Priority Paper Evaluation
Future Rheumatology

Predicting the development of rheumatoid arthritis in patients with recent-onset undifferentiated arthritis

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†Author for correspondence: Leeds Teaching Hospitals, University of Leeds, Academic Unit of Musculoskeletal Diseases, 2nd Floor Chapel Allerton Hospital, Chapeltown Road, Leeds, LS7 4SA, UK ■ Tel.: +44 0113 392 4334 ■ Fax: +44 0113 392 4991 ■ P.Emery@leeds.ac.uk

Evaluation of: van der Helm-van Mil AH, Detert J, le Cessie S *et al.*: Validation of a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis, moving toward individualized treatment decision-making. *Arthritis Rheum.* 58(8), 2241–2247 (2008). The decision to start disease-modifying antirheumatic drugs in patients with undifferentiated arthritis (UA) is not always easy, as the natural disease progression is variable. Van der Helm-van Mil and colleagues have recently developed a prediction rule to estimate the chance of progression to rheumatoid arthritis in individual patients presenting with early UA. In this study, the prediction score was calculated and validated in three independent cohorts of patients with UA, and has been shown to have a good discriminative ability for assessing the likelihood of progression to rheumatoid arthritis in approximately 75% of individual patients with recent-onset UA.

The disease course for patients with undifferentiated arthritis (UA) is variable. Predicting outcomes in patients presenting with this condition is therefore an important issue for clinicians in order to determine the best treatment options for each individual patient. Van der Helm-van Mil and colleagues have recently validated a prediction rule to estimate the chance of progression to rheumatoid arthritis (RA) in individual pateints presenting with early UA [1]. In the original model that the group developed [2], a total of 570 patients with UA were followed-up for 1 year, and monitored for the progression to RA or another diagnosis. Clinical characteristics at baseline were evaluated for their predictive value in the development of RA. The prediction rule consists of nine clinical variables, with a total score ranging from 0 to 14. Using upper and lower cutoff values of 8.0 and 6.0 corresponded with positive predictive values (PPVs) and negative predictive values (NPVs) of 84 and 91%, respectively.

To assess the accuracy of this recently developed prediction rule, a further study was undertaken in three independent cohorts of patients with recent-onset UA from the UK, Germany and The Netherlands. The first group consisted of 99 patients with UA recruited to the Birmingham Early Arthritis Cohort (EAC), UK. Patients were included if they had synovitis in at least one joint and a duration of symptoms (defined as inflammation-related joint pain, swelling or morning stiffness) of 3 months or less [3]. Patients were followed up for at least 18 months and were classified as having RA if they fulfilled the ACR criteria for RA [4]. The second cohort of 155 patients was from Berlin, Germany. Patients were included if they had synovitis of two or more joints and symptom duration between 1 and 12 months [5], and were assessed for fulfillment of the ACR criteria for RA after 1 year of follow-up. The third cohort consisted of 34 Dutch patients [6] who were not included in the initial Leiden EAC cohort that had been used to derive the original prediction rule [2].

In two of these cohorts, data on the baseline severity of morning stiffness (measured on a visual analog scale) were not available. The original prediction rule was therefore rederived with the duration of morning stiffness as a substitute using data from the original derivation cohort (the Leiden EAC). As duration of morning stiffness was found to be a less powerful predictor than severity of morning stiffness, the maximal prediction score for duration of morning stiffness was adjusted to 1 (compared with 2 in the original prediction rule). The maximal total score was 13 instead of 14 (see Table 1).

The prediction score and the chance of developing RA were calculated in each of the cohorts. These data were compared with the observed disease outcome after a year or more of follow-up. PPVs and NPVs were calculated

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Table 1. Predicting progression to RA in patients with UA.

Predictive factor	Score
Age in years. Multiply by 0.02	
Female sex	1
Distribution of involved joints	
Small joints hands/feet	0.5
Symmetric	0.5
Upper extremities OR	1
Upper and lower extremities	1.5
Length of morning stiffness (min)	
30–59	0.5
≥60	1
Number of tender joints (out of 68)	
4–10	0.5
≥11	1
Number of swollen joints (out of 66)	
4–10	0.5
≥11	1
CRP level (mg/l)	
5–50	0.5
≥51	1.5
RF positivity	1
Anti-CCP positivity	2

anti-CCP: Anticyclic citrullinated peptide antibody; CRP: C-reactive protein; RA: Rheumatoid arthritis; RF: Rheumatoid factor; UA: Undifferentiated arthritis.

and the overall discriminative ability of the prediction rule was assessed using area under the receiver operating characteristic curves (AUCs). For each validation cohort, the AUC was 0.83 (SEM 0.041), 0.82 (SEM 0.037) and 0.95 (SEM 0.031) in the British, German and Dutch cohorts, respectively. The NPVs (for a prediction score of 6.0 or less) in these three cohorts were 83, 83 and 86%, respectively; the PPVs (for a prediction score of 8.0 or more) were 100, 93 and 100%, respectively.

When pateints from all three cohorts were combined, the overall AUC was 0.84 (SEM 0.024). A total of 83% of patients with a score of 6.0 or less did not develop RA (compared with 89% using the rederived prediction rule of the original cohort). A total of 97% of patients with a score of 8.0 or more progressed to RA. However, 24% of patients fell in the intermediate group (scoring between 6.0 and 8.0), for whom no accurate prediction could be made. Data on radiologic joint destruction and various genetic risk factors for RA were studied in the original derivation cohort and found to be of no additional value in assessing those patients with a score between 6 and 8.

The authors also looked at the data on rheumatoid factor (RF) and anticyclic citrullinated peptide antibody (anti-CCP) in their ability to predict progression to RA, and compared this with the prediction rule. The PPV for the development of RA was 95.7% in those who were seropositive for both antibodies (45 of 47 patients developed RA), 39.4% in those who were seropositive for either antibody and 18.9% (33 of 75 patients) in those who were negative for both antibodies. The prediction model was found to perform better than the autoantibody status alone, with the AUC for the prediction rule AUC 0.84 (SEM 0.024) higher than using the data on CCP and RF of 0.73 (SEM 0.033).

Discussion

Rheumatoid arthritis is a destructive inflammatory arthritis. However, its outcome has improved considerably in recent years [7]. The recognition that early treatment results in better outcomes has emphasized the need for early diagnosis [8–10].

Rheumatologists now aim to see patients within weeks of symptom onset. As a consequence, a sizeable proportion of patients with an inflammatory arthritis who are seen at this early stage may present with UA – a form of arthritis that does not fulfill the classification criteria for a more definitive diagnosis [11]. Early initiation of methotrexate in a subgroup of these patients has been shown to delay development of RA [6]; however, the natural history of patients with UA is variable. Estimates from the Leiden early arthritis clinic suggest that of the patients that present with UA, 40–50% will have a spontaneous remission, while a third will develop RA [12]. Differentiating patients with self-limiting disease from those at risk of developing RA will enable clinicians to individualize treatment decision-making, and allow the initiation of appropriate therapeutic measures for those that will progress and prevent unnecessary treatment for those that will resolve.

Several models have previously been developed to predict radiographic damage in early RA [13–15]. There is also a model for predicting self-limiting, persisting or erosive arthritis [16], which was developed in a cohort of patients with early arthritis. This was not limited to patients with UA, but also included those who fulfilled criteria for a definitive diagnosis at first presentation. More recently, El Miedany and colleagues have published a scoring system to assess the outcome of early UA [17] that uses the percentage change in the health

assessment questionnaire (HAQ) score between baseline and 3 months. The prediction rule by Van der Helm-van Mil and colleagues, however, is the first to have been validated in different cohorts to predict development of RA in patients with UA. It utilizes clinical and laboratory data that can be readily collected at the first visit in most centers.

Results from this study suggest that this prediction model can be used in different clinical practices. It accurately predicted the outcome of UA in all three independent cohorts, despite some noticeable differences between them. These included the baseline patient characteristics, in particular the maximum symptom duration at entry as well as the different countries of origin. There were also differences in the use of DMARDs in each cohort, which may have slowed the rate of progression to RA. Disease-modifying antirheumatic drugs were started in 22% of the patients in the Birmingham cohort and 25% in the Berlin cohort whose disease did not progress to RA. No DMARDs were used in the Dutch cohort.

Further use of this rule in general clinical practice will be required to determine whether it will add to physician judgment and whether use of this tool will result in better clinical outcomes than the general standard of care. In this study, no adequate estimation of risk could be made in approximately 25% of patients (those with an intermediate score between 6 and 8). In clinical practice, it is in these patients, who have some but not many clinical features that make a clinician suspect RA, that the prognostic and treatment difficulties lie. Identifying patients in this group who will progress to RA, as well as those with a persistent UA who may also experience increased morbidity and require treatment [18], remains an important research goal. The use of newer imaging modalities with ultrasound and magnetic resonance imaging, and the identification of novel markers, may prove to be of additional value to facilitate the prediction of outcome in this group of patients.

In summary, this prediction rule is the first validated tool for application in patients with recent-onset UA to predict the risk of developing RA. It has been shown to accurately estimate the risk of developing RA in approximately 75% of individual patients with recent-onset UA. Further evaluation of its use in clinical practice will determine whether it will result in better clinical outcomes and a reduction in the under- and over-treatment of patients with UA. Predicting clinical outcomes in intermediate-risk groups of patients with UA remains an area for further research.

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Executive summary

- Approximately a third of patients with undifferentiated arthritis (UA) progress to rheumatoid arthritis (RA), whereas 40–50% of patients experience spontaneous remission.
- Predicting progression of UA will allow for more tailored treatment and prevent over-treatment.
- Van der Helm-van Mil and colleagues have introduced the first validated prediction rule to estimate the chance of progression to RA in individual patients presenting with UA.
- The presence of autoantibodies, in particular the anticyclic citrullinated peptide antibody, confers an increased risk of progression of UA to RA.

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- ▪ of interest
- ▪▪ of considerable interest

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