Remission in Rheumatoid Arthritis: Must It Be Our Objective?

Raimon Sanmartí Sala

Unidad de Artritis, Servicio de Reumatología, Hospital Clínic, Barcelona, Spain

The treatment of rheumatoid arthritis (RA) is changing and there is no doubt that these changes are producing notable clinical benefits. We are beginning to prove that the patients with RA who are diagnosed during the last few years are evolving better and have a more favorable prognosis than in past decades.[1,2] In my opinion, the circumstances that are collaborating to this improved horizon of hope for the patients with RA have been diverse: the new knowledge and approach strategies of patients with new onset arthritis, the early introduction of antirheumatic therapies, a better use of classical disease-modifying drugs (DMARDS) and the appearance of new biologic treatments. Nevertheless, another 2 aspects are and have been crucial to attain a better control of the disease in patients with RA: the acquisition of consensus disease activity scores, which have resulted useful in the clinical practice, and the development of concrete therapeutic goals, which have to be reachable in a short amount of time.

In the present issue of *Reumatología Clínica,* Balsa[3] elaborates an excellent review of the disease activity measures that should be used in clinical practice. Some of these measurement scales, such as the Disease Activity Score (original DAS and DAS28) or the Simplified Disease Activity Index (SDAI), have been accepted in the rheumatology clinical practice. With them, inflammatory activity levels are defined and are useful for the follow-up of individual patients though time and, more importantly, are the main tool used to determine if a patient is susceptible to a change in antirheumatic therapy. Arguably, one can be lead by the degree of disease activity as determined by these scores to decide which will be the DMARD of first choice.[4] Some studies show that intensive treatment given after using these scores as therapeutic objectives produce undeniable, with high remission rates.[5] Most studies,[5,6] independently of the therapeutic strategy employed, try to reach what could be denominated as a *minimal degree of inflammatory activity* (which would correspond to, for example, an original DAS of less than 2.4 or a DAS28 less than 3.2). But, could a step forward be taken and could we fix as a definitive therapeutic objective the complete remission of the illness?

The first problem is defining remission. We agree that it could be defined as a state in which no inflammatory activity is found and, therefore, without synovitis or clinical symptoms, and no evidence of structural damage progression. If this situation could be achieved in a permanent manner with time and after having abandoned antirheumatic therapy we could even talk about a cure. Unfortunately, these circumstances are not the ones that are found in everyday rheumatologic practice.

As commented by Balsa,[3] remission criteria in chronic RA are very conservative and of little use in the daily practice. On the other hand, the criteria according to DAS, especially when using the DAS28, seem scarcely specific, with a considerable number of false positives.[7] Furthermore, if we take into account the fact that some patients seemingly in remission do have radiographic progression[8] and that a subclinical synovitis can exist in them, as detected by imaging methods such as ultrasound,[9] the definition of a state of remission is even more complex. Besides, the therapeutic strategy employed can influence the quality of remission. According to the same criteria, remission achieved with biologic therapy can be of a better *quality* (absence of synovitis by imaging techniques, absence of structural damage progression) than that achieved by, for example, classical DMARDS.[10]

Independently of the criteria used to define remission, recent studies show that these can be achieved in approximately 25%-50% of patients with RA and a time since the onset of disease of 2 to 5 years, if these patients have been treated exclusively with DMARDS[11-13] or tumor necrosis factor (TNF) alpha inhibitors.[6,14-16] In the TICORA, where intensive therapy is used and combined with DMARDS and glucocorticoids, and with a regular and frequent follow-up visits, this number is increased to 67% at 18 months.[5] Though it is still unknown how these patients will fare in the long term and it is probable that many will not be in remission

Correspondence: Dr. R. Sanmartí Sala.
Unidad de Artritis. Servicio de Reumatología. Hospital Clínic.
Villarroel, 170. 08036 Barcelona. España.

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during the different phases of their disease,[17] there is no doubt that these are numbers that are filled with hope and would have been difficult to imagine a few years back.

Following the thread of this same argument, would a change in antirheumatic therapy in a patient treated with DMARDS and who is not in remission, but whose disease activity is very moderate be justified? It would be the case, for example, of a patient with a very good response after a maximum dose of methotrexate, going from an initial DAS28 of 6.78 to one of 3.50 (equivalent to having one swollen joint, one tender joint, an erythrocyte sedimentation rate [ESR] of 28 and a global health evaluation by the patient of 25 mm). Though it is evident that each case must be approached in an individual manner and other parameters could be taken into account, such as the degree of pain and physical limitation, the type of joint affected and the evidence or lack thereof of radiographic progression, when it comes to decision-making time it is very probable that different opinions will exist among our rheumatologists community, taking into account that a few years ago nobody would have advocated such a modification in therapy. According to the actual consensus of the SER,[18] this patient could be a candidate to anti-TNF-alpha therapy, but, not if we follow the British consensus,[19] which is much more restrictive. Would it be then justified to try to reach in these patients, using continuing changes in the therapeutic strategy, this hypothetical remission? The question is difficult to answer, but there is no doubt that the appearance of the currently registered anti-TNF-alpha therapies (infliximab, etanercept, adalimumab), and the new biologic drugs which have shown efficacy (rituximab, abatacept...), forces us to demand even more, with ever more ambitious objectives in the quest to obtain a stricter control of the illness, without forgetting that a significant number (the majority), of patients that receive these treatments will not achieve remission.[14-16]

In conclusion, I would not advocate that our final objective must be to achieve remission (abstract as this concept may seem, as discussed beforehand), but that it is fundamental and must be a priority to set clear and precise therapeutic objectives when starting a treatment to a patient with RA. These objectives can be created according to the disease activity indexes, validated and useful in the clinical practice, and one must be more demanding in the control of illness. Such an objective must be very close to what today is understood as remission in RA. On the other hand, there is no doubt that the recent papers on the very early treatment of the disease with biologic drugs, where some patients persist in remission after abandoning such therapies,[20] though preliminary, will reopen the field of therapeutic strategy in RA and the final objective of attaining remission.

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