Autoantibody Profiling as Early Diagnostic and Prognostic Tool For Rheumatoid Arthritis

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Objective. Early therapy prevents progression of joint damage in rheumatoid arthritis (RA), but diagnosis in early disease is impeded by lack of appropriate diagnostic criteria. Our main objective was to study the value of rheumatoid factor (RF), anti-cyclic citrullinated peptide autoantibodies (anti-CCP) and anti-RA33 autoantibodies for diagnosis of RA and prediction of outcome in patients with very early arthritis.

Methods. The prospective follow-up inception cohort included 200 patients with very early (<3 months) inflammatory joint disease. Autoantibodies were measured at baseline and analyzed in a tree-based model aiming to determine the added diagnostic value of testing for anti-CCP and anti-RA33 as compared to RF alone.

Results. RA was diagnosed in 102 patients, while 98 developed other inflammatory arthropathies. Receiver operator curve analysis revealed an optimum cut-off level for RF at 50 U/ml, above which anti-CCP and anti-RA33 had no additional diagnostic value. Remarkably, RF≥50 U/ml and anti-CCP showed similar sensitivity and high specificity for RA, but overlapped considerably. Anti-RA33 was less specific and did not correlate with RF or anti-CCP. Among RA patients, 72% showed at least one of these three autoantibodies, compared to 15% of non-RA patients. RF≥50 U/ml and anti-CCP were predictors of erosive disease, while anti-RA33 was associated with mild disease.

Conclusions. These data suggest stepwise autoantibody testing in early inflammatory joint disease, starting with RF followed by anti-CCP (in patients with RF<50 U/ml), and finally anti-RA33 as a sensitive and effective strategy for distinguishing RA patients at high risk for poor outcome.
Introduction

During the last decade the therapeutic paradigms in rheumatoid arthritis (RA) have changed considerably. Evidence for the occurrence of joint erosions within the first few months in the course of RA has led to recognition of the importance of early institution of disease modifying antirheumatic drugs (DMARDs), which can retard the progression of disability [1-3]. Such advantage was shown in several early RA trials, which often included patients with symptom duration of less than one year [4;5]. Furthermore, it has been demonstrated that such therapy initiated within only 3 months of symptom onset is more efficient when compared to even short delays of therapy with an ongoing beneficial effect in long-term follow-up [6;7].

However, early treatment of RA requires reliable differential diagnosis, which may be difficult in the initial stage of inflammatory joint disorders. The clinical presentation of RA and other arthritides early in their course is not always characteristic; moreover, classification criteria for RA, developed in established disease [8], are frequently not fulfilled in early stages [9;10]. Thus, instead of searching for fulfillment of classification criteria among early inflammatory joint diseases, it remains important to predict joint destruction, which primarily relates to RA, as early in the disease course as possible.

Among the seven classification criteria of the American College of Rheumatology (ACR) for RA, rheumatoid factor (RF) is the only serological marker [8]. RF has been shown to be associated with unfavourable outcome in terms of joint destruction and disability [11], particularly when present in high titer [12]. However, RF is often negative or low-titred in the early disease stages. Among several novel autoantibodies described in recent years in patients with RA, anti-cyclic citrullinated peptide antibodies (anti-CCP), which bind antigenic determinants containing the unusual amino acid citrulline, appear to be the most promising [13]. Such determinants have been found in several proteins including filaggrin, fibrinogen/fibrin and vimentin [14;15]. Another autoantibody of potential diagnostic value is anti-RA33 which is directed to the heterogeneous nuclear ribonucleoprotein A2; although less specific for RA than anti-CCP, anti-RA33 may nevertheless prove helpful for the diagnosis of RA [16].

Production of RF, anti-CCP and anti-RA33 may occur early in the disease and even can precede the development of clinical manifestations in RA by several years [17-19]. Concerning anti-CCP, recent studies have described their occurrence in 41-68% of patients with early RA [20-26]. However, up to 90% of anti-CCP positive patients were also positive for RF [20;21;24] and co-occurrence of both antibodies was not more specific for RA than either antibody alone [25;27].

Given this frequent concurrence of RF and anti-CCP as well as the economic impact of broad anti-CCP testing, we investigated if autoantibody profiling by sequential testing at first presentation might have diagnostic and prognostic value in differentiating RA from other arthritic disorders in an inception cohort of patients with very early inflammatory joint disease.
Patients and Methods

Patients
An inception cohort of patients recruited within the Austrian Early Arthritis Action was followed prospectively. Details of this patient population have been described elsewhere [10;28;29]. Briefly, patients were included into this study if they fulfilled the following criteria: symptom duration <3 months, non-traumatic synovitis of at least one joint, and erythrocyte sedimentation rate >20mm or C-reactive protein >0.5mg/dl. Informed consent was obtained from all patients enrolled. The study was approved by the local Ethical Committee and followed the Good Clinical Practice–International Congress of Harmonization guidelines. The first 200 consecutive patients who had follow-up examinations over at least 6 months were included in the present analysis.

Initial preliminary diagnoses were based on the appropriate diagnostic or classification criteria and clinical judgment. When such preliminary diagnosis could not be established the disease was classified as undifferentiated arthritis. All diagnoses were ascertained clinically in the course of the disease and/or by chart review after 6 or 12 months by an experienced rheumatologist (KPM). RA was diagnosed in patients with persistent arthritis of more than 12 weeks, if the ACR criteria for RA were fulfilled at baseline and/or cumulatively during the first year of follow-up [30-32].

Detection of autoantibodies
RF was measured by nephelometry; a level of >20 U/ml was considered positive. Anti-CCP antibodies were measured by ELISA (Axis Shields Diagnostics, Dundee, UK) and considered positive above a cut-off value of 5 arbitrary units as suggested by the manufacturer. Anti-RA33 was assessed by immunoblotting using recombinant and natural antigens as described previously [33;34]. Antibodies were determined at first visit, i.e. in patients with <3 months of symptom duration and additionally at 6 and 12 months from baseline, and every 6 months thereafter, when applicable.

Clinical and radiographic assessments
Clinical and laboratory data were collected every three months according to the core set of disease activity measures for RA [35]. The disease activity score DAS28 was calculated as a measure of RA activity [36]. In patients with RA, initial and yearly follow-up radiographs of hands and feet, blinded for group and sequence, were assessed by a rheumatologist (KPM) and a radiologist (MU). In order to account for any fortuitous findings of singular erosions, only patients with at least two erosions in at least two different joints were classified as erosive. Erosions were defined as follows: presence of at least two unequivocal lesions on any hand or foot joint except the DIP joint with unequivocal cortical break of at least one millimetre in width in one of the erosions or, if the erosion or the cortical break was smaller, presence of at least two such lesions on different joints. In addition, radiographs were scored according to the Larsen method on 42 joints in the hands and feet: firstly, films were scored using the traditional Larsen scoring with 0 (normal) to 5 (mutilating changes) for each individual joint [37]; secondly, grade 1 scores were abandoned and the total scores recalculated [38]. Only the latter modified Larsen score will be shown in our analyses. Precision of assessment was ascertained by re-assessing a subset of 40 randomly chosen X-rays: the correlation coefficient between both assessments was 0.86 (95% CI: 0.805 to 0.906).
Statistical analysis

The SPSS statistical software was used for statistical analysis (SPSS Inc., Chicago, IL). The reported p-values are the results of two-sided tests. A p-value \( \leq 0.05 \) was considered significant. To determine the added diagnostic value of testing for anti-CCP and anti-RA33 in addition to RF, as opposed to RF testing alone, for differentiation of RA vs. non-RA, we used a tree-based approach by taking into account the continuous RF levels and the corresponding dichotomous anti-CCP and anti-RA33 status (0 for negative, 1 for positive test). The RF level with the highest accuracy (sum = sensitivity plus specificity), determined from a receiver operating characteristics curve (ROC) [39], was used as a candidate cut-off level that would split samples into two clusters: above this candidate RF level, the additional information from anti-CCP and/or anti-RA33 testing would not add significant predictive value in distinguishing RA from non-RA; below this level, a positive anti-CCP and/or anti-RA33 test would be of further diagnostic value. The area under the ROC for the tree based model was computed, indicating, for a randomly chosen RA patient and a non-RA control patient, the probability that the RA patient will have a higher test value than the control: a value of 0.5 indicates no discrimination and a value of 1 perfect discrimination.

The presence of erosions in RA patients with at least one-year follow-up and complete sets of X-rays of hands and feet was used as the major outcome variable (erosive vs. non-erosive disease) for determination of the prognostic value of autoantibodies at baseline. In addition, changes from baseline in Larsen scores were analyzed in patient groups with different autoantibody profiles at baseline and analyzed by employing the summary measures approach by Matthews et al [40]. For Larsen scores the regression of score over time was computed for each patient and the resulting regression coefficients were considered to summarize individual progression over time. Differences in regression coefficients between the groups were non-parametrically tested using the Wilcoxon ranked sum test (\( p_{sm} \)). Binary variables were analyzed using the Chi Square test (\( p \)).

Results

Diagnoses at baseline and after follow-up

Among the 200 patients enrolled in this study 75 patients had at first visit a preliminary diagnosis of RA with 35 of them fulfilling the ACR criteria for RA at baseline. After 1 year 102 patients had a final diagnosis of RA and all fulfilled the ACR criteria within the first year. As soon as RA was suspected patients were started on traditional DMARDs. Among the 98 non-RA patients, 37 patients were finally diagnosed as undifferentiated arthritis, 36 as reactive arthritis, and 25 had other diagnoses. For further analyses, the 98 non-RA patients were seen as one group.

RA patients were slightly older at symptom onset, with a mean age of 50 (range 18-83) years as opposed to 43 (range 18-87) years in non-RA patients. The proportion of female patients, median symptom duration until first presentation in clinics and disease activity scores were similar for RA and non-RA patients. Follow-up time for RA patients was 27 months median (range 6-48 months ), and 18 months median (range 6-48 months) for non-RA patients.
Determination of the optimum cut-off value for RF in a tree-based model and diagnostic value of RF, anti-CCP and anti-RA33

RF, anti-CCP and anti-RA33 was measured at baseline in all patients. To determine the added diagnostic value of anti-CCP and anti-RA33 as compared to RF alone, the data were entered into a tree-based model, which found a candidate cut-off level for RF at 49.75 U/ml as deduced from a ROC curve (Fig.1): only below this RF level, a positive anti-CCP and/or anti-RA33 test would add significant further diagnostic value. RF values ≥50 U/ml will be referred to as “high-titre” RF.

Based on this finding sensitivity, specificity and positive predictive values (PPV) of total RF (>20 U/ml), high-titre RF (≥50 U/ml), anti-CCP and anti-RA33 were calculated (Table 1A): RF>20 U/ml was present in 55% of RA and in 11% of non-RA patients resulting in a specificity of 89%. High-titre RF, however, occurred in 45% of RA but in only 4% of non-RA patients, while “low-titre” RF (<50 U/ml) was detected with similar frequency in both groups (10% and 7%, respectively) and therefore of little diagnostic value. Therefore in subsequent analyses patients with negative or low-titre RF were grouped together. For anti-CCP a sensitivity of 41% and a very high specificity of 98% was found which was remarkably similar to the values obtained for high-titre RF. The resulting PPVs were 92% for high-titre RF and 96% for anti-CCP. Compared to these two antibodies anti-RA33 was less sensitive (28%) and less specific (90%) resulting in a PPV of 74%. Noteworthy, while high-titre RF and anti-CCP overlapped considerably with 28% of early RA patients showing both antibodies (p<0.0001), anti-RA33 was not associated with either antibody. Importantly, anti-RA33 and anti-CCP occurred with identical frequencies (14%) in patients with low-titre or negative RF, with only a single of the 28 patients being positive for both specificities (Table 1B).

Table 1. Diagnostic value of RF, anti-CCP and anti-RA33 autoantibodies.

(A) Data in the overall patient population. High-titre RF (≥50 U/ml) and anti-CCP both showed high specificity and comparable sensitivity, whereas low-titre RF occurred with similar frequency in the RA and in the non-RA group. (B) Anti-CCP and anti-RA33 in the subgroup of patients with negative or low-titre RF. In this group both antibodies showed the same prevalence and did not concur.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=200)</th>
<th>RA n=102</th>
<th>Non-RA n=98</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF (&gt;20 U/ml)</td>
<td>56</td>
<td>11</td>
<td>55</td>
<td>89</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>High-titre RF (≥50U/ml)</td>
<td>46</td>
<td>4</td>
<td>45</td>
<td>96</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>42</td>
<td>2</td>
<td>41</td>
<td>98</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Anti-RA33</td>
<td>29</td>
<td>10</td>
<td>28</td>
<td>90</td>
<td>74</td>
<td></td>
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</tbody>
</table>

*PPV positive predictive value

B.

<table>
<thead>
<tr>
<th></th>
<th>Patients with RF&lt;50 U/ml (n=150)</th>
<th>RA n=56</th>
<th>Non-RA n=94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CCP</td>
<td>14</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Anti-RA33</td>
<td>14</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Both antibodies</td>
<td>1</td>
<td>0</td>
<td></td>
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</tbody>
</table>
**Prognostic value of autoantibodies: correlation with erosive disease**

Complete X-ray sets were available from 66 RA patients. Unfortunately, films of the remaining 36 patients were not available for analysis due to logistic reasons. However, baseline values of these patients did not differ significantly from the values of patients available for analysis (data not shown). After a median follow-up time of more than 2 years, 36 patients (55%) had erosive disease, but only 4 (6%) of them had erosions already at first visit. The initial distribution of DMARDs was similar in erosive and non-erosive patients. However, DMARD switches were significantly more frequent in patients who developed erosive disease. High-titre RF and anti-CCP were significantly associated with an increased risk to develop erosions as demonstrated by PPVs of 78% for RF and 88% for CCP (Table 2A). In contrast, anti-RA33 was similarly distributed among the erosive and the non-erosive group and therefore not associated with erosive disease (Table 2A and B).

**Table 2. Prognostic value of autoantibodies for development of erosive disease in RA patients.**

(A) High-titre RF, anti-CCP and anti-RA33 in RA patients with erosive and non-erosive disease. (B) Anti-CCP and anti-RA33 in the subgroup of patients with negative or low-titre RF.

<table>
<thead>
<tr>
<th></th>
<th>Erosive (n=36)</th>
<th>Non-erosive (n=30)</th>
<th>PPV</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-titre RF, n</strong></td>
<td>21</td>
<td>6</td>
<td>78%</td>
<td>p=0.002</td>
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<tr>
<td><strong>Anti-CCP, n</strong></td>
<td>22</td>
<td>3</td>
<td>88%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Anti-RA33, n</strong></td>
<td>11</td>
<td>7</td>
<td>61%</td>
<td>p=0.51</td>
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</tbody>
</table>

**B.**

<table>
<thead>
<tr>
<th>RA patients with RF&lt;50 U/ml (n=39)</th>
<th>Erosive (n=15)</th>
<th>Non-erosive (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CCP, n</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Anti-RA33, n</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Both, n</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

In predicting erosive disease in RA patients with low-titre or negative RF, anti-CCP appeared to be of particular value (Table 2B): 15 patients of this group developed bone erosions and 7 of them were anti-CCP positive at first visit, while among the 24 non-erosive patients only 2 showed this antibody (p=0.006).

Mean Larsen scores at baseline were similar in all groups, irrespectively of their autoantibody status (Fig. 2). However, Larsen scores were significantly higher in high-titre RF patients than in patients with low-titre or negative RF ($p_{sm}<0.0001$, Fig. 2A); the same was found for anti-CCP positive versus anti-CCP negative patients (data not shown). Importantly, within the subgroup of patients with low-titre or negative RF, anti-CCP positive patients showed significantly more rapid radiographic progression ($p_{sm} = 0.038$, Fig. 2B). To evaluate the independent value of RF as predictive marker for radiographic progression, we additionally analysed the subgroup of anti-CCP negative patients: again, patients with high-titre RF showed significantly higher Larsen scores ($p_{sm} = 0.0014$, Fig. 2C). Thus, the slope of progression of joint destruction was much steeper in patients presenting with high-titre RF and/or anti-CCP at baseline than in those negative for these autoantibodies.
Prognostic value of autoantibodies: correlation with disease activity

Disease activity at baseline (as measured by DAS28) was similar in all patients, irrespective of the antibody status (Fig. 3). However, improvement was significantly better in patients with low-titre or negative RF than in patients with high-titre RF (p=0.004). Among patients with RF<50 U/ml, the anti-CCP positive ones showed higher disease activity than anti-CCP negative patients, but the difference did not reach the level of significance, presumably due to the relatively small number of patients in this group. Anti-RA33 positive patients on the other hand, improved on DMARDs from baseline to a significantly higher degree than RF or anti-CCP positive patients. Noteworthy, improvement in anti-RA33 positive patients was even better than in patients negative for all three autoantibodies (p=0.044). Thus, anti-RA33 (when occurring alone) appears to characterize patients with mild disease and a more favourable outcome.

Development of an algorithm for serological testing

The data obtained suggested stepwise testing for the three autoantibodies as an efficient strategy for identifying patients with early RA at high risk for developing erosive disease (Fig. 4). Since 45% of the 102 RA patients and only 4% of the 98 non-RA patients had high-titre RF there would have been no further need to test these patients for anti-CCP or anti-RA33 in order to assess the diagnosis of RA and the risk of an unfavourable outcome. Among the 150 remaining patients however, anti-CCP testing was of great diagnostic benefit because 14 additional RA patients could be identified with only 2 non-RA patients being positive. This resulted in 59% of RA and 6% of non-RA patients positive for high-titre RF and/or anti-CCP. Moreover, RA patients showing either of the two antibodies had a significantly increased risk for development of erosive disease. Among the 134 patients (42 RA and 92 non-RA) negative for these two antibodies, anti-RA33 testing revealed an additional 13 RA patients but was also positive in 9 non-RA patients.

In summary, only 28% of RA patients were negative for all three autoantibodies compared to 85% of non-RA patients. This model of stepwise testing for 3 different autoantibodies therefore yields an overall sensitivity of 72% for the diagnosis of RA in patients with very early inflammatory joint disease.

Discussion

The ability to identify those patients who will develop progressive, erosive disease remains the major objective in early arthritis because these patients may particularly benefit from early, more intensive treatment. Patients treated with DMARDs within the first few weeks to months after symptom onset have shown a long-lasting benefit regarding retardation of disease progression compared to RA patients with delayed onset of therapy [1-7]. Since only patients with inflammatory joint disease of less than three months symptom duration were studied here, we were able to investigate the autoantibody profiles within only a few weeks from onset of clinically apparent synovitis both in RA patients and in an inherent control group meeting the same inclusion criteria, but developing other forms of inflammatory arthritis.

The proposed diagnostic algorithm for autoantibody testing in patients with very early inflammatory joint disease (Figure 4) is not only helpful in establishing a diagnosis of RA in more than 70% of the patients, but also allows to define patients at increased risk for developing erosive disease. The first step of this algorithm, the presence of high-titre RF,
conformed with the diagnosis of RA in 45% of the RA patients and showed high disease specificity which was surprisingly similar to that found for anti-CCP. While the high specificity of anti-CCP is undisputed, RF is often considered a reasonably sensitive but relatively non-specific marker of RA which - as the data clearly demonstrate - depends on the choice of the cut-off level. The optimum cut-off level for RF calculated in the tree-based model was in very good agreement with previous reports showing that only RF ≥50 U/ml was significantly associated with RA [12;25;27]. Together, these findings suggest to consider redefinition of RF positivity for RA since RF<50 U/ml seems to be of little if any diagnostic usefulness. Thus, in an early arthritis clinic only patients with high-titre RF should be considered RF positive. This justifies the proposed step-wise approach to autoantibody determination which is also in line with previous notions that RF and anti-CCP frequently concur [20;21] and that the presence of both antibodies is not more specific for RA than either antibody alone [25;27]. Since also the prognostic values of high-titre RF and anti-CCP for erosive disease were comparable, testing patients with high-titre RF additionally for anti-CCP seems to be of limited diagnostic benefit. However, when RF is of low-titre or negative, anti-CCP is an extremely helpful diagnostic marker being not only highly specific for RA but also strongly associated with erosive disease, which is in full agreement with other reports [25-27]. Overall, it should be be noted that despite the excellent performance of high-titre RF, anti-CCP proved slightly superior and this both with respect to disease specificity and prognostic value. Thus, if there were no financial restrictions it might be more advisable to determine anti-CCP first and RF additionally in anti-CCP negative patients, or ideally, both antibodies in parallel. Considering costs, even though anti-CCP testing is considerably more expensive than RF determination, one could argue that in case of a positive anti-CCP result follow-up testing would not necessarily be required.

Taken together, for now the proposed algorithm may help to establish in an effective manner diagnosis and prognosis in the majority of patients with very early inflammatory joint disease, which needs to be confirmed in other cohorts of very early arthritis patients. Since both high-titre RF and anti-CCP are strong predictors of erosive disease, therapeutic strategies in patients showing such antibodies may have to be adapted in terms of a more aggressive approach, including use of the most efficient compounds available today [41-43]. Anti-RA33 on the other hand, despite its limited specificity, may be of usefulness in patients negative for high-titre RF and anti-CCP allowing to identify patients with a good prognosis who will respond well to treatment with DMARDs. Thus, autoantibody signatures convey diagnostic and prognostic insights that may allow designing appropriate therapeutic strategies already at first visit, a time point most challenging in the course of RA.

Acknowledgements

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References


Figure 1. Receiver operating curve (ROC) for the tree-based model.

Using a computer based tree model we determined the optimum cut-off value for RF above which performing anti-CCP and/or anti-RA33 would add no significant benefit in identifying patients with RA. This value was found at 49.75 IU/l (indicated by an arrow) and RF values $\geq$50 U/ml were subsequently called “high-titer” RF. The ROC revealed an area under the curve for this model of 0.78.

Figure 2. High-titre RF and anti-CCP are associated with rapid radiographic progression of RA.

Boxplots showing the difference in Larsen scores (grade 1 abandoned) in (A) RA patients with high-titre RF vs. low-titre or negative RF, (B) RA patients with low-titre or negative RF, positive or negative for anti-CCP, and (C) anti-CCP negative RA patients with high-titre RF vs low-titre or negative RF. The box shows median values and 25th/75th percentiles. $p_{sm}$ values indicate differences in regression coefficients between the groups. Baseline values were similar in all groups, but Larsen score progression was significantly higher in patients with high-titre RF than in patients with low-titre or negative RF, and this both in the overall RA population ($p_{sm}$<0.0001; Fig.2A), and also in the subpopulation of anti-CCP negative patients ($p_{sm}$ = 0.0014; Fig. 2C); a significant difference in progression was also seen between anti-CCP positive and anti-CCP negative patients in the subpopulation of patients with low-titre or negative RF ($p_{sm}$=0.038; Fig. ‘2B).

Figure 3. Prognostic value of autoantibodies for predicting improvement of disease activity.

Baseline disease activity (DAS28) was similar in all patient groups (grey columns). At study endpoint, DAS28 (striped columns) was significantly lower in patients with RF<50 U/ml than in patients with high-titre RF. In patients with RF<50 U/ml the difference between anti-CCP positive and anti-CCP negative patients was not significant. DAS28 in anti-RA33 positive patients was markedly lower than in high titre RF or anti-CCP positive patients and even significantly lower than in patients negative for all three autoantibodies. $p$ values represent the difference in DAS28 at study endpoint between the autoantibody positive versus negative group.

Figure 4. Decision tree to determine risk of RA and erosive disease in patients with early arthritis.

All patients with early arthritis are tested for RF. High-titre RF ($\geq$ 50 U/ml) is highly predictive for the diagnosis of RA and for developing erosive disease, and there is no benefit of determination of additional autoantibodies. In patients with low-titre or negative RF, anti-CCP determination helps to identify additional RA patients at high risk for developing erosive disease. In patients negative for RF and anti-CCP, anti-RA33 testing may allow to identify patients with a more favourable outcome. Percentages shown correspond to the total numbers of RA and non-RA patients.
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Figure 2B

Larsen score

Low titre or negative RF
- anti-CCP negative
- anti-CCP positive

baseline 1 year 2 years 3 years
Patients presenting with early arthritis
102 RA* 98 non-RA*

Rheumatoid factor

RF > 50 U/ml
45% of RA, 4% of non-RA
High risk to develop RA
High risk to develop erosive disease
Positive
14% of RA, 2% of non-RA

RF < 50 U/ml

Anti-CCP

Positive
14% of RA; 2% of non-RA

Negative

Anti-RA33

Positive
13% of RA; 9% of non-RA

Negative
28% of RA; 85% of non-RA

Increased risk to develop RA
Good prognosis

Decreased risk to develop RA

*Final diagnoses

Figure 4
Autoantibody Profiling as Early Diagnostic and Prognostic Tool For Rheumatoid Arthritis

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