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Prediction and prevention of rheumatoid arthritis

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Summary

A substantial proportion of patients who present with probable rheumatoid arthritis (probable RA or undifferentiated arthritis = UA) progresses to RA.

In a randomized trial we demonstrated that in patients with UA methotrexate is an effective drug to inhibit symptoms, structural damage, and progression towards RA. However 40-50% of UA-patients remit spontaneously. Therefore adequate treatment decision-making in early-UA necessitates identification of the UA-patients that will develop RA. We developed a prediction rule using data from the Leiden Early Arthritis Clinic, an inception cohort of patients with recent-onset arthritis (n=1700). The patients that presented with UA were selected (n=570); progression to RA or other diagnosis was monitored after one-year follow-up. The prediction rule consisted of nine clinical variables: gender, age, localization of symptoms, morning stiffness, tender and swollen joint count, C-reactive protein, rheumatoid factor and anti-CCP antibodies. Each prediction score varies between 0 and 14 and corresponds to a chance (percentage) RA development. Thus, in early-UA the risk to develop RA can be predicted, thereby allowing individualized treatment decisions to initiate disease-modifying antirheumatic drugs in patients who present with UA.

Key words: rheumatoid arthritis, undiffertiated artritis, prediction, prevention.

Resumen

Una buena proporción de pacientes que se presentan con artritis reumatoide probable (AR probable) o artritis indiferenciada (AI), progresan a AR. En un estudio aleatorizado, nosotros demostramos que en pacientes con AI, el metotrexate es un medicamento efectivo para mejorar los síntomas, evitar el daño estructural y la progresión hacia AR. Sin embargo, 40-50% de los pacientes con AI remiten espontáneamente. De esta manera, para hacer una buena decisión terapéutica en pacientes con artritis temprana indiferenciada, necesitamos identificar mejor aquellos pacientes con AI que desarrollarán AR. Nosotros desarrollamos una regla de predicción, utilizando datos del "Leiden Early Artritis Clinic", una cohorte de pacientes con artritis de reciente comienzo (n= 1700). Se seleccionaron los pacientes que se presentaron con AI (n= 570); la progresión a AR u otros diagnósticos fue monitoreada después de un año de seguimiento. La regla de predicción consistió en nueve variables clínicas: género, edad, localización de los síntomas, rigidez matinal, conteo de articulaciones inflamadas y dolorosas, proteína C reactiva, factor reumatoide, y anticuerpos antipéptido citrulinado cíclico (anti-CCP). Cada conteo de predicción varia entre 0 y 14 y corresponde a una probabilidad (porcentaje) de desarrollar AR. De

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este modo, en AI temprana, el riesgo de desarrollar AR puede predecirse, permitiendo individualizar las decisiones terapéuticas para iniciar medicamentos modificadores de la enfermedad en pacientes que se presenten con AI.

Palabras clave: artritis reumatoide, artritis indiferenciada, predicción, prevención.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that may have a high impact on patients´ quality of life as it is associated with disability, (co)morbidity and an increased mortality rate[1]. The last decade it has been recognized that RA needs to be diagnosed early and treated promptly with disease modifying antirheumatic drugs in order to successfully interfere with the disease process. This new treatment paradigm in combination with new treatment options have already improved the prospects for RA patients in general and have lead to a reduction in the level of joint destruction, disability and mortality. Although rheumatologist are nowadays successful in reducing the level of disease activity patients in with RA, the ultimate challenge for the future is to initiate therapy in such an early phase that the actual development of RA is prevented. This indicates that patients should be treated in a phase that they have not fully developed the disease. It might well be that in such an early phase the mechanisms that drive chronicity are less settled and that interference with the disease process will induce remission more easily. To achieve this rheumatologists require two tools. First, they should be able to identify the patients that will develop RA and, second, drugs that are proven to be effective in preventing the development of RA should be available.

Currently clinical trial are designed in order to assess treatment efficacy in patients with early undifferentiated arthritis (UA), this manuscript appraises the definition of UA, the natural course of UA, clinical characteristics that predict the progression from UA to RA and pathophysiological differences between UA and RA. Finally, results on the first trial investigating the effect of DMARD therapy in patients with UA are presented.

Definitions of early arthritis and UA

The published trials evaluating treatment strategies in RA all include patients classified according to the 1987 ACR-criteria for RA. These criteria are generally accepted and are developed by experts that compared characteristics of patients with longstanding ´classical' RA (mean disease duration 8 years). In clinical practice, patients presenting with an early arthritis frequently have an undifferentiated disease that in time may progress to a polyarthritis fulfilling the ACR-criteria for RA or may have a more benign disease course. The ACR criteria have been criticized as they have low discriminative ability in patients presenting with recent onset arthritis[2-5]. This is not surprising considering the method by which the criteria were formulated and the components of the ACR-criteria. One of the criteria is the presence of erosions on the radiographs of hands and wrists. In the early phases of RA only 13% of the patients have erosive disease[6]. Additionally, erosions often initially present in the small joints of the feet and appear in the small joints of the hands at a later point in the disease course[7]. Also rheumatoid nodules are very rare in the early phases of RA and rheumatoid factor is present in only 50% of the patients with early RA[8]. This indicates that at present a set of criteria is needed that applies to early undifferentiated arthritis and that differentiate the UA-patients that will progress to RA from those that will have a more benign disease course. Before the characteristics that predict the disease outcome in UA-patients can be identified, a general acceptance on the definition for early UA is needed. In the literature several terms that refer to arthritis of recent onset are used, but they refer to distinct categories of patients and should therefore be separated. Most frequently used are the terms 'early arthritis', 'early RA' and undifferentiated arthritis. *Early arthritis* is the description of a state in which there is a (mono-, oligo- or poly) arthritis that has a recent onset. In case of early arthritis the disease can be undifferentiated or differentiated (Figure 1). For example, about 20% of the patients that present with an early arthritis directly fulfill the ACR-criteria and thus can be classified as RA. This indicates that in *early RA* per definition the ACR-criteria for RA are fulfilled. Since the ACR criteria also state that the patients fulfill the criteria for at least 6 weeks, shorter

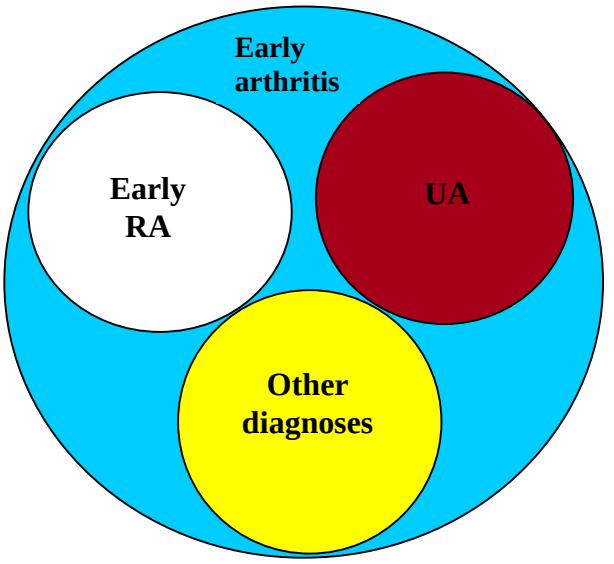

Figure 1. The term early arthritis may refer to early undifferentiated arthritis, early RA and other classified diagnosis.

disease duration than six weeks is by definition impossible in case of early RA. Patients with an early arthritis may also fulfill classification criteria for other diagnoses. Finally, those early arthritis patients that can not be classified according to ACR-criteria and in whom the arthritis is not septic or reactive in origin have per exclusionem an *undifferentiated arthritis*. Discerning UA from early arthritis and early RA is relevant when comparing studies that describe models that predict the disease outcome or studies that assess therapeutic efficacy as the generalizability of these studies depends on the patient group that is included. This manuscript focuses on UA as patients with UA may advance to RA. Therefore, these patients may provide an opportunity as it is to be expected that the process that drives chronicity can be influenced more effectively when it is less established.

Natural disease course of UA

The natural disease course of UA is variably reported in several inception cohorts. This is not only due to the use of different definitions for UA, but is also a result of differences in inclusion criteria for several early arthritis cohorts. For example, inclusion in the Norfolk Arthritis Registry (UK) required the presence of at least two swollen joints[9], whereas for inclusion in the Leeds early arthritis clinic (UK)[10] or the arthritis cohort from Wichita (USA) the presence of synovitis was not required[11]. On the other hand, some early arthritis clinics did not include patients with UA but only patients that fulfilled the criteria for RA[12,13]. Inclusion criteria from early arthritis cohorts differ not only in the presence/absence of arthritis, but also in the required symptom duration. Patients could be included in the NOAR when the arthritis was present for at least 4 weeks, whereas a symptom duration of more than 12 weeks was an exclusion criteria for the early arthritis cohort from Birmingham. Different inclusion and exclusion criteria instigate the enrolment of different groups of patients and clarifies that different results are observed when the natural disease course is studied.

Early arthritis cohorts that included all patients with at least one swollen joint reported that at initial presentation about 20% of the patients fulfilled the criteria for RA and that 35%-54% of the patients presented with UA[14,15]. In case of UA the disease course was divers: 40-55% remitted spontaneously[15-18], 35%-50%[6,14] developed RA and the remaining patients developed other diagnoses or remained undifferentiated (Figure 2).

These data also illustrate that when evaluating studies on UA-patients the duration of symptoms are of importance for the outcome of the patient group. In other words, an undifferentiated arthritis from recent onset (several weeks) has a different natural course than an arthritis that after one year of follow-up is still unclassified (persistent undifferentiated arthritis). In the Leiden Early Arthritis Clinic, patients that after 1 year of follow-up had persistent undifferentiated arthritis developed only in a minority (10%) RA later on in the disease course.

Intriguingly, the reported rates of spontaneous remission patients in case of UA are importantly different from those in RA. Whereas remission was achieved in 40-55% of the patients with recent-onset undifferentiated arthritis, the remission rate in RA is at most 10-15%[19, 20]. Apparently, the chance to achieve a natural remission becomes smaller when the disease process is more matured. This supports

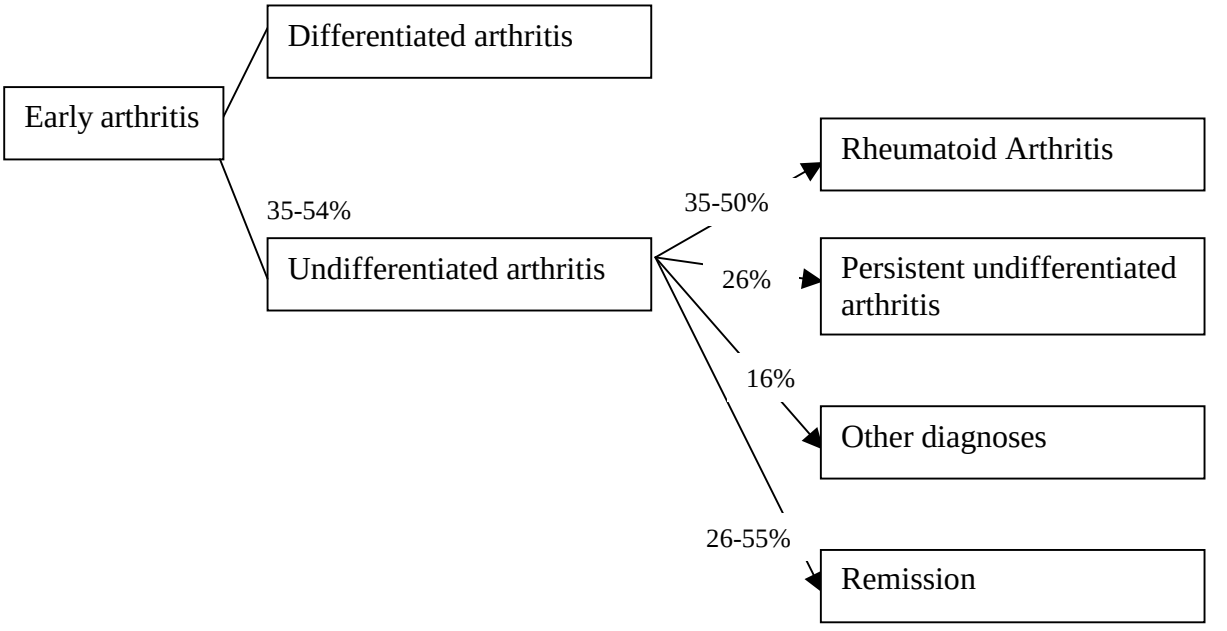

Figure 2. The natural disease course of patients with early arthritis and UA. Reported percentages differ between several early arthritis cohorts, explaining the total may add to more than 100%.

the notion that chronicity might be more easily reversed in the phase of UA.

Predicting progression from UA to RA

As UA has a variable disease course and DMARD-therapy is potentially toxic, only the UA-patients that have a high chance to develop RA are preferentially treated with DMARDs, whereas the patients that will achieve a spontaneous remission will preferentially not receive these drugs. This underlines that a model that is able to predict the disease outcome in individual patients with UA is needed. Initial attempts to define such prognostic criteria have been made by Visser et al. based on the Leiden Early Arthritis Cohort[21]. This model predicts disease persistency and erosiveness. For the development of this model all early arthritis patients were included and not only patients with UA. Consequently, patients that at first presentation were classified as e.g. reactive arthritis or RA were also included. However, the natural course of these diseases is already known as reactive arthritis is in most cases remitting and RA is in most cases a persistent disorder, indicating that patients with a diagnosis of which the disease course is well-known may skew a model that predicts the disease outcome. As the model of Visser et al. was not developed using specifically patients with UA, this model is not optimal to guide individualized treatment decision in UA. Recently, a model that predicts the disease outcome in individual patients with UA was developed, also based on the Leiden Early Arthritis Cohort[22]. From a total cohort of 1700 early arthritis patients, 570 patients presented with UA. After one year of follow-up 31% of the UA-patients had progressed to RA. The remaining two-third had developed other diagnoses (16%), had achieved spontaneous remission (26%) or remained unclassified (26%). Clinical characteristics between the UA-patients that had and had not developed RA were compared and using logistic regression analysis the variables that were independent predictors for the development of RA were selected. This resulted in the construction of a prediction rule (Figure 3)[22]. The discriminative ability of this prediction rule was assessed by the area under the receiver operator curve, which was 0.89 for the derivation

cohort and 0.97 for the replication cohort. The total prediction score ranged between 0 and 14. All patients with a score < 4 did not progress and all patients with a score > 10 did progress to RA. With the cut-off levels < 6 and > 8 the negative and positive predictive values were 91% and 84% respectively. As this prediction rule consists of 9 variables that are regularly assessed at the outpatient clinic (age, gender, distribution of involved joints, morning stiffness severity, number of tender and swollen joints, C-reactive proteins, rheumatoid factor and anti-CCP antibodies), this prediction rule can be easily applied in daily practice. Moreover, as the prediction rule estimates the chance for an individual patient to progress to RA in a percentage, application of this rule might facilitate the involvement of patients themselves in treatments decision-making.

Biological mechanisms in UA and RA

Subsequently, the question arises which biological mechanism are responsible for the progression from UA to RA. The identified nine risk factors may provide clues. Therefore possible mechanisms underlying the association with each of these variables and RA-development are shortly discussed.

1. Age

Ageing is associated with a decline in a large number of physiological functions as well as immune function. Impairment in cellular, humoral and innate immunity might predispose persons with an increasing age to amongst others RA. Relevant changes in the innate immune system are an altered phagocyte function and an increased production of pro-inflammatory cytokines such as Il-1, TNF-alpha and IL-6 (the latter is responsible for the increase in CRP that is seen in elderly persons)[23]. Modification of the adaptive immune system is exemplified by the development of a polyreactive antibody production at higher age[24]. The immunosenescence is further discussed in reference 25 but might predispose to arthritis or mediate an aggressive disease course.

2. Gender

Sex hormones influence the predisposition to autoimmune diseases. In general, men are less prone than women. This might be caused by anti-inflammatory effects of androgens. Recently it was demonstrated that PPARá, a gene in CD4+ T cells, is sensitive to androgen levels and is higher expressed in males, which induced higher levels of Th2 cytokines and consequently a lower susceptibility to Th1-mediated autoimmune diseases[26]. Estrogen are also able to suppress arthritis in mouse models[27] and the use of oral anticontraceptives might be associated with a lower risk on RA-development[28]. However, this finding was not replicated in the Nurses' Health study[29]. Additionally, both estrogen and androgen inhibit bone resorption[30]. Moreover, sex hormones may have local effects which seems to consist mainly in modulation of cell proliferation and cytokine production (i.e., TNF-alpha, IL-1). Altogether, these data suggest that postmenopausal women exhibit a proinflammatory cytokine profile, that might contribute to the higher incidence of RA in these women.

3. Distribution of involved joints

RA particularly affects the small joints of the hands and feet, whereas in some other rheumatologic diseases the large joints are preferentially inflamed. At present the reason for this predilection is not clear. It has recently been suggested that differential accumulation of regularly T cells in different joints may dictate the anatomic spectrum seen in arthritis syndromes[31]. However this hypothesis is based on animal models and whether this might explain the distribution of inflamed joints in human is not known.

4. Severity of morning stiffness

Although in clinical practice the presence of morning stiffness is a specific maker for RA, the anatomical substrate causing morning stiffness is ample examined. Straub et al. recently proposed that the symptom stiffness is due to edema formation mediated by circulating proinflammatory cytokines[32]. The observations that the pro-inflammatory cytokines TNFα and Il-6 exhibit a circadian rhythm and that these levels peak level around 6.00 -7.00 in RA-patients might support this hypothesis and explain why stiffness is most severe in the early morning.

5. C-reactive protein, number of tender and swollen joints

As already discussed IL-6 enhances the hepatic production of CRP, explaining that in situations in

1. What is the age in years?	Multiply with 0.02		
2. What is the gender?	In case female:	1 point	_____
3. How is the distribution of involved joints?	In case small joints hands / feet:	0.5 point	_____
	In case symmetric:	0.5 point	_____
	In case upper extremities	1 point	_____
	or in case upper & lower extremities:	1.5 points	_____
4. What is the length of the VAS morning stiffness (range 0-100 mm)?			
	In case 26-90 mm:	1 point	_____
	In case > 90 mm:	2 points	_____
5. What is the number of tender joints?	In case 4-10:	0.5 point	_____
	In case 11 or higher:	1 point	_____
6. What is the number of swollen joints?	In case 4-10:	0.5 point	_____
	In case 11 or more:	1 point	_____
7. What is the C-reactive protein level (mg/L)?	In case 5-50:	0.5 point	_____
	In case 51 or higher:	1.5 points	_____
8. Is the Rheumatoid factor positive?	If yes:	1 point	_____
9. Are the anti-CCP antibodies positive?	If yes:	2 points	_____
		Total score	_____

Figure 3A.

Prediction Score	Non- RA n (%)	RA n (%)
0	1 (100)	0 (0)
1	8 (100)	0 (0)
2	42 (100)	0 (0)
3	58 (100)	0 (0)
4	78 (93)	6 (7)
5	73 (85)	13 (15)
6	63 (74)	22 (26)
7	37 (49)	38 (51)
8	16 (33)	33 (67)
9	6 (14)	36 (86)
10	5 (23)	17 (77)
11	0 (0)	8 (100)
12	0 (0)	1 (100)
13	0 (0)	1 (100)
14	0	0
Total	387	175

Figure 3B.

Figure 3A & 3B. The form used to calculate the prediction score in points for individual patients with UA (figure 3A) and the observed chances to progress to RA for the different prediction scores (figure 3B).

which IL-6 is increased (older age, inflammation) CRP-levels are elevated. Therefore, the CRP-level directly reflects the level of proinflammatory cytokines. Additionally, also the number of tender joints and the number of swollen joint may mirror the level of the proinflammatory processes. It is reasonable to suggest that in case of increased (local) pro-inflammatory activity the biological processes that generate RA are boosted.

6. Rheumatoid factor and anti-CCP antibodies

The association between most of the above mentioned factors and RA are (in part) mediated by an increase in pro-inflammatory cytokines, and thus reflect a quantitative trait. The last two items of the prediction model, the presence of autoantibodies, are primarily a qualitative trait. Although it is still uncertain whether these autoantibodies are of pathophysiological importance or the result of a bystander effect, the specificity of anti-CCP antibodies for the development of RA is extensively reported. A recent study revealed that not only the presence of anti-CCP antibodies, but in case of anti-CCP-positivity also the level of these antibodies, is correlated with an increased risk on progressing from UA to RA[33]. Moreover, not only the level but also the nature of the autoantibody response is different in UA and RA. Patients with UA have a lower number of anti-CCP isotypes than patients with RA and, similarly, the UA-patients that progressed to RA had a higher number of isotypes compared to the UA-patients that did not develop RA[34].

In conclusion, the biological mechanisms underlying UA and RA differ both in quantity (e.g. level proinflammatory cytokines) and quality (e.g. autoantibody response). Apparently, UA-patients that have more of these quantitative or qualitative traits have a concomitant higher risk to progress to RA.

Outcomes of treatment in UA

Almost all clinical trials on therapeutic strategies have included patients with (early of longstanding) RA. At present there is one study that assessed the efficacy of methotrexate in patients with UA[35]. In this double blind clinical trial patients were randomized for treatment with either methotrexate or placebo. The aim of the PROMPT study was to determine whether patients with UA benefit from treatment with methotrexate (MTX). The main outcomes were progression to RA and radiographic joint damage.

The PROMPT study was a prospective double-blind placebo-controlled randomized multicenter trial in 110 patients with UA who fulfilled the ACR 1958 criteria for probable RA. Treatment started with MTX 15 mg/wk or placebo tablets, and dose increase was dictated by 3-monthly calculations of the disease activity score (DAS), aiming at a DAS= 2.4. After 12 months, the study medication was tapered to nil. Patients were followed up for 30 months. When a patient fulfilled the ACR 1987 criteria for RA, the study medication was changed to MTX.

In the MTX-group, 22/55 patients had progressed to RA versus 29/55 in the placebo-group, the criteria were fulfilled at a later time point ($p=0.04$), and patients showed less radiographic progression over 18 months ($p=0.046$). Subsequently, patients were followed for 30 months and both the progression towards RA and the level of joint destruction were measured. A significant lower number of UA-patients that was treated with methotrexate had progressed to RA compared to the placebo treated patients. In addition, the UA-patients that were treated with methotrexate had a significantly lower lever of radiological joint destruction, indicating a less severe disease course. Interestingly, after the cessation of methotrexate at 18 months the difference in the number of patients that developed RA remained statistically significant but the difference became smaller. This suggests that in some patients methotrexate had hampered the progression of the disease but had not been able to totally stop the underlying pathophysiological mechanisms. These data have to be replicated in other studies and hopefully future targeted therapies will be able to fully halt the development of persistent arthritis. Nevertheless, the data of this study is promising as they indicate that treatment in an early phase of RA, before the disease is established, is effective.

Conclusion

UA is a diagnosis per exclusionem and refers to arthritis that cannot be classified according to current criteria. The term UA is different from ‘early

arthritis' and 'early RA'. The disease course of UA is variable and about one third of the UA-patients are in an early phase of RA. These UA-patients provide an opportunity, as the disease process in UA is less established and treatment in this early phase might result in halting the progression towards RA. To achieve this, physicians should be able to predict which UA-patients will progress to RA and will benefit from drugs that are proven to be effective in UA. A rule that predicts the chance to develop RA in individual patients with UA has recently been developed and clinical trials evaluating the effects of DMARD-therapy in UA are being designed. Hopefully, in the next decade personalized medicine will be achieved and the impact of arthritis on patients' quality of life will be further diminished.

Parts of this manuscript have been published before, for an extensive literature search see papers published by prof. Dr. TWJ Huizinga via www.pubmed.com

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