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THE NUMBERS GUY

Medicine's Dangerous Guessing Game

Different Methods of Weighing the Risks and Benefits of Medical Treatments Lead to Varying Conclusions About Their Safety

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Updated Sept. 9, 2009 11:59 p.m. ET

Ever since the powerful multiple sclerosis drug Tysabri returned to the market in July 2006, a key issue for patients has been the risk of contracting progressive multifocal leukoencephalopathy, or PML, a dangerous brain infection associated with the drug.

PML's appearance in three of the 3,000 patients who took Tysabri during clinical trials was the reason the drug was pulled from the market in 2005 -- and its return was made possible only under patient-monitoring rules imposed on Tysabri maker Biogen Idec Inc. by the Food and Drug Administration.

Despite these rules, it has been hard for many MS patients to get a clear picture of the odds of getting PML during long-term Tysabri use since the drug is relatively new. In the three years since the drug's return, Biogen reported 11 new PML cases among 56,500 patients who have tried the drug.

Tysabri underscores a central mathematical issue in assessing risks and benefits of medical treatment -- one that has also shown up in calculating the risk of blood clots among heart-stent users, and in figuring out how beneficial chemotherapy is in treating lung cancer.

Simply put, the issue is a matter of whether to adjust for time. In other words, should the chances of contracting a harmful side effect be calculated by figuring out the simple percentage of all those taking the drug who have come down with the side effect? Or should those calculations be adjusted for the duration that patients have been treated?

The former method calculates what's called an "absolute" percentage. The latter, used widely in medical studies and by insurance actuaries, takes into account that risk changes over time: For example, someone who drives a car only one day during his lifetime is less likely to be in a crash than someone who drives for 20 years.

Using the absolute method, Biogen in late April said cases of PML that had occurred since the drug's return were 1.2 per 10,000 -- or about one in 8,700 -- extrapolated from the six then-known cases among 52,000 Tysabri takers.

Biogen says now that the rate of PML among Tysabri users "remains very low and well below the rate suggested by the U.S. product label," which discloses the three cases among 3,000 patients in clinical trials, and was revised in late 2008 to say there have been more cases since reintroduction. A spokeswoman said Tuesday that the company won't be disclosing new cases of PML and won't recalculate the risk unless it changes significantly.

But taking into account the five additional cases the company has reported since April, and using the actuarial method, the risk comes out to about one in 1,200 -- much closer to the one-in-1,000 threshold that some analysts have said might cause doctors to become more cautious about prescribing the drug. Biogen says the absolute method is more appropriate to measure rare risks.

Some doctors have begun using actuarial calculations to estimate Tysabri's risks. For a chronic disease like MS, where treatment can last eight or 10 years, the long-term risk is probably different than for somebody who has only a short course of the drug.

Robert Fox, a neurologist and director of the MS center at the Cleveland Clinic, calculates that for patients on Tysabri for more than 30 months, the risk is higher than one in 1,000, while for those on it for 18 months it is only 0.21 per 1,000. He says the clinic has been suggesting to patients on the drug for two or three years should "rotate off" the drug and onto a different therapy.

Mark Schoenebaum, an analyst at Deutsche Bank who follows Biogen, has said that a one-in-1,000 incidence rate would amount to a level that would cause patients to be more reluctant to take the drug, and doctors to be more reluctant to prescribe it.

The Wall Street Journal's analysis, based on standard actuarial methods commonly used in medical research, was reviewed by David Harrington, a biostatistics professor at Harvard University's School of Public Health who specializes in calculating medical risks. He said the calculations were accurate and an appropriate way to calculate the risk.

Biogen reviewed a copy of the calculations and disagrees with them. "The WSJ methodology is flawed because it uses the wrong type of model...in the wrong manner," the company said in a statement.

The two mathematical methods in calculating risks have led to prior disputes. In 2006, Boston Scientific Corp. and Johnson & Johnson disagreed over whether their models of drug-coated heart stents -- tiny scaffolds that prop open clogged arteries -- caused blood clots years after implantation.

J&J found no increase in the percentage of patients with clots in its coated stent. Boston Scientific used the actuarial method to measure its coated stent and did find an increase, by about one clot per 200 people per year. That led to unwelcome headlines for Boston Scientific. But a later study, in the New England Journal of Medicine, analyzed both stents with the same technique. Both products showed the same increase in clots. Representatives for Boston Scientific and J&J declined to comment.

Similarly in 2005, a Canadian clinical trial inaugurated the use of chemotherapy to treat lung cancer after demonstrating that the treatment reduced mortality by 31%. Half the people in the study were given chemo, and half weren't.

But the results didn't mean that chemo decreased actual lung-cancer deaths -- only that it would extend the life of patients. In fact, after eight years, the study estimated that the same fraction of people would die with treatment as without -- about half. Since people on chemo lived longer, by about 21 months, the study could truthfully report that treatment reduced the average death rate during the study.

Trying to estimate Tysabri's risks runs into the same issue of accounting for risks over time. The drug, also sold by Elan Corp. of Ireland, is widely considered the most potent MS treatment on the market.

Although the company declines to quantify the risk based on current data, using the absolute method it applied in April, the rate would come out to one in 5,140 -- or 11 of the 56,500 patients who have taken the drug since its return.

That lumps together everybody who has tried Tysabri, no matter how long. Biogen says about 200 new patients keep starting every week. Since the drug was relaunched only in 2006, fewer than half of the patients taking it have been using it for more than 18 months. It takes time for the infection to develop and to be recognized. Mathematically, averaging all the patients together, irrespective of how long they have been observed taking Tysabri, underestimates the risk to a long-term patient.

But using the actuarial method, which takes into account that different patients have been observed on the drug for different amounts of time, the rate comes out to one in 1,200 for three years of use.

The actuarial method estimates the chance of making it through various time periods without getting PML. For example, according to Biogen, nobody got PML in the first year of treatment, so the chance is 100% -- risk free. About 30,600 people received at least a year of Tysabri, and four of them were infected before they reached 18 months. So the chance of successfully making it through that period is about 99.99%. About 10,000 people have been observed on Tysabri for between two and three years, and seven got PML -- a 99.93% chance of not getting PML during the third year.

Multiplying the figures together -- 100% times 99.99% times 99.93% -- results in a 99.92% chance of not getting PML during the first three years of treatment. In other words, there's an 0.08% chance of getting the infection. That works out to one in 1,200.

