Anti-cyclic citrullinated peptide antibodies are associated with radiographic damage but not disease activity in early rheumatoid arthritis diagnosed in 2006–2011

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Anti-cyclic citrullinated peptide antibodies are associated with radiographic damage but not disease activity in early rheumatoid arthritis diagnosed in 2006–2011

M Ziegelasch\(^1\), A Boman\(^2\), K Martinsson\(^1\), I Thyberg\(^1\), C Jacobs\(^1\), BM Nyhäll-Wåhlin\(^3\), A Svärd\(^3\), E Berglin\(^2\), S Rantapää-Dahlqvist\(^2\), T Skogh\(^1\), A Kastbom\(^1\)

\(^1\)Department of Rheumatology in Östergötland, and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden
\(^2\)Department of Public Health and Clinical Medicine, Rheumatology, Umeå University, Umeå, Sweden
\(^3\)Department of Rheumatology, Falun Hospital, Falun, Sweden
\(^4\)Center for Clinical Research Dalarna, Uppsala University, Uppsala, Sweden

Objective: The discovery of anti-citrullinated protein antibodies (ACPAs) and the introduction of new therapeutic options have had profound impacts on early rheumatoid arthritis (RA) care. Since ACPA status, most widely assessed as reactivity to cyclic citrullinated peptides (CCPs), influences treatment decisions in early RA, we aimed to determine whether anti-CCP remains a predictor of disease activity and radiographic joint damage in more recent ‘real-world’ early RA.

Method: Two observational early RA cohorts from Sweden enrolled patients in 1996–1999 (TIRA-1, n = 239) and 2006–2009 (TIRA-2, n = 444). Clinical and radiographic data and ongoing treatment were prospectively collected up to 3 years. Two other cohorts served as confirmation cohorts (TRAM-1, with enrolment 1996–2000, n = 249; and TRAM-2, 2006–2011, n = 528). Baseline anti-CCP status was related to disease activity, pharmacotherapy, and radiographic joint damage according to Larsen score.

Results: In the TIRA-1 cohort, anti-CCP-positive patients had significantly higher 28-joint Disease Activity Score, swollen joint count, C-reactive protein level, and erythrocyte sedimentation rate during follow-up compared with anti-CCP-negative patients. In TIRA-2, no such differences were found, but baseline anti-CCP positivity was associated with higher 3 year Larsen score (5.4 vs 3.5, p = 0.039). In TRAM-2, anti-CCP also predicted radiographic damage (8.9 vs 6.7, p = 0.027), with no significant differences in disease activity.

Conclusion: In the early RA cohorts recruiting patients in 2006–2011, baseline anti-CCP positivity was not associated with disease activity over time, but was associated with increased radiographic damage at follow-up. Hence, close radiographic monitoring is warranted in early anti-CCP-positive RA regardless of disease activity.

The management of early rheumatoid arthritis (RA) has improved substantially in recent decades thanks to treat-to-target strategies and novel pharmaceutical options (1, 2). Major breakthroughs were made in the late 1990s with the identification of citrulline residues as key antigenic determinants for RA-specific autoantibodies (3, 4) and the development of easily available detection assays, such as the anti-cyclic citrullinated peptide (anti-CCP) test. Subsequently, the occurrence of immunoglobulin G (IgG)-class anti-CCP was shown to precede the onset of RA (5) and to be associated with a worse prognosis in terms of disease activity (6–8), extra-articular manifestations (9–11), and radiographic joint damage (12–14). Furthermore, anti-CCP-positive patients in clinical remission appear to have a higher risk of radiographic progression compared with anti-CCP-negative patients (15–17).

Clinical use of the anti-CCP test increased rapidly following its introduction at the beginning of the twenty-first century. Today, the diagnostic and prognostic values of anti-CCP are well known among rheumatologists, and influence both treatment decisions and follow-up procedures in early RA. More potent treatment options have also been introduced. Taken together, the clinical outcomes associated with a positive anti-CCP test are potentially different today from those in the era during which anti-CCP was...
Table 1. Patient characteristics at baseline.

<table>
<thead>
<tr>
<th>Period of enrolment</th>
<th>Primary cohorts</th>
<th>Confirmation cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TIRA-1 (N = 239)</td>
<td>TIRA-2 (N = 444)</td>
</tr>
<tr>
<td>Age (years), mean ± sd</td>
<td>54.9 ± 15.4</td>
<td>58.7 ± 14.5</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>163 (68.2)</td>
<td>297 (66.9)</td>
</tr>
<tr>
<td>Symptom duration until inclusion and diagnosis (months), median (IQR)</td>
<td>&lt; 12</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Anti-CCP positive, n (%)</td>
<td>156 (65.3)</td>
<td>303 (68.2)</td>
</tr>
<tr>
<td>RF positive, n (%)</td>
<td>155 (64.9)</td>
<td>264 (59.5)</td>
</tr>
<tr>
<td>Smoking, ever, n (%)</td>
<td>90/155 (58.1)</td>
<td>147/212 (63.4)</td>
</tr>
<tr>
<td>Proportion of patients fulfilling ARA 87 at inclusion, n (%)</td>
<td>231 (96.7)</td>
<td>421 (94.8)</td>
</tr>
<tr>
<td>Larsen score, median (IQR)</td>
<td>–</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Presence of erosions, n (%)</td>
<td>–</td>
<td>75/419 (17.9)</td>
</tr>
</tbody>
</table>

ARA, American Rheumatism Association; CCP, cyclic citrullinated peptides; RF, rheumatoid factor; IQR, interquartile range; ns, not significant.

Introduced. To characterize the predictive value of anti-CCP in a more recent era of early RA management, we analysed clinical and radiographic outcomes in early RA cohorts recruited in 2006–2011, and related the findings to cohorts recruited in 1996–2000.

**Methods**

**Patients**

Two multicentre prospective observational early RA cohorts, denoted ‘TIRA’ (a Swedish acronym for ‘tidiga insatser vid reumatoid artrit’) were enrolled 10 years apart and followed up prospectively over 3 years (henceforth called the primary cohorts). The inclusion criteria were identical in the two cohorts: symptom duration (defined as first observed joint swelling < 12 months), and either fulfilment of the 1987 American Rheumatism Association (ARA) criteria (18) or suffering from morning stiffness > 60 min, symmetrical arthritis, and small joint engagement. TIRA-1 enrolled 239 patients in 1996–1999 and TIRA-2 enrolled 444 patients in 2006–2009 from southeast–central Sweden. To confirm our findings, we used independent cohorts (henceforth called confirmation cohorts) with early RA (symptoms < 12 months) fulfilling 1987 ARA criteria (18) from the Northern Region of Sweden: TRAM-1 (n = 249, enrolment 1996–2000) and TRAM-2 (n = 528, enrolment 2006–2011) (TRAM is a Swedish acronym for ‘tidig reumatoid artrit mottagning’). During the enrolment of patients in the more recent cohorts TIRA-2 and TRAM-2, anti-CCP status was available to clinicians making treatment decisions at baseline. All cohorts had similar follow-up routines scheduled after

Table 2. Multivariable linear regression analysis in three early rheumatoid arthritis cohorts with radiographic damage (defined as Larsen score) at follow-up as the dependent variable.

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>TIRA-2 (N = 237)</th>
<th>TRAM-1 (N = 93)</th>
<th>TRAM-2 (n = 255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>p</td>
<td>B</td>
<td>p</td>
</tr>
<tr>
<td>Larsen score</td>
<td>1.13</td>
<td>&lt; 0.001*</td>
<td>1.16</td>
</tr>
<tr>
<td>Anti-CCP status</td>
<td>1.05</td>
<td>0.039*</td>
<td>1.32</td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
<td>ns</td>
<td>0.08</td>
</tr>
<tr>
<td>ESR</td>
<td>0.01</td>
<td>ns</td>
<td>0.03</td>
</tr>
</tbody>
</table>

The models include baseline factors that correlated trend-wise (p < 0.1) with radiographic damage at follow-up in the primary cohort (TIRA-2) using univariable analysis. CCP, cyclic citrullinated peptides; ESR, erythrocyte sedimentation rate; ns, not significant.

*Significant values (p < 0.05).
6, 12, and 24 months, and 36 months in the TIRA cohorts. At baseline and scheduled follow-up visits, tender joint count (TJC), swollen joint count (SJC), patient’s global assessment (100 mm visual analogue scale), erythrocyte sedimentation rate (ESR) (mm/h), 28-joint Disease Activity Score (DAS28) (19), ongoing medication, and response to treatments at 6, 12, and 24 months according to the European League Against Rheumatism (EULAR) criteria (20) were recorded. Patient-reported pain (visual analogue scale), physician’s global assessment of disease activity (PGA), and functional ability according to the Swedish version of the Stanford Health Assessment Questionnaire (HAQ) (21) were also registered.

The study protocol was approved by the regional ethics review board in Linköping (TIRA-1 and TIRA-2) and in Umeå (TRAM-1 and TRAM-2). All participating patients gave their written informed consent.

Laboratory analyses

Serum samples were drawn at baseline and stored (3—6 years for TIRA-1, 4—7 years for TIRA-2, 4—8 years for TRAM-1, 0—2 years for TRAM-2) at −70 to −80°C until analysed. Anti-CCP antibodies were detected using second generation immunonasays (Immunoscan CCP; Euro-Diagnostica, Malmö, Sweden). We used the cut-off level recommended by the manufacturer (25 AU/mL). IgM-class rheumatoid factor (RF), ESR (mm/h), and C-reactive protein (CRP, mg/L) were analysed according to routine methods at the local hospitals.

Radiographic evaluation

Radiographs of the hands and feet taken at baseline (n = 419, 94%) and after 36 months (n = 265, 60%) in TIRA-2, and at baseline and after 24 months in TRAM-1 and TRAM-2 (available from 38.2% and 54% of the patients at baseline, respectively, and 37.3% and 48.3% of the patients at 24 months, respectively) were evaluated in chronological order and graded according to the Larsen score (22) by experienced readers. In total, 254 (63%) of TIRA-2 patients had radiographs available from both time-points, and in TRAM-1 97% and in TRAM-2 90% of the patients. Analyses of dropouts of the radiological examinations showed that in TIRA-2 the patients with complete radiographic data were significantly younger than those without (mean 56.8 vs 61.0 years, p = 0.02), had significantly lower baseline ESR (29.8 vs 35.3 mm/h, p = 0.014), and were more often anti-CCP positive (72.5% vs 62.9%, p = 0.04). In TRAM-1, there were no significant differences concerning DAS28, ESR, gender, or age in those with X-rays compared with those without (data not shown), while in TRAM-2, patients with radiographs compared with those without were younger at inclusion (mean 56.0 vs 61.1 years, p = 0.006) and baseline DAS28 was lower (mean 4.6 vs 4.8, p = 0.027). Radiographs were not available from TIRA-1.

The number of erosions [defined as a break of cortical bone > 1 mm (22)] was also calculated for each individual on the radiographs of the hands and feet.

Statistical analyses

Statistical calculations were performed using SPSS software (version 23; IBM Corp., Armonk, NY, USA). Two-sided p-values < 0.05 were considered significant. Missing data points for CRP, DAS28, ESR, TJC, and SJC were considered to occur at random, and except for baseline values, we adopted the last observation carried forward (LOCF) method in the TIRA cohorts, whereas in TRAM missing values were imputed using chained equations (23). Sensitivity analyses regarding DAS28 at the different time-points showed differences in mean values between 0.86% and 2.9% before and after imputations, and between 0.54% and 1.76% regarding LOCF. In the TIRA cohorts, LOCF was carried out on 11.6% of occasions, and in the TRAM cohorts 20.0% of the values were imputed. Radiographic data were not subject to LOCF or imputations.

Measures of disease activity, function, and pain were compared between anti-CCP-positive and anti-CCP-negative patients by the Student’s t-test at baseline, and the general linear model for repeated measurements regarding the follow-up period. The p-values have been corrected for the number of performed comparisons according to the method of Bonferroni (p.) for DAS28 and the components related to DAS28 (n = 8). Categorical data were compared using the chi-squared method.

The Mann–Whitney U-test was used to compare baseline and follow-up radiographic joint damage (measured as Larsen score) according to anti-CCP status. Associations between anti-CCP as an independent predictor of radiographic damage at follow-up were investigated using simple and multiple regression analysis including baseline clinical and laboratory data that were related trend-wise (p < 0.1) with Larsen score in univariable analysis in TIRA-2. These factors were age, baseline ESR, and baseline Larsen score, besides anti-CCP antibodies. There were no relationships between Larsen score at 24 months and being an ever-smoker or body mass index in either TRAM-1 or TRAM-2 (data not shown).

Results

Demographic and clinical characteristics of the cohorts

Baseline characteristics of all cohorts are shown in Table 1. Of note, mean age at inclusion had increased in both of the more recent cohorts. In the TRAM cohorts, the rate of RF-positive patients was lower in the more recent cohort, while no difference could be
observed between TIRA-1 and TIRA-2. However, the proportion of anti-CCP-positive patients remained similar between the historical and more recent cohorts of both TIRA and TRAM. The proportion of smokers was higher in TIRA-2 than in TIRA-1, while the proportion of smokers decreased in the more recent TRAM cohort.

Anti-CCP status and clinical course

In the primary historical cohort (TIRA-1), CRP, ESR, DAS28, and SJC were significantly higher among anti-CCP-positive cases values throughout follow-up (p < 0.05 for all), but not at baseline (Figure 1). The TJC and HAQ did not differ significantly in relation to anti-CCP status in TIRA-1 (Supplementary figure S1).

In TIRA-2, which recruited patients in 2006–2009, anti-CCP-positive patients had lower baseline mean SJC compared with anti-CCP-negative cases (10 vs 7, p = 0.008), and borderline significance regarding CRP and DAS28 (p = 0.056 for both). No significant differences remained during follow-up concerning these variables (Figure 1). No significant differences were seen regarding TJC or the self-reported outcomes PGA, pain, and HAQ (Supplementary figure S1).

In the confirmation cohorts, TRAM-1 and TRAM-2, no differences in disease activity measures remained significant after correction for the number of comparisons performed (Supplementary figure S2).

Baseline anti-CCP status and radiographic joint damage

Baseline Larsen scores in TIRA-2 did not significantly differ between anti-CCP-positive and anti-CCP-negative patients (3.0 vs 2.4, p = 0.28). At 36 months, however, anti-CCP-positive patients had significantly higher Larsen score than anti-CCP-negative patients (mean 5.4 vs 3.5, p = 0.027) (Figure 2). In the confirmation cohorts, anti-CCP was associated with higher Larsen scores at baseline (TRAM-1, mean 5.8 vs 2.7, p = 0.01; and TRAM-2, mean 6.6 vs 5.1, p = 0.03) as well as at follow-up (TRAM-1, mean 11.3 vs 6.4, p = 0.001; and TRAM-2, mean 8.9 vs 6.7, p = 0.009) (Figure 2). In multivariable analysis, baseline Larsen score was independently associated with Larsen score at follow-up in all cohorts, while baseline anti-CCP status included in the multivariable analysis reached statistical significance only in the two more recent cohorts, TIRA-2 and TRAM-2 (Table 2). In both TIRA-2 and TRAM-2, baseline anti-CCP status was associated with Larsen score at follow-up also after adding EULAR response to treatment at 6 months as an adjustment. As sensitivity analyses, we performed a linear regression analysis restricted to TIRA-2 patients fulfilling ARA 1987 initiating methotrexate (MTX) monotherapy at baseline (n = 213). Here, we found radiographic damage at 36 months (as graded according to Larsen) to remain significantly increased among anti-CCP-positive patients also after adjusting for baseline damage [B = 1.2, 95% confidence interval (CI) 0.04–2.4, p = 0.042]. In TRAM-2, all patients fulfilled ARA 1987, but restricting the analysis to patients initiating MTX monotherapy at baseline (n = 419) yielded very similar results (B = 1.1, 95% CI 0.09–2.1, p = 0.034). The number of erosions calculated for the cohorts with X-rays performed (TIRA-2, TRAM-1 and TRAM-2) increased significantly from baseline to follow-up in all three cohorts with radiographs available (p < 0.001 for all), and this remained significant when analysing anti-CCP-positive patients only (p < 0.01 for all).

Anti-rheumatic treatment and response according to anti-CCP status

In TIRA-1, the pattern of treatment was significantly different between anti-CCP-positive and anti-CCP-negative patients at all time-points of the study period except for baseline, consistent with a more aggressive treatment approach among the anti-CCP-positive patients (Figure 3A). In TIRA-2, the pattern of treatment was significantly different from year 2 onwards, with the appearance of more aggressive pharmacotherapy among anti-CCP-positive patients (Figure 3B). The treatment was generally more intense in TIRA-2 compared to TIRA-1 (Figure 3A, B). The frequencies of treatment with conventional disease-modifying anti-rheumatic drugs (DMARDs) were similar in both TRAM-1 and TRAM-2 during the 24 months (Figure 3C, D). In TRAM-2, treatment with biologics had increased to 13% in anti-CCP-positive patients, compared with 6% in the anti-CCP-negative patients (p < 0.028).

In both discovery cohorts TIRA-1 and TIRA-2, a significantly higher number of anti-CCP-positive patients received glucocorticoids (GC) after 24 and 36 months (Supplementary figure S3A, B).

At baseline, more anti-CCP-negative patients received GC in both TRAM cohorts, while in TRAM-2 more anti-CCP-positive patients received GC after 24 months (Supplementary figure S3C, D).

EULAR response rates evaluated at 6, 12, and 24 months were significantly superior (p < 0.001 for all occasions) in the more recent cohorts (TIRA-2 and TRAM-2) versus their historical counterparts (TIRA-1 and TRAM-1, respectively) (Supplementary figure S4A, B). The frequencies of good response were 20–35% for TIRA-1/TRAM-1 versus 39–59% for TIRA-2/TRAM-2 (Supplementary figure S4A, B). Differences between historical and more recent cohorts remained statistically significant at all time-points after stratifying for anti-CCP antibodies (data not shown).

Discussion

The present study shows that the evolution of early RA treatment attenuates the association between baseline anti-
Figure 1. Disease activity over time in relation to baseline anti-cyclic citrullinated protein (CCP) antibody status in early rheumatoid arthritis patients enrolled in 1996–1998 (TIRA-1) and 2006–2009 (TIRA-2). Circles show mean values and error bars show standard error of the mean. The exact p-values are presented after correction for the number of performed tests. DAS28, 28-joint Disease Activity Score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
CCP status and disease activity over time, but despite this, patients with anti-CCP antibodies remain at increased risk of radiographic joint damage. These findings highlight the need for careful radiographic monitoring of anti-CCP-positive early RA patients even when disease activity is brought under control and treatment response is achieved. The findings are consistent with the hypothesis that antibodies to citrullinated proteins/peptides (ACPAs) can mediate bone-degrading effects.

At the time of inclusion in our historical cohorts, neither anti-CCP tests nor the therapeutic use of biologics had been established in clinical routine. Also, the concept of early aggressive therapy and the ‘window of opportunity’ had not been fully implemented. This fact has been taken into account in our modern study cohorts as well as the knowledge of anti-CCP status at baseline, and may have influenced the rheumatologists making treatment decisions. Thus, it is not surprising that the more recently recruited early RA patients were subject to more aggressive pharmacotherapy and more often achieved EULAR responses than in the historical cohorts. However, we had expected the differences in anti-rheumatic therapy according to baseline anti-CCP status to be more pronounced and to appear earlier in the disease course than was the case in the more recent cohorts. In TIRA-2, the treatment pattern was not significantly different until 2 years after inclusion, while in the TRAM-2, no significant differences were found except for the proportion of biological treatment at 24 months. This was possibly because disease activity measures were not higher among anti-CCP-positive patients either at baseline or during follow-up in TIRA-2 or TRAM-2. There was a difference in DMARD prescription pattern between the two historical cohorts, with DMARD treatment being more prevalent in TRAM-1 than in TIRA-1. These regional differences in treatment may explain why a clear association between baseline anti-CCP and disease activity over time was seen in TIRA-1, but not in TRAM-1 (or in the more recent cohorts). The treatment strategy in the more recent cohorts differs slightly from the current practice today. The introduction of biosimilars and Janus kinase inhibitors may have contributed to even more intense treatment in early disease (24).

The current study describes two independent cohorts of early RA patients diagnosed in 2006–2009/2011 where baseline anti-CCP status was independently associated with radiographic joint damage after 2 and 3 years, respectively. This association emerged despite rheumatologists’ awareness of anti-CCP status and despite very similar disease activity measures during follow-up. The association remained after adjusting for response to treatment after 6 months, but it should be noted that initial treatment with biological disease-modifying anti-rheumatic drugs (bDMARDs) was rare, and hypothetically, more frequent early bDMARD use could have attenuated the radiographic damage associated with anti-CCP. A study from Norway showed that in the context of 2010 criteria-based

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**Figure 2.** Radiographic damage in different cohorts of early rheumatoid arthritis patients versus baseline anti-cyclic citrullinated protein (CCP) antibody status. The presented p-values result from the Mann–Whitney U-test.
enrolment and a strict treat-to-target protocol, anti-CCP positivity was not associated with increased radiographic damage (25). In the Swedish Swefot trial, however, where early RA patients according to ARA 1987 with inadequate response to MTX were randomized to either triple therapy or infliximab, baseline anti-CCP positivity was indeed associated with increased 2 year radiographic damage (13). Thus, both recruitment criteria and treatment context may influence the prognostic value of anti-CCP. Although radiographic damage, analysed as Larsen score, in the more recent cohorts of this study was less pronounced compared to the historical cohort TRAM-1 (Figure 2), we believe that our findings call for a careful radiographic monitoring of anti-CCP-positive patients even in the case of limited disease activity. These findings also imply a need for drugs with modes of action other than being directed against pro-inflammatory activity.

The radiographic results in the current study are in line with previous work showing bone-specific effects of ACPAs. For instance, Bugatti showed an association between ACPA, RF, and low bone mass (26). Llorente et al described similar results, but they could not find any association with RF, strengthening the particular involvement of ACPAs in the pathogenesis of bone destruction in early RA and undifferentiated arthritis (27). Carpenter et al investigated radiographic damage in RA in two large cohorts enrolling patients in 1986–2001 and 2002–2013 (28). Instead of ACPAs, that study assessed the contribution of RF, which was associated with greater radiographic progression in both cohorts, although the newer cohort had a lower absolute difference regarding mean annual change in Sharp–van der Heijde score. Identical to our study, more patients were treated earlier and partly with new, more aggressive anti-rheumatic drugs, resulting in improvement of disease outcome. These observations are in line with our results as well as the results from previous studies (29–34). However, when studying recent-onset patients classified according to the 2010 RA criteria, anti-CCP-positive disease does not appear to be associated with more severe outcomes (25, 35).

The well-characterized ‘real-world’ patients, including replication and historical cohorts, are strengths of
the current study. Limitations include missing follow-up data, particularly concerning radiographs, since differences were seen in the more recent cohorts regarding baseline characteristics between those who had radiographic data and those who did not. Furthermore, radiographs were not available in the TIRA-1 cohort. In addition, patients were not enrolled based on the 2010 American College of Rheumatology/EULAR criteria and therefore may not completely align with current practice in the clinics.

Conclusion

In early RA patients recruited in 2006–2011, baseline anti-CCP positivity was associated with increased radiographic damage at follow-up, without signs of increased disease activity over time. This calls for careful radiographic monitoring of early RA patients with anti-CCP antibodies also when an early clinical treatment response is achieved. Furthermore, these findings support the hypothesis of direct bone-degrading effects of ACPAs.

Acknowledgements

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Disclosure statement

All the authors declare that they have no competing interests.

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Supporting information

Additional Supporting Information may be found in the online version of this article.

Supplementary figure S1. Measures of disease activity and functional ability according to baseline anti-CCP status in TIRA-1 and TIRA-2 cohorts. Pp = Bonferroni corrected p-value.

Supplementary figure S2. Measures of disease activity and functional ability according to baseline anti-CCP status in the TRAM cohorts. Pp = Bonferroni corrected p-values.

Supplementary figure S3. Treatment with glucocorticoids in the early rheumatoid arthritis patients enrolled in the primary cohorts (A) TIRA-1, (B) TIRA-2; and in the confirmation cohorts (C) TRAM-1 (1996–2000), (D) TRAM-2 (2006–2011).

Supplementary figure S4. EULAR responses in historical cohorts TIRA-1 and TRAM-1 compared to the more recent cohorts TIRA-2 and TRAM-2, respectively.

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