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REVIEW ARTICLE

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.

USO DE FÁRMACOS BIOLÓGICOS EN DERMATOSIS FUERA DE LA INDICACIÓN APROBADA. SEGUNDA PARTE: ETANERCEPT, EFALIZUMAB, ALEFACEPT, RITUXIMAB, DACLIZUMAB, BASILIXIMAB, OMALIZUMAB Y CETUXIMAB

Resumen. En los últimos años han aparecido una serie de nuevos fármacos desarrollados por biología molecular. Estos medicamentos actúan bloqueando moléculas específicas del sistema inmunológico y se desarrollan para actuar sobre dianas específicas que tienen un papel importante en la fisiopatología de determinadas enfermedades para cuyo tratamiento son aprobadas. Con el tiempo se ha ido adquiriendo experiencia con estos medicamentos en el tratamiento de dermatosis para las que no han sido diseñados, pero para las que, por compartir un mismo mecanismo fisiopatológico, pueden ser útiles. El empleo de estos medicamentos en el tratamiento de casos difíciles de numerosas enfermedades dermatológicas para las cuales no están aprobados es creciente. Esta segunda parte de la revisión analiza el uso, fuera de indicación, en el tratamiento de la dermatosis de los siguientes fármacos biológicos: etanercept, efalizumab, alefacept, rituximab, daclizumab, basiliximab, omalizumab y cetuximab.

Palabras clave: biológicos, dermatosis, fuera de indicación.

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

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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 al[27] 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 al[28] 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 al[31] 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.[32] 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 al[33] 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 subsequently. 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 al[34] 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 25 mg 3 times a week for 3 weeks without success.

Roy et al[35] 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 al[36] 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

Collagen Disease
Lupus erythematosus
Dermatomyositis
Scleroderma
Neutrophilic Skin Diseases
Sweet syndrome
Pyoderma gangrenosum
Graft-Versus-Host Disease
Acute
Chronic
Spongiotic Dermatitis
Dyshidrotic eczema
Atopic dermatitis
Blistering Diseases
Bullous pemphigoid
Cicatricial pemphigoid
Pemphigus vulgaris
Pemphigus foliaceus
Benign familial pemphigus (Hailey-Hailey disease)
Granulomatous Skin Diseases
Sarcoidosis
Granuloma annulare
Necrobiosis lipoidica
Silicone granulomas
Cutaneous granulomas in patients with common variable immunodeficiency
Vasculitis
Behçet disease
Wegener granulomatosis
Polyarteritis nodosa
Miscellaneous
Multicentric reticulohistiocytosis
Toxic epidermal necrolysis
Acne vulgaris
Hidradenitis
Aphthous stomatitis
Alopecia areata
Centrifugal annular erythema
Primary amyloidosis
Erythroderma-related pruritus in Sézary syndrome
Cutaneous T-cell lymphoma
Inflammatory linear verrucous epidermal nevus
SAPHO syndrome

Goldenberg et al[37] 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[39] 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/m^2 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 dapsone, 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 al[56] 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, triamcinolone 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.[65] 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 al[67] 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 al[71] 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 al[78] 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 al[79] 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]

Polyarteritis nodosa. 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.[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 al[83] 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.[85] 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.[84]

Toxic epidermal necrolysis. TNF-induced apoptosis is partly responsible for the erosion of mucosal surfaces and epidermal shedding associated with toxic epidermal necrolysis.[86] Famularo et al[87] 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.[88] 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.

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[90] 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.[91]

Aphthous stomatitis. Robinson et al[92] 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.[93] In another reported case, a 44-year-old patient with universal alopecia areata did not respond to treatment with etanercept.[94]

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.[95]

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.[96] 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.[97]

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.[98] 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. Tsimberidou et al[99] 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.[100] 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[101] 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.[102,103] 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.[104]

Table 2. Off-label Uses of Efalizumab in Skin Diseases

Granuloma annulare
Lichen planus
Atopic dermatitis
Dermatomyositis
Graft-versus-host disease
Alopecia areata
Lupus erythematosus

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.[105]

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[106] 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.[107] 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.[108]

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.[109] 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[110] 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[111] 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.[112] 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[113] 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.[114] 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.[114]

Alopecia Areata

Several years ago, efalizumab was suggested as a drug that might be useful in treatment of alopecia areata.[115] However, it was not until 2006 that the first studies evaluating this indication were published.[116,117]

In 1 reported case, a 19-year-old man with alopecia universalis showed significant improvement after receiving the usual dose of efalizumab.[116] 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.[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.[117]

Subacute Lupus Erythematosus

Clayton et al[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, leflunomide, 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.[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.[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.[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.[122] Self-limiting flu-like symptoms occur during the initial weeks of treatment. Injection site reactions have been reported to be minimal.[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.[122]

Approximately 3% of patients develop antialefacept antibodies.[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.[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.[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.[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/m^2 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 is safe and beneficial.[142-147]

Some authors report that, in addition to improvement in systemic manifestations, clinical improvement in skin symptoms is also observed.[139,148-152] A case has also been reported of urticarial vasculitis and angioedema in a patient with systemic lupus erythematosus that was refractory to several treatments (mycophenolate mofetil, high-dose methylprednisolone, and intravenous immunoglobulin) but responded rapidly to treatment with rituximab.[153] 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.[154] 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.[155,156,157] In a study by Levine et al[155] 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[156] 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,[157] 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 periungual 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.[158,159] 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.[160] In another study of 9 patients, 8 showed complete response.[161]

Cases have been reported of patients with treatment-resistant Wegener disease who responded to treatment with rituximab. Ferraro et al[162] 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.[163-169] 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,[166] in other cases the response was lasting.[170,171] The combination of leflunomide and rituximab may have a synergistic effect in maintenance therapy.[172] In a prospective study, 10 patients with vasculitis secondary to Wegener disease were treated with a course of 4 weekly doses of rituximab.[173] 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 response[177] or even worsening of the disease and an increase in cryoagglutinin titers.[178] 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).[190] 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 depletion 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

Author	No. of Patients	Age Sex	Concomitant Therapy	Response	Follow-Up Side Effects
Salopek 2002[190]	1	29 W	C, MM, CS	Improvement, occasional flares	160 d
Virgolini 2003[191]	1	53 W	C, CS	Complete remission	40 wk
Cooper 2003[192]	1	54 W	C, MM	Complete remission	Unknown
Hermann 2003[193]	1	54 W	C	Complete remission	Unknown
Morrison 2004[194]	3	51 M 37 M 47 W	C, CP C, CP CP	Complete remission Complete remission Improvement	18 mo 5 mo 9 mo
España 2004[195]	1	39 M	C	Complete remission	40 wk
Dupuy 2004[196]	3	34 W 42 W 20 M	C, AZ C,CS, MM C	Partial response Partial response Complete remission	40 wk 72 wk 40 wk
Cecchi 2005[197]	1	44 W	C	Complete remission	10 mo
Kong 2005[198]	1	17 W	C	Complete remission	17 mo
Arin 2005[199]	4	60 W 26 W 27 W 57 W	C, MM C, MTX C, MTX C, MM	Complete response Improvement, occasional outbreaks Improvement, occasional outbreaks Complete response	24 mo 10 mo 10 mo 18 mo
Schmidt 2005[200]	1	14 W	C, MM, IVIg	Complete response	2 y
Wenzel 2005[201]	1	55 W	C	Complete response	3 mo
Ahmed 2006[202]	11	Mean 38 y 5 M; 6 W	C, IVIg	9 Complete responses 2 Partial responses	22-37 mo
Domínguez 2006[203]	1	60 W	C	Partial response	1 mo
Niedermeier 2006[204]	1	26 W	C, MM	Delayed complete response	15 mo
Esposito 2006[205]	2	45 M 49 M	Monotherapy	Complete response Complete response	7 mo 6 mo
Pitarch 2006[206]	1	64 M	C	Complete response	7 mo
Belgi 2006[207]	1	37 W	C, MM	Late complete response	11 mo
Antonucci 2006[208]	5	30 M 31 M 28 M 35 W 29 M	C in all 5 cases	Complete response in all cases	12 mo 12 mo 13 mo 12 mo 11 mo
Marzano 2007[209]	3	51 M 50 W 55 M	Unknown	Complete response Partial response Minimal response	24 mo 21 mo 2 mo
Goh 2007[210]	5	48 M 62 W 57 M 46 W 57 M	C, MM, CS C, MM C, CS C, AZ C	No response Complete response No response Complete response Complete response	13-18 mo
Borel 2007[211]	2	52 W 50 W	C, MM C, AZA, CS, IVIg	Complete response Complete response	15 mo 8 mo
Schmidt 2007[212]	4	39 W 81 W 68 W 17 W 17 W	C, AZ C, CP C, MM C, MM C, MM	Partial response Complete response Complete response Partial response	21 mo 16 mo 9 mo 7 mo

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,[204,207,209] giving rise to the hypothesis that this type of involvement is more resistant to treatment with rituximab.[209] The period during which response was sustained varied from case to case, from a few months before a relapse[196] to a maximum of 3 years after treatment.[199,209]

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.[199]

Only 2 cases have been reported of a drop in immunoglobulin levels in circulating blood.[198,212] 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 discontined.[192]

Of the 56 patients, 37 achieve complete remission making it possible to discontinue treatment with other drugs.[192-194,199,200,202,205,209,210,212] Monotherapy with rituximab was used in only 2 patients.[205]

In the largest study, which was undertaken by Ahmed et al,[202] 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.[202]

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.[210] 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.[209]

Rituximab was generally well tolerated, although severe adverse effects did occur in some patients, including serious infections, fatal pneumonia caused by *Pneumocystis carinii,*[194] *Pseudomonas aeruginosa* hip arthritis,[196] community-acquired pneumonia, [196,210,212] polymicrobial sepsis,[190] noninfectious enteropathy, pneumonia caused by *Haemophilus influenzae,* sepsis related to the herpes zoster virus,[212] nosocomial pneumonia,[212] and cytomegalovirus.[210] 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.

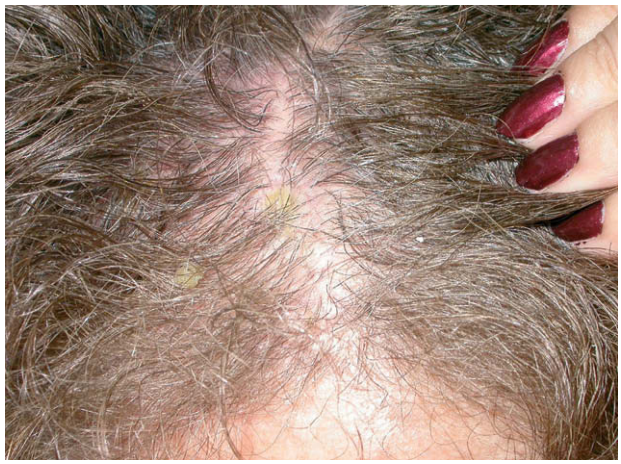

Figure 1. Pemphigus vulgaris blistering on scalp. Source: Esposito M, et al.[205]

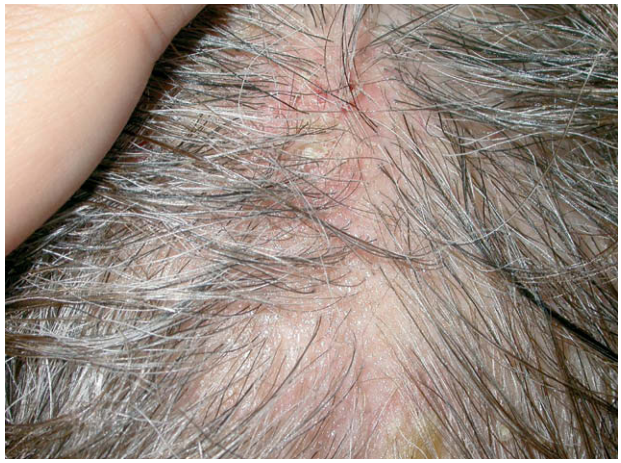

Figure 2. Residual lesions on the scalp of the same patient after 3 intravenous infusions of rituximab. Source: Esposito M, et al.[205]

Rituximab has also been used in the treatment of paraneoplastic pemphigus, and in some cases patients showed significant improvement after treatment with this agent.[213,214,218] 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.[214] By contrast, 4 cases have been reported of paraneoplastic pemphigus associated with non-Hodgkin lymphomas that did not respond to treatment.[216,217,219,228]

Rituximab was also effective in the treatment of 3 cases of pemphigus foliaceus in which it obtained a rapid response.[221,222]

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 al[226] 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 (prednisone, azathioprine, dapsone, and colchicine). He achieved complete remission after a single cycle of rituximab, remained disease free during the 1-year follow-up period, and was able to discontinue treatment with other drugs. The case reports of 3 more patients were published at a later date. Two showed a good response to combined treatment with immunoadsorption and rituximab[225] and 1 had a partial response to combined treatment with rituximab and mycophenolate mofetil during a 1-year follow-up period.[224]

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.[229] They treated 8 patients who had sclerodermiform changes with rituximab (a 4-week cycle at a dose of 375 mg/m^2/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 al[234] 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] This was the first report of an improvement in this disease in response to rituximab.

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[242] and allergic rhinitis.[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.[246-249] The formation of antibodies against omalizumab has not been reported.[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.[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.[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).[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.[254] Beck et al[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[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[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.[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[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.[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 50 mg/d and prednisone 5 mg/d. 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 al[264] 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 al[266] 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 al[271] 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 al[274] 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/m^2 of body surface area. All subsequent weekly doses are 250 mg/m^2 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]

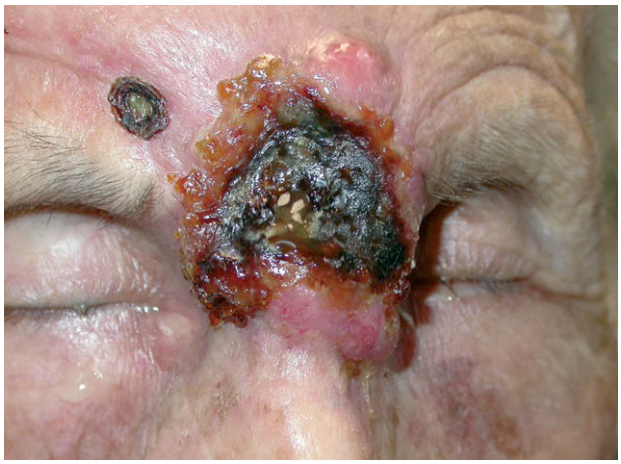

Figura 3. Squamous cell carcinoma in a 94-year-old patient previously treated with radiation therapy, before treatment with cetuximab.

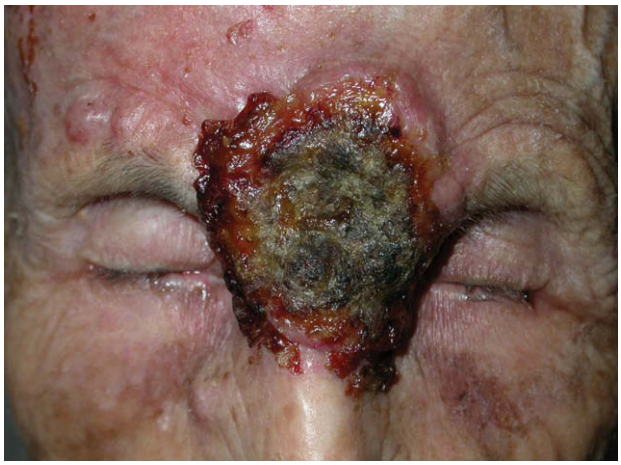

Figura 4. Squamous cell carcinoma in the same patient as Figure 3 after 6 weekly cycles of intravenous cetuximab. Tumor progression and an absence of any improvement can be observed.

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.[280] 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.[281] 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).[282]

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 [283]and basal cell carcinoma.[284]

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

1. Graves JE, Nunley K, Heffernan MP. Off-label uses of biologics in dermatology: rituximab, omalizumab, infliximab, etanercept, adalimumab, efalizumab, and alefacept (part 2 of 2). J Am Acad Dermatol. 2007;56:e55-79.
2. Kerns MJ, Graves JE, Smith DI, Heffernan MP. Off-label uses of biologic agents in dermatology: a 2006 update. Semin Cutan Med Surg. 2006;25:226-40.
3. Jacobi A, Manger B, Schuler G, Hertl M. [Therapeutic application of TNF-alpha inhibitors infliximab and etanercept in inflammatory skin disorders]. J Dtsch Dermatol Ges. 2003;1:259-72.
4. Trent JT, Kerdel FA. Tumor necrosis factor alpha inhibitors for the treatment of dermatologic diseases. Dermatol Nurs. 2005;17(2):97-107.
5. Williams JD, Griffiths CE. Cytokine blocking agents in dermatology. Clin Exp Dermatol. 2002;27:585-90.
6. Scheinfeld N. The medical uses and side effects of etanercept with a focus on cutaneous disease. J Drugs Dermatol. 2004;3:653-9.
7. Alexis AF, Strober BE. Off-label dermatologic uses of anti-TNF-α therapies. J Cutan Med Surg. 2005;9:296-302.
8. Gamo R, López-Estebaranz JL. Biologic therapy and psoriasis. Actas Dermosifiliogr. 2006;97:1-17.
9. Nanda S, Bathon JM. Etanercept: a clinical review of current and emerging indications. Expert Opin Pharmacother. 2004;5:1175-86.
10. Goffe B, Cather JC. Etanercept: an overview. J Am Acad Dermatol. 2003;49Suppl:S105-11.
11. Goffe B. Etanercept (Enbrel)—an update. Skin Therapy Lett. 2004;9:1-4, 9.
12. http://emea.europa.eu/humandocs/Humans/EPAR/enbrel/enbrel.htm.
13. Hamilton CD. Infectious complications of treatment with biologic agents. Curr Opin Rheumatol. 2004;16(4):393-8.
14. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. N Engl J Med. 2004;350:2167-79.
15. Swale VJ, Perrett CM, Denton CP, Black CM, Rustin MH. Etanercept-induced systemic lupus erythematosus. Clin Exp Dermatol. 2003;28:604-7.
16. Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. Lancet. 2002;359:579-80.
17. Richez C, Blanco P, Dumoulin C, Schaeverbeke T. Lupus erythematosus manifestations exacerbated by etanercept therapy in a patient with mixed connective tissue disease. Clin Exp Rheumatol. 2005;23:273.
18. Mor A, Bingham C, Barisoni L, Lydon E, Belmont HM. Proliferative lupus nephritis and leukocytoclastic vasculitis during treatment with etanercept. J Rheumatol. 2005;32: 740-3.
19. Lepore L, Marchetti F, Facchini S, Leone V, Ventura A. Drug-induced systemic lupus erythematosus associated with etanercept therapy in a child with juvenile idiopathic arthritis. Clin Exp Rheumatol. 2003;21:276-7.
20. Kang MJ, Lee YH, Lee J. Etanercept-induced systemic lupus erythematosus in a patient with rheumatoid arthritis. J Korean Med Sci. 2006;21:946-9.
21. Debandt M, Vittecoq O, Descamps V, Le Loet X, Meyer O. Anti-TNF-alpha-induced systemic lupus syndrome. Clin Rheumatol. 2003;22:56-61.
22. De Bandt M, Sibilia J, Le Loet X, Prouzeau S, Fautrel B, Marcelli C, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther. 2005;7:R545-51.
2 3. Carlson E, Rothfield N. Etanercept-induced lupus-like syndrome in a patient with rheumatoid arthritis. Arthritis Rheum. 2003;48:1165-6; author reply 1166.
24. Cairns AP, Duncan MK, Hinder AE, Taggart AJ. New onset systemic lupus erythematosus in a patient receiving etanercept for rheumatoid arthritis. Ann Rheum Dis. 2002; 61:1031-2.
25. Bleumink GS, ter Borg EJ, Ramselaar CG, Ch Stricker BH. Etanercept-induced subacute cutaneous lupus erythematosus. Rheumatology (Oxford). 2001;40:1317-9.
26. Benucci M, Li Gobbi F, Fossi F, Manfredi M, Del Rosso A. Drug-induced lupus after treatment with infliximab in rheumatoid arthritis. J Clin Rheumatol. 2005;11:47-9.
27. Norman R, Greenberg RG, Jackson JM. Case reports of etanercept in inflammatory dermatoses. J Am Acad Dermatol. 2006;54Suppl2:S139-42.
28. Fautrel B, Foltz V, Frances C, Bourgeois P, Rozenberg S. Regression of subacute cutaneous lupus erythematosus in a patient with rheumatoid arthritis treated with a biologic tumor necrosis factor alpha-blocking agent: comment on the article by Pisetsky and the letter from Aringer et al. Arthritis Rheum. 2002;46:1408-9; author reply 1409.
29. Hall HA, Zimmermann B. Evolution of dermatomyositis during therapy with a tumor necrosis factor alpha inhibitor. Arthritis Rheum. 2006;55:982-4.
30. Efthimiou P, Schwartzman S, Kagen LJ. Possible role for tumour necrosis factor inhibitors in the treatment of resistant dermatomyositis and polymyositis: a retrospective study of eight patients. Ann Rheum Dis. 2006;65:1233-6.
31. Iannone F, Scioscia C, Falappone PC, Covelli M, Lapadula G. Use of etanercept in the treatment of dermatomyositis: a case series. J Rheumatol. 2006;33:1802-4.
32. Ellman MH MP, HAyes FA. Etanercept as treatment for diffuse scleroderma: a pilot study. Arthritis Rheum. 2000; 43:392.
33. Yamauchi PS, Turner L, Lowe NJ, Gindi V, Jackson JM. Treatment of recurrent Sweet's syndrome with coexisting rheumatoid arthritis with the tumor necrosis factor antagonist etanercept. J Am Acad Dermatol. 2006;54Suppl2: S122-6.
34. Hubbard VG, Friedmann AC, Goldsmith R Systemic pyoderma gangrenosum responding to infliximab and adalimumab. Br J Dermatol. 2005;152:1059-61.
35. Roy DB, Conte ET, Cohen DJ. The treatment of pyoderma gangrenosum using etanercept. J Am Acad Dermatol. 2006; 54Suppl2:S128-34.
36. McGowan JWt, Johnson CA, Lynn A. Treatment of pyoderma gangrenosum with etanercept. J Drugs Dermatol. 2004;3:441-4.
37. Goldenberg G, Jorizzo JL. Use of etanercept in treatment of pyoderma gangrenosum in a patient with autoimmune hepatitis. J Dermatolog Treat. 2005;16:347-9.
38. Pastor N, Betlloch I, Pascual JC, Blanes M, Banuls J, Silvestre JF. Pyoderma gangrenosum treated with anti-TNF alpha therapy (etanercept). Clin Exp Dermatol. 2006;31:152-3.
39. Disla E, Quayum B, Cuppari GG, Pancorbo R. Successful use of etanercept in a patient with pyoderma gangrenosum complicating rheumatoid arthritis. J Clin Rheumatol. 2004; 10:50-2.

40. Holler E, Kolb HJ, Moller A, Kempeni J, Liesenfeld S, Pechumer H, et al. Increased serum levels of tumor necrosis factor alpha precede major complications of bone marrow transplantation. Blood. 1990;75:1011-6.
41. Holler E, Kolb HJ, Hintermeier-Knabe R, Mittermuller J, Thierfelder S, Kaul M, et al. Role of tumor necrosis factor alpha in acute graft-versus-host disease and complications following allogeneic bone marrow transplantation. Transplant Proc. 1993;25:1234-6.
42. Holler E, Kolb HJ, Eissner G, Wilmanns W. Cytokines in GvH and GvL. Bone Marrow Transplant. 1998;22Suppl4: S3-6.
43. Schmaltz C, Alpdogan O, Muriglan SJ, Kappel BJ, Rotolo JA, Ricchetti ET, et al. Donor T cell-derived TNF is required for graft-versus-host disease and graft-versus-tumor activity after bone marrow transplantation. Blood. 2003; 101: 2440-5.
44. Jacobsohn DA, Vogelsang GB. Anti-cytokine therapy for the treatment of graft-versus-host disease. Curr Pharm Des. 2004;10:1195-205.
45. Andolina M, Rabusin M, Maximova N, Di Leo G. Etanercept in graft-versus-host disease. Bone Marrow Transplant. 2000;26:929.
46. Wolff D, Roessler V, Steiner B, Wilhelm S, Weirich V, Brenmoehl J, et al. Treatment of steroid-resistant acute graft-versus-host disease with daclizumab and etanercept. Bone Marrow Transplant. 2005;35:1003-10.
47. Kennedy GA, Butler J, Western R, Morton J, Durrant S, Hill GR. Combination antithymocyte globulin and soluble TNF-alpha inhibitor (etanercept) +/- mycophenolate mofetil for treatment of steroid refractory acute graft-versus-host disease. Bone Marrow Transplant. 2006;37:1143-7.
48. Uberti JP, Ayash L, Ratanatharathorn V, Silver S, Reynolds C, Becker M, et al. Pilot trial on the use of etanercept and methylprednisolone as primary treatment for acute graft-versus-host disease. Biol Blood Marrow Transplant. 2005; 11:680-7.
49. Busca A, Locatelli F, Marmont F, Ceretto C, Falda M. Recombinant human soluble tumor necrosis factor receptor fusion protein as treatment for steroid refractory graft-versus-host disease following allogeneic hematopoietic stem cell transplantation. Am J Hematol. 2007;82:45-52.
50. Chiang KY, Abhyankar S, Bridges K, Godder K, Henslee-Downey JP. Recombinant human tumor necrosis factor receptor fusion protein as complementary treatment for chronic graft-versus-host disease. Transplantation. 2002;73: 665-7.
51. Ogden S, Clayton TH, Goodfield MJ. Recalcitrant hand pompholyx: variable response to etanercept. Clin Exp Dermatol. 2006;31:145-6.
52. Buka RL, Resh B, Roberts B, Cunningham BB, Friedlander S. Etanercept is minimally effective in 2 children with atopic dermatitis. J Am Acad Dermatol. 2005;53:358-9.
53. Yamauchi PS, Lowe NJ, Gindi V. Treatment of coexisting bullous pemphigoid and psoriasis with the tumor necrosis factor antagonist etanercept. J Am Acad Dermatol. 2006; 54Suppl2:S121-2.
54. Sacher C, Rubbert A, Konig C, Scharffetter-Kochanek K, Krieg T, Hunzelmann N. Treatment of recalcitrant cicatricial pemphigoid with the tumor necrosis factor alpha antagonist etanercept. J Am Acad Dermatol. 2002;46:113-5.
55. Prey S, Robert PY, Drouet M, Sparsa A, Roux C, Bonnet-blanc JM, et al. Treatment of ocular cicatricial pemphigoid with the tumour necrosis factor alpha antagonist etanercept. Acta Derm Venereol. 2007;87:74-5.
56. Canizares MJ, Smith DI, Conners MS, Maverick KJ, Heffernan MP. Successful treatment of mucous membrane pemphigoid with etanercept in 3 patients. Arch Dermatol. 2006;142:1457-61.
57. Lin MH, Hsu CK, Lee JY. Successful treatment of recalcitrant pemphigus vulgaris and pemphigus vegetans with etanercept and carbon dioxide laser. Arch Dermatol. 2005;141:680-2.
58. Berookhim B, Fischer HD, Weinberg JM. Treatment of recalcitrant pemphigus vulgaris with the tumor necrosis factor alpha antagonist etanercept. Cutis. 2004;74:245-7.
59. Gubinelli E, Bergamo F, Didona B, Annessi G, Atzori F, Raskovic D. Pemphigus foliaceus treated with etanercept. J Am Acad Dermatol. 2006;55:1107-8.
60. Utz JP, Limper AH, Kalra S, Specks U, Scott JP, Vuk-Pavlovic Z, et al. Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. Chest. 2003;124: 177-85.
61. Baughman RP, Lower EE, Bradley DA, Raymond LA, Kaufman A. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. Chest. 2005;128: 1062-47.
62. Khanna D, Liebling MR, Louie JS. Etanercept ameliorates sarcoidosis arthritis and skin disease. J Rheumatol. 2003;30: 1864-7.
63. Tuchinda C, Wong HK. Etanercept for chronic progressive cutaneous sarcoidosis. J Drugs Dermatol. 2006;5:538-40.
64. González-López MA, Blanco R, González-Vela MC, Fernández-Llaca H, Rodríguez-Valverde V. Development of sarcoidosis during etanercept therapy. Arthritis Rheum. 2006;55:817-20.
65. Kudrin A, Chilvers ER, Ginawi A, Hazleman BL, Griffiths MH, Thiru S, et al. Sarcoid-like granulomatous disease following etanercept treatment for RA. J Rheumatol. 2007; 34:648-9.
66. Verschueren K, Van Essche E, Verschueren P, Taelman V, Westhovens R. Development of sarcoidosis in etanercept-treated rheumatoid arthritis patients. Clin Rheumatol. 2007;26:1969-71.
67. Shupack J, Siu K. Resolving granuloma annulare with etanercept. Arch Dermatol. 2006;142:394-5.
68. Kreuter A, Altmeyer P, Gambichler T. Failure of etanercept therapy in disseminated granuloma annulare. Arch Dermatol. 2006;142:1236-7.
69. Cummins DL, Hiatt KM, Mimouni D, Vander Kolk CA, Cohen BA, Nousari CH. Generalized necrobiosis lipoidica treated with a combination of split-thickness autografting and immunomodulatory therapy. Int J Dermatol. 2004;43: 852-4.
70. Zeichner JA, Stern DW, Lebwohl M. Treatment of necrobiosis lipoidica with the tumor necrosis factor antagonist etanercept. J Am Acad Dermatol. 2006;54Suppl 2:S120-1.
71. Pasternack FR, Fox LP, Engler DE. Silicone granulomas treated with etanercept. Arch Dermatol. 2005;141:13-5.
72. Desai AM, Browning J, Rosen T. Etanercept therapy for silicone granuloma. J Drugs Dermatol. 2006;5:894-6.
73. Rapaport MJ. Silicone granulomas treated with etanercept. Arch Dermatol. 2005;141:1171.
74. Lin JH, Liebhaber M, Roberts RL, Dyer Z, Stiehm ER. Etanercept treatment of cutaneous granulomas in common

variable immunodeficiency. J Allergy Clin Immunol. 2006; 117:878-82.
75. Melikoglu M, Fresko I, Mat C, Ozyazgan Y, Gogus F, Yurdakul S, et al. Short-term trial of etanercept in Behcet's disease: a double blind, placebo controlled study. J Rheumatol. 2005;32:98-105.
76. Sommer A, Altmeyer P, Kreuter A. A case of mucocutaneous Behcet's disease responding to etanercept. J Am Acad Dermatol. 2005;52:717-9.
77. Atzeni F, Sarzi-Puttini P, Capsoni F, Mecchia M, Marrazza MG, Carrabba M. Successful treatment of resistant Behcet's disease with etanercept. Clin Exp Rheumatol. 2005;23: 729.
78. Estrach C, Mpofu S, Moots RJ. Behcet's syndrome: response to infliximab after failure of etanercept. Rheumatology (Oxford). 2002;41:1213-4.
79. Stone JH, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, Hoffman GS. Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety. Arthritis Rheum. 2001; 44:1149-54.
80. Wegener's granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med. 2005;352:351-61.
81. Kleinert J, Lorenz M, Kostler W, Horl W, Sunder-Plassmann G, Soleiman A. [Refractory Wegener's granulomatosis responds to tumor necrosis factor blockade]. Wien Klin Wochenschr. 2004;116:334-8.
82. Feinstein J, Arroyo R. Successful treatment of childhood onset refractory polyarteritis nodosa with tumor necrosis factor alpha blockade. J Clin Rheumatol. 2005;11:219-22.
83. Kovach BT, Calamia KT, Walsh JS, Ginsburg WW. Treatment of multicentric reticulohistiocytosis with etanercept. Arch Dermatol. 2004;140:919-21.
84. Lovelace K, Loyd A, Adelson D, Crowson N, Taylor JR, Cornelison R. Etanercept and the treatment of multicentric reticulohistiocytosis. Arch Dermatol. 2005;141:1167-8.
85. Matejicka C, Morgan GJ, Schlegelmilch JG. Multicentric reticulohistiocytosis treated successfully with an anti-tumor necrosis factor agent: comment on the article by Gorman et al. Arthritis Rheum. 2003;48:864-6.
86. Chave TA, Mortimer NJ, Sladden MJ, Hall AP, Hutchinson PE. Toxic epidermal necrolysis: current evidence, practical management and future directions. Br J Dermatol. 2005;153:241-53.
87. Famularo G, Di Dona B, Canzona F, Girardelli CR, Cruciani G. Etanercept for toxic epidermal necrolysis. Ann Pharmacother. 2007;41:1083-4.
88. Campione E, Mazzotta AM, Bianchi L, Chimenti S. Severe acne successfully treated with etanercept. Acta Derm Venereol. 2006;86:256-7.
89. Cortis E, De Benedetti F, Insalaco A, Cioschi S, Muratori F, D'Urbano LE, et al. Abnormal production of tumor necrosis factor (TNF)—alpha and clinical efficacy of the TNF inhibitor etanercept in a patient with PAPA syndrome [corrected]. J Pediatr. 2004;145:851-5.
90. Cusack C, Buckley C. Etanercept: effective in the management of hidradenitis suppurativa. Br J Dermatol. 2006;154: 726-9.
91. Henderson RL, Jr. Case reports: treatment of atypical hidradenitis suppurativa with the tumor necrosis factor receptor-Fc fusion protein etanercept. J Drugs Dermatol. 2006;5: 1010-1.
92. Robinson ND, Guitart J. Recalcitrant, recurrent aphthous stomatitis treated with etanercept. Arch Dermatol. 2003; 139:1259-62.
93. Strober BE, Siu K, Alexis AF, Kim G, Washenik K, Sinha A, et al. Etanercept does not effectively treat moderate to severe alopecia areata: an open-label study. J Am Acad Dermatol. 2005;52:1082-4.
94. Abramovits W, Losornio M. Failure of two TNF-alpha blockers to influence the course of alopecia areata. Skinmed. 2006;5:177-81.
95. Posten W, Swan J. Recurrence of alopecia areata in a patient receiving etanercept injections. Arch Dermatol. 2005;141: 759-60.
96. Minni J, Sarro R. A novel therapeutic approach to erythema annulare centrifugum. J Am Acad Dermatol. 2006;54Suppl 2:S134-5.
97. Hussein MA, Juturi JV, Rybicki L, Lutton S, Murphy BR, Karam MA. Etanercept therapy in patients with advanced primary amyloidosis. Med Oncol. 2003;20:283-90.
98. Querfeld C, Guitart J, Kuzel TM, Rosen S. Successful treatment of recalcitrant, erythroderma-associated pruritus with etanercept. Arch Dermatol. 2004;140:1539-40.
99. Tsimberidou AM, Giles FJ, Duvic M, Kurzrock R. Pilot study of etanercept in patients with relapsed cutaneous T-cell lymphomas. J Am Acad Dermatol. 2004;51:200-4.
100. Bogle MA, Sobell JM, Dover JS. Successful treatment of a widespread inflammatory verrucous epidermal nevus with etanercept. Arch Dermatol. 2006;142:401-2.
101. Wagner AD, Andresen J, Jendro MC, Hulsemann JL, Zeidler H. Sustained response to tumor necrosis factor alpha-blocking agents in two patients with SAPHO syndrome. Arthritis Rheum. 2002;46:1965-8.
102. van Noesel C, Miedema F, Brouwer M, de Rie MA, Aarden LA, van Lier RA. Regulatory properties of LFA-1 alpha and beta chains in human T-lymphocyte activation. Nature. 1988;333:850-2.
103. Shear NH, Langley RG, Ho V. Efalizumab, a reversible T-cell modulator for psoriasis. J Cutan Med Surg. 2006; 9Suppl1:4-9.
104. http://emea.europa.eu/humandocs/Humans/EPAR/raptiva/raptiva.htm. Accessed June 30, 2007.
105. Langley RG, Carey WP, Rafal ES, Tyring SK, Caro I, Wang X, et al. Incidence of infection during efalizumab therapy for psoriasis: analysis of the clinical trial experience. Clin Ther. 2005;27:1317-28.
106. Goffe BS. Disseminated granuloma annulare resolved with the T-cell modulator efalizumab. Arch Dermatol. 2004;140: 1287-8.
107. Cheng A, Mann C. Oral erosive lichen planus treated with efalizumab. Arch Dermatol. 2006;142:680-2.
108. Heffernan MP, Smith DI, Bentley D, Tabacchi M, Graves JE. A single-center, open-label, prospective pilot study of subcutaneous efalizumab for oral erosive lichen planus. J Drugs Dermatol. 2007;6:310-4.
109. Bohm M, Luger TA. Lichen planus responding to efalizumab. J Am Acad Dermatol. 2007;56Suppl:S92-3.
110. Weinberg JM, Siegfried EC. Successful treatment of severe atopic dermatitis in a child and an adult with the T-cell modulator efalizumab. Arch Dermatol. 2006;14:555-8.

111. Hassan AS, Kaelin U, Braathen LR, Yawalkar N. Clinical and immunopathologic findings during treatment of recalcitrant atopic eczema with efalizumab. J Am Acad Dermatol. 2007;5 6:217-21.
112. Takiguchi R, Tofte S, Simpson B, Harper E, Blauvelt A, Hanifin J, et al. Efalizumab for severe atopic dermatitis: a pilot study in adults. J Am Acad Dermatol. 2007;56:222-7.
113. Huber A, Gaffal E, Bieber T, Tuting T, Wenzel J. Treatment of recalcitrant dermatomyositis with efalizumab. Acta Derm Venereol. 2006;86:254-5.
114. Dedrick RL, Walicke P, Garovoy M. Anti-adhesion antibodies efalizumab, a humanized anti-CD11a monoclonal antibody. Transpl Immunol. 2002;9:181-6.
115. McMichael AJ. The new biologics in psoriasis: possible treatments for alopecia areata. J Investig Dermatol Symp Proc. 2003;8:217-8.
116. Kaelin U, Hassan AS, Braathen LR, Yawalkar N. Treatment of alopecia areata partim universalis with efalizumab. J Am Acad Dermatol. 2006;55:529-32.
117. Tosti A, Pazzaglia M, Starace M, Bellavista S, Vincenzi C, Tonelli G. Alopecia areata during treatment with biologic agents. Arch Dermatol. 2006;142:1653-4.
118. Clayton TH, Ogden S, Goodfield MD. Treatment of refractory subacute cutaneous lupus erythematosus with efalizumab. J Am Acad Dermatol. 2006;54:892-5.
119. Bentley DD, Graves JE, Smith DI, Heffernan MP. Efalizumab-induced subacute cutaneous lupus erythematosus. J Am Acad Dermatol. 2006;54Suppl:S242-3.
120. Usmani N GM. Efalizumab in the treatment of discoid lupus erythematosus. Arch Dermatol. 2007;143:873-7.
121. http://www.fda.gov/cder/biologics/products/alefbio013003.htm. Accessed June 30, 2007.
122. Hodak E, David M. Alefacept: a review of the literature and practical guidelines for management. Dermatol Ther. 2004; 17:383-92.
123. Fivenson DP, Mathes B. Treatment of generalized lichen planus with alefacept. Arch Dermatol. 2006;142:151-2.
124. Heffernan MP, Hurley MY, Martin KS, Smith DI, Anadkat MJ. Alefacept for alopecia areata. Arch Dermatol. 2005;141:1513-6.
125. García-Zuazaga J, Korman NJ. Cutaneous sarcoidosis successfully treated with alefacept. J Cutan Med Surg. 2006;10: 300-3.
126. Chi GC, Hsu FS, Yang CC, Wei JC. Scleroderma and failed response to alefacept. Rheumatology (Oxford). 2005;44: 1328-30.
127. Shapira MY, Resnick IB, Bitan M, Ackerstein A, Tsirigotis P, Gesundheit B, et al. Rapid response to alefacept given to patients with steroid resistant or steroid dependent acute graft-versus-host disease: a preliminary report. Bone Marrow Transplant. 2005;36:1097-101.
128. Grillo-López AJ, White CA, Varns C, Shen D, Wei A, McClure A, et al. Overview of the clinical development of rituximab: first monoclonal antibody approved for the treatment of lymphoma. Semin Oncol. 1999;26Suppl14:66-73.
129. http://www.emea.europa.eu/humandocs/Humans/EPAR/mabthera/mabthera.htm.
130. Maloney DG, Grillo-López AJ, Bodkin DJ, White CA, Liles TM, Royston I, et al. IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. J Clin Oncol. 1997;15:3266-74.
131. Maloney DG, Grillo-López AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, et al. IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood. 1997; 90:2188-95.
132. Golay J, Zaffaroni L, Vaccari T, Lazzari M, Borleri GM, Bernasconi S, et al. Biologic response of B lymphoma cells to anti-CD20 monoclonal antibody rituximab in vitro: CD55 and CD59 regulate complement-mediated cell lysis. Blood. 2000;95:3900-8.
133. Foran JM, Rohatiner AZ, Cunningham D, Popescu RA, Solal-Celigny P, Ghielmini M, et al. European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. J Clin Oncol. 2000;18:317-24.
134. Schulz H, Bohlius JF, Trelle S, Skoetz N, Reiser M, Kober T, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst. 2007;99:706-14.
135. Mohrbacher A. B cell non-Hodgkin's lymphoma: rituximab safety experience. Arthritis Res Ther. 2005;7Suppl3:S19-25.
136. Pérez-Gala S, Delgado-Jiménez Y, Goiriz R, Fraga J, García-Díez A, Fernández-Herrera J. Cytokine-release syndrome related to rituximab limited to lesions and excision scars of lesions of primary cutaneous lymphoma. Arch Dermatol. 2006;142:1516-7.
137. Heinzerling LM, Urbanek M, Funk JO, Peker S, Bleck O, Neuber K, et al. Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. Cancer. 2000;89:1835-44.
138. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006;54:1390-400.
139. Looney RJ, Anolik JH, Campbell D, Felgar RE, Young F, Arend LJ, et al. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. Arthritis Rheum. 2004;50:2580-9.
140. Cambridge G, Leandro MJ, Teodorescu M, Manson J, Rahman A, Isenberg DA, et al. B cell depletion therapy in systemic lupus erythematosus: effect on autoantibody and antimicrobial antibody profiles. Arthritis Rheum. 2006;54: 3612-22.
141. Looney RJ, Anolik J, Sanz I. B cells as therapeutic targets for rheumatic diseases. Curr Opin Rheumatol. 2004;16: 180-5.
142. Looney RJ. B cells as a therapeutic target in autoimmune diseases other than rheumatoid arthritis. Rheumatology (Oxford). 2005;44Suppl2:ii13-7.
143. Looney RJ. B cell-targeted therapy in diseases other than rheumatoid arthritis. J Rheumatol Suppl. 2005;73:25-8.
144. Looney RJ, Anolik J, Sanz I. Treatment of SLE with anti-CD20 monoclonal antibody. Curr Dir Autoimmun. 2005;8: 193-205.
145. Tahir H, Rohrer J, Bhatia A, Wegener WA, Isenberg DA. Humanized anti-CD20 monoclonal antibody in the

treatment of severe resistant systemic lupus erythematosus in a patient with antibodies against rituximab. Rheumatology (Oxford). 2005;44:561-2.
146. Lehembre S, Macario-Barrel A, Musette P, Carvalho P, Joly P. Rituximab treatment for immune thrombocytopenia associated with systemic lupus erythematosus. Ann Dermatol Venereol. 2006;133:53-5.
147. Tanaka Y, Yamamoto K, Takeuchi T, Nishimoto N, Miyasaka N, Sumida T, et al. A multicenter phase I/II trial of rituximab for refractory systemic lupus erythematosus. Mod Rheumatol. 2007;17:191-7.
148. Sabugo F, Llanos C, Soto L, Gutiérrez J, Cuchacovich M. Rituximab (anti-CD20 monoclonal antibody) for refractory systemic lupus erythematosus: report of one case. Rev Med Chil. 2005;133:681-4.
149. Saito K, Nawata M, Iwata S, Tokunaga M, Tanaka Y. Extremely high titer of anti-human chimeric antibody following re-treatment with rituximab in a patient with active systemic lupus erythematosus. Rheumatology (Oxford). 2005;44:1462-4.
150. Van den Bergh B, Selleslag D, Boelaert JR, Matthys EG, Schurgers M, Vandecasteele S, et al. Management of therapy-resistant systemic lupus erythematosus with rituximab: report of a case and review of the literature. Acta Clin Belg. 2005; 60:102-5.
151. Kneitz C, Wilhelm M, Tony HP. Effective B cell depletion with rituximab in the treatment of autoimmune diseases. Immunobiology. 2002;206:519-27.
156. Tokunaga M, Fujii K, Saito K, Nakayamada S, Tsujimura S, Nawata M, et al. Down-regulation of CD40 and CD80 on B cells in patients with life-threatening systemic lupus erythematosus after successful treatment with rituximab. Rheumatology (Oxford). 2005;44:176-82.
153. Saigal K, Valencia IC, Cohen J, Kerdel FA. Hypocomplementemic urticarial vasculitis with angioedema, a rare presentation of systemic lupus erythematosus: rapid response to rituximab. J Am Acad Dermatol. 2003; 49Suppl:S283-5.
154. Greenberg SA, Amato AA. Uncertainties in the pathogenesis of adult dermatomyositis. Curr Opin Neurol. 2004;17: 359-64.
155. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum. 2005;52: 601-7.
156. Chung L, Genovese MC, Fiorentino DF. A pilot trial of rituximab in the treatment of patients with dermatomyositis. Arch Dermatol. 2007;143:763-7.
157. Dinh HV, McCormack C, Hall S, Prince HM. Rituximab for the treatment of the skin manifestations of dermatomyositis: a report of 3 cases. J Am Acad Dermatol. 2007;56: 148-53.
158. Noss EH, Hausner-Sypek DL, Weinblatt ME. Rituximab as therapy for refractory polymyositis and dermatomyositis. J Rheumatol. 2006;33:1021-6.
159. Chiappetta N, Steier J, Gruber B. Rituximab in the treatment of refractory dermatomyositis. J Clin Rheumatol. 2005;11:264-6.
160. Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2005;52:262-8.
161. Eriksson R Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. J Intern Med. 2005;257:540-8.
162. Ferraro AJ, Day CJ, Drayson MT, Savage CO. Effective therapeutic use of rituximab in refractory Wegener's granulomatosis. Nephrol Dial Transplant. 2005;20:622-5.
163. Specks U, Fervenza FC, McDonald TJ, Hogan MC. Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy. Arthritis Rheum. 2001;44: 2836-40.
164. Memet B, Rudinskaya A, Krebs T, Oelberg D. Wegener granulomatosis with massive intracerebral hemorrhage: remission of disease in response to rituximab. J Clin Rheumatol. 2005;11:314-8.
165. Cheung CM, Murray PI, Savage CO. Successful treatment of Wegener's granulomatosis associated scleritis with rituximab. Br J Ophthalmol. 2005;89:1542.
166. Omdal R, Wildhagen K, Hansen T, Gunnarsson R, Kristoffersen G. Anti-CD20 therapy of treatment-resistant Wegener's granulomatosis: favourable but temporary response. Scand J Rheumatol. 2005;34:229-32.
167. Bachmeyer C, Cadranel JF, Demontis R. Rituximab is an alternative in a case of contraindication of cyclophosphamide in Wegener's granulomatosis. Nephrol Dial Transplant. 2005;20:1274.
168. Tamura N, Matsudaira R, Hirashima M, Ikeda M, Tajima M, Nawata M, et al. Two cases of refractory Wegener's granulomatosis successfully treated with rituximab. Intern Med. 2007;46:409-14.
169. Kallenbach M, Duan H, Ring T. Rituximab induced remission in a patient with Wegener's granulomatosis. Nephron Clin Pract. 2005;99:92-6.
170. Tektonidou MG, Skopouli FN. Sustained 3-year remission after rituximab treatment in a patient with refractory Wegener's granulomatosis. Clin Exp Rheumatol. 2006;24Suppl 41:S103.
171. Stasi R, Stipa E, Del Poeta G, Amadori S, Newland AC, Provan D. Long-term observation of patients with antineutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. Rheumatology (Oxford). 2006;45: 1432-6.
172. Henes JC, Fritz J, Koch S, Klein R, Horger M, Risler T, et al. Rituximab for treatment-resistant extensive Wegener's granulomatosis-additive effects of a maintenance treatment with leflunomide. Clin Rheumatol. 2007. 26:1711-5.
173. Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, Specks U. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. Am J Respir Crit Care Med. 2006;173:180-7.
174. Aries PM, Hellmich B, Voswinkel J, Both M, Nolle B, Holl-Ulrich K, et al. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. Ann Rheum Dis. 2006;65:853-8.
175. Aries PM, Lamprecht P, Gross WL. Rituximab in refractory Wegener's granulomatosis: Favorable or not? Am J Respir Crit Care Med. 2006;173:815-6.
176. Brihaye B, Aouba A, Pagnoux C, Cohen P, Lacassin F, Guillevin L. Adjunction of rituximab to steroids and immunosuppressants for refractory/relapsing Wegener's granulomatosis: a study on 8 patients. Clin Exp Rheumatol. 2007; 25Suppl44:S23-7.

177. Chu D, Stevens M, Gladstone DE. Severe, refractory, non-malignant type I cryoglobulinemia treated with alemtuzumab. Rheumatol Int. 2007.27:1173-5.
178. Nehme-Schuster H, Korganow AS, Pasquali JL, Martin T. Rituximab inefficiency during type I cryoglobulinaemia. Rheumatology (Oxford). 2005;44:410-1.
179. Mantha S, Jacobs MI, Savage DG. Unusual leukemia presentations. Case 3. Type I IgGlambda cryoglobulinemia associated with chronic lymphocytic leukemia. J Clin Oncol. 2005;23:5841-3.
180. Sansonno D, De Re V, Lauletta G, Tucci FA, Boiocchi M, Dammacco F. Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon alpha with an anti-CD20. Blood. 2003;101:3818-26.
181. Zaja F, De Vita S, Mazzaro C, Sacco S, Damiani D, De Marchi G, et al. Efficacy and safety of rituximab in type II mixed cryoglobulinemia. Blood. 2003;101:3827-34.
182. Zaja F, De Vita S, Russo D, Michelutti A, Fanin R, Ferraccioli G, et al. Rituximab for the treatment of type II mixed cryoglobulinemia. Arthritis Rheum. 2002;46:2252-4; author reply 2254-5.
183. Zaja F, Russo D, Fuga G, Patriarca F, Ermacora A, Baccarani M. Rituximab for the treatment of type II mixed cryoglobulinemia. Haematologica. 1999;84:1157-8.
184. Arzoo K, Sadeghi S, Liebman HA. Treatment of refractory antibody mediated autoimmune disorders with an anti-CD20 monoclonal antibody (rituximab). Ann Rheum Dis. 2002;61:922-4.
185. Cai FZ, Ahern M, Smith M. Treatment of cryoglobulinemia associated peripheral neuropathy with rituximab. J Rheumatol. 2006;33:1197-8.
186. Ghijsels E, Lerut E, Vanrenterghem Y, Kuypers D. Anti-CD20 monoclonal antibody (rituximab) treatment for hepatitis C-negative therapy-resistant essential mixed cryoglobulinemia with renal and cardiac failure. Am J Kidney Dis. 2004;43:e34-8.
187. Koukoulaki M, Abeygunasekara SC, Smith KG, Jayne DR. Remission of refractory hepatitis C-negative cryoglobulinaemic vasculitis after rituximab and infliximab. Nephrol Dial Transplant. 2005;20:213-6.
188. Lamprecht P, Lerin-Lozano C, Merz H, Dennin RH, Gause A, Voswinkel J, et al. Rituximab induces remission in refractory HCV associated cryoglobulinaemic vasculitis. Ann Rheum Dis. 2003;62:1230-3.
189. Cohen H, Green S, Jones S, Amos N, William BD. Lack of efficacy of rituximab in a patient with essential mixed cryoglobulinaemia. Rheumatology (Oxford). 2007;46: 366-7.
190. Salopek TG, Logsetty S, Tredget EE. Anti-CD20 chimeric monoclonal antibody (rituximab) for the treatment of recalcitrant, life-threatening pemphigus vulgaris with implications in the pathogenesis of the disorder. J Am Acad Dermatol. 2002;47:785-8.
191. Virgolini L, Marzocchi V. Anti-CD20 monoclonal antibody (rituximab) in the treatment of autoimmune diseases. Successful result in refractory Pemphigus vulgaris: report of a case. Haematologica. 2003;88:24.
192. Cooper HL, Healy E, Theaker JM, Friedmann PS. Treatment of resistant pemphigus vulgaris with an anti-CD20 monoclonal antibody (Rituximab). Clin Exp Dermatol. 2003;28:366-8.
193. Herrmann G, Hunzelmann N, Engert A. Treatment of pemphigus vulgaris with anti-CD20 monoclonal antibody (rituximab). Br J Dermatol. 2003;148:602-3.
194. Morrison LH. Therapy of refractory pemphigus vulgaris with monoclonal anti-CD20 antibody (rituximab). J Am Acad Dermatol. 2004;51:817-9.
195. Espana A, Fernández-Galar M, Lloret P, Sánchez-Ibarrola A, Panizo C. Long-term complete remission of severe pemphigus vulgaris with monoclonal anti-CD20 antibody therapy and immunophenotype correlations. J Am Acad Dermatol. 2004;50:974-6.
196. Dupuy A, Viguier M, Bedane C, Cordoliani F, Blaise S, Aucouturier F, et al. Treatment of refractory pemphigus vulgaris with rituximab (anti-CD20 monoclonal antibody). Arch Dermatol. 2004;140:91-6.
197. Cecchi R, Gasperini U. Severe pemphigus vulgaris treated with rituximab (Mabthera). J Dermatol. 2005;32:862-4.
198. Kong HH, Prose NS, Ware RE, Hall RP, 3rd. Successful treatment of refractory childhood pemphigus vulgaris with anti-CD20 monoclonal antibody (rituximab). Pediatr Dermatol. 2005;22:461-4.
199. Arin MJ, Engert A, Krieg T, Hunzelmann N. Anti-CD20 monoclonal antibody (rituximab) in the treatment of pemphigus. Br J Dermatol. 2005;153:620-5.
200. Schmidt E, Herzog S, Brocker EB, Zillikens D, Goebeler M. Long-standing remission of recalcitrant juvenile pemphigus vulgaris after adjuvant therapy with rituximab. Br J Dermatol. 2005;153:449-51.
201. Wenzel J, Bauer R, Bieber T, Tuting T. Successful rituximab treatment of severe pemphigus vulgaris resistant to multiple immunosuppressants. Acta Derm Venereol. 2005;85: 185-6.
202. Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med. 2006;355: 1772-9.
203. Domínguez-Fernández I, Pérez-Gala S, Goiriz R, Sánchez-Pérez J, Fernández-Herrera J. [Pemphigus vulgaris treated with rituximab]. Actas Dermosifiliogr. 2006;97:221-2.
204. Niedermeier A, Worl P, Barth S, Schuler G, HertlM. Delayed response of oral pemphigus vulgaris to rituximab treatment. Eur J Dermatol. 2006;16:266-70.
205. Esposito M, Capriotti E, Giunta A, Bianchi L, Chimenti S. Long-lasting remission of pemphigus vulgaris treated with rituximab. Acta Derm Venereol. 2006;86:87-9.
206. Pitarch G, Sánchez-Carazo JL, Pardo J, Torrijos A, Roche E, Fortea JM. [Treatment of severe refractory pemphigus vulgaris with rituximab]. Actas Dermosifiliogr. 2006;97: 48-51.
207. Belgi AS, Azeez M, Hoyle C, Williams RE. Response of pemphigus vulgaris to anti-CD20 antibody therapy (rituximab) may be delayed. Clin Exp Dermatol. 2006;31:143.
208. Antonucci A, Negosanti M, Tabanelli M, Varotti C. Treatment of refractory pemphigus vulgaris with anti-CD20 monoclonal antibody (rituximab): Five cases. J Dermatolog Treat. 2007;18:178-83.
209. Marzano AV, Fanoni D, Venegoni L, Berti E, Caputo R. Treatment of refractory pemphigus with the anti-CD20 monoclonal antibody (rituximab). Dermatology. 2007;214: 310-8.
210. Goh MS, McCormack C, Dinh HV, Welsh B, Foley P, Prince HM. Rituximab in the adjuvant treatment of

pemphigus vulgaris: a prospective open-label pilot study in five patients. Br J Dermatol. 2007;156:990-6.
211. Borel C, Launay F, Garrouste C, Astudillo L, Bazex J, Arlet P, et al. [Rituximab induced remission of pemphigus vulgaris: 2 cases]. Rev Med Interne. 2007;28:266-8.
212. Schmidt E, Seitz CS, Benoit S, Brocker EB, Goebeler M. Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. Br J Dermatol. 2007;156:352-6.
213. Heizmann M, Itin P, Wernli M, Borradori L, Bargetzi MJ. Successful treatment of paraneoplastic pemphigus in follicular NHL with rituximab: report of a case and review of treatment for paraneoplastic pemphigus in NHL and CLL. Am J Hematol. 2001;66:142-4.
214. Borradori L, Lombardi T, Samson J, Girardet C, Saurat JH, Hugli A. Anti-CD20 monoclonal antibody (rituximab) for refractory erosive stomatitis secondary to CD20(+) follicular lymphoma-associated paraneoplastic pemphigus. Arch Dermatol. 2001;137:269-72.
215. Gergely L, Varoczy L, Vadasz G, Remenyik E, Illes A. Successful treatment of B cell chronic lymphocytic leukemia-associated severe paraneoplastic pemphigus with cyclosporin A. Acta Haematol. 2003;109:202-5.
216. Rossum MM, Verhaegen NT, Jonkman MF, Mackenzie MA, Koster A, Van Der Valk PG, et al. Follicular non-Hodgkin's lymphoma with refractory paraneoplastic pemphigus: case report with review of novel treatment modalities. Leuk Lymphoma. 2004;45:2327-32.
217. Imataki O, Tamai Y, Abe Y, Ito I, Yoshikawa S, Kawakami K. [A case of follicular lymphoma complicated with lethal pemphigus]. Gan To Kagaku Ryoho. 2006;33:1677-80.
218. Barnadas M, Roe E, Brunet S, García P, Bergua P, Pimentel L, et al. Therapy of paraneoplastic pemphigus with Rituximab: a case report and review of literature. J Eur Acad Dermatol Venereol. 2006;20:69-74.
219. Hoque SR, Black MM, Cliff S. Paraneoplastic pemphigus associated with CD20-positive follicular non-Hodgkin's lymphoma treated with rituximab: a third case resistant to rituximab therapy. Clin Exp Dermatol. 2007;32:172-5.
220. Taintor AR, Leiferman KM, Hashimoto T, Ishii N, Zone JJ, Hull CM. A novel case of IgA paraneoplastic pemphigus associated with chronic lymphocytic leukemia. J Am Acad Dermatol. 2007;56Suppl:S73-6.
221. Goebeler M, Herzog S, Brocker EB, Zillikens D. Rapid response of treatment-resistant pemphigus foliaceus to the anti-CD20 antibody rituximab. Br J Dermatol. 2003;149: 899-901.
222. Connelly EA, Aber C, Kleiner G, Nousari C, Charles C, Schachner LA. Generalized erythrodermic pemphigus foliaceus in a child and its successful response to rituximab treatment. Pediatr Dermatol. 2007;24:172-6.
223. McGinness JL, Bivens MM, Greer KE, Patterson JW, Saulsbury FT. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) associated with pemphigoid nodularis: a case report and review of the literature. J Am Acad Dermatol. 2006;55:143-8.
224. Crichlow SM, Mortimer NJ, Harman KE. A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titre epidermolysis bullosa acquisita. Br J Dermatol. 2007;156:194-6.
225. Niedermeier A, Eming R, Pfutze M, Neumann CR, Happel C, Reich K, et al. Clinical response of severe mechanobullous epidermolysis bullosa acquisita to combined treatment with immunoadsorption and rituximab (anti-CD20 monoclonal antibodies). Arch Dermatol. 2007;143:192-8.
226. Schmidt E, Benoit S, Brocker EB, Zillikens D, Goebeler M. Successful adjuvant treatment of recalcitrant epidermolysis bullosa acquisita with anti-CD20 antibody rituximab. Arch Dermatol. 2006;142:147-50.
227. Bhol K, Natarajan K, Nagarwalla N, Mohimen A, Aoki V, Ahmed AR. Correlation of peptide specificity and IgG subclass with pathogenic and nonpathogenic autoantibodies in pemphigus vulgaris: a model for autoimmunity. Proc Natl Acad Sci U S A. 1995;92:5239-43.
228. Schadlow MB, Anhalt GJ, Sinha AA. Using rituximab (anti-CD20 antibody) in a patient with paraneoplastic pemphigus. J Drugs Dermatol 2003;2:564-7.
229. Ratanatharathorn V, Ayash L, Reynolds C, Silver S, Reddy P, Becker M, et al. Treatment of chronic graft-versus-host disease with anti-CD20 chimeric monoclonal antibody. Biol Blood Marrow Transplant. 2003;9:505-11.
230. Rouquette-Gally AM, Boyeldieu D, Prost AC, Gluckman E. Autoimmunity after allogeneic bone marrow transplantation. A study of 53 long-term-surviving patients. Transplantation. 1988;46:238-40.
231. Saito E, Fujimoto M, Hasegawa M, Komura K, Hamaguchi Y, Kaburagi Y, et al. CD19-dependent B lymphocyte signaling thresholds influence skin fibrosis and autoimmunity in the tight-skin mouse. J Clin Invest. 2002;109:1453-62.
232. Canninga-van Dijk MR, van der Straaten HM, Fijnheer R, Sanders CJ, van den Tweel JG, Verdonck LF. Anti-CD20 monoclonal antibody treatment in 6 patients with therapy-refractory chronic graft-versus-host disease. Blood. 2004; 104:2603-6.
233. Okamoto M, Okano A, Akamatsu S, Ashihara E, Inaba T, Takenaka H, et al. Rituximab is effective for steroid-refractory sclerodermatous chronic graft-versus-host disease. Leukemia. 2006;20:172-3.
234. Cutler C, Miklos D, Kim HT, Treister N, Woo SB, Bienfang D, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. Blood. 2006;108:756-62.
235. Zaja F, Bacigalupo A, Patriarca F, Stanzani M, Van Lint MT, Fili C, et al. Treatment of refractory chronic GVHD with Rituximab: a GITMO study. Bone Marrow Transplant. 2007;40:273-7.
236. Kamble R, Oholendt M, Carrum G. Rituximab responsive refractory acute graft-versus-host disease. Biol Blood Marrow Transplant. 2006;12:1201-2.
237. Ratanatharathorn V, Carson E, Reynolds C, Ayash LJ, Levine J, Yanik G, et al. Anti-CD20 chimeric monoclonal antibody treatment of refractory immune-mediated thrombocytopenia in a patient with chronic graft-versus-host disease. Ann Intern Med. 2000;133:275-9.
238. Szabolcs P, Reese M, Yancey KB, Hall RP, Kurtzberg J. Combination treatment of bullous pemphigoid with anti-CD20 and anti-CD25 antibodies in a patient with chronic graft-versus-host disease. Bone Marrow Transplant. 2002; 30:327-9.
239. Carella AM, Biasco S, Nati S, Congiu A, Lerma E. Rituximab is effective for extensive steroid-refractory chronic graft-vs.-host-disease. Leuk Lymphoma. 2007;48:623-4.
240. Milgrom H, Fick RB, Jr., Su JQ, Reimann JD, Bush RK, Watrous ML, et al. Treatment of allergic asthma with

monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. N Engl J Med. 1999;341:1966-73.
241. http://emea.europa.eu/humandocs/Humans/EPAR/xolair/xolair.htm. Accessed June 30, 2007.
242. Leynadier F, Doudou O, Gaouar H, Le Gros V, Bourdeix I, Guyomarch-Cocco L, et al. Effect of omalizumab in health care workers with occupational latex allergy. J Allergy Clin Immunol. 2004;113:360-1.
243. Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. Jama. 2001;286:2956-67.
244. Kaliner MA. Omalizumab and the treatment of allergic rhinitis. Curr Allergy Asthma Rep. 2004;4:237-44.
245. Okubo K, Ogino S, Nagakura T, Ishikawa T. Omalizumab is effective and safe in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. Allergol Int. 2006; 55:379-86.
246. Deniz YM, Gupta N. Safety and tolerability of omalizumab (Xolair), a recombinant humanized monoclonal anti-IgE antibody. Clin Rev Allergy Immunol. 2005;29:31-48.
247. Dreyfus DH, Randolph CC. Characterization of an anaphylactoid reaction to omalizumab. Ann Allergy Asthma Immunol. 2006;96:624-7.
248. Lanier BQ. Unanswered questions and warnings involving anti-immunoglobulin E therapy based on 2-year observation of clinical experience. Allergy Asthma Proc. 2005; 26: 435-9.
249. Scheinfeld N. Omalizumab: a recombinant humanized monoclonal IgE-blocking antibody. Dermatol Online J. 2005;11:2.
250. Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J. 2001;18:254-61.
251. http://emea.europa.eu/humandocs/PDFs/EPAR/Xolair/ H-606-PI-es.pdf. Accessed June 30, 2007.
252. Schmitt J, Schakel K. Omalizumab as a therapeutic option in atopic eczema. Current evidence and potential benefit. Hautarzt. 2007;58:128, 130-2.
253. Johansson SG, Haahtela T, O'Byrne PM. Omalizumab and the immune system: an overview of preclinical and clinical data. Ann Allergy Asthma Immunol. 2002;89:132-8.
254. Simpson EL, Hanifin JM. Atopic dermatitis. J Am Acad Dermatol. 2005;53:115-28.
255. Beck LA, Saini S. Wanted: A study with omalizumab to determine the role of IgE-mediated pathways in atopic dermatitis. J Am Acad Dermatol. 2006;55:540-1.
256. Krathen RA, Hsu S. Failure of omalizumab for treatment of severe adult atopic dermatitis. J Am Acad Dermatol 2005; 53:338-40.
257. Lane JE, Cheyney JM, Lane TN, Kent DE, Cohen DJ. Treatment of recalcitrant atopic dermatitis with omalizumab. J Am Acad Dermatol. 2006;54:68-72.
258. Vigo PG, Girgis KR, Pfuetze BL, Critchlow ME, Fisher J, Hussain I. Efficacy of anti-IgE therapy in patients with atopic dermatitis. J Am Acad Dermatol. 2006;55:168-70.
259. Carter MC, Robyn JA, Bressler PB, Walker JC, Shapiro GG, Metcalfe DD. Omalizumab for the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis. J Allergy Clin Immunol. 2007;119:1550-1.
260. Mankad VS, Burks AW. Omalizumab: other indications and unanswered questions. Clin Rev Allergy Immunol. 2005;29:17-30.
261. http://emea.europa.eu/humandocs/PDFs/EPAR/Zenapax/H-198-PI-es.pdf. Accessed June 30, 2007.
262. Mockenhaupt M, Grosber M, Norganer J. Daclizumab: a novel therapeutic option in severe bullous pemphigoid. Acta Derm Venereol. 2005;85:65-6.
263. Renkl A, Mockenhaupt M, Technau K, Herouy Y, Norgauer J. A novel therapeutic option in pemphigus vulgaris: humanized monoclonal anti-CD25 antibody. Br J Dermatol. 2004;150:1220-2.
264. Egan CA, Brown M, White JD, Yancey KB. Treatment of epidermolysis bullosa acquisita with the humanized anti-Tac mAb daclizumab. Clin Immunol. 2001;101:146-51.
265. Osborne GE, Pagliuca A, Ho A, du Vivier AW. Novel treatment of Sezary-like syndrome due to adult T-cell leukaemia/lymphoma with daclizumab (humanized anti-interleukin-2 receptor alpha antibody). Br J Dermatol. 2006; 155: 617-20.
266. Krueger JG, Walters IB, Miyazawa M, Gilleaudeau P, Hakimi J, Light S, et al. Successful in vivo blockade of CD25 (high-affinity interleukin 2 receptor) on T cells by administration of humanized anti-Tac antibody to patients with psoriasis. J Am Acad Dermatol. 2000;43:448-58.
267. Wohlrab J, Fischer M, Taube KM, Marsch WC. Treatment of recalcitrant psoriasis with daclizumab. Br J Dermatol. 2001;144:209-10.
268. Dichmann S, Mrowietz U, Schopf E, Norgauer J. Humanized monoclonal anti-CD25 antibody as a novel therapeutic option in HIV-associated psoriatic erythroderma. J Am Acad Dermatol. 2002;47:635-6.
269. http://emea.europa.eu/humandocs/PDFs/EPAR/Simulect/H-207-PI-es.pdf. Accessed June 30, 2007.
270. Haufs MG, Haneke E. Epidermolysis bullosa acquisita treated with basiliximab, an interleukin-2 receptor antibody. Acta Derm Venereol. 2001;81:72.
271. Bagel J, Garland WT, Breneman D, Holick M, Littlejohn TW, Crosby D, et al. Administration of DAB389IL-2 to patients with recalcitrant psoriasis: a double-blind, phase II multicenter trial. J Am Acad Dermatol. 1998;38: 938-44.
272. Owen CM, Harrison PV. Successful treatment of severe psoriasis with basiliximab, an interleukin-2 receptor monoclonal antibody. Clin Exp Dermatol. 2000;25:195-7.
273. Bell HK, Parslew RA. Use of basiliximab as a cyclosporin-sparing agent in palmoplantar pustular psoriasis with myalgia as an adverse effect. Br J Dermatol. 2002;147:606-7.
274. Mrowietz U, Zhu K, Christophers E. Treatment of severe psoriasis with anti-CD25 monoclonal antibodies. Arch Dermatol. 2000;136:675-6.
275. Salim A, Emerson RM, Dalziel KL. Successful treatment of severe generalized pustular psoriasis with basiliximab (interleukin-2 receptor blocker). Br J Dermatol. 2000;143: 1121-2.
276. Rebora A, Parodi A, Murialdo G. Basiliximab is effective for erosive lichen planus. Arch Dermatol. 2002;138: 1100-1.
277. Guhl G, González-de Arriba A, Dauden E. [Epidermal growth factor receptor inhibitors side effects]. Actas Dermosifiliogr. 2006;97:296-310.
278. http://emea.europa.eu/humandocs/Humans/EPAR/erbitux/erbitux.htm. Accessed June 30, 2007.

279. http://emea.europa.eu/humandocs/PDFs/EPAR/erbitux/H-558-PI-es.pdf. Accessed June 30, 2007.
280. Suen JK, Bressler L, Shord SS, Warso M, Villano JL. Cutaneous squamous cell carcinoma responding serially to single-agent cetuximab. Anticancer Drugs. 2007;18:827-9.
281. Bauman JE, Eaton KD, Martins RG. Treatment of recurrent squamous cell carcinoma of the skin with cetuximab. Arch Dermatol. 2007;1:889-92.
282. http://clinicaltrials.gov/ct/show/NCT00240682? Accessed July 30, 2007.
283. Ben-Bassat H. Biological activity of tyrosine kinase inhibitors: novel agents for psoriasis therapy. Curr Opin Investig Drugs. 2001;2:1539-45.
284. Mueller H, Eisendle K, Fritsch P. Basal-cell carcinoma. N Engl J Med. 2006;354:769-71.