Review

Etanercept in spondyloarthropathies. Part I: current evidence of efficacy

C. Palazzi[1], S. D'Angelo[1,2], F. Cantini[3], E. Lubrano[4], A. Marchesoni[5], A. Mathieu[6], C. Salvarani[7], R. Scarpa[8], A. Spadaro[9], I. Olivieri[1]

[1]Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera; [2]Department of Health Sciences, University of Molise, Campobasso; [3]Rheumatology Unit, 2nd Division of Medicine, Prato Hospital, Prato; [4]Academic Rheumatology Unit, Department of Health Science, University of Molise, Campobasso, Italy; [5]UOC Day Hospital di Reumatologia, Istituto Ortopedico G. Pini, Milano; [6]Chair of Rheumatology, Department of Medical Sciences, University of Cagliari, Cagliari; [7]Rheumatology Unit, "Arcispedale S. Maria Nuova", Reggio Emilia; [8]Academic Rheumatology Unit, University of Naples Federico II, Napoli; [9]Department of Internal Medicine and Medical Specialties, Division of Rheumatology, "Sapienza" University of Rome Roma, Italy.

Carlo Palazzi, MD
Salvatore D'Angelo, MD
Fabrizio Cantini, MD
Ennio Lubrano, MD
Antonio Marchesoni, MD
Alessandro Mathieu, MD
Carlo Salvarani, MD
Raffaele Scarpa, MD
Antonio Spadaro, MD
Ignazio Olivieri, MD

Please address correspondence to:
Dr Ignazio Olivieri,
Rheumatology Department of Lucania,
San Carlo Hospital,
Contrada Macchia Romana,
85100 Potenza, Italy.
E-mail: i.olivieri@ospedalesancarlo.it

Received on April 16, 2011; accepted in revised form on July 11, 2011.

Clin Exp Rheumatol 2011; 29: 858-864.

Key words: etanercept, spondiloarthropathies, efficacy, ankylosing spondylitis, psoriatic arthritis

Competing interests: none declared.

ABSTRACT

Etanercept is a recombinant soluble tumour necrosis factor alpha receptor administered subcutaneously at the dose of 50 mg weekly (or 25 mg/twice weekly) for the treatment of the main chronic arthritides: rheumatoid arthritis and spondyloarthropathies. It shows high qualities in terms of efficacy and manageability. Favourable results were reported in all localisations of spondyloarthropathies: axial disease, peripheral arthritis, and enthesitis. In particular, several studies demonstrated its efficacy on the clinical and functional indicators of ankylosing spondylitis. Similar data were also reported for psoriatic arthritis in which, in addition, a significant reduction in the progression of erosive damages was widely described. Furthermore, although only a few studies are available, very interesting results have been obtained in patients suffering from undifferentiated spondyloarthropathies and severe enthesitis.

Introduction

The availability of anti-tumour necrosis factor alpha (TNF-α) drugs revolutionised the treatment of the most important inflammatory arthropathies: rheumatoid arthritis (RA) and spondyloarthropathies (SpA) (1). In SpA, they uniquely allow to treat the axial involvement and to reduce the progression of the erosive damage of peripheral joints. Moreover, their action on all musculoskeletal symptoms of SpA is much more satisfactory when compared with previously used drugs. Although anti-TNF-α agents lead to regression of active inflammatory lesions of the spine, as detected by MRI, long-term follow-up studies are needed in order to investigate the prevention of spinal structural damage.

ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis as also ASAS/EULAR recommendations for the management of ankylosing spondylitis have been recently published (2, 3).

Among anti-TNF-α agents, etanercept (ETN) is a molecule administered subcutaneously at the dose of 50 mg weekly (or 25 mg/twice weekly) that shows interesting peculiarities. In the present review, we have summarised the main aspects concerning the efficacy of ETN in the SpA therapy.

ETN, a recombinant soluble TNF receptor, is a fusion protein composed of two extracellular domains of the human p75-TNF-receptor (sTNFRII), linked to the Fc portion of human IgG1 (4, 5).The mechanisms of action of ETN include blockade of TNFR and induction of transmembrane-TNF mediated process. In fact, the two sTNFRII arms of ETN bind two of the three receptor-binding sites on the TNF trimer in a 1:1 ratio, leaving the third receptor binding site open (5, 6). This feature and the fast association/dissociation rates of the p75-TNF-receptor with TNF-α suggest that ETN may only transiently neutralise the activity of an individual TNF molecule (7). Concerning the mechanism of action of ETN on bone and cartilage damage it must be considered that the role of TNF may be different in diseases in which the damage is predominantly proliferative (*i.e.* ankylosing spondylitis) or destructive (*i.e.* RA). However, ETN generally showed beneficial effects on biological markers of cartilage degradation/turnover in SpAs (8).

Efficacy of etanercept in ankylosing spondylitis

The therapeutic role of ETN in ankylosing spondylitis (AS) was primarily

Table I. Main studies concerning etanercept 25 mg/twice weekly in AS.

Studies	Significant response
ETN *vs*. PL, RCT (13) (4 months, 40 Pts) OLE (6 months) (14)	ASAS 20
ETN *vs*. PL, RCT (15) (6 months, 30 Pts)	ASAS 20; BASDAI; BASFI; BASMI
ETN *vs*. PL, RCT (16) (24 weeks, 277 Pts) OLE (192 weeks) (18)	ASAS 20, 50, 70
ETN *vs*. PL, RCT (19) (12 weeks, 84 Pts) OLE (96 weeks) (20)	ASAS 20
ETN *vs*. SSZ, RCT (21) (16 weeks, 566 Pts)	ASAS 20, 40, 5/6; BASDAI; BASFI; BASMI

AS: ankylosing spondylitis; ETN: etanercept; PL: placebo; Pts: patients; OLE: open-label extension; RCT: randomized clinical trials; SSZ: sulphasalazine.

assessed through the evaluation of its efficacy on symptoms defined as 20% or greater improvement of Assessments in Ankylosing Spondylitis Working Group (ASAS) response, and separate analyses of individual ASAS items including the acute-phase reactants, the inflammation degree as expressed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the mobility by the Bath Ankylosing Spondylitis Metrology Index (BASMI), and the functional status by the Bath Ankylosing Spondylitis Functional Index (BASFI) (9-12).

Five randomised clinical trials (RCTs) have provided evidence of efficacy and safety of ETN 25 mg/twice weekly subcutaneously in the treatment of active AS (Table I). The first, historical RCT was published in 2002 (13). In this 4-month study, 40 patients with long-standing, active AS were randomised in a 1:1 ratio to receive twice weekly subcutaneous injections of ETN 25 mg or placebo. The ASAS 20 response rate at month 4 was 80% in the ETN group and 30% in the placebo group (p=0.004) with significant improvement of all secondary outcome measures in the active treatment arm. A 6-month, open-label extension of the study demonstrated a prompt response to ETN in 18 patients previously allocated in the placebo and a sustained response in 18 patients of study drug group (14). In June 2003, another single-centre, 6-month, double-blind, placebo-controlled trial on 30 AS patients confirmed the short-term efficacy of ETN with 78% ASAS 20 response rate (15). The drug was rapidly effective reaching statistical significance compared to placebo at the 6th week of treatment. All secondary outcome measures including BASDAI, BASFI and BASMI improved significantly. Five months later, a 24-week, multicentre, randomised, double-blind, placebo-controlled trial performed in the US confirmed the efficacy of ETN on a larger number (277) of AS patients (16). At week 24, 57% of ETN group versus 22% of controls (p<0.0001) achieved the ASAS 20 response. In the active study group, the ASAS 50 and 70 responses were achieved in 40% and 20% of patients respectively with a statistically significant difference compared to the placebo group. After the first 24-week controlled phase, also the placebo group patients received ETN in an open-label extension study. After 96 weeks the proportion of patients achieving the ASAS 20 response had increased to 78% demonstrating the sustained durability and tolerability of the treatment (17). The results of a 192-week study extension have been recently published and show an impressive durability of efficacy and tolerability of ETN with 81% of patients maintaining the ASAS 20 response (18). In a multicentre, double-blind, randomised, 12-week study 45 patients received ETN 25 mg/twice weekly/subcutaneously and 39 received placebo (19). At week 12 significantly more ETN patients (60%) than placebo patients (23%) (p<0.001) were ASAS 20 responders, with simultaneous significant improvement of functional status and metrology. Recently, a 96-week open-label extension of this study has been published confirming the long-term efficacy and tolerability of ETN in AS patients (20). The fifth RCT was a 16-week, randomised, double-blind study designed to compare the efficacy of ETN and sulphasalazine (SSZ) in 566 patients with AS. The proportion of ASAS 20 responders was greater (p<0.001) in the ETN group compared to the SSZ group from week 2. At week 16, an ASAS 20 response was observed in 75.5% of ETN-treated patients and in 51.3% of SSZ-treated patients (p<0.001). ASAS 40, ASAS 5/6, partial remission for AS, BASFI, BASDAI, BASMI, nocturnal back pain, and modified Schober's were all improved (p<0.001) in the ETN group compared with the SSZ group at all time points (21). Data from the Czech national registry ATTRA concerning AS patients, showed that the proportion of patients with a BASDAI <4 was higher in the ETN group in comparison with infliximab (IFX) group (p 0.001) (22).

Similarly to what was observed in RA, also in AS, a 12-week RCT demonstrated comparable results in terms of efficacy when ETN was administered either as 50 mg/once weekly or as 25 mg/twice weekly (23-25). Probably due to its low immunogenicity, ETN is efficacious in the long-term and safe after re-administration in patients with AS (26). A recent retrospective analysis performed in a Korean tertiary hospital reported that extending the dosing interval of ETN 25 mg up to 12.1±7.0 days, at 21 months of treatment, the BASDAI continued to decrease (27). An innovative therapeutic approach to AS sacroiliitis was described by Chinese Authors. They obtained good clinical, MRI and SPECT results in 16 AS patients with CT-guided intra-articular injections of ETN 25 mg at 0, 4 and 8 weeks. The long-term efficacy of this treatment remains to be demonstrated (28).

The reduction of inflammation induced by ETN in patients with AS has also been confirmed by MRI examinations (29, 30).

A recent report seems to indicate that ETN therapy, despite its rapid and sustained efficacy on inflammation-related symptoms, does not influence the radiographic progression of AS (31). The long duration of AS, the selection of patients, and the use of a historical

control group have probably negatively influenced the results of this study, and these preliminary findings should be confirmed by properly designed studies on patients with early onset AS. Controlled studies in patients with AS have also demonstrated the efficacy of ETN therapy in improving the health-related quality of life, which directly reflects the reduction of disease activity (32, 33). In a very recent small double-blind placebo-controlled trial enrolling 40 AS patients, the effectiveness of ETN 25 mg twice weekly in improving work instability as measured by the Ankylosing Spondylitis Work Instability Scale (AS-WIS) was reported (34).

Efficacy of etanercept in psoriatic arthritis

The efficacy of ETN in psoriatic arthritis (PsA) has been demonstrated since 2000 in a placebo controlled, randomised trial in which 60 PsA patients received either ETN (25 mg subcutaneously twice a week) or placebo (35). A subgroup of PsA patients (47%) were on methotrexate (MTX) and they were randomly allocated to receive placebo or ETN. The primary arthritis endpoint was the Psoriatic Arthritis Response Criterion (PsARC); the secondary endpoints were the American College of Rheumatology (ACR) 20% improvement criteria (ACR20), and ACR 50 and 70 responses modified for PsA. At week 12 of the study, 87% of ETN treated patients were responders, compared to 23% of those on placebo. In 77% of the patients, the response to ETN was quite rapid, since they were considered responders at 4 weeks. Similar positive responses were noted when ACR 20, 50 and 70 criteria were applied. Furthermore, no statistically significant difference was observed between patients who were receiving MTX and those who were not. In 2004, a multicentre placebo-controlled double-blind trial, involved 205 patients randomly assigned to receive ETN (25 mg subcutaneously twice a week) or placebo for 24 weeks, and then treated with ETN open-label in a 48-week extension phase (36). At 12 weeks ACR20 was achieved by 59% of the patients treated with ETN compared to 15% of those in the placebo group ($p<0.0001$). The same results were obtained for the other clinical outcome measures. Moreover, the primary radiographic endpoint, the annualised rate of change in the modified TSS (total Sharp score) showed at 12 months that the disease progression was inhibited in the ETN group (-0.03 unit) compared to the placebo group, which conversely showed a worsening of disease (+1.00 unit) ($p=0.0001$). Annualised changes in the erosion score and joint space narrowing were also significantly different between groups in favour of ETN. A 26-week observational study measured the efficacy, effectiveness and safety of ETN monotherapy in refractory PsA (37). At week 26, PsARC response was obtained in 85% of the 20 enrolled patients. Effectiveness in the individual patient was demonstrated, since at least 50% of the patients had 90% and 85% improvement in swollen and tender joint count, respectively and 71% improvement in the Health Assessment Questionnaire (HAQ) score. Four patients reached complete remission. In 2006, Mease *et al*. showed the results of an additional 48 weeks, open-label treatment period available to patients originally randomised to ETN or placebo who completed the first phase of the study (38). They found a sustained benefit of ETN treatment, including inhibition of radiographic progression.

The efficacy of ETN, measured in terms of drug survival, was also considered by the Spanish Register BIOBADASER (39). The study, aimed to compare drug survival and safety of IFX, ETN and adalimumab (ADA) in SpA, showed a good efficacy and safety profile of ETN. The South Swedish Arthritis Treatment Group Register showed that patients treated with ETN had about half the risk of discontinuing therapy when compared to IFX ($p=0.01$) (40). Spadaro *et al*. evaluated the cumulative probability of carrying on ETN treatment with or without MTX in a large cohort of 82 patients (41). Clinical peripheral assessment was performed according to the PsARC criteria and axial response was evaluated by the BASDAI. The rate of withdrawals was not significantly different in patients on ETN alone compared to patients treated with the combination ETN plus MTX. The authors concluded that their results did not confirm the previous data obtained by the Swedish register and that ETN can be used with or without MTX. The concomitant use of MTX did not seem a predictor of sustained anti TNF therapy survival in PsA patients.

Recently, more data were obtained from the British Society of Rheumatology Biologics Register, in a study aimed at assessing the persistence on treatment with a first and second course of anti-TNF in a prospective cohort of PsA patients (42). Data were obtained from 566 biologics-naive patients including 316 (55.8%) treated with ETN, 162 (28.6%) with IFX and 88 (15.6%) with ADA. The multivariate Cox proportional hazard model showed that being female [HR 1.3 (95% CI 1.0, 1.7)], having a comorbidity [HR 1.5 (95% CI 2.1, 3.7)] and using IFX rather than ETN [HR 2.8 (95% CI 2.1, 3.7)] were associated with significantly higher overall drug discontinuation rates. Moreover, treatment with IFX was associated with significantly earlier drug discontinuation for inefficacy [adjusted HR 3.8, (95% CI 2.0, 7.3)] as compared to ETN and this is in keeping with data published from the Swedish and Spanish registers.

Very recently, the PRESTA study evaluated the efficacy of two different dose regimens of ETN (50 mg twice a week *vs*. 50 mg once a week) over 12 weeks in patients with both psoriasis and psoriatic arthritis (43). Results showed that ETN 50 mg twice a week compared to ETN 50 mg once a week had similar efficacy on joint manifestations. The step down and the usual dose for psoriasis were equivalent by week 24. At 12 weeks, quality of life, measured by the Dermatology Life Quality Index (DLQI), improved more rapidly with ETN 50 mg twice a week than once a week, but this difference was not significant. Both treatment groups continued to improve and achieved comparable DLQI scores at week 24.

A 3-year open-label, non controlled, prospective study including 32 PsA patients, performed in a dermatological setting, showed the long-term ef-

fectiveness of the unusual ETN dose of 50 twice weekly for 12 weeks followed by 25 mg twice weekly. Twenty-seven subjects completed the study. At week 144, mean disease activity score in 28 joints (DAS-28) decreased from 5.3 to 1.8, while the pain visual analogue scale (pain-VAS) score decreased from 64.2 to 2 (44).

Patients-reported outcomes (PRO) were evaluated in a double-blind comparison to placebo (n=205) followed by a 48-weeks open-label phase (n=169) in which all eligible subjects received ETN. PRO were measured by the HAQ Disability Index (HAQ-D1), the Medical Outcomes Short-Form (SF-26), the EQ-5D VAS, and the ACR patient pain assessment. PsA patients treated with ETN reported a significant improvement in physical function that was almost 10-fold greater than the placebo-related one. Almost 50% of the ETN treated subject showed no disability by the end of this study (45).

In a very recent Italian multicentre observational study, 32 patients with axial manifestations of PsA were treated with ETN. Effectiveness of ETN was observed in 72% of subjects for the BASDAI ($p<0.001$), in 68% for the BASFI ($p<0.001$), in 76% for ESR ($p<0.001$) and in 68% of patients for CRP ($p<0.01$). ACR 20 and 50 was reached in 78 and 56% of patients with peripheral involvement respectively (46).

Etanercept in undifferentiated spondyloarthritides and enthesitis

Undifferentiated spondyloarthritides (uSpA) include forms that do not meet criteria for the established categories of the SpA complex (47). uSpA include incomplete forms of definite entities, the early phase of definite SpA (*i.e.* the pre-radiological phase of sacroiliitis in AS) and forms that remain undifferentiated for a very long time. The clinical spectrum of uSpA is wide and results from various combinations of the clinical and radiological manifestations of SpA. uSpA are as common in men as in women and can occur in every age group.

The first study on ETN in SpA including uSpA patients was published in 2001 (48). In this study SpA patients were treated with 25 mg ETN twice weekly for 6 months. The only patient with uSpA and a disease duration of 8 months remained in clinical remission more than 9 months after stopping ETN, suggesting a potential important role for TNF-α-inhibition in the early disease. In the same study MRI-detectable entheseal lesions were seen in the sacroiliac joints in 6 patients (n=15 lesions), in the lumbar or cervical spine in 9 patients (n=22 lesions), and in peripheral joints in 5 patients (n=7 lesions). Overall, 86% of MRI-detected entheseal lesions either regressed completely or improved. No new lesions developed. In 2004 Brandt *et al*. treated 10 patients with severe and active uSpA with ETN at a dosage of 25 mg twice weekly, for 12 weeks, followed by an observation period of 12 weeks (49). Treatment with ETN resulted in a >50% improvement of the BASDAI (primary outcome variable) in 60% of the patients. The mean BASDAI dropped significantly from 6.1 (range 3.7–9.2) at baseline to 3.5 at week 12 (0.8–8.7; $p=0.01$). Function, spinal pain, peripheral arthritis, enthesitis, quality of life, and acute phase reactants improved similarly. After ETN discontinuation, 2 patients went into longstanding remission. The authors concluded that ETN treatment is effective in patients with severe and active uSpA. They also suggested that the discontinuation of anti-TNF-α therapy may be tried in some patients and that long-term studies are needed to prove that transition to AS may be prevented by early anti-TNF-α treatment. In 2005 Rudwaleit *et al*. published the first study assessing the changes in inflammatory lesions of the spine and the sacroiliac joints as detected by MRI, in patients with uSpA with predominant axial symptoms, during treatment with ETN (30). Twenty-five out of 40 patients (30 suffering from AS and 10 from uSpA) were investigated by MRI of the spine and/or sacroiliac joints that was performed at baseline, after 6 weeks, and after 24 weeks of treatment. The 30 patients with AS were randomly allocated to either ETN or placebo, whereas all 10 patients with uSpA were treated with ETN. By the use of definite short tau inversion recovery (STIR) sequences, significant regression of spinal inflammation was seen already after 6 weeks in the patients treated with ETN, but not in those treated with placebo. Continuous treatment with ETN for 24 weeks reduced active spinal changes by 69%. There was only a trend towards a decrease of active inflammatory lesions of the sacroiliac joint. The conclusion of the study was that ETN leads to significant regression of active inflammatory spine lesions in patients with active AS and uSpA. Flagg *et al*. treated with ETN for 6 months (25 mg subcutaneous twice weekly) 16 patients with undifferentiated or reactive arthritis in a prospective study (50). The 9 patients with undifferentiated arthritis had persistent disease in at least 1 peripheral joint. Five of the 16 patients showed evidence of chlamydial nucleic acid in synovial biopsy samples at some time during the study. Ten of the 16 patients completed the study. Six patients withdrew, but none had worsening of arthritis or infection. Of the 10 completers, 9 could be classified as treatment responders, despite the evidence of bacterial organisms at polymerase chain reaction (PCR) analysis prior to initiating ETN in 3 patients; 2 patients became PCR negative on ETN. Five of the 6 patients with adequate synovial biopsy specimens showed improvement, but not normalisation of histology. In 2007, Olivieri *et al*. described a case of severe HLA-B27-positive heel enthesitis which responded partially and temporarily to ADA but was cured with ETN (51). This report also outlined the possibility of administering treatment for limited periods in this kind of patients. Very recently, Dougados *et al*. performed the first randomised placebo-controlled, double-blind study concerning the treatment with an anti-TNF agent in refractory heel enthesitis proven by MRI (52). In this 12-week study, 24 patients with SpA were enrolled according to Amor's criteria. The primary efficacy endpoint was the normalised net incremental area under the curve (AUC) between randomisation and week 12 for the patient's global assessment (PGA) of disease activity. Secondary endpoints included changes from baseline in PGA, heel pain, the Western Ontario and McMaster Univer-

sities Osteoarthritis index (WOMAC) function subscale and improvement in enthesitis as measured by MRI. Mean normalised net incremental AUC for PGA of disease activity over 12 weeks was significantly greater in the ETN *versus* the placebo group: -28.5 *versus* -11.1, respectively (p=0.029). Significant improvements were also reported for PGA, -37.6 *versus* -11.6 (p=0.007); heel pain, -36.7 *versus* -13.1 (p=0.022); and WOMAC function, -23.2 *versus* -7.8 (p=0.024). No significant changes were observed in the MRI findings between groups.

Etanercept in extra-articular manifestations

The extra-articular involvement in SpA consists of relatively frequent, clinically overt (ocular) or sub-clinical (intestinal) manifestations, and less frequent (cutaneous, renal, pulmonary) or infrequent (cardiac) disease features. At present, there are no controlled, prospective studies with ETN specific in any of the mentioned extra-articular disturbances. However, some data from retrospective or meta-analyses of studies with ETN in SpA are available mainly for ocular involvement and summarised hereafter. Data concerning psoriasis and inflammatory bowel disease (IBD) are not included in the present review.

Anterior uveitis (AU) occurs in about 30% of patients with AS (53,54). This manifestation is associated with the presence of HLA-B27 gene in a wide proportion (50%) of cases (55).

The results of 3 studies on small series of patients, reported by JT Rosenbaum (56), have shown a reduced rate (by about three times) of iritis episodes in AS patients treated with ETN as compared with those receiving placebo (56). In a retrospective analysis, the frequency of episodes of uveitis flares during ETN therapy remained unchanged in comparison with the pre-treatment period (57). Braun *et al*. performed a meta-analysis of the incidence of AU on a total of 717 patients with AS (297 on ETN, 90 on IFX, and 190 without biologicals) during the course of clinical trials with biological agents, 397 of whom were specifically followed up for ocular manifestations (58). They observed that the frequency of flares of AU among patients treated with a biological agent was 6.8 per 100 patient-years (7.9 with ETN and 3.4 with IFX) *versus* 15.6 per 100 patient-years in the placebo group. The difference between the two agents was not significant. It was impossible to exclude that co-medication with effective DMARDs (MTX, SSZ) or corticosteroids could have played a role in reducing the incidence of AU flares in the two subgroups of patients treated with anti-TNF-α drugs. From the global data analysed, a reduction to one quarter and to one half of the expected incidence of AU flares can be expected with IFX and ETN, respectively. Dijckmans *et al*. observed an incidence of 12% of AU episodes in patients undergoing ETN for a 96-weeks treatment as compared with 32% resulting from the pre-therapy clinical history in the same subjects (20). A recent analysis of AU incidence from clinical trials of ETN in AS (4 placebo-controlled, 1 active-controlled, 3 open-label for a total of 1323 subjects) showed that AU rate was lower with ETN than with placebo in the double-blind, placebo-controlled trials (8.6 *vs*. 19.3, p=0.03), and similar to SSZ in the active-controlled trial (10.7 and 14.7, p=0.49) (59). AU was mainly observed in men (83% of AS patients); no study discontinuation was caused by AU and the adverse events were defined as mild or moderate in the 96% of cases.

In contrast with these reports, the prospective investigation of Cobo-Ibanez *et al*. showed a trend towards the increase in AU occurrence on ETN treatment; the study included 4/19 cases of SpAs different from AS (60). Regarding the AU features, in 5 cases the ocular involvement was bilateral. Previously, a review of two spontaneous databases on AU occurrence during TNF-blocking treatments was published by Lim *et al*., supporting the conclusion that the greater number of AU cases observed with ETN may be due to a drug-specific and not a class-dependent effect (61). In the series of 350 SpA patients treated with ETN and retrospectively analysed by Scrivo *et al*., 4 AU flares were observed; 2 of them had AS, and only one was a new onset episode (62). A report by Coates *et al*. on new onset AU during treatment with TNF inhibitors showed that the occurrence of AU in 5 out of 130 AS patients was not restricted to ETN-treated cases, that only 3/5 patients were HLA-B27 positive, and that all but one were females (63). Interestingly, in all patients AU was bilateral. Some of these features may suggest that these cases may refer to a clinical entity distinct from the typical AS-associated AU, possibly related to the therapy with TNF-blockers. The genetic background might contribute to the development of AU occurring in AS patients under anti-TNF alpha treatment. As regards PsA- and IBD-related AU, a retrospective study has been published on 296 patients with SpAs including also PsA and SpA associated with IBD. Interestingly, the incidence of paradoxical adverse effects (AU, psoriasis, IBD) was not significantly lower in the 112 SpA patients not treated with TNF-blocking agents (64).

According to some authors, an AS-associated renal involvement is considered rare and questionable, while others recommend to actively investigate it, since it may be as frequent as 10% of cases (excluding nephrolithiasis); among AS-associated nephropathies, secondary renal amyloidosis is the most common (62% of cases) (65-68). Interestingly, in some cases of amyloidosis secondary to AS, ETN treatment was able to improve both joint and kidney involvement, similarly to what described in some case reports of amyloidosis secondary to RA and other autoimmune inflammatory diseases (69, 70).

Conclusions

The 10-year experience concerning the use of ETN in the SpA field is extremely positive. Favourable results were reported in all localisations of SpA: axial disease, peripheral arthritis, and enthesitis. At present, despite our rather profound knowledge of ETN-therapy, other aspects deserve to be analysed, such as the effect on radiological progression of axial involvement, the temporary treatment for enthesitis, the prolonged dosing interval in patients showing a sustained response and the intra-articular administration of this molecule.

References

1. BRAUN J, KALDEN JR: Biologics in the treatment of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009; 27 (Suppl. 55): S 164-7.
2. VAN DER HEIJDE D, SIEPER J, MAKSYMOWYCH WP *et al*.: for the Assessment of SpondyloArthritis international Society. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011; 70: 905-8.
3. BRAUN J, VAN DEN BERG R, BARALIAKOS X *et al*.: 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011; 70: 896-904.
4. TRACEY D, KLARESKOG L, SASSO EH, SALFELD JG, TAK PP: Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. *Pharmacol Ther* 2008; 117: 244-79.
5. WONG M, ZIRING D, KORIN Y *et al*.: TNF-α blockade in human diseases: Mechanisms and future directions. *Clin Immunol* 2008; 126: 121-36.
6. SANTORA LC, KAYMAKCALAN Z, SAKORAFAS P, KRULL IS, GRANT K: Characterization of noncovalent complexes of recombinant human monoclonal antibody and antigen using cation exchange, size exclusion chromatography, and BIAcore. *Anal Biochem* 2001; 299: 119-29.
7. SCALLON B, CAI A, SOLOWSKI N *et al*.: Binding and functional comparisons of two types of tumor necrosis factor antagonists. *J Pharmacol Exp Ther* 2002; 301: 418-26.
8. HOY SM, SCOTT LJ: Etanercept. A review of its use in the management of ankylosing spondylitis and psoriatic arthritis. *Drugs* 2007; 67: 2609-33.
9. 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.
10. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondilytis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
11. JENKINSON TR, MALLORIE PA, WHITELOCK H, KENNEDY LG, GARRETT S, CALIN A: Defining spinal mobility in ankylosing spondylitis (AS): the Bath AS Metrology Index. *J Rheumatol* 1994; 21: 1694-8.
12. CALIN A, GARRETT S, WHITELOCK H *et al*.: A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994; 21: 2281-5.
13. GORMAN JD, SACK KE, DAVIS JC: Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor α. *N Engl J Med* 2002; 346: 1349-56.
14. DAVIS JC, WEBB A, LUND S, SACK K: Results from an open-label extension study of etanercept in ankylosing spondylitis. *Arthritis Rheum* 2004; 52: 302-4.
15. BRANDT J, KHARIOUZOV A, LISTING J *et al*.: Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum* 2003; 48: 1667-75.
16. DAVIS JC, VAN DER HEIJDE D, BRAUN J *et al*.: Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis. *Arthritis Rheum* 2003; 48: 3230-6.
17. DAVIS JC, VAN DER HEIJDE D, BRAUN J *et al*.: Sustained durability and tolerability of etanercept in ankylosing spondylitis. *Ann Rheum Dis* 2005; 64: 1557-62.
18. DAVIS JC, VAN DER HEIJDE D, BRAUN J *et al*.: Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. *Ann Rheum Dis* 2008; 67: 346-52.
19. CALIN A, DIJKMANS BAC, EMERY P *et al*.: Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. *Ann Rheum Dis* 2004; 63: 1594-600.
20. DIJKMANS BAC, EMERY P, HAKALA M *et al*.: Etanercept in the longterm treatment of patients with ankylosing spondylitis. *J Rheumatol* 2009;36: 1256-64.
21. BRAUN J, HUANG F, BURGOS-VARGAS R *et al*.: Assessment of clinical efficacy in a randomized, double-blind study of etanercept and sulphasalazine in patients with ankylosing spondylitis. *Arthritis Rheum* 2008; 58: S415.
22. PAVELKA K, FOREJTOVÁ S, STOLFA J *et al*.: Anti-TNF therapy of ankylosing spondylitis in clinical practice. Results from the Czech national registry ATTRA, *Clin Exp Rheumatol* 2009; 27: 958-63.
23. KEYSTONE EC, SCHIFF MH, KREMER JM *et al*.: Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis : results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004; 50: 353-63.
24. VAN DER HEIJDE D, DA SILVA JC, DOUGADOS M *et al*.: Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006; 65: 1572-7.
25. BRAUN J, MCHUGH N, SINGH A, WAJDULA JS, SATO R: Improvement in patient-reported outcomes from patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. *Rheumatology* (Oxford) 2007; 46: 999-1004.
26. BRANDT J, LISTING J, HAIBEL H *et al*.: Long-term efficacy and safety of etanercept after readministration in patients with ankylosing spondylitis. *Rheumatology* (Oxford) 2005; 44: 342-8.
27. LEE J, NOH JW, HWANG JW *et al*.: Extended dosing of etanercept 25 mg can be effective in patients with ankylosing spondylitis: a retrospective analysis. *Clin Rheumatol* 2010; 29: 1149-54.
28. CUI Y, XIAO Z, SHUXIA W *et al*.: Computed tomography guided intra-articular injection of etanercept in the sacroiliac joint is an effective mode of treatment of ankylosing spondylitis. *Scand J Rheumatol* 2009; 27: 958-63.
29. BARALIAKOS X, DAVIS J, TSUJI W, BRAUN J: Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor alpha receptor fusion protein etanercept. *Arthritis Rheum* 2005; 52: 1216-23.
30. RUDWALEIT M, BARALIAKOS X, LISTING J, BRANDT J, SIEPER J, BRAUN J: Magnetic resonance imaging of the spine and the sacroiliac joints in ankylosing spondylitis and undifferentiated spondyloarthritis during treatment with etanercept. *Ann Rheum Dis* 2005; 64: 1305-10.
31. VAN DER HEIJDE D, LANDEWÉ R, EINSTEIN S, ORY P *et al*.: Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis Rheum* 2008; 58: 1324-31.
32. DAVIS JC, VAN DER HEIJDE D, DOUGADOS M, WOOLLEY JM: Reductions in health-related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy. *Arthritis Rheum* 2005; 53: 494-501.
33. BOONEN A, PATEL V, TRAINA S, CHIOU CF, MAETZEL A, TSUJI W: Rapid and sustained improvement in health-related quality of life and utility for 72 weeks in patients with ankylosing spondylitis receiving etanercept. *J Rheumatol* 2008; 35: 662-7.
34. BARKHAM N, COATES LC, KEEN H *et al*.: Double-blind placebo-controlled trial of etanercept in the prevention of work disability in ankylosing spondylitis. *Ann Rheum Dis* 2010; 69: 1926-8
35. MEASE PJ, GOFFE BS, METZ J, VANDERSTOEP A, FINCK B, BURGE DJ: Etanercept in the treatment of psoriatic arthritis and psoriasis; a randomised trial. *Lancet* 2000; 356: 385-90.
36. MEASE PJ, KIVITZ AJ, BURCH FX *et al*.: Etanercept treatment of psoriatic arthritis. Safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004; 50: 2264-72.
37. DE VLAM K, LORIES RJU: Efficacy, effectiveness and safety of etanercept in monotherapy for refractory psoriatic arthritis: a 26-week observational study. *Rheumatology* (Oxford) 2006; 46: 321-4.
38. MEASE PJ, KIVITZ AJ, BURCH FX *et al*.: Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J Rheumatol* 2006; 33: 712-21.
39. CARMONA L, REINO-GOMEZ JJ ON BEHALF OF THE BIOBADASER GROUP: Survival on TNF antagonists in spondyloarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. *Arthritis Res Ther* 2006; 8: R72.
40. KRISTENSEN LE, GULFE A, SAXNE T, GEBOREK P: Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register *Ann Rheum Dis* 2008; 67: 364-9.
41. SPADARO A, CECCARELLI F, SCRIVO R, VALESINI G: Life-table analysis of etanercept with or without methotrexate in patients with psoriatic arthritis. *Ann Rheum Dis* 2008; 67: 1650-1.
42. SAAD AA, ASHCROFT DM, WATSON KD, HYRICH KL, NOYCE PR, SYMMONS DPM: Persistence with anti-tumour necrosis factor

therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. *Arthritis Res Ther* 2009, 11: R52
43. KIRKHAM BW, STERRY W, ORMEROD A *et al*.: Etanercept benefits skin, joints, and entheseal symptoms in patients with psoriasis and psoriatic arthritis. the PRESTA trial. *Arthritis Rheum* 2009; 60 (Suppl. 10): S194
44. MAZZOTTA A, ESPOSITO M, SCHIPANI C, CHIMENTI S: Long-term experience with etanercept in psoriatic arthritis patients: a 3-year observational study. *J Dermatolog Treat* 2009; 20: 354-8.
45. MEASE PJ, WOOLEY JM, SINGH A, TSUJI W, DUNN M, CHOIU CF: Patients reported outcomes in a randomized trial of etanercept in psoriatic arthritis. *J Rheumatol* 2010; 37: 1221-7.
46. LUBRANO E, SPADARO A, MARCHESONI A *et al*.: The effectiveness of a biologic agent on axial manifestations of psoriatic arthritis. A twelve months observational study in a group of patients treated with etanercept. *Clin Exp Rheumatol* 2011; 29: 80-4.
47. OLIVIERI I, VAN TUBERGEN A, SALVARANI C, VAN DER LINDEN S: Seronegative spondyloarthritides. *Best Pract Res Clin Rheumatol* 2002; 16: 723-39.
48. MARZO-ORTEGA H, MCGONAGLE D, O'CONNOR P, EMERY P: Efficacy of etanercept in the treatment of the entheseal pathology in resistant spondylarthropathy: a clinical and magnetic resonance imaging study. *Arthritis Rheum* 2001; 44: 2112-7.
49. BRANDT J, KHARIOUZOV A, LISTING J *et al*.: Successful short term treatment of patients with severe undifferentiated spondyloarthritis with the anti-tumor necrosis factor-alpha fusion receptor protein etanercept. *J Rheumatol* 2004; 31: 531-8.
50. FLAGG SD, MEADOR R, HSIA E, KITUMNUAYPONG T, SCHUMACHER HR JR.: Decreased pain and synovial inflammation after etanercept therapy in patients with reactive and undifferentiated arthritis: an open-label trial. *Arthritis Rheum* 2005; 53: 613-7.
51. OLIVIERI I, SCARANO E, PADULA A, D'ANGELO S, CANTINI F: Switching tumor necrosis factor α inhibithors in HLA-B27-associated severe heel enthesitis. *Arthritis Rheum* 2007; 57: 1572-4.
52. DOUGADOS M, COMBE B, BRAUN J *et al*.: A randomised, double-blind, placebo-controlled trial of etanercept in adults with refractory heel enthesitis in spondyloathritis: the HEEL trial. *Ann Rheum Dis* 2010; 69: 1430-5.
53. GRAN JT, SKOMSVOLL JF: The outcome of ankylosing spondylitis: a study of 100 patients. *Br J Rheumatol* 1997; 36: 766-71.
54. ZEBOULON N, DOUGADOS M, GOSSEC L: Prevalence and characteristics of uveitis in the spondyloarthropathies: a systematic literature review. *Ann Rheum Dis* 2008; 67: 955-9.
55. GRAN JT, HUSBY G: HLA-B27 and spondyloarthropathy: value for early diagnosis? *J Med Genet* 1995; 32: 497-501.
56. ROSENBAUM JT: Effect of etanercept on iritis in patients with ankylosing spondylitis [letter]. *Arthritis Rheum* 2004; 50: 3736-7.
57. SAMSON CM, WAHEED N, BALTATZIS S, FOSTER CS: Methotrexate therapy for chronic noninfectious uveitis: an analysis of a case series of 160 patients. *Ophthalmology* 2001; 108: 1134-9.
58. BRAUN J, BARALIAKOS X, LISTING J, SIEPER J: Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum* 2005; 52: 2447-51.
59. SIEPER J, KOENIG AS, BAUMGARTNER S *et al*.: Analysis of uveitis rates across all etanercept ankylosing spondylitis clinical trials. *Ann Rheum Dis* 2010; 69: 226-9.
60. COBO-IBANEZ T, DEL CARMEN ORDONEZ M, MUNOZ-FERNANDEZ S, MADERO-PRADO R, MARTIN-MOLA E: Do TNF-blockers reduce or induce uveitis? *Rheumatology* (Oxford) 2008; 47: 731-2.
61. LIM LL, FRAUNFELDER FW, ROSENBAUM JT: Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. *Arthritis Rheum* 2007; 56: 3248-52.
62. SCRIVO R, SPADARO A, SPINELLI FR, VALESINI G: Uveitis following the use of tumor necrosis factor α inhibitors: comment on the article by Lim *et al*. *Arthritis Rheum* 2008; 58: 1555-6.
63. COATES LC, MCGONAGLE DG, BENNETT AN, MARZO-ORTEGA M: Uveitis and tumor necrosis factor blockade in ankylosing spondylitis. *Ann Rheum Dis* 2009; 67: 729-30.
64. FOUACHE D, GOËB V, MASSY-GUILLEMANT N *et al*.: Paradoxical adverse events of anti-tumour necrosis factor therapy for spondyloarthropaties: a retrospective study. *Rheumatology* (Oxford) 2009; 48: 761-4.
65. LANGE U, STAPFER G, DITTING T *et al*.: Pathologic alterations of the heart and the kidney in patients with ankylosing spondylitis. *Eur J Med Res* 2007; 14: 573-81.
66. JONES DW, MANSELL MA, SAMUELL CT, ISENBERG DA: Renal abnormalities in ankylosing spondylitis. *Br J Rheumatol* 1987; 26: 341-445.
67. BEN TAARIT C, AJLANI H, BEN MOUSSA F, BEN ABDALLAH T, BEN MAIZ H, KHEDHER A: Renal involvement in ankylosing spondylitis: concerning 210 cases. *Rev Med Interne* 2005; 26: 966-9.
68. STROBEL ES, FRITSCHKA E: Renal diseases in ankylosing spondylitis: review of the literature illustrated by case reports. *Clin Rheumatol* 1998; 17: 524-30.
69. KOBAK S, OKSEL F, KABASAKAL Y, DOGANAVSARGIL E: Ankylosing spondylitis-related secondary amyloidosis responded well to etanercept: a report of three patients. *Clin Rheumatol* 2007; 26: 2191-4.
70. BELLISSIMO S, FERRUCCI MG, GALLO A, STISI S: Response to anti-TNF-alpha treatment for secondary renal amyloidosis in a patient with ankylosing spondylitis. *Reumatismo* 2007; 59: 240-3.