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FROM THE ANALYST'S COUCH

Rheumatoid arthritis market

Claire Mount and James Featherstone

In patients who suffer from rheumatoid arthritis (RA), the body, for unknown reasons, directs a hostile autoimmune response against joint cavities, which results in progressive, painful destruction of joint tissues. Worldwide, approximately 1–2% of the population is thought to be affected by RA, and one in three patients is likely to become severely disabled within 20 years. Onset often occurs between the ages of 25 and 50 years and is three times more prevalent in women than men. There are currently three major product classes being used for the treatment of RA that offer significant clinical and quality-of-life improvements for sufferers.

Treatment trends

Early therapeutics treated the symptoms of the disease and maintained the patient's quality of life, and were generally non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, naproxen and the cyclooxygenase 2 (COX2) inhibitors, all of which reduce pain and inflammation. However, the recent high profile voluntary withdrawal of Merck's COX2 inhibitor Vioxx, due to the increased risk of cardiovascular events, and the temporary withdrawal of Novartis' Prexige, casts a shadow over the entire COX2 inhibitor class. Steroids were often used in conjunction with NSAIDs to further reduce inflammation, and this combination offered the most potent short-term anti-inflammatory activity. However, clinical benefit seems to diminish over time, which is problematic given the chronic nature of RA.

During the past 20 years, the poor prognosis for chronic RA sufferers has spurred a more aggressive approach to the treatment of RA, and has led to the development of disease-modifying antirheumatic drugs (DMARDS) that attempt to halt disease progression. The most popular DMARD is methotrexate, originally used in the treatment of cancer, and others include gold salts, antimalarials, sulphasalazine, tetracyclines and cyclosporine. These are generic products and together consistently generate approximately US $600 million per year in sales. Evidence of early structural damage in RA has lead to a shift in the treatment paradigm, and physicians now prescribe DMARDs at disease onset; moderate-to-severe RA suffers are given NSAIDs, corticosteroids and DMARDs concurrently.

Although methotrexate is effective in the majority of RA patients, many cannot tolerate the side effects of the drug, and roughly 50% of patients eventually fail treatment, subsequently becoming eligible for more recent treatment innovations, such as biologic response modifiers. Leflunomide (Arava; Aventis) was launched in 1998, and was the first drug specifically approved for RA in more than a decade. Leflunomide is similar in mechanism and side effects to methotrexate and is used as a second-line agent in patients that have failed methotrexate therapy.

The most successful of the novel RA therapies are the tumour-necrosis factor-α (TNFα) inhibitors such as etanercept (Enbrel; Amgen), infliximab (Remicade; J&J/Centocor) and adalimumab (Humira; Abbott). Overall, TNFα inhibitors generated more than US $4 billion in sales in 2003, and growth in excess of 30% in 2004 is expected. The market is projected at US $7 billion by 2007, as approximately 30% of the moderate-to-severe patient population will be receiving anti-TNF therapy, with increasing penetration in mild-to-moderate patients.

Amgen's second biologic RA treatment, anakinra (Kineret), an interleukin-1 receptor antagonist (IL-1ra), was approved for the treatment of RA in 2001, although uptake has been slow due to inferior efficacy compared with anti-TNFα therapies. Kineret is generally restricted to use in the 30–40% of cases in which patients fail to respond to anti-TNFα therapies and is then given as a monotherapy or in combination with methotrexate or other non-TNF-targeting DMARDs.

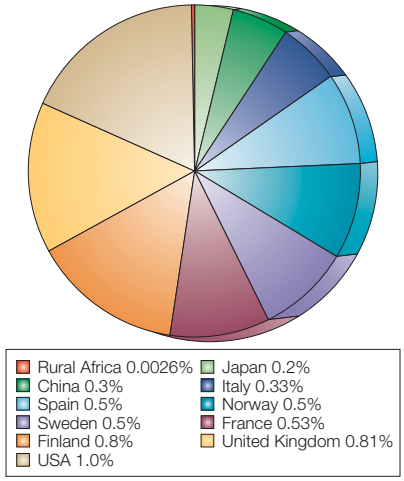

Figure 1 | **Population prevalence.** The prevalence of rheumatoid arthritis is relatively constant in many populations at between 0.5 and 1%. There are, however, exceptions, indicating the need for further elucidation of both genetic and environmental risk factors and their interactions.

What's in the pipeline?

The RA market is set to become more competitive in the medium term with the introduction of a number of drugs based on new mechanisms of action that have potential advantages over existing TNFα inhibitors, including longer half-lives and reduced dosing schedules.

The most advanced pipeline products are new-generation TNFα inhibitors such as UCB/Celltech's CDP-870 pegylated TNFα antibody fragment, and Biogen Idec/Genentech/Roche's MabThera/Rituxan, which is currently approved for the treatment of non-Hodgkin's lymphoma. CDP-870 is produced in *Escherichia coli*, which reduces the cost of goods to approximately one-quarter of that of the other TNFα drugs, and MabThera has a highly differentiated dosing regime that could reduce the cost of treatment to less than half that of existing biologic therapies, which is currently upwards of US $10,000 per patient per year.

Other development programmes include Roche's atlizumab (Actemra) treatment, a humanized anti-IL-6 receptor antibody; Bristol-Myers Squibb's CTLA4Ig (Abatacept), a soluble immunosuppressant antibody that is the first in a new class of co-stimulation blockers; and BMS's 561392 (DPC 333), a TNFα-converting enzyme inhibitor which, based on its mechanism of action, has the added advantage of being orally available.

In the longer-term, small-molecule inhibitors of proteases and enzymes will begin to emerge as RA treatments. Examples include Angiotech Pharma's protease inhibitor Paxceed; Wyeth's cell-cycle inhibitor CCI-779; J&J's (Scios) p38 MAPK inhibitor SCIO-469; and AtheroGenics TNF-response-genes modulator AGIX-4207. These products could be complementary to anti-TNFs or target refractory patients, and be easier to administer. Other key areas of interest include further anti-TNF agents, novel cytokines, angiogenic molecules, cell adhesion molecules and IL-1β-converting enzyme inhibitors. ▶

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RHEUMATOID ARTHRITIS MARKET | MARKET INDICATORS

The treatment of RA is dominated in volume by older, generic drugs, but the market for new biologics is growing rapidly (FIG. 2). Indeed, with roughly 165 million sufferers worldwide, and given that only an estimated 15% of US patients with RA are currently being treated with biologics, the market has tremendous potential for growth. Although penetration of the anti-TNFs is likely to increase in the near-term, growth of this class should ultimately begin to tail off, particularly following the approval of the non-TNF-targeted competitors including MabThera and MRA; in addition, novel drug targets are set to influence the future of RA treatment in the next decade (TABLE 1). New product classes have made significant improvements to the treatment of RA and promising developmental candidates have led to much optimism surrounding the chance to control disease progression (TABLE 2). With significant unmet clinical need, there is room for further growth in the RA market. The current growth potential 2003–2008 is predicted to be a 12% increase, with a market size of US $10 billion by 2008.

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doi:10.1038/nrd1611

Online links

FURTHER INFORMATION
The Arthritis foundation: http://www.arthritis.org
National Institutes of Health: http://www.nih.gov/
National Rheumatoid Arthritis Society: http://www.rheumatoid.org.uk/
Access to this interactive links box is free online.

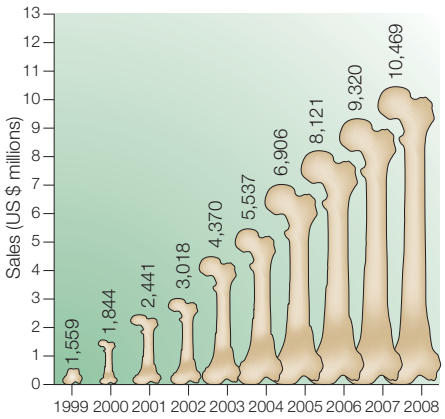

Figure 2 | **Forecast growth rates for the rheumatoid arthritis (RA) market.** 2003–2008 forecast compound annual growth rate = 24.4%. The RA market is expected to expand rapidly, driven by technological advances, increased competition and significant unmet need.

Table 1 | **Performance of key marketed brands and products 2003/2008***

Key products	2003	2008‡
Marketed brands		
Arava	287	385
Enbrel (Amgen)	1,300	2,808
Enbrel (Wyeth)	299	545
Remicade (Johnson & Johnson)	1,169	2,068
Remicade (Schering-Plough)	378	815
Kineret	68	150
Humira	280	2,537
Remicade (Tanabe)	2	66
Development products		
CTLA4-Ig (Abatacept)	0	340
CDP870	0	225

*Figures in US $ millions. ‡Estimated.

Table 2 | **Selected rheumatoid arthritis (RA) products in clinical trials**

Product	Target/mechanism	Status	Company	Comments
Abatacept	Inhibits T-cell activation	Phase III	Bristol-Myers Squibb	First in new class of co-stimulation modulators; also being (CTLA4Ig) tested in combination with Enbrel
Rituxan	Antibody against CD20	Phase III	Genentech/ Roche/ Biogen Idec	Currently used in treatment of B-cell lymphoma; for patients refractory to other DMARDs; IV infusion every 12 weeks
R1569/MRA	Antibody against IL-6 receptor	Phase III	Roche/Chugai	IL-6 significantly increased in RA
CDP-870	Antibody against TNF	Phase III	Celltech/UCB	Once per month dosing due to longer half-life; cheaper manufacturing
Pegsunercept	Pegylated TNF receptor type I	Phase II	Amgen	
AMG 714/ HuMax-IL15	Antibody against IL-15	Phase II	Amgen/ Genmab	
Paxceed	Small-molecule protease inhibitor	Phase II	Angiotech Pharma	
SCIO-469	Small molecule p38 MAPK inhibitor	Phase II	J&J (Scios)	Oral administration
ISIS 104838	Antisense molecule against TNFα	Phase II	ISIS	
Vitaxin	Antibody against vitronectin receptor	Phase II	MedImmune	In patients with suboptimal response to other drugs
AGIX-4207	Small molecule that modulates TNF-response genes	Phase II	Atherogenics	Oral administration
Antegren	Antibody against adhesion molecules	Phase II	Elan/Biogen Idec	
CCI-779	Small-molecule cell-cycle inhibitor	Phase II	Wyeth	
Humira	Antibody against TNF	Phase II	Eisai/Abbott	Developed for Japanese market by Eisai

DMARD, disease-modifying antirheumatic drug; IL, interleukin; IV, intravenous; MAPK, mitogen-activated protein kinase; TNF, tumour-necrosis factor.

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