CONCISE REPORT

Serological changes in the course of traditional and biological disease modifying therapy of rheumatoid arthritis

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ABSTRACT

Objective To investigate changes of rheumatoid factor (RF) and antibodies against citrullinated peptides (ACPA) during therapy with disease modifying antirheumatic drugs.

Methods We obtained clinical and serological data of patients from the treatment start and after 6 months of therapy. With non-parametric tests, we analysed changes of ACPA and RF levels between the two visits and the influence of treatment response. Furthermore, we analysed potential influential factors as disease chronicity, different therapeutics and the trend over 18 months.

Results 143 ACPA and RF positive patients were included. The median (25th/75th percentile) relative changes after 6 months were −35.6% (−63.3; −8.3) for RF and −15.2% (−40.0; 10.0) for ACPA (p<0.001 for both). Changes of RF levels were significantly greater than those seen for ACPA (p<0.001). The decrease of ACPA and RF was significantly higher in treatment responders (p=0.034 and p=0.01, respectively). Aside from changes in disease activity, only a short disease duration showed an independent effect on changes of RF levels (p=0.087).

Conclusions ACPA and RF levels decreased significantly after 6 months of therapy. Reductions of both autoantibodies were closely linked to a reduction of disease activity; RF declined faster, to a larger extent and in greater numbers of patients than ACPA.

Rheumatoid factor (RF) and antibodies against citrullinated peptides (ACPA) are established markers in the diagnostic approach to rheumatoid arthritis (RA).1 Besides their diagnostic relevance, RF and ACPA also have a prognostic value, since both are associated with more aggressive, destructive disease.2–4 Moreover, high RF levels are related to extra-articular manifestations.1 For these reasons, RF and ACPA are part of the 2010 RA classification criteria,5 and considered bad prognostic markers in the European League Against Rheumatism (EULAR) recommendations for the management of RA.6 Several studies examined changes of these autoantibodies (AAB) in the course of therapy; but especially for ACPA, findings were inconsistent.7–9

Given the current efforts to treat RA to a treatment target considering individual risk factors,10 the presence and levels of these AAB are therapeutically highly relevant.6 The aim of the present study was to evaluate the responsiveness of ACPA and RF levels during therapy of RA; in this context, we also aimed to consider the influence of individual therapeutic agents and treatment response with a special focus on the impact of disease duration and trend over time.

METHODS

Patients

We obtained data on RA outpatients who were seen at our clinic where data on every visit are prospectively documented in an observational database.11 All participants fulfilled the 1987 American College of Rheumatology (ACR),12 or more recently, the 2010 ACR/EULAR classification criteria for RA5 and were recruited between February 2006 and October 2011. We selected patients with at least low disease activity, in whom a traditional or biological disease modifying antirheumatic drug (DMARD) was initiated, and identified those who were seropositive for ACPA and RF. For each patient, we selected only the treatment course with the longest follow-up period in order to maintain data independence in our analyses. All patients consented to an anonymous data analysis, and the local ethics committee had approved the data collection.

Study variables

At baseline and after 3, 6, 12 and 18 months of therapy, levels of RF (U/ml; positive >14 U/ml) and ACPA (U/ml; positive ≥8 U/ml) were obtained; ACPA levels >340 U/ml had not been further diluted, and since we were interested in changes in AAB levels, these patients were excluded. Furthermore, we collected patient and evaluator global assessments of disease activity; pain; swollen and tender joint count (SJ28 and TJC28); the Health Assessment Questionnaire Disability Index; C reactive protein (in mg/dl) and erythrocyte sedimentation rate (in mm/h). We mainly used the Simplified Disease Activity Index (SDAI) to measure disease activity.13

Statistical analysis

In most of our analyses, to account for the starting point (baseline level) of RF or ACPA, we evaluated relative rather than absolute changes within the first 6 months. All data were analysed by non-parametric statistics. To facilitate graphical illustration, we used a fractional rank depiction (‘probability plots’) with a 100% cap for worsening. All analyses were performed with SPSS.
We initially investigated whether overall significant serological changes are observable during 6 months of therapy, and if these changes were different for RF compared with ACPA. Next, we investigated the effects of treatment response, defined by SDAI50 criteria,14 in relation to the observed changes in the serological measures. In addition to this categorical approach, we also used Spearman correlation to assess if individual disease activity components were associated with relative changes in AAB.

We then analysed the role of disease duration in AAB reactivity, comparing AAB changes in early (<12 months) and established RA (≥12 months), and of different therapeutics comparing methotrexate (MTX) with other traditional DMARDs, tumour necrosis factor α inhibitors (TNFi) and other biologicals. The analyses of treatment types and chronicity were then also adjusted for the differences in disease activity changes (a suspected major confounder) by calculating the % change of ACPA and RF per % change of SDAI.

Finally, we investigated the trend over time of ACPA and RF levels and of the SDAI. To this end, we selected patients who received the same therapeutic agent throughout a period of at least 18 months. Missing values were estimated by interpolation.

RESULTS

Study population

For our main analyses on changes after 6 months of therapy, data of 143 patients with complete datasets at least these two time points were available. Clinical and demographic characteristics are shown in table 1.

Changes of ACPA and RF levels

The median (quartiles) absolute changes over 6 months of therapy were −9 U/ml (−42; 6) for ACPA (p<0.001) and −52 U/ml (−115; −4) for RF levels (p<0.001), as depicted in figure 1A. Median relative changes compared with baseline were −15.2% for ACPA (−40.0; 10.0) and −35.6% for RF (−65.3; −8.3), respectively. The changes of RF levels were significantly greater than those seen for ACPA (p<0.001).

Effects of treatment response

The decrease of ABB was significantly higher in the 60 patients (42%) with treatment response than in those without (p=0.034 and p=0.01, respectively, figure 1B/C) (see online supplementary table S1 for ORs of improvement in serological markers among patients with different clinical response). The median absolute change for treatment responders was −17 U/ml (−68; 0) for ACPA and −43 U/ml (−143; −12) for RF and the relative changes were −26.5% (−44.4; 0) and −47.9% (−66.7; −18.8), respectively. The serological changes in treatment responders were highly significant (ACPA: p=0.001; RF: p<0.001). In SDAI50, non-responders absolute and relative changes were −5.1 U/ml (−56; 9) and −7.5% (−27.0; 11.1) for ACPA and −18.0 U/ml (−96.0; 4.0) and −26.4% (−57.1; 3.5) for RF respectively. In non-responders, the serological changes were clearly significant for RF (p<0.001), but failed to reach significance for ACPA (p=0.059). Correlations between changes of ACPA/RF and changes of individual disease activity variables are shown in table 2.

Effects of disease chronicity, different therapeutics and temporal trends

RF but not ACPA levels, were more likely to improve within the first year from disease onset (p=0.059; p=0.516; figure 1D,E) than later. After adjusting for disease activity we still found a trend that RF titres decrease more clearly in patients with early RA, although differences were not statistically significant (RF p=0.087; ACPA p=0.802) (see online supplementary text and online supplementary table S2 for AAB changes on different types of treatment).

We could analyse AAB changes of 82 patients over 18 months. After 3 months, ACPA declined about 4.6% in relation to baseline, RF about 13.2% and SDAI about 23.5%; after 12 months, these values were 16.9%, 51.4% and 40.5%; and after 18 months, 23.8%, 35.2% and 44.3%, respectively.

DISCUSSION

In the current study, we show that ACPA as well as RF levels decrease significantly after 6 months of therapy. The findings presented are in line with previous studies, which mainly examined changes under individual TNFi.9 15 16 RF seems to be more reactive than ACPA, as we found significant decreases in RF levels indicating a subclinical therapeutic effect. While the finding could also indicate that ACPA might be a better marker to follow changes in disease activity, or that the decreases in RF levels indicate a subclinical therapeutic effect. The much lower decrease of ACPA than RF in patients experiencing therapeutic efficacy and the correlation of clinical markers of disease activity with RF but not ACPA changes indicate that ACPA are overall less responsive to therapy, whether these effects are clinically visible or only subclinical.

ACPA, anti-citrullinated peptide antibodies; CDAI, clinical disease activity index; CRP, C reactive protein; DAS 28, disease activity score 28; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; PGA, patient global assessment; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.
In simple correlation analyses, acute phase reactant changes were similarly associated with changes of ACPA and changes of RF, while changes of SJC, pain and patient global assessment were only correlated with changes of RF. The latter finding is very intriguing and one can only speculate that RF may be more strongly involved in activating cytokine production within the joints and that these local events are linked with swelling, but also with pain, which has been suggested associated with enhanced release of proinflammatory cytokines, like interleukin (IL)-6. IL-6 is, vice versa, also involved in B cell differentiation and the development of antibody-producing plasma cells. This might constitute a link between all these variables.

RF level declines were greater in patients with a disease onset of less than 12 months; in accordance with the bad prognostic impact of RF, this could indicate that a prognostic difference can be made only at an early stage of the disease in many patients, consistent with the ‘window of opportunity’ theory in RA.

In contrast to a previous study, changes of ACPA were not influenced by disease duration. This may be related to differences in study design and the small sample size of the published study.

One limitation in our study assessments was the fact that ACPA levels >340 U/ml were not further diluted; we were able to show that a comparable exclusion of the patients with the top RF levels did not affect the results (data not shown). In addition, we were not able to address the potential impact of changes in AAB levels on structural progression in our study; since both AAB are linked with radiological progression, this is another limitation.

**Figure 1** Probability plots of relative changes of anti-citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF). Panel A shows the differences between relative changes of ACPA and RF. Panels B (ACPA) and C (RF) depict the influence of treatment response and panels D (ACPA) and E (RF) the differences between patients with early and established rheumatoid arthritis. SDAI, Simplified Disease Activity Index.

**Table 2** Correlations (95% CI) between relative changes of ACPA/RF and relative change of SDAI, CRP, ESR, SJC, TJC, PGA, EGA, HAQ and pain.

<table>
<thead>
<tr>
<th>Change</th>
<th>ACPA (r)</th>
<th>RF (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDAI</td>
<td>0.263** (0.085/0.425)</td>
<td>0.327** (0.154/0.480)</td>
</tr>
<tr>
<td>CRP</td>
<td>0.336** (0.164/0.488)</td>
<td>0.261** (0.082/0.423)</td>
</tr>
<tr>
<td>ESR</td>
<td>0.268** (0.090/0.429)</td>
<td>0.243** (0.063/0.407)</td>
</tr>
<tr>
<td>SJC</td>
<td>0.110 (−0.073/0.287)</td>
<td>0.236* (0.056/0.401)</td>
</tr>
<tr>
<td>TJC</td>
<td>0.174 (−0.009/0.345)</td>
<td>0.179 (−0.004/0.349)</td>
</tr>
<tr>
<td>PGA</td>
<td>0.143 (−0.040/0.317)</td>
<td>0.275* (0.098/0.435)</td>
</tr>
<tr>
<td>EGA</td>
<td>0.210* (0.029/0.378)</td>
<td>0.262* (0.084/0.424)</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.063 (−0.121/0.243)</td>
<td>0.038 (−0.145/0.219)</td>
</tr>
<tr>
<td>Pain</td>
<td>0.054 (−0.129/0.234)</td>
<td>0.231** (0.050/0.396)</td>
</tr>
<tr>
<td>ACPA/RF</td>
<td>0.336** (0.164/0.488)</td>
<td></td>
</tr>
</tbody>
</table>

Only patients with no missing data were used for analysis (n=116). *p<0.05 and **p<0.01.
ACPA, anti-citrullinated peptide antibodies; CRP, C reactive protein; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; PGA, patient global assessment; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SJC, swollen tender joint count; TJC, tender joint count.
Clinical and epidemiological research

In conclusion, we were able to show that ACPA and RF levels decreased significantly after 6 months of therapy as well as subsequently and that decreases were closely linked to an improvement of disease activity. RF declined faster, to a larger extent and in greater numbers of patients than ACPA. Further research is needed to investigate whether reductions of ACPA and RF levels are associated with better structural and functional outcomes of RA in the longer term.

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Contributors CB: Study design, data acquisition, data analysis, manuscript drafting. HR: Data acquisition, data analysis, study design, data analysis, manuscript drafting.

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