over the following 8 months.70

Silicone granulomas. 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.72 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.73

Cutaneous granulomas in patients with common variable immunodeficiency. The formation of granulomas in various organs—including the lungs, spleen, liver, and skin—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-γ, 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.74

Vasculitis

Behçet disease. In a clinical trial carried out in Turkey, 40 patients with Behçet disease were randomized to either etanercept 25 mg twice weekly or placebo. Patients who received etanercept presented a significantly lower number of oral ulcers, nodular lesions, and papulopustular lesions than the controls, but no improvement was observed in genital lesions or pathergy reaction.75 Other isolated cases showing good outcomes have been published.76,77 However, Estrach et al78 published the case of a patient with treatment-resistant disease who showed no improvement after 3 months of treatment with etanercept at a dose of 25 mg twice weekly. The patient was then switched to infliximab with resolution of all lesions.

Wegener granulomatosis. Several trials have studied the use of etanercept in patients with Wegener Granulomatosis. In a clinical trial, Stone et al79 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.80 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.81

Polyarthritis nodosa. A 5-year-old boy who presented with polyarthritis 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.82 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.

Others

Multicentric reticulohistiocytosis. Several authors have documented the use of etanercept in the treatment of this rare systemic illness that causes severe arthritis and cutaneous nodules.83-85 Kovach et al83 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.

**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-year-old 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.

**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. In this patient, combination etanercept 25 mg twice weekly and hydroxychloroquine halted disease progression.

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. Both the acne and the episodes of arthritis disappeared during this period.

**Hidradenitis.** Hidradenitis suppurativa is a treatment-resistant condition with severe negative repercussions on the patient’s quality of life. A number of new therapeutic modalities have been tried, including treatment with etanercept.

Cusack et al tried etanercept 25 mg twice weekly in 6 patients with severe hidradenitis and measured response using self-reported patient evaluation and the Dermatology Quality of Life Index. All 6 patients showed improvement, with a reduction in mean quality-of-life score of 64% at 24 weeks, and all of them rated etanercept as the most effective treatment they had received to date. However, complete resolution of lesions was not achieved in any of these patients.

In an isolated case, treatment with etanercept resulted in an improvement in the patient’s condition.

**Aphthous stomatitis.** Robinson et al reported the case of a 50-year-old woman with a 24-year history of weekly outbreaks of painful aphthous lesions refractory to standard treatments with the exception of thalidomide, which controlled the lesions but had to be discontinued because of neuropathy. After 1 month of treatment with etanercept 25 mg twice weekly, the patient showed significant improvement, and subsequent outbreaks were easily controlled with topical corticosteroid therapy. During 1 of the flares, the patient was given an additional dose of etanercept 25 mg and the lesions resolved the next day.

**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.

**Centrifugal annular erythema.** A 57-year-old patient with a 1-year history of centrifugal annular erythema who had experienced a recurrence after an interruption in repeated cycles of prednisone showed rapid recovery after starting treatment with etanercept 25 mg twice weekly and was asymptomatic within 1 month. The patient remained asymptomatic during the 6 months of treatment with etanercept and relapsed 2 weeks after it was interrupted. When treatment was resumed, the lesions once again disappeared rapidly.

**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.

**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.
Cutaneous T-cell lymphoma. Tsimeridou et al<sup>99</sup> 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).

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.<sup>100</sup> 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.

SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis). Wagner et al<sup>101</sup> reported the cases of 2 patients who had SAPHO syndrome with severe skeletal involvement. One patient had been treated with infliximab with good results but presented symptoms of dyspnea after the infusions and was therefore switched to a regimen of etanercept 25 mg twice weekly, which resulted in substantial improvement. The other was a patient with mandibular osteomyelitis whose symptoms improved during treatment with etanercept at the same dose, making it possible to reduce the daily dose of prednisone from 20 mg to 7.5 mg. Both patients remained in remission during the 9-month follow-up period.

Efalizumab

Efalizumab is a humanized monoclonal antibody that targets the CD11a subunit of LFA-1. The LFA-1 molecule is a ligand of intercellular adhesion molecule (ICAM) 1, and the binding of these 2 molecules triggers numerous pathophysiologic mechanisms in psoriasis, such as the migration of effector-memory T-cells to the epidermis and dermis, activation of these lymphocytes at the site of inflammation, and their adhesion to keratinocytes in the dermis.<sup>102,103</sup> On binding to Cd11a, efalizumab reversibly blocks this molecule from binding to ICAM-1.

Efalizumab is currently approved for the treatment of moderate-to-severe plaque psoriasis in patients who have not responded to, are intolerant to, or have contraindications to conventional systemic therapies.<sup>104</sup>

**Posology**

Efalizumab is administered by subcutaneous injection with an initial dose of 0.7 mg/kg the first week followed by weekly injections of 1 mg/kg.

**Side Effects**

One of the side effects reported is a flu-like syndrome during the first 2 or 3 days after administration, which takes the form of low-grade fever or fever, myalgias, headache, and chills. These reactions usually disappear after the third dose.

In clinical trials with efalizumab, slightly higher infection rates have been reported in treated patients compared to controls. However, most of these infections were mild.<sup>105</sup>

The development of severe thrombocytopenia has been reported in a very small number of patients, generally during the first 12 weeks of treatment. This thrombocytopenia is reversible following withdrawal of the drug and treatment with systemic corticosteroids.

Another reported side effect is transient localized papular eruption taking the form of numerous papules and small erythematous plaques on the flexures, neck and chest characterized histologically as neutrophilic dermatosis. These eruptions usually develop during the first 2 months of treatment and are easily controlled with topical corticosteroids.

More rarely, a generalized inflammatory flare of the existing psoriasis occurs, sometimes accompanied by the appearance of new lesions in previously unaffected areas. These symptoms generally appear during the first 6 months of treatment, and the addition to the regimen of another systemic drug for psoriasis is recommended.

Another relatively common adverse effect is a relapse or flare shortly after stopping treatment with efalizumab.

**Contraindications**

Treatment with efalizumab is contraindicated in immunodeficient patients, patients with active tuberculosis...
or other severe infections, pregnant or breastfeeding women, and patients with a history of malignancy during the previous 10 years.

Off-label Uses in Skin Diseases (Table 2)

**Granuloma Annulare**

Goffe et al reported the case of a 52-year-old patient with disseminated granuloma annulare and psoriasis who had been treated with cyclosporin, clofazimine, PUVA, tazarotene, intralesional corticosteroids, and tacrolimus with varying degrees of efficacy. He enrolled in a trial studying the use of efalizumab in the treatment of psoriasis. After 4 weeks of treatment, there was visible improvement in the granuloma annulare and the lesion healed completely within 3 months. A parallel improvement was observed in the psoriasis.

**Lichen Planus**

A case has been reported of a 54-year-old woman with cutaneous lichen planus and oral erosive lichen of 3 month's standing who had showed modest improvement on treatment with oral corticosteroids and topical tacrolimus. After 10 weeks of treatment with efalizumab at the usual dose, a 75% improvement was observed in the oral erosions; the skin lesions also improved, leaving only residual hyperpigmented macules.

In another study, 4 patients with oral erosive lichen planus treated with the usual dose of efalizumab showed a mean reduction of 71% in the affected mucosal surface area and an 82% improvement in pain.

After treatment with normal doses of efalizumab, a rapid improvement in skin lesions was obtained in another patient with cutaneous lichen planus but no oral erosive lichen. Previous treatments included cyclosporin and corticosteroids. Dramatic improvement in the lesions was observed after only 4 weeks of treatment.

**Atopic Dermatitis**

Several authors have reported the usefulness of efalizumab in the treatment of atopic dermatitis. In 2006, Weinberg et al published the case reports of 2 patients with severe atopic dermatitis who were treated with efalizumab. The first was an 8-year-old boy who had been treated with topical and systemic corticosteroids, cyclosporin, and etanercept with poor results. After starting treatment with the usual dose of efalizumab, progressive improvement was observed in the patient's atopic dermatitis. The second patient, a 48-year-old woman who had been treated with topical tacrolimus and corticosteroids and had refused phototherapy, reported improvement after 7 months of treatment with efalizumab at the usual dose.

Hassan et al reported a good response in a 19-year-old man with a flare of atopic dermatitis previously treated with topical corticosteroids, calcineurin inhibitors, and phototherapy. During the 10 months of treatment with efalizumab, no other therapy was required and the severity of the patient's atopic dermatitis showed progressive improvement. A comparison of biopsies obtained at the start of treatment and after 6 months revealed, among other findings, a reduction in CD4 helper T cells.

More recently, a study was carried out of 10 patients receiving efalizumab at the usual dose for 12 weeks. Six of the 10 patients showed improvement of more than 50% on the Eczema Area and Severity Index. One patient relapsed when treatment was discontinued.

**Dermatomyositis**

Huber et al reported the case of an 82-year-old woman with dermatomyositis refractory to systemic corticosteroids and methotrexate. When treatment was begun with a combination of efalizumab 1 mg/kg/wk and prednisolone 40 mg/d, rapid improvement was observed in the patient's skin lesions and general condition. A month later, the dose of efalizumab was increased to 1.8 mg/kg, that of prednisolone was reduced to 10 mg/d, and azathioprine 50 mg/d was added to the regimen. The patient's condition remained stable during the 12-month follow-up period.

**Graft-Versus-Host Disease**

The adhesion of T-cells to endothelium and subsequently to affected tissue is one of the pathophysiologic mechanisms of graft-versus-host-disease. There is no experience with cutaneous graft-versus-host-disease, but studies are underway to evaluate the use of efalizumab in the prevention of this disease in renal transplant patients.

**Alopecia Areata**

Several years ago, efalizumab was suggested as a drug that might be useful in treatment of alopecia areata. However, it was not until 2006 that the first studies evaluating this indication were published. In 1 reported case, a 19-year-old man with alopecia universalis showed significant improvement after receiving the usual dose of efalizumab. This patient had previously been treated with topical corticosteroids alone. One month after starting treatment with efalizumab, abundant hair growth was observed on the scalp and this continued over the following months. After 3 months,
hair had grown on 50% of the scalp, and at 6 months, on 90%.

An 8-year-old boy with atopic dermatitis and alopecia areata who received efalizumab for the atopic dermatitis experienced partial regrowth on the areas affected by the alopecia areata.\textsuperscript{110}

Somewhat paradoxically, a case has been reported of a patient with psoriasis who developed alopecia areata affecting 70% of the body surface during treatment with efalizumab.\textsuperscript{117}

Subacute Lupus Erythematosus

Clayton et al\textsuperscript{118} described the case of a 47-year-old woman who presented with erythematous plaques in photoexposed areas. Histologic and serologic findings were consistent with a diagnosis of subacute lupus erythematosus. The patient's condition responded poorly to a broad range of treatments (topical and systemic corticosteroids, antimalarials, dapsone, gold salts, azathioprine, thalidomide, methotrexate, isotretinoin, lefunomide, and mycophenolate mofetil). Treatment was then started with efalizumab at a dose of 1 mg/kg/wk and striking improvement was observed after 6 months of treatment. A flare-up after 4 months of treatment was controlled by raising the dose of efalizumab to 1.25 mg/kg/wk. The disease was still under control after 5 months of treatment.

By contrast, in another reported case, a 65-year-old woman treated with efalizumab for erosive oral lichen planus experienced an outbreak of skin lesions after 8 weeks of treatment. The lesions were indicative of subacute lupus erythematosus and the patient tested positive for antinuclear (1:160) and anti-Ro antibodies.\textsuperscript{119}

In a recently published retrospective study, 13 patients with discoid lupus refractory to normal immunosuppressive therapies were treated with efalizumab with encouraging results: a good to excellent overall response in 11 patients, a mean time to response of 5.5 weeks, a reduction in antinuclear antibody titers in 6 patients, and few side effects.\textsuperscript{120}

Alefacept

Alefacept is a dimeric recombinant fusion protein in which the binding domain is derived from LFA-3, the ligand for CD2. Alefacept binds to CD2 on effector-memory T-cells, thereby inhibiting their activation. Moreover, the constant fraction of IgG1 binds to macrophages and natural killer cells giving rise to apoptosis of T8 cells.

This drug is approved in the United States for use in the treatment of moderate-to-severe plaque psoriasis.\textsuperscript{121} It is currently not approved for use in the European Union.

Posology

The approved dosage regimen is weekly intramuscular administration of 15 mg doses of alefacept for 12 weeks. Further cycles may be administered after a minimum interval of 12 weeks without treatment.

Side Effects

No increased incidence of infections or malignancies has been reported in alefacept-treated patients compared to placebo-treated patients.\textsuperscript{122} Self-limiting flu-like symptoms occur during the initial weeks of treatment. Injection site reactions have been reported to be minimal.\textsuperscript{122}

CD4 counts decline during treatment. If this count falls below 250 cells/µL, treatment should be suspended and only resumed when the CD4 count rises above this minimum threshold. If the count remains below 250 cells/µL for more than 4 weeks, alefacept treatment must be discontinued permanently.\textsuperscript{122}

Approximately 3% of patients develop antialefacept antibodies.\textsuperscript{8}

Contraindications

Treatment with alefacept is contraindicated in patients with a history of malignant disease and in those who have a CD4 count below normal or have had a severe infection during the 2 weeks prior to treatment.\textsuperscript{122}

Off Label Uses in Skin Diseases

Lichen Planus

There are 2 case reports in the literature of patients with treatment-refractory generalized lichen planus who responded to treatment with alefacept.\textsuperscript{123} The dose used was 15 mg/wk for 12 weeks, and both patients improved substantially after 1 month of treatment. By week 12, new lesions had stopped appearing, and existing lesions had healed to some degree in both patients. Pruritus had also resolved completely in both patients.

Alopecia Areata

Four patients with extensive alopecia areata or alopecia universalis were treated with 15 mg/wk of alefacept for 3 months and received intralesional corticosteroids in the affected areas.\textsuperscript{124} They all experienced some improvement, but this was very modest in most patients and none of them obtained complete remission. Time to initial
response was between 3 and 15 weeks after start of treatment.

**Sarcoidosis**

A 46-year-old man with recalcitrant lupus pernio experienced modest improvement 8 weeks after starting treatment with alefacept.125

**Scleroderma**

A 58-year-old woman with progressive scleroderma refractory to multiple therapies (systemic corticosteroids, antimalarials, colchicine, and methotrexate) was treated with alefacept for 3 months without improvement.126

**Graft-Versus-Host Disease**

One article in the literature reported a study undertaken to evaluate the use of alefacept in 7 patients with corticosteroid-resistant graft-versus-host-disease.127 The systems affected were the skin in all 7 patients, gastrointestinal tract in 5, and the liver in 3. All 7 patients responded to treatment, but in 3 of them initial response was followed by renewed exacerbation and complete response was not achieved. Initial response was very rapid, with improvement being noted the day after treatment was started. Only 1 patient achieved complete remission, which was observed after 40 days of treatment.

**Rituximab**

Rituximab, a chimeric anti-CD20 monoclonal antibody that causes in vivo depletion of CD20+ B cells, was the first antibody approved for the treatment of cancer.128 It is currently approved for use in the treatment of follicular or diffuse CD20+ large B cell lymphoma refractory to chemotherapy and as a maintenance treatment in patients who have responded to induction treatment. In combination with methotrexate, it is also indicated for the treatment of rheumatoid arthritis in patients refractory to standard therapies, including anti-TNF agents.129

The CD20 molecule is a transmembrane antigen expressed on mature B cells, but not on plasma cells, stem cells, or immature lymphocytes.128 Consequently, immunoglobulin concentrations are maintained, and mature B cell counts are reestablished through the maturation of pre-B cells after each treatment cycle.130,131 Antibody-dependent cell-mediated cytotoxicity and complement-mediated cell lysis appear to be the chief mechanisms that bring about the depletion of CD20+ B cells.132

**Posology**

The standard regimen for rituximab is intravenous infusions of 375 mg/m² administered weekly for 4 weeks. The course can be repeated.129

**Side Effects**

Rituximab has a relatively good safety profile, and the most commonly reported side affects are mild allergic reactions to the first infusion (urticaria, fever, and angioedema).130,133,134 It is estimated that these reactions occur in 18% of patients.135 Cases have also been reported in which local reactions occurred following treatment due to the localized release of cytokines at the tumor sites.136,137

A higher than normal incidence of infections has been reported in patients treated with this drug.138 The development of human antichimeric antibodies is highly variable and appears to depend on the underlying disease. Development of these antibodies is associated with a reduction in the efficacy of the drug.139

**Off-Label Uses**

The idea of using this monoclonal antibody in the treatment of autoimmune diseases originated shortly after the commercial release of the drug in 1997 for the treatment of low-grade lymphoma.140 The rationale for such off-label use is that treatment with rituximab depletes both malignant and normal CD20+ cells without affecting plasma cells. This means that the aim of treatment is not to reduce autoantibody levels but rather to modify the immune response mechanism by changing and renewing the CD20+ memory cells.

Consequently, rituximab has been used to treat various autoimmune diseases, including the skin diseases commented on below.

**Lupus Erythematosus**

Rituximab appears to work in the treatment of systemic lupus erythematosus by interfering with the interaction between B cells and T cells, ultimately leading to a reduction in the production of autoreactive B cells.141 Thus a correlation exists between response to rituximab and B cell depletion.

Rituximab has mainly been used to treat lupus erythematosus in patients with highly active disease, cytopenia, and serious involvement of vital organs, such as the central nervous system or the kidneys. While no large studies have yet been published, the use of this drug in the treatment of systemic lupus erythematosus appears to be safe and beneficial.142-147
Some authors report that, in addition to improvement in systemic manifestations, clinical improvement in skin symptoms is also observed. A case has also been reported of urticarial vasculitis and angioedema in a patient with systemic lupus erythematosus that was refractory to several treatments (methylprednisolone, high-dose methylprednisolone, and intravenous immunoglobulin) but responded rapidly to treatment with rituximab. The patient experienced no new episodes of urticaria or angioedema after treatment and was able to discontinue treatment with boluses of methylprednisolone.

**Dermatomyositis**

Rituximab has proved useful in the treatment of some patients with dermatomyositis, a disease in which antibodies deposited in the blood vessel endothelium play an important role. After activating the complement cascade, these antibodies cause the release of inflammatory mediators, leading to necrosis, and ultimately, muscular ischemia and skin damage. Rituximab has been used in the treatment of dermatomyositis to reduce the titers of these autoantibodies.

Three studies in the literature evaluated the efficacy of rituximab in the treatment of dermatomyositis with varying results. In a study by Levine et al, good results were obtained in 6 patients with refractory dermatomyositis treated with a standard regimen of rituximab, with improvement in cutaneous and muscle symptoms in all of the patients. At a later date, Chung et al treated 8 patients with refractory dermatomyositis. They used a regimen of 2 infusions (1 g each) of rituximab administered 2 weeks apart. Partial improvement in muscle strength was noted in only 3 patients, and skin disease showed improvement in only 1. In a more recent study of 3 patients with treatment-refractory dermatomyositis published by Dinh et al, the investigators carefully evaluated the response of cutaneous disease. One patient with palmar hyperkeratosis and poikiloderma responded to treatment and remained free of lesions with infusions at 4-month intervals during a 2-year period. Another patient with erythema and poikiloderma on the trunk, heliotrope erythema, and Gottron papules presented only mild symptoms after 4 months of treatment with rituximab at the standard dose and was able to discontinue treatment with immunosuppressive agents during the 20-month follow-up period. The last patient in this series, who had periungual erythema, alopecia, poikiloderma, and heliotrope erythema, showed improvement in all cutaneous symptoms 2 months after completing treatment with rituximab with the exception of the erythema on the fingers and periungal area.

In addition to these studies, 2 isolated cases have been published in which treatment with rituximab resulted in improvement of symptoms and decreased muscle enzyme levels. It is difficult to come to any firm conclusions because of the scant number of patients with dermatomyositis who have been treated with rituximab. However, the literature does provide some indications that while rituximab treatment produces an improvement in muscle symptoms, skin symptoms appear to be more resistant to treatment, notwithstanding reports of a rapid and lasting response in some cases.

**Vasculitis**

Rituximab has been used to treat different types of vasculitis, especially cases of disease associated with antineutrophilic cytoplasmic antibodies (ANCA) and cryoglobulinemia.

Although rituximab does not act on the mature plasma cells, the beneficial effect obtained in this disease appears to be due to its interference with the CD20+ lymphocytes that are the precursors of the plasma cells, giving rise to a reduction in autoantibody levels and the formation of the immunocomplexes involved in the genesis of vasculitis. In a study of 11 patients with ANCA+ vasculitis, all the patients achieved complete remission after treatment with standard doses of rituximab. In another study of 9 patients, showed complete response.

Cases have been reported of patients with treatment-resistant Wegener disease who responded to treatment with rituximab. Ferraro et al reported the case of a patient with Wegener disease initially controlled with cyclophosphamide and plasmapheresis who subsequently developed a high-grade non-Hodgkin lymphoma. As a result of this development, cyclophosphamide was withdrawn and the patient was treated with rituximab. After 2 cycles of rituximab at the standard dose, the patient remained in remission and did not require treatment with other drugs during the 10-month follow-up period. Other authors have described similar responses to treatment with rituximab in patients with treatment-refractory Wegener disease and in patients in whom immunosuppressive therapy was contraindicated because of side effects. These patients responded rapidly to treatment with rituximab, and remission was achieved after the first cycle, allowing corticosteroid therapy to be discontinued. Moreover, patients who experienced a recurrence of disease responded well to a repeat course of treatment. Although many of these patients only achieved a transient response, in other cases the response was lasting. The combination of leflunomide and rituximab may have a synergistic effect in maintenance therapy. In a prospective study, 10 patients with vasculitis secondary to Wegener disease were treated with a course of 4 weekly doses of rituximab. In all cases, c-ANCA levels returned to normal and clinical remission was achieved, allowing gradual withdrawal of corticosteroid therapy. Five
of these patients were given a second course of treatment with rituximab because of a rise in autoantibody titers. Only 1 patient experienced a flare after normal CD20+ lymphocyte levels were reestablished.

In contrast to these cases in which good outcomes were obtained after treatment of Wegener disease with rituximab, some rather less promising results have also been reported. In a study of 8 patients, only 3 responded with clinical improvement, while disease remained stable in 3 and continued to progress in 2.174 CD20 levels decreased but c-ANCA titers remained stable. The explanation for the poor response in some of the patients in this case series may be that these patients presented clinical manifestations of granulomatous disease (retro-orbital masses, pulmonary nodules, and tracheal stenosis) while the patients who showed a better response had small vessel vasculitis (glomerulonephritis, episcleritis, pulmonary hemorrhage).175

In a recent study of 8 patients, vasculitis activity was also observed to respond better than granulomatous lesions to treatment with rituximab.176

Rituximab has also been used to treat vasculitis associated with cryoglobulinemia. While some authors have reported a good response in patients with type I cryoglobulinemia treated with rituximab, others have observed no response177 or even worsening of the disease and an increase in cryoagglutinin titers. In one case, a patient with type I cryoglobulinemia and chronic lymphocytic leukemia responded to treatment with rituximab and fludarabine.179

Type II and type III cryoglobulinemia are, in most cases, associated with hepatitis C virus (HCV) infection. In addition to the skin, vasculitis can also affect vital organs, such as the kidneys. Treatment with interferon and ribavirin is not effective in many cases, and immunosuppressive therapy gives rise to multiple adverse effects. Rituximab is therefore seen as a promising new treatment option.

In the largest case series to date of patients with mixed cryoglobulinemia (II and III), 20 patients were treated with rituximab. All of them were HCV-positive and resistant to interferon-α therapy.180 Sixteen of the 20 patients showed a complete response with reduced cryoglobulin levels. This response was, however, accompanied by a sharp decrease in anti-HCV antibodies and an increase in viral RNA levels. For this reason, although rituximab appears to be an effective treatment for mixed cryoglobulinemia, it should be used with caution in this context. An earlier study enrolled 15 patients diagnosed with mixed type II cryoglobulinemia that had not responded to conventional management.181 All the patients with cutaneous symptoms showed a positive response to treatment with rituximab. In a study of 4 patients with type II cryoglobulinemia treated with rituximab, 1 patient had a complete remission after treatment and the other 3 a partial response; disappearance of cryoglobulins was noted in 2 patients.182

Another patient with type III cryoglobulinemia unconnected with lymphoma presented with purpuric lesions and joint pains that proved refractory to corticosteroids, cyclophosphamide, and plasmapheresis, but he responded to treatment with rituximab.183 Similarly, cases have been reported of patients with type II essential mixed cryoglobulinemia that also responded to treatment with rituximab,184-186 and a patient who responded to treatment with combination rituximab and infliximab.187

In 1 case, a patient receiving treatment with rituximab for a non-Hodgkin lymphoma also showed improvement in type III mixed cryoglobulinemia.188 These cases reporting a good response contrast with a case of essential mixed cryoglobulinemia in which the disease failed to respond to treatment with rituximab.189

### Autoimmune Blistering Diseases

One of the most studied models among the autoimmune diseases is that of the blistering diseases, and in most cases the specific antigen and the type of antibody that reacts to it thereby causing the disease have been identified.

In the literature reviewed, most of the reports on autoimmune blistering disease treated with rituximab were cases of pemphigus vulgaris. Altogether, 56 case reports have been published involving cases of pemphigus vulgaris (Table 3, Figures 1 and 2).190-212 8 of paraneoplastic pemphigus,213-220 3 of pemphigus foliaceus,221,222 3 of bullous pemphigoid,212,223 1 of IgA pemphigus,220 1 of cicatricial pemphigoid,212 and 5 of epidermolysis bullosa acquisita.224-226

A close association has been found between pemphigus vulgaris—a blistering autoimmune disease—and levels of circulating autoantibodies (antidesmoglein 3 and antidesmoglein 1).189 In view of the fact that rituximab does not deplete mature plasma cells, the good response obtained with this drug may be related to the deletion of autoreactive CD20+ lymphocyte clones.196 Other authors have hypothesized that pemphigus antibodies are produced by both CD20+ lymphocytes and plasma cells, but that the latter produce IgG1 subclass antibodies, which are less pathogenic than the IgG4 antibodies produced by CD20+ lymphocytes.192,195,227 Moreover, this B-cell depletition interferes with other functions of these lymphocytes, such as antigen presentation and interaction with T-cells and dendritic cells, and this interference may be another mechanism of action in pemphigus vulgaris and other autoimmune diseases.142

To date, most of the articles in the literature about the use of rituximab in pemphigus vulgaris are case reports.190-212 In most cases of pemphigus vulgaris treated with rituximab, disease responds rapidly to treatment with improvement of symptoms within 1 or 2 weeks of the first
### TABLE 3. Cases of Pemphigus Vulgaris in the Literature Reviewed

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Concomitant Therapy</th>
<th>Response</th>
<th>Follow-Up Side Effects</th>
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<tr>
<td>Salopek 2002</td>
<td>1</td>
<td>29</td>
<td>W</td>
<td>C, MM, CS</td>
<td>Improvement, occasional flares</td>
<td>160 d</td>
</tr>
<tr>
<td>Virgolini 2003</td>
<td>1</td>
<td>53</td>
<td>C</td>
<td></td>
<td>Complete remission</td>
<td>40 wk</td>
</tr>
<tr>
<td>Cooper 2003</td>
<td>1</td>
<td>54</td>
<td>W</td>
<td>C, MM</td>
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<td>Unknown</td>
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<td>3</td>
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<td>C, CP</td>
<td>Complete remission</td>
<td>18 mo</td>
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<tr>
<td>España 2004</td>
<td>1</td>
<td>39</td>
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<td></td>
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<tr>
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<td>3</td>
<td>34</td>
<td>W</td>
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<td>W</td>
<td>C</td>
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<tr>
<td>Belgi 2006</td>
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</tr>
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<td>Antonucci 2006</td>
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<td>C, MM</td>
<td>Complete response in all cases</td>
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<td>C, MM, CS</td>
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<td>13-18 mo</td>
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<td>Borel 2007</td>
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<td>52</td>
<td>M</td>
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<td>Schmidt 2007</td>
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<td>39</td>
<td>W</td>
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| Abbreviations: AZ, azathioprine; C, systemic corticosteroids; CP, cyclophosphamide; CS, cyclosporin; IVIg, intravenous immunoglobulin; M, man; MM, mycophenolate mofetil; MTX, methotrexate; W, woman.
infusion. Patients achieved clinical remission between the first and ninth month after start of treatment. The patients who experience delayed response to rituximab were those whose disease mainly involved the mucous membranes, giving rise to the hypothesis that this type of involvement is more resistant to treatment with rituximab. The period during which response was sustained varied from case to case, from a few months before a relapse to a maximum of 3 years after treatment.

Rapid depletion of circulating B cells was observed in all patients, and this depletion persisted for months or even years after treatment was completed, with reestablishment of these levels coinciding in some cases with a recurrence of the disease.

Only 2 cases have been reported of a drop in immunoglobulin levels in circulating blood. These levels remained stable in all the other cases, and clinical improvement was accompanied by a decrease in antidesmoglein antibody levels. Only 1 case has been reported in which antibody levels not only failed to decline but actually increased in a patient who achieved practically complete remission, allowing other pharmacotherapy to be discontinued.

Of the 56 patients, 37 achieve complete remission making it possible to discontinue treatment with other drugs. Monotherapy with rituximab was used in only 2 patients.

In the largest study, which was undertaken by Ahmed et al., good results were achieved in 11 patients with treatment-refractory pemphigus vulgaris treated with a combination of rituximab and intravenous immunoglobulin. Nine patients achieved complete remission of disease for a long follow-up period averaging 31 months, a result that suggests a possible synergistic effect between these 2 drugs.

The first prospective study in treatment-resistant pemphigus vulgaris was recently published. Of the 5 patients who received 4 doses of rituximab in addition to their ongoing immunosuppressive therapy, 3 achieved complete remission. Two of these patients developed serious infectious complications (community-acquired pneumonia and cytomegalovirus infection).

A case has also been reported of vegetative pemphigus vulgaris in which treatment with rituximab was not satisfactory, a result that can be explained in part by the tendency of such lesions to become superinfected.

Rituximab was generally well tolerated, although severe adverse effects did occur in some patients, including serious infections, fatal pneumonia caused by Pneumocystis carinii, Pseudomonas aeruginosa, hip arthritis, community-acquired pneumonia, polymicrobial sepsis, noninfectious enteropathy, pneumonia caused by Haemophilus influenzae, sepsis related to the herpes zoster virus, nosocomial pneumonia, and cytomegalovirus. Some authors consider that patients with autoimmune diseases who are treated with rituximab develop infections more easily than patients with cancer or blood dyscrasias. This may be due to the immunosuppression these patients acquire as a result of repeated courses of immunosuppressive therapy.

Rituximab has also been used in the treatment of paraneoplastic pemphigus, and in some cases patients showed significant improvement after treatment with this agent. One of these cases was a patient with paraneoplastic pemphigus and a non-Hodgkin lymphoma, although it is difficult to determine whether the improvement in the paraneoplastic pemphigus was due to rituximab or to the regression of the tumor after treatment with this biologic agent. By contrast, 4 cases have been reported of paraneoplastic pemphigus associated with non-Hodgkin lymphomas that did not respond to treatment.
Rituximab was also effective in the treatment of 3 cases of pemphigus foliaceus in which it obtained a rapid response.212,222

The only case of IgA pemphigus treated with rituximab was that of a 79-year-old woman with chronic lymphocytic leukemia who developed vesiculobullous skin lesions and mucosal erosions, the latter more severe.220 Disease was controlled after 3 months treatment with rituximab and fludarabine.

Only 2 cases have been reported of patients with bullous pemphigoid who responded to treatment with rituximab.212 The first of these was a boy who received 2 courses of 4 infusions of rituximab. This regimen achieved control of the disease despite various adverse effects (noninfectious enteropathy, pneumonia caused by Haemophilus influenzae, and sepsis caused by the herpes zoster virus). The other patient was a 63-year-old woman who died from nosocomial pneumonia 2 weeks after treatment with rituximab with a good response.

In a curious case, a 14-year-old boy with IPEX syndrome (immunodysregulation, polyendocrinopathy, enteropathy, X linked disease) developed bullous pemphigoid in the context of treatment-resistant chronic dermatitis with prurigo nodularis-like lesions. He responded to treatment when rituximab was added to the existing immunosuppressive regimen.223

Only 1 case has been reported in which rituximab was used to treat cicatricial pemphigoid. The patient’s nasopharyngeal lesions healed after treatment with 1 course of rituximab, while the ocular lesions failed to improve, probably because they were in a very advanced phase.212

In 2006, Schmidt et al226 published the first case of epidermolysis bullosa acquisita treated with rituximab. The patient was a 46-year-old man whose disease had failed to respond to immunosuppressive therapy and achieved clinical improvement after treatment with rituximab.230-239 The first of those cases, published in 2000, was a patient with graft-versus-host-disease whose skin symptoms improved after treatment.236-239 The first of those cases, published in 2000, was a patient with graft-versus-host-disease receiving rituximab to treat autoimmune thrombocytopenia who experienced a related improvement in the cutaneous symptoms of her disease, including lichenoid changes.237

This was the first report of an improvement in this disease in response to rituximab.

**Graft-Versus-Host Disease**

T cells and natural killer cells play a leading role in graft-versus-host-disease. However, B cells are also involved in the development of this disease.229,230 Using a murine model of systemic sclerosis, it has been shown that the development of fibrosis depends to a large degree on the expansion of B cells activated by interaction with T cells.231 This model has been proposed as one of the pathogenic mechanisms of the sclerodermiform changes associated with graft-versus-host-disease.232 Moreover, autoantigens similar to those associated with autoimmune disease have been found in patients with graft-versus-host-disease.230,232

Rituximab has been used in the treatment of graft-versus-host-disease to interfere with the mechanisms of humoral immunity associated with this entity. The first series of patients with chronic graft-versus-host-disease refractory to conventional immunosuppressive therapy who were treated with rituximab was reported by Ratanatharathorn et al.239 They treated 8 patients who had sclerodermiform changes with rituximab (a 4-week cycle at a dose of 375 mg/m²/wk) in combination with ongoing immunosuppressive therapy and achieved clinical improvement in 4 cases. Good results were also reported in other published case series.232,233 In a recent study, Cutler et al244 treated 21 patients with chronic and refractory graft-versus-host-disease who had either sclerodermatous or lichenoid changes. The overall response rate was 70%, with 2 patients showing complete remission during the 1-year follow-up period. Greater improvement was found in cutaneous and musculoskeletal symptoms than in those affecting mucosal membranes and internal organs. The largest study carried out was that of Zaja et al,235 who treated 38 patients and achieved a 63% response rate in the cutaneous manifestations of the disease and a lower response rate in those affecting mucous membranes.

In some of the patients in these studies, clinical improvement after treatment with rituximab was accompanied by the reduction of autoantibodies to undetectable levels.

In addition to these series, case reports have been published relating to individual patients with graft-versus-host-disease whose skin symptoms improved after treatment.236-239 The first of those cases, published in 2000, was a patient with graft-versus-host-disease receiving rituximab to treat autoimmune thrombocytopenia who experienced a related improvement in the cutaneous symptoms of her disease, including lichenoid changes.237

**Omalizumab**

Omalizumab is a humanized monoclonal antibody that targets the constant region of IgE, reducing serum IgE concentrations and preventing these antibodies from binding to mast cells and other immune cells.240

This drug is approved for the treatment of severe persistent allergic asthma in patients over 12 years of age who have positive allergy tests, reduced lung function, and frequent daily symptoms despite treatment with β-agonists.241 It has
also proved effective in patients with latex allergy\textsuperscript{242} and allergic rhinitis\textsuperscript{243-245}.

**Posology**

The appropriate dose of omalizumab is determined by the patient’s weight and baseline IgE concentration; IgE levels greater than 1000 IU/mL are considered too high to be neutralized. Administration is subcutaneous, and the drug is given every 2–4 weeks.

**Side Effects**

Omalizumab has a very acceptable safety profile, with injection site reactions being the most commonly reported side effect. However, severe anaphylactic reactions have been reported in 0.1\% of patients treated. As these reactions typically occur during the first hour after infusion, the drug should be administered under medical supervision\textsuperscript{246-249}. The formation of antibodies against omalizumab has not been reported\textsuperscript{250}.

**Contraindications**

Omalizumab should not be used to treat asthma exacerbations. Since IgE is involved in the immune defense against helminth infections, omalizumab should not be given to patients at high risk for helminth infection, particularly when they travel to areas where such infections are endemic\textsuperscript{251}. Omalizumab should not be used in patients with known allergy to the active substance or any of the excipients.

**Off-Label Uses**

**Atopic Dermatitis**

A number of case series have been published relating to patients with atopic dermatitis treated with omalizumab\textsuperscript{252}. The rationale for using omalizumab to treat atopic dermatitis is based on the presence of elevated IgE levels in patients with atopic dermatitis and the fact that this entity shares the same atopic spectrum as rhinitis and asthma (both conditions in which treatment with omalizumab has proved useful).\textsuperscript{253} Other experts hold the contrary view that IgE does not play an important role in eczema and that the IgE levels characteristic of atopic dermatitis are too high to be neutralized with omalizumab.\textsuperscript{254} Beck et al\textsuperscript{255} consider that the lack of efficacy of efalizumab in some patients with atopic dermatitis may be due to excessively high serum concentrations of IgE. For this reason, they suggest that a study should be carried out enrolling only patients with atopic dermatitis and IgE concentrations under 700 IU/mL.

Krathen et al\textsuperscript{256} published a case series of 3 adults with severe recalcitrant dermatitis who were treated with omalizumab 450 mg every 2 weeks. Serum IgE concentrations prior to treatment were between 5440 and 24 400 IU/mL. None of the 3 patients showed any improvement.

Lane et al\textsuperscript{257} reported the cases of 3 children aged between 10 and 13 year with severe refractory atopic dermatitis. The dose of omalizumab used in this study ranged from 150 mg to 450 mg with administration every 2 weeks. All 3 patients showed significant clinical improvement. These 3 patients were treated concurrently with topical medication including corticosteroids.

Finally, the largest study undertaken to date included 7 patients aged between 7 and 58 years who had serum IgE levels between 265 and 2020 IU/mL\textsuperscript{258}. Six of these patients were treated with doses of omalizumab 375 mg every 2 weeks and the other patient received 300 mg every 2 weeks. All 7 patients continued to take their usual medication. The eczema was moderate in 4 patients, severe in 1, and mild in the other 2. Patients were assessed at 3 and 7 months after starting treatment with omalizumab. All 7 patients improved and none of them experienced a flare during treatment. The authors concluded by suggesting that their findings should be confirmed by randomized clinical trials.

**Mastocytosis**

Carter et al\textsuperscript{259} reported their experience with omalizumab in the treatment of anaphylactic reactions in 2 patients with systemic mastocytosis. The first was a 17-year-old woman who had a history of urticaria pigmentosa from the age of 3 months. From the age of 5 years she had suffered frequent episodes of syncope. After monthly treatment with omalizumab 300 mg, the episodes of syncope disappeared. The second case was that of a 51-year-old man with a history of urticaria pigmentosa with bone marrow involvement from the age of 14 years. Since the age of 48 years, he had experienced 14 or 15 anaphylactic episodes annually requiring treatment with adrenaline. The anaphylactic symptoms did not recur during the 5 months of treatment with omalizumab 300 mg administered monthly.

**Chronic Urticaria**

In view of the pathogenic mechanisms involved in chronic urticaria, it has been suggested that omalizumab could be useful in the treatment of this disorder.\textsuperscript{260} At present, however, there are no published cases of such use in the literature.
Daclizumab

Daclizumab is a humanized monoclonal antibody against the IL-2 receptor CD25. The inhibiting action of this agent blocks the activation of T cells. It is approved for use in combination with other immunosuppressive agents (cyclosporin and corticosteroids) to prevent acute organ rejection after allogenic renal transplantation.261

Posology

The dose is 1 mg/kg, which is given during the 24 hours before transplantation and every 14 days after the intervention until 5 doses have been received.

Side Effects

On rare occasions, severe and acute hypersensitivity reactions during the 24 hours after administration have been reported. In a clinical trial of heart transplant patients, a greater risk of death due to infection was observed in the group receiving daclizumab.

Contraindications

Daclizumab is contraindicated in patients with known hypersensitivity to the active substance or any of the excipients.

Off-Label Uses

**Bullous Pemphigoid**

Two cases of patients with bullous pemphigoid treated with daclizumab have been reported. The first was a 52-year-old man with extensive bullous pemphigoid who had previously been treated with oral corticosteroids, azathioprine, cyclosporin, and mycophenolate and had developed diabetes mellitus.262 Treatment was started with daclizumab 100 mg every 15 days (6 doses) in combination with azathioprine and prednisone. The bullous lesions started to disappear 2 weeks after the patient started this regimen. The lesions reappeared when treatment with daclizumab was interrupted and resolved again when it was resumed.

The second was a 10-year-old boy who underwent bone marrow transplantation for acute lymphocytic leukemia and presented a bullous pemphigoid 7 months after receiving the transplant despite immunosuppressive therapy and prednisone at doses of up to 2 mg/kg.238 Treatment with a combination of rituximab and daclizumab resulted in rapid improvement of the pemphigoid. A new bulla that developed 2 months after withdrawal of treatment with daclizumab disappeared after a second course of treatment.

**Pemphigus Vulgaris**

Only 1 case has been reported of pemphigus vulgaris treated with daclizumab. The patient was a 64-year-old woman with extensive pemphigus vulgaris refractory to treatment with cyclosporin and azathioprine who had developed diabetes mellitus as a result of corticosteroid therapy.263 She received daclizumab at a dose of 1 mg/kg every 2 weeks (6 cycles) in combination with azathioprine and prednisolone. Her mucous membrane and skin lesions improved after 3 weeks of treatment and resolved completely after 30 days.

**Epidermolysis Bullosa Acquisita**

Egan et al264 used daclizumab to treat epidermolysis bullosa acquisita in 3 men aged between 33 and 44 years. Lymphocyte expression of CD25 was reduced in all 3 patients after treatment. While 2 patients showed no clinical improvement, the third, who had more inflammatory symptoms, did respond. Moreover, his disease flared when daclizumab was suspended, and once again responded favorably when treatment was resumed.

**Adult Erythrodermic T-cell Leukemia**

A 48-year-old patient with treatment-resistant erythroderma secondary to adult T-cell leukemia-lymphoma received daclizumab 1 mg/kg/wk, with rapid resolution of the erythroderma and pruritus and histological remission of the cutaneous lesions.265 He remained symptom free for 6 months, and lesions reappeared when the interval between doses of daclizumab was increased. Once the number of doses was again increased, the lesions disappeared only to reappear after 14 months of treatment.

**Psoriasis**

Krueger et al266 reported a case series of 19 patients with psoriasis treated with daclizumab. The initial dose was 2 mg/kg and this was followed by 1 mg/kg in weeks 2, 4, 8, and 12. A 30% reduction of the psoriasis area and severity index (PASI) was achieved without significant adverse effects.

Several isolated cases with good responses have also been reported.267,268 In a patient infected with human immunodeficiency virus, a case of psoriatic erythroderma resolved completely within a month.268
Basiliximab

Basiliximab is an anti-CD25 chimeric monoclonal antibody similar to daclizumab described above and approved for the same indications.269

Posology

The standard dosage regimen is two 20 mg doses, the first administered during the 4 hours before the transplantation surgery and the second 4 days after the intervention.

Side Effects

Severe acute hypersensitivity reactions have been observed within 24 hours of administration both on initial exposure to basiliximab and on re-exposure to a subsequent course of therapy.

Contraindications

Hypersensitivity to the active substance or any of the excipients.

Off-Label Uses

Epidermolysis Bullosa Acquisita

A 55-year-old man with epidermolysis bullosa acquisita refractory to azathioprine and cyclosporin was treated with a combination of cyclosporin 200 mg/d and a single 20 mg dose of intravenous basiliximab.270 The bullous lesions stopped appearing 2 weeks after treatment, allowing tapering of the dose of cyclosporin. The lesions healed completely within 10 weeks.

Psoriasis

Bagel et al271 undertook a placebo controlled trial in volunteers with psoriasis. Of the patients treated with basiliximab, 24% showed a 50% improvement in PASI scores compared to 17% of the control group. This difference was statistically significant. Treatment was discontinued in 10 patients because of adverse effects, generally flu-like syndrome. The authors concluded that basiliximab is not a reasonable treatment for psoriasis patients because of its poor risk-benefit profile.

Isolated cases of patients with a good response have been published, but rapid relapse occurred after withdrawal of treatment.272 In 1 reported case, a patient with recalcitrant palm–plantar psoriasis refractory to a large number of treatments, including radiation therapy, responded very favorably to basiliximab during the 4 months of treatment.273 Mrowietz et al274 treated 2 patients with different dose regimens. The first patient received 2 doses of 20 mg and no response was observed. The second patient, who received a 20 mg initial dose and 40 mg doses on days 21 and 42, experienced an 83% improvement in PASI score. The authors suggest that higher doses may be necessary for the treatment of psoriasis than those given to transplant patients.

Finally, in the case of an 80-year-old man with extensive refractory psoriasis, basiliximab was added to the patient’s existing treatment—prednisolone, acitretin, and cyclosporin—a combination regimen that had not been successful in controlling his disease.275 After only 2 doses of basiliximab, the patient showed rapid improvement, which was sustained during the 5-month follow-up period.

Erosive Lichen Planus

A 67-year-old woman with oral and genital lesions of erosive lichen planus had received treatment with cyclosporin for 2 years.276 She received two 20 mg doses of basiliximab 4 days apart. The lesions healed but reappeared 1 month later; treatment was not repeated because of its high cost.

Cetuximab

Cetuximab is a chimeric monoclonal antibody that targets the EGFR.277 It is approved for the treatment, in combination with irinotecan, of patients with EGFR-positive colorectal cancer refractory to conventional chemotherapeutic regimens that include irinotecan. Its use is also approved, in combination with radiation therapy, in patients with locally advanced squamous cell cancers of the head and neck.278

Posology

In all indications, cetuximab is administered once a week. The first dose is 400 mg/m² of body surface area. All subsequent weekly doses are 250 mg/m² each.

Side Effects

Infrequent reactions to the infusion have been reported; these tend to develop within 1 hour of administration and may be accompanied by dyspnea.279 An acne-like skin rash is the most commonly reported side effect, occurring in over half the patients. Other types of skin lesions reported are paronychia, eczematous reactions, and trichomegaly.277
Contraindications

It is contraindicated in patients with known severe hypersensitivity reactions (grade 3 or 4) to cetuximab.

Off-Label Uses

Cutaneous Squamous Cell Carcinoma

A case has been published of a patient with locally advanced squamous cell carcinoma who responded well to monotherapy with cetuximab. Recently, 2 cases have been reported of patients with squamous cell carcinoma of the skin and in-transit metastasis despite multiple surgical interventions and radiation therapy. Both these patients showed a very good response to weekly treatment with cetuximab (disappearance of tumor nodules and enlarged nodes in 1, and reduction in tumor size in the other) during follow-up periods of 16 and 12 weeks. One of these patients developed an acneiform reaction as a side effect.

A phase II clinical trial is currently under way in patients with squamous cell carcinoma of the skin expressing EGFR (currently in the recruitment phase). There is very scant experience with treatment of squamous cell carcinoma of the skin. In our hospital, the only patient receiving this drug is being treated for squamous cell carcinoma on the forehead with satellite metastasis and cervical node involvement. Since the tumor has continued to progress despite several surgical interventions and radiation therapy up to the maximum dose, it was decided to initiate treatment with cetuximab. Although the treatment cycles have not yet been completed, the response obtained to date has been poor (Figures 3 and 4).

Other Skin Diseases

There is no experience of the use of cetuximab in other skin diseases, but in light of the pathogenic mechanisms involved it has been suggested that this agent may be useful in other diseases, such as psoriasis and basal cell carcinoma.

Conclusion

The development of these new biologic agents represents a great advance in the treatment of many diseases. Their use is advocated because they target specific pathophysiologic mechanisms and are therefore much more specific than conventional nonbiologic immunosuppressants. In our opinion they differ from standard immunosuppressive agents not so much in their greater specificity but rather because they have been developed to act against a specific target thanks to new molecular biology techniques. The specificity of these agents is, however, relative. TNF, for example, plays a role in the regulation of numerous aspects of the immune system, and this multiplicity of roles provides the rationale for the off-label uses of various different biologic agents.

The aim of this article was to present the information currently available on off-label uses of these agents in the treatment of skin diseases. We are, however, aware that a large number of new cases of diseases treated with these agents will soon be added to the cases included in this review. Our aim was to review the currently available data, although it is clear that by the time this article is published, it will be necessary to complement this information with a review of the evidence published in the intervening period.

Conflict of Interest

The authors declare no conflicts of interest.
REFERENCES


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