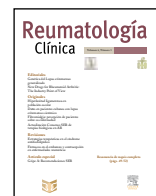




Reumatología Clínica

www.reumatologiaclinica.org



Editorial

New drugs for rheumatoid arthritis: The industry point of view

Nuevos medicamentos contra la artritis reumatoide. El punto de vista de la industria

Stephen H. Polmar

Polmar Pharma Consulting, Woodbridge, Connecticut, USA

During the past decade there has been impressive progress in the treatment of rheumatoid arthritis (RA). Beginning with the regulatory approvals of etanercept and leflunomide in 1998, a total of 10 new disease-modifying anti-rheumatic drugs (DMARDs) have been approved for the treatment of RA. Of these 10 drugs, 9 are biologicals (i.e. monoclonal antibodies, soluble receptors or fusion proteins) and only one, leflunomide, is a small molecule, non-biological DMARD. The biologicals include 5 TNF-blocking agents (etanercept, infliximab, adalimumab, golimumab and certolizumab pegol), an IL-1 beta blocking recombinant soluble receptor (anakinra), a T-cell costimulatory receptor blocking fusion protein (CTLA4-Ig, abatacept), a B-cell depleting monoclonal antibody (anti-CD20, rituximab) and most recently, a monoclonal antibody directed against the IL-6 receptor (tocilizumab). This is an impressive record for this sector of the pharmaceutical industry during a period when the overall productivity of the industry, as measured by the introduction of new drugs to the market, declined.

While currently therapy for new patients with RA is initiated with one or more non-biological DMARDs (most frequently methotrexate), supplemented with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, the advent of the biological agents has fostered earlier and more aggressive therapy.¹ For many patients with an inadequate response to non-biological DMARDs, addition of a TNF blocking agent results in a significant improvement in signs and symptoms of disease as measured by American College of Rheumatology (ACR) scores. Furthermore, as demonstrated in the Premier study, the combination of methotrexate with an anti-TNF alpha monoclonal antibody showed superior efficacy compared to either drug used as monotherapy for patients with early aggressive disease who are naïve to methotrexate.² The most stringent regulatory criterion of efficacy in clinical development is "Major Clinical Response", defined as the patient achieving an ACR 70 response for a continuous period of six months. In the Premier study after 2 years, 49% of patients in the combination therapy group achieved a Major

Clinical Response compared to 28% and 25% for methotrexate alone and adalimumab alone, respectively. In the development of new drugs for RA, pharmaceutical companies chose a so-called "Gold Standard" therapy to which all new therapeutic agents will be compared with respect to efficacy and safety. For this purpose, most pharmaceutical companies now consider the combination of methotrexate with a TNF-blocking agent as the Gold Standard for RA treatment.

When considering investment in a drug discovery and drug development program, a pharmaceutical company must consider the unmet medical need in a particular disease, the size of the patient population anticipated at the time the new drug will enter the market and the competition from other companies. Most importantly the pharmaceutical company must attempt to determine if the mechanism of action of the new drug will translate into increased efficacy and an acceptable safety profile to permit both the approval of the drug by regulatory authorities and allow it to compete successfully against drugs that will be on the market. Ultimately, the success or failure of a new drug depends upon its ability achieve "market penetration", that is to gain a larger share of the market than its competitors.

At the present time rheumatologists and their patients are reasonably satisfied with the Gold Standard therapy with respect to both its degree of efficacy and safety, but clearly there is room for improvement. Gold Standard therapy achieves a Major Clinical Response in only half of the patients and approximately 30% do not even achieve an ACR 20 response. However, the consensus among pharmaceutical companies is that the new biologicals currently in clinical development are unlikely to displace the TNF blocking agents which they consider "first-line biological therapy". This is due both to their efficacy and the generally favorable 15-year safety record of these agents. In contrast, the biologicals currently used in "second-line biological therapy" such as anakinra, abatacept, rituximab and tocilizumab may be vulnerable to replacement due either to sub-optimal efficacy or unanswered questions about their long-term safety. Two anti-CD20 B-cell depleting antibodies, ocrelizumab and ofatumumab, are being positioned as replacements for rituximab. However, a potential complicating factor, not only for the companies developing anti-CD 20 monoclonal antibodies, but also for those companies currently marketing and developing other biologicals, is the possible entry of generic biologicals into the market place in near

E-mail address: stephen@polmarconsulting.com

future. Starting with the expiry of the etanercept patent in 2012 in the US, the patents for all current first and second line biologicals will expire by 2018. The potential impact of generic biologicals on the market is unknown at this time and will depend to a great extent upon the regulatory requirements for generic biologicals and the ability of pharmaceutical companies to delay their entry into the market by legal action. Nonetheless, there should still be opportunities for new biologicals that act on new targets or by novel mechanisms to penetrate the RA market provided that they can demonstrate superior efficacy to currently available biologicals and acceptable safety profiles. For example, anti-IL-17 monoclonal antibodies, which has shown remarkable efficacy in psoriasis, are now in clinical trials in RA. Other biologicals in early clinical development include anti-IL-18, anti-IL-18 receptor, anti-CD 16, anti-GMCSF and anti-IP-10.

Many in the pharmaceutical industry believed that the era of biological DMARD therapy for RA would be relatively short and would be a transitional period after which the biologicals would be largely replaced by oral small molecule therapies. This has been shown to be incorrect. The development of new oral therapies has proven to be extremely challenging both with respect to achieving adequate efficacy and acceptable safety. The attrition of new small molecule drugs in RA clinical development has been extremely high. For example, in 2007 seven pharmaceutical companies had p38 MAP kinase inhibitors in phase II and now only one remains. There is a long list of compounds whose development has been recently discontinued including chemokine inhibitors (CCR1 and CCR2), an iNOS inhibitor, IKK-2 inhibitor and P2X7 receptor antagonists. There are, however, two small molecule drug classes that are currently in late stage clinical development, janus-associated kinase (JAK) inhibitors and spleen tyrosine kinase (SYK) inhibitors. These drugs have shown efficacy similar to TNF-blocking agents in phase II clinical trials, but safety concerns exist such as elevation of liver enzymes and LDL cholesterol, the clinical significance of which remain to be determined. The goal of pharmaceutical companies developing oral small molecule therapeutic agents is to attempt to replace the first-line biologicals in patients who have had an inadequate response to methotrexate. To achieve this goal, these new drugs will have to be at least as efficacious as the TNF-blockers and also have an acceptable safety profile that permits co-administration with methotrexate without an additional risk of hepatotoxicity. Alternatively, such compounds would have to show efficacy as monotherapy comparable to a TNF-blocking agent + methotrexate. These new oral DMARDS would have a potential competitive advantage of convenience for patients and

would be expected to cost less than the biologicals, therefore being favored by health authorities and insurance companies. However, the extent to which some of the new oral agents will ultimately penetrate the market will depend on their efficacy in phase III trials and safety profiles, the degree to which patients will favor daily oral therapy versus every other week or monthly injections and also the possible entry of generic biologicals into the market at a substantially lower cost than current brand-name biologicals.

The pharmaceutical industry, together with academic researchers, has explored many potential drug targets for RA therapy. While there have been some successes there have been many more failures, nonetheless, pharmaceutical companies continue to invest in research and development of new drugs for RA. At the present time, approximately 65 drugs are in phase I or phase II, 63% of these are biologicals and 37% are small molecules. The overwhelming majority of these drugs target the immune system. In a disease such as RA in which combination therapy is frequently employed, addition of yet another drug that targets the immune system along with the Gold Standard therapy can result in an unacceptably high incidence of severe infections. In recognition of the limit to which the immune system can be safely manipulated, academic researchers, biotech companies and some pharmaceutical companies are starting to focus on other tissues (e.g. synovial fibroblasts and osteoclasts) or processes (e.g. angiogenesis) which play an important role in the pathogenesis of RA but which are not critical for host defence against infection or malignancy.

In the next 5–10 years, rheumatologists and their patients should not expect a rate of introduction of new drugs for RA as high as that which occurred during the last decade. However, since a substantial number of patients still do not have their disease fully controlled by current therapy, one can anticipate that the pharmaceutical industry will continue to invest in research and development of both biological- and non-biological drugs to meet the needs of these patients.

References

1. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59:762-84.
2. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, Van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind, clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* 2006;54:26-37.