

Death and Dividends: The Tysabri Debacle

For the last three to four years neurologists have been talking about the coming of a much more effective drug for MS. That drug was first called Antegren and then Tysabri. The story of Tysabri illustrates some risky and unsavory aspects of the search for an effective drug for MS.

Tysabri is a humanized, monoclonal antibody that is produced by transgenic goats in their milk. A monoclonal antibody is a designer drug that targets one specific protein in the body and basically knocks it out of action. MS research has led to the concept that MS is driven by activated T cells that are sensitized to myelin. Such autoreactive T cells are activated in the blood mainly through an immune encounter with a foreign protein from an infectious agent or food. The activated, myelin-aggressive T cells then migrate to the brain, pass through the blood-brain barrier and lead an attack on the myelin. It was reasoned if a drug could stop or greatly hinder the passage of these autoaggressive T cells across the blood-brain barrier, then the MS disease process could be substantially short-circuited. Activated T cells cross the blood-brain barrier by sticking on the blood vessel wall and then pushing through it. A monoclonal antibody, which was to become Tysabri, was developed to knock out the protein on the T cells (VLA-4) that allows them to stick on the blood vessel wall.

Preliminary studies indicated that Tysabri was seemingly safe over the short term with a few bad allergic reactions being the only notable adverse effect. By 2001, Elan and Biogen, the drug companies which were producing Tysabri, predicted billions of dollars in future revenue and their stocks started to soar. The Phase III trial began in late 2002 and, after only one year, the companies applied to the Food and Drug Administration (FDA) in the USA to approve the drug despite the fact that there wasn't any evidence that it slowed disease progression. At the same time the drug was also tested for Crohn's Disease, a gastrointestinal autoimmune disease, but was found to have no significant effect. One person on Tysabri in the Crohn's trial died of apparent brain cancer.

In November of 2004 the FDA approved Tysabri for use on the basis of the first year result of fewer attacks and MRI-detected lesions and soon afterwards neurologists were infusing their patients with this new, very expensive drug. The company stocks climbed to new heights.

The last two weeks of February, 2005 were very eventful. On February 14 Biogen director, Robert Pangia, sold 15,570 shares for a profit of \$954,844. On Feb 15, Biogen's executive chairman, William Rastetter, sold more than 120,000 shares, yielding a \$7.45-million profit. On February 18 Thomas Bucknum, a Biogen executive vice president and the company's general counsel, sold 89,700 shares for a profit of \$1.9 million. Later that same day Biogen informed the FDA that one Tysabri patient had died of a very rare brain disease known as PML (progressive multifocal leukoencephalopathy) and that another patient also likely had the disease.

PML occurs when the JC virus, which most people carry, rises from a dormant state due to a weakened immune system and destroys the myelin in the brain at a very rapid rate. PML is a very ugly disease which usually ends in death over a few months. Given that Tysabri prevents T cells from entering the brain and thus reduces immunological control of the JC virus, it is extremely likely that it is the main cause of the PML.

On February 27, Elan and Biogen issued a glowing press release describing the results of the two-year Tysabri clinical trials. It sounded like the promised drug had arrived. On February 28 the FDA

issued a terse statement stating that two Tysabri patients had PML and that the drug was being voluntarily withdrawn from use by Elan and Biogen. Both stocks fell like rocks with Elan losing 60% of its value and Biogen 40%. When questioned about the executives who had possibly made illegal stock trades, Biogen stated "All these trades preceded that quick and decisive action, which was guided exclusively by concern for patient safety and our commitment to the MS community". The Securities Exchange Commission will likely investigate whether or not insider-trading laws were violated.

Throughout most of March it was widely agreed that Tysabri would likely make a comeback as early as the fall. Then at the end of March came the news that the patient in the Crohn's/Tysabri study who had supposedly died of cancer had actually died of PML. As I write this they are still debating whether or not Tysabri will be brought back despite its potentially fatal side effects.

There are a number of incidents connected with the Tysabri saga that need clarification. It is surprising the Biogen doctors misdiagnosed PML as brain cancer in 2003 especially when PML is a possibility with any drug that has a major effect on the immune system of the brain. Also it is unclear why it took at least a month after the PML cases were identified in the Tysabri and MS trials for the drug's withdrawal to be announced. This delay put many people at great risk. Furthermore, is it just coincidence that the Biogen executives unloaded their stock during this questionable delay? It is also surprising that Elan and Biogen put out a press release saying how fantastic Tysabri is, knowing full well that the next day the FDA was going to announce the suspension of the drug because of ties to a deadly brain disease. And why did the FDA approve Tysabri after only one year of the Phase III trial given the potential of long-term side effects of such a powerful drug as well as the less than stellar results. These are all troubling questions without answers.

Persons with MS should realize that participating in a clinical trial is somewhat like playing Russian Roulette and that a drug company's desire for maximum profits may compromise their efforts to ensure maximum protection against harm. Drugs that short-circuit the immune system have bad side effects and death is always a possibility. Copaxone and the beta-interferon drugs are cakewalks compared to what is coming down the pipe. The drug companies know that any new "blockbuster" drug, such as Tysabri, has to be significantly more effective than the current drugs and that means they will likely be much more damaging to the immune system.

I always find it incredible that many people recently diagnosed with MS will choose a potentially deadly drug over nutritional strategies that are completely safe and likely more effective. Luckily there are still some people with common sense who do not allow themselves to be sacrificed for profit.