Early treatment of rheumatoid arthritis: rationale, evidence, and implications

In recent years the therapeutic attitude towards rheumatoid arthritis (RA) has changed considerably. Now, the disease is treated in an increasingly earlier phase and also more aggressively.[1] As is often the case in medicine, the process leading to this change in therapeutic attitude is not easy to unravel, as it might consist of a mixture of (seemingly) rational arguments and instinctive feelings, including dissatisfaction with current therapeutic modalities, new therapeutic options, changed insights into the pathogenesis, new hypotheses, etc.

In this article we will focus on the early treatment principle, being related to, but definitely distinct from the topic of more aggressive treatment of the disease, which will not primarily be dealt with here. We will briefly mention the rationale for treating patients with RA as early as possible, and thereafter review the current evidence available for this change in therapeutic attitude. Finally, we mention possible consequences of early treatment of RA, both for teaching and training as well as for the health care system.

Rationale for early treatment

A number of observations and arguments have led in the recent past to earlier (and more aggressive) treatment of RA. It has become clear that the way of treatment prevailing until recently, was insufficient to prevent ultimate disability and joint destruction.[2] Furthermore, RA, especially its more severe and systemic forms, is not only a disabling disease, but also associated with increased mortality.[2 3]

In the past years, it has become clear from a number of studies that in the "natural history" of RA, joint destruction occurs relatively early in the disease—that is, in the first years after onset.[4] A hopeful finding of some years ago, was that in those patients that were apparently treated successfully (or had a spontaneous remission) progression of joint destruction had decreased or even stopped.[5] As it has been shown that increased mortality, among others, depends on the severity and extent of the polyarthritis, it could be hoped that adequate treatment of the inflammatory process will not only influence joint destruction and disability, but will also increase the live span in these patients.

Apart from attempting to improve treatment (by starting earlier in the disease course), there have been concurrent developments that have led to better measurements of disease activity and outcome parameters, allowing for better monitoring of the disease. This in itself has opened the way to improve treatment and therefore better treatment results.

Increased treatment possibilities

Until some years ago treatment of RA had been, compared with today, rather conservative. There were several reasons for that therapeutic attitude. Firstly, a number of patients with polyarthritis of a few weeks duration will go into spontaneous remission, and thus exposed unnecessarily to the risks of treatment. Secondly, the number of second line agents (also called disease modifying antirheumatic drugs (DMARDs), slow acting antirheumatic drugs (SAARDs)) was rather small, were considered to be very toxic, and had unfavourable drug survival curves.[6] This usually led to rather late institution of these drugs—that is, at the time when considerable joint destruction had already taken place.[7] It therefore is not surprising that studies on the influence of these drugs on progression of radiographic joint damage were either negative or not very impressively positive.[8]

The chance of starting second line treatment in patients who would reach spontaneous remission early in the disease course will be small. Even within the "early treatment principle" there is still a period of trying to control the disease with non-steroidal anti-inflammatory drugs alone. The larger part of potential "spontaneous remission" patients will remain in this group. If not, it is questionable whether second line treatment will be undesirable, as there was an initial period of high disease activity leading to this treatment decision. Furthermore, the percentage of patients reaching sustained remission is small. Harrison *et al* reported a figure of 9% of early RA patients (symptoms for less than one year) who were in sustained remission at both one and two years of follow up.[9]

Recently, the pharmacotherapeutic armamentarium has been enlarged considerably. The classic second line agents (including antimalarials, gold, D-penicillamine, and azathioprine) have been supplemented with the "newer" ones, including sulphasalazine, methotrexate, and cyclosporine. In addition, ongoing studies indicate that the number will increase further in the not too distant future. Another important finding is that some of these "newer" drugs, namely sulphasalazine and methotrexate, differ in their effectivity characteristics from those of the "classic" ones. They tend to have a faster mode of action, which allows for better monitoring and therefore timely treatment adjustment. In addition, they have a definitely better drug survival curve.[10] With these tools in hand, the improved possibilities for disease assessment, and new insights in how disease activity, namely the area under the curve, is associated with ultimate disease outcome,[11] will be beneficial.

These developments have led to new hope, and to the fact that more patients are currently treated for a longer period of time, which at least decreases their cumulative disease activity over time. Whether this in the end will also decrease ultimate disability and joint destruction, is a point of current discussion and further studies and will be briefly discussed.

Early treatment: real evidence for better results?

More and more rheumatologists are convinced that early (and aggressive) treatment is necessary to achieve the best long term results. The reasoning behind the early initiation of disease controlling antirheumatic treatment is sensible, but is there enough clinical evidence?

Mötönen *et al*[12] compared their early RA cohort, treated according to the "sawtooth" strategy, with the results of previously published (historical) cohorts who had been treated with more conventional drug regimens. They conclude that the difference in response rate and joint erosions, which were in favour of their sawtooth policy, might be at least partly because of the different treatment strategies. However, such a historical comparison is liable to bias because of interobserver variation and different patient populations. Randomised trials are less subject to these forms of bias. Borg *et al*[13] conducted a 24 months "intention to treat" clinical trial of early RA patients randomised to auranofin or placebo. Despite the fact that only 24 of the original 65 patients still used placebo at the end of the study, a significant difference between the groups in several end point measures, including radiological progression, was found. The patients in the placebo (or delayed DMARD) group did worse than the auranofin (or

early DMARD) group. Egsmose *et al*[14] reinvestigated a representative subgroup of these trial patients five years after start of the original study. They demonstrated continued improvement in the early treatment (auranofin) group despite three more years of open DMARD treatment. Van der Heijde *et al*[15] analysed, in patients who had participated in a 52 weeks trial comparing sulphasalazine and hydroxychloroquine, the progression of joint damage two years after the end of the study. They found that the original benefit of sulphasalazine was sustained two years later. Van der Heide *et al*[16] studied immediate versus delayed introduction of SAARD treatment in recent onset RA patients using intention to treat analysis. After 12 months most clinical variables significantly improved, all in favour of the early treatment group. No difference in radiological progression was found. These studies all confirm a sustained effect of early active treatment, however the follow up, with respect to the chronic nature of the disease, was short. In addition, it should be noted that established longstanding disease can also be treatment responsive, not only in clinical terms but also in terms of diminishing progression of joint damage.[17] Apart from the long term efficacy of early or delayed treatment, another question should be answered: is there a "treatment window" early in the disease? Does the efficacy of treatment depend on the duration of the disease? Studies in murine collagen induced arthritis[18] suggest different roles of cytokines, thus different mechanisms, in early and established arthritis. We have searched the literature for comparable early and late RA patient trials. Disappointingly, no clear comparison could be made because all studies used their own, thus different, trial design. Frequently the inclusion criteria did not match and different disease activity variables and/or different measurement techniques were used. The core set of disease activity variables is a step towards better comparability of trials. In the past more trials have included these measures. In future these trials might be used to answer the question whether early treatment gives better direct and long term results.

In conclusion, more research is necessary including larger patient populations and especially longer follow up periods to evaluate the possible beneficial effect of early treatment. It might be possible to re-evaluate the combined data of standardised placebo controlled trials of recent onset RA five, 10, or even 15 years after study completion.

Possible implications for teaching, training, and the health care system

With the abovementioned caveats in mind, extrapolating recent improvements in treatment, including promising data with biological agents[19–21] to the future it seems reasonable that treatment of RA as early as possible will become a standard procedure. This in itself will have profound consequences for teaching and training of students and doctors, as well as for the health care system as a whole. Currently, textbooks usually focus on the classic picture of RA, with the well known malformations of peripheral joints. In the future this focus will have to shift to teach and recognise the symptoms and signs of early disease. In addition, both students and doctors as well as the lay public, should be made aware that recognising early disease is worthwhile because effective treatment modalities are available indeed. Finally, skills to monitor disease activity will have to be taught and trained because adjustments of treatment in case of flare of the disease are certainly as important as early treatment itself. Also the functioning of the health care system has to meet the new requirements. Most important in this respect is that patients suspected of having a diagnosis of RA have easy access to a rheumatologist without delay. Although part of the delay to get the right treatment relates to a delay in the diagnosis,[22] there is also a delay in several western countries because of waiting lists, which reflects a shortage in the number of rheumatologists available. It is important that this shortage is met, especially in the light of the expected demographic changes. Recent studies have indicated that a treatment delay of three to six months may already result in considerable joint damage,[13] which is largely irreversible. Early treatment as a measure of (secondary) prevention of disabling late disease, seems to be within reach. Creating the right conditions for implementing this new principle is one of the great challenges of future medicine.

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1 American College of Rheumatology ad hoc committee on clinical guidelines. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum 1996;39:713–22.
2 Pincus-T. Long-term outcomes in rheumatoid arthritis. Br J Rheumatol 1995;34 (suppl 2):59–73.
3 Mitchell DM, Spitz PW, Young DY, Bloch DA, McShane DJ, Fries JF. Survival, prognosis, and causes of death in rheumatoid arthritis. Arthritis Rheum 1986;29:706–14.
4 van der Heijde DMFM. Joint erosions and patients with early rheumatoid arthritis. Br J Rheumatol 1995;34:74–8.
5 van Leeuwen MA, van der Heijde DMFM, van Rijswijk MH, Houtman PM, van Riel PLCM, van de Putte LBA, *et al.* Interrelationship of outcome measures and process variables in early rheumatoid arthritis. J Rheumatol 1994;21:425–9.
6 Wolfe F. The epidemiology of drug treatment failure in rheumatoid arthritis. Baillieres Clin Rheumatol 1995;9:619–32.
7 Louie JS. Additional drugs for rheumatoid arthritis. In: Bluestone R, ed. *Rheumatology.*. Boston: Houghton Mifflin Professional Publishers, 1980:246.
8 Ianuzzi L, Dawson N, Zein N, Kushner J. Does drug therapy slow radiographic deterioration in rheumatoid arthritis? N Engl J Med 1983;309:1023–8.
9 Harrison BJ, Symmons DPM, Brennan P, Barrett EM, Silman AJ. Natural remission in inflammatory polyarthritis; issues of definition and prediction. Br J Rheumatol 1996;35:1096–100.
10 van Gestel AM, Haagsma CJ, Furst DE, van Riel PLCM. Treatment of early rheumatoid arthritis patients with slow-acting anti-rheumatic drugs (SAARDs). Baillieres Clin Rheumatol 1997;11:65–82.
11 van der Heijde DMFM, van't Hof M, van Riel PLCM, van de Putte LBA. Validity of single variables and indices to measure disease activity in rheumatoid arthritis. J Rheumatol 1993;20:538–41.
12 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.
13 Borg G, Allander E, Lund B, Berg E, Brodin U, Petterson H, *et al*. Auranofin improves outcome in early rheumatoid arthritis. Results from a 2 year double blind placebo controlled study. J Rheumatol 1988;15:1747–54.
14 Egsmose C, Lund B, Borg G, Pettersson H, Berg E, Brodin U, Trang L. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. J Rheumatol 1995;22:2208–13.
15 van der Heijde DMFM, van Riel PLCM, Nuver-Zwart HH, van de Putte LBA. Sulphasalazine versus hydroxychloroquine in rheumatoid arthritis: 3-year follow-up. [Letter]. Lancet 1990;335:539.
16 van der Heide A , Jacobs JWG, Bijlsma JWJ, Heurkens AHM, van Booma-Frankfurt C, van de Veen MJ, *et al*. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized controlled trial. Ann Intern Med 1996;124:699–707.
17 Jeurissen MEC, Boerbooms AMTh, van de Putte LBA, Doesburg WH, Lemmens AM. Influence of methotrexate and azathioprine on radiologic progression in rheumatoid arthritis. A randomized, double-blind study. Ann Intern Med 1991;114:999–1004.
18 Joosten LA, Helsen MM, van de Loo FA, van den Berg WB. Anticytokine treatment of established type II collagen-induced arthritis in DBA/1 mice. A comparative study using anti-TNF alpha, anti-IL-1 alpha/beta, and IL-1Ra. Arthritis Rheum 1996;39:797–809.
19 Moreland LW, Heck LW Jr, Koopman WJ. Biologic agents for treating rheumatoid arthritis. Concepts and progress. Arthritis Rheum 1997;40:397–409.
20 Strand V, Keystone E, Breedveld F. Biologic agents for the treatment of rheumatoid arthritis. Rheum Dis Clin North Am 1997;22:117–32.
21 Maini RN. A perspective on anti-cytokine and anti-T cell-directed therapies in rheumatoid arthritis. Clin Exp Rheumatol 1995;13:S35–40.
22 Chan KW, Felson DT, Yood RA, Walker AM. The lag time between onset of symptoms and diagnosis of rheumatoid arthritis. Arthritis Rheum 1994;37: 814–20.