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Multiple sclerosis woes

The multiple sclerosis drug Tysabri showed such efficacy in two Phase III clinical trials over one year that the US Food and Drug Administration (FDA) granted it accelerated approval in November. Only three months later, the drug was withdrawn after two patients in ongoing trials developed an exceedingly rare—and often deadly—viral brain infection called progressive multifocal leukoencephalopathy (PML). A third patient was later confirmed to have died in 2003 from PML. Doctors and drug companies are searching for a way to safely reintroduce Tysabri, but we must ensure that such efforts are based on solid science rather than hope.

Multiple sclerosis (MS) affects up to 2.5 million people worldwide. It typically begins in young adults with benign neurological symptoms that come and go. Relapses can cause severe symptoms, but they tend to resolve within weeks. Five to twenty years after diagnosis, in most patients, the disease switches to a chronic progressive course that can cause severe disability. Even in the early stages when quality of life is good, chronically activated pro-inflammatory T lymphocytes attack myelin in brain and spinal cord, causing lesions detectable by MRI (magnetic resonance imaging) scans.

MS frustrates doctors and patients for many reasons. Its course is unpredictable, and lesion severity, as seen by MRI, is not reliably correlated with symptom severity. Despite decades of study, the pathogenic mechanisms of MS remain poorly understood, hobbling drug design and development. Finally, available treatments—three interferon-β preparations, a peptidomimetic of myelin basic protein, a chemotherapy drug and steroids—do some good, but they can only delay long-term disability.

Tysabri was all set to lift the gloom. The drug approval had come two days before the Thanksgiving holiday. "My family needled me all weekend that I should be roasted and served as the Thanksgiving turkey," jokes Lawrence Steinman from Stanford University, whose laboratory contributed to the scientific groundwork[1] for Tysabri, but who did not participate in its commercial development by Elan Pharmaceuticals of Dublin, Ireland, and Biogen Idec of Cambridge, Massachusetts.

The drug is a humanized monoclonal antibody to the α4 integrin subunit. Activated T lymphocytes express an α4β1 integrin dimer that interacts with the receptor VCAM-1 on blood vessel endothelial cells to enable T cells to cross from the bloodstream into inflamed tissue. Tysabri inhibits the integrin-VCAM interaction and thereby blocks pathological T cells from entering the CNS and damaging myelin sheaths. In clinical trials, it reduced MRI lesions and relapse frequency about twice as well as the most commonly prescribed MS drug, a version of interferon-β-1a.

By its mechanism of action, Tysabri is a powerful immunomodulator. Thus researchers fully expected infections—common or opportunistic—to turn up in clinical trials. However, none had become apparent before FDA approval, after 3,000 participants had received monthly doses of Tysabri for a year or longer.

Nevertheless, PML is an opportunistic infection, caused by a normally harmless virus, JCV, to which most people are exposed in infancy. JCV persists in kidney epithelial cells, where it typically remains in a latent state. However, immunosuppression may allow it to spread; up to 5% of AIDS patients develop PML. About 80% of people carry antibodies to JCV. The latent viral genome is difficult to detect, but its prevalence is estimated at 50%.

We do not yet know how Tysabri activates JCV to cause PML. Perhaps the drug simply increases susceptibility to opportunistic infections across the board, but only PML has been reported so far. The other possibility is that Tysabri specifically affects JCV or the cells that harbor it. Latent JCV must undergo genomic rearrangement before it can become virulent, and Tysabri might affect rearrangement frequency. Hematopoietic cell types other than activated T cells express α4β1 integrin, and JCV may reside in hematopoietic cells. PML is such a rare condition that few laboratories work on JCV. This may change now as this exotic virus threatens to derail a promising treatment for a large patient group.

Can Tysabri—and the promise it brought to MS patients—be salvaged? Representatives from Biogen Idec, in a recent letter to the New England Journal of Medicine[2], expressed hope that stringent testing for JCV load could catch active virus before it reaches the brain. If this were possible, some patients might choose to take the risk, and Tysabri, though it might never be a first-line MS drug, could become a useful arrow in our unsatisfactory arsenal.

Other experts are less optimistic. Richard Ransohoff, an MS clinician and researcher from the Cleveland Clinic Foundation, believes that Tysabri triggers JCV through a specific mechanism, which would augur badly for it or any other drug aimed at α4β1 integrin. Indeed, pharmaceutical companies GlaxoSmithKline and Antisense Therapeutics have stopped Phase II trials of two drugs that were also designed to interfere with α4. Ransohoff believes that attention should turn to other targets involved in T lymphocyte homing, such as chemokine receptors. Steinman fears that the PML debacle may put a lasting chill on development and clinical testing of therapies for MS and other autoimmune diseases, if regulatory agencies demand more extensive trials and monitoring—which adds substantial cost and could discourage investment. FDA spokesperson Lenore Gelb states that the agency is not considering any changes to the accelerated approval procedure at this time.

Yet, some encouragement can be drawn from this sad story. Tysabri has proven that highly effective drugs against MS are possible, and researchers may be able to rehabilitate the drug once we understand its mechanistic link to PML. In addition, phase II trials are underway for drugs based on other mechanisms, among them a sphingosine-1-phosphate receptor agonist that affects lymphocyte homing[3,4], chemotherapeutic drugs that inhibit lymphocyte proliferation, and monoclonal antibodies to different lymphocyte surface antigens. The disappointing outcome of the Tysabri trials should not reduce our efforts to find an effective treatment for this serious disease.

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3. Mandala, S. et al. Science **296**, 346–349 (2002).
4. Brinkmann, V. et al. J. Biol. Chem. **277,** 21453–21457 (2002).