Review

TNF-α antagonists beyond approved indications: stories of success and prospects for the future

M.P. KARAMPETSOU¹, S.-N.C. LIOSSIS¹ and P.P. SFIKAKIS²

From the ¹Division of Rheumatology, Department of Internal Medicine, University of Patras Medical School, Patras and ²First Department of Propedeutic and Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece

Address correspondence to Dr S.-N.C. Liossis, Department of Medicine, University of Patras, 26504, Patras, Greece. email: snliossis@med.upatras.gr

Summary

Tumour necrosis factor alpha (TNF-α) is a key molecule of the inflammatory response and data derived from studies in experimental animal models and humans suggest that TNF-α may be implicated in the pathogenesis of various autoimmune and non-infectious inflammatory conditions. Over the past decade pharmaceutical agents directed against TNF-α (infliximab, adalimumab and etanercept) have been widely and successfully employed for the management of rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis, psoriatic arthritis, juvenile idiopathic arthritis and inflammatory bowel disease, whereas two novel anti-TNF-α agents, golimumab and certolimumab pegol, recently entered the market for the treatment of RA, AS, Crohn’s disease and psoriasis. Encouraged by the positive results obtained from the use of TNF-α antagonists in terms of efficacy and safety and due to the increasingly accumulating evidence regarding the implication of TNF-α in the pathogenesis of numerous disorders, anti-TNF-α agents have been considered for the management of diseases other than the ones they were initially approved for. Although in the case of multiple sclerosis and chronic heart failure the outcome from the administration of TNF-α blockers had been less than favourable, in other cases of non-infectious inflammatory conditions the response to TNF-α inhibition had been fairly beneficial. More specifically, according to well-documented clinical trials, anti-TNF-α agents demonstrated that TNF-α mediates a broad range of cellular activities, including proliferation, survival, differentiation and apoptosis, and is considered to be essential for the induction and maintenance of the inflammatory immune response. Since the generation of transgenic mice that constitutively overexpressed human TNF-α...
and developed a polyarticular inflammatory syndrome reminiscent of human rheumatoid arthritis (RA) in 1991, accumulating data from humans and experimental models suggested that TNF-α may play a central role in the pathogenesis of autoimmune inflammatory disorders and that inhibition of TNF-α may represent a reasonable therapeutic approach.4

Currently, TNF-α antagonists (infliximab, adalimumab and etanercept) are approved and widely employed for the management of moderately to severely active RA, ankylosing spondylitis (AS), Crohn’s disease, plaque psoriasis, psoriatic arthritis and juvenile idiopathic arthritis (JIA).5 Etanercept is a fusion protein consisting of the binding part of the human type II receptor of TNF-α linked to the Fc portion of IgG1. Infliximab and adalimumab are monoclonal antibodies (mAbs) directed against TNF-α. Infliximab is a chimeric mAb consisting of a human constant region of IgG1 and a variable murine binding site for TNF-α, whereas adalimumab is a fully humanized IgG1 mAb. Etanercept, as well as infliximab and adalimumab may bind both soluble and transmembrane TNF-α. Two novel anti-TNF-α agents, certolizumab pegol and golimumab recently entered the market. Certolizumab pegol is a humanized F(ab)0 fragment of an antibody directed against membrane and soluble TNF-α conjugated to polyethylene glycol and golimumab is a fully humanized IgG1κ mAb. Certolizumab pegol is approved for the treatment of Crohn’s disease, whereas golimumab is indicated for the management of RA, AS and psoriatic arthritis. Treatment with TNF-α blockers has displayed considerable efficacy in reducing signs and symptoms of inflammation in patients with such conditions when administered either in combination with disease modifying anti-rheumatic drugs (DMARDs) or even as a monotherapy. Over the years, TNF-α antagonists have also displayed a rather satisfactory safety profile, with the main concern being an increased susceptibility to opportunistic infections, reactivation of latent tuberculosis infection and infusion reactions. Up to date more than 2 000 000 patients worldwide have received treatment with either one of the first three anti-TNF-α biologic agents.5 In certain conditions, even though TNF-α initially appeared to be a promising target according to existing experimental evidence, the actual response to anti-TNF-α treatment varied from indifferent to deleterious (summarized in Table 1).6–22 Two distinct examples stem from the treatment of patients with multiple sclerosis with anti-TNF-α agents resulting in exacerbation of the disease19,20 and TNF-α inhibition in patients with chronic heart failure that caused worsening of their disease.21,22

However, the response to TNF-α blockers has been beneficial in a number of non-infectious inflammatory conditions, thus introducing a novel therapeutic approach when conventional treatments failed or were not tolerated by the patients. Behçet’s disease (BD), non-infectious ocular inflammation, pyoderma gangrenosum and hidradenitis suppurativa have successfully been treated with anti-TNF-α agents, according to well-documented clinical data. We discuss herein on the successful outcomes from the off-label use of anti-TNF-α agents, as well as the future prospects from the administration of TNF-α inhibitors in conditions other than the ones already approved for.

**Behçet’s disease**

An example of striking success has been the administration of anti-TNF-α agents for the induction of remission in patients with sight-threatening uveitis, especially in the context of BD. BD is an inflammatory chronic, relapsing, multisystem disorder characterized by ulcers of the oral and genital mucocutaneous tissue, skin lesions and non-erosive arthritis. Ocular inflammation, manifested as anterior and/or posterior uveitis or necrotic retinal vasculitis, is one of the most common and severe manifestations of BD affecting ~70% of the patients and recurrent uveitic attacks may eventually result in permanent loss of vision.23 During 2001 a small open-label study in five patients with BD and acute panuveitis demonstrated that a single infusion of 5 mg/kg of infliximab, administered within 48 h from the onset of the relapse, sufficed to induce rapid clinical remission with improvement in visual acuity within the first 24 h following anti-TNF-α administration. Almost complete clinical remission of inflammation was evident within a week and, at the same time, concomitant extra-ocular manifestations of BD such as oral ulcers and/or arthritis subsided as well.24 The rapid remission-inducing effect of infliximab in acute ocular inflammation, as well as the beneficial effect of TNF-α inhibition in the management of concurrent BD-related manifestations, has been verified by subsequent prospective open-label trials in small numbers of patients.25–37 In a limited number of patients with uveitis secondary to BD, one to four infusions of infliximab not only induced, but even sustained clinical remission of inflammation for long periods of time that extended for up to 3 years.27,33,35 In the majority of patients, however, repeated injections of infliximab (5 mg/kg) q6–8 weeks were required for efficient prevention of uveitic relapses, suggesting that even though infliximab...
may lead to immediate clinical improvement of ocular inflammation, the effect is not permanent and continuous treatment may be necessary.25,26,35 The efficacy of infliximab in BD-associated uveitis was examined in most of the previously mentioned studies almost exclusively as an add-on therapy to DMARDs and, according to a subsequent retrospective, non-randomized comparative study combination of infliximab and conventional DMARDs significantly reduced the frequency of uveitis flares compared to administration of DMARDs alone.38 More specifically, in the study by Tabbara et al., a comparison was retrospectively performed among patients that received treatment with immunosuppressive agents (prednisone, cyclosporine and azathioprine or methotrexate) or with infliximab (5 mg/kg, q2 weeks for six infusions) during every uveitic attack in case previously administered conventional treatment had failed to induce remission. During periods of remission all patients were kept on maintenance therapy with prednisone and azathioprine. Patients that were treated with infliximab displayed significantly fewer uveitic flares and achieved better visual acuity compared to patients that were treated with DMARDs alone.38 Of interest are the results from two clinical trials addressing the efficacy of infliximab in patients with refractory uveitis secondary to BD as a monotherapy.28,33 In these studies, treatment with conventional immunosuppressants had been discontinued prior to the initiation of the infliximab regimen and patients were receiving only corticosteroids at baseline, thus any potentially beneficial outcomes could be attributed to infliximab and not to additional immunosuppressive treatment. As previously reported, both studies demonstrated that TNF-α blockade resulted in rapid resolution of ocular inflammation. In the first study that included five patients with BD with retinal vasculitis and vitritis, all patients rapidly displayed a significant amelioration of uveitis resulting in improvement of visual acuity and vitreous haze, following three i.v. infusions of infliximab.28 However, most patients experienced uveitic flares during the 3-year follow-up period that were successfully treated with additional infliximab infusions.28 In the second trial, 12 patients with BD and chronic, refractory posterior uveitis received nine infusions of infliximab over a period of 12 months and were followed-up for another 12 months; immunosuppressive treatment had been discontinued at baseline and patients were being treated with corticosteroids alone.33 A significant reduction in the frequency of ocular attacks was seen during the infliximab administration period and 9 out of 12 patients achieved complete remission. Remission was sustained to the end of the evaluation period in seven out of these nine patients.33 Visual acuity was also significantly improved. The few patients (n = 2) that experienced uveitic relapses during the follow-up period were successfully treated with corticosteroids and additional infliximab infusions.33 In all of the studies, infliximab exhibited a significant steroid-sparing effect, allowing for tapering and even cessation of

<table>
<thead>
<tr>
<th>Condition</th>
<th>Anti-TNF-α agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren’s syndrome</td>
<td>Infliximab&lt;sup&gt;6,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>Etanercept&lt;sup&gt;7,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>Infliximab&lt;sup&gt;8,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>Infliximab&lt;sup&gt;9,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Autoimmune inner ear disease</td>
<td>Etanercept&lt;sup&gt;10,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pulmonary sarcoidosis</td>
<td>Infliximab&lt;sup&gt;11,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>Infliximab&lt;sup&gt;12,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Asthma</td>
<td>Golimumab&lt;sup&gt;13,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hemiated disc</td>
<td>Infliximab&lt;sup&gt;14,15,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Infliximab&lt;sup&gt;16,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Infliximab&lt;sup&gt;17,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Idiopathic membranous nephropathy</td>
<td>Etanercept&lt;sup&gt;18,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Monoclonal anti-TNF antibody cA2&lt;sup&gt;19,c&lt;/sup&gt; and Lenercept&lt;sup&gt;20,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>Infliximab&lt;sup&gt;21,a&lt;/sup&gt;, Etanercept&lt;sup&gt;22,a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Lenercept = fusion protein consisting of the binding part of the human type I receptor of TNF-α (p55TNFR) and IgG1 immunoglobulin.
<sup>a</sup>Double blind, placebo-controlled study.
<sup>b</sup>Open-label trial.
<sup>c</sup>Case-report study.

Table 1  Reported off-label anti-TNF-α administration with indifferent or unfavourable responses

919 TNF-α antagonists beyond approved indications
corticosteroid administration and many patients were also allowed to reduce the doses of co-administered DMARDs. So far, data regarding the use of infliximab in BD are obtained from independent open-label trials in small numbers of patients. Data on etanercept and adalimumab are similarly encouraging yet limited, and are mainly derived from case-reports, thus no definitive conclusions can be drawn.\(^4\) Even though larger, multicentered, double-blind clinical studies for the use of anti-TNF-\(\alpha\) agents in ocular BD are still awaited, infliximab has been approved in Japan for the management of severe, sight-threatening BD-related uveoretinitis that fails to respond to standard immunosuppressive regimens (Osaka, Japan, 26 January 2007, Newswire). TNF-\(\alpha\) inhibitors have also displayed considerable efficacy in the management of extra-ocular manifestations of BD. There is one double-blind, randomized, placebo-controlled study addressing the efficacy of anti-TNF-\(\alpha\) agents in extra-ocular BD. More specifically, short-term treatment with etanercept (4 weeks) in 20 male patients with BD ameliorated mucocutaneous and articular manifestations, compared to 20 patients treated with placebo.\(^40\) Moreover, similarly to what has been reported for the management of BD-related uveitis, infliximab rapidly induced remission and ameliorated clinical symptoms in patients with steroid-dependent, refractory gastrointestinal BD.\(^41-45\) Infliximab had an immediate response, within hours, in life threatening situations, such as refractory bleeding. Also, no increases of infectious complications after abdominal surgery in anti-TNF-treated patients were noted. Naganuma et al.\(^46\) reported the induction of remission in four out of six patients with entero-Behçet, manifested with ulcers of the gastrointestinal tract, severe abdominal pain, diarrhoeas and fever, after administration of infliximab at 0, 2 and 6 weeks. Remission was sustained for periods of time ranging from 9 months to 3 years with repeated injections of infliximab every 8 weeks.\(^46\) In a subsequent open-label study infliximab was continuously administered in 10 patients with refractory entero-BD for a period of time ranging from 1 year to 39 months. Intestinal manifestations subsided within the first month of treatment and complete remission was maintained for more than one year in 9 out of 10 patients.\(^37\) It should be noted however, that despite the initially favourable response, a dose escalation from 3 to 5 mg/kg of infliximab and shorter infusion intervals (every 6 weeks) were required to sustain remission in two patients.

With regard to CNS involvement in BD, there have been several case-reports from patients with new-onset or relapsing neuro-BD refractory to conventional immunosuppressive therapy, that have successfully been treated with infliximab (reviewed in ref.\(^45\)). Moreover, a small 24-week trial in five patients with chronic, progressive neuro-Behçet syndrome demonstrated that administration of infliximab and methotrexate resulted in amelioration, or at least stabilization, of the neurological symptoms in all patients.\(^59\)

Finally, infliximab has also been reported to achieve remission in two patients with pulmonary aneurysms in the context of BD,\(^50,51\) but was inefficient in the management of patients with BD with the Budd-Chiari syndrome.\(^52\)

**Other non-infectious ocular inflammation**

Apart from the promising data regarding the usefulness of anti-TNF-\(\alpha\) agents in uveitis secondary to BD, there is also evidence that TNF-\(\alpha\) inhibition may be effective in the treatment of ocular inflammation irrespectively of the existence or the nature of an underlying systemic condition.\(^30,53-56\) A strong correlation between anterior uveitis and the HLA-B27 haplotype has repeatedly been described.\(^57,58\) Unilateral anterior uveitis is a common manifestation in patients with SpA, affecting \(\sim 30-40\%\) of patients with AS, psoriatic arthritis or reactive arthritis.\(^59-61\) Administration of 10 mg/kg of infliximab as a single dose suppressed ocular inflammation in six out of seven patients with HLA-B27-associated uveitis within 24 h.\(^62\) Complete remission was evident 17 days following treatment with infliximab, yet uveitis flares occurred in four out of seven patients 5 months following treatment. Recurrences were successfully controlled with topical corticosteroids. Methotrexate, oral prednisone and additional doses of infliximab were needed in one patient for the efficient management of macular oedema and uveitis flares.

In patients with SpA, the frequency of uveitic flares appears to be lower following treatment with either infliximab or etanercept.\(^63,64\) In accordance, administration of adalimumab for 12–20 weeks was able to prevent flares of anterior uveitis by 50\% in 1250 patients with AS.\(^65\) Even though a direct head-to-head comparison among the different anti-TNF-\(\alpha\) agents is not available, retrospectively collected data comparing the efficacy of all three TNF-\(\alpha\) antagonists in preventing uveitis attacks in patients with SpA demonstrated that uveitis flares were significantly lower with infliximab or adalimumab, but not with etanercept.\(^64\) In another retrospective study, however, comparing data from four placebo-controlled trials, both infliximab and
etanercept reduced the frequency of ocular attacks in patients with AS, compared to treatment with placebo. Even though the effect appeared to be more prominent in patients treated with infliximab, the difference between infliximab and etanercept was not statistically significant.53

The possibility that etanercept may be less effective than the anti-TNF-α monoclonal antibodies for the treatment of ocular inflammation has been implied by other studies as well. There are two double-blind placebo-controlled trials testing the efficacy of etanercept in ocular sarcoidosis and JIA-associated uveitis. Etanercept was not proven superior to placebo for the treatment of chronic ocular sarcoidosis.66 Infliximab on the other hand, has shown more promising results in ocular sarcoidosis, according to case-reports and small open-label studies, however these studies need to be verified by larger controlled trials before drawing any definitive conclusions.67–70 Similarly, in patients with uveitis secondary to JIA, which is a common cause of blindness in children,71 etanercept did not add to the benefit of conventional treatment with regard to manifestations from the eyes,72 whereas infliximab and adalimumab presented a more beneficial therapeutic effect.73–75 The underlying mechanisms regarding the reported differences in the efficacy between the anti-TNF-α mAbs and the fusion protein are not yet fully elucidated. However, it has been postulated that the anti-TNF-α mAbs bind to the membrane-bound TNF-α expressed on the surface of immune cells, and by triggering a reverse-signalling cascade induce cell cycle arrest and cell apoptosis, in addition to their complement-dependent-cytotoxic activities (CDC) and antibody-dependent-cytotoxic activities (ADCC) activities. Etanercept, on the other hand, exhibits ADCC activity, but not CDC or reverse-signalling activity.76

Moreover, it has also been reported that new-onset uveitis was seen in patients with JIA already receiving treatment with etanercept.74,77,78 It should be noted, however, that a paradoxical development of uveitis has been reported with the use of all three anti-TNF-α agents. Preliminary data point to a potential stronger correlation of etanercept use and the development of this manifestation.79

Skin disorders

Hidradenitis suppurativa

Hidradenitis suppurativa (HS), or acne inversa, is a relatively rare chronic inflammatory dermatological condition of unknown aetiology. HS initially presents with tender nodules usually in the axillae, perianal, submammary and/or inguinal region that evolve to painful subcutaneous abscesses and, eventually, to the formation of sinus tracts, skin fibrosis and scarring. HS mainly affects young females during the second or third decade of life and may be a significant cause of morbidity especially due to severe pain of the lesions and to psychological parameters because of the location and the persistent nature of the disease.80 Although HS is seen in otherwise healthy individuals, HS may also be associated with Crohn’s disease and spondyloarthropathy, suggesting that a potentially common immunopathological basis may exist,81,82 and also with SAPHO syndrome, a systemic rheumatologic disorder characterized by synovitis, acne, pustulosis, hyperostosis and osteitis.83

The beneficial effect of anti-TNF-α treatment in patients with HS was initially established in patients that were treated with infliximab for the management of concomitant Crohn’s disease. Administration of infliximab was efficacious in controlling both gastrointestinal and cutaneous manifestations.84–86 Regardless of the existence or not of an underlying disease treatment of HS with either infliximab, etanercept or adalimumab has yielded encouraging results according to many case-report studies (reviewed in ref.87). Up to date more than 100 patients have reportedly been treated with a TNF-α antagonist for the management of HS either as a monotherapy or in addition to immunosuppressants and/or antibiotics, displaying various degrees of improvement. In an open-label study by Lee et al. treatment of 15 patients with moderate or severe HS with etanercept for 14 weeks (50 mg/week for 12 weeks and 25 mg/week for another 2 weeks) did not result in significant clinical improvement, which was defined as at least 50% improvement in physician’s global assessment scores (PGA) and Dermatology Life Quality Index (DLQI) and >50% reduction of pain according to visual-analogue scales (VAS); however a statistically significant amelioration of DLQI was recorded. Discontinuation of etanercept at Week 14 was accompanied by worsening of the symptoms during the 1-month follow-up period of the study.88 The outcome from treatment with etanercept (50 mg/week for 12 weeks), although assessed with a different disease activity scoring system, was more favourable in another open-label clinical trial in 10 patients, however cessation of treatment also resulted in recurrence of the symptoms during the follow-up period, indicating that long-term administration should be considered in order to maintain
remission in patients with HS.\textsuperscript{89} Recently, the efficacy and safety of infliximab was evaluated in a double-blind placebo-controlled cross-over trial analysing 38 patients.\textsuperscript{90} Infliximab was well tolerated and clinical improvement measured by PGA, DQLI and VAS was accompanied by a significant reduction in erythrocyte sedimentation rate levels as well, indicating that administration of infliximab may be an effective therapeutic option for this otherwise difficult-to-treat condition.

**Neutrophilic dermatoses**

Pyoderma gangrenosum (PG) along with Sweet’s syndrome, subcorneal pustular dermatosis (Sneddon–Wilkinson disease) and erythema elevatum diutinum, belongs to a group of rare non-infectious diseases known as neutrophilic dermatoses sharing common clinical, histopathological and pathogenetic features.\textsuperscript{91} Neutrophilic dermatoses are commonly associated with underlying systemic conditions, such as inflammatory bowel disease, RA, haematological disorders (myeloproliferative malignancies and myelodysplastic syndrome) and/or solid cancers. Data regarding the use of an anti-TNF-\(\alpha\) agent in Sweet’s syndrome and subcorneal pustular dermatosis, although positive, are scant and usually derive from limited case-report studies, whereas there is no report of anti-TNF-\(\alpha\) administration with respect to erythema elevatum diutinum to our knowledge.\textsuperscript{92–95} This is not the case, however, for PG. PG is characterized by painful deep ulcerations usually located at the lower extremities. The clinical course of PG may be quite aggressive and may potentially cause severe morbidity, occasionally leading to amputation. Treatment is empirical and systemic administration of corticosteroids and/or treatment with immunosuppressive agents, such as cyclosporine A, have been applied for the management of widespread and aggressive disease.\textsuperscript{96} In fact, infliximab is the only therapeutic approach that underwent a randomized, double-blind, placebo-controlled evaluation in 30 patients with PG.\textsuperscript{97} In this study, infliximab was shown to be superior to placebo in patients with PG irrespectively of the existence of concomitant inflammatory bowel disease. Almost half of the patients improved following a single infusion of infliximab (5 mg/kg) at Week 2. Almost 70% of the patients displayed improvement and 21% was able to achieve complete remission at Week 6, although a second course of infliximab was required in seven patients, whereas no response was seen in 31% of the patients.

**Future prospects**

**Ophthalmology**

In the face of promising preliminary results regarding the beneficial effects of TNF-\(\alpha\) antagonists in ocular inflammation, double-blind, placebo-controlled studies are currently under way to evaluate the efficacy and safety of anti-TNF-\(\alpha\) agents in childhood uveitis (infliximab), as well as in refractory uveitis in adults (adalimumab), whereas etanercept is currently being evaluated for the treatment of ocular BD. Systemic administration of anti-TNF-\(\alpha\) agents has shown encouraging preliminary results in uveitic and diabetic cystoid macular oedema and age-related macular degeneration.\textsuperscript{98–100} In a recently completed small but double-blind randomized, placebo-controlled crossover trial of infliximab for diabetic macular oedema refractory to all currently available therapy a significant improvement of visual acuity was indeed found.\textsuperscript{101} Of particular interest are trials which are currently planned to address the efficacy and safety of intravitreal injections of infliximab and adalimumab in patients with diabetic macular oedema, diabetic retinopathy and choroidal neovascularization. Experimental data from an animal model of age-related macular degeneration provided evidence that intravitreal infliximab inhibited choroidal neovascularization.\textsuperscript{102} Data from the intravitreal administration of TNF-\(\alpha\) antagonists in humans with age-related vascular degeneration or diabetic macular oedema are conflicting and insufficient due to the small number of patients. More specifically, even though low-doses of intravitreal injections of infliximab, adalimumab or etanercept in animal models were considered to be safe,\textsuperscript{103–106} a small open-label study including two patients with diabetic macular oedema and two patients with choroidal neovascularization due to age-related macular degeneration demonstrated that infliximab was associated with induction of ocular inflammation (vitritis or panuveitis).\textsuperscript{107} Moreover, intravitreal adalimumab and etanercept injections were of no benefit in eight patients with chronic cystoid macular oedema secondary to non-infectious uveitis and seven patients with diabetic macular oedema respectively.\textsuperscript{108,109} However, intravitreal injections of infliximab were well tolerated and were associated with improvement in visual acuity in another study that included three patients with neovascular age-related macular degeneration.\textsuperscript{110}

**Dermatology**

According to preliminary data, TNF-\(\alpha\) antagonists may also be of value in the treatment of a number
of skin diseases. Up to date, psoriasis is the only disease for which anti-TNF-α agents are approved for. Briefly, positive results have been obtained from the treatment with TNF-α antagonists in multicentric reticulohistiocytosis,111,112 pyotria rubra pilaria,113 eosinophilic fasciitis,114 panniculitis,115,116 necrobiosis lipoidica diabeticorum,117,118 and cicatricial pemphigoid.119 The vast majority of such data have accumulated from case-reports and small case-series studies, and the results should be validated by larger organised clinical trials before considering the off-label use of anti-TNF-α agents for treating these conditions, whereas safety issues should also be carefully examined.

Rheumatology

Initial open-label studies regarding the use of anti-TNF-α agents in systemic lupus erythematosus (SLE) reported that inhibition of TNF-α (four infusions of infliximab over a period of 10 weeks) was associated with significant improvement of proteinuria within a week following administration of infliximab, which lasted for several months. Arthritis also subsided following treatment with infliximab; however a relapse was seen 2–3 months following discontinuation of anti-TNF-α administration.120,121 A subsequent study, however, demonstrated that although short-term treatment of patients with SLE with infliximab was efficient in controlling lupus nephritis and was generally well-tolerated, long-term treatment was accompanied by severe side-effects, such as CNS lymphoma and Legionella pneumonia.122 Up to date, the use of anti-TNF-α agents in SLE remains a matter of debate, especially due to the fear that TNF-α inhibition may lead to severe disease exacerbation, since treatment of patients with RA or SpA with TNF-α blockers has repeatedly been associated with a transient induction of anti-nuclear and anti-dsDNA autoAbs and, occasionally, with the induction of a SLE-like syndrome.123–125 Administration of TNF-α antagonists has also yielded encouraging preliminary results in the treatment of adult-onset Still’s disease126,127 and various forms of systemic vasculitis.128 A prospective open-label study in patients with ANCA-associated vasculitis demonstrated that although infliximab was able to induce remission and was a steroid-sparing agent in the majority of the patients, continuous treatment was not effective in preventing relapses of the disease.129 Administration of adalimumab as an adjuvant to corticosteroids and cyclophosphamide did not add to the benefit of conventional treatment, but similarly to infliximab, allowed for tapering of corticosteroids,130 whereas etanercept was not superior to placebo for maintaining remission in Wegener’s granulomatosis.7 Moreover, treatment with etanercept according to the WGET study was associated with serious adverse events such as the development of solid tumours, yet the fact that all of the patients that eventually developed cancer had also been exposed to cyclophosphamide should be taken into account.7 Favourable preliminary responses to TNF-α blockade that need to be further explored were seen in patients with Takayasu disease.131,132 Treatment with TNF-α antagonists induced and maintained remission for >1 year in 10 out of 15 patients with Takayasu arteritis.131 Finally, encouraging results have also been obtained from the use of anti-TNF-α agents in SAPHO syndrome.133

Conclusions

Anti-TNF-α agents have proven useful for the management of several autoimmune inflammatory diseases and emerging data suggest that treatment with TNF-α antagonists may be a safe and efficacious alternative for the treatment of disorders other than the ones already approved for. So far, accumulated data from the off-label use of anti-TNF-α agents indicate that TNF-α inhibition may result in rapid control of the inflammatory process and in certain cases, such as BD, non-infectious ocular inflammation, hidradenitis suppurativa and pyoderma gangrenosum, continuous treatment may contribute to maintaining remission. However, despite promising experimental data TNF-α blockade has not always been successfully used in the clinic suggesting that much knowledge remains to be gained regarding the role of TNF-α in physiology as well as in human disease. Moreover, even when administration of anti-TNF-α agents appears to be beneficial, several patients do not adequately respond to treatment, thus highlighting the necessity for treatment individualization.134 Further research is also warranted in order to address issues of optimal dosage regimens, duration of treatment and long-term safety. Currently, results from ongoing trials are still awaited for the usefulness of anti-TNF-α agents in the treatment-resistant major depression, Alzheimer’s disease, pemphigus vulgaris, cutaneous manifestations of sarcoidosis, toxic epidermal necrolysis (infliximab as a single dose), lichen planus, inclusion body myositis and Kawasaki disease.

Conflict of interest: None declared.
References


28. Benitez-del-Castillo JM, Martinez-de-la-Casa JM, Patocur E, Mendez-Fernandez R, Lopez-Abad C, Matilla M,


