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REVIEW ARTICLE

Off-Label Use of Biologic Agents in the Treatment of Dermatosis, Part 1: Infliximab and Adalimumab

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Abstract. In recent years, the therapeutic armamentarium available to dermatologists has been extended thanks to the development of numerous biologic agents. In our field, immunomodulators—although currently only approved for psoriasis—have given rise to new therapeutic possibilities in a number of inflammatory skin diseases. Since these new agents have more specific immunologic mechanisms of action, their efficacy and safety is an improvement on traditional immunosuppressants. Consequently, it is very likely that they will play an important role in dermatology in the next few years. This article, the first part of a review of off-label use of biologic agents in dermatology, describes the anti-tumor necrosis factor-α antibodies infliximab and adalimumab.

Key words: infliximab, adalimumab, off-label, dermatosis.

USO DE FÁRMACOS BIOLÓGICOS EN DERMATOSIS FUERA DE LA INDICACIÓN APROBADA. PRIMERA PARTE: INFLIXIMAB Y ADALIMUMAB

Resumen. En los últimos años el armamento terapéutico de los dermatólogos se ha incrementado como consecuencia de la introducción de múltiples fármacos biológicos. En Dermatología los inmunomoduladores están aprobados únicamente para la psoriasis. No obstante todos estos medicamentos han abierto nuevas posibilidades de tratamiento para numerosas dermatosis inflamatorias. La eficacia y el perfil de seguridad de estos fármacos puede considerarse mejor al de los inmunosupresores clásicos, dado que actúan sobre mecanismos inmunológicos más específicos, siendo muy probable que en los próximos años estos medicamentos biológicos adquieran un importante papel en el campo de la Dermatología. Este artículo, primera parte de la revisión de usos fuera de indicación de fármacos biológicos en Dermatología, describe los anticuerpos anti-factor de necrosis tumoral (TNF): infliximab y adalimumab.

Palabras clave: infliximab, adalimumab, fuera de indicación, dermatosis.

Introduction

Biologic agents have represented a major advance in the treatment of numerous skin diseases such as psoriasis.

In recent years, numerous drugs of this type have been added to the dermatologic pharmacopeia. Biologic agents are defined as proteins derived from living organisms (be they animals, microorganisms, or humans) that are used in the prevention, treatment, or cure of diseases.

In dermatology, psoriasis is the only entity for which various drugs of this type are authorized. This group of drugs acts on various immunologic processes and has a good efficacy and safety profile. Two different groups of biologic agents are used in psoriasis: antagonists of tumor necrosis factor (TNF) and inhibitors of T lymphocytes or antigen-presenting cells. However, these drugs have also been used off-label in numerous skin diseases, on the basis of their pathophysiology, and various reviews have been published previously on this subject.[1-7] The increasing use of these drugs currently extends the number of possible indications in numerous skin diseases. This article reviews these new indications.

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Table 1. Approved and Off-Label Uses of Infliximab in Dermatology

Approved Uses
Crohn disease
Ulcerative colitis
Rheumatoid arthritis
Ankylosing spondylitis
Psoriatic arthritis
Moderate-severe psoriasis
Off-Label Uses in Dermatology
Sarcoidosis
Necrobiosis lipoidica
Granuloma annulare
Pityriasis rubra pilaris
TEN
Vasculitis
Hidradenitis suppurativa
SAPHO syndrome
Pyoderma gangrenosum
Sweet syndrome
Subcorneal pustulosis
Pemphigus vulgaris
Bullous pemphigoid
Lupus erythematosus
Scleroderma
Dermatomyositis
Sjögren disease
Behçet disease
GVHD

Abbreviations: TEN, toxic epidermal necrolysis; GVHD, graft-versus-host disease; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis.

Infliximab

Infliximab is a chimeric immunoglobulin (Ig) G1 monoclonal antibody containing human constant regions and murine variable regions.

It binds and inhibits both soluble and transmembrane TNF-α and activates lysis of cells that express transmembrane TNF-α via antibody-dependent and complement-dependent cytotoxic mechanisms.[8,9]

The uses currently accepted by the European Medicines Evaluation Agency are Crohn disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and moderate or severe cutaneous psoriasis in which other systemic drugs such as cyclosporin, methotrexate, or psoralen-UV-A (PUVA) are contraindicated or ineffective[10] (Table 1).

Dosage

In most diseases in which the drug has been used, it has been administered at a dose of 3 or 5 mg/kg in weeks 0, 2, and 6, and subsequently every 8 weeks.[1]

Side Effects

Infliximab is well tolerated and most of the side effects that have been described correspond to infusion reactions, which occur in around 10% of patients and tend not to be serious.[11,12]

Part of the infliximab molecule is murine in origin, and consequently, the development of neutralizing antibodies has been described in between 15% and 50% of cases, depending on the study.[13-16] The presence of neutralizing antibodies is associated with an increased risk of adverse effects and a higher dose is required to control the disease.[13,16]

The dose of infliximab is not associated with the development of antibodies, although an association has been described between low plasma levels of infliximab and the presence of antibodies.[16,18]

The concomitant use of immunosuppressant drugs such as cyclosporin or methotrexate has been shown to reduce the rate of formation of neutralizing antibodies.[18-20]

In terms of the safety profile of infliximab, patients treated with anti-TNF agents have been reported to have a higher rate of tuberculosis, which can also present as disseminated or atypical disease.[21] This is due to the important role played by TNF in granuloma formation as a response to tuberculosis.[22]

In addition, cases have also been described in which lymphoma[23] and demyelinating disease[24-27] occurred during treatment with anti-TNF agents.

Infliximab in Skin Diseases Other Than Psoriasis

Sarcoidosis

In vitro and in vivo studies have demonstrated the importance of TNF-α in the formation of granulomas.[22,28-30] Increased levels of TNF-α have been observed in alveolar fluid from patients with sarcoidosis[31,32] and the levels of

TNF-α are also predictive of disease severity and treatment resistance.[33]

Various case series have been reported in which the efficacy and safety of this drug was assessed in the treatment of systemic sarcoidosis. Most of the published cases involving treatment of sarcoidosis show that infliximab improves the symptoms and has an efficacy and safety profile similar to that seen in other diseases, and they conclude that the drug is both effective and safe.[34-43]

However, large case series or placebo-controlled trials are currently unavailable, meaning that this drug should still be used with caution in cases of sarcoidosis, especially regarding the possibility of developing tuberculosis, which may be difficult to diagnose in patients with sarcoidosis.[37,44]

In terms of the improvement of cutaneous symptoms of sarcoidosis, the first cases were published in 2001, and since then, various patients have been described in whom cutaneous symptoms improved following treatment with infliximab.[45-55] Recently, a series of 12 patients with sarcoidosis refractory to multiple treatments was published in which 5 patients had extensive cutaneous involvement.[56] Following treatment with infliximab at a dose of 3 mg/kg in weeks 2, 4, 6, 10, and 14, there was a clear improvement of cutaneous and systemic symptoms, allowing suspension or reduction of corticosteroid therapy in most of the patients. Nevertheless, once the treatment was withdrawn, the lesions reappeared, making new courses of treatment necessary.

In another case series comprising 10 patients, 6 of whom presented cutaneous symptoms as the primary manifestation of the disease, treatment was provided with infliximab at a dose of 5 mg/kg in weeks 0, 2, and 6, and then every 8 weeks.[57] In all patients, a rapid and significant improvement in cutaneous symptoms was observed, along with improvement of systemic symptoms. The drug was well tolerated, except in 1 patient who developed a hypersensitivity reaction that was assumed to be due to the production of antibodies against infliximab; that patient was the only one in whom concomitant immunosuppressant therapy was not used.

Necrobiosis Lipoidica

Inhibition of granuloma formation by drugs that antagonize the action of TNF-α can have beneficial effects.

We have only found 1 case in the literature in which necrobiosis lipoidica was treated with infliximab. The case involved a patient with an ulcerated plaque due to necrobiosis lipoidica that was refractory to multiple treatments and that displayed a marked improvement following treatment with 2 doses of infliximab (5 mg/kg), a response that was sustained despite having to suspend treatment because of diagnosis of miliary tuberculosis.[58]

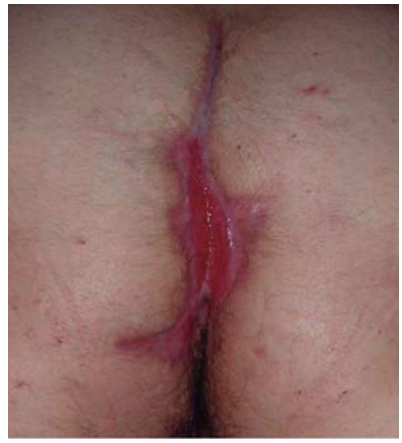

Figure 1. Hidradenitis, baseline situation.

Granuloma Annulare

Granuloma annulare is another granulomatous disease of unknown etiology with an unpredictable clinical course. It is sometimes refractory to standard treatments and can represent a therapeutic challenge. A case has been reported of a patient with disseminated granuloma annulare that began 4 years previously and was refractory to various treatments (topical corticosteroids, topical retinoids, PUVA therapy with dapsone and clofazimine), in whom treatment with systemic corticosteroids was ruled out due to poorly controlled diabetes.[59] In that patient, treatment with infliximab at a dose of 5 mg/kg in weeks 0, 2, and 6, and every 4 weeks for the following 4 months led to complete remission of the lesions in the sixth week, with improvement observed from the second week and continued absence of symptoms a year after discontinuation of treatment.

Hidradenitis Suppurativa and Acne

Some case series and isolated cases have been described in which hidradenitis suppurativa was treated with infliximab with highly variable results, ranging from complete cure to absence of response. In addition, the results are difficult to interpret, since in many of the cases hidradenitis suppurativa was associated with inflammatory bowel disease, making it impossible to determine whether the improvements were due to improvement of chronic intestinal inflammation (Figures 1 and 2).

The most recent and extensive case series was a retrospective study of 7 patients with hidradenitis suppurativa treated with infliximab in whom an initial response was obtained in 5 patients following 3 infusions (5 mg/kg).[60] The response was only sustained after induction therapy in 2 of the patients, and treatment had to be suspended in 1 of those patients due to the appearance of

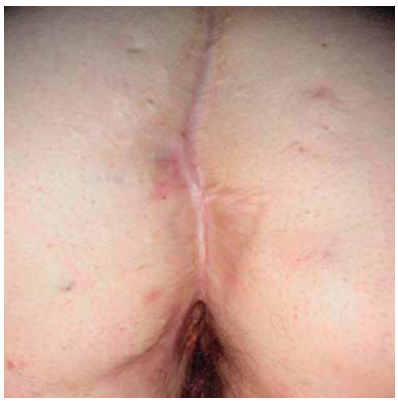

Figure 2. Hidradenitis after 5 infusions of intravenous infliximab, showing scars.

side effects, and in the other due to a lack of response after 8 infusions. The poor results obtained in that study could be due to the presence of very advanced, chronic hidradenitis suppurativa, and that none of them had associated intestinal disease for which improvement could partly explain the response of the hidradenitis suppurativa. In addition, 3 of the patients presented serious side effects related to the use of infliximab.

Usmani et al[61] reported 4 patients with treatment-refractory hidradenitis suppurativa in whom treatment with infliximab led to improvement in 2 of them (1 of whom had associated Crohn disease). In both cases the treatment had to be discontinued due to side effects associated with the drug (lupus-like reaction and hypersensitivity reaction following infusion).

The most promising results were obtained in a retrospective study of 5 patients with refractory hidradenitis suppurativa.[62] Following treatment with a single infusion of infliximab (5 mg/kg) in 2 of the patients and 2 infusions in the others, a moderate-to-excellent response was obtained in all of the patients, none of whom had associated inflammatory bowel disease.

Thielen et al[63] reported the case of a patient with highly disfiguring hidradenitis suppurativa and without associated inflammatory bowel disease in whom treatment with infliximab led to a marked, rapid, and sustained improvement. The patient was treated with infliximab at a dose of 5 mg/kg, with a total of 13 infusions, along with methotrexate, and complete remission of the disease was observed.

In addition to these case series, another 6 cases have been published of hidradenitis suppurativa treated with infliximab,[64-69] all of whom showed complete remission and all associated with chronic inflammatory bowel disease, namely Chrohn disease[64-66,68,69] or ulcerative colitis.[67]

Only 1 case has been described of treatment of acne conglobata with infliximab.[70] The patient had rheumatoid arthritis and nodulocystic acne that had displayed a partial response to oral isotretinoin. Due to the development of hypertriglyceridemia and hypercholesterolemia, treatment was initiated with infliximab at a dose of 3 mg/kg, which led to clear improvement that remained stable throughout the follow-up period (6 months with infusions every 8 weeks) and allowed treatment with isotretinoin to be progressively suspended.

SAPHO syndrome

SAPHO syndrome involves a combination of synovitis, acne, pustulosis, hyperostosis, and osteitis of unknown etiology.

In 2002, Olivieri et al[71] reported the first 2 cases of SAPHO syndrome treated with infliximab. Both patients displayed a good response both in terms of symptoms and analytical variables following the first 3 doses of the drug. They suffered relapse after withdrawal of the drug and finally a complete sustained response during 18 months of follow-up following a fourth infusion, with no side effects in either of the patients.

Subsequently, 6 patients have been described in whom treatment with infliximab proved effective over a follow-up period of between 10 and 21 months.[72-74] Two of those patients suffered a relapse following discontinuation of treatment.[74] One of the patients who responded to treatment with infliximab was a 10-year-old child with long-standing, treatment-resistant disease and in whom treatment options were limited by the child's age.[72]

Pyoderma Gangrenosum

Pyoderma gangrenosum is a neutrophilic dermatosis that is associated with inflammatory bowel disease in 1% to 5% of cases[75] and for which the first-line treatment involves systemic corticosteroids and other immunosuppressant drugs (Figures 3 and 4).

The treatment of inflammatory bowel disease with TNF-α inhibitors has represented a major step forward and has created new therapeutic options for the treatment of cutaneous manifestations such as pyoderma gangrenosum.

The most extensive case series published on patients with pyoderma gangrenosum treated with infliximab involved a retrospective analysis of 13 patients in whom the disease was associated with inflammatory bowel disease.[76] Of all the patients studied, 3 showed a complete response after induction therapy (3 infusions) and remained asymptomatic throughout follow-up, without the need for further treatment. The other 10 patients responded to induction therapy but required periodic infusions of the drug every 4 to 12 weeks. All of the patients who were previously treated with corticosteroids no longer needed them.

Another study that also obtained good results was undertaken in 8 patients with pyoderma gangrenosum and Crohn disease treated with infliximab.[77] All of the patients responded after 1 to 4 months of treatment. Three patients showed complete cure of the lesions with no need for further treatment, another 3 showed a complete response but required maintenance treatment, and 2 patients only showed a partial response.

Rispo et al[78] reported 15 patients with Crohn disease treated with infliximab (5 mg/kg) in whom the response of the extraintestinal manifestations of the disease was studied. All patients showed improvement of the extraintestinal symptoms at 10 weeks. Four of the 15 patients presented cutaneous symptoms and only 1 had pyoderma gangrenosum, which responded rapidly and was cured.

Kaufman et al[79] undertook a prospective study of cutaneous manifestations in patients with inflammatory bowel disease following a single dose of infliximab at 5 mg/kg. Of the 23 patients included in the group, 4 had pyoderma gangrenosum, and in all of those patients there was a marked and rapid response following infusion (with complete cure observed in 1 of the patients).

In addition to these patient series, 38 cases of pyoderma gangrenosum have been published in which improvement was observed following treatment with infliximab, most of them small case series or isolated cases.[80-99]

In addition, cases have been described in which treatment with infliximab was satisfactory in complicated or peculiar cases of pyoderma gangrenosum, such as ulcerated or infected forms,[100] PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome,[101] or vegetating pyoderma gangrenosum.[86]

A case has been described of treatment-refractory idiopathic systemic pyoderma gangrenosum with neutrophilic infiltrates in the psoas muscle and spleen that showed a spectacular response to treatment with infliximab (5 mg/kg).[102] However, following the fourth infusion (16 weeks after the first), the patient developed an anaphylactoid reaction and became refractory to the drug. Treatment was then provided with etanercept (75 mg/week), without success, and resolution of the symptoms was ultimately achieved following treatment with adalimumab (40 mg every 2 weeks).

Infliximab has proved to be a safe and effective drug for the treatment of pyoderma gangrenosum, with or without associated inflammatory bowel disease, and is currently a first-line treatment for the disease, especially in those cases associated with inflammatory bowel disease.

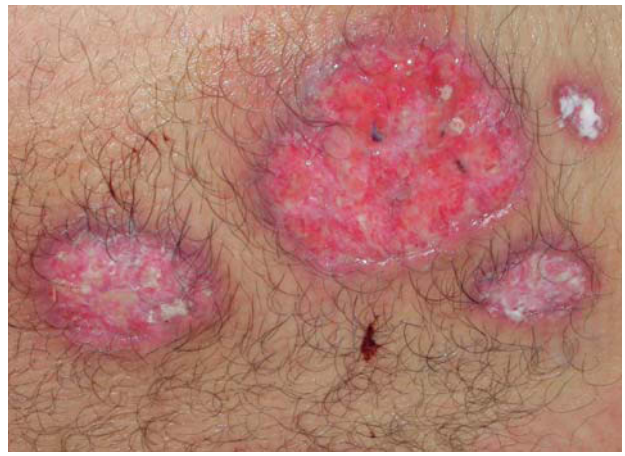

Figure 3. Pyoderma gangrenosum in a patient with ulcerative colitis.

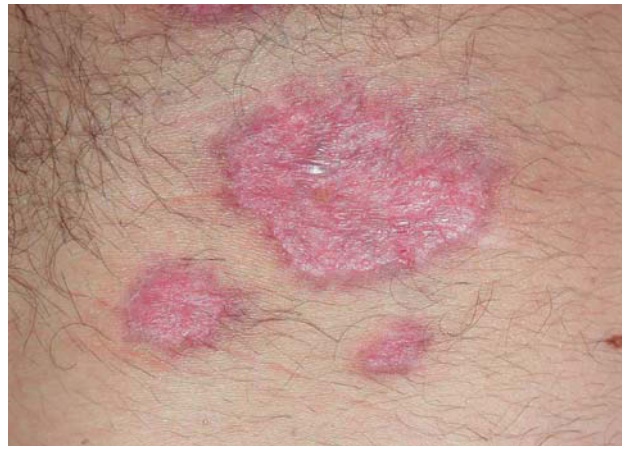

Figure 4. Pyoderma gangrenosum 6 weeks after initiating treatment with intravenous infliximab, showing visible healing of the lesions.

Sweet Syndrome

To date, only 5 cases of Sweet syndrome treated with infliximab have been described, 4 of which responded adequately and 1 of which only showed an initial transient response.

Two cases have been described in which Sweet syndrome associated with erythema nodosum was treated with infliximab.[103,104] In both cases, a good response was obtained at the dose and with the regimen normally employed with this drug.

Two cases have also been described of Sweet syndrome associated with Crohn disease, 1 of which was also associated with Sjögren disease, and which responded to infliximab with resolution of the lesions.[105]

Despite these good results, a case has also been described in which the result was more disappointing. The case involved a patient with long-standing polychondritis who subsequently developed Sweet syndrome during corticosteroid therapy, and who, following treatment with infliximab (3 mg/kg), despite a good initial response, relapsed

within a few days and following a second infusion developed septicemia and died.[106]

Subcorneal Pustulosis

Only 2 cases have been described of subcorneal pustulosis treated with infliximab. The first involved a woman in whom the disease was refractory to multiple treatments (corticosteroids, azathioprine, retinoids, phototherapy, colchicine, and sulfadiazine) and who did not tolerate dapsone.[107] This patient's disease could be controlled following introduction of infliximab, which led to a rapid improvement that required only 2 infusions of 5 mg/kg and remained controlled with acitretin over a follow-up period of 6 months. The second case involved a woman aged 54 years who presented with the disease 8 years previously.[108] The disease was refractory to multiple treatments but responded rapidly to treatment with infliximab (5 mg/kg), allowing the dose of methylprednisolone and acitretin to be reduced. However, after 12 weeks of treatment (3 doses), the patient became refractory to the drug.

Blistering Diseases

To date, 2 cases have been described of recalcitrant pemphigus vulgaris that was refractory to multiple immunosuppressant treatments and that responded rapidly to treatment with infliximab.[109,110] In both cases, the patients showed a lasting response (4 months and 104 weeks).

Only 1 case has been described of bullous pemphigoid of the mucous membranes.[111] The process was highly aggressive and refractory to multiple immunosuppressant treatments, in which treatment with infliximab at standard dose and regimen led to remission of the disease in the oral and pharyngeal mucosa and stabilized the ocular involvement, which had led to the loss of an eye.

Lupus Erythematosus

The proinflammatory role of TNF-α as an early cytokine able to activate the complement cascade and involved in various connective tissue diseases has been demonstrated in various studies. Thus, TNF-α inhibition could have a beneficial effect in the treatment of such diseases.[112-114]

However, this is still the subject of some debate, and some cases of lupus associated with anti-TNF-α agents have been described,[115-131] in addition to the more common side effect of the development of autoantibodies in patients treated with infliximab for diseases such as rheumatoid arthritis or Crohn disease.[132-138] In most cases, the development of autoantibodies does not have clinical repercussions, apparently because the antibodies produced during treatment with infliximab are predominantly IgM against double-stranded DNA (dsDNA), whereas those that appear to be responsible for the disease are IgG.[139]

In terms of how the levels of autoantibodies are altered in patients with systemic lupus erythematosus (SLE) treated with infliximab, a study was published recently on 7 patients with SLE in whom increased plasma levels of anti-dsDNA (5 of the 7 patients), antihistone (4 of the 7 patients), and antichromatin antibodies (6 of the 7 patients), along with anticardiolipin IgM (4 out of the 7 patients) were observed following 3 doses of infliximab.[140] This increase in the plasma levels of autoantibodies occurred in parallel to clinical improvement, and the levels of autoantibodies returned to baseline within a few weeks. The authors of the study suggested that the observed increase in the levels of autoantibodies was due to the release of antigens from cells that underwent apoptosis following inhibition of TNF-α.[140]

Other cases have been described in which a clinical response was observed along with changes in analytical parameters in patients with SLE treated with infliximab.[141-143]

Aringer et al[144] published a study that included the largest number of patients with SLE treated with infliximab (4 doses of 300 mg), in whom a marked and rapid improvement in systemic symptoms and analytical variables was observed. The response was sustained for at least 8 weeks and coincided with an increase in the levels of autoantibodies.

Scleroderma

Various lines of evidence support a pathogenic role for TNF-α in scleroderma.[145-151] However, few cases have been reported of systemic or localized scleroderma treated with infliximab and many are descriptions of cases in which, despite the drug being effective, treatment had to be suspended as a result of side effects (thrombocytopenia associated with the development of anticardiolipin IgM,[152] pancytopenia followed by fungal infection,[153] lupus-like syndrome with autoantibodies and hypocomplementemia[154]). Somewhat paradoxically, there is even a case in which scleroderma-like symptoms appeared following the use of infliximab in a patient with rheumatoid arthritis in whom human antichimeric antibodies were observed.[155]

Magro et al[156] described a series of patients with connective tissue disease associated with cytomegalovirus infection, 1 of whom (a 66-year-old woman) exhibited generalized scleroderma and was treated with infliximab over the course of a year, leading to marked improvement.

Recently, a series of 4 patients with pulmonary fibrosis as a result of collagen vascular disease (3 with rheumatoid arthritis and 1 with systemic sclerosis) was described in which treatment with infliximab at a dose of 3 mg/kg in weeks 0, 2, and 6, and every 8 weeks for at least 12 months led to stabilization of the pulmonary disease with good tolerance of the drug.[157] A case of systemic sclerosis with pulmonary fibrosis and pulmonary hypertension has been described in which 6 months of treatment with infliximab led to a marked clinical improvement and a reduction in pulmonary arterial pressure, with improvement in the results of lung function tests.[158]

Given the limited experience, it is difficult to draw conclusions regarding the efficacy of infliximab in this disease or regarding the hypothetical increased risk of side effects associated with treatment in these patients.

Dermatomyositis

TNF-α also appears to play an important role in dermatomyositis,[159-163] but as in other connective tissue diseases, few cases have been published in which it was treated with infliximab.

The first case was described in 2002 by Roddy et al.[164] The case involved a 48-year-old woman with treatment-refractory dermatomyositis who presented symptoms of sepsis after the third infusion of infliximab (5 mg/kg), leading to discontinuation of the treatment, and who was diagnosed with non-Hodgkin lymphoma 4 months later. The possible relationship between the lymphoma and treatment with infliximab is doubtful, since the patient had been treated with immunosuppressant drugs and the lymphoma could also be the primary cause of the dermatomyositis. This case illustrates the complexity involved in treatment of this disease—which can be paraneoplastic in origin—with a drug that has been associated with the development of malignant processes.

Four cases have been reported in which improvement was observed following treatment with infliximab.[165-167] In addition, 2 cases have been described in which spectacular results were observed following the use of infliximab in patients with severe treatment-refractory dermatomyositis. One of those cases involved a 19-year-old woman who was treated with 3 doses of infliximab at 8 mg/kg (along with intravenous boluses of methylprednisolone, 1 g/d, and methotrexate) after being placed on a mechanical ventilator due to treatment-refractory hypoventilation.[168] In that patient, spontaneous respiration was recovered after 8 days of treatment and symptoms disappeared completely following the fourth infusion. The other case involved a 58-year-old woman suffering from severe dermatomyositis that led to tetraparesis and necessitated the use of a nasogastric tube.[169] The patient had not responded to multiple treatments (boluses of methylprednisolone, cyclophosphamide, and immunoglobulins; cyclosporin; and methotrexate) but did respond to treatment with infliximab associated with methotrexate, cyclosporin, and prednisone, and remained asymptomatic after 1 year of follow-up.

A retrospective study has been published based on 8 patients diagnosed with dermatomyositis or polymyositis treated with anti-TNF agents.[170] Two of the patients were treated with infliximab, with only a partial response in 1 and no response in the other, and 6 patients were treated with etanercept, leading to a positive response in 5 of them. The limited number of patients included meant that comparisons could not be made between the 2 drugs.

Sjögren Disease

TNF-α plays a central role in Sjögren disease and elevated levels of the cytokine have been observed in the salivary glands of patients with this disease.[171]

However, although TNF-α appears to be involved in the disease, no differences were observed between patients who received infliximab and those receiving placebo in a randomized trial involving 103 patients (no differences were observed in symptoms of fatigue, arthralgia, or mucosal dryness).[172]

Behçet Disease

Relatively extensive experience has been gained with anti-TNF-α agents in the treatment of the different manifestations of Behçet disease, suggesting that this cytokine is implicated in the pathogenesis of the disease and its inhibition may be beneficial. Various cases have been published in which patients were treated with infliximab to control the different manifestations of the disease (ocular, neurologic, etc) and in whom improvements were also seen in the mucocutaneous symptoms.[173-183]

To date, at least 8 patients treated with infliximab have been described,[184-191] in whom the main manifestations were long-standing oral and genital ulcers that had serious repercussions for the patient and that had been refractory to treatment with standard immunosuppressants (Table 2). In most cases the drug was used at a similar dose to that employed in other diseases (3 or 5 mg/kg). In all cases, complete cure of the ulcers was observed and in most cases the response to treatment was rapid (within 6 weeks of the first infusion). In 1 case, a response was observed 3 days after the first infusion.[189] In most patients the response was sustained for various weeks following the first infusion; in 3 cases the patients remained asymptomatic at 1-year follow-up[184,186, 188] and another patient was asymptomatic at 20 months.[189] Only 1 case of relapse following withdrawal

Table 2. Cases of Behçet Disease Treated With Infliximab

Authors, y	*No.*	*Symptoms*	*Previous Treatment*	*Infliximab Dose/Regimen*	*Response (Ulcers)*	*Length of Follow-up*
Goossens et al[184] 2001	1	Ulcers of the skin, anus, mouth, and scrotum	Prednisone, MTX, cyclophosphamide, thalidomide, AZA	10 mg/kg monthly 2 doses	Improvement in 2 weeks Remission following second infusion	12 months without symptoms
Robertson and Hickling[185] 2001	1	Ulcers Arthralgia, phlebitis, erythema nodosum	Topical drugs, thalidomide, ciclosporin, AZA	5 mg/kg 3 doses (0, 2, 6 wk)	Remission	–
Estrach et al[186] 2002	1	Ulcers Arthralgia, phlebitis, erythema nodosum, iritis	Thalidomide, ciclosporin, AZA, chlorambucil, methylprednisolone	3 mg/kg 0, 2, and every 8 weeks, in combination with MTX	Remission	12 months without symptoms
Rozenbaum et al[187] 2002	1	Ulcers Arthritis, papulopustular cutaneous manifestations	Sulfasalazine, colchicine, corticosteroids, auranofin	3 mg/kg, 0, 2, 4, and 6, and subsequently every 8 weeks	Remission Response in the second week	–
Gulli et al[188] 2003	1	Ulcers Arthritis, retinal vasculitis	Prednisone, colchicine, AZA, cyclosporin	5 mg/kg 2, 6, 14, and 22, and subsequently every 8 weeks	Improvement in 24 h. Remission on the eighth day	12 months without symptoms
Saulsbury and Mann[189] 2003	1	Ulcers Arthritis, rash	Prednisone, colchicine, penicillin, pentoxifylline	5 mg/kg (0, 2, 6, 10 wk)	Relapse 10 wk after the fourth infusion and treatment reinitiated every 4-6 wk	–
Haugeberg et al[190] 2004	1	Genital ulcers Arthritis Uveitis	Prednisolone, AZA, colchicine	5 mg/kg (4 infusions) 0, 2, 6, 15 wk	Remission, improvement from first infusion	2 months of follow-up following the fourth infusion
Connolly et al[191] 2005	1	Genital ulcers Arthritis Uveitis, cutaneous rash, pustules, fatigue, myalgia, paresthesia, diarrhea	Prednisolone, AZA, colchicine, sulfasalazine, MTX, leflunomide, thalidomide	3 mg/kg, 0, 2, 6, 12 and every 8 wk 1 year of treatment	Remission Improvement from first infusion	A year of treatment and remission after 20 wk of follow-up

Abbreviations: MTX, methotrexate; AZA, azathioprine.

of treatment has been described (10 weeks after the last infusion), although the patient responded rapidly to reinitiation of treatment.[189]

None of the cases reported side effects associated with the treatment and only 1 patient had to modify the regimen due to a mild infection.[190]

In all cases the extracutaneous symptoms also responded satisfactorily to treatment.

Although treatment of Behçet disease with infliximab has achieved excellent results in most of the patients described, 2 cases have been reported in which the response was not satisfactory.[192] Both patients had extracutaneous involvement (ileitis and colitis with musculoskeletal involvement in 1 and ocular involvement in the other) along with urogenital ulcers and recurrent outbreaks of erythema nodosum affecting the legs in both cases. In both patients, treatment was initiated with infliximab at standard dose (5 mg/kg) and regimen, and despite rapid improvement of the ulcers and extracutaneous manifestations (except diarrhea caused by ileitis/colitis in the first patient) both patients

developed a severe outbreak of erythema nodosum lesions on the legs (with scleritis in 1 of the cases), leading to suspension of treatment.

Finally, a case of Behçet disease has been reported in which no response was obtained after 3 months of treatment with etanercept (25 g twice weekly) but a rapid response was observed with infliximab (3 mg/kg) associated with methotrexate (7.5 mg/wk).[186] The authors suggested that in Behçet disease, as in Crohn disease, with which it shares certain similarities, these 2 treatments, despite blocking the same inflammatory molecule, have a different efficacy that is partly explained by the capacity to block transmembrane TNF-α displayed by infliximab but not etanercept.

Graft-Versus-Host Disease

TNF-α plays a central role in graft-versus-host disease. Various studies in animal models have shown that it is involved both in the acute and the chronic disease, and that decreased levels after genetic modification or inhibition using anti-TNF antibodies in mice acting as bone-marrow transplant donors reduces development of the disease.[193-197]

In addition, it appears also to play an important role in the development of the graft-versus-leukemia effect; consequently, animals that receive transplants free of TNF-α are less likely to develop graft-versus-host disease but their overall survival is shorter, since they die as a result of the tumor.[193,194] Thus, treatment of graft-versus-host disease with inhibitors of the TNF-α pathway, which are in principle effective for this purpose, could worsen the overall result of the transplant. It has recently been shown that mice that had received a bone-marrow transplant that was able to produce soluble but not transmembrane TNF-α were less likely to develop graft-versus-host disease but without any reduction in the capacity of the graft to treat the tumor, suggesting that transmembrane TNF-α was responsible for graft-versus-host disease whereas soluble TNF-α would be implicated in the antitumor effects.[198] This point is important, since if it were to be confirmed in humans it could imply marked differences in the indications for anti-TNF agents, such that in principle etanercept would be more indicated since it does not bind transmembrane TNF-α.

It has been demonstrated in humans that increased levels of TNF-α are more often associated with both acute[199,200] and chronic graft-versus-host disease.[201-203]

Acute Graft-Versus-Host Disease

Acute graft-versus-host disease has 3 different phases. TNF-α is implicated both in the first phase, in which it is released from tissues damaged by the conditioning, and the third phase, in which it is released by effector T lymphocytes from the donor, previously activated by antigen-presenting cells from the recipient and that lead to cell death via a mechanism of cytotoxicity involving TNF-α.[204]

Graft-versus-host disease is a serious condition in which the first-line treatment involves high doses of systemic corticosteroids followed by maintenance treatment with tacrolimus or ciclosporin, and failure to control the disease with these drugs represents a difficult therapeutic challenge.[205] Biologic agents acting against TNF-α have proven to be effective in some cases and represent a first-line option for the treatment of refractory cases. Some authors have observed greater efficacy with infliximab in cases of gastrointestinal graft-versus-host disease,[206,207] suggesting that TNF-α is the main cytokine involved in the gastrointestinal disease, whereas in cutaneous and hepatic graft-versus-host disease, other cytokines also play an important role.[207,208]

Some case series have been published on the treatment of acute graft-versus-host disease with infliximab. Most involve patients in whom severe acute disease that was refractory to traditional treatments (immunosuppressant drugs and corticosteroids) developed following bone-marrow transplant. In these case series the treatment consisted of 4 infusions of 10 mg/kg infliximab per week.

The most extensive series is that of Couriel and Ipolotti,[206] which included 37 patients with graft-versus-host disease treated with infliximab, of whom 28% had corticosteroid-resistant disease. In that series the complete-response rate was 75% in the patients with cutaneous symptoms, 81% in those with extensive gastrointestinal tract involvement, 91% in patients with colon involvement, and 35% in those with liver disease. Twenty-two of the 37 patients died; in 13 cases, death was attributed to progression of graft-versus-host disease.

Two retrospective studies have been published in which very promising results were obtained with this disease in patients refractory to corticosteroid therapy. The first was a series of 21 patients (14% grade I, 67% grade II, and 19% grade III/IV) treated with infliximab as monotherapy.[205] An overall response of 70% was obtained for cutaneous disease (67% complete response), 75% for intestinal involvement (65% complete response), and 25% for hepatic disease (25% complete response). The overall survival was 38% but all of the patients went on to develop chronic graft-versus-host disease. The second study reported similar results in a series of 32 patients diagnosed with grade II-IV graft-versus-host disease.[208] An adequate response to infliximab was obtained in 59% of the patients (19% complete responses and 40% partial responses).

Other series published on acute or refractory graft-versus-host disease treated with infliximab encompass a total of 12 patients, of which 10 died during follow-up, despite 8 having shown improvement with treatment.[209-211] Only 2

cases have been reported in which treatment of acute graft-versus-host disease with infliximab (in both cases associated with adalizumab) led to a good response.[212]

A phase III study has been published comparing the efficacy of infliximab with that of standard treatment in previously untreated patients.[213] Fifty-eight patients were randomized to 2 treatment groups: infliximab plus methylprednisolone or methylprednisolone alone. The authors found no statistically significant differences between the 2 treatment arms (63% response to methylprednisolone alone compared with 66% response to a combination of methylprednisolone and infliximab).

Chronic Graft-Versus-Host Disease

Couriel and Iplotti[206] described 22 patients with chronic graft-versus-host disease who were treated with infliximab in combination with prednisone or other immunosuppressant drugs. The response rate was 92% for gastrointestinal manifestations and 57% for cutaneous ones. Eleven patients died, 7 due to progression of the disease.

Infliximab is well tolerated in most cases. It is not easy to reach a conclusion regarding whether it increases the risk of infection, since patients with refractory graft-versus-host disease are immunocompromised and it is difficult to determine the extent to which infliximab is involved. Some authors have reported an increased risk of fungal infections associated with the treatment of graft-versus-host disease with infliximab.[214]

These studies appear to indicate that treatment with infliximab can be a good therapeutic alternative for those patients who have not responded to previous treatments. Infliximab can improve the symptoms of the disease, although without achieving complete control in most patients, while it does not appear to offer improvements over standard treatments in previously untreated patients.

There are no human studies available to resolve the important issue of whether infliximab may be associated with reduced transplant efficacy as confirmed in animals following inhibition of transmembrane TNF-α.

Pityriasis Rubra Pilaris

Four patients with pityriasis rubra pilaris treated with infliximab have been described. In 2005, Liao and Mutasim[215] reported 2 cases with generalized disease that began in adulthood and was refractory to various attempts at treatment (ciclosporin combined with acitretin in 1 patient and acitretin alone in the other). Both were treated with infliximab at the standard dose and with the standard regimen, which led to a marked improvement that became apparent 2 weeks after the first dose in both cases. Following this treatment, the patients continued with acitretin as monotherapy at a lower dose than used previously.

Subsequently, Manoharan et al[216] described a woman with pityriasis rubra pilaris who, having been treated previously with various oral and topical drugs, showed a marked and rapid response to infliximab leading to almost total absence of symptoms and continued management only with emollients.

In contrast, a case of pityriasis rubra pilaris has been described in which no improvement was obtained following combined treatment with infliximab (5 mg/kg, 4 infusions) and acitretin.[217]

Toxic Epidermal Necrolysis

TNF-α appears to be important in the pathogenesis of toxic epidermal necrolysis (TEN), although its exact role is not completely clear. Various studies have found that blister fluid from patients with TEN has an elevated concentration of TNF-α compared with fluid from patients with thermal burns.

The first case of TEN treated satisfactorily with a single dose of infliximab (5 mg/kg) was published in 2002 by Fisher et al.[218] Since then, 5 more cases have been reported,[219-221] all with a satisfactory response. The most recent publication reported 3 cases of drug-induced skin disease with characteristics compatible with exanthematous pustulosis and TEN that had not responded to corticosteroids or suspension of the drug responsible for the symptoms and in which a single dose of infliximab led to a rapid and significant improvement.[221]

Vasculitis

The use of infliximab for the treatment of systemic vasculitides is an area that requires further research, since the majority of cases described correspond to isolated cases or very small case series, and in addition, the few prospective studies performed have yielded variable results. Thus, while some studies report a beneficial effect of this treatment in patients with refractory systemic vasculitis,[222] others have observed poor results with a high rate of adverse effects.[223]

Wegener Disease

The most extensive experience with the use of infliximab for the treatment of vasculitis has been obtained with Wegener disease, in which the mechanism of action of the drug is similar to that of other granulomatous diseases mentioned previously. The role of TNF-α in this necrotizing

disease has been established in a study assessing endothelial dysfunction in patients with antineutrophil cytoplasmic antigen-associated vasculitis.[224] In that study, the forearm blood flow response to acetylcholine was less than in healthy subjects and improved when the patients were treated with infliximab.

Three prospective clinical trials have been performed with 32 patients, [222] 10 patients,[225] and 6 patients[226] in whom infliximab at a dose of 3-5 mg/kg at 2-8 week intervals was effective in the treatment of cytoplasmic antineutrophil antibody-associated vasculitis that was refractory to standard immunosuppressant treatment. The study including the largest number of patients obtained an overall response rate of 88%, with 20% relapse in patients who showed an initial response,[222] indicating that the treatment is effective in this disease. However, 2 patients died and 7 suffered a severe infection, emphasizing the risk of side effects in patients who follow this treatment whilst immunocompromised as a result of treatments they have received or are currently receiving. Cases have also been described in which patients with this disease developed severe infections,[227] perhaps suggesting a particular risk associated with this type of vasculitis.

In addition, various isolated cases have been described with a variety of manifestations, including severe central nervous system disease,[228,229] ocular involvement,[230,231] and renal failure,[232] that responded to treatment with infliximab, and 3 cases of pediatric disease in which a good response was also obtained.[233]

However, in addition to these cases in which treatment with infliximab led to a satisfactory response, there are others in which it did not succeed in controlling the disease.[223,224]

As in the case of Crohn disease, infliximab appears to be more effective in the treatment of Wegener disease than is etanercept, for which the outcomes have not been so favorable.[235,236]

In summary, infliximab is a treatment that can be effective in those patients with Wegener disease in whom the disease is not controlled with other treatments, thus offering an alternative to conventional treatment in this disease.

Giant Cell Arteritis

Some cases of giant cell arteritis have been described in which there was a rapid response to treatment with infliximab.[237,238] However, in a prospective study of 44 patients with this disease who responded to corticosteroids, no difference could be observed between patients treated with corticosteroids alone and those who also received periodic infusions of infliximab (there was no reduction in the dose of corticosteroids in this group of patients).[239] Although only a small number of subjects were included in the study, it appears that treatment with infliximab is not beneficial in patients who respond adequately to corticosteroids.

Polyarteritis Nodosa

Infliximab has been used with excellent results in 2 pediatric cases of polyarteritis nodosa that were resistant to immunosuppressant treatment and highly aggressive, allowing the previously used treatments to be reduced over a number of years of follow-up.[240,241]

Adult cases of refractory polyarteritis nodosa with a good response to treatment with infliximab have also been described.[242, 243]

Churg-Strauss Granulomatosis

Two cases of Churg-Strauss granulomatosis with central nervous system involvement and refractory to treatment with corticosteroids and cyclophosphamide have been described in which improvement of the symptoms was observed following introduction of infliximab.[244] However, a case has also been reported of a patient in whom the disease did not improve following treatment and who also had a lupus-like reaction that led to suspension of the treatment.[223]

Leukocytoclastic Vasculitis

The cases of leukocytoclastic vasculitis treated with infliximab that have been reported in the literature showed good results in all patients.[225,245,246]

Some cases of vasculitis associated with rheumatoid arthritis have shown a good response,[247-249] although in 1 case the response could not be maintained.[248]

Takayasu Arteritis

Various cases of Takayasu arteritis refractory to conventional treatment have been described in which treatment with infliximab was effective and allowed patients to be managed with low doses of corticosteroids.[250-252]

In addition to the cases described, a prospective study has been carried out in 15 patients with severe refractory disease in whom the long-term effect of adding an anti-TNF-α agent to their previous treatment was studied (7 patients treated with etanercept and 8 with infliximab).[253] All except 1 of the 15 patients included in the study responded (10 complete responses), and in 10 patients the response was sustained, allowing corticosteroids to be withdrawn. This study suggests anti-TNF-α agents to be a very important treatment option, but does not allow conclusions to be drawn regarding differences between the 2 drugs due to the small sample size.

Adult Still Disease

The effect of treatment with infliximab on Still disease is unclear. Furthermore, only 3 patients treated with this drug have been described in the literature.

In a case of Still disease treated with infliximab no improvement was observed, and in addition, the patient suffered a severe outbreak of the disease despite treatment with the drug and died after 6 months as a result of myocardial infarction, for which the relationship with treatment remains to be established.[223]

Bonilla-Hernán et al[254] reported 2 cases of Still disease that responded to treatment with infliximab at a standard dose and regimen, and that displayed both clinical improvement and improvements in analytical parameters indicative of disease activity.

Schönlein-Henoch Purpura

We have only identified 1 case described in the literature of Schönlein-Henoch purpura treated with infliximab, in which no improvement was observed and treatment had to be suspended due to adverse effects.[223]

Kawasaki Disease

Various cases of Kawasaki disease have been described in which treatment with infliximab was initiated after failure of conventional treatment (intravenous immunoglobulins, aspirin, and methylprednisolone), leading to a rapid response and achieving remission of the disease.[255-258]

In a retrospective study of 17 patients with refractory disease (resistant to intravenous immunoglobulins with or without associated corticosteroids) who were treated with 1 or 2 infusions of 5-10 mg/kg infliximab, according to the severity of the disease, a rapid response (within 24 hours) was observed in terms of both symptoms and analytical parameters in 13 of the 17 patients, with no observed adverse reactions to the drug.[259]

Familial Mediterranean Fever

Four cases have been described in the literature in which familial Mediterranean fever was treated with infliximab.[260-263] All of these patients responded to treatment despite lack of response to standard treatments and, in 2 of them, renal dysfunction due to amyloidosis also improved (reduced proteinuria) following treatment.[261,263]

Table 3. Approved and Off-Label Uses of Adalimumab

Indications
Psoriatic arthritis
Rheumatoid arthritis
Ankylosing spondylitis
Off-Label Uses in Dermatology
Pyoderma gangrenosum
Behçet disease
Hidradenitis suppurativa
Vasculitis
Sarcoidosis
Multiple familial trichoepithelioma
Multicentric reticulohistiocytosis
Subcorneal pustular dermatosis

Adalimumab

Adalimumab is the most recent anti-TNF antibody to be developed. Its efficacy profile is more similar to that of infliximab than that of etanercept.

The drug is an IgG1 monoclonal antibody that is completely human in origin and is therefore thought to be less immunogenic than murine or chimeric anti-TNF-α antibodies.[264] However, its use leads to the formation of human antihuman antibodies, the mechanism of which remains unclear.[265,266]

Like infliximab, it binds to both soluble and transmembrane TNF-α and fixes complement, leading to lysis of the cells expressing TNF-α.[267]

The drug is administered subcutaneously or intravenously usually at a dose of 40 mg every 2 weeks.

It has a good safety profile, with local reactions to the injection representing the most commonly described side effects.[267]

It is currently approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis[268] (Table 3).

Uses in Diseases Other Than Psoriasis

Pyoderma Gangrenosum

Only 2 cases have been described of pyoderma gangrenosum treated with adalimumab. One involved a woman who had developed inflammatory bowel disease 2 years earlier and who despite treatment with azathioprine and infliximab developed a leg ulcer that responded to treatment with

80 mg adalimumab every 2 weeks; treatment with standard immunosuppressants had not achieved a response.[269] The other case involved a 47-year-old woman with no associated intestinal disease who had an ulcer that was refractory to conventional topical and systemic treatment.[270] Following initiation of adalimumab as the only systemic treatment at a dose of 20 mg/wk for 2 weeks and then at a dose of 40 mg/wk, complete remission of the lesion was observed after 5.5 months of treatment, with improvement observed from the second month.

A case has also been described in which pyoderma gangrenosum with systemic neutrophilic infiltrates in the spleen and psoas muscle showed an initial response to treatment with infliximab and was subsequently resolved with adalimumab at standard dosage.[102]

Behçet Disease

A series of 6 patients with Behçet disease has been published in which an adequate initial response to infliximab was observed, allowing suspension of treatment with the drug.[271] The patients went on to suffer a severe relapse that was treated with adalimumab at standard doses, leading to a rapid response in all of the patients. Three of the patients developed a lichenoid reaction.

In addition, a series of 3 cases has been published involving patients with uveitis caused by this disease.[272] Having achieved remission and control of the disease with infliximab, the decision was made to switch to adalimumab at 40 mg every 2 weeks due to the greater ease of administration. All 3 patients continued in remission following the change.

Hidradenitis Suppurativa

We identified 2 cases in the literature of hidradenitis suppurativa treated with adalimumab. The first involved a woman with long-standing highly disfiguring disease in which numerous treatments, including surgery, had been unsuccessful. A marked improvement was observed from the first injection of adalimumab (40 mg every 2 weeks) and an almost complete response (with no signs of inflammation and disappearance of fistulae and pain) at 1 month.[273]

Recently, another case of hidradenitis suppurativa presenting with arthritis and nodulocystic acne was reported in which clear clinical improvement was observed with adalimumab (at a maintenance dose of 40 mg/wk).[274]

Vasculitis

Thirion et al[275] reported the case of a patient with a cutaneous ulcer due to leukocytoclastic vasculitis that was refractory to conventional treatment and that responded to treatment with adalimumab, achieving complete closure, although recurrence was observed with a few months.

Isolated cases have also been reported of different vasculitides (temporal arteritis[276] and Takayasu disease[277]) that were refractory to conventional treatments but responded to adalimumab.

Sarcoidosis

The first case of cutaneous sarcoidosis treated with adalimumab was described by Philips et al.[278] It involved a woman with cutaneous sarcoidosis who presented with an ulcer that had appeared some months previously and was refractory to treatment with prednisone, hydroxychloroquine, and methotrexate. Marked improvement was observed with adalimumab (40 mg/wk) and closure of the ulcer was achieved after 9 weeks of treatment.

Another case of extensive treatment-refractory cutaneous sarcoidosis treated with adalimumab has since been described.[279] Five weeks after addition of adalimumab to the previous treatment (hydroxychloroquine and pentoxifylline) control of the disease was achieved that lasted over a follow-up period of 10 weeks.

A case of pulmonary sarcoidosis has been described in which improvement was also obtained with adalimumab.[280]

Others

Adalimumab has been used in combination with aspirin for the treatment of multiple familial trichoepitheliomas.[281] In this disease, there is a genetic defect in a molecule that inhibits synthesis of TNF-α. The combination of these drugs would act on the TNF pathway at 2 levels, the TNF-α ligand and nuclear factor κB, thereby compensating for the defective inhibition of the synthesis of this molecule. The patient was a woman who had received multiple sessions of laser resurfacing and in whom adalimumab treatment (initially at 40 mg every 2 weeks and subsequently weekly) had been initiated in combination with 325 mg aspirin every 12 hours due to the limited improvements that had been obtained. After 8 months of treatment there was a marked improvement (reduced size of the tumors and less thickening of the skin).

Adalimumab has also been used for the treatment of multicentric reticulohistiocytosis, leading to improvement of cutaneous and articular symptoms after 8 weeks of treatment.[282]

The drug has also been used to treat subcorneal pustular dermatosis (IgA pemphigus) in a young woman who showed an almost complete response to treatment at a dose of 40 mg every 2 weeks in combination with mycophenolate

mofetil (which had not achieved a response when provided as monotherapy).[283] The response was sustained throughout a follow-up period of 5 months.

Conclusion

Infliximab and adalimumab are 2 molecules whose therapeutic properties reside in their capacity to block the proinflammatory molecule TNF-α. Both act in a similar fashion and it is therefore to be expected that the benefits obtained with adalimumab, a molecule supported by less cumulative experience, are similar to those seen with infliximab, but with fewer side effects, because the molecule does not contain sequences of nonhuman origin.

As with other recently developed biologic agents, both drugs have opened the door to the treatment of numerous cutaneous diseases other than psoriasis that are often difficult to treat, and as such, they offer hope for patients in whom few therapeutic options are left available. However, they not only offer an alternative when conventional treatments are ineffective, they also appear to offer a safety profile that is better than conventional immunosuppressant treatments, at least in the short term.

Nevertheless, we should not be blinded by the novelty of these drugs and the attractive features they offer, since the available information in most diseases other than psoriasis in which they have been used is based on isolated cases or small series of patients, and in some, such as systemic vasculitides or some connective tissue diseases, a significant number of side effects have been described. Furthermore, we should not lose sight of their high cost.

This is the first part of a review of the newly developed biologic agents that in recent years have begun to be incorporated in the therapeutic arsenal available to dermatologists and that in the next few years will probably constitute first-line treatments in cutaneous diseases other than psoriasis.

Conflicts of Interest

The authors declare no conflicts of interest.

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