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Artículo 173.352

Recent evidence for the achievement of remission in rheumatoid arthritis through early aggressive therapy

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Introduction

The outlook for patients presenting with rheumatoid arthritis has improved greatly in recent years with the recognition that the most favourable outcomes are achieved when synovitis is optimally suppressed at the earliest stages of disease. In a proportion of patients, this can be achieved with conventional oral disease-modifying anti-rheumatic drugs. For those not responding adequately to conventional treatment, the combination of a biologic targeting TNFα together with once-weekly methotrexate is particularly effective in the majority of patients only achieving a partial response to conventional oral DMARD treatment. The potency of anti-TNF therapies in combination with methotrexate is such that remission induction has become an achievable goal in a significant proportion of patients.

Defining disease remission

Disease remission may be defined in a number of ways at any given point during the disease course but is most clinically meaningful when it is sustained over time. The most rigorous definition of remission at a single time point remains the ACR remission criteria, which require six parameters to be normal. This includes the absence of fatigue, which is one of the more difficult criteria to fulfil. Other definitions of remission at a single time point include composite scores of disease activity, such as the DAS 28 or DAS 44. For DAS 28, a score of less than 2.6 is defined as being within the remission range, although it is still possible to have a number of swollen joints and yet meet this definition. For the DAS 44, the definition of remission is less than 1.6 and this is in fact a more conservative measure than the DAS 28. Sustained ACR 70 responses over time have also been used as a surrogate for remission or near remission.

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Although remission is in itself a desirable goal, it is essentially a clinical definition. A number of research studies and clinical experience indicate that patients can meet these remission criteria despite imaging evidence of ongoing structural damage to joints[1]. For this reason, the ideal treatment goals include not only the achievement of remission but also prevention of structural damage to joints and preservation of joint function.

Studies supporting the case for early suppression of synovitis

In the Finnish RA combination (FIN-RA-Co) study, 195 patients with recent onset rheumatoid arthritis in the active phase of disease were randomized to treatment with either a combination of DMARDs and prednisolone, or to a single DMARD with or without predisolone[2]. At the end of two years, progression in radiographic damage was significantly less in the combination therapy group than in the sulfasalazine monotherapy group. Further sub-analyses indicated that for the monotherapy group, a treatment delay of greater than 4 months after disease diagnosis resulted in a significantly reduced rate of remission. As in the case of the COBRA study, the FIN-RA-Co cohort have been monitored over time, with the finding that early and aggressive combination therapy gives better results than conventional monotherapy with respect to symptoms and signs, five-year radiographic progression, and importantly, the incidence of work disability[3].

The hypothesis that the best patient outcomes can be achieved by depressing the inflammatory component of disease as optimally as possible with conventional DMARD therapy and steroid was tested in the tight control for rheumatoid arthritis (TICORA) trial, in which routine outpatient care was compared with a strategy of individualized intensive outpatient management, using a step-up combination therapy regime, together with intra-articular and/or intramuscular steroid as determined by the patient's Disease Activity Score assessed at monthly review[4]. In this study, remission rates were highly significantly greater in the intensive therapy group at 65% vs. 16% in the routine care group. Similarly, radiographic outcomes were superior in the

intensive therapy group. Nonetheless, there was still radiographic progression over four Sharp score points in the intensive therapy group.

A number of recent studies have utilized biologics targeting TNFα to test the hypothesis that early treatment intervention with this potent class of therapies gives rise to superior outcomes to conventional DMARDs alone. In the case of infliximab, in the ASPIRE study, methotrexate-naive patients with early rheumatoid arthritis were randomized to one of three treatment groups. These comprised methotrexate once weekly, rapidly escalated to a dose of 20 mg, together with placebo infusions; methotrexate once weekly, escalated to a dose of 20 mg together with a dose of infliximab infusions at 3 mg per kg; or methotrexate once weekly rapidly escalated to a dose of 20 mg with infliximab infusions at 6 mg per kg[5]. At one year, a higher proportion of patients achieved ACR 20, 50, and 70 responses in the infliximab and methotrexate combination groups compared with methotrexate alone. The remission criterion at one year, as defined by a DAS 28 of less than 2.6, was achieved by 15% of patients on methotrexate monotherapy, 21% of patients receiving infliximab at 3 mg per kg together with methotrexate, and 31% of patients receiving infliximab at 6 mg per kg together with methotrexate. A sustained major clinical response in the form of an ACR 70 was achieved for greater than six consecutive months in 17.3% of patients treated with the higher dose of infliximab together with methotrexate.

In an hypothesis-generating study, assessing the use of ultrasonographic measures in a randomized placebo-controlled trial of infliximab in early rheumatoid arthritis patients already on methotrexate, synovial vascularity measured by power Doppler was found to be rapidly suppressed in the group receiving infliximab and methotrexate[6]. Synovial thickening was slower to suppress when measured by high-frequency ultrasound[7]. After the first year of treatment, all patients received infliximab infusions, with subsequent reduction in synovial vascularity and thickening in those patients receiving methotrexate monotherapy in the first year. However, the consequence of a delayed introduction of infliximab was the occurrence of marked progression in structural damage to joints over the first year. Findings of this study suggest that this could have been prevented by early introduction of infliximab.

In another small study of early rheumatoid arthritis, Quinn et al[8] randomized twenty patients to receive either placebo plus methotrexate or infliximab plus methotrexate for one year. At the end of the one-year period infliximab therapy was withdrawn. Of the ten patients receiving infliximab, one showed no response, two initially responded and then relapsed, one showed a partial response, but six patients remained in remission for the subsequent year. Although this is a small study, the findings point to the possibility of use of infliximab to induce a biologic-free remission.

A recent remarkable Dutch multi-centre study compared treatment strategies designed to optimally suppress synovitis in early onset disease. A single-blind multicentre randomized clinical trial compared four different treatment strategies. These comprised sequential substitution monotherapy; step-up add-on combination therapy; initial combination therapy, with a short course of high-dose prednisolone (as employed in the COBRA study); and initial combination therapy with the TNF inhibitor infliximab and methotrexate[9]. The treatment goal for each of these strategies was to obtain a low level of disease activity of clinical relevance as determined by the DAS 44 score of < or = 2.4. Patients in the two combination therapy groups achieved a sustained low level of disease activity and functional improvement more rapidly than the groups receiving sequential monotherapy or step-up combination therapy. At one year of follow-up, patients treated with both initial combinations had less radiographic progression than the groups receiving sequential monotherapy or step-up combination therapy. In a sub-analysis of the patients without erosive disease at baseline, there was a statistically significant difference in the rate of radiographic progression favouring patients receiving initial treatment with infliximab and methotrexate as compared to the strategy of starting with the COBRA regime. Further data on the BeST trial presented at international meetings indicate that of 120 patients receiving initial treatment with infliximab and methotrexate, 77 were responders and able to discontinue infiximab according to protocol. Many of these patients had to recommence infliximab therapy, but 67 of 120 were able to maintain a biologic-free remission. As in the case of the Quinn study[8] this preliminary data raises the possibility that very early intervention with infliximab and methotrexate might allow induction of biologic-free remission.

In conclusion, early and optimal suppression of synovitis greatly improves clinical outcomes. The best radiographic outcomes are seen with early TNFα blockade. New data suggest that early infliximab therapy may permit induction of a period of biologic-free remission. Further studies are required to optimize remission maintenance.

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