Supplement Review

Perspectives for TNF-α-targeting therapies

Hanns-Martin Lorenz and Joachim R Kalden

Institute for Clinical Immunology and Rheumatology, Department of Medicine, University of Erlangen-Nuremberg, Erlangen, Germany

Correspondence: Dr Hanns-Martin Lorenz, Inst. for Clin. Immunology and Rheumatology, Dept of Medicine III, University of Erlangen-Nuremberg, Krankenhausstr. 12, 91054 Erlangen, Germany. Tel: +49 9131 853 6387 or -9107; fax: +49 9131 853 4770; e-mail: Hannes.Lorenz@med3.imed.uni-erlangen.de

Received: 12 March 2002
Revisions requested: 12 March 2002
Revisions received: 13 March 2002
Accepted: 18 March 2002
Published: 9 May 2002

Arthritis Res 2002, **4 (suppl 3)**:S17-S24

(Print ISSN 1465-9905; Online ISSN 1465-9913)

Chapter summary

Rheumatoid arthritis (RA) is the most common chronic autoimmunopathy, clinically leading to joint destruction as a consequence of the chronic inflammatory processes. The pathogenesis of this disabling disease is not well understood, but molecular events leading to tissue inflammation with cartilage and bone destruction are now better defined. Therapy with slow-acting, disease-modifying antirheumatic drugs (DMARDs), such as low-dose methotrexate, which is generally accepted as a standard, leads to a significant amelioration of symptoms but does not stop joint destruction. Due to these disappointing treatment options and the identification of certain inflammatory mediators as therapeutic targets, novel therapeutic agents such as monoclonal antibodies, cytokine-receptor/human-immunoglobulin constructs or recombinant human proteins have been tested in RA with some success. Clinical trials testing anti-TNF-α agents, alone or in combination with methotrexate, have convincingly shown the feasibility and efficacy of these novel approaches to the therapy of RA. A clinical trial testing combination therapy with chimeric (mouse/human) anti-TNF-α monoclonal antibody infliximab and methotrexate showed, for the first time in any RA trial, that there was no median radiological progression in the groups given infliximab plus methotrexate over a 12-month observation period. Similar encouraging results might arise from trials employing other TNF-α-directed agents, such as the fully human monoclonal antibody D2E7, the p75 TNF-α-receptor/Ig construct, etanercept, or others, as discussed in this review. Combination partners other than methotrexate will be established as suitable cotreatment along with anti-TNF-α biologicals. Forthcoming new indications for TNF-α-targeted therapies are discussed.

Keywords: D2E7, etanercept, infliximab, TNF-α, therapy

Introduction

The central role of tumour necrosis factor (TNF-α) in the initiation and/or perpetuation of the inflammatory processes in rheumatoid arthritis (RA), Crohn's disease (CD) and many more chronic inflammatory diseases has been suggested by experimental *in vitro* and *in situ* data. This has been clearly verified by the overwhelming success of TNF-α-targeted therapies. Thus, a lot of enthusiasm has been put into the development of further strategies aimed at blocking TNF-α with new and innovative drugs (immunobiologicals and synthetic inhibitors of TNF-α synthesis or signal transduction). Furthermore, new indications for TNF-α-targeted treatment are forthcoming.

Rheumatoid arthritis and Crohn's disease: future directions

Further studies with immunobiologicals

After TNF-α-targeting immunobiologicals like etanercept and infliximab have been approved for the treatment of Crohn's disease, rheumatoid arthritis and juvenile chronic

A glossary of specialist terms used in this chapter appears at the end of the text section.

arthritis, further steps will be taken to establish this therapeutic principle for treatment of other chronic inflammatory diseases. These developments may include additional clinical trials with the established agents, or clinical studies with new TNF-α-targeting immunobiologicals, such as the human D2E7 antibody [1]. Other TNF-α blocking agents are also being developed (e.g. polyethylenglycol [PEG]-bound p55 TNF-receptor [PEG-TNFRI] [2] or the PEGylated TNF-α antibody fragments [CDP-870]). A soluble type 1 p55 TNF-receptor (onercept) is currently being tested in CD. Further long-term observations are required concerning side effects and efficacy of these agents, focusing particularly on radiological progression under therapy with anti-TNF agents in combination with methotrexate. This information is required specifically for the combinations of etanercept plus methotrexate and D2E7 plus methotrexate in patients with RA, but needs to be determined for all new agents.

To date, TNF-α blockade is only recommended for therapy-resistant cases. A clinical trial has been initiated testing efficacy in RA patients in an early phase of their disease. This will be especially interesting since one could hypothesize that early and effective blockade of the chronic inflammatory processes in RA will be more efficient. This should lead to the prevention of tissue destruction and disability as well as higher frequencies of long-term remissions, compared to situations where treatment is semi-efficient with perpetuating inflammation over years. These studies might, therefore, help to define criteria that prospectively characterize an RA patient as one with better prognosis (and defensive therapeutic strategy) versus a worse prognosis with a requirement for aggressive treatment from the beginning of his/her disease. Prospective parameters could include HLA type, radiological signs of joint desruction early after disease onset or a high number of involved joints at the beginning of the disease. It is unclear to date whether the presence of TNF-α-promoter polymorphisms can predict the severity of RA, but certain promoter polymorphisms could be another discriminator that might dictate early, aggressive therapy.

Alternative combination partners

Since methotrexate is generally accepted as the standard first line disease-modifying antirheumatic drug (DMARD) in RA, most of the anti-TNF-α trials have been performed with this combination partner. However, not all patients respond to, or tolerate, methotrexate, so alternative combination partners substituting methotrexate are warranted. Leflunomide is currently being tested along with infliximab in RA patients. Azathioprin, cyclosporin A or sulfasalazine might be alternative candidates [3]. This will considerably increase the spectrum of therapeutic modalities affiliated with the TNF-α-targeting drugs.

New indications for TNF-α-targeting therapies

Psoriatic arthritis and psoriasis

The prevalence of psoriasis is reported as 1–3% of adults in the United States, and psoriatic arthritis (PsA) occurs in approximately 6–20% of psoriasis patients [4]. Psoriatic arthritis is an inflammatory arthropathy that may develop before skin involvement. It presents in a symmetric or asymmetric polyarticular form, with or without onycholysis. The current therapeutic approaches for PsA are similar to those for RA and include nonsteroidal anti-inflammatory drugs (NSAIDs), DMARDs and immunosuppressive agents. Only two DMARDs, methotrexate and sulfasalazine, have demonstrated efficacy in the treatment of PsA.

Circulating T lymphocytes and macrophages isolated from PsA patients produce an increased amount of TNF-α compared with macrophages isolated from healthy controls [5]. Furthermore, the levels of TNF-α are elevated in the synovial fluid [6], tissue [6,7] and skin lesions [8,9] in PsA patients, with TNF-α levels correlating with disease activity [10,11].

As a logical consequence, studies with TNF-α-blocking biologicals were initiated. Several open-label studies have investigated the use of anti-TNF-α agents in the treatment of PsA and psoriasis [12–16]. In a single-centre, open-label report on the treatment of spondyloarthropathies, van den Bosch *et al.* [12] reported that nine PsA patients treated with infliximab (5 mg/kg at weeks 0, 2 and 6) experienced significant improvement in physician's global assessment (PGA), erythrocyte sedimentation rates (ESR), and C-reactive protein (CRP) levels. Of these patients, eight had psoriasis at baseline. After 12 weeks of infliximab treatment, baseline Psoriasis Area and Severity Index (PASI) scores were significantly improved. The clinical improvements in all PsA and psoriasis disease manifestations were maintained over a follow-up period of 1 year [13]. In another open-label study, eight out of 10 heavily pretreated PsA patients experienced improvements in Health Assessment Questionnaire scores and PGA scores after 12 months of treatment with etanercept (25 mg given subcutaneously twice a week). All four patients in this trial with active psoriasis had significant improvement in their psoriatic skin lesions, including complete resolution in three patients [14].

In our open-label experience, infliximab treatment was efficacious and safe in PsA and psoriasis [15,16]. With infliximab treatment (5 mg/kg at weeks 0, 2, and 6), all 10 patients in our study achieved 20% improvement in arthritis according to the American College of Rheumatology response criteria (ACR20) by week 2. After 10 weeks of treatment, eight patients achieved 70% improvement (ACR70), six of whom maintained this improvement to week 54. In addition, magnetic resonance imaging showed an 82% reduction in perfusion of inflamed joints, and mean PASI scores were reduced by 71% at week 10. After 10

weeks of infliximab therapy, six patients experienced nearly complete clearing of erythematous psoriasis plaques. Histopathological analysis of psoriatic plaques showed a reduction in epidermal hyperplasia and inflammation by week 10 [16]. This reduction in hyperplasia was associated with a decrease in plaque size and was evident by the near-normal epidermal structure after infliximab treatment. In a more detailed analysis we recently showed that, besides a decrease of the cellular infiltration (lymphocytes, granulocytes), the protein expression of TNF-α, intercellular adhesion molecule-1 and leukocyte function-associated antigen-1, the mRNA expression of IL-8, IL-20 and TNFR type I were significantly lower in psoriatic plaques after 4 weeks of treatment (Ogilvie *et al*., submitted). The use of anti-TNF-α agents in treating PsA and psoriasis has also been investigated in a randomized, double-blinded, placebo-controlled study. Mease *et al.* [17] reported that 87% patients receiving etanercept (25 mg subcutaneously twice a week) achieved PsA response criteria, compared with 23% of placebo patients ($P < 0.0001$). In addition, 73% of etanercept-treated patients achieved ACR20 compared with 13% of placebo-treated patients ($P < 0.0001$). Of 19 patients in each treatment group with active psoriasis, the median improvement in PASI scores was significantly higher in etanercept-treated patients than in placebo-treated patients. Of psoriasis patients treated with etanercept, 26% achieved a 75% improvement, whereas no patients improved when treated with placebo. In an open-label extension study, etanercept continued to effectively reduce clinical signs and symptoms of PsA and psoriasis for up to 36 weeks [18].

Recently, Chaudhari *et al.* [19] described the first reported placebo-controlled, randomized study designed to investigate the efficacy of an anti-TNF agent in psoriasis patients. In this study, 30 patients ware randomized to receive infliximab (5 or 10 mg/kg) or placebo. Nine of 11 (82%) patients treated with infliximab at 5 mg/kg achieved good, excellent, or clear ratings on PGA, compared with only 2/11 (18%) patients receiving placebo ($P = 0.0089$). In addition, 10/11 (91%) patients treated with infliximab at 10 mg/kg achieved these ratings ($P = 0.0019$ compared to placebo). A significantly higher proportion of patients treated with infliximab obtained a 75% improvement in PASI scores compared with placebo ($P = 0.0089$, infliximab 5 mg/kg versus placebo; $P = 0.03$, infliximab 10 mg/kg versus placebo). The results of these studies suggest that TNF-α plays a pivotal role in the pathogenesis of PsA and psoriasis. In addition, anti-TNF-α therapy offers patients with PsA and psoriasis a new therapeutic option for the control of their disease.

Ankylosing spondylitis

Ankylosing spondylitis (AS) is an inflammatory arthropathy that preferentially affects the axial skeleton, usually manifesting in the sacroiliac joints and then ascending to involve the back bone, frequently accompanied by peripheral arthritis. Treatment for AS includes NSAIDs and sulfasalazine, which is the only DMARD that shows activity in the disease, albeit only for peripheral joints.

Only limited evidence exists to support a role for TNF-α in the pathophysiology of AS. Braun *et al.* [20] showed that TNF-α mRNA and protein were present in inflamed sacroiliac joints of AS patients. Lange *et al*. [21] reported significantly increased TNF-α plasma levels in AS patients, with a positive correlation between TNF-α plasma levels and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). In addition, the strong link between AS and inflammatory bowel disease, where 20–60% of spondyloarthropathy patients have gastrointestinal lesions resembling those in CD, provides circumstantial evidence for a role of TNF-α in AS [22].

In an open-label study, 11 patients with AS of short duration were treated with infliximab (5 mg/kg at weeks 0, 2, and 6) [23]. Improvements in activity, function and pain scores of ≥50% were reported in 9/10 eligible patients. The median CRP level decreased to normal and the median improvement in BASDAI score after 4 weeks was 70%. In another open-label study of patients with different subtypes of spondyloarthropathy, 10 AS patients treated with infliximab at 5 mg/kg every 14 weeks achieved significant improvements in morning stiffness, tender and swollen joint counts, ESR, CRP, BASDAI score, Bath Ankylosing Spondylitis Functional Index score, and Bath Ankylosing Spondylitis Metrology Index score. Improvement in the other endpoints were significant at days 3–14 and were maintained to day 84 or longer [13].

In a larger open-label study, 48 patients with severe AS were treated with infliximab. At week 8, significant improvements in mean disease activity, global pain, BASDAI score, Bath Ankylosing Spondylitis Functional Index score, and CRP levels were observed [24]. The results of the aforementioned open-label studies were recently confirmed in a double-blind, placebo-controlled, phase III clinical trial [25]. A total of 70 patients with active AS were enrolled in the study and randomized to receive placebo ($n = 35$) or infliximab at 5 mg/kg ($n = 35$) at weeks 0, 2 and 6, and then every 6 weeks until week 48. At the time of the report, 66 patients had completed 3 months of treatment. A 50% improvement in BASDAI score was achieved by 53% of patients treated with infliximab, compared with 9% of patients treated with placebo ($P < 0.01$). Interestingly, only patients with elevated serological markers of inflammation responded to anti-TNF-α therapy. Similar data have recently been reported with etanercept in AS patients [26].

Adult-onset Still's disease

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology. Clinical

symptoms of this disease are high spiking fever, arthritis, transient cutaneous rashes, hepatosplenomegaly, leukocytosis and sore throat. A markedly elevated serum ferritin correlates with disease activity and several inflammatory cytokines are elevated in these patients. Furthermore, Hoshino *et al.* [27] reported elevated serum levels of TNF-α in AOSD patients. Recently, Kawashima *et al.* [28] demonstrated that the proinflammatory cytokine IL-18 is markedly, and in this quantity rather specifically, elevated in the serum of AOSD patients during the acute phase of their disease. Because it has been shown that TNF-α induces the expression of IL-18 in synovial tissues [29], anti-TNF agents may lead to a reduction of IL-18 in AOSD patients. Bombardieri *et al.* [30] recently demonstrated that infliximab reduced IL-18 serum levels in RA patients. Therefore, studies to determine if infliximab also reduces IL-18 serum levels in AOSD are warranted.

The current treatment for AOSD is mostly limited to the use of NSAIDs and, in severe cases, prednisone. However, many patients become dependent on high-dose prednisone or are refractory to corticosteroid treatment. In a retrospective analysis of 26 AOSD patients, methotrexate was an effective second-line treatment for patients who had not responded to prednisone. However, controlled studies of methotrexate and other DMARDs in the treatment of AOSD have not been performed. Thalidomide, a known inhibitor of TNF-α, was reported to markedly improve clinical symptoms in a patient with treatment-resistant AOSD [31].

Systematic investigation of anti-TNF-α therapy in AOSD is in its early stages. An open-label trial evaluated the efficacy of infliximab in the treatment of AOSD refractory to conventional therapy [32]. Three patients with chronic and active AOSD who were unresponsive to corticosteroids and methotrexate were administered infliximab at 3 mg/kg at weeks 0, 2, and 6, and then every 8 weeks thereafter, along with concomitant methotrexate (15 mg/week). At 50 weeks of follow up, disease activity improved in all three patients, and two patients experienced reductions in ESR, CRP, prednisone dose and PGA. In a recent pilot study conducted at our institution, six AOSD patients treated with infliximab reported marked improvements in the clinical signs and symptoms of AOSD [33]. Patients were treated with infliximab at 5 mg/kg at weeks 0, 2, and 6, and thereafter at intervals of 6–8 weeks. In all six patients, fever, arthralgias, myalgias, splenomegaly and rash were resolved within the first three courses of infliximab treatment. Although the results of these open-label trials need to be confirmed in randomized, placebo-controlled studies, preliminary results suggest that infliximab is effective in managing relapses in refractory AOSD patients. This has meanwhile been confirmed by another group [34]. Tamesis *et al.* [35] treated five AOSD patients with etanercept (2 × 25 mg/week, subcutaneously) with good success in all disease parameters up to 12 months. Weinblatt *et al.* [36] treated 12 patients with etanercept (initial dosage 2 × 25 mg/week, subcutaneously). Of these 12 patients, two withdrew because of disease flares and four had to increase their etanercept dosage to 3 × 25 mg/week. In the three patients with fever and rash, only one improved in these features.

Polymyositis and dermatomyositis

Polymyositis and dermatomyositis are idiopathic inflammatory myopathies that are characterized by proximal muscle weakness, skeletal muscle inflammation and damage, and elevated serum levels of muscle-derived proteins such as creatinine kinase. Polymyositis is associated with lymphocyte invasion of muscle fibres, predominantly cytotoxic CD8+ T lymphocytes, which leads to muscle fibre necrosis, degeneration and fibrosis. The current first-line therapy for polymyositis is prednisone. However, many patients only achieve partial response or do not respond at all to high dose corticosteroids. Because early recognition and treatment of polymyositis is critical to prevent irreversible muscle damage, second-line therapies such as methotrexate or azathioprine should be administered to patients who fail to respond to corticosteroid treatment. Alternatively, or in addition, high dose immunoglobulins have been proven efficacious in refractory cases.

Using monoclonal antibodies to TNF-α, Tateyama *et al.* [37] demonstrated that TNF-α positive macrophages and lymphocytes invade the endomysium in the muscles of polymyositis patients. In addition, the authors describe a correlation between TNF-α levels in the endomysium and muscle fibre atrophy. Kuru *et al.* [38] also demonstrated infiltration of TNF-α-positive CD8+ lymphocytes and macrophages into the muscle fibres of polymyositis patients.

The apparent involvement of cytokine-producing T lymphocytes in polymyositis has initiated interest in treating these patients with anti-TNF agents. Saadeh [39] treated four refractory patients with dermatomyositis with satisfying benefit. Hengstman *et al.* [40] treated two dermatomyositis patients with infliximab (10 mg/kg every second week) with good responses. We recently treated a patient with polymyositis refractory to immunosuppressive regimens with infliximab (4 mg/kg every 6 weeks) and concomitant methotrexate therapy. This patient showed a significant response to infliximab treatment, including a significant improvement in mobility. The skeletal muscle-specific enzymes returned to normal serum levels, indicating a substantial reduction in inflammation. However, this could not be confirmed in another patient. Although this is a single case, it suggests that anti-TNF-α therapy may be a viable treatment alternative for certain patients with refractory polymyositis. Further studies to fully investigate the potential for anti-TNF-α therapy in treating polymyositis are warranted .

Vasculitis (Behçet's disease, Wegener's granulomatosis)
Behçet's disease is a chronic autoimmune disorder characterized by systemic vasculitis. This disease is associated with mucocutaneous, ocular, articular, vascular, gastrointestinal and central nervous system manifestations. Approximately 70% of patients experience relapsing ocular inflammation that can lead to blindness. The etiology of Behçet's disease is unknown, although a genetic association to human leukocyte-associated antigen-B5 has been described [41]. However, some evidence suggests that increased levels of TNF-α and soluble TNF receptors are associated with active disease [42,43]. Thalidomide has been successfully used in the treatment of Behçet's disease, possibly by accelerating the degradation of TNF-α mRNA [44].

Recently, anti-TNF therapy has been used for the treatment of these patients. Travis *et al.* [45] reported the successful use of infliximab in two Behçet's disease patients with rare gastrointestinal ulcerations; this has been confirmed by others [46]. Within 10 days of infliximab treatment, the ulcers had healed and all extraintestinal manifestations had resolved. Furthermore, five patients with relapsing panuveitis were successfully treated with infliximab. Remission of ocular inflammation was evident within the first 24 hours and complete suppression was observed within 7 days of infliximab therapy [47]. This has been confirmed in case reports by other authors [48,49]; treatment with infliximab (10 mg/kg, twice at week 0 and 4) has resulted in long-term remission over more than 12 months [49]. Clearly, the rapid and effective response of this handful of Behçet's disease patients to infliximab warrants further studies of the use of anti-TNF therapy in treating this disease.

Wegener's granulomatosis (WG) is a chronic necrotizing vasculitis involving small to middle-sized vessels. Virtually every organ can be involved, but typically eyes, lungs, joints and kidneys are affected. It is characterized by the occurrence of cytoplasmic antineutrophil cytoplasmic antigen antibodies directed against proteinase 3. The production of TNF-α in peripheral blood mononuclear cells and CD4+ T cells isolated from patients with WG was elevated, when compared with healthy donors [50]. Moreover, Noronha *et al.* [51] found expression of TNF-α at active sites of inflammation in kidney biopsies.

Consequently, a clinical study with infliximab in patients with WG was initiated [52]. Six patients who were refractory to therapy with cyclophosphamide were treated with infliximab at 3–5 mg/kg (day 0, weeks 2 and 6, every fourth week thereafter). Three patients had imminent visual loss due to progressive retroorbital granulomas, two patients had progressive glomerulonephritis, and one patient suffered from progressive pulmonary granulomas. Infusion of infliximab resulted in a rapid and significant improvement in five patients, one patient was withdrawn due to suspected infection. Similar results were reported by Bartolucci *et al.* in 10 patients (seven with WG, two with RA-associated systemic vasculitis and one with cryoglobulinemic vasculitis) [53]. In a randomized trial with active WG, 20 patients were enrolled for treatment with etanercept (2 × 25 mg/week, subcutaneously) on methotrexate background. All patients could taper their steroid dosage within 6 months. Long-term efficacy data are not available so far [54]. In another study, Stone *et al.* [55] included 20 active WG patients. Etanercept was added to the standard therapeutic regime including cyclophosphamide in six patients. Nineteen out of the 20 patients remained on the drug over the observation period of 6 months, one patient developed retroorbital granulomas at 4 months. Birmingham Vasculitis Activity Score decreased from 3.6 to 0.6, and the mean daily prednisolone dosage could be reduced from 19 mg to 7.4 mg. However, persistently active disease was common and present in 15/19 patients; one patient developed renal involvement and mesenteric vasculitis while taking etanercept.

New nonbiological TNF-α-targeting agents

Given the high costs associated with immunobiologicals and the need for saving expenses in virtually every health care system worldwide, a specific TNF-α blockade employing synthetic (and therefore less expensive) agents is most desirable. Another advantage would be the possible oral availability of these drugs. In this context, inhibition of TNF-α gene transcription, inhibition of TNF-α mRNA translation or blockade of TNF-α-specific signal transduction could be envisioned. A 10 amino acid peptide could block TNF-α synthesis at the translational level both *in vitro* and *in vivo* (rat arthritis model; murine colitis model) through unknown mechanisms. A TNF-α mRNA antisense construct (ISIS 25302) might qualify as a further drug with high specificity. However, both drugs must be evaluated for efficacy and safety in preclinical and clinical trials in both animals and humans.

Insights into signal transduction events associated with TNF-α and/or other proinflammatory cytokines enable targeting of intracellular key molecules, thereby blocking consequences of TNF-α signaling at the subreceptor level. One needs to keep in mind, however, that, so far, there are no chemical signal transduction inhibitors that are 100% specific for one certain kinase; so the side effects might be less favorable than the immunobiologicals. Moreover, many (probably most) intracellular signaling enzymes are not completely specific for one certain signalling cascade, but are redundantly employed by various receptor-associated signalling cascades. This is not necessarily a disadvantage, but bears the risk for a broader spectrum of side effects.

One of the therapeutic target structures involved in the TNF-α associated signalling cascades is p38 mitogen-

activated protein kinase (MAPK), which is important for the initiation of TNF-α synthesis [56]. Thus, 'specific' inhibitors of p38 MAPK were developed (SCIO-469; VX-745; BIRB 796), which are currently being evaluated in animal models. At high dosage, BIRB 796 has been shown to effectively inhibit arthritis progression in established collagen-induced arthritis [57].

Thalidomide has TNF-α inhibiting properties which might be centrally mediated through inhibition of phosphodiesterase IV. Disadvantages of this old drug are obviously affiliated to its teratogenicity and sedative properties. Several companies are in the course of developing phosphodiesterase-IV-dependent or -independent thalidomide derivatives with similar TNF-α neutralising efficacy, but lower toxicity. Roflumilast, an orally available selective phosphodiesterase IV inhibitor, has been shown to decrease TNF-α concentrations in a lipopolysaccharide model, both *in vivo* and *in vitro*, and to protect mice in the collagen-induced arthritis model, especially in combination with methotrexate [58].

Nuclear factor (NF)-κB is responsible for both synthesis of TNF-α as well as transmission of TNF-α-mediated effects [56,59]. NF-κB is a p50/p65 heterodimer which is bound to, and inactivated by, its inhibitor, IκB. After activation of the cell, IκB-kinases (IκK) phosphorylate and degrade IκB, enabling NF-κB to translocate into the nucleus and to bind to its specific promoter sites. An inhibition of IκK will thereby indirectly block transmission of TNF-α-associated intracellular signals [60]. Several IκK inhibitors have been developed, but to our knowledge none is yet in preclinical trials in humans. In DBA/1 mice, collagen-induced arthritis was treated with two IκK inhibitors, AS 2868 or AS 2920, at occurrence of first signs of the disease [61]. Disease severity was dose-dependently decreased, particularly by AS 2920. In an adjuvant arthritis model in Lewis rats, the IκK inhibitor, SPC-839, was orally given in various doses once daily. The authors describe a dose-dependent decrease in paw swelling and a near complete inhibition of radiographic damage, associated with improvement of histological features [62].

Another strategy focuses on TNF-α converting enzyme (TACE), a metalloproteinase that is important for cleavage of membrane-bound TNF-α. Inhibitors of TACE could prevent secretion of TNF-α and possibly decrease concentrations of (soluble) TNF-α at the inflammatory site. On the other hand, Kollias and his group have shown that overexpression of only the membrane-bound TNF-α in mice still leads to a chronic destructive arthritis [63]. In addition, TACE is responsible for the cleavage of TNF-α receptors, thereby preventing solubilization of these natural TNF-α binding and neutralizing proteins. Therefore, TACE inhibitors might not only have anti-inflammatory properties.

An orally available TACE inhibitor, DPC 333, has been successfully tested in several mouse and rat models of arthritis. A double-blind, placebo-controlled, phase IIa study in RA patients was initiated, but has been put on hold after the merging of Bristol-Myers Squibb and DuPont Pharmaceuticals.

Concluding remarks

The overwhelming success of TNF-α-targeting therapies in treatment of RA, CD and juvenile chronic arthritis has lead to an avalanche of new therapeutic trials aiming at neutralising TNF-α, including long-term treatment in RA patients, introduction of new anti-TNF-α immunobiologicals, new indications for TNF-α blockade and (yet still quite early in development) orally available inhibitors of TNF-α synthesis or signal transduction. Both patients and physicians can optimistically await the next years, as new agents and study results will considerably broaden the range of improved therapeutic options in chronic inflammatory diseases.

Glossary of terms

ACR 20 (50) (70) = American College of Rheumatology criteria for 20% (50%)(70%) improvement; AOSD = Adult onset Still's disease; AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CD = Crohn's disease; PASI = psoriasis area and severity index; PDE = phosphodiesterase; PGA = physician's global assessment; PsA = psoriatic arthritis; TACE = TNF-α converting enzyme; WG = Wegener's granulomatosis.

References

1. van de Putte LBA, Rau R, Breedveld FC, Kalden JR, Malaise MG, Schattenkirchner M, Emery P, Burmester GR, Zeidler H, Moutsopoulos HH, Compagnone D, Kempeni J, Kupper H: **Efficacy of the fully human anti-TNF antibody D2E7 in rheumatoid arthritis [abstract].** *Arthritis Rheum* 1999, **42**:S400. [general reference]
2. Davis MW, Feige U, Bendele AM, Martin SW, Edwards III CK: **Treatment of rheumatoid arthritis with PEGylated recombinant human soluble tumour necrosis factor type I: a clinical update.** *Ann Rheum Dis* 2000, **59**:i41-i43. [key review]
3. Grünke M, Schiller M, Hieronymus T, Geiler T, Kalden JR, Manger B, Lorenz H-M: **Synergistic effects of combinations of established DMARDs and immunobiological drugs in vitro [abstract].** *Arthritis Rheum* 2000, **43**:S364. [general reference]
4. Boumpas D, Tassiulas IO: **Psoriatic arthritis.** In: *Primer on the Rheumatic Diseases.* Edited by Klippel JH, Weyand CM, Wortmann RL. Atlanta, GA: Arthritis Foundation; 1997:175-179.
5. Austin LM, Ozawa M, Kikuchi T, Walters IB, Krueger JG: **The majority of epidermal T cells in psoriasis vulgaris lesions can produce type 1 cytokines, interferon-gamma, interleukin-2, and tumor necrosis factor-alpha, defining TC1 (cytotoxic T lymphocyte) and TH1 effector populations: a type 1 differentiation bias is also measured in circulating blood T cells in psoriatic patients.** *J Invest Dermatol* 1999, **113**:752-759. [general reference]
6. Ritchlin C, Haas-Smith SA, Hicks D, Cappuccio J, Osterland CK, Looney RJ: **Patterns of cytokine production in psoriatic synovium.** *J Rheumatol* 1998, **25**:1544-1552. [general reference]
7. Danning CL, Illei GG, Hitchon C, Greer MR, Boumpas DT, McInnes IB: **Macrophage-derived cytokine and nuclear factor kappaB p65 expression in synovial membrane and skin of patients with psoriatic arthritis.** *Arthritis Rheum* 2000, **43**:1244-1256. [general reference]

8. Ettehadi P, Greaves MW, Wallach D, Aderka D, Camp RD: **Elevated tumour necrosis factor-alpha (TNF-alpha) biological activity in psoriatic skin lesions.** *Clin Exp Immunol* 1994, **96**: 146-151. [archival reference]
9. Uyemura K, Yamamura M, Fivenson DF, Modlin RL, Nickoloff BJ: **The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type 1 cell-mediated response.** *J Invest Dermatol* 1993, **101**:701-705. [archival reference]
10. Bonifati C, Carducci M, Cordiali Fei P, Trento E, Sacerdoti G, Fazio M, Ameglio F: **Correlated increases of tumour necrosis factor-alpha, interleukin-6 and granulocyte monocyte-colony stimulating factor levels in suction blister fluids and sera of psoriatic patients—relationships with disease severity.** *Clin Exp Dermatol* 1994, **19**:383-387. [archival reference]
11. Mussi A, Bonifati C, Carducci M, D'Agosto G, Pimpinelli F, D'Urso D, D'Auria L, Fazio M, Ameglio F: **Serum TNF-alpha levels correlate with disease severity and are reduced by effective therapy in plaque-type psoriasis.** *J Biol Regul Homeost Agents* 1997, **11**:115-118. [general reference]
12. van den Bosch F, Kruithof E, Baeten D, De Keyser F, Mielants H, Veys EM: **Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthropathy: an open pilot study**. *Ann Rheum Dis* 2000, **59**:428-433. [general reference]
13. Kruithof E, van den Bosch F, Baeten D, De Keyser F, Mielants H, Veys EM: **TNF-alpha blockade with infliximab in patients with active spondyloarthropathy: follow-up of one year maintenance regimen [abstract].** *Ann Rheum Dis* 2001, **60**:59. [general reference]
14. Yazici Y, Erkan D, Lockshin MD: **A prelirninary study of etanercept in the treatment of severe, resistant psoriatic arthritis.** *Clin Exp Rheumatol* 2000, **18**:732-734. [general reference]
15. Antoni C, Dechant C, Lorenz H-M, Ogilvie A, Kalden-Nemeth D, Kalden JR: **Successful treatment of severe psoriatic arthritis with infliximab.** *Arthritis Rheum* 1999, **42**:S371. [general reference]
16. Ogilvie AL, Antoni C, Dechant C, Manger B, Kalden JR, Schuler G, Luftl M: **Treatment of psoriatic arthritis with antitumour necrosis factor-alpha antibody clears skin lesions of psoriasis resistant to treatment with methotrexate.** *Br J Dermatol* 2001, **144**:587-589. [general reference]
17. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ: **Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial.** *Lancet* 2000, **356**:385-390. [general reference]
18. Mease PJ, Goffe BS, Metz J, van der Stoep A, Burge DJ: **Enbrel® (etanercept) in patients with psoriatic arthritis and psoriasis [abstract].** *Ann Rheum Dis* 2001, **60**:146. [general reference]
19. Chaudhari U, Rornano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB: **Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial.** *Lancet* 2001, **357**: 1842-1847. [general reference]
20. Braun J, Bollow M, Neure L, Seipelt E, Seyrekbasan F, Herbst H, Eggens U, Distler A, Sieper J: **Use of immunohistologic and in situ hybridization techniques in the examination of sacroillac joint biopsy specimens from patients with ankylosing spondylitis.** *Arthritis Rheum* 1995, **38**:499-505. [archival reference]
21. Lange U, Teichmann J, Stracke H: **Correlation between plasma TNF-alpha, IGF-1, biochemical markers of bone metabolism, markers of inflammation/disease activity, and clinical manifestations in ankylosing spondylitis.** *Eur J Med Res* 2000, **5**: 507-511. [general reference]
22. Mielants H, Veys EM, Cuvelier C, De Vos M: **Course of gut inflammation in spondyloarthropathies and therapeutic consequences.** *Baillieres Clin Rheumatol* 1996, **10**:147-164. [key review]
23. Brandt J, Haibel H, Cornely D, Golder W, Gonzales J, Reddig J, Thriene W, Sieper J, Braun J: **Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab.** *Arthritis Rheum* 2000, **43**:1346-1352. [general reference]
24. Breban MA, Vignon E, Claudepierre P, Saraux A, Wendling D, Lespesailles E, Euller-Ziegler L, Sibilia J, Perdringer A, Alexandre C, Dougados M: **Efficacy of infliximab in severe refractory ankylosing spondylitis (AS). Results of an open-label study [abstract].** *Ann Rheum Dis* 2001, **59**:58. [general reference]
25. Brandt J, Alten R, Burmester G, Gromnica-Ihle E, Kellner H, Schneider M, Sörensen H, Zeidler H, Thriene W, Sieper J, Braun J: **Three months results of a double-blind placebo controlled, phase-111 clinical trial of infiximab in active ankylosing spondylitis [abstract].** *Ann Rheum Dis* 2001, **61**:63. [general reference]
26. Gorman JD, Sack KE, Davis JC: **A randomized, double-blind, placebo-controlled trial of etanercept in the treatment of ankylosing spondylitis [abstract].** *Arthritis Rheum* 2001, **44**: S90. [general reference]
27. Hoshino T, Ohta A, Yang D, Kawamoto M, Kikuchi M, Inoue Y, Kamizono S, Ota T, Itoh K, Oizumi K: **Elevated serum interleukin 6, interferon-gamma, and tumor necrosis factor-alpha levels in patients with adult Still's disease.** *J Rheumatol* 1998, **25**:396-398. [general reference]
28. Kawashima M, Yamamura M, Taniai M, Yamauchi H, Tanimoto T, Kurimoto M, Miyawaki S, Amano T, Takeuchi T, Makino H: **Levels of interleukin-18 and its binding inhibitors in the blood circulation of patients with adult-onset Still's disease.** *Arthritis Rheum* 2001, **44**:550-560. [general reference]
29. Gracie JA, Forsey RJ, Chan WL, Gilmour A, Leung BP, Greer MR, Kennedy K, Carter R, Wei XQ, Xu D, Field M, Foulis A, Liew FY, McInnes IB: **A proinflanimatory role for IL-18 in rheumatoid arthritis.** *J Clin Invest* 1999, **104**:1393-1401. [general reference]
30. Bombardieri M, Pittoni V, Conti F, Spinelli FR, Spadaro A, Riccieri V, Alessandrini C, Scrivo R, Valesini G: **Reduction of IL-18 serum levels in rheumatoid arthritis during short term-treatment with infliximab [abstract].** *Ann Rheum Dis* 2001, **99**:54. [general reference]
31. Stambe C, Wicks IP: **TNF alpha and response of treatment-resistant adult-onset Still's disease to thalidomide.** *Lancet* 1998, **352**:544-545. [general reference]
32. Cavagna L, Caporali R, Epis O, Bobbio-Pallavicini F, Montecucco C: **Infliximab in the treatment of adult Still's disease refractory to conventional therapy.** *Clin Exp Rheumatol* 2001, **19**:329-332. [general reference]
33. Dechant C, Antoni C, Lorenz H-M, Kalden-Nemeth D, Kalden JR, Manger B: **Treatment of severe adult onset Still's disease with infliximab [abstract].** *Ann Rheum Dis* 2000, **59**:162. [general reference]
34. Aurrecoechea E, Blanco R, Gonzales S, Martinez-Taboada VM, Rodriguez.Valverde V: **Successful therapy with infliximab in refractory Adult Onset Still's Disease [abstract].** *Arthritis Rheum* 2001, **44**:S118. [general reference]
35. Tamesis ER, Reginato AM, Hubscher O, Reginato AJ: **Etanercept in recalcitrant Adult Onset Still's Disease [abstract].** *Arthritis Rheum* 2000, **43**:S229. [general reference]
36. Weinblatt ME, Maier AL, Overman SS, Mease PJ, Fraser PA, Gravallese EM: **Etanercept in Still's disease in the adult [abstract].** *Arthritis Rheum* 2000, **43**:S391. [general reference]
37. Tateyama M, Nagano I, Yoshioka M, Chida K, Nakamura S, Itoyama Y: **Expression of tumor necrosis factor alpha in muscles of polymyositis.** *J Neurol Sci* 1997, **146**:45-51. [general reference]
38. Kuru S, Inukai A, Liang Y, Doyu M, Takano A, Sobue G: **Tumor necrosis factor alpha expression in muscles of polymyositis and dermatomyositis.** *Acta Neuropathol* 2000, **99**:585-588. [general reference]
39. Saadeh CK: **Etanercept is effective in the treatment of polymyositis/dermatomyositis which is refractory to conventional therapy including steroids and other disease-modifying agents [abstract].** *Arthritis Rheum* 2000, **43**:S193. [general reference]
40. Hengstman G, van den Hoogen F, van Engelen B, Barrera P, Netea M, van de Putte L: **Anti-TNF blockade with infliximab in polymyositis and dermatomyositis [abstract].** *Arthritis Rheum* 2000, **43**:S193. [general reference]
41. Paul M, Klein T, Krause I, Molad Y, Narinsky R, Weinberger A: **Allelic distribution of HLA-B*5 in HLA-B5-positive Israeli patients with Behçet's disease.** *Tissue Antigens* 2001, **58**:185-186.
42. Kosar A, Haznedaroglu S, Karaaslan Y, Buyukasik Y, Haznedaroglu IC, Ozath D, Sayinalp N, Ozcebe O, Kirazli S, Dundar S: **Effects of interferon-alpha2a treatment on serum levels of tumor necrosis factor-alpha, tumor necrosis factor-alpha2 receptor, interleukin-2, interleukin-2 receptor, and E-selectin in Behcet's disease.** *Rheumatol Int* 1999, **19**:11-14. [general reference]
43. Turan B, Gallati H, Erdi H, Gurler A, Michel BA, Villiger PM: **Systemic levels of the T cell regulatory cytokines IL-10 and IL-12 in Behcet's disease; soluble TNFR-75 as a biological marker**

of disease activity. *J Rheumatol* 1997, **24**:128-132. [general reference]
44. Calabrese L, Fleischer AB: **Thalidomide: current and potential clinical applications.** *Am J Med* 2000, **108**:487-495. [general reference]
45. Travis SP, Czajkowski M, McGovern DP, Watson RG, Bell AL: **Treatment of intestinal Behcet's syndrome with chimeric tumour necrosis factor alpha antibody.** *Gut* 2001, **49**:725-728. [general reference]
46. Hassard PV, Binder SW, Nelson V, Vasiliauskas EA: **Anti-tumor necrosis factor monoclonal antibody therapy for gastrointestinal Behcet's disease: a case report.** *Gastroenterology* 2001, **120**:995-999. [general reference]
47. Sfikakis PP, Theodossiadis PG, Katsiari CG, Kaklamanis P, Markomichelakis NN: **Effect of infliximab on sight-threatening panuveitis in Behcet's disease.** *Lancet* 2001, **358**:295-296. [general reference]
48. Robertson LP, Hickling P: **Treatment of recalcitrant orogenital ulceration of Behcet's syndrome with infliximab.** *Rheumatology* 2001, **40**:473-474. [general reference]
49. Goossens PH, Verburg RJ, Breedveld FC: **Remission of Behcet's syndrome with tumour necrosis factor alpha blocking therapy [abstract].** *Ann Rheum Dis* 2001, **60**:637. [general reference]
50. Ludviksson BR, Sneller MC, Chua KS, Talar-Williams C, Langford CA, Ehrhardt RO, Fauci AS, Strober W: **Active Wegener's granulomatosis is associated with HLA-DR+ CD4+ T cells exhibiting an unbalanced Th1-type T cell cytokine pattern: reversal with IL-10.** *J Immunol* 1998, **160**:3602-3609. [general reference]
51. Noronha IL, Kruger C, Andrassy K, Ritz E, Waldherr R: **In situ production of TNF-alpha, IL-1 beta and IL-2R in ANCA-positive glomerulonephritis.** *Kidney Int* 1993, **43**:682-692. [archival reference]
52. Lamprecht P, Voswinkel J, Lilienthal T, Noelle B, Heller M, Gross W, Gross W, Grause A: **Successful treatment of refractory Wegener's granulomatosis with infliximab [abstract].** *Arthritis Rheum* 2001, **44**:S56. [general reference]
53. Bartolucci P, Ramanoelina J, Cohen P, Le Hello C, Guillevin L**: Pilot study on infliximab for 10 patients with systemic vasculitis not responding to steroids and immunosuppressants [abstract].** *Arthritis Rheum* 2001, **44**:S56. [general reference]
54. Langford CA, Talar-Williams C, Barron KS, McCabe KE, Sneller MC: **Phase I/II trial of etanercept in Wegener's granulomatosis: safety and preliminary experience [abstract].** *Arthritis Rheum* 2000, **43**:S163. [general reference]
55. Stone J, Uhlfelder M, Hellmann D, Crook S, Bedocs N, Hoffman G: **Etanercept in Wegener's granulomatosis: a six month open-label trial to evaluate safety [abstract].** *Arthritis Rheum* 2000, **43**:S404. [general reference]
56. Van den Berghe W, Vermeulen L, De Wilde G, De Bosscher K, Boone E, Haegeman G: **Signal transduction by tumor necrosis factor and gene regulation of the inflammatory cytokine interleukin-6.** *Biochem Pharmacol* 2000, **60**:1185-1195. [general reference]
57. Nabozny G, Souza D, Raymond E, Pargellis C, Regan J: **Inhibition of established collagen-induced arthritis with BIRB 796, a selective inhibitor of p38 MAP kinase [abstract].** *Arthritis Rheum* 2001, **44**:S368. [general reference]
58. Barsig J, Leung BP, Bundschuh DS, Wollin L, Marx D, Beume R, Beume R, Liew FY: **The novel phosphodiesterase-4 inhibitor Roflumilast suppresses TNF-α production and efficiently protects mice against collagen-induced arthritis alone and in combination with methotrexate [abstract].** *Arthritis Rheum* 2001, **44**:S367. [general reference]
59. Umezawa K, Ariga A, Matsumoto N: **Naturally occurring and synthetic inhibitors of NF-kappaB functions.** *Anticancer Drug Des* 2000, **15**:239-244. [general reference]
60. Yamamoto Y, Gaynor RB: **Therapeutic potential of inhibition of the NF-kappaB pathway in the treatment of inflammation and cancer.** *J Clin Invest* 2001, **107**:135-142. [general reference]
61. Sagot Y, Sattonnet-Roche P, Bhagwat SS, Grimshaw CE, Dreano M, Plater-Zyberk C: **Two IκK inhibitors are orally active small molecules decreasing severity of collagen-induced arthritis in DBA/1 mice [abstract].** *Arthritis Rheum* 2001, **44**:S368. [general reference]
62. Bhagwat SS, Bennett BI, Satoh Y, O'Leary EC, Leisten J, Firestein GS, Boyle DS, Dreano M, Anderson DW, Grimshaw CE: **The small molecule IkK2 inhibitor SPC-839 is efficacious in an animal model of arthritis [abstract].** *Arthritis Rheum* 2001, **44**: S213. [general reference]
63. Alexopoulou L, Pasparakis M, Kollias G: **A murine transmembrane tumor necrosis factor (TNF) transgene induces arthritis by cooperative p55/p75 TNF receptor signaling.** *Eur J Immunol* 1997, **27**:2588-2592. [general reference]