Pretreatment serum levels of anti-cyclic citrullinated peptide antibodies are associated with the response to methotrexate in recent-onset arthritis

K. Visser
K.N. Verpoort
H. van Dongen
S.M. van der Kooij
C.F. Allaart
R.E.M. Toes
T.W.J. Huizinga
A.H.M. van der Helm-van Mil

To direct individual treatment decisions in recent-onset rheumatoid arthritis (RA), predictors of treatment response to methotrexate (MTX) need to be identified. Disease activity at baseline, gender and genetic polymorphisms have already been found to be associated with the effect of MTX treatment, but the predictive value of autoimmune antibody status remains less clear (1;2). It has been shown, however, that both the presence and level of anti-cyclic citrullinated peptide antibodies (ACPA) are strongly associated with a worse disease course (3). Therefore, we investigated the potential predictive effect of levels of ACPA in ACPA-positive patients for the response to MTX treatment. As observations from our cohort and others indicate that ACPA levels decrease during treatment, we studied two selected populations of disease-modifying antirheumatic drug (DMARD)-naïve, ACPA-positive patients with recent-onset arthritis, for whom pretreatment ACPA levels were available (4;5).

All ACPA-positive patients with undifferentiated arthritis (UA) who were included in the PROMPT study (PRObable RA: Methotrexate versus Placebo Treatment) (MTX group n = 12, placebo group n = 15) were enrolled (5). MTX treatment was started with 15 mg/week and every 3 months the dosage was increased according to the Disease Activity Score (DAS44) to a maximum of 30 mg/week. Responders were defined as patients whose UA did not progress to RA (according to the American College of Rheumatology criteria) during the use of MTX (n = 6/12). MTX responders had lower levels of pretreatment IgG ACPA than non-responders (median (interquartile range) 428 (214–643) AU/ml. 

Figure 1. (A) Pretreatment anti-cyclic citrullinated peptide antibodies (ACPA) levels in methotrexate (MTX) responders versus non-responders within ACPA-positive patients with recent-onset, undifferentiated arthritis from the PROMPT study (n = 12, p = 0.024). (B) Percentage of responders to MTX in ACPA-positive patients with recent-onset rheumatoid arthritis from the BeSt study with low, intermediate and high pretreatment ACPA levels (n = 26, p = 0.062).
ml vs 1594 (781–4495) AU/ml, respectively) (p=0.024, Mann–Whitney test, figure 1A. Further univariate analysis did not show any significant differences in baseline clinical measures of disease activity, or in rheumatoid factor levels, between responders and non-responders. In addition, the risk of progression to RA, as analysed by survival analysis, was lower in patients with low or intermediate pretreatment ACPA levels than in patients with high levels (stratified by tertiles) (p<0.001, log-rank test, figure 2).

Similar associations were found in a second cohort of ACPA-positive patients with recent-onset RA, who were treated with initial MTX monotherapy (15–25 mg) aiming at a DAS44 ≤2.4 in the BeSt study and from whom pretreatment serum samples were available (n=26/131) (6). Responders were defined as patients achieving a DAS44 ≤2.4 after 6 months. The percentage of responders decreased from 63% and 56% in patients with low and intermediate levels, respectively, to 11% in patients with high levels (stratified by tertiles) (p=0.062, χ2 test, figure 1B). In a multivariate logistic regression analysis, low and intermediate ACPA levels predicted responsiveness, independently of baseline DAS, gender and age (odds ratio=37, 95% confidence interval 0.8 to 1692, p=0.064).

Despite the limited number of patients, these data from two distinct cohorts suggest that low and intermediate pretreatment levels of ACPA are associated with a more favourable response to MTX treatment in recent-onset, ACPA-positive arthritis, whereas high levels are associated with an insufficient response. Although these findings have to be confirmed in larger studies, quantitative evaluation of ACPA levels might be an additional tool to determine which patients will benefit most from MTX treatment. Therefore, we propose that pretreatment ACPA levels should be used in future prediction analyses.

Figure 2. Kaplan–Meier survival curves for the progression of undifferentiated arthritis to rheumatoid arthritis (RA) in anti-cyclic citrullinated peptide antibody (ACPA)-positive patients with undifferentiated arthritis. Placebo group (broken line, n=15); methotrexate group (solid lines, n=12; categorised into patients with low (light line), intermediate (semi-dark line) and high (dark line) pretreatment ACPA levels by tertiles). p<0.001 for the comparison of low/intermediate versus high levels.
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References


