Trends-in-Medicine

March 2005
by Lynne Peterson & D. Woods

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

MULTIPLE SCLEROSIS DRUG WITHDRAWN FROM THE MARKET

On Monday, February 28, 2005, Biogen Idec and Elan made a surprise announcement that they were taking their new multiple sclerosis (MS) drug, Tysabri (natalizumab, antegren), off the market just three months after it was launched. Both companies hosted conference calls with reporters and analysts about the decision, and Biogen Idec CEO James Mullen was interviewed live on CNBC. In addition, FDA officials, neurologists who treat MS, patients, consumer groups, and media sources were interviewed. Following is a recap of the key take-aways from these sources.

The bottom line is that Tysabri is unlikely to return to the market soon, despite company predictions that it will. The companies insisted no additional clinical trials will be required, but that may be wishful thinking – and it is hard to imagine that, at a minimum, additional animal studies won't be required. Even if the drug does get back on the market, it is likely to get a black box warning, be restricted to rapidly-deteriorating interferon-failures, and/or have a time limit on use. Patients are still anxious for the drug and willing to take some risk, and neurologists also would like to see Tysabri available, but the regulatory hurdles appear high.

Agreement on the action taken

Both companies said they suspended supplies from commercial distribution and dosing of Tysabri in all clinical trials (MS, rheumatoid arthritis, and Crohn's Disease), based on one confirmed progressive multifocal leukoencephalopathy (PML) death and one suspected but not confirmed case of PML. Biogen Idec is the official biologic license application (BLA) holder of Tysabri in the U.S., and CEO Mullen said, "In light of these two cases, we believe it is prudent to take a step back and assess the risk of PML."

The patient who died had been on Tysabri plus Biogen Idec's Avonex (interferon beta-1a) for 38 months. Another patient suspected to have PML had been on combination therapy for 27 months.

Characterization of the withdrawal

Biogen Idec officials couched the Tysabri withdrawal as a "pause" or "step back." They emphasized that when it comes to safety, a signal is assumed to be related until proven otherwise.

Confusion over the role of the FDA in the withdrawal decision

Both companies claimed the decision to withdraw Tysabri was "voluntary," but they agreed the decision was made "in collaboration" and "consultation" with the FDA. They quite pointedly did not say that they had taken the action on their

own, as Merck did when it removed Vioxx (rofecoxib) from the market last year. The implication was that the decision was less voluntary than the companies implied, that the FDA let them do it as a voluntary withdrawal. Elan President and CEO Kelly Martin said, "I emphasize that our U.S. license has not been withdrawn and is still in existence." Another Elan official said "unequivocally" that he doesn't believe the FDA wants Tysabri ultimately removed from the market for good, "The FDA did not call up and mandate this, it was more collaborative."

The companies learned of the two patients about a week ago and notified the FDA within 24 hours. Elan's CEO said, "From notification of the first adverse event to the decision between Biogen Idec, us, and the FDA was a matter of days – four or five days in total…We learned of both adverse events within about 18 hours of each other. We and Biogen Idec spoke at length about both (cases) over the next several hours. Then, several hours later, we had a call with the FDA…So, within 24 hours of having the information from both adverse events, there were discussions with the FDA. Then, in subsequent days, we got more data on the adverse events and had more discussions with the FDA, to the point where there was a rapid and accelerating decision to get to the point where we announced this morning (February 28th)."

Tysabri was approved through the accelerated approval process after it showed a 66% reduction in relapses at one-year vs. placebo. In combination with Avonex, Tysabri cut relapses by 54% more than Avonex alone. Normally the FDA requires two-year data on MS drugs, and questions may be raised over the FDA's decision not to wait for two-year data on Tysabri. However, Dr. Karen Weiss, Director of the FDA's Office of Drug Evaluation (ODE) VI, CDER, said, "There was no signal of this potential problem in the pre-marketing database, including the safety update submitted to the BLA before approval. There was an extensive evaluation of the infections in particular to determine whether there were any opportunistic infections which could be a signal of a serious underlying problem with immunosuppression, and none were identified."

Little information on PML

PML was described as a rare, demyelinating disease that is frequently fatal. It is a disorder in which the insulating sheaths on nerves in the brain are damaged and affect conduction. Primarily, PML affects immunosuppressed patients (e.g., transplant patients, cancer patients undergoing extensive chemotherapy, and patients with advanced HIV/AIDS). PML is caused by activation of the JC virus (a polyomavirus), which is present but latent in ≥80% of people. Patients present with impaired cognition, difficulty thinking, cortical blindness, and/or hemiparesis (weakness on one side or the other of the body). An Elan official said, "More than 90% of patients with PML are AIDS patients." Another Elan official estimated that the prevalence in the general population is: 3 in a million, 5% of the HIV population, and <1% of people with hematologic malignancies. (For more information on PML see **www.ninds.nih.gov**)

No one really knows the typical latency to onset of PML. A Biogen Idec official explained, "Usually those patients don't get a screening MRI…It is diagnosed at the time the patient presents with clinical symptoms and is then followed up clinically…So, we don't know anything about latency."

There is an assay for the JC virus that can be done on cerebrospinal fluid (CSF) and tissue specimens, and there may be a PCR assay that can be done on circulating peripheral white cells. However, 80% of the population is sero-positive to the JC virus, so that assay is not informative about active infection. Asked if this is similar to uncommon but serious side effects seen with other immunosuppressive drugs, such as Amgen's Enbrel (etanercept) or Johnson & Johnson's Remicade (infliximab), a Biogen Idec official said, "In some of those drugs, there may be one or two odd cases reported. The issue is that organ transplant patients who may develop PML have undoubtedly been on multiple products, and we don't know ultimately how these cases are reported or put in the package insert. We are not aware of any immuno-suppressive or chemotherapy regimen that is uniquely associated with PML."

There is no antiviral therapy demonstrated to be active to treat PML. However, a Biogen Idec official held out some hope for delaying therapy, saying, "In the HIV literature some patients put on high dose antiretroviral therapy with rapid reconstitution of CD4+ T-cells appear – a good number appear – to be able to suppress the disease…There is indirect evidence that…those who contract PML and are put on a high dose antiretroviral…that up to 50% can have arrest of disease." An Elan official added, "There is evidence patients can recover, using the experience in late-stage HIV patients."

No known mechanism of action of Tysabri in PML

Mullen said, "We took this action to work through what are the possible implications, and what might be the mechanism…Right now, there is not a strong plausible hypothesis. We've not seen (PML) with Tysabri (monotherapy), but the experience with Tysabri is much shorter than that with Avonex." An Elan official said, "The factors leading to activation (of the JC virus) are not fully understood…Tysabri, if anything, affects the translocation of T-lymphocytes and is not seen as compromising the immune system…We actually see increased T-lymphocytes in the plasma of these patients …So, I don't think it will be as easy as seeing a signal in an MRI, and then going back and seeing to what extent that leads to changes in lymphocyte counts."

There apparently is some intersection between immune regulation and activation of the JC virus. A Biogen Idec official said, "This is a very, very rare disorder, and if the second case is truly PML…Then, one might say isn't there a signal with combination therapy and perhaps long-term

therapy? That is something we will examine…We need to tell what risk is in monotherapy and what the risk is in combination therapy…We have no evidence in humans or in animal studies that short-term or long-term treatment with Tysabri is associated with a decline in lymphocyte numbers or any real other signal of significant immune disregulation. We thought of this product as predominantly impacting transit across the microvasculature of immune cells bearing the receptor, rather than as a drug whose major mechanism of action was to alter immune cell activation or function…What I understand is that the brain does not have lymphatics…So, the only way for immune cells to gain access to the brain is through the microvasculature."

Asked whether the thinking that this is a problem of (a) Tysabri, (b) the combination of Tysabri and Avonex, or (c) the combinaton of Tysabri and any interferon, a senior FDA official said, "A very good question. We don't have enough information at this time to know the answer."

Disagreement on how sick the PML patients were/are

The two PML patients came from different geographic locations and were reported completely independently. Beyond that, the two companies paint different pictures of these patients.

A Biogen Idec official described the patients as: "Both with MS…both ***in good health***…and both had been treated for more than two years." He insisted the patients, to the best of their knowledge, did not have HIV/AIDS and were ELISA negative, adding, "Outside of having MS and being in a trial, there are no shared characteristics."

Elan officials suggested the PML patients were sicker and had concomitant medication use in common – steroids. One said, "I am not pointing specifically at the steroids…At this point we don't know the causality of these patients and PML… Identifying PML is not easy. It is a very difficult differential diagnosis, and you need several tools to confirm the diagnosis: a combination of MRI, morphology, and PCR confirmed CSF." An Elan official also claimed Biogen Idec officials had not said both the PML patients were in good health, only that they fulfilled the criteria to enter the study – but that is not what the Biogen Idec official clearly said.

Among the points Elan officials made about the PML patients were:

- "Patient No. 1 who died showed signs of deterioration six months prior to the adverse event being reported…This is…a complicated and rare condition…It is possible that without informing the neurologist specifically what to look for, that certain things could be misinterpreted. On Patient No. 2, the data and facts are inconclusive. Given the rarity of this disease and this virus, that is only a potential case. Case No. 2 may remain an inconclusive event."
- "Both were quite complicated patients on multiple therapies for multiple medical issues."
- "An inclusion factor (in the combination trial) was that patients be on Avonex and still breaking through from a relapse point of view, so patients were worsening on the product (Avonex)."
- "These patients had MS, had been on Avonex, were so-called 'partial failures,' had the disease for a number of years, and obviously met the diagnostic criteria for MS, or they wouldn't have been included. What we are saying is that is it difficult to speculate on whether it was combination therapy, whether the concurrent medications, or all of those things. We don't want to speculate until there is a total investigation. With one confirmed case and one possible case, there is limited data to work from."
- "These (two PML) patients were on a long list of medications, but they had one thing in common – very substantial doses of steroids. If you have PML or a virus infection, it is well documented that steroids should be handled with great caution."
- "I don't think you can draw the conclusion that Tysabri alone or Tysabri+Avonex was the cause of either adverse event, but because we can't rule it out, we took an extraordinary step to make sure we know more."

Asked about a pharmacokinetic (PK) interaction between Tysabri and Avonex that is mentioned in the labeling, a Biogen Idec official responded, "There are data on a potential interaction between these two. I don't think that interaction is clinically important with respect to a super-effect of Tysabri on patients. That is a PK observation, but I don't think we have any evidence it has any meaningful pharmacodynamic significance."

Extent of patients potentially affected

About 3,000 patients were treated in the MS, Crohn's, and RA trials, and another ~5,000 patients have started treatment since the drug was approved in November 2004. That means these patients prescribed Tysabri outside clinical trials have gotten one, two or, in a few cases, three infusions of Tysabri. Biogen Idec officials did not know how many of these patients are on combination therapy, but they cited Wall Street estimates that perhaps a third are on combination therapy.

To date, in the clinical trials, there are no reports of PML in MS patients receiving monotherapy or in Crohn's or RA patients. In addition, Biogen Idec has no reports of PML in patients treated with Avonex alone at any point in time.

- ~500 MS patients have been on monotherapy with Tysabri more than two years.
- ~500 MS patients have been on combination therapy with Tysabri+Avonex more than two years.

- >1,300 patients have been dosed with Tysabri, either monotherapy or combination therapy, for >2 years.
- ~75 Crohn's patients in an open label extension study have been receiving Tysabri for perhaps as long as two years.
- <100 patients have been on combination therapy for three years.

What happens next

According to the companies, the next steps are:

1. **Complete the investigation into the two patients in question.**
2. **Do an extensive review of the MRI scans of Tysabri-treated patients in the clinical trials,** to detect any early signals of PML. A Biogen Idec official said, "The good news with respect to MRIs…is our ability to re-examine them…All MRIs were read through two central labs, obtained through a standard technique, and electronically transferred to those two facilities, run by two of the foremost neuroradiologists in the world, so we will have an opportunity to review the data quickly."
3. **Get a physical exam and a new brain MRI of each MS clinical trial patient,** working with clinical investigators to evaluate the patients. The companies expect this to be done "expeditiously," and Elan thinks it could be complete in three to four months. A Biogen Idec official said, "It will not take us a long time to go back and re-evaluate all the people in clinical trials because we are well set up to do that." Asked how easy it is to identify PML by MRI, a Biogen Idec official said, "My understanding is that there are significantly different characteristics between PML lesions on MRI vs. MS lesions. In particular, in almost every instance, the PML lesions will not gadolinium enhance, whereas MS new lesions, in particular, invariably enhance with gadolinium. There are also important differences in the location of lesions, rate of progression, and the fact that they can be multifocal (with PML)." An Elan official said the physicals would be done in "the near future."
4. **Work with experts (in virus biology and immune regulation/disregulation) to understand PML and any link to Tysabri.** The companies are convening a panel of experts the first week of March 2005, and FDA officials plan to attend as well.
5. **Work with regulatory authorities.**
6. **Inform patients and doctors using Tysabri outside of clinical trials.** An Elan official said, "Patient outreach and patient education is extremely important to us."

Interestingly, the companies have no plans to do special exams or MRIs on the patients who got Tysabri outside of a clinical trial, whether as monotherapy or combination therapy with an interferon. A Biogen Idec official said, "It is not obvious all those patients need to get emergency MRIs…They have all had limited exposure, and probably in that setting, as long as the patient is feeling well and has no suspicious complaints, we would probably follow them and not recommend an MRI."

FDA advice to patients and doctors

- Discontinue Tysabri until further notice.
- Patients who were on Tysabri should discuss alternative treatments with their doctors.
- Any patient who has taken Tysabri and has symptoms that suggest PML should have a thorough evaluation. Doctors should report potential cases to Biogen Idec or FDA's MedWatch.
- Intensive discussions are underway with outside experts and a meeting with the experts, Biogen Idec, and FDA representatives, will take place the end of this week to discuss, among other scientific issues, what types of evaluations should be performed in the patients who were in the Tysabri clinical trials, whether there are risk factors and appropriate screening tests to try and minimize risks, etc.
- There will be further communications from Biogen Idec and FDA as information and/or new recommendations become available.

Will additional clinical trials be needed?

Both Biogen Idec and Elan officials are denying they are likely to have to do more clinical trials to return Tysabri to the market. On the conference call, Biogen Idec's Mullen suggested post-marketing surveillance might be required (a registry?): "Any time we see a safety signal, the starting assumption is it is associated until you can demonstrate it is not. With this and any product post-marketing surveillance continues forever and is always an evolving situation. This (PML) may well be a particular item we want to think about how to monitor in a post-marketing setting." Later, on CNBC he said, "If we see more signals of PML, that will guide us in one direction. If there are no additional signals, I don't think there will be extensive additional clinical trials, and I'm not sure additional trials would be all that useful because we don't know causality and there is a low frequency of events."

Emphasis on the benefits of Tysabri and the need to consider risk:benefit

Both companies pointed out repeatedly that there are strong efficacy benefits with Tysabri. A Biogen Idec official said, "We've been looking at a product with a very exciting efficacy profile, and the safety profile was also quite well understood until this one or two events. So, we are taking a step back to see if there is more out there or if we have seen

everything...We need to reassess the risk:benefit profile… Until a few days ago we thought we had a good understanding of the risk, so we could clearly inform patients about the risk:benefit, so they could make a decision on whether or not to take the drug. Now, we don't understand the risk…because we don't know the factors that lead to PML – if there is a risk …So, we believe that until we can tell physicians and patients to the best of our knowledge what the risk:benefit is, that you really can't sell it (Tysabri)."

The outlook for re-introducing Tysabri

Both companies believe Tysabri will be able to return to the market, but Biogen Idec officials appear to think it will take longer than Elan officials do. An Elan official said, "There have been no issues with monotherapy from an adverse event point of view…We have one-year and two-year data showing strong efficacy and safety for Tysabri monotherapy...I think it is very plausible that, in the absence of anything new, this product would easily be back on the market by fall."

On CNBC, Mullen said, "It is not the FDA's intention to remove (Tysabri) from the market or the FDA would have withdrawn the license. In terms of time lines, it is more speculative and we need to see how the information unfolds …If these are the only two cases, I think there is a way to bring it back, with appropriate warnings." An Elan official agreed, "I won't speak for the FDA…but it is not their intention to have this drug removed from the market…The intension is to 'pause'…It is important to remember that in autoimmune disease, most drugs have serious adverse events. The critical topic is how to manage, diagnose, and treat those – and to give guidance. Then, physicians can make balanced judgments on whether a therapy can be used. Look at the anti-TNFs. You see a string of CNS events, tumors, etc., and I think the fact that a drug has adverse events doesn't mean you can't use the drug. You have to understand what it means… There clearly remains a significant, very high, unmet medical need in the MS space…The data on Tysabri in MS suggest it is exceptionally strong from an efficacy point of view…We want to either eliminate or completely understand (the safety challenge), so we can advise the neurological community how to proceed."

Both companies insisted that they will be able to quickly review patient safety in the clinical trials, but Biogen Idec officials suggested the time frame for any re-introduction of Tysabri may be longer than Elan was suggesting, which was fall 2005. A Biogen Idec official said, "What we find there will guide our actions going forward. If we find little there, we'll see…It won't take us that long to evaluate the situation …but it may take some time to evaluate the path forward because we have to work with regulators."

An FDA official was asked whether, if the PML is proven to be a problem with the combination of Tysabri and Avonex and/or other interferons, it is possible that Tysabri could eventually come back with a black box warning against combination therapy. The response, "That is a possibility."

Is there any acceptable level of PML in this patient population? On the conference call Mullen said, "Certainly, in general, this is not something you want to put people at risk for…but MS is a serious disease, and some patients die of acute MS exacerbations. So, the fundamental issue is to have a clear understanding of the risk:benefit so patients and physicians can choose these therapies. Currently, patients are treated with Imuran (GlaxoSmithKline, azathioprine), mitoxantrone (OSI Pharmaceuticals' Novantrone, which is potentially very toxic), etc…So, some potentially very toxic agents are being used to treat these patients." On CNBC he said, "It is premature to say it is not possible to bring it back. Even if the association is confirmed with PML, we will learn more about how to detect the disease and who is at risk, and there may be a way to go forward with appropriate warnings."

Tysabri for MS in Europe and Tysabri for Crohn's Disease in the U.S. are now both on hold

A Biogen Idec official said, "At the least, it will delay them….We are in close communication with the EMEA, and surely they will want to see the additional data we collect before deciding how to move forward with the package insert…It will be a few weeks before we can begin to understand if they want things different from the FDA or if we have one plan everyone can work with."

What this means for Avonex

Both companies insisted that there has been no signal of any PML risk in Avonex monotherapy patients despite nine years of marketing (Avonex was launched in the U.S. in 1996). A Biogen Idec official said, "We have extensively re-analyzed our safety data on Avonex since 1996 and before looking for any possibility that a case potentially of PML was entered into the database and not appreciated, and we found no evidence of that…We understand the FDA also looked across some of their databases."

The status of Tysabri in Crohn's, RA, and MS combination therapy trials

The trials were stopped, but the companies suggested they may ***not*** have to be started all over again. The MS trial was within a month of completion, so a Biogen Idec official said they may have an adequate database. Elan, which is managing the Crohn's and RA trials, said, the Crohn's trial was three-quarters completed, and there will be a statistical analysis over the next couple of weeks to see how much power is in the trial with the reduced completion, but he insisted the trial would not have to be re-done. Rather, he suggested they might only "have to recruit the number of patients we lost to complete the trial." However, is there a precedent for allowing a company

to stop a trial and then only have to re-do the missing number of patients?

In RA, about half the patients were recruited, and that is a longer trial than Crohn's (six-months). An Elan official said this is a more complicated situation, "To say the RA study is invalidated is not correct. We will see how many patients we have and how many completed."

How the companies will manage patient/doctor concerns

Biogen Idec's Mullen said, "I know the news will cause anxiety in the MS community…but we still believe this is the best step. We have put patient safety as our first and only consideration." Among the steps the company is taking are:

- As a first step, Biogen Idec immediately sent a Dear Health Care Provider (DHCP) letter to every prescribing neurologist in the U.S., informing them of the company's action, along with "preliminary guidance" on what to do with patients. Doctors were asked to evaluate patients with signs and symptoms of PML and immediately report any potential case to Biogen Idec at 1-888-489-7227 or to the FDA's MedWatch at 1-800-FDA-1088.
- Doctors were told they will be notified "regarding the procedure for returning unused product."
- The company also sent a similar Dear Investigator letter to all the physicians with patients in Tysabri trials.
- The Tysabri sales force will be working with doctors and patients to "work through" this "shock wave."

No layoffs planned at either company – yet

For now, the companies plan to re-direct their sales forces to Tysabri outreach and other products.

EARLY PHYSICIAN REACTION

Doctors interviewed were distressed at the news that Tysabri has been pulled from the market, but they appear to have gotten the message and think the companies did the correct thing in withdrawing Tysabri until more is known. Comments included:

- *Washington D.C. neurologist:* "The company has been quite responsive in voluntarily determining that they should tell doctors to stop dosing the drug until further notice, with the idea that, once we learn more about what's happening, a decision can be made as to whether this drug is something that can be reasonably used in some or all people with MS in the future, or whether there are ways to determine if there are certain people who are at higher risk than others for developing some sort of complication."
- *Neurologist:* "It's not entirely clear (whether the issue is Tysabri or a combination of Tysabri and Avonex). As best I know, PML has not occurred in Tysabri alone, and it may well be that it would be a strong FDA recommendation not to use the drug in combination with anything else. Obviously, it's all going to come out. I think people are going to think twice about it. Right now, we're not going to do anything until we get more information."
- *Philadelphia neurologist:* "It's very distressing that this has occurred." Another doctor said, "This is a very demoralizing blow for MS. The two cases of PML among 1,000 people are very bothersome. The data looked wonderful, and this is a significant potential complication. The reaction is to stop use of the drug until they can look at the data with regard to potential causal links and other factors. You have to ask the questions: Is there a true link? Is it related to how long the drug is used? Is it related to combined use of the drug? This is completely sufficient to stop use of the drug…The first thing, however, is that everyone is coming off the drug, and that's the obvious thing to do."

Doctors are informing their patients about the withdrawal and talking with them about what to do next. One doctor said he will put his patients back on what they were taking before they went on Tysabri. A hospital-based neurologist said, "Patients have to have a discussion with their neurologists, number one. They also have to keep in mind that there are several different options for treatment of MS. This isn't a situation where Tysabri was the only treatment. There are several approved and well-used, respected treatments available. We are notifying our patients and telling them what's known thus far. The drug has been temporarily halted, and at this point in time, for most of our MS patients, we're reassessing their treatment and making recommendations…The good news is that there are several other excellent treatments available." Another physician said, "We're clearly taking patients off Tysabri and holding the doses of Tysabri at the moment. What we decide with every patient is very individual, and a lot depends on how they were doing on other drugs before going onto Tysabri."

Several doctors said they have had problems getting insurance to pay for Tysabri, so they didn't have to stop a great number of patients. A California hospital neurologist said, "We've had a lot of problems getting the infusion center financed and set up because of insurance. We'll just probably have to stop everyone who's on it and have no new patients go on it."

Concern with Tysabri does not appear to be negatively impacting the opinion of the interferons. A Philadelphia neurologist said, "There's nothing wrong with interferons. If there were something wrong with Avonex, it would have happened many times over with Betaseron (Schering AG/Berlex, interferon beta-1b) or Rebif (Ares Serono, recombinant human beta interferon)…If anything, they'd be even more immunosuppressive, and I'm not aware of any documented case of PML occurring with interferons…It's

probably got something to do with the combination of the immune-modifying defense of both compounds together, and that would probably be an issue with all interferons (in combination with Tysabri). As far as Copaxone (Teva Pharmaceuticals, copolymer-1) is concerned, there is a small safety study of 100 people – I don't know how long they've been in that study – comparing the combination of Copaxone and Tysabri with the combination of Avonex and Tysabri. I think that there is some potential risk to using that as a combination as well because they obviously modify the immune system. Right now, I think it's not really clear where we should be going other than that we shouldn't be using Tysabri until we get a little more information." Another doctor said, "I don't think there are any data that interferons are at issue here. They've been used for a long time."

Physicians are concerned about PML. The head of a hospital neurology department said, "PML is basically a death sentence. It's a relatively rare disease. Even if they investigate the patients carefully and find that both are HIV positive or there's an explanation, PML is something that typically occurs in pretty significantly immune-compromised individuals, so that's why this is peculiar. We didn't know of any risk of infection with Tysabri. This is an unusual infection and not something that I would have expected." A California neurologist said, "PML has been reported in immunosuppressive conditions. It's more frequent in patients who receive immunotherapies for transplantations, lymphomas, Hodgkin's disease, and, sometimes, spontaneously for no reason. The company has certainly been worried about long-lasting immunosuppressive effects…This could be a manifestation of the immunosuppression for Tysabri…The incidence of spontaneous PML has to be really uncommon, so the fact that they didn't see it in the 300-600 patients in the original study doesn't necessarily mean anything. When they go to post-marketing, and they have several hundred thousand people exposed to the drug, you may see a blip in the incidence of PML, so I don't think we have enough data, and I'm not sure they'll be able to find out."

A doctor suggested there may be some good in the news. He said, "Another way to look at it is: Are they unmasking, with the treatment, the primary cause of MS? The JC polyomavirus specifically infects (certain) cells and produces myelins. So maybe, at least in some people suffering from MS, the JC polyomavirus could be causing the demyelinization, and that could be a clue as to cause (of MS)."

The same doctor also speculated that companies marketing monoclonal antibodies might be in trouble as well, saying, "Any time you jigger the immune response, something's going to happen. It's particularly enticing that it's only in the combination that we've seen it yet. Beta interferon certainly has immune response modification potential, so maybe it's the combination that's the critical step. Whatever it is, it's going to take a while to find out."

Another neurologist said she would be shocked if the Tysabri patients were diagnosed with PML six months ago. She said, "This is such a striking neurological disease I don't think it takes that long to diagnose. Initially, you'd have enough difference that it would be hard to be believed. I don't know the cases at all, but you can do spinal fluid and PCR for the JV virus if you have a suggestive patient or a patient who is going downhill rapidly. There are many ways to make the diagnosis."

Asked about Elan suggesting steroids might be involved, a neurologist said, "Steroids would have to be looked at, but all the patients who have MS use steroids. This is very peculiar and comes out of the blue and makes you wonder."

Doctors were split on whether they think Tysabri could go back on the market. One neurologist who treats >1,500 MS patients said, "I think it's quite possible the FDA would allow it to be used on its own. We have a trial with people on monotherapy, and we have not seen any cases of PML, so it suggests that it's due to the combination rather than just the agent itself. Having said that, that's about as speculative as anybody is going to get right now…PML occurs in very many different immune conditions…This is not a unique Tysabri occurrence. To me, it seems to be a major concern with regard to the combination rather than just Tysabri alone." Another neurologist said, "I think there's a chance Tysabri may come back. If you could identify a group of patients, for example, who would be at little or no risk, or if the PML investigation committee identifies a subset of people who wouldn't be at risk, that would be one scenario…As experts look at the data they will try to determine if there is any way to identify people who are high risk versus low risk of having a side effect, and, if they're successful at doing that, that would be one of the ways it might make its way back into our treatment armamentarium." The head of another hospital neurology department disagreed, saying, "I don't think it will come back in the fall. There are too many questions that have to be answered, and that's going to take some time."

One neurologist came down hard on the FDA, saying the Tysabri recall "gives the FDA another black eye." He added, "This is very peculiar, and it makes you wonder about the FDA. The FDA set a precedent and gave (accelerated) approval to Tysabri on one-year treatment, when all they had to do was wait a few more months for the two-year data. The FDA broke precedent at a time when we had all these problems with Vioxx and Cox-2 inhibitors. Why did they break that precedent? We would have known about this before it got to widespread use. The causal exposure may mean nothing, but it's almost like it's coming back to bite them. I don't know of any other precedent of a brand new agent for MS being approved on one-year (data)." However, another neurologist defended the FDA's decision to put Tysabri on a fast track. He said, "There were two-year data from the European study. I don't think the FDA made a mistake in fast-tracking. MS is a devastating disease, and we don't treat it nearly as well as we'd like to be able to. The

efficacy and safety data we had looked very good, and I think the decision the FDA made at the time was appropriate. You have to remember the FDA has a caveat in that approval of is based on continued monitoring for efficacy and for safety, so the FDA and the investigators were on the same page. You can't absolutely be sure about a drug until you monitor it over the long term. That's why these long-term safety extension studies are always set up to continue to follow patients who are on the drug long-term."

Media and Public Reaction

The questions were (1) how the media would play this story, and (2) whether they would blame the FDA for lack of oversight. So far, this is being played as more of a financial story than anything else. CNBC repeatedly discussed the story, but another network's radio news simply reported highlights from the conference call.

So far, there has been no negative fallout for the FDA on this, but that may change over the next few days as the press looks at the implications. A lot of which depends on whether any consumer groups or Congress take up the issue – but it is too early to predict this. However, FDA Vioxx whistleblower Dr. David Graham said he was unaware of the withdrawal and was not following this issue. Dr. Sidney Wolfe of Public Citizen has not spoken out on the issue or called for a permanent ban on Tysabri.

Patient Reaction

Patients on Tysabri, whether alone or in combination, are shocked, confused, upset, and worried. Among patients comments were:

- "I was waiting to call and see if I got approval yet (for Tysabri)…I was looking so forward to starting it. How sad, but it leaves me confused to know what to do."
- "I guess I'd rather the drug company be extra-cautious at this point."
- "I applaud Biogen and Elan for acting with apparent swiftness in suspending sales so that they can hopefully determine what happened in the two cases mentioned. It's a shame that so many people were either taking or planning to take Tysabri and have now had the rug pulled out from under them, at least temporarily. It makes me wonder if fast-tracking a drug for FDA approval is worth it…Would this potential complication have occurred and been investigated before the release of the drug if it hadn't been fast-tracked for approval and marketing?"
- "I am absolutely in shock. I have felt so good on this new drug. I was scheduled for (infusion) number three this week. I don't know what I'm going to do. I faxed the article to my doctor with a big NOW WHAT on it. Guess it's back to Betaseron for me or trying something else. I just don't know."
- "I'm a long-timer with MS and have seen so many things come, go, and come back again. This is a blip, a BIG one because deaths were involved. Time and lots of investigation will tell if Tysabri can be added to our arsenal."
- "I had so much hope pinned on Tysabri that I'm having a lot of trouble changing my direction. I do believe that I'll give Tysabri a shot when they've determined that it is safe to do so. My instincts tell me that it isn't purely coincidental that both patients were on the combination therapy."

Several patients said they would go back on Tysabri if it returns to the market, saying they were pleased with their results so far. However, they said they wouldn't take it in combination with another drug.

- "I think I will go back on Tysabri when it is back on the market. I wasn't taking it in combination. I wouldn't want to take two drugs anyway. Those cases are probably pretty isolated, so I am not giving up hope. A new drug has to start somewhere, and there can be horrible side effects with any drug. Just pull up the warnings on any drug. You would never take anything if you worried about everything that could happen. I hope this does not deter any advancements in the area of MS."
- "I was taking Copaxone, but switched to Tysabri several months ago. So far I've felt really great on Tysabri. This news comes as a total shocker to me. I love Tysabri and don't want to give it up for anything…If it goes back on the market, I'm first in line."
- "I will go back on Tysabri the minute that I can. My second infusion dose is awaiting me at the neurologist's office…I am extremely upset about this, to say the least."

So far, there does not appear to be any patient demand for MRIs and physicals similar to what is being offered to patients in the Tysabri trials. However, one neurologist, when told of the companies' plan to give MRIs only to patients who had been in the combination trials, said, "I think patients who are on combination and who are not in the trials will probably ask for MRIs. There is already a lot of discussion about the indications for 'routine' or 'follow-up' MRIs. How often will you do them? Every three months? Six months? A year? What change will mandate changing your therapeutic intervention?"

The Litigation Outlook

It is too early to tell how much the personal injury lawyers will latch onto Tysabri – and the potential litigation liability for Biogen Idec and Elan. However, Tysabri has caught the attention of some lawyers, and they are already advertising for Tysabri patients on the Internet. Others are considering their marketing strategy.

♦