EDITORIALS

PREDICTING AND DECIDING ON REMISSION IN RHEUMATOID ARTHRITIS

INFLAMMATION in rheumatoid arthritis (RA) seems greatest at the onset of disease with the number of swollen joints maximal at this time and a high probability of developing joint damage or erosions within 2 yr of the onset of disease [1–3]. Early aggressive treatment of RA may alter the disease course [4–6]. Thus, initiation of disease-modifying anti-rheumatic drug (DMARD) therapy should not be delayed beyond 3 months [1, 7].

However, the diagnosis of RA may be difficult in early disease [8] and the prognosis varies within wide limits: some cases have a tendency to spontaneous (natural) remission, while others result in chronic inflammation with destruction of joints, functional disability, morbidity and mortality. Also, conventional therapies have significant adverse side-effects. Ideally, one could thus recognize patients with self-limiting disease to avoid unnecessary exposure to drug side-effects.

Many studies examined the course and outcome of patients with established RA, and investigated the role of variables measured at the patient's initial visit as prognostic factors [9]. While several sociodemographic, clinical and laboratory variables have been shown to be associated with a poor outcome in terms of decreased survival, development of physical and work disability, and worse quality of life, their usefulness in clinical decision-making has not been demonstrated.

The study by Harrison *et al.* [10] on predicting remission in this issue of the *British Journal of Rheumatology* is unique, because it is based on a true inception cohort of patients with inflammatory polyarthritis in the community and because it examines the usefulness of information currently available in clinical practice. In a methodologically sound approach using a prediction and validation set, Harrison *et al.* could confirm the known association of male gender and fewer than six tender joints at baseline with remission. However, it was not possible to construct a prediction rule of enough certainty to be useful in clinical decision-making. It remains to be shown whether additional information gained from immunogenetic markers allows a prediction rule useful for the clinician to be derived.

The importance of predicting remission is dependent on the rate of remission. The more frequent remission occurs, the more often we may unnecessarily treat a patient. To identify the risk of unnecessary treatment, we would need to know the rate of 'spontaneous remission' occurring without second-line or steroid treatment. For ethical reasons, this cannot be studied empirically, and because of confounding by treatment and selection bias (treated patients are likely to have

more severe and progressive disease), spontaneous remission cannot be studied epidemiologically. Closest to the concept of 'spontaneous remission' comes 'natural remission' which Harrison *et al.* [10] studied and defined as 'no arthritis on examination in a patient who has not taken second-line drugs or steroids in the preceding 3 months'. It is important to note that remission in this population may not only occur spontaneously, but may be induced by second-line drugs.

The rates of 'natural remission' found by Harrison *et al.* [10] are telling. Although the study was community based, which was reflected by the relatively low prevalence of rheumatoid factor positivity indicating less severe disease, the rate of remission in patients with inflammatory polyarthritis after 2 yr was only 25%. Furthermore, only 9% of all patients were in 'sustained remission' both at 1 and 2 yr. If remission had been defined as 'no arthritis' on examination, including treated patients would have given more patients in remission. These data demonstrate that while 'natural remission' (truly spontaneous or induced with a sustained effect over 3 months) is rare, remission can be achieved in a subset of patients treated with second-line drugs at some point in the course of the disease. The rates of remission in treated patients found in a study by Prevoo *et al.* [11] in this issue of the journal are similar. While 25% of patients fulfilled at least once the criteria for remission during the study period only 15% fulfilled the criteria at two consecutive visits. In exemplary case studies, Prevoo *et al.* [11] show that visits in which patients are in remission are not always consecutive. Remission may thus be best understood as an, often temporary, state at the lower end on the continuum of systemic inflammation or disease activity.

Although 'disease activity' and 'damage' have long been used in rheumatology, only recently have these concepts been operationalized and studied empirically [12–14]. The Nijmegen group clearly showed that what physicians describe as disease activity and use in their decision-making regarding DMARD treatment can be measured with few, weighted variables. With their algorithm called the Disease Activity Score (DAS), which integrates the number of swollen, tender joints and sedimentation rate, disease activity can be quantified. The DAS places disease activity on a continuum from 0 to 10. The index is advantageous because it provides a more reliable estimate than each individual measure [12, 14]. The precision is ~0.6: a change of >0.6 is unlikely to be by chance. For patients with mild disease activity, a change of 0.6 represents a clinically relevant change. With more

pronounced disease activity, a larger response of 1.2 is required to be of clinical relevance.

The definition of remission in terms of the DAS proposed by Prevoo et al. [11] is based on our current understanding of systemic inflammation and its consequences. Within this framework, control of systemic inflammation reduces pain in the short term, and damage and consequently disability in the long term. In this understanding, disease activity and damage are intermediate clinical outcomes, while pain and disability are primary patient-orientated health outcomes. The DAS is the target dimension which needs to be adjusted as best as possible; and to define remission in terms of the DAS one may contrast the DAS against patient-orientated health-outcomes and damage [15]. Depending on the selected external standard, different cut-offs in terms of DAS are to be expected.

Avoidance of damage and disability are the final arbiters of disease control. In an earlier paper, van Gestel et al. [13] showed that in group analysis a DAS ≤2.4 was associated with halted X-ray progression. Improved, more sensitive methods to show change in bone density as a first indicator of damage may allow an improved definition of the cut-off required to prevent joint destruction [7]. In the current paper, Prevoo et al. [11] gauged the DAS with the ARA criteria for remission [16], which include the same variables as used in the DAS, but in addition include pain, fatigue and morning stiffness which are primary patient-orientated health outcomes. The cut-off for remission in terms of the DAS was 1.6. Both cut-offs are most useful guidelines in clinical practice. Our goal must be to reduce permanently disease activity below 2.4 or even 1.6.

While remission cannot be predicted with clinical information currently available and while complete remission may not be achieved, we are challenged to optimize management. The DAS is a valid, precise and sensitive measure of disease activity; and the new empirically derived decision rules on response and remission are invaluable for the rheumatologist to best possibly control for disease activity and to alleviate pain, maintain function, and slow the rate of joint damage.

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REFERENCES

1. Kent Kwoh C, Simms RW, Anderson LG et al. Guidelines for the management of rheumatoid arthritis. American College of Rheumatology ad hoc committee on clinical guidelines. Arthritis Rheum 1996;39:713–22.
2. Möttönen TT. Prediction of erosiveness and rate of development of new erosions in early rheumatoid arthritis. Ann Rheum Dis 1988;47:648–53.
3. Van der Heijde DMFM, van Leeuwen MA, van Riel PLCM et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum 1992; 35:26–34.
4. Van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulfasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;i:1036–38.
5. Van der Heijde A, Jacobs JWG, Bijlsma JWJ et al. The effectiveness of early treatment with 'second line' antirheumatic drugs: a randomized, controlled trial. Ann Intern Med 1996;124:699–707.
6. Möttönen T, Paimela L, Ahonen J, Helve T, Hannonen P, Leirisalo-Repo M. Outcome in patients with early rheumatoid arthritis treated according to the 'sawtooth' strategy. Arthritis Rheum 1996;39:996–1005.
7. Emery P. The disease course, prognosis and outcome of rheumatoid arthritis. Rheumatol Eur 1995;24(suppl 2): 169–70.
8. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
9. Hochberg MC. Predicting prognosis of patients with rheumatoid arthritis: is there a crystal ball? J Rheumatol 1993;20:1265–7.
10. Harrison BJ, Symmons DPM, Brennan P, Barrett EM, Silman AJ. Natural remission in inflammatory polyarthritis: Issues of definition and prediction. Br J Rheumatol 1996;35:1096–1100.
11. Prevoo MLL, van Gestel AM, van 't Hof MA, van Rijswijk MH, van de Putte LBA, van Riel PLCM. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the Disease Activity Score. Br J Rheumatol 1996;35:1101–5.
12. van der Heijde DMFM, van 't Hof MA, van Riel PLCM, van Leeuwen MA, van Rijswijk MH, van de Putte LBA. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis 1992;51:177–81.
13. van Gestel AM, Prevoo MLL, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League against Rheumatism Response Criteria for Rheumatoid Arthritis. Arthritis Rheum 1996;39:34–40.
14. van Riel PLCM. Provisional guidelines for measuring disease activity in clinical trials on rheumatoid arthritis. Br J Rheumatol 1992;31:793–4.
15. Stucki G. Towards clinical quality management: RA as a case in point. Rheumatol Eur 1996;3:97–103.
16. Pinals RS, Masi AT, Larsen A. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308–15.