A Quantitative Approach to Early Rheumatoid Arthritis

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Abstract
The prognosis of patients with recent onset arthritis may vary from self-limiting disease to severe destructive rheumatoid arthritis (RA). In order to improve outcomes, a great deal of effort has been put into applying a diagnosis that will allow rapid initiation of treatment. The diagnosis of undifferentiated arthritis (UA) for these patients as well as the new ACR-EULAR 2010 criteria for rheumatoid arthritis (RA) are reviewed in the context of pathogenetic and clinical data available from this group of patients.

Recent data suggest that early therapy and achieving low-disease activity improves long-term outcomes in inflammatory arthritis.1,2 These observations have increased awareness among rheumatologists on the importance of early diagnosis and treatment. As a result, considerable pathophysiological research and clinical trials focus on identifying early synovitis as soon as possible. This has led to considerable efforts to identify rheumatoid arthritis (AR) patients earlier. Uniform descriptions of patients and accurate diagnostic criteria for early synovitis are essential for proper interpretation of clinical research. At present, no standardized definition for early synovitis is widely accepted. By the 1990s, duration of symptoms for fewer than 12 to 24 months was considered early. This duration was chosen because most RA patients incur significant damage when treated conventionally.

The window for modifying disease outcome is unknown, but some evidence suggests that treatment within months might be beneficial. For this reason, several early arthritis cohorts in recent years severely restricted the inclusion criterion symptom duration and therefore were comprised of only patients with a symptom onset of less than 12 weeks; this presentation is referred to as “very early synovitis.” Even this definition probably does not capture the earliest phase of disease, however, as circulating antibodies might appear years before the onset of symptoms in RA, and biomarkers reflecting bone destruction are also elevated before arthritis is present.3,4 Although the term synovitis generally refers to a swollen joint detected by physical examination, alternative definitions are also applied. Physical examination might not be sensitive enough, and clinically undetectable synovitis may yet be present and relevant to identify. Therefore, some studies consider tenderness in the absence of swollen joints as synovitis. For instance, early arthritis clinics might include patients with tenderness but no swollen joints. Others determine synovitis not by physical examination but through the use of imaging modalities, such as ultrasound (US) or magnetic resonance imaging (MRI). US appears to be valuable, especially in the absence of abnormalities, and the negative predictive value of a normal US result is high. The prognostic implication of abnormal US findings is less clear.5 More long-term studies are needed to establish what US characteristics have a high positive predictive value for the development of a persistent or erosive arthritis.

Until more data become available, the term early synovitis will generally refer to synovitis that is detected by physical examination. It is important to note that early synovitis refers to a disease symptom, but does not reflect any specific diagnosis.

What is Undifferentiated Arthritis?
The term undifferentiated arthritis (UA) refers to a subpopulation of early synovitis patients who do not meet the criteria for other diseases, including infections, spondyloarthritis-
thymes, crystal diseases, and RA. As a diagnosis of exclusion, no classification criteria for UA currently exist.

Investigators of European early arthritis cohorts have observed that 35% to 54% of the patients included do not meet criteria for other diseases and thus are considered as UA patients. In the remaining early synovitis patients, a definite diagnosis was able to be established at first visits. The frequency of UA is dependent on the duration of symptoms at the time of the first visit to a rheumatologist. The longer symptoms exist, the more likely that sufficient characteristics are evident to support a definite diagnosis and the lower the prevalence of UA will be. In addition, the prevalence of UA will change when classification criteria for rheumatologic diseases change. For example when applying the 1987 ACR criteria for RA to newly presenting early synovitis patients in the setting of an early arthritis clinic in Europe (for instance, Leiden clinic, The Netherlands), about 20% will directly fulfill the 1987 ACR criteria and therefore can be classified as RA patients. At present, few studies evaluating the performance of the 2010 ACR-EULAR criteria are available. Initial data from the Leiden clinic suggest that the percentage of RA diagnoses will increase when the 2010 criteria for RA are applied. The new set of criteria classified this patient as being in remission, or 3) the occurrence of both events. As such, remission resembles a cure of the disease, although longer term follow-up is needed to determine if symptoms do recur many years later. In addition to the difference in frequency of spontaneous remission in UA and RA, the disease duration when spontaneous remission is achieved differs as well. A recent study observed that within UA the median disease duration until spontaneous remission is 17 months, whereas, in RA, it takes a median period of 40 months before remission is achieved. Thus, the chance of achieving a natural remission is reduced as the disease process matures. This supports the notion that chronicity might be more easily reversed in the undifferentiated phase of disease.

**Characteristics of UA**

The characteristics on first presentation between the patients that present with early UA and early RA, using the 1987 criteria, are somewhat different. Patients with recent onset UA are younger (mean age, 48 vs. 57 years) and are less frequently female (F: 58% vs. M: 66%) than early RA patients. UA patients generally have a fewer swollen joints and have a greater likelihood of asymmetric synovitis. UA and RA patients do not differ in the acuteness of the start of the complaints, body mass index (BMI), or frequency of a positive family history for RA. UA patients have fewer bone erosions at baseline; in a recent study, erosions were present in 18% of UA patients and 35% of RA patients. There are also important differences with regard to autoantibodies. UA patients are rheumatoid factor (RF)-positive in only 14% and anti-CCP positive in 12% of cases, whereas these percentages are both 55% in patients with early RA. According to both the 1987 and the 2010 classification criteria for RA, the presence of anti-CCP antibodies in patients with arthritis is not equal to the classification of RA. Particularly in the cases of a mono-arthritis or oligo-arthritis, patients may not fulfill criteria for RA and are labeled as UA. However, early UA patients who have anti-CCP antibodies have an approximately 70% chance of being classified as RA by the 1987 ACR-criteria 1 year following the UA diagnosis.

**Remission Rates in UA and RA**

The natural disease course of UA is variable, depending on the inclusion criteria and the duration of symptoms in several inception cohorts. Spontaneous remission occurs in 40% to 55% of UA patients. In contrast, the remission rate in RA is at most 10% to 15%. In these studies, remission was defined as 1. the absence of swollen joints for 1 year or more following discontinuation of eventual disease-modifying anti-rheumatic drug (DMARD) therapy, 2. discontinuation of the outpatient clinic because the treating rheumatologist classified this patient as being in remission, or 3) the occurrence of both events. As such, remission resembles a cure of the disease, although longer term follow-up is needed to determine if symptoms do recur many years later. In addition to the difference in frequency of spontaneous remission in UA and RA, the disease duration when spontaneous remission is achieved differs as well. A recent study observed that within UA the median disease duration until spontaneous remission is 17 months, whereas, in RA, it takes a median period of 40 months before remission is achieved. Thus, the chance of achieving a natural remission is reduced as the disease process matures. This supports the notion that chronicity might be more easily reversed in the undifferentiated phase of disease.

**Joint Destruction in UA and RA**

In RA, the extent of joint destruction in small joints effectivly reflects joint destruction in larger joints as well. Such data are missing for UA patients. A recent study evaluated the subgroup of UA patients who developed RA later in time. Radiological data were compared to that of patients who, at first presentation of the disease, directly fulfilled the 1987 ACR criteria for RA. The radiographic progression rates between these groups were not different. Health Assessment Questionnaire (HAQ) scores and Disease Activity Score (DAS) measures also were not different between these two groups. Thus, although UA patients on a group level have a higher rate of spontaneous remission compared to patients with RA, the subgroup of UA patients that progress to RA have an equally severe course compared to the patients classified as RA earlier in the disease course. Studies that compare the rate in joint destruction of the total group of early UA patients to patients with early RA have not been performed.

**Biological Mechanisms in UA and Determinants of Progression to RA**

The understanding of the processes responsible for progression from UA to RA is far from complete. Risk factors that were identified as independent predictors for RA development may provide clues, which are summarized in the following points.
Age: The incidence of RA is clearly age-dependent, with a rising incidence from 7/100,000 for the age group 18 to 34 to 107/100,000 for the age group 75 to 84.15

Gender: Females presenting with UA are two-times as likely to develop RA, compared to males presenting with UA.15 Sex hormones influence predisposition to autoimmune diseases; in general, males are less prone than females.

Number of involved joints and C-reactive protein (CRP): Both markers express the level of inflammation and are frequently reported to be associated with synovitis progression and worse disease outcome. Although the number of swollen joints and the level of CRP are correlated at a group level, this is often not the case in individual patients, and both markers have their own independent predictive value. UA patients presenting with CRP levels greater than 50 mg/L have five-times an increased risk to be in an early stage of RA. Likewise, patients classified with UA and having a polyarthritis have a 1.5-times higher chance to fulfill the criteria for RA later on, compared to patients with a mono- or oligo-arthritis. Moreover, in case an early UA patient has more than 10 swollen joints, the risk that this person will develop RA is three-times higher than that of patients with a mono- or oligo-arthritis.

Autoantibodies: Anti-CCP antibodies as well as the RF can be present years before the first clinical symptom of synovitis, and they are also risk factors for a persistent and destructive course of synovitis. Spontaneous remission is scarce in anti-CCP positive patients. Not only the presence but also the level of anti-CCP antibodies is of predictive relevance.

Environmental factors: Smoking is most widely studied. Early UA patients who smoke have a higher risk for the development of RA and for a destructive disease course. This risk is confined to patients who carry HLA-DRB1 alleles that encode for the so-called “shared epitope.” Persons who smoke and also carry a HLA-DRB1-shared epitope allele are particularly prone to develop anti-CCP antibodies, which subsequently are associated with disease persistency and erosiveness.

Genetic factors: Apart from the HLA-DRB1 shared epitope alleles, genetic factors that associate with progression from UA to RA are not clearly identified. The majority of genetic risk factors for RA provide risk to anti-CCP positive RA, when compared to healthy controls. It is not clear whether these factors associate with progression from UA to RA as well and, if so, whether such an association is independent from the strong association between anti-CCP antibodies and RA development. The identification of new genetic factors also fueled the study of their relevance. In a population of UA patients, information on currently known genetic risk factors for RA does not improve prediction of risk for RA, compared to a prediction rule based on common clinical risk factors alone.16

New biomarkers: The role of biomarkers in the diagnosis of UA is quite limited. Within RA, it is known that serological levels of pro-MMP3, RANKL (receptor activator of nuclear factor kappa-B ligand), and OPG (osteoprotegerin) correlate with the rate of joint destruction over time.17

Window of Opportunity

The concept of a window of opportunity suggests that there is a period early in the course of a disease when the disease process can be altered or can even be reversed, with a complete turn to normality. Treatment during this period might have a greater effect than treatment at a later stage, in terms of halting disease progression and achieving remission.18-20 Several different aspects have been studied regarding whether very early UA (fewer than 12 weeks) may be an immunopathologically distinct phase compared with later disease.

Studies that have focused on synovial tissue have not reveal differences.21 It is difficult to come to any certain conclusion from negative studies, because one never knows whether the relevant processes have been identified and evaluated. However studies that focused on the composition of the autoantibody responses have demonstrated that profound maturation of the autoantibody response occurs early during disease.22

UA patients who present to an early arthritis clinic within 12 weeks of symptom onset less often progress towards RA, compared to UA patients with a symptom duration of more than 12 weeks. Similarly, RA patients who had at their first visit to a rheumatologist symptoms fewer than 12 weeks after symptoms started had a lower rate of joint destruction over time and achieved sustained DMARD-free remission more often than RA patients who had a period of more than 12 weeks before seeing a rheumatologist.23

Trial data support the presence of a window of opportunity is also obtained from trials.24 An unblinded study of a single dose of corticosteroids in patients with mild early inflammatory arthritis (median 20 weeks) found the strongest predictor of disease remission at 6 months (defined as the absence of symptoms and signs in patients without antiinflammatory treatment) to be a disease duration of less than 12 weeks at time of therapy.25 Clinical and radiological outcomes were significantly better at 3 years in a patients who started DMARD therapy within 3 months (“very early”) after disease onset, compared with a median duration of 12 months at the start of treatment (“early”).19 Remission was achieved in only 50% of the very early group compared to 15% in the early group. These data suggest that treatment in very early arthritis might have a greater effect on disease progression, underlining the relevance of identification and treatment of arthritis in the very early disease phase.

Only a few trials have been performed in UA patients and are summarized in Table 1. One trial observed an effect of steroids in early UA patients, an observation that was not reproduced in another study. Methotrexate is reportedly beneficial in UA patients and associated with
delayed progression to RA and a reduction in the rate of joint destruction. This effect appeared to be predominant in the anti-CCP positive UA patients but is negligible in anti-CCP negative UA patients. However, when methotrexate was discontinued, the rate that patients evolved to RA returned to the pre-treatment levels.

Some biologicals have also been studied in UA patients. Although a surprising lack of efficacy was observed with anti-TNF blockers, abatacept was beneficial. Both the heterogeneous nature of UA patients and the more favorable disease outcome and spontaneous remission rate make it difficult to observe treatment efficacy in the total UA group. Thus, placebo-treated groups can have a good remission rate and differences with the treatment group might be difficult to detect. None of the published randomized trials in UA patients addressed this problem of heterogeneity and stratified the patients into those having a high chance to develop RA or to have a spontaneous remission.

**Individualized Treatment of UA**

UA has a variable disease course, ranging between spontaneous remission and severe destruction. Due to this and because DMARD therapy is potentially toxic, the treatment of UA patients should be personalized. The chance...

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**Table 1** Randomized Controlled Trials in Patients with Early UA

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Treatment</th>
<th>Follow-up Duration</th>
<th>Outcome</th>
<th>Effect Compared to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVE trial</td>
<td>389</td>
<td>Single IM injection 120 mg methylprednisolon</td>
<td>52 weeks</td>
<td>Drug-free clinical remission</td>
<td>No effect</td>
</tr>
<tr>
<td>STIVEA trial</td>
<td>265</td>
<td>Three IM injections 80 mg methylprednisolon</td>
<td>6 and 12 months</td>
<td>Need to start DMARDs</td>
<td>At 6 months 61% vs 76% had started DMARDs</td>
</tr>
<tr>
<td>PROMPT trial</td>
<td>110</td>
<td>Methotrexate therapy during 12 months</td>
<td>30 months</td>
<td>Fulfilling the 1987 ACR criteria</td>
<td>40% vs. 53% developed RA, lower radiologic progression</td>
</tr>
<tr>
<td>Adjust trial</td>
<td>56</td>
<td>Abatacept treatment during 6 months</td>
<td>12 months</td>
<td>Fulfilling the 1987 ACR criteria</td>
<td>46% vs. 67% developed RA; no effect on radiographic progression</td>
</tr>
<tr>
<td>Saleem et al.</td>
<td>17</td>
<td>Infliximab at 0, 2, 4, and 16 weeks</td>
<td>26 weeks</td>
<td>Clinical remission</td>
<td>No effect observed</td>
</tr>
</tbody>
</table>

IM, intramuscular; SAVE, Stop Arthritis Very Early; STIVEA, Steroids in Very Early Arthritis; PROMPT, Probable Rheumatoid Arthritis Methotrexate versus Placebo Therapy

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**Table 2** Form to Calculate a Patient’s Prediction Score

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>What is the age? Multiply by 0.02</td>
<td>1 point</td>
</tr>
<tr>
<td>2</td>
<td>What is the gender? In case female:</td>
<td>1 point</td>
</tr>
<tr>
<td>3</td>
<td>How is the distribution of involved joints?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In case small joints hands and feet:</td>
<td>0.5 point</td>
</tr>
<tr>
<td></td>
<td>In case symmetric</td>
<td>0.5 point</td>
</tr>
<tr>
<td></td>
<td>In case upper extremities</td>
<td>1 point</td>
</tr>
<tr>
<td></td>
<td>Or:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In case upper and lower extremities</td>
<td>1.5 points</td>
</tr>
<tr>
<td>4</td>
<td>What is the length of the VAS morning stiffness (range 0-100 mm)?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In case 26-90 mm</td>
<td>1 point</td>
</tr>
<tr>
<td></td>
<td>In case &gt; 90 mm</td>
<td>2 points</td>
</tr>
<tr>
<td>5</td>
<td>What is the number of tender joints?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In case 4-10</td>
<td>0.5 point</td>
</tr>
<tr>
<td></td>
<td>In case 11 or higher</td>
<td>1 point</td>
</tr>
<tr>
<td>6</td>
<td>What is the number of swollen joints?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In case 4-10</td>
<td>0.5 point</td>
</tr>
<tr>
<td></td>
<td>In case 11 or more</td>
<td>1 point</td>
</tr>
<tr>
<td>7</td>
<td>What is the C-reactive protein level (mg/L)?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In case 5-50</td>
<td>0.5 point</td>
</tr>
<tr>
<td></td>
<td>In case 51 or higher</td>
<td>1.5 points</td>
</tr>
<tr>
<td>8</td>
<td>Is the Rheumatoid factor positive? If yes:</td>
<td>1 point</td>
</tr>
<tr>
<td>9</td>
<td>Are the anti-CCP antibodies positive? If yes:</td>
<td>2 points</td>
</tr>
</tbody>
</table>

**Total score**
for individual patients to progress towards RA or to have a persistent erosive disease course can be estimated using prediction models.\(^26,27\) One of the current prediction rules (Table 2) is validated using data from early arthritis clinics from Germany, the UK, Canada, Russia, and Japan, and this algorithm is currently used in daily practice as well in several countries.\(^26,28-33\) The discriminative ability of the model is high. The prediction rule consists of nine variables: age, gender, distribution of involved joints, morning stiffness, number of tender and swollen joints, CRP level, and the presence of RF and anti-CCP antibodies. It calculates the risk of developing RA for every UA patient (Fig. 1). Such information can facilitate the decision on whether or not to initiate DMARD therapy and might facilitate patient involvement in decision making. In general, a score of six or lower is related to a low chance of developing RA (91% chance to not develop RA) and may be reason not to initiate DMARD therapy. In contrast, patients with a score of eight or higher have a chance of 84% to develop RA, which might be a reason to initiate DMARD therapy in some these patients.

**Can the 2010 ACR-EULAR Criteria\(^37\) Be Used to Identify the UA Patients Who Actually Have Early RA?**

The development of the new criteria for RA is relevant and important, as the absence of up-to-date classification criteria have hampered progression with regards to treatment strategies in early RA. The 1987 ACR criteria for RA were not equipped to classify RA early on and did not include the more modern autoantibody tests or imaging modalities. The majority of randomized clinical trials included patients fulfilling the 1987 criteria, this implies patients with established RA. It is not clear whether the efficacy observed in these trials is the same for patients with early RA or UA. The new criteria are mainly derived for classification and research purposes\(^34\) and require validation for use in clinical practice for early synovitis. The 2010 criteria can only be used as diagnostic criteria when it is demonstrated that patients who fulfill them have a high chance for a persistent or destructive disease course. Although the 2010 criteria were developed with the idea that patients should receive methotrexate, the currently available evidence that patients who fulfill the 2010 criteria benefit from the start of disease modifying drugs is limited.

**Disclosure Statement**

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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