Reumatol Clin. 2011;7(5):339–342

Reumatología Clínica

www.reumatologiaclinica.org

Continuing Medical Education

Are Prognostic Factors Useful in Rheumatoid Arthritis?☆

Montserrat Robustillo Villarino*, Jesús Rodríguez Moreno

Servicio de Reumatología, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

ARTICLE INFO

Article history:
Received 26 October 2010
Accepted 17 November 2010
Available online 9 September 2011

Keywords:
Rheumatoid arthritis
Prognosis of disease

ABSTRACT

Rheumatoid arthritis (RA) is an inflammatory disease of unknown etiology, which predominantly affects joints and that confers poor functional and vital outcome. In many patients the inflammatory process is maintained for years, and results in joint destruction and long-term functional disability. Prognostic factors (PF) are demographic, clinical, laboratory and/or radiographic and should be evaluated at the onset of the disease, providing the physician prospective information on patient outcome. The challenge for the rheumatologist is to identify patients who present a poor prognosis in early rheumatoid arthritis and formulate treatment accordingly.

¿Son útiles los factores pronóstico en la artritis reumatoide?

Palabras clave:
Artritis reumatoide
Factores pronóstico

RESUMEN

La artritis reumatoide (AR) es una enfermedad inflamatoria de etiología desconocida y de predominio articular que condiciona mal pronóstico funcional y vital. En muchos pacientes el proceso inflamatorio mantenido durante años se traduce en destrucción articular e impotencia funcional a largo plazo. Los factores pronósticos (FP) son datos sociodemográficos, clínicos, analíticos y/o radiológicos presentes al inicio de la enfermedad que nos proporcionan información prospectiva de la evolución del paciente. El reto del especialista en reumatología es identificar a los pacientes que presenten signos de mal pronóstico en el inicio de la enfermedad y desarrollar una estrategia terapéutica apropiada.

Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory disease of unknown etiology that preferentially affects joints in a symmetric manner. The course of the disease is variable because it leads to functional compromise from the onset, progressing over time along with joint destruction and deformity, which may lead to severe disability in a large percentage of affected personas, work loss and even shortened survival.

Prognostic factors (PF) are sociodemographic, clinical, analytical and/or radiological data present at the beginning of the disease that provide prospective information of the patients' progress. This information is useful in order to guide therapeutic decision. The importance of PF is settled mainly in three aspects:

- Classification: allows the stratification of patients into homogeneous groups.
- Therapeutic: facilitate therapeutic choices for each patient, as well as the comparison of these options between each group of patients with different prognostic characteristics.
- Prevention: the knowledge of PF allows us to initiate specific preventive actions.

We can classify PF into two groups: those which are modifiable (erythrocyte sedimentation rate [ESR], C reactive protein [CRP], DAS28, HAQ, and treatment), and non modifiable (gender, age, rheumatoid factor [RF], anti-CCP, and shared epitope).

One can talk about PF in relation to different aspects:

- Functional prognosis.
- Radiologic progression.
- Disease remission.
- Mortality.

☆ Please cite this article as: Robustillo Villarino M, Rodríguez Moreno J. ¿Son útiles los factores pronóstico en la artritis reumatoide? Reumatol Clin. 2011. doi:10.1016/j.reuma.2010.11.006.

* Corresponding author.
E-mail address: mrobustillo@bellvitgehospital.cat (M. Robustillo Villarino).

2173-5743/$ – see front matter

Functional Prognosis

Functional prognosis of disease refers to the degree of disability developed by a patient in the long term. The possibility that a patient develops severe disability reaches 33% in studies performed before the availability of anti-TNF,[1] and said disability is reflected on the patients capacity to work, which may be reduced in 50% at 10 years since the onset of disease.[2]

PF associated with a greater disability and identified in several studies are age (OR=1058 [1017–1101]),[3] positive RF (OR=3772 [1204–11 813]),[3] elevated baseline DAS28 (OR=2)[4] and baseline HAQ>1 (OR=4023 [1373–11 783]).[3]

Radiologic Progression

Radiographic remission is defined as the lack of progression of structural damage. Irreversible structural lesions appear from the onset of the diseases. Many of the patients attain clinical remission according to current remission criteria, but in spite of a strict control of the disease or the minimum of joint clinical manifestations and normalization of the acute phase reactants, a proportion of patients present progression of the structural damage, joint deformity and reduction in quality of life. This radiologic progression may be explained by maintained subclinical inflammation of the bone and cartilage during the course of disease.[5] In a review of the validity of remissions predictive value[6] there was a relationship between remission of the disease and structural damage and long-term disability, concluding that the patients who reach clinical remission according to current criteria have a tendency to show less functional impairment and slower radiographic progression.

PF predicting radiologic progression as identified in different studies are: female gender (OR=3.3 [1.3–7.6])[7] (OR=5.5 [1.1–28.2])[8]; baseline ESR (OR=3.2 [1.2–7.6])[7]; baseline CRP;[9] positive RF (OR=3.1 [1.2–7.6])[7]; baseline anti-CCP titers (OR=4.03 [1.65–9.82])[5] (low OR=2.6 [0.9–7.2], elevated OR=9.9 [2.7–36.7])[7] (OR=3.6 [0.9–14.5])[8]; bone edema seen on magnetic resonance (MR) (OR=1.44 [0.95–2.20])[5]; sharp score (OR=1.12 [1.03–1.21]); shared epitope (OR=2.0 [1.8–2.2])[10] (OR=3.1 [1.1–9]).[8]

Disease Remission

Disease remission is generally a synonym of minimal clinical affection, absence of synovitis and normal acute phase reactants. If disease remission is achieved, it will be more likely that the degree of long-term disability of the patient will be minimized.

A recent systematic review[11] outlining the variables that act as predictive factors of disease remission has been published. The magnitude of association of each of them is variable in relation to the design and number of included patients in the analyzed studies, as well as the variables used to adjust each model. Factors identified can be grouped into three areas: sociodemographic, disease associated and treatment associated. The factors most commonly associated with disease remission are rheumatoid factor, disease activity as quantified by DAS28, functional status (HAQ) and early onset of treatment.

1. Sociodemographic factors:
   - Gender: among the studies evaluating the effect of gender on disease remission, 5 of 11 studies, among them TEMPO[12] and ReAct,[13] conclude that male gender is an independent predictive factor of disease remission in a maintained manner. The rest of the evaluated studies did not show gender as a remission-predicting factor.
   - Age and age at onset of disease: it has been observed that age acts as a significant predictor of disease remission in an inverse manner, in 2 cohorts of patients treated with anti-TNF.
     1. GISEA[14] trial: patients treated with anti-TNF over 53 years of age have less probability of achieving remission after adjusting for gender, RF and baseline disease activity (OR=0.64 [0.4–0.9]).
     2. ReAct trial[13]: patients treated with adalimumab under 40 years of age have a higher tendency to achieve remission after 3 years of follow up versus those older than 40 (HR=0.61–0.87).
     3. FIN-RACo[15] trial: did not confirm age at onset of disease as an independent prediction factor for remission.

   The study by Pease et al.[16] concludes that onset of disease in persons over 65 acts as an independent remission factor in patients treated with DMARD (OR=2.99 [1.8–5]).

   After gender and age, one may deduce that female gender and advanced age have less chance to achieve remission. These data must be used relatively because of the limited the parameters used to measure the degree of disease activity and remission criteria have in these populations.
   - Genetic markers: their use is restricted to clinical trials. It has been shown that the presence of shared epitope, both specific predisposing alleles HLA-DQB1/HLA-DQA,[1] and the protective HLA-DRB[1] allele are not associated with remission in RA when adjusted for RF and the use of DMARD.[17]
   - Smoking: The results obtained in two studies are contradictory and the effect of tobacco on disease activity must be confirmed by future research.[13,18]
   - Comorbidity:
     1. ReAct trial[13]: the presence of more than one comorbidity is related to a lessened probability of achieving clinical remission (HR=0.85 [0.78–0.93]).
     2. The study by Hyrich et al. did not show a significant association between the presence of comorbidity and disease remission in patients treated with ETN and IFX.
2. Disease dependent factors:
   - Disease activity: most of the studies showed that the degree of disease activity quantified by DAS28 is inversely related to disease remission.[13,19–21]
   - Functional status (HAQ): numerous studies on cohorts of patients treated with DMARD or anti-TNF have shown that the functional status as quantified by the baseline HAQ behaves as an independent predictor of disease remission in all models in an inverse manner.[13,21] This association has not been documented in early onset RA.[19]

   Occasionally, disease activity measures or remission criteria may not truly reflect the degree of disease because they take into account the patient's perception of pain or the global disease activity evaluation. For example, it has been shown that women with RA have a tendency to evaluate in a more severe way than the disease with respect to men and these data may reflect less precision on the evaluation of disease activity by this specific population.
   - Duration of disease: patients with longer diseases have less chances of achieving persistent clinical remission (OR=0.87–0.91; $P \leq .004$).[21] In other cohort studies using anti-TNF it has been impossible to determine if the time since the onset of disease is a predictor of remission.[13,22]
   - Rheumatoid factor: most of the studies have shown that RF is inversely related to disease remission. However, the predictive value of baseline RF disappears when adjusted for anti-CCP titers, the treatment strategy employed (combination DMARD or anti-TNF) and the presence of shared epitope.[21]
   - Anti-CCP: Baseline anti-CCP titers have been inversely related with the probability of remission at 24 months since onset

(OR=0.6 [0.5–0.9]),[21] adjusted for DAS,[28] duration of disease, HAQ and male gender.
- Acute phase reactant plasma levels: patients with a baseline CRP plasma determination equal or over 20 mg/l have a reduced probability of achieving disease remission (HR=0.8 [0.8–0.9]).[13]
- Radiologic affection: a Sharp score under 4 behaves as an independent remission factor when adjusting for other variables (DAS, morning stiffness, HAQ<1.25, Ritchie score) (OR=1.99 [0.98–4.0]).[19]

3. Treatment dependent factors: numerous published studies show that patients receiving early treatment with DMARD, anti-TNF or combinations of DMARD and anti-TNF have a greater probability of achieving disease remission.[13,15,23] On the other hand, the number of DMARDs employed prior to anti-TNF is inversely related to the probability of disease remission.[23,24]

Lastly, patients in which the start of treatment is delayed for more than 4 months since the onset of disease have a reduced chance of attaining clinical remission.[25]

Mortality

While the general population mortality rate has substantially decreased during the past 4–5 decades, this improvement in survival has not been shown to occur in patients with RA, with survival remaining constant.[26] One of the main causes of mortality in patients with RA is that of cardiovascular origin, but classic cardiovascular risk factors by themselves do not justify this increase in RA patient mortality with respect to the general population. However, disease inflammatory activity does play an important role in it.

In studies prior to the use of anti-TNF and in current disease incidence cohorts it has been demonstrated that there is a difference between life expectancy between the general population and patients with RA which has increased in recent decades.[26,27]

Studies evaluating the influence of RF on survival of patients with RA observed an inversely proportional relationship in patients with positive RF, while those negative to RF had a mortality on par with the general population. The increase in the mortality rate between patients with RA and the general population is confirmed for patients with RA and positive RF.[26] The other mortality associated PF identified in RA are[26]:

- Age (HR=1.1 [1.09–1.12]).
- Male gender (OR=1.90 [1.43–2.52]).
- Elevated HAQ scores maintained throughout the progression of the disease (OR=1.46 [1.19–1.79]).
- Comorbidities (OR=1.83 [1.38–2.42]).
- Low schooling levels: lack of secondary schooling is associated with a reduction of over 50% in the functional status or 9 year mortality rates (OR=7.5).[28]
- Depression: patients with depression have higher mortality (HR=2.2 [1.2–3.9]).[29]

Conclusion

We have identified predictors of disease among which are age, rheumatoid factor, the degree of disease activity (DAS[28]), functional status (HAQ) and early treatment. These prognostic factors present at the onset of the disease help us to identify patients most likely to present a more aggressive course of RA. In these patients combination therapy with DMARDs and anti-TNF at the onset of disease[30] may be indicated to achieve as low an inflammatory activity as possible, maintaining it during activity and minimizing morbidity and mortality attributable to RA. However, more studies are needed to establish long-term benefits of aggressive treatment strategies.

References

1. Spector TD. Rheumatoid arthritis. Rheum Dis Clin North Am. 1990;16:513–37.
2. Mau W, Bornmann M, Weber H, Weidemann HF, Hecker H, Raspe HH. Prediction of permanent work disability in a follow-up study of early rheumatoid arthritis: results of a tree structured analysis using recpam. Mau Semin Arthritis Rheum. 1991;21:4–12.
3. Graell E, Vazquez I, Larrosa M, Rodríguez-Cros JR, Hernández MV, Sanmartí R, et al. Disability measured by the modified health assessment questionnaire in early rheumatoid arthritis: prognostic factors after two years of follow-up. Clin Exp Rheumatol. 2009;27:284–91.
4. Schneeberger EE, Citera G, Maldonado Cocco JA, Salcedo M, Chiardola F, Paira SO, et al. Factors associated with disability in patients with rheumatoid arthritis. J Clin Rheumatol. 2010;16:215–8.
5. Hetland ML, Stengaard-Pedersen K, Junker P, Østergaard M, Ejbjerg BJ, Jacobsen S, et al. Radiographic progression and remission rates in early rheumatoid arthritis—MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised CIMESTRA trial. Ann Rheum Dis. 2010;69:1789–95.
6. Vvan Tuyl LH, Felson DT, Wells G, Smolen J, Zhang B, Boers M, American College of Rheumatology. European League against Rheumatism Committee to Define Remission for Clinical Trials. Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. Arthritis Care Res. 2010;62:108–17.
8. Sanmarti R, Gomez A, Ercilla G, Gratacos J, Larrosa M, Canete JD, et al. Radiological progression in early rheumatoid arthritis after DMARDS: a one-year follow-up study in a clinical setting. Rheumatology. 2003;42:1044–9.
9. Lindqvist E, Eberhardt K, Bendtzen K, Heinegård D, Saxne T. Prognostic laboratory markers of joint damage in rheumatoid arthritis. Ann Rheum Dis. 2005;64:196–201.
10. Gorman JD, David-Vaudey E, Pai M, Lum RF, Criswell LA. Lack of association of the HLA-DRB1 shared epitope with rheumatoid nodules: an individual patient data meta-analysis of 3,272 caucasian patients with rheumatoid arthritis. Arthritis Rheum. 2004;50:753–62.
11. Katchamart W, Sindhu Johnson MD, Lucy Lin HJ, Phumethum V, Salliot C, Bombardier C. Predictors for remission in rheumatoid arthritis patients: a systematic review. Arthritis Care Res. 2010;62:1128–43.
12. Van der Heijde D, Klareskog L, Singh A, Tornero J, Melo-Gomes J, Fatenejad S, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis. 2005;65:328–34.
13. Burmester GR, Ferraccioli G, Flipo R-M, Monteagudo-Saez I, Unnebrink K, Kary S, et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum. 2008;59:32–41.
14. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, Falappone PC, Ferrante A, Malesci D, et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol. 2007;34:1670–3.
15. Sokka T, Mäkinen H, Puolakka K, Möttönen T, Hannonen P. Remission as the treatment goal—the FIN-RACo trial. Clin Exp Rheumatol. 2006;24:74–6.
16. Pease CT, Bhakta BB, Devlin J, Emery P. Does the age of onset of rheumatoid arthritis influence phenotype? A prospective study of outcome and prognostic factors. Rheumatology. 1999;38:228–34.
17. Molenaar ETH, Voskuyl AE, Van der Horst-Bruinsma IE, Schreuder GMT, Zanelli E, Dijkmans BAC. Influence of HLA polymorphism on persistent remission in rheumatoid arthritis. Ann Rheum Dis. 2002;61:351–3.
18. Hyrich KL, Watson KD, Silman AJ, Symmons DPM. British Society for Rheumatology Biologics R. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology. 2006;45:1558–65.
19. Gossec L, Dougados M, Goupille P, Cantagrel A, Sibilia J, Comber B. Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. Ann Rheum Dis. 2004;63:675–80.
20. Vazquez I, Graell E, Gratacos J, Canete JD, Vinas O, Ercilla MG, et al. Prognostic markers of clinical remission in early rheumatoid arthritis after two years of DMARDs in a clinical setting. Clin Exp Rheum. 2007;25:231–8.
21. Forslind K, Hafstrom I, Ahlmen M, Svensson B, the BSG. Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis. 2007;66:46–52.
22. Van der Heijde D, Klareskog L, Landewe R, Bruyn GAW, Cantagrel A, Durez P, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum. 2007;56:3928–39.
23. Liang GC, Cordero M, Dyer A, Chang RW. Current tumor necrosis factor-alpha inhibitor use is associated with a higher probability of remissions in patients with rheumatoid arthritis. J Rheum. 2005;32:1662–5.
24. Hyrich KL, Symmons DPM, Watson KD, Silman AJ. British Society for Rheumatology Biologics R. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006;54:1786–94.

25. Mottonen T, Hannonen P, Korpela M, Nissila M, Kautiainen H, Ilonen J, et al. Delay to institution of therapy and induction of remission using single-drug or combination-disease modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum. 2002;46: 894–8.
26. Radovits BJ, Fransen J, Al Shamma S, Eijsbouts AM, Van Riel PLCM, Laan RFJM. Excess mortality emerges after 10 years in an inception cohort of early rheumatoid arthritis. Arth Care Res. 2010;62:362–70.
27. Gonzalez A, Kremers HM, Crowson CS, Nicola PJ, Davis 3rd JM, Gabriel SE, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arth Rheumat. 2007;56: 3583–7.
28. Pincus T, Callahan LF, Burkhauser RV. Most chronic diseases are reported more frequently by individuals with fewer than 12 years of formal education in the age 18–64 United States population. J Chronic Dis. 1987;40:865–74.
29. Ang DC, Choi H, Kroenke K, Wolfe F. Comorbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis. J Rheumatol. 2005;32:1013–9.
30. Actualización de guía de práctica clínica para el manejo de la artritis reumatoide (GUIPCAR) en España 2007.