Biological therapies for spondyloarthritis

Ther Adv Musculoskel Dis

2014, Vol. 6(3) 92–101

DOI: 10.1177/1759720X14535512

Vincenzo Bruner, Mariangela Atteno, Angelo Spanò, Raffaele Scarpa and Rosario Peluso

***Abstract*:** Biological therapies and new imaging techniques have changed the therapeutic and diagnostic approach to spondyloarthritis. In patients with axial spondyloarthritis, tumor necrosis factor α (TNFα) inhibitor treatment is currently the only effective therapy in patients for whom conventional therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) has failed. TNFα inhibitor treatment is more effective in preventing articular damage in peripheral joints than in axial ones. It is important to treat patients at an early stage of disease to reduce disease progression; moreover it is necessary to identify causes of therapy inefficacy in preventing joint damage in the axial subset.

Keywords: biological therapy, spondyloarthritis, tumor necrosis factor

Introduction

Spondyloarthritis (SpA), a group of different diseases, consists of psoriatic arthritis (PsA), reactive arthritis, arthritis related to inflammatory bowel disease (IBD), a subgroup of juvenile idiopathic arthritis, and ankylosing spondylitis (AS), according to Moll and colleagues' criteria of 1974 [Moll *et al.* 1974]. Amor and colleagues [Amor *et al.* 1990], the European Spondyloarthropathy Study Group [Dougados *et al.* 1991] and the Assessment of SpondyloArthritis International Society (ASAS) [Rudwaleit *et al.* 2009b, 2011] established their classification criteria over time, reaching the present classification that identifies two large SpA subtypes, axial and peripheral SpA.

Biological therapies and new imaging techniques have changed both the therapeutic and the diagnostic approach. Magnetic resonance imaging (MRI) in SpA reveals a new subset of patients with early and nonradiographic phases and verifies the efficacy and structural damage of therapies [Soscia *et al.* 2009; Pedersen *et al.* 2012; Peluso *et al.* 2012].

In this review, our purpose is to evaluate and update the opportunity of biological therapies in SpA.

Tumor necrosis factor α inhibitors

Five different tumor necrosis factor α (TNFα) inhibitors, etanercept, infliximab, adalimumab, golimumab and certolizumab pegol, differ in their molecular structure and administration route. Only infliximab is administered intravenously and has an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen for every 6–8 weeks. The others TNFα inhibitors are administered subcutaneously. A particular case is golimumab, also experimentally available in an intravenous formulation.

TNFα inhibitors have the same efficacy in PsA [Ritchlin *et al.* 2009; Atteno *et al.* 2010] and axial SpA [Baraliakos *et al.* 2012; Migliore *et al.* 2012] and are usually administrated after the failure of traditional disease-modifying antirheumatic drugs (DMARDs).

It is not yet known if methotrexate (MTX) gives an additive or synergistic benefit when used in combination with TNFα inhibitors in PsA; nevertheless a recent study [Fagerli *et al.* 2014] revealed that MTX has a role in retention rate of biological therapy but not in response rate and it is useful only in association with infliximab for its potential value to suppress antibody formation against biological therapies [Mease, 2013; Soriano, 2012; De Vries *et al.* 2007].

Certolizumab is the latest biological drug to add another choice for patients with SpA. In the RAPID-ax-SpA study [Landewé *et al.* 2014], certoluzimab was demonstrated to be effective in reducing signs and symptoms of axial involvement

Correspondence to:
Rosario Peluso, MD, PhD
Rheumatology Research Unit, Department of Clinical Medicine and Surgery, University Federico II, via Sergio Pansini 5, 80131 Naples, Italy
rosario.peluso2@unina.it

Vincenzo Bruner, MD
Mariangela Atteno, MD
Angelo Spanò, MD
Raffaele Scarpa. MD
Rheumatology Research Unit, Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy

in patients with SpA, AS and nonradiographic axial SpA (nr-axSpA), with similar efficacy when given either as 200 mg every 2 weeks or 400 mg every 4 weeks. Although only adalimumab has been approved in Europe for nr-ax-SpA [Haibel *et al.* 2008; Sieper *et al.* 2013], etanercept [Song *et al.* 2013], certolizumab pegol [Landewè *et al.* 2014; Song and Rudwaleit, 2013] and infliximab (in a subgroup of the INFAST study) [Sieper *et al.* 2014a, 2014b] show efficacy and safety in patients with this SpA subtype compared with patients with AS. In addition, certolizumab pegol, in the RAPID–PsA study, showed inhibition of radiographic progression in patients with PsA compared with placebo after 24 weeks of therapy [van der Heijde *et al.* 2014].

In arthritis related to IBD, infliximab, adalimumab and golimumab are used to treat bowel disease and joint involvement [Denmark and Mayer, 2013]. Etanercept is effective for spinal symptoms in patients with SpA but not for IBD, and new manifestations of IBD might occur even during etanercept treatment [Sandborn *et al.* 2001; Song *et al.* 2008].

Extra-articular manifestations and TNFα inhibitors

Extra-articular manifestations are a common clinical feature of SpA. They vary widely in terms of both frequency and severity. The most common extra-articular manifestations are uveitis, bowel disease, and lung, heart, skin and kidney involvement.

Recently some authors have reported the efficacy of therapy with TNFα inhibitors in the treatment of uveitis in AS; in particular, it seems that TNFα inhibitors (infliximab and adalimumab) decrease the rate of recurrences [Levy-Clarke and Nussenblatt, 2006; van der Horst-Bruinsma and Nurmohamed, 2012]. A meta-analysis of studies about the use of TNFα inhibitors (etanercept and infliximab) revealed that they significantly reduce the incidence of uveitis flares compared with placebo in patients with AS [Braun *et al.* 2005]. A retrospective study of patients with SpA further confirms the efficacy of TNFα inhibitors in reducing acute uveitis flares [Guignard *et al.* 2006]. However, this analysis demonstrated a clear difference between etanercept and the anti-TNF antibodies (infliximab and adalimumab); the incidence of uveitis remained unchanged with etanercept treatment, whereas it was dramatically reduced after anti-TNF antibody treatment. Reports on the efficacy of adalimumab on uveitis are mainly based on retrospective analysis of placebo-controlled trials which show satisfying results [Rudwaleit *et al.* 2009a]. In a prospective study a significant decrease (73%) in recurrence rate of uveitis during adalimumab treatment was observed [van der Horst-Bruinsma *et al.* 2010]. There has been a recent observational report of the utility of golimumab in SpA-associated refractory uveitis [Miserocchi *et al.* 2013].

TNFα inhibitors (infliximab, etanercept, adalimumab and golimumab) are effective in the treatment of skin and nail lesions of psoriasis [Hoy and Scott, 2007; Barra *et al.* 2009; Brodszky *et al.* 2008; Gladman, 2008]. However, paradoxically between 1.5% and 5% of patients may present an onset or exacerbation of psoriasis during treatment with TNFα inhibitors [Kary *et al.* 2006; Wendling *et al.* 2008].

In contrast to the excellent efficacy of TNFα inhibitors on articular involvement in SpA, infliximab, adalimumab, golimumab and etanercept exert quite different effects on the gut. In fact, infliximab and adalimumab are effective in SpA and IBD, and golimumab is not yet registered for IBD treatment [Hanauer *et al.* 2002; Rutgeerts *et al.* 2005; Braun *et al.* 2007; Sandborn *et al.* 2007]. It has not been proven that etanercept is effective in IBD; while etanercept is effective in treating the axial involvement and peripheral arthritis associated with AS, case reports suggest that associated Crohn's disease remains persistent or flares during etanercept therapy.

A meta-analysis of trials on the use of TNFα inhibitors in patients with AS investigated the incidence of flares or new onset of IBD; in this study there was a significant difference in favor of infliximab over etanercept and adalimumab [Braun *et al.* 2007]. Furthermore, in patients with a history of IBD flares, flares were more likely to occur in patients with AS receiving etanercept or adalimumab than in those treated with infliximab. This difference in clinical efficacy profiles has attracted great interest, but its scientific basis remains uncertain [Tracey *et al.* 2008].

TNFα inhibitors might decrease the cardiovascular manifestations and atherosclerotic cardiovascular risk in SpA [Di Minno *et al.* 2011, 2012; Costa *et al.* 2012].

Table 1. When to start anti-TNF therapy.

Axial SpA	Persistently high disease activity (BASDAI > 4)
	Failure of at least two NSAIDs
Peripheral SpA	Failure of intra-articular steroid injection
	Failure of DMARDs
Poor prognostic factor risk	High CRP/ESR
	Bone edema at MRI
Psoriatic arthritis	Moderate or severe form in case of failure to respond to at least one DMARD
Enthesitis/dactylitis	In severe cases or after failure of traditional therapy

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; SpA, spondyloarthritis; TNF, tumor necrosis factor.

The effect of TNFα inhibitors on lung involvement in SpA has never been evaluated. However, many recent case reports have described contrasting effects on pulmonary fibrosis in patients with rheumatoid arthritis (RA) [Ostor *et al.* 2004; Nouijai *et al.* 2009].

Some case reports suggest the potential role of TNFα inhibitors in improving Amyloid A (AA) amyloidosis [Kobak *et al.* 2007].

Initiating anti-TNFα therapy

According to the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis guidelines (GRAPPA) [Ritchlin *et al.* 2009], in patients with peripheral PsA, administration of at least one DMARD (e.g. sulfasalzine, leflunomide, MTX or cyclosporine) for more than 3 months is useful; more than 2 months with a standard target dose. Even if there is no evidence for using a combined therapy, a combination of two or more agents could be used in patients whose condition fails to respond to a single agent or who present joint damage progression in spite of treatment.

In patients with high disease activity persistence or joint damage progression despite therapy, TNFα inhibitors are recommended. Although no head-to-head trials have been published to directly compare efficacy and safety, all TNFα inhibitors have shown efficacy in phase III randomized controlled trials [Ritchlin *et al.* 2009].

Furthermore, in axial SpA, as well as in axial PsA, no DMARD therapies are recommended as first-line treatment, only nonsteroidal anti-inflammatory drugs (NSAIDs). TNFα inhibitors are recommended only after NSAID failure or in case of severe disease [Baraliakos *et al.* 2012] (Table 1).

Obviously, before starting TNFα inhibitor therapy, screening each patient for latent tuberculosis [Sanduzzi *et al.* 2012] and hepatic viral infections is suggested to promptly identify people at high risk of reactivating the disease. In this subgroup of patients, when suggested, it is useful to start adequate prophylaxis.

The highest response rate during TNFα inhibitor therapy in patients with PsA was achieved in those with elevated C-reactive protein (CRP) level at baseline [Glintborg *et al.* 2011], young age and low Bath Ankylosing Spondylitis Functional Index (BASFI) [Iervolino *et al.* 2012], while male sex was predictive of longer treatment continuation; in addition, a European League Against Rheumatism good response [Song *et al.* 2008], such as a high Health Assessment Questionnaire and visual analogue scale patient score was associated with a higher discontinuation risk [Gratacos *et al.* 2007]. Also in AS, younger age and male sex, and higher levels of inflammatory markers such as CRP were identified as independent baseline predictors of response or continuation of TNFα inhibitors. In contrast, higher baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score was independently associated with treatment discontinuation [Arends *et al.* 2011; Mirjam *et al.* 2009]. Furthermore, in a recent study, TNFα inhibitor therapy seemed to reduce radiographic progression in patients with AS, especially in the case of early treatment and longer duration of follow up [Haroon *et al.* 2013]. In this study, the authors supported the hypothesis that the timing of treatment initiation is important in the ultimate effect on the rate of damage to

the spine of patients with AS, as revealed by Maksymowych and colleagues in an MRI study [Maksymowych *et al.* 2013]. This study confirms that new bone formation is more likely in advanced inflammatory lesions, supporting a window of opportunity concept for disease modification.

Long-term data

Long-term results for biological treatment of SpA are available only for infliximab, etanercept and adalimumab in AS. Overall, biological therapy in AS shows only partial remission or low disease activity, based on ASAS criteria [Anderson *et al.* 2001].

The first TNFα inhibitor available for SpA was infliximab. Recent data show a drug survival rate of 48% after 8 years, with 88% having partial remission of disease or low disease activity [Baraliakos *et al.* 2011] and a low rate of radiographic progression despite therapy [Baraliakos *et al.* 2013b].

Etanercept shows a drug survival rate of 62% after 7 years, with 31% having partial remission and 44% complete remission of disease [Baraliakos *et al.* 2013a]. Five years of treatment with adalimumab in patients with AS resulted in 65% retention rate, and 51% and 61% of Ankylosing Spondylitis Disease Activity Score (ASDAS) partial remission and ASDAS remission. In this open-label extension phase of the ATLAS study, the strongest predictor of remission at 1 and 5 years and of sustained remission was achieving remission at 12 weeks of treatment [Poddubnyy and Rudwaleit, 2013].

Other mechanisms of action

Abatacept

Open-label studies have shown that abatacept has no major influence on clinical features of AS in the short term. Song and colleagues carried out an open-label study of 30 patients with AS (15 patients who were TNFα inhibitor naive and 15 whose disease failed to respond to TNFα inhibitor) who were treated with abatacept 10 mg/kg on days 1, 15, 29 and then every 4 weeks up to 6 months [Song *et al.* 2011]. At 24 weeks, 13% of the TNFα inhibitor naive patients while none of those whose disease failed to respond to TNFα inhibitor were classified as ASAS-40 responders. A total of 27% of the TNFα inhibitor-naive patients (*versus* 20% in the TNFα inhibitor failure group) achieved ASAS-20. This study failed to demonstrate any major improvement in either ASAS-20 or ASAS-40 in patients receiving abatacept [Song *et al.* 2011]. The result is similar to the placebo response reported in the ASSERT and ATLAS trials. More recently, Lekpa and colleagues, in an open-label study performed for 6 months, showed the lack of strong efficacy of abatacept in axial SpA [Lekpa *et al.* 2012b].

Furthermore, only in a case report was a patient with active SpA successfully treated with abatacept. This patient had disease refractory to TNFα inhibitors and all outcome measures including MRI, BASDAI, BASFI and inflammatory markers showed an improvement [Olivieri *et al.* 2009].

Tocilizumab and sarilumab (interleukin-6 receptor inhibitors)

One open-label study failed to demonstrate any clinical improvement in patients with axial SpA treated with tocilizumab [Lekpa *et al.* 2012a]. Dudler and Aubry-Rozier studied 18 patients with axial SpA refractory to anti-TNFα therapy and treated with tocilizumab 8 mg/kg/month [Dudler and Aubry-Rozier, 2011]. Of these 18 patients, 9 had classical AS, 6 had undifferentiated SpA and 3 were affected by PsA. Five out of the eight patients who fulfilled the modified New York criteria discontinued treatment due to the lack of improvement. Neutropenia occurred in four patients (22.4%), while a similar proportion developed abnormal liver function tests; 27.7% and 16.6% had high levels of low-density lipoprotein and triglycerides, respectively. Infections occurred in three patients. After the third infusion, there was an improvement in both erythrocyte sedimentation rate (ESR) and CRP. Recently, Sieper and colleagues demonstrated that there was no difference between patients with AS treated with tocilizumab or placebo at 12 weeks, although a reduction of CRP levels was observed in the tocilizumab arm [Sieper *et al.* 2014c]. However, the fall in inflammatory markers was not associated with any clinical improvement.

Sarilumab, a human immunoglobulin G1 that targets the interleukin-6 (IL6) receptor is currently in two phase III studies as a treatment for RA (RA-MOBILITY study). A phase III study was started in June 2010 to evaluate the long-term safety and efficacy of sarilumab in patients with AS; it was stopped due to lack of improvement in efficacy [Sieper *et al.* 2012].

Rituximab

The efficacy of rituximab needs to be examined in a larger randomized placebo-controlled trial with longer duration of follow up. The biggest experience is by Song and colleagues who performed an open-label study in which 20 patients with active AS were treated with two pulses of rituximab separated by 2 weeks [Song *et al.* 2010]. Of these 20 patients, 10 were TNFα inhibitor naive. At 6 months, 40% achieved ASAS-20 and BASDAI-20, while 25% were ASAS-40 and BASDAI-50 responders. Patients who were TNFα inhibitor naive were found to be better responders, with 50% and 60% achieving ASAS-20 and BASDAI-20 respectively. There were no new safety signals during the study. The positive response observed in the patients who were TNFα inhibitor naive was similar to that reported in patients with AS treated with infliximab [van der Heijde *et al.* 2005], etanercept [Davis *et al.* 2003] and adalimumab [van der Heijde *et al.* 2006]. However, a French study of eight patients with SpA receiving rituximab showed less favorable outcomes [Nocturne *et al.* 2010].

Another observational study reported moderate efficacy in SpA that was more marked in patients who were TNFα inhibitor naive [Wendling *et al.* 2012].

Secukimumab

Baeten and colleagues conducted a study on 30 patients with AS who were assigned randomly to receive secukinumab (2 × 10 mg/kg) or placebo infusion given 3 weeks apart [Baeten *et al.* 2013]. At 6 weeks, 61% of patients receiving secukinumab achieved ASAS-20 compared with 17% of patients treated with placebo. Thirty-five percent of patients treated with secukinumab achieved ASAS-40 and ASAS-5/6 responses respectively. This randomized controlled trial with short duration of follow up showed that secukinumab was clinically effective. However, the efficacy needs to be confirmed in a larger randomized placebo-controlled trial with longer duration of follow up.

Ustekinumab

Ustekinumab is a fully human immunoglobulin monoclonal antibody against a common subunit of IL12 and IL23, approved for patients with moderate to severe plaque psoriasis. Six large clinical trials have shown ustekinumab to be an excellent drug in the management of psoriasis [Gottlieb and Narang, 2013], reporting only few moderate adverse events (i.e. upper respiratory infection, liver enzyme increase or neutropenia). In addition, ustekinumab significantly improved active PsA compared with placebo, and might offer an alternative therapeutic mechanism of action to approved biological treatments [McInnes *et al.* 2013]. Recently, in an open-label clinical trial, ustekinumab was associated with a reduction in signs and symptoms in active AS. In this study, ASAS-20, ASAS-5/6 and ASAS-40 were reached in 75%, 50% and 65% of the patients respectively. Moreover, a significant improvement in other patient-reported outcome parameters and active inflammation as detected by MRI, as well as a significant reduction of NSAID intake, occurred during ustekinumab treatment. Furthermore, ustekinumab was well tolerated [Poddubnyy *et al.* 2014].

Apremilast

Apremilast is an orally available small molecule that specifically targets phosphodiesterase 4. Its effect on lipopolysaccharide-stimulated human peripheral blood mononuclear cells demonstrated a reduction in the number of cytokines, including interferon γ, TNFα, IL12 and IL23 [Palfreeman *et al.* 2013]. Apremilast has been tested in a number of psoriasis, PsA pilot study and phase II trials in order to evaluate its efficacy and safety. More recently, larger double-blind and randomized multicenter studies demonstrated that apremilast is effective in the treatment of psoriasis, PsA and AS, with significantly higher numbers of patients treated with apremilast achieving endpoints compared with baseline [Schett *et al.* 2012; Pathan *et al.* 2013].

Anakinra

Anakinra is an IL1 receptor antagonist currently approved for patients with active RA and it is useful in many rheumatic inflammatory diseases. There are no large trials evaluating its role in SpA but, among available data, some reports showed a clinical benefit only in a small number of treated patients, without MRI improvement. In these studies, carried out in patients with PsA [Jung *et al.* 2010] and AS [Haibel *et al.* 2005; Bennett *et al.* 2008], adverse events were mainly mild and the most frequent were injection site reactions.

Conclusion

In axial SpA, TNFα inhibitor therapy is currently the only effective therapy for patients with disease

that has failed to respond to conventional therapy [Sieper, 2012], although these drugs show different side effects [Peluso *et al.* 2013].

TNFα inhibitor treatment is more effective at preventing articular damage in peripheral joints than in axial ones. It is important to treat patients at an early stage of disease to reduce disease progression; moreover it is necessary to identify causes of therapy inefficacy in preventing joint damage in axial subsets [Barr and Keat, 2010].

Furthermore, although encouraging results from the study of new molecules are in many subtypes of SpA, there is a need for larger and longer studies with imaging results to confirm their efficacy, safety and utility in SpA.

Conflict of interest statement

All the authors revised and approved the present version of this manuscript. No funding and economic support have been received to perform this study. Professor Raffaele Scarpa did not receive specific funding for the preparation of this manuscript. During the last 5 years he served on advisory boards and received honoraria and grants for research unrelated to this study. The other authors have nothing to declare.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

Amor, B., Dougados, M. and Mijiyawa, M. (1990 [Criteria of the classification of spondylarthropathies]. *Rev Rhum Mal Osteoartic* 57: 85–89.

Anderson, J., Baron, G., van der Heijde, D., Felson, D. and Dougados, M. (2001) Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum* 44: 1876–1886.

Arends, S., Brouwer, E., van der Veer, E., Groen, H., Leijsma, M., Houtman, P. *et al.* (2011) Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: prospective longitudinal observational cohort. *Arthritis Res Ther* 13: R94.

Atteno, M., Peluso, R., Costa, L., Padula, S., Iervolino, S., Caso, F. *et al.* (2010) Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. *Clin Rheumatol* 29: 399–403.

Baeten, D., Baraliakos, X., Braun, J., Sieper, J., Emery, P., van der Heijde, D. *et al.* (2013) Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 382: 1705–1713.

Baraliakos, X., Haibel, H., Fritz, C., Listing, J., Heldmann, F., Braun, J. *et al.* (2013a) Long-term outcome of patients with active ankylosing spondylitis with etanercept-sustained efficacy and safety after seven years. *Arthritis Res Ther* 15: R67.

Baraliakos, X., Haibel, H., Listing, J., Sieper, J. and Braun, J. (2013b) Continuous long-term anti-TNF therapy does not lead to an increase in the rate of new bone formation over 8 years in patients with ankylosing spondylitis. *Ann Rheum Dis* 27 March 2013 (Epub ahead of print).

Baraliakos, X., Listing, J., Fritz, C., Haibel, H., Alten, R., Burmester, G. *et al.* (2011) Persistent clinical efficacy and safety of infliximab in ankylosing spondylitis after 8 years – early clinical response predicts long-term outcome. *Rheumatology (Oxford)* 50: 1690–1699.

Baraliakos, X., van den Berg, R., Braun, J. and van der Heijde, D. (2012) Update of the literature review on treatment with biologics as a basis for the first update of the ASAS/EULAR management recommendations of ankylosing spondylitis. *Rheumatology (Oxford)* 51: 1378–1387.

Barr, A. and Keat, A. (2010) Spondyloarthritides: evolving therapies. *Arthritis Res Ther* 12: 221.

Barra, L., Pope, J. and Payne, M. (2009) Real-world anti-tumor necrosis factor treatment in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: cost-effectiveness based on number needed to treat to improve health assessment questionnaire. *J Rheumatol* 36: 1421–1428.

Bennett, A., Tan, A., Coates, L., Emery, P., Marzo-Ortega, H. and McGonagle, D. (2008) Sustained response to anakinra in ankylosing spondylitis. *Rheumatology (Oxford)* 47: 223–224.

Braun, J., Baraliakos, X., Listing, J., Davis, J., van Der Heijde, D., Haibel, H. *et al.* (2007) Differences in the incidence of flares or new onset of inflammatory bowel diseases in patients with ankylosing spondylitis exposed to therapy with anti-tumor necrosis factor alpha agents. *Arthritis Rheum* 57: 639–647.

Braun, J., Baraliakos, X., Listing, J. and Sieper, J. (2005) Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum* 52: 2447–2451.

Brodszky, V., Pentek, M. and Gulacsi, L. (2008) Efficacy of adalimumab, etanercept, and infliximab in psoriatic arthritis based on ACR50 response after 24 weeks of treatment. *Scand J Rheumatol* 37: 399–400.

Costa, L., Caso, F., D'Elia, L., Atteno, M., Peluso, R., Del Puente, A. *et al.* (2012) Psoriatic arthritis is associated with increased arterial stiffness in the absence of known cardiovascular risk factors: a case control study. *Clin Rheumatol* 31: 711–715.

Davis, J. Jr, Van Der Heijde, D., Braun, J., Dougados, M., Cush, J., Clegg, D. *et al.* (2003) Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized controlled trial. *Arthritis Rheum* 48: 3230–3236.

Denmark, V. and Mayer, L. (2013) Current status of monoclonal antibody therapy for the treatment of inflammatory bowel disease: an update. *Expert Rev Clin Immunol* 9: 77–92.

De Vries, M., Wolbink, G., Stapel, S., de Groot, E., Dijkmans, B., Aarden, L. *et al.* (2007) Inefficacy of infliximab in ankylosing spondylitis is correlated with antibody formation. *Ann Rheum Dis* 66: 133–134.

Di Minno, M., Iervolino, S., Peluso, R., Scarpa, R. and Di Minno, G. (2012) TNF-α blockers and carotid intima-media thickness: an emerging issue in the treatment of psoriatic arthritis. *Intern Emerg Med* 7(Suppl. 2): 97–98.

Di Minno, M., Iervolino, S., Peluso, R., Scarpa, R. and Di Minno, G.; CaRRDs Study Group (2011) Carotid intima-media thickness in psoriatic arthritis: differences between tumor necrosis factor-α blockers and traditional disease-modifying antirheumatic drugs. *Arterioscler Thromb Vasc Biol* 31: 705–712.

Dudler, J. and Aubry-Rozier, B. (2011) Tocilizumab in axial spondyarthropathies. *Ann Rheum Dis* 70(Suppl. 3): 128.

Dougados, M., van der Linden, S., Juhlin, R., Huitfeldt, B., Amor, B., Calin, A. *et al.* (1991) The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 34: 1218–1227.

Fagerli, K., Lie, E., van der Heijde, D., Heiberg, M., Lexberg, A., Rødevand, E. *et al.* (2014) The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. *Ann Rheum Dis* 73: 132–137.

Gladman, D. (2008) Adalimumab, etanercept and infliximab are equally effective treatments for patients with psoriatic arthritis. *Nat Clin Pract Rheumatol* 4: 510–511.

Glintborg, B., Hansen, M., Østergaard, M., Dreyer, L., Rifbjerg-Madsen, S., Krogh, N. *et al.* (2011) Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti–tumor necrosis factor therapy. *Arthritis Rheum* 3: 382–390.

Gottlieb, A. and Narang, K. (2013) Ustekinumab in the treatment of psoriatic arthritis: latest findings and clinical potential. *Ther Adv Musculoskelet Dis* 5: 277–285.

Gratacos, J., Casado, E., Real, J. and Torre-Alonso, J. (2007) Prediction of major clinical response (ACR50) to infliximab in psoriatic arthritis refractory to methotrexate. *Ann Rheum Dis* 66: 493–497.

Guignard, S., Gossec, L., Salliot, C., Ruyssen-Witrand, A., Luc, M., Duclos, M. *et al.* (2006) Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. *Ann Rheum Dis* 65: 1631–1634.

Haibel, M., Rudwaleit, M., Listing, J. and Sieper, J. (2005) Open label trial of anakinra in active ankylosing spondylitis over 24 weeks. *Ann Rheum Dis* 64: 296–298.

Haibel, H., Rudwaleit, M., Listing, J., Heldmann, F., Wong, R., Kupper, H. *et al.* (2008) Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum* 58: 1981–1991.

Hanauer, S., Feagan, B., Lichtenstein, G., Mayer, L., Schreiber, S., Colombel, J. *et al.* (2002) Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 359: 1541–1549.

Haroon, N., Inman, R., Learch, T., Weisman, M., Lee, M., Rahbar, M. *et al.* (2013) The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. *Arthritis Rheum* 65: 2645–2654.

Hoy, S. and Scott, L. (2007) Etanercept: a review of its use in the management of ankylosing spondylitis and psoriatic arthritis. *Drugs* 67: 2609–2633.

Iervolino, S., Di Minno, M., Peluso, R., Lofrano, M., Russolillo, A., Di Minno, G. *et al.* (2012) Predictors of early minimal disease activity in patients with psoriatic arthritis treated with tumor necrosis factor-α blockers. *J Rheumatol* 39: 568–573.

Jung, N., Hellmann, M., Hoheisel, R., Lehmann, C., Haase, I., Perniok, A. *et al.* (2010) An open-label pilot study of the efficacy and safety of anakinra in patients with psoriatic arthritis refractory to or intolerant of methotrexate (MTX). *Clin Rheumatol* 29: 1169–1173.

Kary, S., Worm, M., Audring, H., Huscher, D., Renelt, M., Sorensen, H. *et al.* (2006) New onset or exacerbation of psoriatic skin lesions in patients with definite rheumatoid arthritis receiving tumour necrosis factor alpha antagonists. *Ann Rheum Dis* 65: 405–407.

Kobak, S., Oksel, F., Kabasakal, Y. and Doganavsargil, E. (2007) Ankylosing spondylitis-related secondary amyloidosis responded well to etanercept: a report of three patients. *Clin Rheumatol* 26: 2191–2194.

Landewé, R., Braun, J., Deodhar, A., Dougados, M., Maksymowych, W., Mease, P. *et al.* (2014) Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled phase 3 study. *J Ann Rheum Dis* 73: 39–47.

Lekpa, F., Poulain, C., Wendling, D., Soubrier, M., De Bandt, M., Berthelot, J. *et al.* (2012a) Is IL-6 an appropriate target to treat spondyloarthritis patients refractory to anti-TNF therapy? A multicenter retrospective observational study. *Arthritis Res Ther* 14: R53.

Lekpa, F., Farrenq, V., Canouï-Poitrine, F., Paul, M., Chevalier, X., Bruckert, R. *et al.* (2012b) Lack of efficacy of abatacept in axial spondylarthropathies refractory to tumor-necrosis-factor inhibition. *Joint Bone Spine* 79: 47–50.

Levy-Clarke, G. and Nussenblatt, R. (2006) Does anti-TNF therapy decrease the incidence of anterior uveitis in patients with ankylosing spondylitis? *Nat Clin Pract Rheumatol* 2: 72–73.

Maksymowych, W., Morency, N., Conner-Spady, B. and Lambert, R. (2013) Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: evidence for a window of opportunity in disease modification. *Ann Rheum Dis* 72: 23–28.

McInnes, I., Kavanaugh, A., Gottlieb, A., Puig, L., Rahman, P., Ritchlin, C. *et al.* (2013) Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 382: 780–789.

Mease, P. (2013) Methotrexate in psoriatic arthritis. *Bull Hosp Jt Dis* 71: S41–S45.

Migliore, A., Broccoli, S., Bizzi, E. and Laganà, B. (2012) Indirect comparison of the effects of anti-TNF biological agents in patients with ankylosing spondylitis by means of a mixed treatment comparison performed on efficacy data from published randomised, controlled trials. *J Med Econ* 15: 473–480.

Mirjam, K., De Vries, M., Van Eijk, I., Nurmohamed, M., Wolbink, G., Van Der Horst-Bruinsma, I. *et al.* (2009) Levels of ESR, CRP, and SAA and anti-TNF therapy in AS patients. *Arthritis Rheum* 61: 1484–1490.

Miserocchi, E., Modorati, G., Pontikaki, I., Meroni, P. and Gerloni, V. (2013) Long-term treatment with golimumab for severe uveitis. *Ocul Immunol Inflamm* 21 October 2013 (Epub ahead of print).

Moll, J., Haslock, I., Macrae, I. and Wright, V. (1974) Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. *Medicine (Baltimore)* 53: 343–364.

Nocturne, G., Dougados, M., Constantin, A., Richez, C., Sellam, J., Simon, A. *et al.* (2010) Rituximab in the spondyloarthropathies: data of eight patients followed up in the French Autoimmunity and Rituximab (AIR) registry. *Ann Rheum Dis* 69: 471–472.

Nouijai, A., Mounach, A., Ghozlani, I., Achemlal, L., Bezza, A. and El Maghraoui, A. (2009) Fibrosing alveolitis after treatment of rheumatoid arthritis by infliximab. *Presse Med* 38: 17–20.

Olivieri, I., D'Angelo, S., Mennillo, G., Pistone, G., Scarano, E. and Padula, A. (2009) Abatacept in spondyloarthritis refractory to tumour necrosis factor alpha inhibition. *Ann Rheum Dis* 68: 151–152.

Ostor, A., Crisp, J., Somerville, M. and Scott, D. (2004) Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. *BMJ* 329: 1266.

Palfreeman, A., McNamee, K. and McCann, F. (2013) New developments in the management of psoriasis and psoriatic arthritis: a focus on apremilast. *Drug Des Devel Ther* 7: 201–210.

Pathan, E., Abraham, S., Van Rossen, E., Withrington, R., Keat, A., Charles, P. *et al.* (2013) Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis. *Ann Rheum Dis* 72: 1475–1480.

Pedersen, S., Weber, U. and Ostergaard, M. (2012) The diagnostic utility of MRI in spondyloarthritis. *Best Pract Res Clin Rheumatol* 26: 751–766.

Peluso, R., Di Minno, M., Bruner, V., Soscia, E., Castiglione, F., Manguso, F. *et al.* (2012) Discovertebral erosions in patients with enteropathic spondyloarthritis. *J Rheumatol* 39: 2332–2340.

Peluso, R., Cafaro, G., Di Minno, A., Iervolino, S., Ambrosino, P., Lupoli, G. *et al.* (2013) Side effects of TNF-α blockers in patients with psoriatic arthritis: evidences from literature studies. *Clin Rheumatol* 32: 743–753.

Poddubnyy, D., Hermann, K., Callhoff, J., Listing, J. and Sieper, J. (2014) Ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS). *Ann Rheum Dis* 3 January 2014 (Epub ahead of print).

Poddubnyy, D. and Rudwaleit, M. (2013) Adalimumab for the treatment of ankylosing spondylitis and nonradiographic axial

spondyloarthritis – a five-year update. *Expert Opin Biol Ther* 13: 1599–1611.

Ritchlin, C., Kavanaugh, A., Gladman, D., Mease, P., Helliwell, P., Boehncke, W. *et al.* (2009) Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis* 68: 1387–1394.

Rudwaleit, M., Rodevand, E., Holck, P., Vanhoof, J., Kron, M., Kary, S. *et al.* (2009a) 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* 68: 696–701.

Rudwaleit, M., van der Heijde, D., Landewé, R., Akkoc, N., Brandt, J., Chou, C. *et al.* (2011) The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 7: 25–31.

Rudwaleit, M., van der Heijde, D., Landewé, R., Listing, J., Akkoc, N., Brandt, J. *et al.* (2009b) The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 68: 777–783.

Rutgeerts, P., Sandborn, W., Feagan, B., Reinisch, W., Olson, A., Johanns, J. *et al.* (2005) Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 353: 2462–2476.

Sandborn, W., Hanauer, S., Katz, S., Safdi, M., Wolf, D., Baerg, R. *et al.* (2001) Etanercept for active Crohn's disease: a randomized, double-blind, placebo controlled trial. *Gastroenterology* 121: 1088–1094.

Sandborn, W., Rutgeerts, P., Enns, R., Hanauer, S., Colombel, J., Panaccione, R. *et al.* (2007) Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 146: 829–838.

Sanduzzi, A., Bocchino, M., Atteno, M., Costa, L., Ponticiello, A., Matarese, A. *et al.* (2012) Screening and monitoring of latent tubercular infection in patients taking tumor necrosis factor-α blockers for psoriatic arthritis. *J Rheumatol Suppl* 89: 82–85.

Schett, G., Wollenhaupt, J., Papp, K., Joos, R., Rodrigues, J., Vessey, A. *et al.* (2012) Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 64: 3156–3167.

Sieper, J. (2012) Developments in therapies for spondyloarthritis. *Nat Rev Rheumatol* 8: 280–287.

Sieper, J., Inman, R. and Badalamenti, S. (2012) Sarilumab for the treatment of ankylosing spondylitis: results of a phase 2, randomized, double-blind, placebo-controlled, international study (ALIGN). *Ann Rheum Dis* 71(Suppl. 3): 111.

Sieper, J., Lenaerts, J., Wollenhaupt, J., Rudwaleit, M., Mazurov, V., Myasoutova, L. *et al.* (2014a) Maintenance of biologic-free remission with naproxen or no treatment in patients with early, active axial spondyloarthritis: results from a 6-month, randomised, open-label follow-up study, INFAST part 2. *Ann Rheum Dis* 73: 108–113.

Sieper, J., Lenaerts, J., Wollenhaupt, J., Rudwaleit, M., Mazurov, V., Myasoutova, L. *et al.* (2014b) Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, part 1. *Ann Rheum Dis* 73: 101–107.

Sieper, J., Porter-Brown, B., Thompson, L., Harari, O. and Dougados, M. (2014c) Assessment of short-term symptomatic efficacy of tocilizumab in ankylosing spondylitis: results of randomised, placebo-controlled trials. *Ann Rheum Dis* 73: 95–100.

Sieper, J., van der Heijde, D., Dougados, M., Mease, P., Maksymowych, W., Brown, M. *et al.* (2013) Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 72: 815–822.

Song, I., Appel, H., Haibel, H., Loddenkemper, C., Braun, J., Sieper, J. *et al.* (2008) New onset of Crohn's disease during treatment of active ankylosing spondylitis with etanercept. *J Rheumatol* 35: 532–536.

Song, I., Heldmann, F., Rudwaleit, M., Haibel, H., Weiss, A., Braun, J. *et al.* (2011) Treatment of active ankylosing spondylitis with abatacept: an open-label, 24-week pilot study. *Ann Rheum Dis* 70: 1108–1110.

Song, I., Heldmann, F., Rudwaleit, M., Listing, J., Appel, H., Braun, J. *et al.* (2010) Different response to rituximab in tumor necrosis factor blocker naive patients with active ankylosing spondylitis and in patients in whom tumor necrosis factor blockers have failed: a twenty-four-week clinical trial. *Arthritis Rheum* 62: 1290–1297.

Song, I. and Rudwaleit, M. (2013) Certolizumab pegol in axial spondyloarthritis. *Expert Rev Clin Immunol* 9: 1161–1172.

Song, I., Weib, A., Hermann, K., Haibel, H., Althoff, C., Poddubnyy, D. *et al.* (2013) Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. *Ann Rheum Dis* 7: 823–825.

Soriano, E. (2012) The actual role of therapy with traditional disease-modifying antirheumatic drugs in psoriatic arthritis. *J Rheumatol Suppl* 89: 67–70.

Soscia, E., Scarpa, R., Cimmino, M., Atteno, M., Peluso, R., Sirignano, C. *et al.* (2009) Magnetic

resonance imaging of nail unit in psoriatic arthritis. *J Rheumatol Suppl* 83: 42–45.

Tracey, D., Klareskog, L., Sasso, E., Salfeld, J. and Tak, P. (2008) Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther* 117: 244–279.

van der Heijde, D., Dijkmans, B., Geusens, P., Sieper, J., DeWoody, K., Williamson, P. *et al.* (2005) Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 52: 582–591.

van der Heijde, D., Fleischmann, R., Wollenhaupt, J., Deodhar, A., Kielar, D., Woltering, F. *et al.* (2014) Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol. *Ann Rheum Dis* 73: 233–237.

van der Heijde, D., Kivitz, A., Schiff, M., Sieper, J., Dijkmans, B., Braun, J. *et al.* (2006) Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, doubleblind, placebo-controlled trial. *Arthritis Rheum* 54: 2136–2146.

van der Horst-Bruinsma, I. and Nurmohamed, M. (2012) Management and evaluation of extra-articular manifestations in spondyloarthritis. *Ther Adv Musculoskelet Dis* 4: 413–422.

van der Horst-Bruinsma, I., Van Denderen, J., Visman, I., Suttorp-Schulten, M., Dijkmans, B. and Nurmohamed, M. (2010) Decreased recurrence rate of anterior uveitis in ankylosing spondylitis treated with adalimumab – an interim analysis. *Clin Exp Rheumatol* 28: 630.

Wendling, D., Balblanc, J., Briancon, D., Brousse, A., Lohse, A., Deprez, P. *et al.* (2008) Onset or exacerbation of cutaneous psoriasis during TNFalpha antagonist therapy. *Joint Bone Spine* 75: 315–318.

Wendling, D., Dougados, M., Berenbaum, F., Brocq, O., Schaeverbeke, T., Mazieres, B. *et al.* (2012) Rituximab treatment for spondyloarthritis. A nationwide series: data from the AIR registry of the French Society of Rheumatology. *J Rheumatol* 39: 2327–2331.