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. 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. Furthermore, RA, especially its more severe and systemic forms, is not only a disabling disease, but also associated with increased mortality.

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. 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. As it was found. The patients in the placebo (or control) group 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.18 re-investigated 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.17 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.19 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 arthritis18 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 agents19–21 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, 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,21 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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