Uncertainty in Benefit and Risk: Tysabri (natalizumab)

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Tysabri (natalizumab)

Approved in 2004 when the only treatments were copaxone (glatiramer acetate) and interferon; based on 1-year data. The approval was an accelerated approval (first example of AA based on a clinical effect, i.e., not a surrogate), with a requirement to obtain 2-year data. Tysabri is given as a monthly infusion.

The effect size (reduction of annual recurrence rate) was large compared to available therapy, about 68% compared to placebo and about 55% when added to interferon. There was also a strong effect on disability, 42% vs placebo and 25% vs interferon.

Trouble

Four months after approval, in Feb 2005, FDA received 2 reports of progressive multifocal leukoencephalopathy (PML), a usually fatal disease caused by activation of the JC virus, a virus present in most people and known to cause PML in immunosuppressed people. Both patients had been on Tysabri for a long period (36 months and 28 months) and were receiving interferon as well.

At that time about 7,000 patients had received at least one dose of Tysabri, but many fewer for > 2 years.

Biogen Idec suspended marketing and all clinical trials and reviewed all the data.

Biogen Update

In addition to the 2-year data showing continued effectiveness, Biogen Idec in Sept 2005 reported its safety assessment and asked for marketing reauthorization

- No more MS cases among a total of 1869 MS patients treated for a mean of 120 weeks.
- An additional case in a Crohn's Disease patient, for total of about 3 cases among 3000 patients.
- PML not previously associated with MS.
- MS patients all on interferon; Crohn's patient on immunosuppression.

Problems and Major Resolutions

1. Rate – major uncertainty
   All cases had been on Tysabri for > 2 years, but little longer term exposure. Would rate climb with greater exposure?
2. Benefit at 2 years well-established
3. March 2006, Advisory Committee extensive discussion, including powerful personal testimony. Patients, well aware of the lethal risk, nonetheless strongly favored re-introduction and the AC unanimously endorsed this step

But with major restrictions:

Restrictions - AC

1. Monotherapy only
2. Patients with relapsing MS
3. Divided on whether should be second line only

What We Did

June 2006 return to market with RiskMAP. Needed to

1. Identify people at higher risk
2. Find treatment for PML, perhaps by earlier identification
3. Treat only people who really need Tysabri
4. Follow-up

Marketing Requirements

1. Use only as monotherapy in relapsing MS, "generally only in people with inadequate response to, or unable to tolerate, an alternative MS therapy."
2. Boxed warning and detailed safety information on PML.
3. Risk management plan including controlled distribution plan (TOUCH) with Rx by certified healthcare providers, only in enrolled patients, with documented patient counseling and evaluation at 3, 6 months, then every 6 months.
4. Prospective observational post-marketing study, n=5000 followed for 5 years (TYGRIS).

Since 2006

Crohn's Disease approval 2008 (2nd line), part of TOUCH.

2 new PML cases in 2008, after total worldwide exposure of about 39,000 worldwide, with 12,000 Rx'd for ≥ 1 year, both Europe, monotherapy.

As of September 2013, 401 cases, distributed as follows

Tysabri exposure – Anti-JVC Ab positive		
	No immunosup	Prior immunosup
1-24 mos	< 1/1000	1/1000
25-48 mos	3/1000	13/1000
49-72 mos	7/1000	9/1000

Overall - Future

In 2006, return was plainly needed; alternatives were few. There have been recent approvals of fairly well-tolerated drugs (fingolimod, dimethyl fumarate, teriflunomide), all oral. It seems likely that fewer people will need to assume the risk of Tysabri, but there are always non-responders to any given therapy.