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Prognostic evaluation of early rheumatoid arthritis

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Summary

The progression of rheumatoid arthritis (RA) is quite variable, ranging from very mild or subclinical forms (approx. 10%) to rapidly progressing and debilitating forms (10–15%). The majority of patients present with an intermediate stage with episodes of exacerbation separated by periods of relative inactivity, which evolves to progressive functional losses. To optimise the therapeutic management of early RA it is necessary to perform periodic evaluations of the clinical and laboratory test responses to the treatment instituted, as well as the parameters indicating disease prognosis. Composite measures are frequently used to evaluate the disease activity score (DAS), including the response criteria of the American College of Rheumatology (ACR), the response criteria and the DAS according to the European League Against Rheumatism (EULAR) and the composite indices of disease activity (CIDsA): DAS, the index of disease activity based on 28 joints (DAS 28), the simplified disease activity index (SDAI) and the clinical disease activity index (CDAI). The evaluation of prognosis includes investigation of the absence or occurrence of disease and joint damage remission. Due to the multifaceted nature of RA, no single clinical or laboratory parameter is able to describe satisfactorily the level of inflammatory activity or the disease prognosis at any given time.

Key words: *early rheumatoid arthritis; prognostic; remission; joint damage; disease activity*

Introduction

Rheumatoid arthritis (RA) is a systemic condition that is chronic and progressive, and preferentially affects the synovium, possibly leading to osseous and cartilaginous destruction. It is a common disease that affects 1–2% of the world's population [1].

The progression of RA is highly variable and no precise statistics are available for it. RA can be very mild or subclinical, with spontaneous remission which is sometimes not diagnosed (almost 10%), or it can be rapidly progressive and debilitating (10–15%). The majority of patients present with an intermediate form involving episodes of exacerbation separated by periods of relative inactivity, evolving to progressive functional losses [2].

Temporary or permanent work incapacity is a serious consequence of RA, with grave repercussions for the individual and society. During the first years of symptoms it has been reported that up to 30% of RA patients are incapacitated for work, a number that increases to 60% after 5 yrs of disease [3].

Mortality among patients with RA is 1.5 times higher than in the rest of the population [4]. RA patients' survival chances have not improved relative to the general population during the past four decades [5]. Patients with severe forms of the disease have decreased average survival of 10 to 15 yrs. The causes of death include cardiovascular diseases, infections, pulmonary and renal diseases, lymphoproliferative diseases and gastrointestinal bleeding [6]. In addition to clinical indicators, high titres of rheumatoid factor (RF) are also associated with greater mortality [7].

Factors that suggest a worse joint and functional prognosis include early (before age 20) or late (after age 60) onset of the disease, a greater number of involved joints (more than 20), persistently changing inflammatory indicators, high titres of RF, positivity for anti-CCP, extra-joint commitment and early development of radiological erosion [8]. The search for other prognostic indicators is now a vast field of investigation.

To optimise the treatment of early RA, periodical evaluation of the patient's clinical and laboratory responses to treatment is necessary, as well as the parameters that indicate disease prognosis. Due to the multifaceted nature of RA, no clinical or laboratory parameter alone is capable of satisfactorily demonstrating the level of inflammatory activity or disease prognosis at any given time [9].

Evaluation of disease activity

Persistent inflammatory activity in early RA is intimately linked to symptoms such as constant pain and joint oedema. Initially, RA disease activity evaluations were focused on separate measurement of relevant variables, including symptoms such as duration of morning stiffness, number of painful and oedematous joints and measurements to detect inflammatory activity, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [10].

Currently, composite measures are frequently used for a broader evaluation of disease activity. The American College of Rheumatology (ACR) response criteria [11], and the response criteria and the disease activity index of the European League Against Rheumatism (EULAR) [12] are usually used. There are also highly useful instruments measuring RA activity on a continuous basis, including the composite indices of disease activity (CIDsA): the *disease activity score* (DAS) [13], the index of disease activity based on 28 joints (DAS 28) [14], the *simplified disease activity index* (SDAI) [15] and the *clinical disease activity index* (CDAI) [15, 16].

Table 1 reviews the characteristics of the CIDsA, including its elements and what contributes to the total score. Table 2 shows the cut-off values for parameters of disease activity [17].

Several studies have demonstrated that these CIDsA are highly correlated and that they can be used interchangeably depending on the doctor's choice [18–20]. The DAS 28 shows excellent correlation when compared to the original DAS and is much more practical because it evaluates only joints of the upper extremities and the knee [13].

The CIDsA permit the establishment of a therapeutic goal and a target to be reached for both patients and physicians. The value of the CIDsA should be used to direct the treatment of patients diagnosed with RA. Despite their great importance, the CIDsA have some limitations, and certain measurements must be taken [9]. In relation to the painful joint count, the CIDsA having been drawn up from the analysis of patients with a short duration of RA, pain, when present, predominantly indicates the presence of an inflammatory process. In patients with a long disease evolution who present with variable degrees of destruction and/or joint deformities, pain may not necessarily reflect disease activity [9]. Similarly, the observation of joint oedema without inflammatory activity represents a positive finding whether or not it resembles "residual synovitis". On the other hand, an increase in joint volume secondary to joint deformity and/or possible associated osteoarthritis should not be considered for the calculation of joints with oedema [19]. In some cases, when emotional factors are shown to be relevant, in particular when anxiety or depression are present, the painful joints count, the global health assessment and the patient's disease activity do not necessarily indicate a rheumatic inflammatory process. Following the same rationale, patients diagnosed with fibromyalgia also need special attention [9].

The evaluation of disease activity by the physician can and should take into consideration all of the limitations described, as well as all laboratory results that are available at the time of consultation [9].

It is of fundamental importance to have a reference parameter to guide the therapeutic path of a patient with RA. In particular, when a biological agent is used, it is mandatory that some CIDsA be used to determine when to initiate the use of medication [21].

A Dutch observational study by Welsing and collaborators [22] demonstrated that after an improvement in the first months of treatment the DAS scores remained stable during the subsequent course of RA. In this study, the mean of the initial DAS was 3.6 and decreased to approximately 3.0 after 6 to 9 months' follow-up and remained at this level thereafter. A similar pattern was seen in an Austrian report of early RA [23], in which the DAS score decreased from an initial mean value of 5.5 to an average of 3.2. Studies of changes in isolated measurements of disease activity, such as the joint count indices or the response measurements during the acute phase, showed a similar pattern. Initially, disease activity is suppressed by treatment but does not reach remission. For example, a report of 684 patients in the United Kingdom by Wiles and colleagues [24] demonstrated that the initial mean count of oedematous joints fell from 6 to 2 after 12 months' monitoring, and remained at that level during the subsequent follow-up.

When patients are evaluated early in the course of the disease, there is a potentially greater improvement in the DAS score. In Austria a small group of patients with very early RA symptoms, who were evaluated within the first 3 months of onset of symptoms and who received a disease-modifying antirheumatic drug (DMARD) as required, showed an improvement in the DAS of 2.8, compared to an improvement in the DAS of 1.7 among patients seen in the first 12 months of symptoms and who had received similar treatment [25].

Remission

Remission, which means the absence of disease activity, is the therapeutic target during the treatment of patients with RA, especially in its initial stages [26]. However, like the diagnosis of early RA, the definition of remission is controversial.

Many specialists use the ACR remission criteria, which are relatively restricted. According to the ACR, at least five of the following criteria should be present for at least two consecutive months for a patient to be considered in remission: 1) morning stiffness less than 15 min; 2) absence of fatigue; 3) absence of joint pain through clinical history; 4) lack of joint sensitivity to movement; 5) absence of joint or tendon oedema; and 6) an ESR value lower than 30 mm/h for men and 20 mm/h for women [27].

A variety of other less rigid definitions (the so-called stages of low disease activity) have been used to define early RA remission. The definition of disease remission by the EULAR, a definition that is currently widely used, is simpler and is based upon a DAS 28 below 2.6. An SDAI below 5 or a CDAI below 2.8 equally constitute remission [28].

An additional problem is the fact that remission may occur independently of therapy, a situation called "natural

remission", or can be the result of effective drug treatment when RA is essentially in a persistent state of low disease activity [29]. Although about one third of patients with undifferentiated arthritis develop spontaneous remission, this percentage is lower in patients diagnosed with early RA [30]. The majority of studies suggest that around 10% of patients with RA go into "natural remission". For example, an American study by Wolfe and colleagues, who followed more than 1000 patients/year, found that 14% of 458 RA patients achieved remission even without treatment [31]. Another study reported a long-term remission of 7% [32]. On the other hand, a Dutch study by Prevoo and colleagues reported that 10% of 227 RA patients followed for 4 yrs achieved remission [33].

The percentage of patients who achieve remission due to the therapy instituted is highly variable. Table 3 [33–45] illustrates the occurrence of remission in several prospective observational studies of patients with early RA. These studies cannot be compared because the definition and criteria of remission used are not uniform. Another variable are the different therapeutic schemes used by patients over time. Even in those studies in which there was no planned therapeutic intervention it is possible to observe higher remission indices in recent cohorts. This fact can also be explained by the changes in therapeutic approaches that have occurred in recent years (the use of therapeutic goals, such as a stage of low disease activity; more frequent evaluations; and therapeutic regimens including combinations of DMARD and biological therapy in the early phases) [46].

Joint damage

One of the possible outcomes for patients with early RA is the development of erosive joint disease, which can be evaluated through conventional radiographs or other imaging methods such as ultrasound and MRI. Radiographic alterations, especially the occurrence of juxta-joint erosion, are an important indicator of progressive damage because they have been shown to correlate well with subsequent incapacity [2].

In 1977, Brooks and Corbett [47] summarised the radiographic alterations observed in 94 patients with early RA followed up over a 5-yr period. Radiographic damage was detected in the early stages of disease evolution and affected 73% of the population evaluated. The erosive alter-

Table 1
Characteristics of the composite indices of activity of rheumatoid arthritis: elements and contribution to the total score.

Elements	SDAI	CDAI	DAS	DAS28
Number of swollen joints	Simple count (0–28)	Simple count (0–28)	More extensive joint count (0–2.86)	Square root of simple count (0–1.48)
Number of tender joints	Simple count (0–28)	Simple count (0–28)	Square root of the Ritchie index (0–4.77)	Square root of simple count (0–2.96)
Reagents of acute phase	CRP in mg/dl (0.1–10)	–	Transformed logarithm of ESR (0.23–1.51)	Transformed logarithm of ESR (0.49–3.22)
Assessment of global health by the patient	–	–	EVA in mm (0–0.72)	EVA in mm (0–1.40)
Assessment of disease activity by the patient	VAS in cm (0–10)	VAS in cm (0–10)	–	–
Assessment of disease activity by the physician	VAS in cm (0–10)	VAS in cm (0–10)	–	–-
Total score	Simple count (0.1–86)	Simple count (0–76)	Requires a calculator (0.23–9.87)	Requires a calculator (0.49–9.07)
Comments	The calculation is simple, but not immediate (CRP)	Simple and immediate calculation	In addition to a calculator, the ESR is needed	in addition to a calculator, the ESR is needed

SDAI – Simplified disease activity index; CDAI – Clinical disease activity index; DAS – Disease activity score; DAS 28 – Disease activity score (28 joints); CRP – C-reactive protein; ESR – Erythrocyte sedimentation rate; VAS – Visual analogue scale 2 and 100 mm/h for ESR and between 0.1 and 10 mg/dL for CRP.

Table 2
Characteristics of the composite indices of activity of rheumatoid arthritis: cutoff values for disease activity stage.

Index	Stage of disease activity	Definition
SDAI	Remission Low disease activity Moderate disease activity High disease activity	<5 <20 <40 ≥40
CDAI	Remission Low disease activity Moderate disease activity High disease activity	<2.8 <10 <22 ≥22
DAS28	Remission Low disease activity Moderate disease activity High disease activity	<2.6 <3.2 <5.1 ≥5.1

SDAI – Simplified disease activity index; CDAI – Clinical disease activity index; DAS – Disease activity score; DAS 28 – Disease activity score (28 joints); CRP – C-reactive protein; ESR – Erythrocyte sedimentation rate; VAS – Visual analogue scale 2 and 100 mm/h for ESR and between 0.1 and 10 mg/dL for CRP.

ations preceded joint space reduction and were particularly present in the feet.

Since then, several groups have reported the frequency of erosive alterations in patients with early RA followed for at least 12 months. On average, 44% of the patients presented with erosions in the early evaluation of these observational studies. After an average follow-up period of 4 yrs, the percentage of patients who presented with erosions increased to approx. 63%, although there was considerable variation among the studies [48]. Machold and collaborators [49] assessed 108 patients with very early RA who were evaluated in the first 3 months of symptoms, and reported that 13% presented with erosions at the time of first evaluation; after 2 yrs of follow-up this value increased to 28%. In contrast, the largest British study, the *Early Rheumatoid Arthritis Study* (ERAS), involving a cohort of 866 patients with RA receiving conventional treatment, found that 32% of patients presented with radiographic erosion at the first evaluation, and 70% of patients displayed radiographic erosion after 3 yrs [50]. Radiographic erosions on conventional radiographs remain the key measurement in the structural outcome of early RA; hence the use of radiography was recommended by a European committee of rheumatologists after a detailed review of all available evidence [51].

MRI and ultrasound are promising techniques that may become valuable for monitoring disease activity and the response to treatment during early RA. Several studies suggest the use of these techniques [52], although the expert opinion is that they are still experimental and their merits in routine clinical practice still need to be defined; the findings reported with these methods may therefore be controversial.

Quality of life

Patient quality of life (QOL) outcome-based studies are performed to assess whether patient health has been enhanced as measured by physical, mental, and social tools. Generic and disease-specific patient-reported QOL instruments, such as the Health Assessment Questionnaire (HAQ) Disability Index and the SF-36, are of proven power and sensitivity for the measurement of changes in QOL in clinical trials of disease-modifying antirheumatic drugs [53]. However, these instruments are little used in clinical practice, and patients have reported that the actual clinical assessments alone do not address important parameters such as fatigue and disturbed sleep, which significantly affect QOL. In spite of this, these instruments are widely used in clinical trials and the results are used to evaluate therapeutic response in RA.

Conclusion

In the wide spectrum of RA, attempting to define which patients will progress to more severe symptoms is of fundamental importance. It will allow the institution of more aggressive therapy in the early stages of the disease for the group with a higher risk of progressing to severe disease. The occurrence of remission and the evaluation of disease activity and joint damage are ways of establishing disease prognosis.

Given the complexity of the disease, only the sum of several parameters such as the currently available composite indices of activity, a more comprehensive definition of remission and more modern methods of verification of joint damage will allow approximate determination of the inflammatory activity level or the disease prognosis at any given time.

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Table 3
Remission in prospective observational studies of early rheumatoid arthritis patients.

Study (reference)	Year	Cases	Follow up (years)	Remission n (%)
Mottonen et al. [33]	1996	142	6	45 (32)
Prevoo et al. [32]	1996	162	2	32 (20)
Sokka and Hannonen [34]	1999	135	15	32 (24)
Harrison and Symmons [35]	2000	231	3	42 (18)
Young et al. [36]	2000	732	5	94 (13)
Lindqvist et al. [37]	2002	183	10	30 (18)
Visser et al. [38]	2002	156	2	16 (10)
Schumacher et al. [39]	2004	20	5	2 (10)
Tengstrand et al. [40]	2004	844	2	279 (33)
Vázquez et al. [41]	2007	105	2	34 (32)
Forslind et al. [42]	2007	698	5	269 (38)
Pascual-Ramos et al. [43]	2009	75	2	48 (64)
Verschueren et al. [44]	2009	89	1	61 (69)

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