FROM THE ANALYST'S COUCH

Rheumatoid arthritis: current and future trends

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Rheumatoid arthritis (RA) is a chronic autoimmune condition of the connective tissue in synovial joints characterized by inflammation that can lead to impaired movement and disability. The underlying disease mechanisms remain unclear but are generally triggered by infections and inflammatory mediators. The incidence of RA increases with age, with women being more prone to the disease; approximately 0.3–1% of people are affected worldwide (see Further information).

Current treatments

Current clinical guidelines recommend a combination of small-molecule disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate as a first-line therapy. Such regimens are effective in easing symptoms but their ability to suppress disease progression and joint destruction is limited for a substantial proportion of patients.

The arrival of targeted biologics was a major advance in the treatment of RA, with greater success in disease remission and protection against joint destruction. Biological DMARDs work by blocking the activity of key inflammatory mediators that give rise to the main characteristics of RA. These include inhibitors of tumour necrosis factor (TNF) (a pro-inflammatory cytokine known to mediate most of the joint damage) such as infliximab (Remicade; Johnson & Johnson/Merck & Co.), adalimumab (Humira; AbbVie), etanercept (Enbrel; Amgen/Pfizer), golimumab (Simponi; Johnson & Johnson/Merck & Co.) and certolizumab pegol (Cimzia; UCB).

Several other biological response modifiers are currently on the market. These include abatacept (Orencia; Bristol-Myers Squibb), which is a fusion protein composed of the Fc region of the immunoglobulin IgG1, linked to the extracellular domain of the checkpoint inhibitor cytotoxic T lymphocyte-associated protein 4 (CTLA4). By dampening T cell co-stimulation, it inhibits the production of inflammatory cytokines such as TNF, interferon-γ and interleukin-2 (IL-2). Rituximab (MabThera; Genentech) targets the B cell antigen CD20, leading to the depletion of B cells and thereby the abrogation of antibody production. Tocilizumab (Actemra/RoActemra; Roche) targets IL-6, a pleiotropic cytokine with a pivotal role in the pathophysiology of RA. These costly biologics are often reserved as later-line agents for patients with an inadequate response to conventional DMARDs.

Tofacitinib (Xeljanz; Pfizer) became the first oral small-molecule DMARD to be approved by the FDA in more than a decade in 2012. It is a first-in-class inhibitor of Janus kinase 1 (JAK1) and JAK3, which mediate cytokine signal transduction. In March 2016, Pfizer announced it has re-filed its marketing application for tofacitinib in the EU, where it had failed to secure approval because of concerns over safety, with additional data from the Phase III ORAL global development program. In the United States, the drug carries a boxed warning for serious infections and malignancies.

Emerging therapies

A number of promising RA therapies are in development (TABLE 1), including three late-stage small-molecule JAK inhibitors. Despite the limited success of tofacitinib, the interest in other JAK inhibitors has not diminished; baricitinib (Eli Lilly/Incyte), an oral JAK1 and JAK2 inhibitor, currently leads the race in this class with a marketing application submitted to the FDA in January 2016. Baricitinib has demonstrated superior head-to-head efficacy versus adalimumab in the Phase III RA-BEAM study. However, baricitinib is likely to face strong competition from the JAK inhibitors filgotinib (Galapagos) and ABT-494 (AbbVie). Filgotinib, a highly selective JAK1 inhibitor, is also under development for Crohn disease. The drug showed promising results in RA in a Phase II trial (DARWIN-2). It was originally developed in collaboration with AbbVie; however, following withdrawal of support from AbbVie in September 2015, Galapagos entered into an agreement with Gilead to develop filgotinib. In the meantime, AbbVie's in-house JAK inhibitor ABT-494 achieved impressive responses in two placebo-controlled Phase II (BALANCE-I and BALANCE-II) trials in patients that were intolerant to methotrexate as well as anti-TNF drugs, resulting in improvements in the conditions of up to 82% and 73% of patients, respectively, on the American College of Rheumatology criteria ≥ 20%

Table 1 | **Selected late-stage rheumatoid arthritis products in development**

Drug	Developer(s)	Mode of action	Status
JAK inhibitors			
Baricitinib	Incyte Corp., Eli Lilly	JAK1/2 inhibitor	Pre-registration
Filgotinib	Galapagos NV	JAK1 inhibitor	Phase II
ABT-494	AbbVie	JAK1/2/3 inhibitor	Phase II
IL-6 inhibitors or IL-6R antagonists			
Sarilumab	Sanofi	IL-6R antagonist	Pre-registration
Sirukumab	Centocor, Janssen Biotech	IL-6 inhibitor	Phase III
ALX 0061	Ablynx, AbbVie	IL-6R antagonist	Phase II
Clazakizumab	Alder Biopharmaceuticals	IL-6 inhibitor	Phase II
Others			
Denosumab	Daiichi Sankyo	RANKL inhibitor	Phase III
Mavrilimumab	MedImmune	GM-CSF antagonist	Phase II

GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; ILR, interleukin receptor; JAK, Janus kinase; RANKL, receptor activator of NF-κB ligand.

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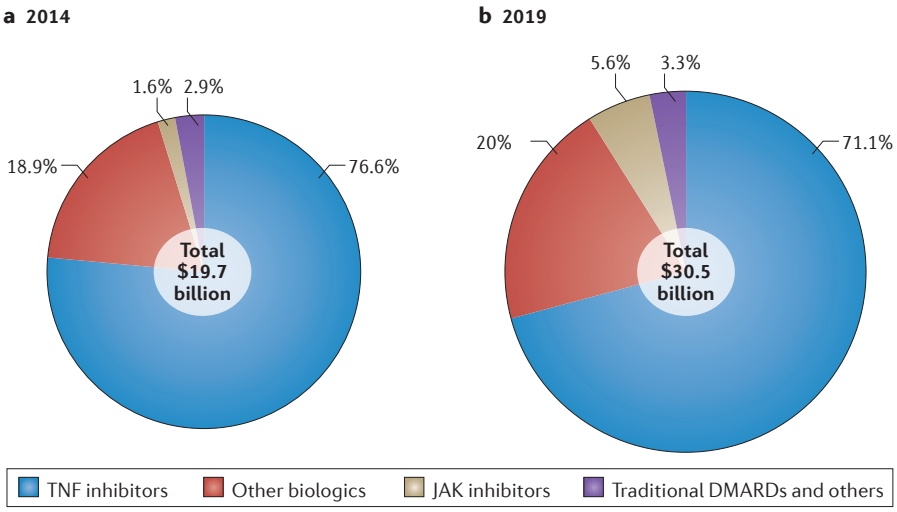

Figure 1 | **Rheumatoid arthritis global sales ($US) in 2014 and 2019.** In 2014, tumour necrosis factor (TNF) inhibitors had sales of $15.1 billion, followed by 'other biologics' (rituximab, abatacept and tocilizumab) with collective sales of $3.7 billion. The 'traditional disease modifying anti-rheumatic drugs (DMARDs) and others' class generated sales of $0.57 billion. Janus kinase (JAK) inhibitors, with tofacitinib as the only approved product, contributed just under 2% of total rheumatoid arthritis market, generating $308 million.

improvement (ACR20) scale. It has now entered Phase III development. These newer JAK inhibitors, with their improved safety and efficacy, are anticipated to outperform tofacitinib in market uptake.

Following in the footsteps of tocilizumab, several biologics that target the IL-6 pathway are also under development for RA. While this mechanism of action is considered more attractive, as dysregulated persistent production of IL-6 has a crucial role in both joint destruction and systemic manifestations, anti-IL-6 therapies can cause more severe adverse effects. Nevertheless, sarilumab (Regeneron/Sanofi), a fully humanized monoclonal antibody (mAb) targeted at the IL-6 receptor, has shown considerable promise. Positive Phase III data from the SARIL-RA-TARGET study of sarilumab, announced in May 2015, showed significant improvement in symptoms of RA in ACR20 scores. These data follow positive results from the Phase III SARIL-RA-EASY and SARIL-RA-ASCERTAIN trials, in which sarilumab also met primary end points. The drug has been filed for regulatory approval with a decision expected in early 2016.

Sirukumab (Janssen/GlaxoSmithKline), a fully human IgG1κ mAb that targets IL-6, has also demonstrated positive efficacy data in Phase II trials. A head-to-head Phase III trial (SIRROUND-H) against adalimumab in biologic-naive RA patients is currently underway with expected completion in August 2016. The long-term safety and efficacy of sirukumab is also being tested in the Phase III SIRROUND-LTE trial in patients that have inadequate responses to DMARDs and anti-TNF drugs. Although details of the clinical results for the Phase III trials have not been revealed, GSK expects to file for approval in 2016.

Two other anti-IL-6 products have entered Phase II development. Clazakizumab (Alder Biopharmaceuticals), a humanized mAb, showed significant improvements versus placebo in ACR20 scores in Phase IIb trials. ALX-0061 (Ablynx), a nanobody (consisting of a single monomeric variable antibody domain (VHH)) with a strong affinity for soluble IL-6 receptor, achieved clinical proof-of-concept in a Phase IIa RA study. Ablynx has signed exclusive global licensing agreements with AbbVie; Phase IIb studies are currently underway with results expected in the later half of 2016.

Other biologics that have reached advanced stages of clinical development for RA include denosumab (Daiichi Sankyo) and mavrilimumab (MedImmune/AstraZeneca). Denosumab is a fully humanized mAb that binds to receptor activator of NF-κB ligand (RANKL) and thus inhibits bone removal. It is already approved for osteoporosis (Prolia, Amgen) and skeletal disorders following bone metastases (Xgeva, Amgen), and it is currently in a Phase III trial (DESIRABLE) as a maintenance therapy in RA patients that are taking DMARDs. Mavrilimumab, a first-in-class mAb that targets granulocyte–macrophage colony-stimulating factor (GM-CSF) receptor, demonstrated positive data in Phase IIb (EARTH-EXPLORER-1). Mavrilimumab met the primary and secondary end points of improvement in disease symptoms (ACR20 and Disease Activity Score 28–joint Disease Activity Score based on C-reactive protein (DAS 28–CRP) scores) and sustained improvement in several RA symptoms.

Market indicators

The global RA market generated revenues worth US$19.7 billion in 2014, demonstrating considerable growth from a 2010 value of $10.8 billion (with a 2010–2014 compound annual growth rate (CAGR) of 16.2%) (FIG. 1).

The RA market is projected to reach $30.5 billion by 2019 (CAGR of 9.1%, 2014–2019), driven mainly by premium-priced anti-TNF drugs and other targeted biologics. JAK inhibitors, with the expected launch of baricitinib, filgotinib and ABT-494, are forecast to contribute ~6% of the market by 2019. However, with the loss of exclusivity for a number of anti-TNF biologics, growth is likely to be restricted by biosimilars; biosimilars of infliximab and etanercept are already approved in a number of markets, and biosimilar adalimumab will probably launch during the forecast period.

The low rates of disease remission and the lack of durable response to current medicines remain a challenge. Identification of biomarkers to determine personalized (or stratified) treatment will improve response, durability and reduce costs.

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