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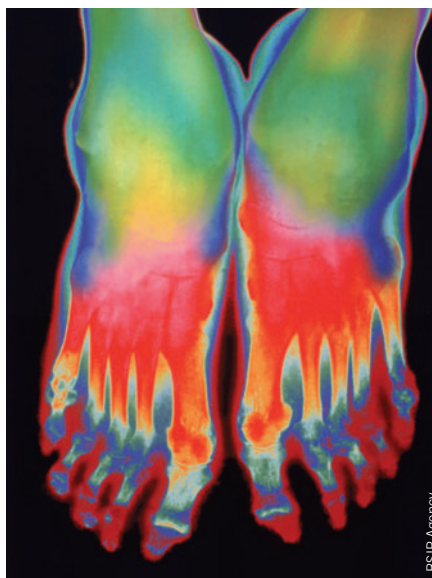
First-in-class biologic to enter rheumatoid arthritis fray

A completely novel biologic for the treatment of rheumatoid arthritis (RA) is poised to enter the US market following a September US Food and Drug Administration (FDA) committee approval recommendation for Bristol-Myers Squibb's fusion protein Orenzia (abatacept). Other novel treatments will soon follow, challenging the dominance of tumor necrosis factor (TNF) blockers, such as Centocor's Remicade (infliximab), Amgen/Wyeth's Enbrel (etanercept) and Abbott's Humira (adalimumab). Meanwhile, pipeline attrition also continues unabated, with Regeneron's interleukin-1 trap molecule the latest casualty in the highly crowded and competitive field.

In September, the Arthritis Advisory Committee of the FDA voted unanimously to recommend approval for Orenzia, a fusion of cytotoxic T lymphocyte antigen-4 (CTLA4) and a fragment of the Fc portion of IgG1. Orenzia's imminent approval culminates a long and tortuous history dating back to 1989, when scientists at Oncogen in Seattle made a fusion protein that blocked the 'costimulatory signal' between antigen-presenting cells and T cells, preventing T-cell activation (*Nat. Biotechnol.* 22, 145–147, 2004). In RA, infiltrating T cells generate inflammatory molecules that attack joints.

Phase 3 results, published in the *New England Journal of Medicine* (353, 1114–1123, 2005) in September, demonstrate that half of Orenzia patients who failed anti-TNF therapy achieved at least a 20% improvement in the signs and symptoms of the disease, compared with one-fifth of patients receiving placebo. But only one patient in ten experienced 70% improvement. "Efficacy is definitely demonstrated, but it is not dramatic," commented advisory committee member Norman Ilowite, from Schneider Children's Hospital in New York.

Still, Orenzia will be an obvious choice to treat patients failing anti-TNF therapy. Almost 10% (130,000) of the estimated 1.5 million diagnosed with moderate or severe disease fall into that category. In most RA patients "it'll be a TNF blocker that'll be used first, and then [Orenzia] will be the fallback, for now, until we have more direct experience or some direct



Keeping on their toes: biotechs will have to be nimble to take advantage of the RA market, which is already crowded.

comparison to show that it's at least as good as a TNF blocker," said David Fox, rheumatologist at the University of Michigan in Ann Arbor. Only then, could Orenzia be used as first-line therapy (see **Box 1**).

Approval for Orenzia and Rituxan (rituximab; see **Box 1**), will give rheumatologists three mechanistically distinct biologic treatments for RA, benefiting patients but complicating the worldwide market, which already exceeds \$5 billion a year for biologics alone. "It's going to be interesting to have a B-cell target [Rituxan], and a T-cell target [Orenzia] and a pro-inflammatory target [TNF blockers]," says Fox. Meanwhile, Chugai's anti-IL-6 MRA antibody, which showed outstanding results in a randomized phase 2 trial, is now in phase 3 and could provide yet another new kind of agent. And several other RA drugs are moving up the pipeline (see **Table 1**).

Should Orenzia gain approval, its market stakes are high. Albert Rauch, a pharmaceutical analyst at A.G. Edwards & Sons in St. Louis, Missouri, predicts Orenzia will reach \$500 million in sales in three to five years. "It's going to be difficult to capture market share [in] a crowded market," he says. That market will grow as more doctors use the biologics earlier in the disease, says Rauch, but there are limits. With anti-TNF treatment costing \$15,000 or more annually, insurance companies are increasingly vigilant. "If these drugs get too widely used, they'll certainly try to find ways to limit their usage," says Rauch.

Box 1 Adverse events could still cast a shadow on Orenzia's approval

Although Orenzia appeared safe in clinical trials, long-term safety remains an issue. Bristol-Myers Squibb will conduct several post-marketing trials, including a prospective safety trial involving 5,000 new patients. Researchers will be watching for infections, cancer and new autoimmune disease, which paradoxically could arise—in theory—because regulatory T cells, which help keep the immune system in check, are highly dependent on the same costimulatory signals blocked by Orenzia.

TNF blockers have their own safety problems. Rare adverse effects include the development of unrelated autoimmune diseases like lupus, as well as malignancies and tuberculosis. So a new, safer agent with comparable efficacy, in theory, could supplant them, at least for subsets of patients. "What we don't know at this point, because there have been no direct comparison trials, is whether [Orenzia] is as good as...any of the TNF blockers," says Fox.

The same is true for Rituxan, a B-cell-targeted chimeric antibody from Cambridge, MA-based Biogen Idec, approved in 1997 for non-Hodgkin's lymphoma, now in trials for RA. Biogen announced impressive phase 3 results in April 2005 and submitted its supplemental biologic license application to the FDA in August.

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Table 1 The pretenders: RA drugs in advanced development

Company	Agent	Stage
Amgen (Thousand Oaks, California), GenMab (Copenhagen)	AMG-714 (anti-IL-15 mAb)	Phase 2
Androclus Therapeutics, San Diego, California.	dnaJP1 (epitope-specific immunotherapy peptide)	phase 2
Biogen Idec (Cambridge, MA), Genentech (S. San Francisco, California), Roche (Basel)	Rituxan (anti-CD20 mAb)	Phase 3 complete
Bristol-Myers Squibb (New York)	Orencia (CTLA4-Ig)	Phase 3 complete
Can-Fite (Petach Tikva, Israel)	CF101 (adenosine A3 receptor agonist)	Phase 2a
UCB Celltech (Brussels)	CDP 870 (pegylated anti-TNF Fab)	Phase 3
Centocor (Horsham, PA), Schering-Plough	CNTO 148 (anti-TNF antibody)	Phase 2 complete
Chugai (Tokyo), Roche	MRA (anti-IL 6 receptor mAb)	Phase 3
Genmab	Humax-CD20 (anti-CD20 mAb)	Phase 2
Human Genome Sciences (Rockville, Maryland)	LymphoStat B (anti-BlyS mAb)	Phase 2
Incyte (Wilmington, Delaware)	3284 (chemokine receptor 2 antagonist)	Phase 2a
Merrimack Pharmaceuticals (Cambridge, Massachusetts)	MM-093 (recombinant human alpha-fetoprotein)	Phase 2a
Millennium Pharmaceuticals (Cambridge, Massachusetts)	MLN1202 (mAb against CCR2 chemokine receptor)	Phase 2
Scios (Fremont, California)	SCIO-469 (p38 MAP kinase inhibitor)	Phase 2
Vertex Pharmaceuticals (Cambridge, Massachusetts)	VX-702 (oral p38 MAP kinase inhibitor)	Phase 2

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In the long run, Clare Churchill, analyst at Data Monitor, predicts the market for RA biologic treatment could reach \$10 billion by 2010, based on extrapolating current trends, while Orencia could peak at \$800 million by then. But she agrees that restrictions on reimbursement by insurance companies will probably keep it from getting to that point—a hurdle that's higher in Europe than in the US. "These drugs are very expensive. Whether the markets can sustain those kinds of sales is something we're going to have to wait and see, really," says Churchill. Governments in Europe, said Rauch, will be

somewhat more resistant to paying for new biologics like Orencia than will payers in the US.

In the race to provide new alternative treatments to tap the lucrative RA market, attrition remains high. In November, 2003, Vertex Pharmaceuticals killed its interleukin-1-converting enzyme inhibitor in phase 2. Isis Pharmaceuticals did the same for its anti-TNF antisense drug the following year and Amgen has stopped developing its pegylated soluble TNF receptor. Several companies have abandoned p38 MAP kinase inhibitors in advanced development, although Vertex and Scios con-

tinue to develop their versions. Finally, in September, Regeneron terminated its IL-1 trap program in phase 2. "RA is a very crowded field," comments Regeneron CEO Leonard Schleifer. "We thought our resources could be better spent."

The surviving drugs, starting with Orencia, will make an undeniable impact. But a cure remains elusive. "There's no agent, so far, which we can give for a short time, then stop it, and the disease won't come back," says Fox. "We're still ten to twenty years away from curing the disease."

Ken Garber, Ann Arbor, Michigan