A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis

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Objectives. Identifying patients with RA at high risk of rapid radiographic progression (RRP) is critical for making appropriate treatment decisions. We developed an exploratory prediction model for the risk of RRP using an RA study population undergoing either conservative or aggressive disease management.

Methods. Using data from the active-controlled study of patients receiving infliximab for the treatment of rheumatoid arthritis of early onset (ASPIRE) early RA study, RRP was defined as a threshold change in modified Sharp/van der Heijde score (SHS) of ≥ 5 U/year. Spearman's rank analysis was used to identify baseline risk factors for RRP. Logistic regression was used to calculate the probability of RRP in 1 year. The results were combined into a matrix model that consisted of risk factors and initiated treatment arranged in increasing risk of RRP. Data from the anti-TNF trial in rheumatoid arthritis with concomitant therapy (ATTRACT) established RA study were applied to the model to test its generalizability in another population.

Results. The 28 swollen joint count, RF, CRP and ESR are included as trichotomous variables and initiated treatment (monotherapy or combination therapy) as a dichotomous variable. Two models, one incorporating all risk factors except CRP and another incorporating all risk factors except ESR, were developed to adjust for collinearity. These models identify subpopulations of RA patients at higher predicted risk for RRP.

Conclusions. These preliminary matrix models predict the risk of RRP using initiated treatment and easily accessible clinical and laboratory variables. Further testing in other populations and with other therapies is needed to obtain a definitive risk model that will guide rheumatologists in making treatment decisions for individual RA patients.

KEY WORDS: Risk model, Radiographic progression, Infliximab, TNF-α, RA, MTX.

Introduction

RA is a chronic systemic inflammatory disease predominantly characterized by joint inflammation and frequent progression of joint destruction resulting in decreased functional capacity, work disability and reduced quality of life [1–4]. Rapid radiographic progression (RRP) in RA usually occurs in a minority of treated patients. In these patients, effective therapy can reduce the odds of progression by as much as 78% [5], and both early and intensive treatment can alter the course of the disease by slowing the rate of radiographic progression [6–8]. The identification of individual RA patients at high risk of RRP is therefore critical to making appropriate treatment choices. Various clinical and biological markers have been identified as baseline risk factors for the progression of joint damage in patients with RA [8–12]. Although the use of any single baseline variable has limited value [13], combining multiple markers has been shown to improve predictive power [12–16].

One of the most widely used risk models in medicine is the Systematic Coronary Risk Evaluation (SCORE) Risk Chart [17]. This model predicts the 10-year probability of cardiovascular mortality based on a number of widely accepted risk factors (e.g. sex, blood pressure, lipid levels and tobacco use) that have been organized into a simple, visual, colour-coded matrix relative to an individual’s specific risk profile. However, a limitation of the SCORE chart is that it does not account for the associated adverse effects of the therapies that may influence the risk of adverse outcomes.

We aimed to create a similar visual matrix model that would predict the 1-year risk of RRP for individual RA patients based on associated risk factors and the type of initiated therapy (conservative vs aggressive management). We describe the first stage of development of this exploratory model using data from the active-controlled study of patients receiving infliximab for the treatment of rheumatoid arthritis of early onset (ASPIRE) from an early RA study population [18] and test whether the proposed method for outcome prediction could also be used in the anti-TNF trial in rheumatoid arthritis with concomitant therapy (ATTRACT) from an established RA study population [19]; both these groups were receiving either DMARD monotherapy or intensive anti-TNF plus DMARD combination therapy.

Methods

The ASPIRE and ATTRACT studies

In ASPIRE, 1049 MTX-naïve, early RA patients (disease duration 3 months–3 years) were double-blinded to randomly receive MTX monotherapy or MTX in combination with 3 or 6 mg/kg infliximab through 46 weeks [18]. In ATTRACT, 428 established RA patients with active disease despite treatment with stable-dose MTX (≥ 12.5 mg/week) were continued on MTX and additionally double-blinded to randomly receive placebo or 3 or 10 mg/kg infliximab through 54 weeks [19]. For this analysis, the infliximab plus MTX groups were combined in each respective study, since all dose groups within each study were well balanced for demographics and baseline disease characteristics and showed similar rates of radiographic progression through Week 54. This study is a subanalysis of the ASPIRE and the ATTRACT studies, both of which had ethical approval and informed patient consent. The authors had full access to the data of these studies. Relevant baseline demographics and disease characteristics are summarized in Table 1.

In both studies, patients were assessed at baseline for the 68 tender joint count (TJC), the 66 swollen joint count (SJC), ESR, CRP, RF and radiographs of the hands and feet.
The Westergren method was used to determine ESR at the local laboratory. CRP was measured by nephelometry. IgM-RF was evaluated at the central laboratory. Two readers blinded to treatment and timepoint scored the radiographs independently. The average of the two readers’ scores at each timepoint was used to calculate joint damage progression as defined by the change in the van der Heijde modification of the Sharp score (SHS) [20] from baseline to Week 54. In ASPIRE, the intraclass correlation coefficients were 0.87 at baseline and 0.88 at Week 54. The smallest detectable difference in SHS was defined at 9.0 and 8.6 U from baseline, respectively, in the ASPIRE and the ATTRACT studies.

**Determination of RRP**

To define RRP for the model, the proportions of patients in ASPIRE who rapidly progressed according to a range of thresholds of annual change in SHS (≥0 to ≥9) were compared with the mean/median progression rate and to the proportion of patients who had any progression. Sensitivity analyses using other thresholds of annual change in SHS were done to determine whether using an equally higher or lower definition of RRP would significantly affect the multivariate model.

**Selection of baseline risk factors**

Baseline risk factors to be included in the model were identified from the ASPIRE data set. The ASPIRE study design, which allowed for the inclusion of a range of RA patients (e.g. those with normal CRP, negative RF or no erosive disease) [18], provides an apt data set for examining 1-year radiographic progression in relation to various clinical and biological variables as well as administered therapy. Without making any assumptions on the distribution of the variables, Spearman’s correlation coefficients were used to evaluate the relationship between all available baseline variables and radiographic progression. Any two risk factors having a correlation coefficient >0.3 were investigated for collinearity to minimize the inclusion of duplicative factors. A comparison of the maximum rescaled $R^2$ was used to evaluate whether including only one of any pair of collinear factors would improve the face validity of the model without significantly reducing the predictive power.

Logistic regression analyses were performed to predict the risk of RRP from the selected baseline risk factors after adjustment for treatment group. These baseline risk factors include SJC, RF, and ESR or CRP, treated as ordinal variables. No adjustments were made for multiple testing. Predicted probability of RRP was calculated using a logistic regression analysis. For selected risk factors that are continuous variables, treatment group differences in the change in SHS from baseline to Week 54 were further explored using analysis of variance on van der Waerden normal scores to test for interaction among baseline characteristics. Statistical analyses were done using the SAS system (SAS Institute, Cary, NC, USA). All statistical tests were two-sided and tested at $\alpha = 0.05$.

**Development of the matrix risk model**

The selected baseline risk factors and initiated treatments were combined and arranged so that the risk of RRP increases from left to right and from bottom to top in the matrix model. Each continuous risk factor was presented in approximate tertiles based on clinical utility and the ability to identify subgroups of relevant size. A colour scheme ranging from blue (low risk) to red (high risk) was used to enhance visual readability. Patient baseline and radiographic data from ASPIRE were then used to generate the probabilities of RRP to populate the exploratory matrix risk model. Absolute and relative risk ratios and numbers needed to treat (NNT) were calculated using this generated model to evaluate the relative benefit of MTX monotherapy vs MTX plus infliximab in ASPIRE.

**Application of the matrix risk model**

To assess whether our matrix risk model—i.e. the method we used to arrange the combination of selected risk factors for risk prediction in an early RA data set—would be similarly predictive of the same definition of RRP in more advanced RA populations undergoing similar treatment, patient baseline and radiographic data from the ATTRACT study were used to generate the probabilities of RRP in a second, exploratory matrix risk model. Finally, to highlight the impact of the choice of conservative vs aggressive management on actual radiographic progression early in the disease course, we show the cumulative probability plots as described by van der Heijde et al. [21] of two ASPIRE patient subgroups selected based on their baseline risk factor profiles.

**Results**

**Determination of RRP**

The observed proportion of patients with radiographic progression in ASPIRE was inversely related to the threshold values tested, i.e. higher proportions for lower thresholds and vice versa (Table 2).

Based on our clinical experience and the fact that the complete destruction of one joint during 1 year is equal to an increase of 5 SHS units [22, 23], we arbitrarily selected this increase in SHS of ≥5 U/year as the definition of RRP for conceptual simplicity. Among patients who showed any radiographic progression, a threshold of ≥5 U/year in the SHS identified ~23% of those on

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**Table 1. Baseline demographics and disease characteristics across treatment groups**

<table>
<thead>
<tr>
<th></th>
<th>ASPIRE</th>
<th>ATTRACT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>1049</td>
<td>428</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>51 (41, 60)</td>
<td>53.5 (45, 60)</td>
</tr>
<tr>
<td><strong>Sex, female</strong></td>
<td>742 (71.1)</td>
<td>332 (77.6)</td>
</tr>
<tr>
<td><strong>Disease duration, years</strong></td>
<td>0.6 (0.4, 1.1)</td>
<td>8.4 (4.3, 14.7)</td>
</tr>
<tr>
<td><strong>HAQ score (scale 0–3)</strong></td>
<td>1.5 (1.0, 1.9)</td>
<td>1.8 (1.3, 2.1)</td>
</tr>
<tr>
<td><strong>TJC</strong></td>
<td>31 (22, 44)</td>
<td>31 (19, 44)</td>
</tr>
<tr>
<td><strong>SJC</strong></td>
<td>19 (14, 26)</td>
<td>20 (13, 29)</td>
</tr>
<tr>
<td><strong>CRP, mg/dl</strong></td>
<td>1.4 (0.4, 4.1)</td>
<td>2.6 (1.1, 5.1)</td>
</tr>
<tr>
<td><strong>ESR, mm/h</strong></td>
<td>40 (23, 61)</td>
<td>42 (32, 65)</td>
</tr>
<tr>
<td><strong>RF, U/ml</strong></td>
<td>178 (30, 357)</td>
<td>178 (48, 425)</td>
</tr>
<tr>
<td><strong>Total modified SHS</strong></td>
<td>5.0 (1.5, 14.0)</td>
<td>51.5 (20.6, 113.0)</td>
</tr>
<tr>
<td><strong>Patients with joint erosion</strong></td>
<td>854 (82.0)</td>
<td>415 (99.1)</td>
</tr>
<tr>
<td><strong>Patients with joint space narrowing</strong></td>
<td>687 (65.9)</td>
<td>402 (95.9)</td>
</tr>
<tr>
<td><strong>Patients with prior joint surgery</strong></td>
<td>3 (0.3)</td>
<td>90 (21.0)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or n (%).

**Table 2. Radiographic progression through Week 54 according to various thresholds in the ASPIRE early RA population**

<table>
<thead>
<tr>
<th></th>
<th>MTX monotherapy</th>
<th>Infliximab plus MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression in the modified SHS, U/year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± s.d.</td>
<td>3.7 ± 0.4</td>
<td>0.5 ± 0.6</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>0.3 (0.0, 4.4)</td>
<td>0.0 (–1.0, 1.3)</td>
</tr>
<tr>
<td>Range</td>
<td>(–22.3, 67.9)</td>
<td>(–34.7, 48.0)</td>
</tr>
<tr>
<td><strong>Patients with progression in SHS, U/year, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0</td>
<td>52.0</td>
<td>39.2</td>
</tr>
<tr>
<td>≥1</td>
<td>42.3</td>
<td>30.4</td>
</tr>
<tr>
<td>≥2</td>
<td>32.9</td>
<td>20.1</td>
</tr>
<tr>
<td>≥3</td>
<td>29.5</td>
<td>13.6</td>
</tr>
<tr>
<td>≥4</td>
<td>25.5</td>
<td>10.7</td>
</tr>
<tr>
<td>≥5</td>
<td>22.8</td>
<td>8.3</td>
</tr>
<tr>
<td>≥6</td>
<td>19.1</td>
<td>6.5</td>
</tr>
<tr>
<td>≥7</td>
<td>17.8</td>
<td>5.2</td>
</tr>
<tr>
<td>≥8</td>
<td>15.4</td>
<td>4.8</td>
</tr>
<tr>
<td>≥9</td>
<td>14.1</td>
<td>3.9</td>
</tr>
</tbody>
</table>

The bold values were calculated from the sensitivity analysis. Higher SHS U/year indicates more severe radiographic progression of joint damage.

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MTX monotherapy and 8% of those on infliximab plus MTX. Sensitivity analysis with the threshold changes in SHS of ≥2 and ≥8 U/year demonstrated the same inversely proportional relationship for the logistic regression modelling of the selected baseline risk factors and the identified subgroups of patients with radiographic progression, i.e. the higher the threshold change, the smaller the identified subgroup. As an example, the sensitivity analysis for CRP is shown in Fig. 1A and B.

Selection of baseline risk factors

In ASPIRE, the following continuous baseline risk factors were selected for inclusion in the model as trichotomous variables: CRP (<0.6, 0.6–3 or >3 mg/dl), ESR (<21, 21–50 or >50 mm/h), SJC (<10, 10–17 or >17) and RF (<80, 80–200 or >200 U/ml) (Fig. 1C–F). CRP and ESR were highly correlated (coefficient = 0.61) and showed limited collinearity. When ESR was excluded from the model, the maximum rescaled $R^2$ decreased only slightly, from 0.1616 to 0.1428. From this decrease, we concluded that the model could be simplified by using just one of the two risk factors without compromising its predictive power. Although both the 66 (data not shown) and the 28 joint counts for SJC correlated similarly with radiographic progression, the 28 joint count was selected for its greater practicality in the clinical setting [24]. RF titre was included as a trichotomous variable, because it contributed significantly to the model as a continuous variable but not as a categorical variable (i.e. RF-positive or -negative). Initiated treatment (MTX monotherapy or infliximab plus MTX) was included in the model as a dichotomous variable. Treatment through 46 weeks with infliximab plus MTX resulted in significantly better radiographic outcome compared with MTX monotherapy for the total sample patient population and for all high-range subgroups defined by risk profile (Fig. 2).
Notably, radiographic damage or radiographic score at baseline was not a prognostic variable. Eighty-two percent and 66% of the patients had erosions and joint space narrowing, respectively, at baseline, which did not allow us to take into account the presence of damage at baseline as a prognostic factor in our model. Radiographic score at baseline was inversely associated with the radiographic progression in patients treated with infliximab plus MTX and was, therefore, not retained as a negative prognostic factor in the model.

Development of the matrix risk model

Using clinical, serological and radiographic data from the ASPIRE early RA population, two alternate models—one incorporating all risk factors except ESR (Fig. 3A) and another incorporating all risk factors except CRP (Fig. 3B)—were generated to enable the interchangeable use of these two acute-phase measures depending on clinical availability. The numbers in each cell of the matrix represent the percentage (95% CI) of patients who had RRP out of all patients who have the baseline characteristics and receive the initiated treatment as indicated by the location of the cell within the matrix. For example, a patient with RA who has 18 swollen joints and 7 mg/dl CRP and 380 U/ml RF serum concentrations would have a 47% (95% CI 36%, 59%) probability of RRP if treated with MTX monotherapy or a 14% (95% CI 9%, 20%) probability if treated with infliximab plus MTX combination therapy. Due to the even distribution of the ASPIRE patient population over each of the selected risk factors (also see patient numbers in Fig. 2), approximate tertiles were used to identify subgroups of relevant size in these matrix models. For example, the subgroup at the highest risk (SJC >17, RF >200 U/ml, CRP >3 mg/dl) comprised 65 patients in the CRP-based model shown in Fig. 3A.

The relative risk reduction of RRP with infliximab plus MTX vs MTX monotherapy was 43 and 71% for those within the low ranges and 70 and 59% for those within the high ranges of all baseline risk factors, respectively, in the CRP- and ESR-based models. The absolute risk reduction of RRP with infliximab plus MTX as compared with MTX monotherapy was 3 and 5%.

Fig. 2. Differences between treatment groups in mean van der Waerden (VW) normal scores of the change of > 5 U/year in total modified SHS for subgroups defined by selected baseline risk factors in the ASPIRE population. Mono: monotherapy; IFX: infliximab.

Fig. 3. Matrix risk model for the probability of RRP in 1 year including all selected baseline risk factors except (A) ESR or (B) CRP, generated from the ASPIRE early RA data set. The numbers in each cell represent the percentage (95% CI) of patients who had RRP out of all patients who have the baseline characteristics and receive the initiated treatment as indicated. Colour scheme: blue: 0–9%; green: 10–19%; yellow: 20–29%; orange: 30–39%; red: 40–100% predicted probability of RRP. Higher percentage indicates more severe radiographic progression of joint damage. Mono: monotherapy; IFX: infliximab.
for those within the low ranges and 33 and 24% for those within the high ranges of all baseline risk factors, respectively, in the CRP- and ESR-based models. The NNT with aggressive management to prevent one patient from rapidly progressing with conservative management was 3 for those within the high ranges for CRP, SJC and RF and 33 for those within the low ranges.

The cumulative probability plots of a subpopulation with a high risk of radiographic progression (CRP >3 mg/dl, RF >200 U/ml, SJC >17; n = 65) and a subpopulation with a low risk of radiographic progression (CRP <0.6 mg/dl, RF <80 U/ml, SJC <10; n = 68) from ASPIRE are presented in Fig. 4A and B.

**Application of the matrix risk model**

As expected, all patients who received conservative management in the ATTRACT study tended to be at high risk of RRP, irrespective of baseline risk factor values (Fig. 5A and B). To a greater extent than observed in the ASPIRE data set, combination therapy with infliximab considerably reduced the proportion of ATTRACT patients with RRP, since these patients were not initiating MTX but rather continuing their pre-study MTX despite having active disease. By contrast, patients receiving aggressive therapy within the low or intermediate ranges of all baseline risk factors tended to be at low risk of RRP; and only those within the highest ranges of baseline risk factors tended to be at high risk, albeit to a lesser degree than patients receiving conservative management.

**Discussion**

We developed two preliminary, exploratory matrix risk models for the prediction of radiographic outcome in RA based on multiple risk factors associated with joint damage and related to treatment type. The uniqueness of our preliminary models lies not in the included baseline risk factors whose prognostic capabilities are well recognized [13, 25–30], but in the way the combination of these markers are arranged into a visual matrix that is able to predict the 1-year risk of RRP based on where a patient’s baseline risk factors fall within the matrix. This preliminary matrix risk model, once refined to a finalized model through further development—using a greater variety of RA populations, such as those seen in daily practice, and treatment options reflective of the daily clinical setting (e.g. treatment adjustment upon non-response), and perhaps in the future the inclusion of genetic markers—may be used in clinical practice to predict the risk of...
RRP in the individual RA patient. Further, the inclusion of conservative vs aggressive management in our models can guide rheumatologists in making appropriate treatment choices for patients, particularly for early RA patients naive to DMARDs. The data sets available to perform this exploratory analysis limited our comparison of the drug regimen (MTX vs infliximab plus MTX). The management choices that can be made in light of the predicted prognosis need not be limited to the choice of drug regimen but can be an adjustment of the frequency and the method for measuring disease activity, the rapidity of including a biological agent in the regimen after an initial course with DMARDs, and the choice of imaging method for detecting joint damage. Rather than defining risk in terms of means, medians, ranges and s.d., we predicted risk in terms of 'probability', as the more practical method to refer to risk (prognosis) in a patient–doctor conversation.

For our matrix model, we chose an annual progression rate of $\geq 5$ SHS U/year as our definition of RRP. Whereas harder endpoints, such as surgery and death, may be interesting to pursue in the future, both are usually very distant outcomes and becoming less prevalent in recent years [31–33]. Prevention of death is not thought to be a primary goal for treatment in RA. With better use of the therapeutic armamentarium that rheumatologists currently have access to, it can also be argued that joint surgery still has a place in the therapy for RA [33]. Although HAQ is an important outcome for clinicians and especially for patients, whether it can be considered an objective hard outcome is debatable. HAQ is primarily determined by disease activity [34], and much of the functional impairment is therefore reversible, especially early in the disease course [35]. However, it is well established that radiographic damage has an important effect on long-term functionality [1, 4, 34]. Therefore, choosing joint damage over a 1-year time-frame as our predicted outcome is a good surrogate of the consequences of disease activity as the driver of destruction and long-term disability resulting from this damage.

Of course, we do not consider progression $<5$ SHS U/year insignificant, given the increase in irreversible disability with the accrual of joint damage [1, 35]. Applying a lower threshold of $\leq 2$ SHS U/year in the sensitivity analysis resulted in models showing the same inversely proportional relationship between threshold value and subgroup size, but with higher probabilities of RRP overall. Conversely, although the smallest detectable difference in SHS U/year was 9 U in ASPIRE, we did not choose a higher threshold value because a threshold of 9 SHS U/year was deemed too high by the advisory board and, as seen in Table 2, using a definition of $\geq 9$ SHS U/year identified much smaller subsets of patients meeting this rigorous definition of extensive RRP. Although $\geq 5$ SHS U/year was also deemed too high a threshold by the advisory board, our chosen definition identified subsets of relevant size.

The 1-year endpoint was chosen because it is the most commonly reported radiographic endpoint and yearly progression rate is therefore likely to be the easiest for clinicians to interpret. Radiographic progression from baseline to Week 52 was the co-primary endpoint in the ASPIRE study [18] and it was the primary radiographic outcome parameter in the ATTRACT study [19]. Epidemiological studies have shown that progression of radiographic damage on the group level is more or less linear [36]. Radiographic data at Week 30 were available for both ASPIRE and ATTRACT studies and confirmed the linearity of progression within the first year at the group level (data not shown). In light of this, as we are reporting on a yearly progression rate rather than the overall SHS, progression times $<1$ year (e.g. 3 and 6 months) or $>1$ year can be extrapolated from the yearly progression rate. Thus, because our aim was to focus on extensive radiographic progression rather than any progression, our definition was chosen based on practicality, clinical experience, and conceptual simplicity to reflect only a subgroup of patients with extensive progression [22, 23].

Interestingly, two types of risk factors were identified from the early RA population in ASPIRE as well as the established RA population in ATTRACT: ‘disease activity-related factors’ such as CRP, ESR and SJC, and ‘serological factors’ such as RF. Indeed, serum markers reflecting acute inflammation have been described to be the most important predictors of radiographic progression [37] and in our models, the probabilities of rapid progression increase mainly with increasing CRP and ESR (i.e. higher slopes in Fig. 1). Similarly, SJC5 but not TJC5 were associated with RRP [18] and, as noted, our findings are in line with existing reports [13, 26, 28] that adduce the ‘serological profile’, i.e. the combination of these serological markers, of a patient is an important contributor to radiographic progression during early RA (e.g. increase in radiographic progression with higher RF when all other risk factors are stable).

Using the results from ASPIRE, we generated two alternate risk models for early RA, one excluding CRP and another excluding ESR. To perform an initial assessment of whether the risk factors selected for the models were generalizable to other RA population samples, we applied data from the established RA patients in ATTRACT to the ASPIRE-based models and generated two very similar matrix risk models. A few important differences between the two data sets are of note. First, RF contributed less to the ATTRACT-based models than to the ASPIRE-based models, possibly due to the differences between the study populations (e.g. disease duration and treatment history). Another explanation may be that ‘serological factors’ are less important in established disease than in early disease and that the progression of joint damage is primarily influenced by current disease activity in patients with established disease. Secondly, differences in the effect of aggressive combination therapy between the ASPIRE- and ATTRACT-based models should be considered in light of the distinct patient sample populations (ATTRACT patients had longer disease duration, higher X-ray scores and disability, etc.), and their treatment history (i.e. MTX-failure vs -naive), as delayed treatment itself is likely to have played a role in disease progression [6]. Thirdly, RRP in all risk groups may not be surprising in ATTRACT, since all patients were refractory to MTX and those assigned to MTX monotherapy essentially received placebo. Regardless, the risk profiles of patients on aggressive therapy in both ASPIRE and ATTRACT were similarly influenced by all selected baseline risk factors.

The utility and widespread success of the SCORE chart [17] motivated us in part to develop a similar risk model for RA. Whereas our matrix risk models predict the risk of joint destruction using correlated risk factors rather than cardiovascular mortality using independent risk factors, they also incorporate treatment as a contributor to the risk of RRP. In the context of the data sets used to build our models, MTX monotherapy can be considered conservative management, whereas infliximab plus MTX can be considered aggressive management. Although our matrix risk models should not be used to determine the appropriateness of initiating biological therapy before a conservative regimen, such as MTX monotherapy, in any individual patient, differential radiographic outcomes resulting from these two treatments were clearly observed and might warrant initiation of an aggressive regimen that includes several DMARDs in combination with corticosteroids. Our models identified subgroups of patients with low predicted risk of RRP in whom conservative management provides effective treatment (Fig. 4B) as well as subpopulations of RA patients in whom it had a high risk of failure to prevent RRP (Fig. 4A). Moreover, patients with values for the selected baseline risk factors exceeding the upper limits of the matrix models (e.g. CRP $>3$ mg/dl in combination with high values for the other factors) had an even higher likelihood of RRP with an NNT that approached 1. It is specifically in these very high-risk subpopulations that aggressive therapy demonstrated improved treatment benefit, and in whom early
established RA sample population. Therefore, the differences RA cohort and, instead, tested the models using the ATTRACT could not test our preliminary matrix models in another early placebo-controlled treatment regimens similar to ASPIRE, we the marker they are most familiar with. RF can likely be interchanged in our model and clinicians can use is considerably more expensive and less available in clinical slightly better for prognostic value [42]. In practice, ACPA testing excellent performance of high-titre RF overall, ACPAs proved however, appears to be of limited prognostic benefit. Despite the available. Research on the relationship between levels of RF and combination therapy may be warranted in light of the worse prognosis. For a risk model to be broadly applicable, it should be easy to use, reflective of current clinical practice, and representative of the range of patients seen in the real-life clinical setting from those with DMARD-naïve, early RA to DMARD-refractory, established RA. An overview of the selected variables in a number of recent publications of large early RA cohorts (Table 3) suggests that the number of swollen joints is lower in clinical practice than in ASPIRE. However, the medians and quartiles of CRP and ESR in ASPIRE (Table 1), i.e. the most important predictors of RRP, do appear representative of what are seen in daily practice (Table 3).

Our study has several important limitations. First, the ASPIRE study was not specifically designed to create a matrix risk model. Unlike the goal-driven strategies used in current clinical practice, treatment assignment was fixed for 1 year for patients in the ASPIRE study to allow for true placebo control. The entry criteria selected a specific group of early RA patients in ASPIRE; it is certain that in daily rheumatological practice the proportion of patients at high risk is smaller than it was in the ASPIRE study. Further, the selected risk factors for RRP were limited to the variables collected and analysed for the ASPIRE study, which may limit their applicability to other data sets. Introducing novel ‘disease activity-related risk factors’ for radiographic progression, such as MMP-3 and IL-8 [38], or ‘serological factors’, such as HLA-DR shared epitope [39], may have improved the predictive value of our models. However, the limited accessibility of tests for some of these parameters restricts their utility in routine practice. Additionally, although anti-cyclic citrullinated peptide antibodies (ACPAs) are now considered one of the most important risk factors for joint progression in RA [40, 41] and their use is becoming increasingly routine in clinical practice, we were unable to include this predictive marker in our models because only a small number of ASPIRE patients had ACPA assessments available. Research on the relationship between levels of RF and ACPA, separately and combined, has shown that the prognostic value of high-titre RF and ACPAs for erosive disease are comparable. Testing patients with high-titre RF additionally for ACPAs, however, appears to be of limited prognostic benefit. Despite the excellent performance of high-titre RF overall, ACPAs proved slightly better for prognostic value [42]. In practice, ACPA testing is considerably more expensive and less available in clinical practice than RF. However, as with CRP and ESR, ACPAs and RF can likely be interchanged in our model and clinicians can use the marker they are most familiar with.

Lastly, due to a lack of available RA patient data sets with placebo-controlled treatment regimens similar to ASPIRE, we could not test our preliminary matrix models in another early RA cohort and, instead, tested the models using the ATTRACT established RA sample population. Therefore, the differences between the ASPIRE- and ATTRACT-based matrix risk models should be interpreted with caution, especially in light of the much smaller sample size in ATTRACT.

In summary, using the radiographic data from the ASPIRE study, we developed two novel models for the risk of RRP in patients with early RA. Our preliminary risk models use some of the established disease characteristics (SJC, ESR, CRP and RF) that are readily available in routine clinical setting to generate easy-to-use, visual matrices that, once refined through future development, can be used to predict the risk of joint damage progression in RA patients, particularly those with DMARD-naïve early disease. Additional exploratory development and testing of the matrix risk models in other populations and with other therapies is needed to finalize a single risk model that can be used to guide rheumatologists in making treatment decisions for individual patients with RA.

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### Disclosure statement

N.V. is currently employed by Schering-Plough and owns Schering-Plough stock. D.A. has received honoraria and research grants/support from Schering-Plough. J.S.S. is a consultant for and has received research grants/support from Centocor and Schering-Plough. S.X. is an employee of Centocor Research & Development, Inc., and owns stock options in Johnson & Johnson. E.W.St.C. has received research grants from Genentech and Amgen and is a consultant for Biogen Idec.

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