Table 1 Selected MS therapies in advanced development

Agent	Company	Likely mechanisms	Status
Small molecules			
FTY720 (fingolimod)	Novartis (Basel)	S1P receptor modulation with immunosuppression	Phase 3 (three trials at various stages)
Leustatin (cladribine)	EMD Serono (Rockland, Massachusetts)	Purine nucleoside analog, depletes lymphocytes	Phase 3
BG-12 (fumarate derivative)	Biogen Idec (Cambridge, Massachusetts)	Activates Nrf2 pathway, anti-inflammatory, neuroprotective	Phase 3
Teriflunomide	Sanofi-Aventis (Paris)	Unknown, pyrimidine synthesis inhibitor	Phase 3
Laquinimod (oral Copaxone)	Teva Pharmaceutical Industries (Jerusalem)	T-helper 2 regulatory cell induction, others possible	Phase 3
Monoclonal antibodies			
Campath 1H (alemtuzumab)	Genzyme (Cambridge, Massachusetts)	Targets CD52, depletes variety of immune cells	Phase 3
Ocrelizumab	Genentech (S. San Francisco, California)	Targets CD20 receptor, depletes mature B cells	Phase 2
Lymphostat B (belimumab)	Human Genome Sciences (Rockville, Maryland)	Targets BLyS, reduces autoantibody levels	Phase 2
Zenapax (daclizumab)	Biogen Idec	Anti-CD25, modulates T cells	Phase 2

the cause. In the phase 3 trial, the patient with herpes encephalitis was taking FTY720 monotherapy, whereas the two Tysabri patients who died several years ago from progressive multifocal leukoencephalopathy (PML) were on combination therapy. If FTY720 alone leads to infections, that would be a serious setback. "I wouldn't be surprised if fingolimod is going to be associated with PML," says Bibiana Bielekova, an MS researcher at the National Institutes of Health. Novartis plans to file for US Food and Drug Administration registration in late 2009, although Kaplan thinks that date may be pushed back about six months, due to the new safety concerns. Timing might be crucial, because three other oral agents for MS are in phase 3 (**Table 1**).

Even if most or all of these drugs win regulatory approval, that won't render obsolete current injectable treatments, such as Biogen Idec's Tysabri and Avonex (interferon (IFN)-beta), Darmstadt, Germany–based Merck Serono's Rebif (IFN-beta) or Jerusalem-based Teva Pharmaceutical's Copaxone (glatiramer acetate). "If you're on an injection therapy, doing well and tolerating it fairly well, you have to ask yourself whether you want to make a switch to a drug where…the long-term safety isn't known," says Mikol. But oral delivery is where the MS field is going. "People hate interferons," says Bielekova. "A really large proportion of patients get tired and achy, and they hate giving themselves a shot. So there is absolutely a huge demand for oral therapies."

Several injectable immunomodulating mAbs are also in advanced development for MS (**Table 1**). But by far the best-performing antibody for MS is Campath IH (alemtuzumab) from Genzyme in Cambridge, Massachusetts. Campath, already approved for treating B-cell chronic lymphocytic leukemia, binds the glycoprotein CD52, which is expressed on the surface of T and B cells, and indirectly kills them. Phase 2 results in MS were dramatic: patients taking Campath had a 73% reduction in the risk of relapse compared to IFN treatment. "That's something that could potentially impact the [MS] landscape," says Aaron Reames, an analyst at Wachovia Capital Markets in Boston. Unfortunately, Campath can cause immune thrombocytopenia purpura, a condition that results in abnormal bleeding from low platelet counts. Campath "is by far the most effective drug for MS," says Caroline Stewart, an analyst at Piper Jaffray in New York. "It's also the most dangerous."

In the end, market dominance will come down to safety, for FTY720 and for its competitors. But none of them is the final answer for MS. "The biggest question is [whether MS is] only immune system driven or is the immune system responding to something that is happening in the brain?" says Bielekova. "If we can completely tackle the immune system part, can we cure the disease? And I think we don't know that."

Ken Garber *Ann Arbor, Michigan*

IN brief

India harmonizes regulations

India will create a single autonomous body for biosafety clearance of genetically modified (GM) products, a move that has been welcomed by the biotech industry. Come September, the National Biotechnology Regulatory Authority (NBRA) will replace the existing committees currently under different ministries. "This is what we have been asking for all these years," Arvind Kapur, managing director of Nunhems Seeds Private Limited, a subsidiary of Bayer Crop Science located in Gurgaon near Delhi. "We will not have to run to different ministries anymore to get approval." The NBRA will have separate divisions to handle issues in agricultural, pharmaceutical and industrial products and GM food under a common chairman. Advising the NBRA will be a panel of delegates from relevant ministries and another 20-member council representing the scientific community, private sector, nongovernmental and farmer organizations. The NBRA will also set up a mechanism for dispute settlement and Kapur says companies may not have to spend huge amounts of money fighting litigations filed by nongovernmental organizations (NGOs). Maharaj Kishan Bhan, secretary to the department of biotechnology, points out that although his department helped create this new regulatory body, it will not control it. *–K S Jayaraman*

FDA probes TNF blockers

The tumor necrosis factor inhibitors Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab) and Cimzia (certolizumab pegol) are being investigated by the US Food and Drug Administration (FDA) after being linked to about 30 cases of cancer. The cancers (mostly lymphomas, though leukemia, melanoma and solid organ cancers also surfaced) occurred between 1998, the year Remicade was approved, and the end of April this year, and were found in children or young adults who began using the drugs before the age of 18 to fight Crohn's, juvenile idiopathic arthritis or other diseases. Though the patients also were taking other immunosuppressive drugs, and cancers can normally occur in children, FDA said the tumor necrosis factor (TNF) inhibitors-cancer connection is "of concern" and deserves "further investigation." Toward that end, FDA asked Enbrel manufacturers Amgen, of Thousand Oaks, California, and Wyeth, of Madison, New Jersey; Humira manufacturer Abbott Laboratories of Abbott Park, Illinois; and Remicade manufacturer Eli Lilly of Indianapolis to provide information on all reported cancers in children taking the inhibitors. UCB, of Brussels, maker of Cimzia, is required to conduct a 10-year study beginning next year, as the product is approved for only Crohn's disease and not yet cleared for use in children. Still, FDA, the companies and the Arthritis Foundation all suggest the benefits of the products outweigh the risks, and so far, sales have not slipped. "The whole [TNF inhibitor] market has been growing really robustly," says Mark Schoenebaum, an analyst in New York with Deutsche Bank. "People thought this market was mature years ago, but it's been growing…year on year." *–Brady Huggett*