Letters to the Editors

Predictive value of ultrasonographic assessment of disease activity in response to tumour necrosis factor-α inhibitor treatment in rheumatoid arthritis: a prospective cohort study

Sirs,

Tumour necrosis factor-α inhibitors (TNFi) represent an important advancement in rheumatoid arthritis (RA). However, there is a large heterogeneity in response and there are still no good response predictors.

Over the last decade, ultrasound (US), a validated and sensitive tool, has been increasingly used to better detect and monitor disease activity in RA. Currently, it is unknown whether better detection of baseline disease activity with US may predict TNFi response. Therefore we designed a prospective study to investigate the ability of the ultrasonographic disease activity parameters to predict which RA patients will benefit from TNFi treatment in terms of EULAR response.

Thirty-nine seropositive, biologic-naive RA patients underwent clinical, laboratory and US evaluation at baseline, 3rd, 6th and 12th months of therapy. DAS28 and EULAR response was evaluated at each visit (1-3). Systematic multiplanar grey-scale (GS) and power Doppler (PD) US examination of 28-joints (included in DAS28) was performed with MyLab70 US machine (Esaote, Italy) using multifrequency linear array transducers (7–12MHz) (sonographer NI). US synovitis GS and PD signals were semiquantitatively graded according to Szkudlarek's definition (0=absent; 1=mild; 2=moderate; 3=marked) (4). Sum of GS and PD synovitis scores of all sites and joints with at least grade 1 synovitis in GS and PDUS were recorded as sum scores of GS and PD, US joint count in GS and PD, respectively. Candidate predictors of EULAR response at 3rd month with a *p*-value of ≤0.20 in univariate analysis were analysed using a stepwise-multivariable logistic regression.

Complete clinical, laboratory and ultrasonographic data were obtained from 39, 38 and 33 patients at 3rd, 6th and 12th months, respectively. Drop-outs were due to lack of efficacy (n=5, at 6th month) and side effects (n=1, at 3rd month). The mean age, disease duration and DAS28 score were 46.7±11.7 years, 9.1±6.5 years, and 5.57±1.19, respectively.

The EULAR response (good/moderate) rate at 3rd month was 64.1% and was similar to 6th and 12th months' (71.8% and 74.4%; *p*=0.22, *p*=0.14, respectively). Baseline characteristics of TNFi responders and non-responders at 3rd month were shown in Table I. Baseline PD synovitis sum score was significantly higher in non-responders compared to responders (*p*=0.035). All patients were receiving concomitant synthetic disease-modifying anti-rheumatic drugs throughout the study and those were similar in both groups. In multivariable analysis, only baseline PD synovitis sum score (OR=0.86; CI:95% 0.75-0.98, *p*=0.023) was independently associated with EULAR response to TNFi at the 3rd month.

Table I. Baseline characteristics of TNFi responders and nonresponders at 3rd month*.

Parameter	Responders (n=24)	Non-responders (n=15)	*p*-value
Female, n (%)	18 (72)	12 (85.7)	0.33
Age (years)	46.4 ± 11.6	47.1 ± 12.4	0.85
Disease duration (years)	7.7 ± 5.7	11.5 ± 7.2	0.080
Current smoker, n (%)	7 (28)	3 (21.4)	0.65
Extra-articular involvement, n (%)	5 (20)	5 (35.7)	0.28
RF titer (IU/mL), median (25p-75p)	94 (33-271)	95 (46-257)	0.97
Anti- CCP titer (U/mL), median (25p-75p)	68.7 (22.4-97.1)	100 (20.5-340)	0.22
DAS28	5.6 ± 1.0	5.6 ± 1.4	0.94
Elevated ESR (>20 mm/h), n (%)	22 (88)	10 (71.4)	0.19
Elevated CRP (>10 mg/L), n (%)	18 (72)	6 (42.9)	0.070
TJC (0-28)	9.5 ± 7.5	12.3 ± 9.4	0.32
SJC (0-28)	6.1 ± 5.1	9.5 ± 7.4	0.10
USJC in GS (0-28)	8.3 ± 2.9	9.2 ± 5.6	0.11
USJC in PD (0-28)	6.9 ± 2.5	9.2 ± 5.6	0.088
HAQ score	1.15 ± 0.67	1.31 ± 0.46	0.37
Prednisolone dose, mg/day	6.7 ± 3.0	5.7 ± 1.8	0.22
Sum score of PD signals (0-84)	13.0 ± 5.1	20.6 ± 11.8	0.035
Sum score of GS signals (0-84)	16.4 ± 6.9	24.9 ± 14.4	0.054

*The values are presented as mean ± SD, unless indicated otherwise.
RF: rheumatoid factor; CCP: cyclic citrullinated peptide; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TJC: tender joint count; SJC: swollen joint count; USJC: Ultrasonographic joint count; GS: Grey-scale; PD: Power Doppler; HAQ: Health Assessment Questionnaire.

Our findings are important as baseline clinical disease activity of responders and non-responders according to DAS28 criteria were similar and the difference in disease activity could only be detected with US. This is the first study evaluating predictive role of baseline US disease activity in TNFi EULAR response. The only study so far, evaluating the predictive value of baseline ultrasonographic disease activity revealed that higher baseline colour Doppler measurements predicted which patients remain on TNFi for 1-year which was interpreted as response (5). The study design (only wrist joint was evaluated) and the end points (TNFi continuation instead of EULAR response) were not exactly the same with our study. That study patients were not all biologic-naive which may affect response to next TNFi, and less than 50% of patients were in high disease activity state. Furthermore, seropositivity may have an effect on TNFi response (6-7).

In conclusion, we have shown that despite similar clinical features and clinical disease activity state as assessed by DAS28, higher baseline PD synovitis scores may predict EULAR-non-response to TNFi therapy in seropositive RA patients. This study indicates that non-responder patients have excess inflammatory activity that is detectable with PDUS but not with clinical examination.

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