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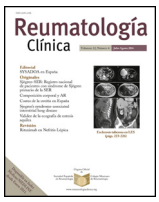

Editorial

Innovations in the therapeutic outlook of rheumatoid arthritis☆

Novedades en el Panorama Terapéutico de la Artritis Reumatoide

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Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized as a cause of chronic inflammation of diarthrodial joints. As a consequence, the patients in whom it is diagnosed undergo a deterioration in the functional capacity and quality of life, as well as an increase in the mortality rate. Given that the prevalence of RA ranges between 0.5% and 1% of the general population,[1] at the present time, between 30 and 60 million people around the world are RA patients, and their treatment constitutes an important economic and social cost.[2,3]

The etiology of RA is unknown, although we know that smoking, high salt intake and obesity increase the risk of developing the disease,[4–6] and genetic variations in more than 100 genes have been reported to predispose individuals to acquire it.[7] Among the genetic factors, most of them are related to T-cell function, with human leukocyte antigen (HLA) class II being the region that accounts for more than 50% of the genetic risk of developing RA. However, it has also been associated with genes involving B-cell function, innate immunity and intracellular signaling related to the production of proinflammatory cytokines.[7]

Due to these factors, its pathophysiology is highly complex, with different degrees of participation of the innate and adaptive immune systems depending on the groups of patients, and even on the phases of the disease. In any case, many of these pathophysiological pathways culminate in common final effector mechanisms, among which we should particularly point out tumor necrosis factor (TNF) and interleukin (IL) 6.[8] In addition, psychosocial factors have a role in making the presentation and clinical course, as well as the response to therapy, extremely heterogeneous. Nevertheless, it is indisputable that the management of RA has improved enormously in recent years as a consequence of the implementation of strategies for early detection and treatment that make it possible to take advantage of the "therapeutic window of opportunity", as well as strategies for the close control and intensification of the treatment until the therapeutic objective, ideally remission, is accomplished. Although the cornerstone of these therapeutic strategies continues to be methotrexate, it is unquestionable that our enhanced ability to achieve the remission of RA is the availability of a therapeutic arsenal that has increased considerably over the last 15 years.

At the present time, we have 3 types or families of slow-acting disease-modifying antirheumatic drugs (DMARD): (1) conventional synthetic (csDMARD) [methotrexate, leflunomide, salazopyrin, hydroxychloroquine and gold salts]; (2) biologic (bDMARD), which include 5 TNF antagonists, a T-cell costimulation blocker, a B-cell depleting agent and a IL-6 receptor antagonist; and (3) directed or *targeted* synthetic (tsDMARD), small molecules capable of crossing the cytoplasmic membrane and inhibiting, in quite a specific manner, different signaling pathways, especially the "Janus kinase/signal transducer and activator of transcription" (JAK/STAT) pathway. Nevertheless, despite the advances introduced, it is estimated that TNF inhibition is effective in only 20–50% of the patients after 6 months of treatment[9] and that only 5–10% of RA patients achieve complete and sustained remission.[10] With these questions still to be successfully addressed, the pharmaceutical industry is making a significant innovative effort to increase our therapeutic arsenal in the endeavor to increment these values. Among the new agents, those that represent a distinctive contribution to the mechanism of action are JAK kinase inhibitors and blockade of the granulocyte macrophage colony-stimulating factor (GM-CSF) cytokine, but we will also have access to novel agents acting as IL-6 antagonists and the number of biosimilars will continue to grow over the next few years.

A number of cytokines relevant to the pathogenesis of RA (IL-6, IL-12, IL-15, IL-23, interferon and GM-CSF) signal through the JAK/STAT1 pathway.[11] Moreover, genetic variants of STAT1, STAT4 and TYK2 confer a higher risk for developing the disease.[7] Thus, it is logical that the European Medicines Agency recently approved, for use in patients with RA, 2 drugs that act on that pathway: tofacitinib (Xeljanz, Pfizer), a dual inhibitor of JAK1 and JAK3, and baricitinib (Incyte, Eli-Lilly), which acts by inhibiting preferentially JAK1 and JAK2. Both have shown excellent results both in csDMARD-naïve patients, and in patients with active moderate to severe RA and previous failure with csDMARD and/or anti-TNF, with a safety profile very much like that associated with IL-6 blockade, although with an incidence of herpes zoster somewhat higher in certain populations than that reported for other biologics. It is estimated that both will be available for use in Spain during the second half of 2017.

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Another 2 inhibitors of the JAK/STAT pathway at an earlier phase of development are filgotinib (Galapagos/Gilead) and ABT-494 (AbbVie), specific JAK1 inhibitors. If they have a safe landing, they will consolidate the inhibition of the JAK/STAT pathway as one of the most competitive upcoming strategies in the treatment of RA in the near future.[12,13]

Other new mechanisms of action being developed for the treatment of RA include the inhibition of colony-stimulating factors, especially GM-CSF, and the use of mesenchymal stem cells. Mavrilimumab (MedImmune/AstraZeneca) is the first monoclonal antibody against GM-CSF receptor α chain, and has aroused a great deal of interest. The excellent results in phase I and II trials in RA have sparked considerable expectations concerning the development of this molecule.[14,15]

With regard to the use of mesenchymal stem cells, recently published data show the findings in a controlled Ib/IIa clinical trial in patients with active RA refractory to ≥2 biologics. They were followed for 24 weeks after undergoing intravenous administration of mesenchymal stem cells from expanded allogeneic adipose-derived tissue.[16] This therapeutic approach, in which the mechanism of action is the induction of immunoregulatory substances and cells, was found to be safe and effective,[16] although the duration of the response was limited. Therefore, its use in clinical practice is uncertain.

On the other hand, given that IL-6 blockade has been shown to enable the control of the disease, on both the local and systemic level,[17] at this time, plans for at least another 5 products that act through this mechanism of action are in the pipeline of several pharmaceutical companies, as occurred after the first anti-TNFα agent was introduced. Of these, we should point out sarilumab (Regeneron/Sanofi) and sirukumab (Janssen/GlaxoSmithKline), both of which are antibodies with a high affinity against IL-6 receptor, to be administered subcutaneously, that show efficacy data that are quite outstanding and safety profiles similar to that of tocilizumab.[9,17,18] Others in less advanced phases of development include clazakizumab (Alder Biopharmaceuticals) and olokizumab (UCB/R-Pharm), which are humanized anti-IL-6 monoclonal antibodies, and ALX 0061 (Ablynx/AbbVie), also directed against IL-6 receptor.[19,20]

In Spain, we currently have access to 3 infliximab biosimilars and 1 approved for etanercept. However, over the coming 2 years, biosimilars of adalimumab and rituximab will also be made available. This means that, in short, there will be 13 or 14 bDMARD and 2 tsDMARD. Undoubtedly, we will find that the number of RA patients that achieve remission will increase but, in turn, decision making will become more complex.

Until now, the prescription of a bDMARD follows an approach that combines the tactic of "trial and error", with the evaluation of factors that are particular for each patient, such as the preference for a certain route of administration, frequency of use, family support, access to a hospital and associated comorbidity, as well as the previous experience of the prescribing physician. However, the arrival of biosimilars and the growing use of innovative therapies have put economic factors on the table that must be taken into account if we want the Spanish health system to be sustainable.

During the next few years, we are going to observe a transformation in the approach to the treatment of RA, with new scenarios and opportunities. On the one hand, we have to see the attitude adopted by the pharmaceutical companies who are the proprietors of the existing innovating drugs whose patents have expired. On the other, the proprietors of new innovating drugs are going to touch down in a very competitive state of affairs. More important, the concept of "pay for performance" is beginning to be introduced. For this reason, we consider that the treatment of RA in the coming years will be a truly exciting field of research, given the challenges involving the need for: (i) biomarkers for the activity, prognoses and response to a given treatment, that make it possible to differentiate risk groups and the phenotypes of patients who may benefit from a certain class of drugs; and (ii) novel concepts of therapeutic response that are an improvement over those existing at the present time, which may be useful in clinical trials, but are found to be difficult to apply in real life. The objective will be to optimize the efforts made by physicians and the costs of the medication, improving the quality of life and safety of our patients.

Conflict of interest

Dr. Castañeda is currently the principal investigator of a research project granted by the *Instituto de Salud Carlos III (ISCIII)*, Madrid, Spain, and Pfizer. Dr. Gonzalez-Álvaro is the principal investigator of several research projects granted by the *ISCIII* throughout the progress of this study. Dr. Gonzalez-Álvaro has also been the recipient of fees from Eli-Lilly, as well as grants, research funds and fees from UCB, BMS, Pfizer, Roche, AbbVie and MSD, not related to the objectives of this report. Dr. Gonzalez-Álvaro is also the holder of the intellectual property rights for patent PCT/ES2015/070182.

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