



Editorial

Considerations on treatment recommendations for rheumatoid arthritis[☆]



Consideraciones a las recomendaciones terapéuticas para la artritis reumatoide

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Given the polyarticular, chronic, progressive, incapacitating, invalidating effects that shorten survival in patients with rheumatoid arthritis (AR), achieving a state of remission, or at least minimal activity, is imperative. In this quest, several guidelines have been published to reach this outcome. Some recommendations, however, may awaken a certain degree of dissent or provide food for thought, while yet other points of interest merit inclusion in these guidelines.

Periodical guideline evaluations have produced clarifications, such as, “monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after treatment start or the target has not been reached by 6 months, therapy should be adjusted.”¹ It is reasonable that adjustments in treatment may be done one month after treatment for those patients with poor prognostic factors,^{2,3} those with high disease activity score with triple therapy, and in cases of persistent or increased activity (number of painful and inflamed joints, elevated acute-phase reactants, positive serology, early radiological changes, extra-articular manifestations). Rheumatologists should make therapeutic modifications without waiting to reach wide-ranging limits to modify treatment, which is also applicable when there is expression of toxicity. Several studies have emphasized the advantages of achieving early remission, even for longer survival.⁴ Despite this, most controlled studies have evaluations for decision-making some 3 months or more after the start of treatment, even with small-molecules and biological therapy, which are treatments that show a response in days or weeks.

Methotrexate is the cornerstone of initial treatment; it is accessible and provides adequate effectiveness and tolerability. The ACR guidelines, which are to be published in 2015, are based on

the analysis of 102 clinical studies selected from 11,705 publications (Singh J, MacAlindon T, Saag K, Bridges SL, Akl E, Bannuru R, et al., 2015. *Recommendations for the treatment of rheumatoid arthritis*; oral presentation at ACR 2014, Boston). Leflunomide and sulfasalazine are mentioned as alternatives that are comparable to methotrexate in effectiveness and safety, although hydroxychloroquine is also considered for use as monotherapy, which may be unacceptable to many, even though it reduces disease progression in combination therapy and improves the metabolic profile.^{5,6} The future guidelines will also suggest that all RA patients should be evaluated by a rheumatologist and that, given the efficacy and fast action of glucocorticoids, these should be used; however, because of their adverse effects and accumulated damage, we should limit their use to the lowest dose and duration possible.

The EULAR recommendations suggest reducing, but not suspending, therapy with conventional synthetic disease-modifying antirheumatic drugs (DMARD) when remission is reached. In a systematic review and meta-analysis of 6 controlled clinical studies, after 24 months O'Mahony et al.⁷ reported that the relative risk of relapse or deterioration of RA was 0.31 (95% confidence interval: 0.16–0.57; $p < 0.001$) when DMARD were suspended; those who remained in treatment had a lower probability of relapse. Wolde et al.⁸ evaluated 285 patients with established RA in treatment with DMARD for an average of 5 years (2–33), in remission during the previous year, who were randomised to continue with DMARD (142) or placebo (143), with an incidence of relapse of 22% and 38%, respectively ($p = 0.002$); factors associated with relapse were high maintenance dose (RR:3) and positive rheumatoid factor (RR:2.9). When Van der Woude et al.⁹ evaluated 2 cohorts, one by Leiden (68 out of 454 patients – 15%) and one from ERAS (84 out of 895 – 9.4%), criteria for remission were reached without the use of DMARD, with an average remission of 43 months; in the univariate analysis, in both cohorts there were 6 factors associated with remission: shorter evolution time, non-smoker, limited radiographic progression at baseline, seronegativity (rheumatoid factor and anti-citrullinated protein antibodies), and absence of shared epitope alleles. In the multivariate analysis from the Leiden cohort, 2 factors were associated with remission: C-reactive protein and anti-citrullinated protein antibody at the baseline evaluation;

[☆] Please cite this article as: Abud-Mendoza C, Coordinators of the Grupo Mexicano de Estudio de Manejo Integral de la Artritis Reumatoide. Consideraciones a las recomendaciones terapéuticas para la artritis reumatoide. *Reumatol Clin*. 2015. <http://dx.doi.org/10.1016/j.reuma.2015.05.002>

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in the ERAS cohort, rheumatoid factor was an independent factor associated with DMARD-free remission.

Due to the infectious processes present in at least double the population exposed to biologics, when faced with a previous history of opportunistic or serious infections, Singh et al. state: keep in mind not to escalate to a TNF inhibitor (iTNF), and abatacept should be considered when a biologic is required, based on its safety; patients should also receive vaccines derived from attenuated living microorganisms before receiving biologics. However, it is interesting that patients with RA have increased risk for chickenpox infections and that the risk for herpes zoster is even greater during treatment with glucocorticoids (≥ 10 mg de prednisone/d), with DMARD or biologics, and higher with the use of small molecules. Nonetheless, in zoster vaccination studies, not one patient out of the hundreds in treatment with biologics had disseminate varicella zoster; furthermore, with vaccination, and in spite of the biologic, the presentation of this infection was substantially reduced.^{10,11}

We have learned that, in general, there is no increased cancer risk associated with current treatment in patients with RA, and patients with a history of non-melanoma skin CA can be treated with DMARD. In the case of melanoma, iTNF is used before tofacitinib; abatacept, tocilizumab or rituximab can be selected when there is a history of lymphoma. As for seropositivity for hepatitis B virus, DMARD are preferable in conjunction with adequate treatment to achieve viral load remission; when a biologic is required, use iTNF; for hepatitis C virus, other biologics and tofacitinib can also be selected. In patients with heart failure, it is preferable to use DMARD, other biologics and tofacitinib before iTNF, although the use of etanercept is acceptable.¹²

The main comorbidities or extra-articular manifestations of RA should be considered, such as cardiovascular and osteoporosis. For both, vitamin D is an incontrovertible option, both for its metabolic effects as well as the potential pleiotropism for autoimmunity and cardiovascular health,¹³ a fact that could be extended to bisphosphonates, which reduce the rate of myocardial infarction by 28%, and potentially denosumab.^{14–17}

Increased cardiovascular risk in autoimmune inflammatory disease, especially RA, are well known.^{18–21} Thus, in patients with RA, consideration should be given to the prevention and treatment of cardio- and cerebrovascular disease, particularly in those with one or more cardiovascular risk factors and in patients with established RA for more than 10 years, with seropositivity and extra-articular manifestations. Treatment, with the aim of also achieving remission of RA, should include smoking cessation, reduction or elimination of non-steroid and steroid anti-inflammatories, blood pressure normalisation, physical exercise and the use of statins.^{22–24}

Indisputably, exercise provides benefits in addition to cardiovascular protection, including improved quality of life, pain, rigidity and fatigue in patients with RA, as well as the decrease in proinflammatory cytokines and, therefore, less local and systemic inflammation.^{24,25}

Thus, while rheumatologists attempt to achieve remission of RA as quickly as possible, we should also contemplate the comorbidities or extra-articular manifestations of the disease and escalate to optimal, complete treatment without restrictions for better quality of life and increased survival, which, in spite of our efforts, we still have not been able to achieve.²⁶

Addendum. Mexican Workgroup for the Integral Management of Rheumatoid Arthritis

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