

Expert Opinion

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Infliximab in dermatological treatment: beyond psoriasis

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Infliximab is a chimeric monoclonal antibody of the IgG1 class. Experience from its use has been accumulated in rheumatology and gastroenterology by the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disease, respectively. Because of its TNF- α binding capacity it has been approved for the treatment of moderate-to-severe plaque psoriasis. Moreover, it has also been evaluated in other inflammatory dermatoses as well as systemic diseases involving the skin such as severe atopic dermatitis, pityriasis rubra pilaris, pyoderma gangrenosum and cutaneous sarcoidosis. The possible future uses of infliximab in dermatology are being reviewed herein.

Keywords: anti-TNF, inflammatory dermatoses, infliximab, TNF- α

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1. Introduction

1.1 Introduction to infliximab

Infliximab is a chimeric IgG monoclonal antibody with human constant and murine variable regions. It belongs to a class of novel therapeutic tools known as biological agents, which were developed as a result of the more precise comprehension of the pathogenesis of inflammatory diseases. Its molecular formula is $C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$ and its molecular weight is 144188.23 g/mol. There is an increasing interest in infliximab as expressed by the rapidly growing literature on the subject. In February 2004 a Medline search using the term 'infliximab' produced 1116 results [1] compared with the 3564 articles in September 2007.

1.2 Indications and dosage

Infliximab is available as soluble powder for intravenous infusion under the trade name Remicade (Remicade, Centocor, Inc.). It was initially approved by the FDA at August 24, 1998 for the treatment of 'moderately to severely active Crohn's disease for the reduction of the signs and symptoms, in patients who have an inadequate response to conventional therapies; and treatment of patients with fistulising Crohn's disease for the reduction in the number of draining enterocutaneous fistula(s)' [2]. In November 1999 it was licensed for the treatment of rheumatoid arthritis and in December 2004 for ankylosing spondylitis. In May 2005 the indication was expanded to include the treatment of psoriatic arthritis and four months later it included ulcerative colitis as well. A new indication involving pediatric patients with moderately to severely active Crohn's disease was added in May 2006. Finally, on January 31, 2007 it was officially approved for chronic plaque psoriasis by the FDA [3]. However, the inclusion of plaque psoriasis had been already approved on August 4, 2005 by the European Medicines Agency (EMA) [4].

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With the exception of rheumatoid arthritis, the recommended scheme by the FDA of initiating infliximab is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. The dose can be adjusted depending on the response [3].

1.3 Mechanisms of action

Infliximab blocks the effects of human TNF- α by binding to it, whereas it does not affect TNF- β , exhibiting a more specific mode of action than etanercept, also an anti-TNF molecule [1,5]. The neutralisation of both soluble and transmembrane TNF- α prevents TNF from binding to its receptor, thus inhibiting cell proliferation and upregulation of pro-inflammatory mediators. This interference modifies the clinical expression of inflammatory autoimmune conditions such as Crohn's disease, rheumatoid arthritis or psoriasis. Especially for psoriasis, the response to infliximab may be attributed to the inhibition of the activation process of psoriatic T lymphocytes and the impairment of the antigen-presenting capacity of dendritic cells [6]. Infliximab also induces both antibody-dependent and complement-related lysis of TNF- α -expressing cells [5]. Additional mechanisms of action include the apoptosis of activated immune cells at sites of inflammation and the infliximab-induced reverse signalling via the transmembrane TNF- α . Especially for Crohn's disease the latter mechanisms may play an important role in the therapeutic process with infliximab [7].

2. Off-label use of infliximab

2.1 Pustular and erythrodermic psoriasis

Infliximab has been licensed for the treatment of chronic, severe plaque psoriasis in adult patients who responded inadequately to conventional systemic drugs and for reducing sign and symptoms and improving physical function in patients with psoriatic arthritis. However, the efficacy of infliximab has been reported in other forms of psoriasis as well, although data from organised clinical trials is lacking. Four patients with generalised pustular psoriasis were treated with infliximab 5 mg/kg intravenous infusion with positive response and no side effects [8]. Pereira *et al.* reported a case of a 3-year-old child with generalised pustular psoriasis treated successfully with infliximab at a dose of 5 mg/kg. However, infliximab had to be ceased after a year of treatment due to the recurrence of the disease [9]. Several cases have been also published reporting the efficacy of infliximab in erythrodermic psoriasis. Heikkilä *et al.* reported four patients with recalcitrant erythrodermic psoriasis and psoriatic arthritis unresponsive to systemic therapies, who effectively maintained treatment with infliximab combined with methotrexate for 9 months to 5 years [10]. Lisby *et al.* successfully treated a patient with erythrodermic psoriasis with infliximab at a dose of 3 mg/kg

with methotrexate. After a 14-week remission, relapse was observed in the form of guttate psoriasis and a session with infliximab was repeated [11]. Infliximab has been also used in a patient with palmoplantar pustulosis resulting in worsening of the condition [12], acrodermatitis continua of Hallopeau with clearance of the pustules [11,13] and has exhibited effects over psoriatic nails [9,13,14]. Furthermore, in a Phase III double-blind trial enrolling 378 patients with plaque psoriasis, infliximab 5 mg/kg was administered to 240 patients with nail psoriasis showing a significantly greater reduction in the baseline Nail Psoriasis Severity Index at weeks 10 and 24 than in the 65 placebo-treated patients with nail involvement [15].

2.2 Immunobullous diseases

This group of autoimmune disorders involves dermatoses characterised by the formation of bullae and blisters resulting from the reaction between autoantibodies and target antigens. Depending on the depth of this interaction into the skin they can be divided into intraepidermal, such as pemphigus vulgaris, and subepidermal immunobullous diseases, such as bullous pemphigoid. It is found that TNF- α is strongly expressed by the acantholytic cells in pemphigus [16] and thus infliximab could be useful in treating these conditions. Still, only case reports have been published showing the complete response of pemphigus vulgaris to infliximab. However, after 13 successful infusions of infliximab 5 mg/kg in a 62 year-old male, pemphigus vulgaris relapsed enforcing the cessation of the drug [17]. In another reported case of pemphigus the rapid response to infliximab was succeeded by the development of zoster infection and the discontinuation of the drug [18]. The usefulness of infliximab was also observed in cicatricial pemphigoid [19] and subcorneal pustular dermatosis [20]. However, in the latter case despite the initially rapid response to infliximab a relapse occurred after 12 weeks and no further benefit was obtained by the treatment.

2.3 Connective tissue diseases

Connective tissue diseases include conditions that can affect multiple organs exhibiting autoimmunity as a common feature. Lupus erythematosus, dermatomyositis and Sjogren's syndrome are some of the conditions with cutaneous involvement treated with infliximab. As TNF- α was found elevated at various stages in the course of systemic lupus erythematosus (SLE) [21], it seems relevant to use infliximab for the TNF blockade in the clinical spectrum of lupus, either systemic or cutaneous. The suspected efficacy of infliximab in SLE was shown in an open-label study that evaluated its effect on lupus nephritis and arthritis [22]. However, although a decline in the disease activity was noted, the levels of autoantibodies against double-stranded DNA (anti-dsDNA) increased, which was correlated with the use of infliximab. The latter was also confirmed by more recent studies [23]. There is also evidence, yet insufficient,

supporting the plausibility of infliximab as a treatment option for dermatomyositis [24,25], focusing primarily on the myositis component of the disease.

Moreover, several studies examining the effect of infliximab in Sjogren's syndrome have been conducted. The syndrome has been divided into primary and secondary. Primary Sjogren's syndrome or sicca syndrome is not associated with any other connective tissue disease in contrast with secondary Sjogren's syndrome. In a multi-centre, randomised, double-blind, placebo-controlled trial three infusions of infliximab 5 mg/kg at weeks 0, 2 and 6 failed to achieve a significantly superior result in alleviating fatigue, arthralgia and dryness compared to placebo in 103 patients with primary Sjogren's syndrome after 22 weeks of follow-up [26]. This outcome was discordant with the results reported three years earlier by Steinfeld *et al.* [27]. In this open-label study, 16 patients with active primary Sjogren's syndrome were treated with infliximab at a dose of 3 mg/kg. After three infusions at weeks 0, 2 and 6 a clinical improvement was observed and persisted for at least 2 months during the follow-up period. In addition, this study was extended for one more year, enrolling ten of the 16 patients who experienced relapse of symptoms. After the administration of the drug at doses of 3 mg/kg or 5 mg/kg in 2 patients, approximately every 12 weeks, the authors concluded that repeated infusions of infliximab could preserve the absence of symptoms of primary Sjogren's syndrome for a long period of time without any serious side effects [28]. The efficacy of infliximab has been also reported in a case of secondary Sjogren's syndrome coexisting with Crohn's disease and Sweet's syndrome [29]. The possibility to treat cutaneous manifestations of adult onset Still's disease [30] and relapsing polychondritis [31] with infliximab has emerged as well.

2.4 Vasculitis

Vasculitides consist of a variety of entities exhibiting clinical and pathogenetic heterogeneity with inflammation and necrosis of blood vessels as a common feature. Although the pathogenesis of vasculitis is complicated and different mechanisms and cascades are involved, the TNF blockade may be of value. There are reports of patients with vasculitis of the deep cutaneous vessels treated with infliximab resulting in remission of the lesions [32]. Furthermore, preliminary results by the use of infliximab in patients with Behcet's disease suggest that it could be a reliable therapeutic option for the cutaneous manifestations [33,34] but also that it may not be so effective for all patients with Behcet's disease [35]. The efficacy of infliximab has been also tested in cases of childhood cutaneous polyarteritis nodosa [36], systemic manifestations of Takayasu arteritis [37], Wegener's granulomatosis [38], Kawasaki syndrome [39], Churg-Strauss syndrome [40] and giant cell arteritis [41]. Treatment failure of infliximab along with other drugs was reported in two patients with refractory vasculitis secondary to hepatitis C-associated mixed cryoglobulinaemia [42].

2.5 Neutrophilic dermatoses

The term 'neutrophilic dermatoses' applies to diseases with similar pathogenesis but distinct clinical manifestations that are associated with internal diseases. Their histopathology is characterised by a neutrophilic infiltrate without signs of vasculitis, although the latter is an issue of debate. Published reports suggest that infliximab could be beneficial for patients with Sweet's syndrome [29,43], pyostomatitis vegetans [44] and pyoderma gangrenosum, both outside the context of inflammatory bowel disease [45] and in coexistence with Crohn's disease or ulcerative colitis [46]. For the latter, data derived from a randomised placebo-controlled trial which enrolled 30 patients with pyoderma gangrenosum is available. The randomisation was applied for the first infusion of infliximab and the non-responders were administered additional doses of open-labelled infliximab. The results were in favour of the drug.

2.6 Acne and hidradenitis suppurativa

Infliximab has been used effectively in a patient with acne conglobata and rheumatoid arthritis [47]. Several case series have been published testing infliximab in hidradenitis suppurativa. In a retrospective evaluation, five patients with hidradenitis suppurativa were treated with infliximab 5 mg/kg. After each infusion any clinical alterations were assessed by a physician and were also rated retrospectively by each patient on a scale of 1 – 10. Both the physicians and the five patients characterised their condition as improved [48]. However, in another retrospective review including four patients with hidradenitis suppurativa the administration of infliximab was less effective. Two of the patients responded temporarily but after the development of a lupus-like reaction in the first and severe infusion reactions in the latter, the drug was discontinued. The remaining two patients exhibited no improvement of their condition [49]. Moreover, infliximab induced a marked or moderate overall improvement at week six in five out of seven patients that were studied with severe chronic hidradenitis suppurativa, but this effect proved transient [50]. At week ten only two of the patients responded to treatment. Unfortunately, serious side effects including multifocal motor neuropathy, grade 3 allergic reaction and abdominal pain related to colon cancer were reported in three patients after three out of four infusions and the evaluation of infliximab was ceased. Hidradenitis suppurativa has been also reported to coexist with inflammatory bowel disease. The efficacy of infliximab in these patients has not been evaluated in clinical trials so far, although single cases [51] have exhibited promising results.

Severe forms of acne can be manifested in patients within the context of the synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome. Along with the articular and skeletal components of the syndrome, the skin can be involved with the presence of palmoplantar pustulosis, pustular psoriasis or acne [52]. Information from clinical

trials regarding the efficacy of infliximab in this syndrome is lacking; however, case reports with this objective have been published. Four patients with the osteoarticular component of SAPHO syndrome at the time of presentation were treated with intravenous infliximab 5 mg/kg [53]. After three infusions, complete remission was observed and the good response was stable for 12 months. Nevertheless, a relapse of palmoplantar pustulosis took place in two of the patients. However, other published cases suggest that infliximab may induce sustained response in patients with cutaneous manifestations of the SAPHO syndrome [54,55].

2.7 Other inflammatory dermatoses

Atopic dermatitis is a chronic inflammatory, pruritic skin condition. Because of its tendency to relapse, long-term treatment is often required. Although for decades corticosteroids have been the therapeutic mainstay, new drugs including infliximab have emerged as treatment options. In an open prospective pilot study, 9 adult patients with moderate-to-severe refractory atopic dermatitis received 7 infusions of infliximab at a dose of 5 mg/kg and were followed for 46 weeks. A significant clinical improvement was noted in all patients, although it was not maintained for all 46 weeks in the vast majority [56].

Furthermore, infliximab may also be of value in pityriasis rubra pilaris, a skin disease which is divided into adult and juvenile forms. An erythrodermic patient with adult-onset pityriasis rubra pilaris (PRP) was benefited by the use of infliximab 5 mg/kg within 2 weeks [57]. On the contrary, an adult patient with PRP did not clinically improve with the combination treatment of oral acitretin and intravenous infliximab 5 mg/kg after four infusions [58]. Finally, moderate improvement was reported in an adult with PRP after two infusions of infliximab 5 mg/kg combined with acitretin [59].

2.8 Sarcoidosis

Sarcoidosis is a chronic multisystem disease of unknown aetiology characterised by noncaseating epithelioid granulomas within the lesions. Several single reports and case series have been published, all exhibiting satisfactory outcomes with the use of infliximab in both systemic and cutaneous sarcoidosis. Doty *et al.* in a retrospective chart review of 10 patients with various manifestations of sarcoidosis, including skin involvement in 6 cases that were treated with infliximab 5 mg/kg in combination with prednisone noted the efficacy and safety of the anti-TNF drug. In five of the patients the skin lesions clinically improved and the sixth one experienced complete resolution of the rash. Only two of the patients with systemic disease, one with granulomatous myositis and the other with skeletal involvement, did not exhibit clinical response. The administration of infliximab was well tolerated by eight patients. On the contrary, one of the patients developed flushing, hypertension and chest pain and another one developed

angioimmunoblastic lymphoma after a 20-year history of ill-defined lymphoproliferative disorder [60]. Similar results were reported in another retrospective chart review of 9 subjects with sarcoidosis that received infliximab 3 – 5 mg/kg. The introduction of infliximab allowed the reduction of the dose of prednisone or methotrexate and induced clinical improvement including remission of the skin lesions. Only one patient developed drug-induced lupus [61]. Baughman *et al.* in a vehicle-controlled trial randomised 138 patients with pulmonary sarcoidosis into subgroups treated with placebo, infliximab 3 mg/kg or infliximab 5 mg/kg, demonstrating a statistically significant increase in forced vital capacity of 2.5% at week 24 in the combined infliximab-treated groups. On the other hand a risk of developing pneumonia was higher in the patients treated with infliximab than placebo. In this study 19 of the patients exhibited skin involvement (lupus pernio) at baseline and were randomised in the treatment subgroups. However, there was no noted statistically significant improvement with infliximab compared with vehicle [62].

2.9 Non-infectious granulomas and hypersensitivity reactions

Infliximab has been administered effectively in cases of non-infectious granulomatous dermatitides. Case reports suggest possible indications for infliximab in necrobiosis lipoidica [63], refractory orofacial granulomatosis [64], interstitial granulomatous dermatitis [65], granulomatous cheilitis [66] and granuloma annulare [67].

Erythema nodosum is believed to represent a hypersensitivity reaction triggered by various factors. The efficacy of infliximab in erythema nodosum associated with inflammatory bowel disease has been discussed in the literature [43,68] in addition to a case of erythema nodosum leprosum in a patient receiving therapy for borderline lepromatous leprosy [69].

2.10 Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN) is a potentially fatal dermatosis, often induced by drugs. Published data demonstrates a possible role for infliximab as rescue therapy in such cases. The TNF-blockade was found useful in three patients with overlapped characteristics of acute generalised exanthematous pustulosis and TEN caused by antibiotics [70]. Also, a single dose of infliximab 3 or 5 mg/kg proved adequate in restraining the evolution of TEN in at least two more patients [71,72].

2.11 Miscellaneous diseases with cutaneous manifestations

Inflammatory bowel diseases often exhibit cutaneous manifestations. The skin may be involved as either a direct extension from the bowel or at distant sites, especially with Crohn's disease, or even by the development of reactive dermatoses such as erythema nodosum. Infliximab is licensed

Table 1. Synopsis of the off-label uses of infliximab in conditions affecting the skin according to the level of evidence.

Disease	Best available evidence	Overall outcomes*
Psoriasis of the nails	Randomised controlled trial (N = 305, n = 240)	Stop of disease, more effective than vehicle
Pyoderma gangrenosum	Randomised controlled trial (N = 30, n = 13)	Stop of disease, more effective than vehicle
Sjögren's syndrome, primary	Randomised controlled trial (N = 103, n = 54), open-label study (n = 16)	Treatment failure (or controversial results)
Sarcoidosis, cutaneous manifestations	Randomised controlled trial (ns = 19), Case series (ns = 6)	Controversial results for cutaneous lesions
Atopic dermatitis	Open-label study (n = 9)	Relapse
Inflammatory bowel disease, extraintestinal manifestations	Open-label study (n = 23), case reports (nt = 12)	Stop of disease
Lupus erythematosus, systemic	Open-label study (n = 6)	Stop of disease, no data for any skin lesions
Acne conglobata	Case report (n = 1)	Stop of disease
Acrodermatitis continua of Hallopeau	Case reports (nt = 2)	Stop of disease
Amyloidosis, secondary	Case series (n = 3, nt = 5)	Stop of systemic disease, no data for skin lesions
Behcet's disease, cutaneous manifestations	Case reports (nt = 4)	Controversial results
Cutaneous vasculitis	Case reports (nt = 3)	Relapse or stop of disease
Dercum's disease	Case report (n = 1)	Relapse
Dermatomyositis	Case reports (nt = 5)	Stop of disease
Erythema nodosum	Case reports (nt = 3)	Stop of disease
Graft-versus-host disease	Case series (n = 21, ns = 9), (n = ns = 11),	Partial response, relapse
Granuloma annulare	Case report (n = 1)	Stop of disease
Granulomatous cheilitis	Case report (n = 1)	Relapse
Hidradenitis suppurativa	Case series and case reports (nt = 30)	Controversial results
Interstitial granulomatous dermatitis	Case report (n = 1)	Stop of disease
Cicatricial pemphigoid	Case report (n = 1)	Stop of disease
Multicentric reticulohistiocytosis	Case reports (nt = 3)	Remission of skin lesions, controversial results for articular involvement
Necrobiosis lipoidica	Case report (n = 1)	Stop of disease
Orofacial granulomatosis	Case report (n = 1)	Stop of disease
Palmoplantar pustulosis	Case reports (nt = 2)	Deterioration of disease
Pemphigus vulgaris	Case reports (nt = 2)	Relapse
Pityriasis rubra pilaris	Case reports (nt = 3)	Controversial results
Polyarteritis nodosa, cutaneous	Case reports (nt = 3)	Stop of disease
Psoriasis, erythrodermic	Case reports (nt = 7)	Stop of disease
Psoriasis, guttate	Case report (n = 1)	Outcome not reported
Psoriasis, pustular	Case reports (nt = 13)	Stop of disease or relapse
Pyostomatitis vegetans	Case report (n = 1)	Stop of disease
Relapsing polychondritis	Case reports (nt = 3)	Stop of disease
SAPHO syndrome	Case reports (nt = 7)	Controversial results for skin lesions, stop of disease for articular involvement

*By the end of the follow-up period.

N: Total number of patients enrolled in the study; n: Total number of patients treated with infliximab in the study; ns: Number of patients with skin manifestations in the study; nt: Total number of patients treated with infliximab in all reports; SAPHO: Synovitis-acne-pustulosis-hyperostosisosteitis.

Table 1. Synopsis of the off-label uses of infliximab in conditions affecting the skin according to the level of evidence (continued).

Disease	Best available evidence	Overall outcomes*
Sjögren's syndrome, secondary	Case report (n = 2)	Stop of disease
Still's disease	Case series (n = 15)	Partial response, relapse
Subcorneal pustular dermatosis (Sneddon-Wilkinson disease)	Case reports (nt = 2)	Controversial results
Toxic epidermal necrolysis	Case reports (nt = 5)	Stop of disease
Sweet's syndrome	Case reports (nt = 4)	Stop of disease
Vasculitides (Wegener's granulomatosis, giant-cell arteritis, etc.)	Case reports (nt > 10), case series (Kawasaki syndrome, n = 16)	Clinical improvement varying

*By the end of the follow-up period.

N: Total number of patients enrolled in the study; n: Total number of patients treated with infliximab in the study; ns: Number of patients with skin manifestations in the study; nt: Total number of patients treated with infliximab in all reports; SAPHO: Synovitis-acne-pustulosis-hyperostosisosteitis.

for the treatment of intestinal Crohn's disease with or without enterocutaneous fistulas and ulcerative colitis as well. It has been also used by physicians for the extraintestinal manifestations of these diseases. In an open study, 22 patients with Crohn's disease and one with ulcerative colitis were treated for their extraintestinal manifestations with infliximab 5 mg/kg. Remission of pyoderma gangrenosum, erythema nodosum and aphthous stomatitis along with the systemic manifestations was observed [73]. Furthermore, infliximab was effective in oral Crohn's disease [74], cutaneous 'metastatic' Crohn's disease [75] and enterocutaneous fistulas outside the context of inflammatory bowel disease [76], whereas a failure of infliximab was reported in a patient with cutaneous Crohn's disease [77].

Graft-versus-host disease (GVHD) occurs when cells from a donor react against tissue of an immunocompromised host. Organs affected by GVHD are the skin, liver and the gastrointestinal tract. Depending on the time of development, GVHD is divided in acute and chronic. As GVHD is T-cell mediated, infliximab could be a useful option. In a retrospective study of a number of patients with acute GVHD treated with infliximab 10 mg/kg once weekly as monotherapy, a good response to treatment was noticed [78]. A partial improvement of the manifestations of the disease by the use of infliximab was shown in additional case series [79,80]. Unfortunately, various complications in some of the patients proved fatal.

In addition, infliximab has shown efficacy in reducing the burden of Dercum's disease [81], secondary amyloidosis [82,83] and familial Mediterranean fever [83]. It was used successfully in cases of multicentric reticulohistiocytosis [84] and it could play a role in the treatment of cutaneous endometriosis [1,85] and wound healing [86].

A synopsis of the off-label uses of infliximab in conditions involving the skin is presented in Table 1.

3. Safety concerns

According to Centocor, Inc., infliximab has been administered to > 843,000 patients worldwide [87]. Although the safety of infliximab has been reported in most cases, it has also been incriminated for the development of side effects which are mentioned hereafter. Infusion reactions, either acute or delayed, have been recorded and they occur in 5 – 10% of all infusions. However, they are easily manageable [88] and > 99% of them are not anaphylactic [3]. As happens with other exogenous substances [89], the development of antibodies against the molecule of infliximab is possible, which increases the risk of infusion reactions and reduces the efficacy of treatment. Nonetheless, concomitant immunosuppressive therapy could limit this problem [90].

An ongoing issue of debate is whether or not TNF blockers increase the risk of malignancies. The so far studied samples may not be representative of the population who has received treatment with infliximab. Nevertheless, a systematic review and meta-analysis including 9 randomised trials and 3493 patients with rheumatoid arthritis who were treated with infliximab or adalimumab but not etanercept concluded on the existence of 'a dose-dependent increased risk of malignancies in patients with rheumatoid arthritis treated with anti-TNF antibody therapy' [91]. In addition, a cohort of 757 patients treated with infliximab or etanercept for rheumatoid arthritis were not found as being at risk of developing tumours in comparison with 800 patients treated with conventional antirheumatic treatment. However, an increased risk for lymphomas by the use of anti-TNF drugs was identified by the investigators, although their result was not interpreted as conclusive [92]. Furthermore, a prospective study of 18,572 patients with rheumatoid arthritis failed to demonstrate a definite correlation between

the development of lymphomas and treatment with infliximab or etanercept [93].

The treatment with infliximab has been associated with the reactivation of latent infections or an increased susceptibility to new ones. A study reviewing 70 patients reported cases of tuberculosis after treatment with infliximab showed the correlation between the treatment and the development of the infection, which occurred soon after three infusions of the drug in most cases [94]. Various infections, including opportunistic ones [91,95], have been also reported. Serious complications such as meningitis [96], sepsis [97] or reactivation of hepatitis [98] also constitute a threat. A careful selection and screening of the candidates for treatment with infliximab is thus required.

Furthermore, it has been observed that TNF-antagonists may exacerbate or induce heart failure [99]. Infliximab has been incriminated for palmoplantar pustular psoriasis, psoriasis-like eruption or eczema-like eruption [100]. It has also been associated with the development of glomerulonephritis [101], systemic lupus erythematosus or lupus-like syndrome [102], acute respiratory distress syndrome [103], optic neuritis [104] and demyelinating disease [105]. Moreover, in a recent study the use of anti-TNF- α antagonists for rheumatoid arthritis was correlated with the development of vasculitis in 39 patients, with skin involvement in 32 of them [106].

4. Expert opinion

Infliximab is a chimeric monoclonal antibody that acts as TNF- α antagonist and consists of human and murine parts. A present, the only skin disease that infliximab has been licensed to treat is plaque psoriasis. However, the better

understanding of the pathogenesis of inflammatory processes and the data that have been published provide arguments for the introduction of infliximab to new indications. Although positive preliminary results have been exhibited in most cases treated with infliximab, strong evidence is still lacking. Nevertheless, it seems possible that infliximab could become a treatment option for pyoderma gangrenosum, cutaneous Crohn's disease, refractory sarcoidosis, chronic recurrent erythema nodosum and TEN. It could also be useful in reducing the dosage of other medications in resistant cases of pustular or erythrodermic psoriasis, pemphigus vulgaris and severe atopic dermatitis, although this issue needs further investigation. However, infliximab cannot become an option in cases of mild atopic dermatitis, acne vulgaris, guttate psoriasis or non-refractory erythema nodosum due to socioeconomic reasons and the existence of effective and cheaper medications in use.

An important parameter that must never be neglected when treating patients with infliximab is the evaluation for tuberculosis risk factors and for the presence of latent infections. Also, the patients under treatment should be closely monitored for the appearance of any adverse events. It seems that most side effects, including infusion reactions, occur until the fourth infusion. However, delayed reactions and side effects can also take place, meaning vigilance is required. A cautious use of this drug will assist physicians to be more successful in their practice.

Declaration of interest

The authors have no conflict of interest to declare and no fee has been received for preparation of the manuscript.

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