Anti-Tumor Necrosis Factor Therapies in Immune-Mediated Rheumatic Diseases. Other Observations from the Clinic

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ABSTRACT. To date, over 2 million patients worldwide have been treated with anti-tumor necrosis factor (TNF) therapies, dramatically improving the treatment outcomes of immune-mediated inflammatory diseases (IMID). Observations from clinicians have identified some curious disconnects between clinical and radiographic outcomes, and the paradoxical occurrence of anti-TNF therapy-induced IMID such as psoriasis or reactivation of uveitis and Crohn's disease. These observations point to the need for a better understanding of the mechanisms underlying the ability of anti-TNF therapies to reduce inflammation and how this is linked to the pathogenesis of IMID. (J Rheumatol 2010;37 Suppl 85:53–62; doi:10.3899/jrheum.091465)

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Many patients benefit from the use of anti-tumor necrosis factor (TNF) therapies to treat immune-mediated inflammatory diseases (IMID). What is surprising is the exacerbation of existing cases, or the occurrence of new cases, of psoriasis and uveitis when anti-TNF therapies are indicated for the treatment of these diseases. In some instances, the condition resolves when the patient is switched to another TNF inhibitor, and in most cases the condition resolves upon discontinuation of treatment. These observations point to a need for more treatment options for patients who develop these paradoxical adverse events.

Of additional interest is the disconnect between clinical and radiographic outcomes in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) patients treated with TNF inhibitors. While TNF inhibitors reduce TNF-associated inflammation, there is not always a concomitant reduction in structural progression in AS patients, suggesting that TNF is not involved in AS-associated spinal structural changes. The opposite is observed in RA patients; i.e., reduction of radiographic progression, sometimes to levels below 0, even when there is residual inflammation. These observations point to a need for better understanding of the links between TNF inhibitors and inflammation and radiographic outcomes.

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THE DISCONNECT BETWEEN THE SKIN AND JOINTS: PSORIASIS TRIGGERED BY TNF INHIBITORS

Recent paradoxical observations that TNF-α inhibitors are capable of inducing psoriasis while also being effective therapy for the very same condition puzzled many clinicians and opened a new area for TNF-related scientific research and discussions. Further, in a recent online survey of rheumatologists, 63% of responders indicated that they have encountered psoriasis or other skin reactions in patients taking anti-TNF-α therapies[1]. It is also important to note that this adverse reaction appears to be a class effect and it is reported mainly in patients treated with TNF antagonist for RA, AS, and Crohn's disease (CD).

Psoriasis Induced by Anti-TNF Therapies: Review of Published Case Studies

A recent review of a series of 127 cases of TNF-inhibitor induced psoriasis observed between 1990 and 2007 showed a prevalence ranging from 0.6% to 5.3% and onset from after a few days to up to 4 years[2]. While psoriasis classically presents as thick, erythematous plaques with an adherent silvery scale on the extensor surfaces of extremities (with over 80% of psoriasis patients having plaque-type), psoriasis occurring during TNF blockade has been mostly reported as the pustular type occurring on the palms and soles (pustular, palmo/plantar type in > 40% of cases vs plaque-type psoriasis in just 33% of the cases).

Similar data were reported by Grinblat and Scheinberg[3]. Of 50 cases of TNF inhibitor-induced psoriasis and psoriasiform skin lesions reported in the literature through to 2007, psoriasis developed following the administration of more than one TNF inhibitor in 7 patients. Fifty-six percent of patients were under treatment for RA, 22% for AS, and

14% for inflammatory bowel disease (IBD). However, according to this report the most common skin eruption reported was plaque psoriasis in 29 patients, followed by pustular psoriasis in 26 patients, and guttate psoriasis in 4 patients. Four patients also reported nail involvement. In all patients the lesions resolved when therapy was discontinued, and conversely, persisted with continuation of therapy.

Harrison, *et al*[4] identified 25 cases of new-onset psoriasis among 9826 anti-TNF-treated patients with severe RA from the British Society for Rheumatology Biologics Register (BSRBR), while none of the 2880 patients with severe RA in a comparison cohort who received only traditional disease-modifying antirheumatic drugs (DMARD) in this database developed psoriasis. The median age of patients with incident psoriasis was 60 (interquartile range 55 to 63) and the female-to-male ratio was 5.3:1. Thirteen of the 25 patients developed psoriasis within the first 6 months of anti-TNF therapy, exhibiting extensive psoriasis of multiple sites or palmoplantar pustulosis. Only one patient reported a positive family history of psoriasis. The crude incidence rate of psoriasis was higher in those treated with TNF-α inhibitor therapy (1.04 per 1000 person-years) than in the comparison cohort based on 0 cases (one-sided 97.5% confidence interval 0.71 per 1000 person-years) in 5207 person-years of followup, or a rate calculated using a hypothetical case of psoriasis (0.19 per 1000 person-years). The unadjusted incidence rate ratio for new-onset psoriasis in patients treated with TNF inhibitors compared to a hypothetical case in the comparison cohort would be 5.4 (95% CI 0.7 to 40.3).

Table 1 provides an overview of common observations that emerged from case studies reporting psoriasis induced by anti-TNF therapies[5].

Table 1. Overview of common observations from case studies reporting psoriasis induced by anti-tumor necrosis factor (TNF) therapies. Adapted from Ritchlin C, Tausk F, Ann Rheum Dis 2006;65:1541–4[5]; with permission from BMJ Publishing Group Ltd.

The psoriatic lesions were confirmed by formal dermatological evaluation in some patients and histological confirmation in more than half the patients
Three forms of psoriasis were observed: vulgaris, palmopustular, and guttate, with palmopustular type being the most prevalent
Most patients had no personal or family history of psoriasis
Psoriasiform skin lesions were noted in patients receiving all 3 TNF antagonists, which supports a class effect rather than a disease mechanism related to the structure or function of a single molecule
Most of the patients had underlying rheumatoid arthritis or ankylosing spondylitis, but no reports of new-onset vulgaris or palmopustular psoriasis were identified in patients with psoriasis or psoriatic arthritis receiving anti-TNF agents
Most psoriatic lesions appeared > 12 weeks after anti-TNF treatment was initiated, and the lesions persisted when the TNF antagonists were continued.

Etiology and Pathogenesis

A number of possible explanations for the paradoxical occurrence of psoriasis as an adverse event of anti-TNF treatment have been explored (Table 2). One theory is that patients were misdiagnosed as having RA or AS but had either psoriatic arthritis (PsA) or psoriasis associated with AS. For example, PsA may precede psoriasis in about 15% of cases[4]. Alternatively, patients with psoriasis as an adverse event may have a genetic predisposition to psoriasis, which is not uncommon (prevalence 2.5%) in addition to their arthritis[6]. It is unlikely, however, that this accounts for the majority of patients. The RA patients had typical clinical and radiographic features of rheumatoid joint disease and almost all of them were rheumatoid factor (RF)-positive[5]. The patients with AS also met the New York diagnostic criteria for this disorder[7], and only 25% of them had a history of psoriasis. Further, palmopustular psoriasis has not been described in patients with PsA receiving TNF antagonists.

A second explanation is the triggering of the cutaneous manifestations by infections[5,8]. Bacterial infections have been described in the genesis of both vulgaris and palmopustular psoriasis. It has been suggested that the palmopustular lesions are actually a form of keratoderma blenorrhagicum triggered by persistent Yersinia or *Chlamydia trachomatis*[9], which may be similar to the palmopustular form of psoriasis. However, the absence of other features of reactive arthritis (e.g., eye disease, mucous membrane involvement, and joint inflammation), coupled with no documented preceding infection in the urogenital or gastrointestinal tract, argues against keratoderma blenorrhagicum in most, if not all, of the cases reported to date.

Immunological Considerations

One plausible explanation for the onset of psoriasis is that the reduction of TNF-α levels may cause a cytokine imbal-

Table 2. Potential etiologies for psoriasiform lesions in patients receiving anti-tumor necrosis factor (TNF) treatment. From Ritchlin C, Tausk F, Ann Rheum Dis 2006;65:1541–4[5]; with permission from BMJ Publishing Group Ltd.

Underlying disease was psoriatic arthritis, not rheumatoid arthritis or ankylosing spondylitis
Systemic infection
Reactive arthritis
Drug-induced lupus
Adverse drug reaction
Acute generalized exanthematous pustulosis
Interstitial granulomatous dermatitis
Adverse drug reaction leading to altered immune response
Inflammation mediated by unopposed interferon-α
Inflammation triggered by suppression of TNF in eccrine glands
Suppression of T-regulatory cell function

ance between TNF-α and interferon-α (IFN-α), which can promote an autoimmune response. Plasmacytoid dendritic cells (PDC), which are natural IFN-α producing cells, have recently been shown to infiltrate the skin of patients with psoriasis[10]. It has also been demonstrated that TNF-α regulates IFN-α production[11] by inhibiting the maturation of PDC from hematopoietic progenitors and by inhibiting IFN-α release by PDC activated by viral infection.

In support of this theory is the fact that other cutaneous eruptions associated with TNF-inhibitor therapy include lupus- and dermatomyositis-like eruptions and cutaneous vasculitis[12]. Both cutaneous lupus erythematosus[13] and dermatomyositis[14] have been associated with dysregulation of IFN-α. Patients using IFN-α for chronic liver disease or certain malignancies are also known to be prone to the development of new-onset psoriasis[15].

In addition, changes in T cell function could potentially trigger a psoriasiform response in patients after TNF inhibition. T cells are believed to play an important role in the initiation and persistence of psoriasis[16]. Changes in T cell function through the subtype that expresses CD4+ CD25+ may play a role, since it suppresses autoinflammatory responses in mice and possibly in humans[17]. Keratinocytes and T-regulatory cells also express a glucocorticoid-induced TNF receptor (GITR) that is involved in apoptotic mechanisms. A decline in TNF levels may be involved in anti-apoptotic activity through the GITR receptor[18]. Finally, decreased TNF expression was recently reported in the palmopustular subtype, suggesting that suppression of TNF can facilitate the development of this subtype[19].

Management of Anti-TNF Therapy-induced Psoriasis

According to published case studies[2], topical corticosteroids were used over 55% of the time but led to resolution in only 25% of cases when used without any other intervention. Switching to a different TNF inhibitor led to resolution in just 15% of cases, compared to discontinuing anti-TNF therapy, which led to improvement in 50% of patients. The most effective treatment option was discontinuation of TNF-inhibitor treatment paired with initiation of systemic therapy, leading to resolution in over 64% of cases.

According to the above evidence, the most logical approach for patients receiving anti-TNF agents who develop psoriatic lesions would be to discontinue anti-TNF therapy. However, as this may result in a significant flare of the underlying disease, careful benefit/risk assessment may be necessary. The diagnosis of psoriasis should be confirmed clinically and histologically. The simultaneous use of topical treatments and occlusive dressings may be beneficial. An alternative to discontinuation is to switch to a different anti-TNF agent. Phototherapy and systemic agents such as cyclosporine may also be useful.

In summary, further work and collaboration between dermatologists, rheumatologists, and gastroenterologists are needed to identify risk factors for TNF antagonist-induced psoriasis, to advance knowledge of the pathophysiological mechanism of this phenomenon, and to determine the best therapeutic strategy.

THE DISCONNECT BETWEEN CLINICAL AND RADIOGRAPHIC OUTCOMES: SUPPRESSION OF THE OSTEOCLAST

Inflammation of rheumatoid joints causes cartilage degradation, bone resorption, and joint destruction that, if left untreated, lead to permanent disability. Progression of erosions and joint-space narrowing has been shown to be most rapid during the early stages of RA, tapering slightly in later years[20]. In a prospective followup study of 147 patients with recent-onset RA[21], 70% of patients developed radiographic damage within 3 years of onset. Thus, a key to successful outcomes is an early and aggressive therapy. The goals of treatment for patients with RA are to reduce inflammation and to prevent radiographic progression. To that end, a variety of useful and practical tools are available to rheumatologists to assess patient prognosis and evaluate response to treatment in clinical practice. The most accepted clinical assessment tools are the response criteria of the American College of Rheumatology (ACR)[22] and the European League Against Rheumatism[23], as well as the Disease Activity Score (DAS)[24] and its simplifications such as the Simplified Disease Activity Index (SDAI)[25] and the Clinical Disease Activity Index[26]. Radiographic progression, on the other hand, is generally assessed by quantifying changes in joint-space narrowing and erosions visible on serial plain radiographs. Evidence from daily clinical practice, however, clearly indicates that clinical remission does not necessarily reflect radiographic remission, and vice versa.

Radiographic Progression in Patients with Clinical Response

Radiographic progression may occur in patients who have met the criteria for clinical remission, suggesting ongoing disease activity. One reason for this disparity is that current definitions of clinical remission, such as the DAS and the ACR criteria, allow for some residual disease activity. Patients may have up to 8 or 13 swollen joints while still meeting the criteria for DAS or ACR remission, respectively[27].

Clinical Disease Activity in Patients with Radiographic Remission

Just as radiographic progression is observed in patients with clinical remission, patients with clinical disease activity may have little or no evidence of radiographic progression. Data from the pivotal trials with infliximab (Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis With Concomitant Therapy, ATTRACT), etanercept (Trial of Etanercept and Methotrexate With Radiographic and Patient Outcomes, TEMPO), and adalimumab (PREMIER) show

the remarkable ability of TNF inhibitors to reduce the mean level of joint destruction[28-30], even in patients with suboptimal clinical response [i.e., those not reaching 20% improvement by ACR criteria (ACR20) or with high DAS].

The ATTRACT trial assessed the relationship between inflammation and joint destruction in RA patients treated with infliximab and methotrexate (MTX) who were previously unresponsive to MTX alone[29]. Patients were followed to Week 54 and assessed for changes in clinical variables. Radiographic progression was compared between patients who received infliximab + MTX and those who received placebo + MTX. Patients receiving infliximab + MTX who did not reach ACR20 response did exhibit mild but statistically significant improvement in clinical variables, including the 28-joint DAS, tender and swollen joint counts, and C-reactive protein (CRP) level. Whereas the clinical and CRP changes among these ACR20 nonresponders were small and much lower compared to ACR20 responders, there was a significant inhibition of radiographic progression among ACR20 nonresponders to infliximab + MTX compared with ACR20 nonresponders to placebo + MTX (Figure 1). Further, patients receiving infliximab + MTX still demonstrated inhibition of structural damage that was statistically significant compared with inhibition in patients who received placebo + MTX whether they were ACR20 nonresponders through Week 54, DAS nonresponders at Weeks 30 and 54, or without any improvement in individual clinical variables[29].

The PREMIER trial[30,31] further demonstrates the clinical/radiographic dissociation with anti-TNF agents (Figure 2). The trial compared a combination of adalimumab and MTX with each of the 2 drugs as monotherapy. Although higher ACR responses were seen with the combination therapy than with either drug as monotherapy, there was no significant difference between the 2 monotherapies in terms of ACR response. However, patients treated with MTX monotherapy showed greater radiographic progression than patients treated with adalimumab. Cumulative probability plots revealed that, overall, the majority of patients had a change in total Sharp scores (TSS) of ≥ 0, and that the combination of MTX and adalimumab decreased both the number of patients with radiographic progression and the extent of progression in those patients[32]. Taken together, these studies indicate that the mechanisms that cause inflammation are not the same as those that cause joint damage. Further, radiographic remission appears to be substantially easier to achieve than clinical remission.

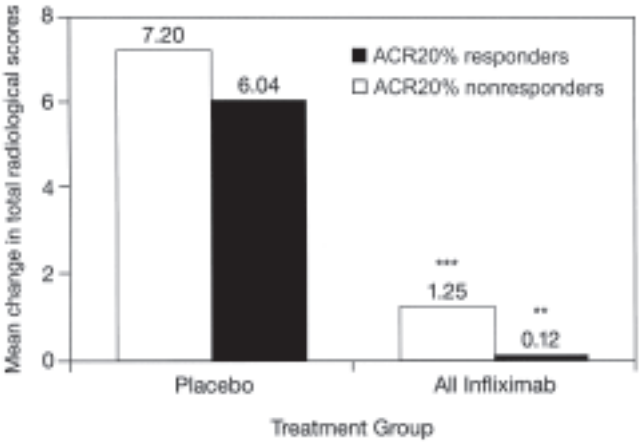

Figure 1. ATTRACT study data: mean change in total radiological scores. Mean change from baseline to Week 54 in the modified Sharp/van der Heijde score among ACR20% criteria responders and nonresponders, by treatment group. Corresponding median changes were 4.02 (nonresponders) and 1.96 (responders) in the methotrexate (MTX) + placebo-treated group (Placebo) and 0.50 (nonresponders) and 0.00 (responders) in the infliximab + MTX-treated group. **p < 0.01, ***p < 0.001, vs MTX plus placebo-treated patients. From Smolen, *et al*, Arthritis Rheum 2005;52:1020-30[29]. With permission from John Wiley and Sons, Inc.

Smolen, *et al*[33] propose that high TNF levels in the synovial joints play a crucial role in joint destruction in RA and that inhibiting TNF might, therefore, retard radiographic progression when clinical manifestations are not lessened in a meaningful way. This hypothesis is based on reports that RA-affected joints have much higher levels of TNF than joints affected with other inflammatory arthritides[34-36], which may play a critical role in initiating osteoclastogenesis[37]. Based on these data, it is postulated that excessive TNF levels are unique in causing joint destruction in RA and that the advent of anti-TNF therapies has revealed an important relationship between TNF and bone erosion that is independent of inflammation.

In summary, a better understanding of the mechanisms responsible for the disconnect between inflammation and radiographic outcomes would provide justification for continuation of anti-TNF therapy in patients who exhibit little or no improvement in clinical symptoms.

THE DISCONNECT BETWEEN RADIOGRAPHIC AND CLINICAL OUTCOMES: SPONDYLOARTHROPATHIES

AS is a chronic rheumatic disease associated with spinal inflammation that subsequently leads to progression of structural damage and loss of function. A hallmark of the disease is new bone formation in the spine, which typically leads to ankylosis across disc spaces and is thought to follow the onset of inflammation[38]. Unlike other inflammatory rheumatic diseases such as RA and PsA, structural progression in AS appears to be independent of TNF, despite the fact that TNF is a key cytokine involved in the inflammation-related signs and symptoms of the disease. Anti-TNF therapies have been shown to increase spinal mobility, decrease the erythrocyte sedimentation rate and CRP levels, and decrease markers of cartilage degradation in patients with AS[39]. Restoration of Th1 cytokine production, decrease in synovial vascularity and infiltration with inflammatory cells, and improvement in magnetic resonance imaging

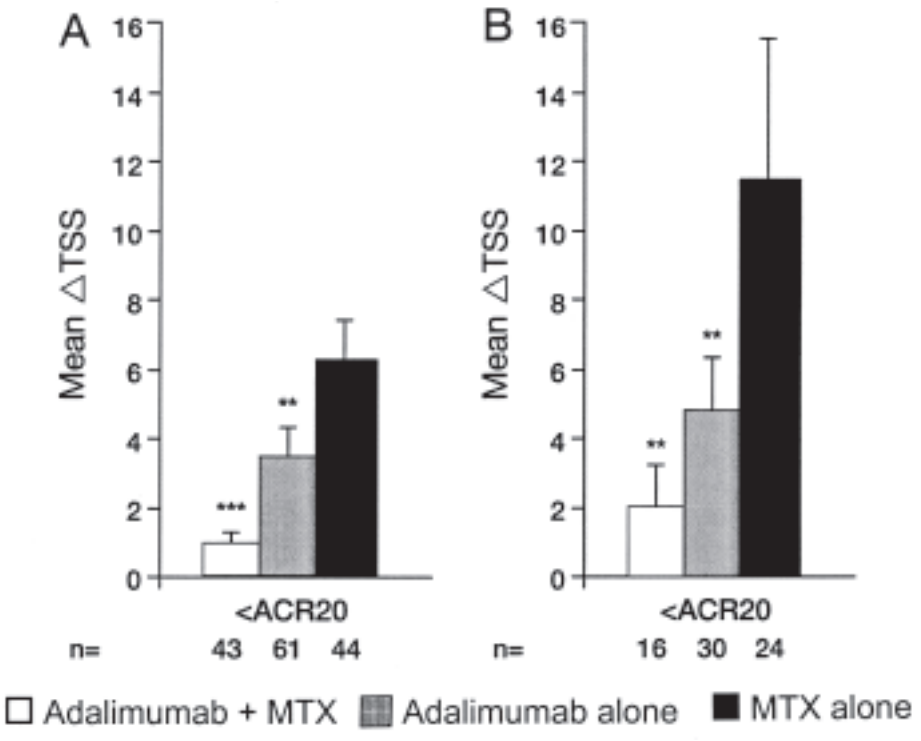

Figure 2. PREMIER study: mean change in Total Sharp Score (TSS) for methotrexate (MTX) treatment alone or in combination therapy with adalimumab at (A) 26 weeks and (B) 104 weeks of treatment. Mean change in TSS at (A) Week 26 and (B) Week 104, for patients with < ACR20% response following 26 or 104 weeks therapy, respectively, with adalimumab + MTX, adalimumab alone, or MTX alone. **p < 0.01, ***p < 0.001 vs MTX alone. From Emery, *et al*, J Rheumatol 2009;36:1429-41[31].

(MRI)-defined lesions with TNF-inhibitor treatment have also been reported[40]. However, prevention of structural damage by TNF inhibitors has yet to be demonstrated.

The effect of anti-TNF therapies on radiographic progression in patients with AS was evaluated by comparing patients treated with an anti-TNF agent to AS patients enrolled in the Outcome Assessments in Ankylosing Spondylitis International Study [OASIS][41]. OASIS patients were treated according to common practice guidelines including the use of nonsteroidal antiinflammatory drugs (NSAID), analgesics, and regular exercise therapy, but not with anti-TNF agents. Radiographic progression was measured using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)[42]. There was no significant difference in the change in mSASSS from baseline to 2 years among patients who received etanercept as compared to patients from the OASIS group (Figure 3A)[43], or infliximab (Figure 3B)[41], or adalimumab (Figure 3C)[44].

The fact that NSAID are shown to reduce radiographic progression further supports the hypothesis that TNF does not play a role in AS-associated structural damage[45]. NSAID are still regarded as the cornerstone of pharmacological intervention for AS, with a good antiinflammatory capacity and the ability to rapidly reduce pain and stiffness[46,47]. Wanders, *et al*[45] demonstrated that longterm, continuous treatment with NSAID significantly slowed radiographic progression in AS patients compared to patients receiving on-demand NSAID therapy. Patients began treatment with celecoxib [a cyclooxygenase-2 (COX-2) inhibitor] at a starting dosage of 100 mg twice daily, and were permitted to increase this dosage to 200 mg twice daily or switch to another NSAID. COX-2, an inducible inflammatory cytokine, plays an important role in regulating osteoblastogenesis in bone formation[48]. Therefore, the mechanism by which COX-2 inhibitors slow radiographic progression is postulated to be through its role in blocking COX-2 and inhibiting new bone formation. In COX-2 knockout mice, the reduced bone formation phenotype can be rescued with the addition of prostaglandin E_2 (PGE_2), the product of the COX-2 enzyme[48].

Interactions Between Inflammation and New Bone Formation

An important observation in AS patients is the development of new syndesmophytes following the resolution of inflammation by anti-TNF therapies. Maksymowych, *et al*[49] observed that an active corner inflammatory lesion (CIL) in AS patients was more likely to evolve into a new syndesmophyte than a vertebral corner demonstrating no active inflammation. New syndesmophytes also developed more

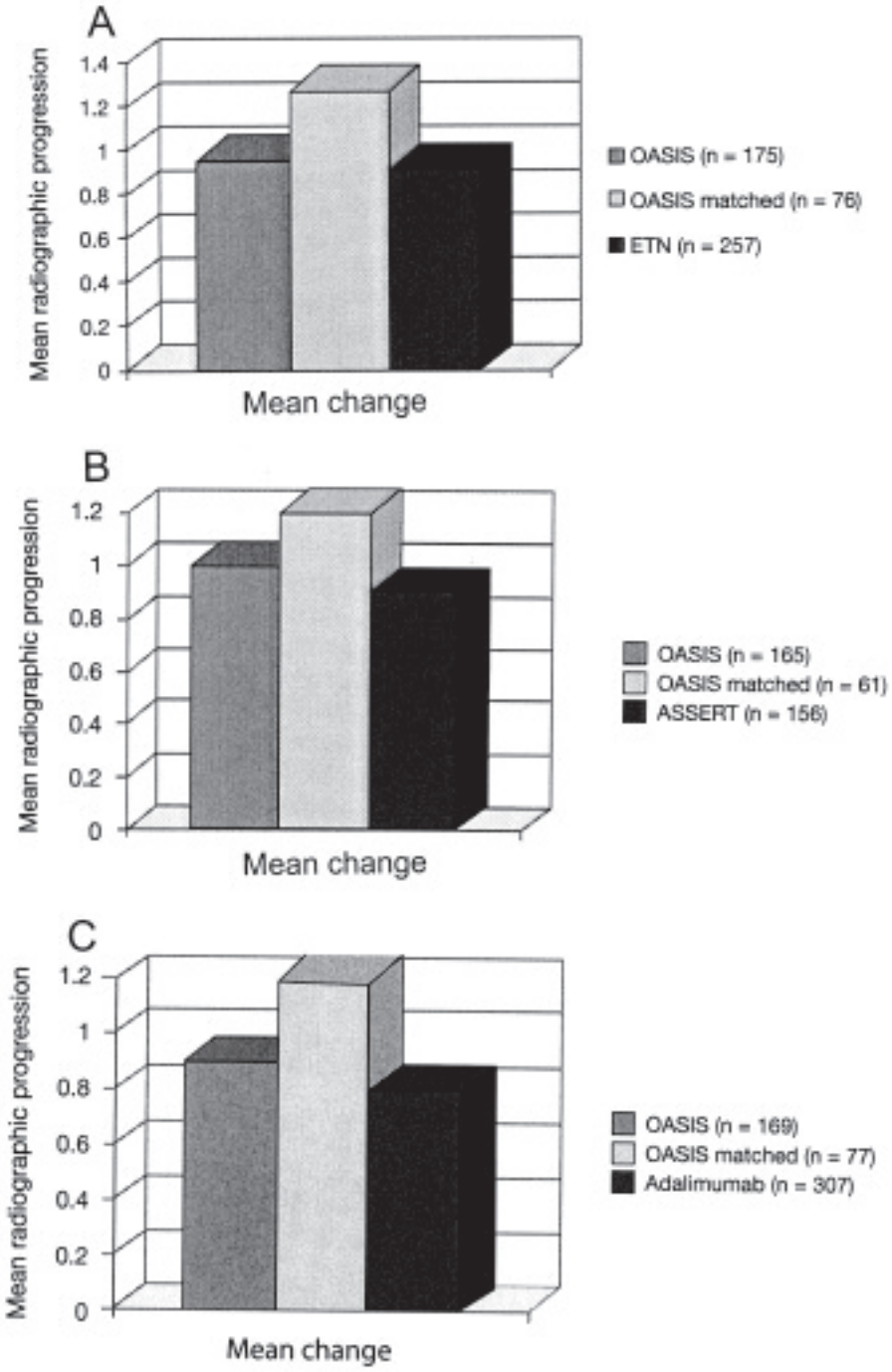

Figure 3. Radiographic progression in AS patients following 2 years of anti-TNF therapies: (A) etanercept; (B) infliximab; (C) adalimumab. From: (A) van der Heijde, *et al*, Arthritis Rheum 2008;58:1324-31[43], with permission from John Wiley and Sons; (B) van der Heijde, *et al*, Arthritis Rheum 2008;58:3063-70[41], with permission from John Wiley and Sons; (C) van der Heijde, *et al*, Arthritis Res Ther 2009;11:R127[44].

frequently in vertebral corners where inflammation had resolved than in those where inflammation persisted despite anti-TNF treatment. The findings support a relationship between inflammation and ankylosis and indicate that a syndesmophyte is more likely to develop from a prior inflammatory lesion.

The interaction between the mechanisms of new bone formation and inflammation is crucial in the pathogenesis of

AS. Diarra, *et al*[50] demonstrated that Dickkopf-1 (DKK1) plays a major role in the stimulation of osteoclasts and in the inhibition of the Wnt/ß-catenin pathway, which activates new bone formation. TNF is a key inducer of DKK1, therefore blocking TNF with anti-TNF therapy results in downregulation of DKK1, which in turn results in new bone formation. These results suggest that TNF inhibitors are unable to block new bone formation, but rather are able to induce new bone formation. Thus, it could be hypothesized that anti-TNF therapies can only prevent new bone formation if this is coupled to inflammation and if this inflammation is treated early. Studies on bone biomarkers in AS patients support the view that suppression of inflammation induces new bone formation[51-53]. Once inflammatory lesions are established, inflammation and osteoblastogenesis are driven by non-TNF signaling pathways and therefore anti-TNF therapies no longer have an effect on radiographic progression.

Recent evidence suggests a link between the Wnt/ß-catenin pathway and the prostaglandin pathway involving downregulation of DKK1 and sclerostin and upregulation of the Wnt pathway by PGE_2[54]. Therefore, new bone formation (Wnt pathway) may be inhibited by prostaglandin inhibitors such as NSAID, which might explain the inhibitory effect of NSAID on new syndesmophyte formation in AS[45].

ORPHAN DISEASES — UVEITIS

The term "uveitis" is used to describe many forms of inflammation of the middle layer of the eye involving the uveal tract (iris, ciliary body, and choroid) and adjacent ocular structures (retina, vitreous, and optic nerve)[55]. Ocular inflammation can lead to permanent loss of vision[56]. A major subset of uveitis is associated with the immune-mediated diseases such as AS[57], Behçet's disease (BD)[58], IBD[59], juvenile idiopathic arthritis (JIA)[60], PsA[61], psoriasis[62], relapsing polychondritis[63], and sarcoidosis[64]. Sugita, *et al*[65] analyzed ocular fluid from patients with active and inactive uveitis, as well as from control subjects without uveitis. Significantly higher levels of TNF and both soluble TNF receptors (sTNFR1 and sTNFR2) were measured in the ocular fluids of patients with active uveitis compared to patients with inactive uveitis and control patients. Further, it was demonstrated that sTNFR had the ability to enhance TNF production by intraocular T cells, suggesting that intraocular sTNFR plays a regulatory role in the ocular inflammation observed in uveitis.

TNF Inhibitors for the Management of Uveitis

It is therefore not surprising that TNF inhibitors, which are effective for many of the systemic diseases associated with uveitis, are also effective in the management of uveitis itself. Infliximab has been reported to be especially successful in the treatment of uveitis in patients with BD, producing a fast-onset therapeutic effect in patients with sight-threatening inflammation, including patients with retinal vasculitis[66,67]. Repetitive infliximab infusions were also reported effective in preventing ocular relapses, maintaining visual acuity, and tapering immunosuppressive therapy in the majority of patients who were intolerant of or who demonstrated an inadequate response to conventional therapy[66]. Infliximab shows efficacy in patients with refractory posterior uveitis and scleritis as demonstrated in a 7-year followup case series study using patients refractory to conventional therapies, i.e., steroids and at least one immunosuppressive agent[68]. Infliximab is effective in reducing acute episodes of uveitis in BD[69] and appears to induce long-lasting remission of BD even after the end of therapy[70]. Infliximab has also demonstrated efficacy in the treatment of ocular inflammation associated with RA, JIA, SpA, CD, sarcoidosis, and Graves' disease ophthalmopathy[71]. However, as infliximab requires intravenous administration some patients are turning to adalimumab with its subcutaneous administration as a therapy for uveitis. Further, in a study conducted by Suhler, *et al*[72] infliximab therapy for uveitis was associated with marked toxicities. One speculation is that this toxicity results from the effect of very high serum drug levels in patients who have localized inflammation and normal baseline serum TNF.

Adalimumab has a substantial preventive effect on the frequency of uveitis flares in patients with AS (Figure 4)[73] and has been reported to show efficacy in the treatment of BD-associated uveitis resistant to infliximab therapy[74] (Figure 4). In their study of the efficacy of adalimumab on chronic anterior uveitis in children, Biester, *et al*[75] found adalimumab to be effective in cases previously unresponsive to combined therapies (including infliximab), with minimal side effects (absence of anaphylactic reaction or infection). Response to adalimumab in JIA uveitis is fast and occurs within the first 2–6 weeks of therapy[76]. Adalimumab also appears to be a safe and effective therapy for the management of refractory uveitis[77].

In summary, in patients with spondyloarthropathy, both adalimumab and infliximab are effective in reducing uveitis flares whereas etanercept has not consistently been found to prevent attacks[78]. Further, several small, randomized, controlled trials comparing etanercept with placebo in the treatment of chronic noninfectious uveitis[79], uveitis associated with JIA[80], and uveitis associated with sarcoidosis[81] concluded that etanercept failed to show a treatment effect.

Uveitis During Treatment with an Anti-TNF Agent

Several studies have revealed new-onset uveitis[82,83] or a worsening of pre-existing uveitis[84] among patients taking anti-TNF treatment. Lim, *et al*[85] analyzed cases of uveitis associated with etanercept, infliximab, and adalimumab therapy that were reported to the World Health Organization adverse drug events database (WHO Uppsala Monitoring

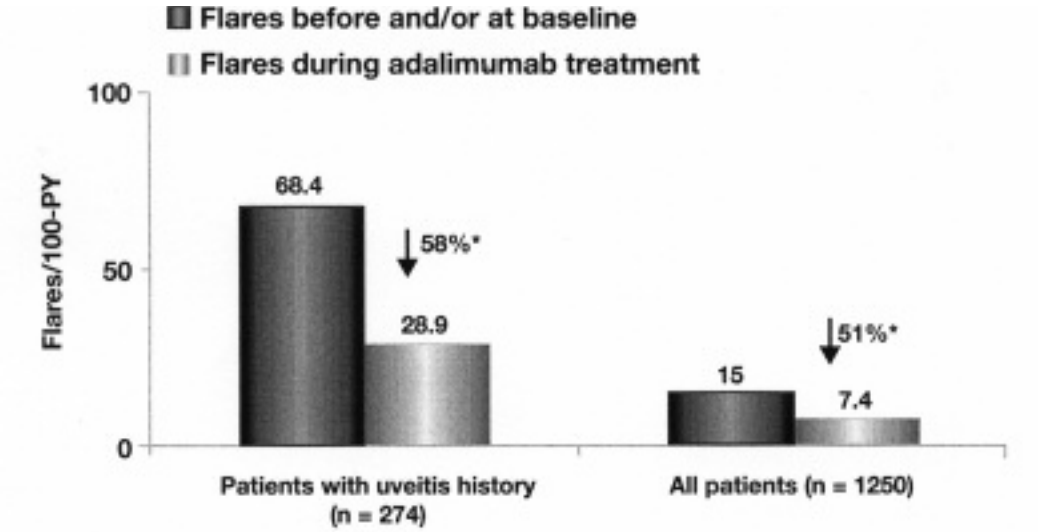

Figure 4. Adalimumab in uveitis therapy. Reduction in uveitis flares at Week 12; *p < 0.001. From Rudwaleit, *et al*, Ann Rheum Dis 2009;68:696-701[73]; with permission from BMJ Publishing Group. PY: patient-years.

Centre, Uppsala, Sweden) or the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Portland, OR, USA) from January 1, 1998, to January 1, 2006. There were 43 cases of uveitis associated with etanercept, 14 with infliximab, and 2 with adalimumab. After normalizing for the estimated number of patients treated with each TNF inhibitor, etanercept showed a significantly greater association with uveitis compared to both infliximab and adalimumab; no significant difference was found between adalimumab and infliximab. A priori criteria were used to exclude patients with an underlying disease associated with uveitis (e.g., AS, CD, PsA), resulting in the identification of 20 cases associated with etanercept, 4 with infliximab, and 2 with adalimumab. Repeat analysis revealed a greater number of uveitis cases associated with etanercept compared to infliximab. These results are consistent with previous studies, and suggest that this is specific to etanercept and not related to TNF inhibitors as a group; however, these observations do not support the use of infliximab over etanercept; rather, if uveitis develops while on etanercept a switch to infliximab may be warranted.

SUMMARY

The development of anti-TNF therapies has revolutionized the treatment of IMID, providing clinicians with a wider choice of effective treatments for their patients. The use of these agents in daily clinical practice, however, has revealed some counterintuitive findings. These include triggering autoimmune diseases such as psoriasis and uveitis, as well as a disconnect between clinical and radiographic outcomes in RA and AS. These observations demonstrate that gaps remain in our understanding of the role of TNF in IMID. Uncovering the underlying mechanisms and connections between inflammation and structural damage will further help clinicians to optimize the use of anti-TNF therapies.

REFERENCES

1. de Gannes GC, Ghoreishi M, Pope J, Russell A, Bell D, Adams S, et al. Psoriasis and pustular dermatitis triggered by TNF-alpha inhibitors in patients with rheumatologic conditions. Arch Dermatol 2007;143:223-31.
2. Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF blockade therapy: a review and analysis of 127 cases. J Dermatolog Treat 2009;20:100-8.
3. Grinblat B, Scheinberg M. The enigmatic development of psoriasis and psoriasiform lesions during anti-TNF therapy: a review. Semin Arthritis Rheum 2008;37:251-5.
4. Harrison MJ, Dixon WG, Watson KD, King Y, Groves R, Hyrich KL, et al. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2009;68:209-15.
5. Ritchlin C, Tausk F. A medical conundrum: onset of psoriasis in patients receiving anti-tumour necrosis factor agents. Ann Rheum Dis 2006;65:1541-4.
6. Fiorentino DF. The yin and yang of TNF-alpha inhibition. Arch Dermatol 2007;143:233-6.
7. Moll JMH, Wright V. New York clinical criteria for ankylosing spondylitis. Ann Rheum Dis 1973;32:354-63.
8. Kary S, Worm M, Audring H, Huscher D, Renelt M, Sörensen H, et al. New onset or exacerbation of psoriatic skin lesions in patients with definite rheumatoid arthritis receiving tumour necrosis factor alpha antagonists. Ann Rheum Dis 2006;65:405-7.
9. Carter JD. Tumour necrosis factor inhibition causing psoriasis? A more plausible explanation exists [letter]. Ann Rheum Dis 2006;65:1680.
10. Nestle FO, Conrad C, Tun-Kyi A, Homey B, Gombert M, Boyman O, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. J Exp Med 2005;202:135-43.
11. Palucka AK, Blanck JP, Bennett L, Pascual V, Banchereau J. Cross-regulation of TNF and IFN-alpha in autoimmune diseases. Proc Natl Acad Sci USA 2005;102:3372-7.
12. Flendrie M, Vissers WH, Creemers MC, de Jong EM, van de Kerkhof PC, van Riel PL. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther 2005;7:R666-R676.
13. Wenzel J, Worenkamper E, Freutel S, Henze S, Haller O, Bieber T, et al. Enhanced type I interferon signalling promotes

Th1-biased inflammation in cutaneous lupus erythematosus. J Pathol 2005;205:435-42.
14. Greenberg SA, Pinkus JL, Pinkus GS, Burleson T, Sanoudou D, Tawil R, et al. Interferon-alpha/beta-mediated innate immune mechanisms in dermatomyositis. Ann Neurol 2005;57:664-78.
15. Seckin D, Durusoy C, Sahin S. Concomitant vitiligo and psoriasis in a patient treated with interferon alfa-2a for chronic hepatitis B infection. Pediatr Dermatol 2004;21:577-9.
16. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. Ann Rheum Dis 2005;64 Suppl 2:ii30-ii36.
17. Jiang H, Chess L. Regulation of immune responses by T cells. N Engl J Med 2006;354:1166-76.
18. Esparza EM, Arch RH. Glucocorticoid-induced TNF receptor functions as a costimulatory receptor that promotes survival in early phases of T cell activation. J Immunol 2005;174:7869-74.
19. Michaelsson G, Kajermo U, Michaelsson A, Hagforsen E. Infliximab can precipitate as well as worsen palmoplantar pustulosis: possible linkage to the expression of tumor necrosis factor alpha in the normal palmar eccrine sweat duct? Br J Dermatol 2005;153:1243-4.
20. Sharp JT, Wolfe F, Mitchell DM, Bloch DA. The progression of erosion and joint space narrowing scores in rheumatoid arthritis during the first twenty-five years of disease. Arthritis Rheum 1991;34:660-8.
21. van der Heijde DM, van Leeuwen MA, van Riel PL, Koster AM, van 't Hof MA, van Rijswijk MH, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum 1992;35:26-34.
22. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
23. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/ International League Against Rheumatism Criteria. Arthritis Rheum 1996;39:34-40.
24. van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20:579-81.
25. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology 2003;42:244-57.
26. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23 Suppl 39:S100-S108.
27. Keystone EC. Clinical implications of understanding radiographic findings in relation to clinical outcomes in rheumatoid arthritis. J Rheumatol 2009;36 Suppl 82:11-6.
28. van der Heijde D, Landewé R, Klareskog L, Rodriguez-Valverde V, Settas L, Pedersen R, et al. Presentation and analysis of data on radiographic outcome in clinical trials: experience from the TEMPO study. Arthritis Rheum 2005;52:49-60.
29. Smolen JS, Han C, Bala M, Maini RN, Kalden JR, van der Heijde D, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis Rheum 2005;52:1020-30.
30. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26-37.
31. Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. J Rheumatol 2009;36:1429-41.
32. Genovese MC, Kavanaugh AF, Cohen SB, Emery P, Sasso EH, Spencer-Green GT. The relationship of radiographic progression to clinical response in patients with early RA treated with adalimumab (Humira®) plus MTX or MTX alone [abstract]. Arthritis Rheum 2005;52 Suppl:S451.
33. Smolen JS, Maini RN, Han C, Baker D, Lipsky P; ATTRACT Study Group. Reply to the editor. Arthritis Rheum 2005;52:4045-7.
34. Firestein GS, Alvaro-Gracia JM, Maki R. Quantitative analysis of cytokine gene expression in rheumatoid arthritis. J Immunol 1990;144:3347-53.
35. Partsch G, Steiner G, Leeb BF, Dunky A, Bröll H, Smolen JS. Highly increased levels of tumor necrosis factor-alpha and other proinflammatory cytokines in psoriatic arthritis synovial fluid. J Rheumatol 1997;24:518-23.
36. Steiner G, Tohidast-Akrad M, Witzmann G, Vesely M, Studnicka-Benke A, Gal A, et al. Cytokine production by synovial T cells in rheumatoid arthritis. Rheumatology 1999;38:202-13.
37. Lam J, Takeshita S, Barker JE, Kanagawa O, Ross FP, Teitelbaum SL. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. J Clin Invest 2000;106:1481-8.
38. Maksymowych WP. Ankylosing spondylitis: pathology, etiology and pathogenesis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. 4th ed. New York: Mosby, Harcourt Health Sciences;2008:1115-30.
39. Maksymowych WP, Rahman P, Shojania K, Olszynski WP, Thomson GT, Ballal S, et al. Beneficial effects of adalimumab on biomarkers reflecting structural damage in patients with ankylosing spondylitis. J Rheumatol 2008;35:2030-7.
40. Lambert RG, Salonen D, Rahman P, Inman RD, Wong RL, Einstein SG, et al. Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2007;56:4005-14.
41. van der Heijde D, Landewé R, Baraliakos X, Houben H, van Tubergen A, Williamson P, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum 2008;58:3063-70.
42. Creemers MC, Franssen MJ, van 't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2005;64:127-9.
43. van der Heijde D, Landewé R, Einstein S, Ory P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum 2008;58:1324-31.
44. van der Heijde D, Salonen D, Weissman BN, Landewé R, Maksymowych WP, Kupper H, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. Arthritis Res Ther 2009;11:R127.
45. Wanders A, Heijde D, Landewé R, Béhier JM, Calin A, Olivieri I, et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum 2005;52:1756-65.

46. Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum 2001;44:1876-86.
47. Song IH, Poddubnyy DA, Rudwaleit M, Sieper J. Benefits and risks of ankylosing spondylitis treatment with nonsteroidal antiinflammatory drugs. Arthritis Rheum 2008;58:929-38.
48. Zhang X, Schwarz EM, Young DA, Puzas JE, Rosier RN, O'Keefe RJ. Cyclooxygenase-2 regulates mesenchymal cell differentiation into the osteoblast lineage and is critically involved in bone repair. J Clin Invest 2002;109:1405-15.
49. Maksymowych WP, Chiowchanwisawakit P, Clare T, Pedersen SJ, Østergaard M, Lambert RG. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. Arthritis Rheum 2009;60:93-102.
50. Diarra D, Stolina M, Polzer K, Zwerina J, Ominsky MS, Dwyer D, et al. Dickkopf-1 is a master regulator of joint remodeling. Nat Med 2007;13:156-63.
51. Appel H, Janssen L, Listing J, Heydrich R, Rudwaleit M, Sieper J. Serum levels of biomarkers of bone and cartilage destruction and new bone formation in different cohorts of patients with axial spondyloarthritis with and without tumor necrosis factor-alpha blocker treatment. Arthritis Res Ther 2008;10:R125.
52. Woo JH, Lee HJ, Sung IH, Kim TH. Changes of clinical response and bone biochemical markers in patients with ankylosing spondylitis taking etanercept. J Rheumatol 2007;34:1753-9.
53. Visvanathan S, van der Heijde D, Deodhar A, Wagner C, Baker DG, Han J, et al. Effects of infliximab on markers of inflammation and bone turnover and associations with bone mineral density in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:175-82.
54. Bonewald LF, Johnson ML. Osteocytes, mechanosensing and Wnt signaling. Bone 2008;42:606-15.
55. Lowder CY, Char DH. Uveitis. A review. West J Med 1994; 140:421-32.
56. Kaklamani VG, Kaklamanis PG. Treatment of Behçet's disease — an update. Semin Arthritis Rheum 2001;30:299-312.
57. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. Ann Rheum Dis 2002;61 Suppl 3:iii8-iii18.
58. Deuter CM, Kötter I, Wallace GR, Murray PI, Stübiger N, Zierhut M. Behçet's disease: ocular effects and treatment. Prog Retin Eye Res 2008;27:111-36.
59. Barrie A, Regueiro M. Biologic therapy in the management of extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2007;13:1424-9.
60. Hamade IH, Al Shamsi HN, Al Dhibi H, Chacra CB, Abu El-Asrar AM, Tabbara KF. Uveitis survey in children. Br J Ophthalmol 2009;93:569-72.
61. Queiro R, Torre JC, Belzunegui J, González C, De Dios JR, Unanue F, et al. Clinical features and predictive factors in psoriatic arthritis-related uveitis. Semin Arthritis Rheum 2002;31:264-70.
62. Durrani K, Foster CS. Psoriatic uveitis: a distinct clinical entity? Am J Ophthalmol 2005;139:106-11.
63. Karim A, Allali F, Tachfouti S, Laghmari M, Cherkaoui W, Hajjaj-Hassouni N, et al. Bilateral uveitis in relapsing polychondritis. A case report. J Fr Ophtalmol 2005;28:530-2.
64. Chung YM, Lin YC, Liu YT, Chang SC, Liu HN, Hsu WH. Uveitis with biopsy-proven sarcoidosis in Chinese: a study of 60 patients in a uveitis clinic over a period of 20 years. J Chin Med Assoc 2007;70:492-6.
65. Sugita S, Takase H, Taguchi C, Mochizuki M. The role of soluble TNF receptors for TNF-alpha in uveitis. Invest Ophthalmol Vis Sci 2007;48:3246-52.
66. Sfikakis PP, Markomichelakis N, Alpsoy E, Assaad-Khalil S, Bodaghi B, Gul A, et al. Anti-TNF therapy in the management of Behcet's disease-review and basis for recommendations. Rheumatology 2007;46:736-41.
67. Munoz-Fernandez S, Hidalgo V, Fernández-Melón J, Schlincker A, Martín-Mola E. Effect of infliximab on threatening panuveitis in Behçet's disease. Lancet 2001;358:1644.
68. Lopez-Gonzalez R, Loza E, Jover JA, Benitez Del Castillo JM, Mendez R, Hernandez-Garcia C, et al. Treatment of refractory posterior uveitis with infliximab: a 7-year follow-up study. Scand J Rheumatol 2009;38:58-62.
69. Yamada Y, Sugita S, Tanaka H, Kamoi K, Kawaguchi T, Mochizuki M. Comparison of infliximab versus cyclosporine during the initial 6-month treatment period in Behcet's disease. Br J Ophthalmol 2009 Aug 18. [Epub ahead of print]
70. Olivieri I, Padula A, Leccese P, D'Angelo S, Giasi V. Long-lasting remission of severe Behçet's disease after the end of infliximab therapy [letter]. J Rheumatol 2009;36:855.
71. Theodossiadis PG, Markomichelakis NN, Sfikakis PP. Tumor necrosis factor antagonists: preliminary evidence for an emerging approach in the treatment of ocular inflammation. Retina 2007;27:399-413.
72. Suhler EB, Smith JR, Giles TR, Lauer AK, Wertheim MS, Kurz DE, et al. Infliximab therapy for refractory uveitis: 2-year results of a prospective trial. Arch Ophthalmol 2009;127:819-22.
73. Rudwaleit M, Rødevand E, Holck P, Vanhoof J, Kron M, Kary S, et al. Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study. Ann Rheum Dis 2009;68:696-701.
74. Mushtaq B, Saeed T, Situnayake RD, Murray PI. Adalimumab for sight-threatening uveitis in Behçet's disease. Eye 2007;21:824-5.
75. Biester S, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, et al. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol 2007;91:319-24.
76. Vazquez-Cobian LB, Flynn T, Lehman TJ. Adalimumab therapy for childhood uveitis. J Pediatr 2006;149:572-5.
77. Diaz-Llopis M, García-Delpech S, Salom D, Udaondo P, Hernández-Garfella M, Bosch-Morell F, et al. Adalimumab therapy for refractory uveitis: a pilot study. J Ocul Pharmacol Ther 2008;24:351-61.
78. Guignard S, Gossec L, Salliot C, Ruyssen-Witrand A, Luc M, Duclos M, et al. Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. Ann Rheum Dis 2006;65:1631-4.
79. Foster CS, Tufail F, Waheed NK, Chu D, Miserocchi E, Baltatzis S, et al. Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. Arch Ophthalmol 2003;121:437-40.
80. Smith JA, Thompson DJ, Whitcup SM, Suhler E, Clarke G, Smith S, et al. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. Arthritis Rheum 2005;53:18-23.
81. Baughman RP, Lower EE, Bradley DA, Raymond LA, Kaufman A. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. Chest 2005;128:1062-7.
82. Scrivo R, Spadaro A, Spinelli FR, Valesini G. Uveitis following the use of tumor necrosis factor alpha inhibitors: comment on the article by Lim et al. Arthritis Rheum 2008;58:1555-6.
83. Fouache D, Goëb V, Massy-Guillemant N, Avenel G, Bacquet-Deschryver H, Kozyreff-Meurice M, et al. Paradoxical adverse events of anti-tumour necrosis factor therapy for spondyloarthropathies: a retrospective study. Rheumatology 2009;48:761-4.
84. Suzuki J, Goto H. Uveitis associated with sarcoidosis exacerbated by etanercept therapy. Jpn J Ophthalmol 2009;53:439-40.
85. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheum 2007;56:3248-52.