Presse Med. 2016; 45: e179–e192

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New therapeutic approaches in rheumatoid arthritis

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Available online: 27 May 2016

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Summary

The treatment of rheumatoid arthritis (RA) has changed dramatically over the past two decades. The combination of better insights into the pathophysiological and immunological mechanisms of RA and the possibilities offered by biotechnology led to the development and introduction into clinical practice of a new class of antirheumatic biologic therapies, which along with earlier and more aggressive treatment contributed to dramatically better outcomes for patients with RA. To date, nine biologic agents have been approved for the treatment for RA, and a first Janus kinase (JAK) inhibitor has also been approved in the United States and various other countries in the world (but not by the European Medicines Agency [EMA]). Many additional molecules with distinct mechanisms of action are currently being tested in laboratories and in clinical trials. In addition, considerable improvements have been made in the optimal use of all these agents through treatment strategies such as treating-to-target, induction-maintenance, and dose individualization.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic disease of the joints characterized by synovial inflammation that can lead to cartilage and bone destruction. The disease is associated with various extra-articular inflammatory complications (scleritis, pleurisy, vasculitis) and often features systemic inflammation as well. RA is generally thought to be autoimmune in nature, and it is believed that genetic predisposition (HLA-DR4 and the "shared epitope") and environmental factors (smoking, certain exposures) interact to bring about the full-blown disease. RA occurs in all age groups and has an overall prevalence of around 0.8% in Europe; the incidence peaks around the fifth decade of life and women are affected three times as often as men.

When left untreated, RA usually has a chronic course characterized by undulating pain and stiffness as well as general malaise, and it may also cause progressive destruction of cartilage and bone in the joints (*figure 1*), resulting in typical deformities, loss of function, and handicap. Treatment for RA is therefore based on the dual principle of controlling the inflammatory process so as to provide relief of symptoms for the patient, and preventing the destructive process so as to preserve

http://dx.doi.org/10.1016/j.lpm.2016.05.004

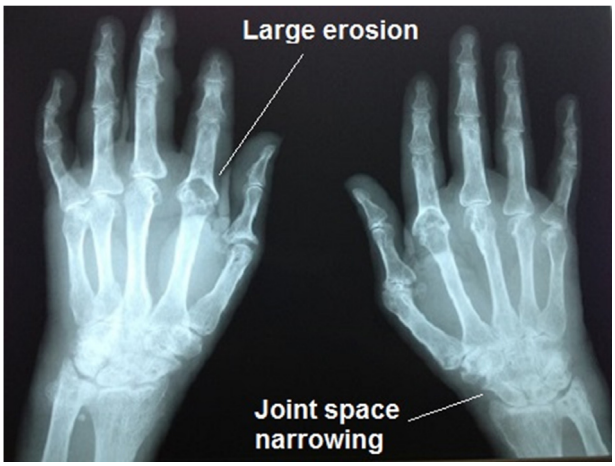

FIGURE 1
Rheumatoid arthritis: destruction of cartilage and bone in the joints

functional status. Simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) may provide the first but not the second of these objectives, and therefore it is generally held that RA should be treated with proper antirheumatic medications. These medications, usually referred to as conventional disease-modifying antirheumatic drugs (DMARDs), are a small group of chemically unrelated compounds that have been shown to achieve at least some degree of both symptom control and prevention of damage progression. The most widely used DMARDs are methotrexate (MTX), an antimetabolite with powerful anti-inflammatory effects that are possibly mediated through the local release of adenosine, sulfasalazine (SSZ; *figure 2*), and leflunomide.

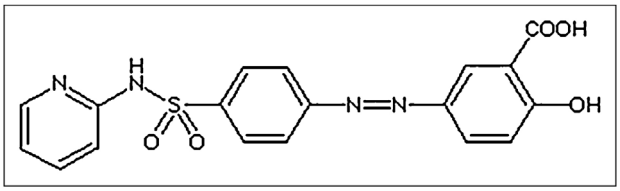

FIGURE 2
Sulfasalazine

New treatments for RA

Over the past two decades, a whole new class of antirheumatic biologic therapies or biologic DMARDs (bDMARDs) has been introduced into the clinic, based on better insights into the pathophysiological and immunological mechanisms of the disease and the possibilities offered by biotechnology. These drugs, along with earlier and more aggressive treatment, brought about a true revolution in this therapeutic area with major improvements in the outcomes of the disease. To date, nine biologic agents have been approved for the treatment for RA (*figure 3*), and a first Janus kinase (JAK) inhibitor, a small-molecular compound with biologic-like efficacy, has also been approved in the United States and various other countries in the world (but not by the European Medicines Agency [EMA]). Many additional molecules with distinct mechanisms of action are currently being tested in laboratories and in clinical trials. The approved biologics were shown to have very good clinical efficacy and safety in large, randomized, controlled clinical trials leading to regulatory approval; and biological therapies for RA have become widely used and have been intensively studied. The approved biological treatments include five tumor necrosis factor inhibitors (TNFi) and four agents with other mechanisms of action (*figure 4*).

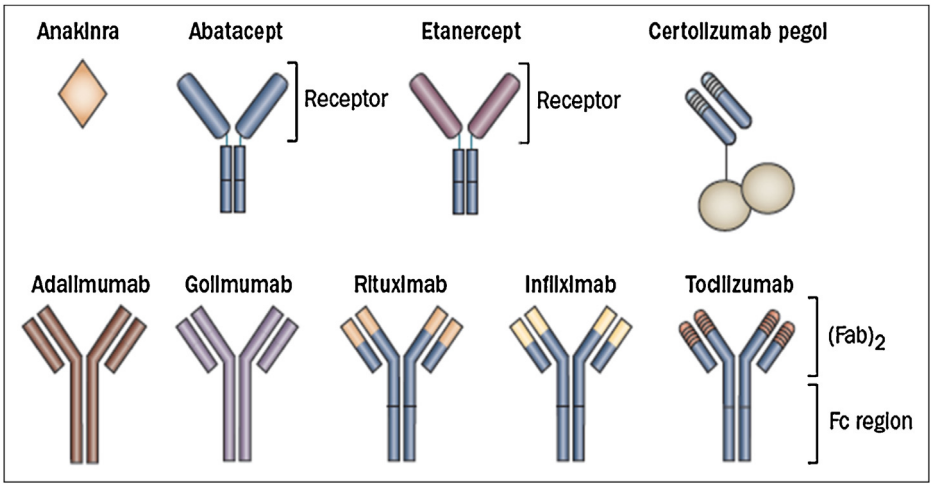

FIGURE 3
Biologic agents approved for the treatment of rheumatoid arthritis