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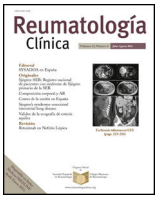

Editorial

What lies in the near future for the treatment of rheumatoid arthritis?

¿Qué pasará en un futuro próximo para el tratamiento de la artritis reumatoide?

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The treatment of rheumatoid arthritis (RA) changed dramatically with the appearance of biological drugs more than 15 years ago. The release of the first anti-TNF agents, including infliximab (chimeric), adalimumab (humanized) and etanercept (soluble receptor) represented a paradigm shift in the treatment of a chronic inflammatory disease that had few treatment options and, for many, a poor prognosis. Soon after, the appearance of new therapeutic medications such as tocilizumab (inhibitor of IL-6), rituximab (anti-CD20), abatacept (T cell co-stimulation blocker), along with new subcutaneous anti-TNF drugs (golimumab and certolizumab pegol), has completed the arsenal of commonly used biologic disease-modifying anti-rheumatic drugs (b-DMARDs). Parallel to the appearance of those therapies, we have improved the management of older drugs such as methotrexate, with optimization of the dose or improving bioavailability with the subcutaneous route of administration.

Based on recent publications, the treatment of RA may be headed for yet another shift in paradigm. After years of experience with b-DMARDs and the availability of extensive records such as Biobadaser,[1] we have reassuring safety data. In addition, we have studies comparing the effectiveness of different anti-TNF agents as the first b-DMARDs in large populations of naïve patients, with no noticeable differences between them in usual clinical practice.[2] Not only have new and more effective drugs been developed but the entire approach to treatment has been revolutionized by the adoption of treat-to-target (T2T) strategies.[3] Since then, multiple trials have been released to propose variations of this approach. Aligned to the T2T strategy, the recent *Strategy* study recommends initial MTX treatment optimization before initiation of a biologic agent and emphasizes the importance of treat-to-target strategy.[4] And a recent meta-analysis of different randomized controlled trials evaluated 13 studies out of 44,651 citations to compare cycling strategies between different anti TNF agents (including adalimumab, etanercept, certolizumab, golimumab, and infliximab) with swapping strategies (including tocilizumab, abatacept, rituximab, and tofacitinib) and found that cycling to a different anti-TNF drug after an initial anti-TNF failure can be effective and should be considered before switching to a different targeted therapy. These data suggest that many patients who fail a specific agent will not fail anti-TNF drugs as a class.[5] For those who are treated with biologic agents other than an anti-TNF, monotherapy may be just as effective as combination with a conventional, synthetic DMARD: at the 2016 American College of Rheumatology meeting, Gottenberg et al. presented long-term registry data from 4498 patients with RA demonstrating that in a real world setting, monotherapy with abatacept, rituximab or tocilizumab was not associated with lower long term retention than combination with synthetic DMARDs.[6]

One of the biggest complaints about research in RA in recent years has been the lack of head to head studies between biological therapies. At last, the results of such studies are beginning to appear: the Ample study compared abatacept with adalimumab[7] and, recently, the results of a new trial comparing certolizumab and adalimumab was released. The EXXELERATE study is the first trial to directly compare two anti-TNF agents and confirms similar early and long-term efficacy of both certolizumab and adalimumab in combination with MTX.[8]

Considering that cost is a major impediment to the treatment of patients with RA who warrant biologic therapy, the development of biosimilars represents an important advance. Several studies of therapeutic bioequivalence have demonstrated equal safety and efficacy for biosimilars as compared with the original molecule. A study comparing etanercept (ETN) with a biosimilar (SB4) version confirmed that long-term efficacy (as assessed by DAS28, SDAI, CDAI, and HAQ-DI) and safety were comparable between both agents during the trial, as well as during the extension period. In addition, efficacy was sustained after switching from etanercept to SB4.[9]

What should we expect from the future of RA treatment? Since 2014, a new oral therapy, tofacintinib, a Janus kinase (JAK1, JAK3) inhibitor, has been available in the US though it is not yet available in Europe. At the recent meeting of the ACR, several studies presented data about this new agent. We have learned that a lack of early change in disease activity score in patients treated with tofacitinib, predicts a low likelihood of achieving low disease activity at month 6.[10] Recent open-label, long-term

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extension studies have released valuable data regarding the safety and efficacy of tofacitinib over 8 years, including the risk of major adverse cardiovascular events (MACE).[11] In the pooled analyses of tofacitinib-treated patients, increases in HDL-cholesterol appeared to offset the increases in total and LDL cholesterol, so that MACE risk was actually reduced.[12]

Interest is growing in the promise of combining biologic therapies. Tumor necrosis factor (TNF) and interleukin 17 (IL-17) appear to independently contribute to the pathophysiology of rheumatoid arthritis (RA), synergistically inducing inflammatory mediators leading to joint destruction. In a mouse model of RA, dual neutralization of TNF and IL-17 conferred superior joint protection compared with inhibition of either target individually. A recent abstract presented at the 2016 ACR meeting showed the usefulness of ABT-122, a drug that inhibits both TNF and IL-17.[13] The authors found that dual cytokine inhibition of TNF-α and IL-17 demonstrated good tolerability and maintenance of benefit in the open label extension period when continued for up to 36 weeks in patients with RA receiving background methotrexate. This included those switching from ADA to ABT-122.

Recent studies of a new oral JAK1/JAK2 inhibitor, baricitinib, have reported positive efficacy and safety data among elderly patients with moderate to severe rheumatoid arthritis.[14] A recent trial from Taylor et al.[15] found similar results among RA patients switching from adalimumab to baricitinib in a phase 3 trial. A systematic review and meta-analysis presented by Zamora et al.[16] suggests that baricitinib alone or combined with methotrexate was more effective than methotrexate alone at 12–24 weeks. Moreover, baricitinib had similar effects as adalimumab, but slightly higher rates of severe adverse reactions. Thus, baricitinib could become an additional therapeutic option to treat patients with moderate to severe disease with an inadequate response to other agents. Some concerns have been recently raised regarding the incidence of herpes zoster and unfavorable lipid changes among baricitinib-treated patients. Integrated analyses have shown that treatment with baricitinib was associated with an increased risk of herpes zoster compared with placebo, with an overall rate of 3.3/100 patient-years. Rates appeared to diminish with prolonged exposure.[17] Secondly, in a trial from McInnes et al., baricitinib was associated with increased LDL-C, HDL-C, and TG levels, with a stable LDL-C/HDL-C ratio. In patients initiating statin therapy during the study, the elevation in total cholesterol, LDL-C, and TG decreased to pretreatment levels, while HDL-C remained elevated with statin therapy.[18]

Besides tofacitinib and baricitinib, other new targeted therapies were presented at the recent ACR meeting that may soon be available. Olokizumab, an interleukin-6 (IL-6)-targeting monoclonal antibody[19] and sirukumab, another anti-IL-6 monoclonal antibody have shown promising results in reducing joint inflammation and fatigue as well as other signs and symptoms of RA.[20,21] Sarilumab (150 or 200 mg every 2 weeks subcutaneously) has also shown promising clinical outcome results after 3 years of treatment and, in addition, pooled safety and efficacy data have been recently presented for elderly patients with RA.[22,23] A new selective JAK1 inhibitor, filgotinib, is another treatment that could become a viable option for RA therapy in the future.[24]

Presentations at the most recent ACR and EULAR meetings suggest that a number of new drugs and targets may change and advance our approach to RA. Complementing treatments targeting TNF, IL-6, CTL4/CD28 co-stimulation blocker, or B-cells, our patients with RA may soon benefit from the development of new molecules directed against G-CSF, JAK kinase or even monoclonal antibodies directed against 2 or more targets. Recently, Kalden[25] reviewed older biologic agents (now considered "classic"), as well as new small molecules, combination therapies (such as kinase inhibitors and b-DMARDs), and b-DMARDs directed against interleukin-17 or complement component 5. Finally, a proteasome inhibitor such as bortezomib, has also been proposed as a potential antirheumatic agent; proteasomes degrade proteins in mammalian cells and are established targets of anticancer drugs, such as multiple myeloma.[26]

Keeping up with new and emerging therapeutic strategies will require frequent updates by clinicians and researchers. However, in the near-run, one of the biggest changes we are likely to see is the growing presence of biosimilars. Additional research, clinical experience and time will reveal their importance and usefulness.

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