Etanercept treatment in resistant spondyloarthropathy: Imaging, duration of effect and efficacy on reintroduction

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ABSTRACT

Biologic blockade of tumour necrosis factor alpha is an exciting new development in the treatment of the spondyloarthropathies (SpA). Recent reports suggest that both infliximab and etanercept are potent suppressors of inflammation in SpA and this has been confirmed by studies showing suppression of inflammatory indices as well as complete regression or improvement in the inflammatory lesions as shown by magnetic resonance imaging (MRI). Whilst limited follow up data have been reported in the case of infliximab there are no data on how patients on etanercept fare after a years' treatment.

The spondyloarthropathies (SpA) have an estimated prevalence of between 0.6% to 1.9% (1) which is similar to that of rheumatoid arthritis (RA) with recent studies suggesting a grade of disability of affected patients equivalent to that of RA (2). Despite this, treatment options have traditionally been less numerous and less satisfactory than in RA. Indeed, there is a general perception that DMARDs which are effective in RA have, at best, only a modest benefit in SpA. This is particularly true in the case of enthesopathy, the hallmark of these diseases. Recent reports of the presence of TNF alpha or mRNA for TNF on the peripheral blood and sacroiliac joints in patients with SpA suggested a role for this cytokine in the pathogenesis of these diseases. Following the first studies demonstrating the efficacy of TNF alpha blockade in RA, a number of reports suggesting equal or superior efficacy in SpA have now been published (3, 4).

In our unit, we have recently reported in an open label study the efficacy of the recombinant fusion protein etanercept in the treatment of patients with resistant SpA (5). In this observational study, 10 patients with a diagnosis of SpA according to the ESSG criteria and secondary AS who had failed to respond to long-term treatment with non-steroidal anti-inflammatory drugs and disease modifying agents such as sulphasalazine and methotrexate, were treated with a standard dose of etanercept (Wyeth, UK) (25 mg/sc twice weekly) for 24 weeks. Six patients already receiving methotrexate prior to study entry were allowed to continue this medication and received etanercept in combination. Diagnoses in the study group included seven patient with AS, 2 patients with Crohn's spondylitis and 1 patient with undifferentiated SpA. Mean disease duration was 12 years (range: 0.6-34) and 80% of the patients were HLA-B27 positive.

Our primary outcome was clinical and looked at the improvement among others of BASDAI and quality of life as measured by the ankylosing spondylitis quality of life questionnaire or ASQoL (6). Our results showed that etanercept was efficacious at suppressing the symptoms and signs of inflammation in SpA (Table I). As previously reported, a marked response was seen in clinical signs and symptoms at all sites of disease with all patients achieving > 50% improvement on global parameters of disease activity such as the BASDAI by week 4. This improvement was maintained throughout the study period and was comparable to that reported with infliximab (3,4). In particular, for the first time a therapy has been shown to be very effective in the case of enthesopathy, as shown by the VAS enthesopathy scores (median baseline 62 of a total of 100, median follow-up 3, $p = 0.008$).

Magnetic resonance imaging (MRI) was used as a secondary outcome measure. Recently, it has been shown by different groups that MRI identifies inflammatory changes in the enthesis, the bone and synovium in patients with SpA (7-9). We used MRI to assess response to therapy as shown by resolution of bone oedema at entheseal sites with sequential MRI showing that 90%

Table I. Summary of clinical outcomes showing percentage of involvement at different endpoints.

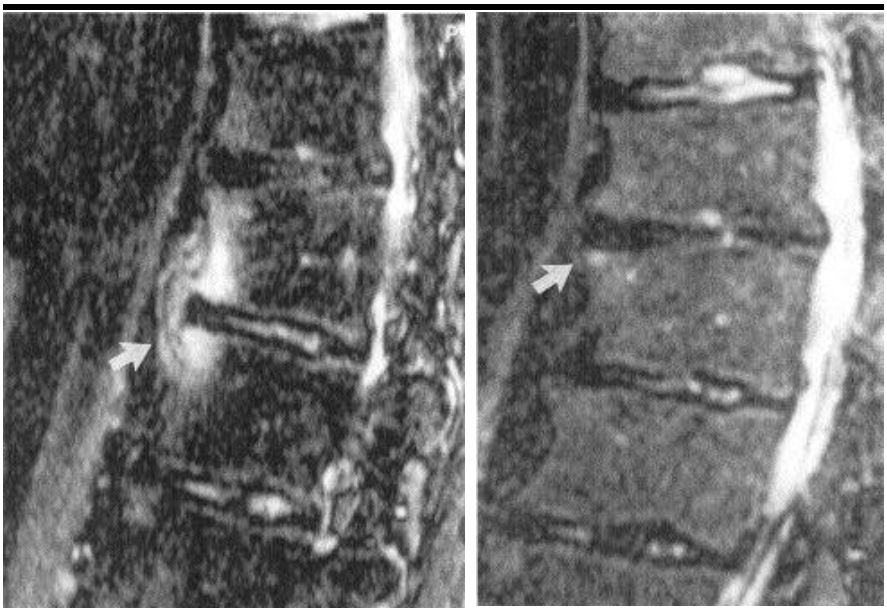
	Baseline		Week 24		% change from baseline	Flare		Week 24 (after re-starting therapy)		% change
BASDAI	6.25	(3.4-9.3)	1.3	(0-6.2)	79	6.74	(2.3-8.2)	4.21	(0-7.3)	37
VAS enthesopathy	62	(23-100)	11	(0-77)	95	57.5	(11-87)	6	(0-68)	89
ASQoL	14	(13-18)	3	(0-9)	78	12	(14-17)	2	(0-16)	83
CRP	43.5	(16-58)	11	(0-28)	65	57	(12-116)	6	(0-16)	89

BASDAI:Bath Ankylosing spondylitis disease activity index (0-10); VAS:visual analogue score (0-100); ASQoL:ankylosing spondylitis quality of life questionnaire (0-18); CRP: C-reactive protein, normal value < 5 mg/l. All values are given as median with range.

Table II. Summary of scoring results of MRI lesions at the different sites assessed pre- and post-treatment with etanercept.

	Baseline	Week 24		
		-3 Regressed	-2 or –1 Improved	0 No change
Sacro-iliac joint	15	6 (40)	3 (20)	6
Spine	22	17 (71)	5 (23)	0
Peripheral joints	7	4 (57)	3 (42)	0
TOTAL	27 (61)	11 (25)		6 (14)
	44		38 (86)	6 (14)

Numbers represent total number of lesions with % in brackets.



(a) **(b)**

Fig. 1. (a) T2 fat suppressed sagittal image of the lumbar spine of a patient with AS showing the typical appearances of MR Romanus lesions (**white arrows**). **(b)** Follow up scan after therapy.

of regions of enthesitis/osteitis either regressed completely or markedly improved (Fig. 1, Table II) and this has been reported in detail elsewhere (5).

Disease flare following cessation of etanercept

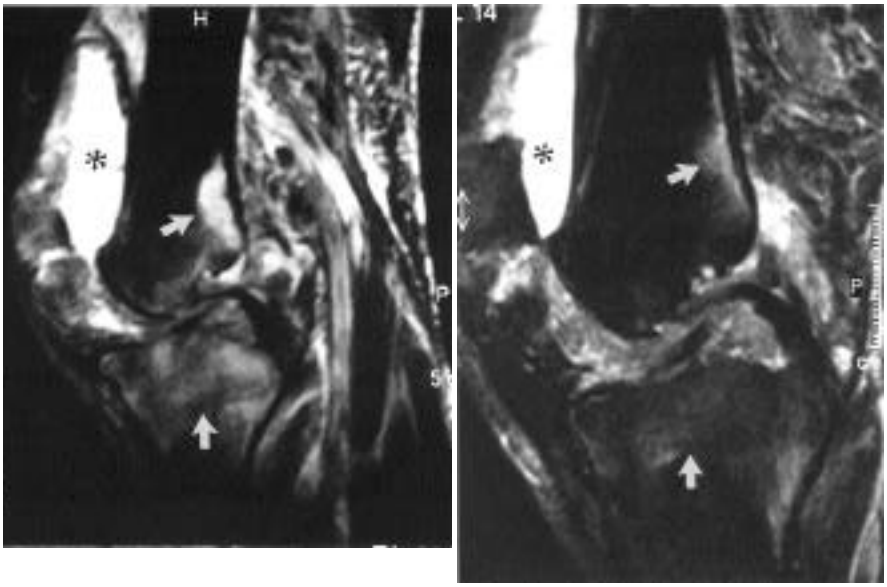
According to our study protocol, all patients in our cohort stopped treatment after 24 weeks. Patients were followed up 12 weekly or were seen on request if symptoms returned. Here we report on their evolution. A flare of disease was defined as a BASDAI score of >60% of the initial baseline value at week 0 before the first infusion. Overall, symptoms and signs of disease returned at a median of 10 weeks (range: 4-36) after stopping therapy in all 10 patients. Interestingly, 3 patients reported a flare that was of worse severity than disease prior to initially starting etanercept. In these patients, disease flare was associated with a rebound in C-reactive protein (CRP) levels that were between 51% and 125% higher than values at study entry.

Retreatment with etanercept

Two of the patients had a mild flare of disease with a BASDAI < 60% from baseline and were treated with sulphasalazine. A third patient with Crohn's related spondylitis whose bowel symptoms did not respond to etanercept on the first phase of the study was treated with infliximab as part of a different protocol. Seven patients were re-started on regular etanercept at the original dose of 25 mg/sc twice weekly and were assessed every 12 weeks with repeat BASDAI, VAS enthesopathy and CRP measurement as well as quality of life assessments (ASQoL). In these patients the response was again prompt and sustained. At week 24, all outcomes including quality of life achieved a degree of response equivalent to that achieved at the end of the first study period (% improvement: BASDAI 37, VAS enthesopathy 89.5, CRP 89.4, ASQoL: 83.3) (Table I).

Toxicity

Only one significant complication was noted with one patient developing refractory anterior uveitis that necessitated discontinuation of etanercept. At 30 week follow up no other major side effects have been reported and injections are well tolerated. No significant ANA seroconversion has been found in these patients.



(a) **(b)**

Fig. 2. (a) T2 fat suppressed sagittal image of the knee joint of a patient with AS before treatment with etanercept. There is a retropatellar knee effusion (**black asterisk**) as well as extensive bone oedema in the area of insertion of posterior cruciate ligament and at the tibial condyle (**white arrows**). **(b)** The follow up scan showing effusion and bone oedema appearances much improved but not completely resolved.

MRI imaging

Whilst enthesitis and osteitis improved or disappeared following initial therapy these lesions returned following disease flare. We also noted that the 3 patients who flared most rapidly after stopping etanercept (mean 7 weeks) had MRI evidence of persistent enthesitis/ osteitis at the end of the original study period (Fig. 2) suggesting that MRI may have a role in predicting the likelihood of disease flare following discontinuation of therapy.

These findings suggest that etanercept is efficacious in suppression of enthesitis and osteitis and clinical symptoms in resistant SpA over a 1-year period. Likewise, similar to what has been reported with the monoclonal antibody infliximab (10,11), these findings also suggest that once initiated, etanercept therapy will probably need to be continued. The use of etanercept in AS is increasing and other reports are currently appearing (12). Results from a double-blind randomised controlled trial from San Francisco looking at the use of etanercept in AS have recently been reported (13). Also, although preliminary, our data suggest that MRI may have a role in the identification of poor responders. Clearly further studies are needed to determine its value in this respect.

In conclusion, although our numbers are small, these results are the first long-term follow up data on SpA patients treated with etanercept and suggest that sustained improvement can be achieved in severe, active and refractory SpA even after re-introduction of etanercept after a severe flare. Longer follow-up of larger number of patients is needed particularly to assess long-term safety of this drug.

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