



Anti-collagen type II antibodies in patients with very early synovitis

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Could tumour necrosis factor blockers inhibit the progression of future structural damage in ankylosing spondylitis?

We read with great interest the editorial article by Schett *et al*,¹ where the authors discuss the role of tumour necrosis factor (TNF) α blockers in reducing new bone formation in ankylosing spondylitis (AS). They described the pathophysiological process, where TNF- α is a key proinflammatory cytokine, but is also a potent inhibitor of bone formation. Therefore, it is unlikely that TNF- α blockers are effective in reducing syndesmophyte growth and bridging. In other words, would TNF- α blockers inhibit the progression of structural damage even though they are proven to be very efficient in diminishing the clinical parameters of AS activity, acute-phase reactants and also active inflammation visible on magnetic resonance imaging?²

We recently performed a study³ in 10 patients with AS with rather early (mean duration of 5.0 years, range 1–14) and active disease according to either clinical and/or laboratory parameters (table 1). Patients were treated with regular infusions of infliximab (5 mg/kg body weight at baseline, weeks 2 and 6, and every 6–8 weeks thereafter). For each patient, one inflamed lesion was qualitatively selected at baseline by short τ inversion recovery (STIR) and pre-contrast T1-weighted spin-echo (T1SE) magnetic resonance imaging of the spine and sacroiliac joints as the region of interest (ROI). The same selected inflamed lesion (ROI) was followed from baseline through control visits at months 2 and 12; this was done quantitatively by diffusion-weighted imaging (DWI) measuring an apparent diffusion coefficient (ADC) and by dynamic contrast-enhanced imaging (DCEI) with evaluation of the enhancement factor (f_{enh}) and enhancement gradient (g_{enh}). ADC values reflect the diffusion of free water. In the inflamed tissues they are influenced by the proportion of less restricted extracellular water (as in inflammatory oedema) and more restricted intracellular water (as in infiltrated inflamed cells). Furthermore, f_{enh} and g_{enh} reflect the distribution profile of the paramagnetic contrast agent in microvessels and in the interstitial space of inflamed tissues.⁴ In accordance with marked clinical improvement at months 2 and 12, there was also a statistically significant decrease in the f_{enh} and g_{enh} at both control times ($p < 0.05$), while the decrease in ADC reached statistical significance only at month 12 (table 1).

The results are in accordance with previously reported good efficacy of TNF- α blockers.² Importantly, despite rapid clinical improvement and the complete disappearance of inflammatory lesions on STIR or T1SE images, ADC values diminished much more slowly, which probably reflects the persistence of inflammation (with some oedema and inflammatory cell infiltration remaining). Additionally, in DCEI the almost complete flattening of the signal intensity curve (which according to categories

Table 1 Clinical, laboratory and magnetic resonance imaging parameters in patients with ankylosing spondylitis, treated with infliximab, at three end points

	Baseline	Month 2	P Value	Month 12	p Value
BASDAI	5.96 (3.4–7.8)	1.79 (0.0–4.6)	0.005*	1.43 (0.0–4.5)	0.005*
BASFI	5.56 (1.6–8.5)	1.87 (0.0–4.8)	0.005*	1.13 (0.0–3.2)	0.005*
BAS-G	7.23 (3.7–9.7)	4.1 (0.0–9.4)	0.009*	1.97 (0.0–8.3)	0.011*
ESR (mm/h)	28.8 (4–96)	6.8 (1–20)	0.008*	8.2 (1–28)	0.009*
CRP (mg/l)	25.6 (0–107)	2.6 (0–5)	0.043*	2.0 (0–4)	0.028*
ADC (10^{-3} mm ² /s)	1.31 (0.6–2.3)	1.15 (0.7–1.6)	0.508	0.88 (0.4–1.6)	0.022*
f_{enh} (1)	1.85 (0.5–5.5)	0.96 (0.3–2.1)	0.013*	0.60 (0.2–0.9)	0.007*
g_{enh} (%/s)	3.09 (1.1–5.9)	1.81 (0.6–4.2)	0.022*	1.40 (0.3–3.4)	0.013*

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index 0–10; BASFI, Bath Ankylosing Spondylitis Functional Index 0–10; BAS-G, Bath Ankylosing Spondylitis Patient Global Score 0–10; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ADC, apparent diffusion coefficient; f_{enh} , enhancement factor; g_{enh} , enhancement gradient.

Values are given as mean (range). Statistically significant values are in bold type.

* $p < 0.05$, Wilcoxon signed rank test comparing baseline data with data at control month.

proposed by Braun *et al*⁴ reflects the level of no inflammation) was observed in only one patient ($f_{\text{enh}} = 0.19$, $g_{\text{enh}} = 0.27\%/s$), while in other patients quantitative measurements showed at least persistent latent inflammatory activity even at month 12. DCEI and more recently DWI⁵ provide additional quantitative information about inflammatory activity that, in our study, shows residual inflammation in the ROI of TNF- α blocker treated patients with AS. It seems possible that this residual inflammation, left over TNF- α blocker treatment, could be responsible for the progression of future structural damage in AS.

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Anti-collagen type II antibodies in patients with very early synovitis

Anti-type II collagen (anti-CII) antibodies have been reported in between 3% and 27% of patients with rheumatoid arthritis

(RA).^{1–3} In contrast with anti-cyclic citrullinated peptide (anti-CCP) antibodies,^{4,5} anti-CII antibodies are absent before the onset of synovitis⁶ and decrease over the first few years of disease.^{2,3} Anti-CII antibody levels thus appear to peak around the time of diagnosis of RA when they are associated with active inflammation.³ The pathological processes operating in

the joints of patients with very early synovitis who develop RA are distinct from those in other patients with early synovitis and are characterised by a cytokine profile that includes interleukins 2, 4 and 13.⁷ Consequently we sought to assess whether anti-CII antibodies were more prevalent in patients with very early synovitis who subsequently developed RA than in patients with other outcomes.

Patients with synovitis of ≤ 3 months duration were recruited, and data collected from them, as previously described.^{7,8} Ethical permission was obtained and all patients gave written informed consent. Patients were followed for 18 months and assigned to their final diagnostic groups. Patients were classified as having RA according to established criteria.⁹

Antibodies against native human CII were measured in duplicate wells with enzyme-linked immunosorbent assay, as described previously, in serum samples that had been obtained at initial presentation and had been stored at -80°C .³ A level of ≥ 29 U/ml (95th percentile among 100 healthy controls) was considered positive.³

A total of 177 patients were recruited (details shown in table 1); 64 patients developed RA and 113 did not (70 unclassified; 11 reactive arthritis; 10 psoriatic arthritis; 10 crystal arthritis; 12 other). Two patients without RA were anti-CCP antibody positive (both were classified as psoriatic arthritis, one was rheumatoid factor positive and neither had elevated anti-CII antibody levels).

Twelve of 177 patients were anti-CII antibody positive (fig 1). Three of these developed RA (two were rheumatoid factor positive and none were anti-CCP antibody positive), three developed a persistent unclassified synovitis and in six the synovitis resolved (three reactive arthritis; two gout; one unclassified). Of the nine non-RA patients, two were rheumatoid factor positive and none were anti-CCP antibody positive. The prevalence of anti-CII antibody positivity was not different between the patients with and without RA ($p = 0.40$; χ^2). There was no relationship between the ESR, CRP or swollen joint count and the anti-CII antibody level (Spearman test; data not shown).

The prevalence of anti-CII antibodies in patients who developed RA (5%) is towards the lower end of the range previously reported for patients with established RA. None of our patients had the very high levels of anti-CII antibody

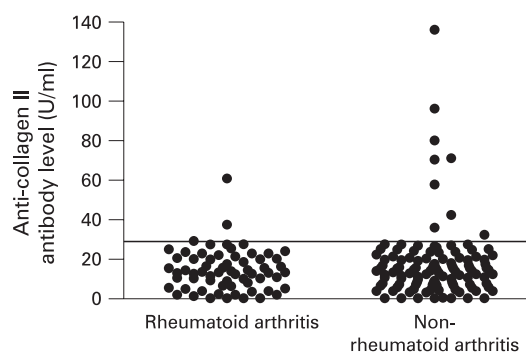


Figure 1 Anti-collagen II antibody levels in patients with very early synovitis divided according to final outcome (rheumatoid arthritis and non-rheumatoid arthritis).

reported previously in a small subgroup (about 3%) of patients with early RA.³ These data suggest that the prevalence of anti-CII antibodies is no higher in patients with very early synovitis who develop RA than in those with other very early synovitides. The measurement of this antibody is unlikely to be useful in the prediction of outcome in patients with very early synovitis of less than 3 months duration.

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Table 1 Characteristics of patients with very early synovitis divided according to final clinical outcome

	Very early RA	Other very early synovitis	p Value
Number	64	113	
Female; number (%)	38 (59%)	51 (45%)	0.07†
Age, years; median (IQR)	61 (46–71)	43 (31–57)	<0.0001*
Swollen joint count; median (IQR) (n = 177)	4 (2–7)	2 (1–3)	<0.0001*
Tender joint count; median (IQR) (n = 177)	6 (3–13)	2 (1–5)	<0.0001*
CRP; median (IQR) (n = 173)	21 (9–42)	23 (6–61)	0.73*
ESR; median (IQR) (n = 159)	28 (14–50)	23 (9–60)	0.47*
Rheumatoid factor positive; number (%) (n = 177)	36 (56%)	13 (12%)	<0.0001†
Anti-CCP antibody positive; number (%) (n = 175)	31 (48%)	2 (of 111) (1%)	<0.0001†
Anti-CII antibody positive; number (%) (n = 177)	3 (5%)	9 (8%)	0.40†

CCP, cyclic citrullinated peptide; CII, collagen II; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; RA, rheumatoid arthritis.

*Mann-Whitney test.

† χ^2 test.