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Quick Pulse

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TWO NEW PML CASES WITH TYSABRI LIKELY TO DECREASE TYSABRI USE SLIGHTLY

Biogen Idec and Elan disclosed on July 31, 2008, that two multiple sclerosis (MS) patients in Europe taking Tysabri (natalizumab) were diagnosed with confirmed cases of progressive multifocal leukoencephalopathy (PML). These are the first new PML cases since Tysabri was reintroduced in the U.S. and launched in Europe in 2006. Both patients are still alive, one in the hospital and the other at home. The patients are in two different European countries, but Biogen Idec officials would not identify which countries, citing patient confidentiality reasons.

In a conference call, Biogen Idec officials emphasized that they have been educating doctors to be alert for the signs and symptoms of PML. Dr. Cecil Pickett, president of R&D for Biogen Idec, said, "The heightened vigilance around Tysabri and the efforts to educate physicians were critical in identifying these two patients and to ensure that the necessary steps were taken. Tysabri remains an important therapeutic option for patients. It has established a new level of efficacy for MS therapies, and we believe its risk management profile continues to be favorable, offering hope to many patients suffering from MS." Dr. Carmen Bozic, vice president of drug safety at Biogen Idec, said, "We feel very comfortable that doctors are looking out for PML and that if they suspect it, they are working up their patients appropriately…I'm very confident that, as of today, these are the only confirmed cases we have."

An FDA official commented that "the cases were submitted to the Agency by the company, and the FDA is reviewing the data and is in discussions with the sponsor."

Tysabri was pulled from the U.S. market in February 2005, only a few months after the FDA approved it, because two patients developed PML, a usually deadly disorder. A third case of PML was later reported in a Crohn's disease patient. Two of the patients died. In March 2006 an FDA advisory committee recommended that Tysabri be allowed to return to the market under a strict – and mandatory – risk management program (RiskMAP), named TOUCH, and in June 2006 the FDA agreed. The FDA approved use of Tysabri as ***monotherapy*** for ***adult*** relapsing-remitting MS patients who have not responded adequately to, or cannot tolerate, other MS treatments.

As of the end of June 2008, nearly 32,000 patients were on Tysabri worldwide: 13,900 of these had been on it more than 12 months, and 6,600 had been on it more than 18 months. Officials have not said how many patients have been on it for 2 years. The percentage of Tysabri patients who have never taken another disease-modifying drug was said to be "still in the single digits."

On July 24, 2008 – just a week before the new PML cases were announced – Biogen Idec released its quarterly earnings report and held a conference call with analysts. No mention of the PML cases was made at that time. Company officials said that was because they had not yet been informed of the ***confirmed*** cases. However, they declined to provide any details on what they know about patients reported to have ***suspected*** PML or about patients getting plasmapheresis. And an official did admit that one of the PML patients had gotten plasmapheresis in July 2008, presumably before the earnings announcement.

The PML Patients

Biogen Idec officials also would not discuss the clinical prognosis for the two new PML patients, but Alfred Sandrock PhD, senior vice president of neurology R&D at Biogen Idec offered a few details on each of the cases:

- ***Patient #1 – remains clinically stable and ambulatory at home.*** On July 30, 2008, Biogen Idec received confirmation of PML in this patient. The diagnosis was made on JC virus (JCV) DNA in the cerebrospinal fluid (CSF) in a setting of clinical signs and symptoms and a clinical diagnosis of PML. The patient has not returned to baseline status; he continues to have the left upper extremity weakness and twitching, but those neurological deficits were described as "stable."

Dr. Sandrock said the patient was diagnosed in late 2006 with aggressive MS, "The patient was naïve to disease-modifying therapies. He received Tysabri for ~17 months and responded well to Tysabri. Focal twitching and weakness of the left upper extremities developed over a period of 2.5 months… There were no cognitive symptoms. Clinical vigilance led to early identification of possible PML…and a workup included CSF and MRI testing…JCV DNA was ***not*** detected in the cerebrospinal fluid at that time. Given the continuing clinical suspicion, plasma exchange was initiated, and Tysabri was discontinued. Five plasma exchanges were performed over 10 days."

However a second CSF sample sent to the National Institutes of Health (NIH) did test positive for JCV, though with low copy numbers. Dr. Sandrock said, "The diagnosis (of PML) was based on this. This was reported to the company on July 30th. HIV testing was negative as far as we know…The patient is ambulatory, has been an outpatient throughout the entire workup, and remains an outpatient." He added that a noted PML expert, Dr. Eugene Major of NIH, concurred with the PML diagnosis.

- ***Patient #2 – remains hospitalized and clinically stable.*** On July 31, 2008, Biogen Idec was notified of a diagnosis of PML in this second European patient who was receiving Tysabri in the post-marketing setting. The diagnosis was based on JCV in the CSF in a setting of clinical signs and symptoms consistent with PML. The patient is currently in an open ward in a hospital.

Dr. Sandrock said, "The patient was diagnosed in 1992 with relapsing-remitting MS. He received approximately 10 years of azathioprine along with intervals of beta-interferon. He had received Tysabri monotherapy for ~14 months. Left hemiparesis was treated with steroids for presumed MS relapse… The symptoms increased, leading to hospitalization…Enhancing white lesions not appropriate for MS (were seen on MRI)…JCV was determined (in CSF) by two labs and repeated a week later."

The Implications of These PML Cases

Biogen Idec officials would not say how many suspected PML patients there have been or how many patients have been through part of the diagnostic workup for PML but do not yet meet the criteria for a confirmed case of PML. Dr. Bozic said, "Doctors are encouraged to report suspected cases, but none of them have turned into confirmed cases except these two…We don't comment on specific numbers reported to us." Another official said, "We have no comment on the number of suspected cases…What we've seen in these two cases is clinical vigilance led to rapid identification…These cases were identified early based on clinical vigilance, and the diagnostic workup included MRI and CSF testing for JCV, which is what we've been educating physicians about."

There has been concern that development of PML may be related to extended (perhaps two years or longer) exposure to Tysabri. Since the U.S. reintroduction of Tysabri has just reached the two year mark, Biogen Idec officials were asked if more patients are expected to present with PML symptoms in the next few months. Dr. Sandrock said, "No comment on that…Every patient in the U.S., before starting Tysabri, is made aware of the risk of PML, and they sign something that they understand that risk, so every patient is aware of that risk, and clinical vigilance is certainly working, as we've seen in these two cases." Dr. Pickett added, "As we've said in the past, we expect to see cases of PML."

Biogen Idec officials insisted that the risk management programs in the U.S. and Europe are similar, though not identical. Dr. Bozic said, "Both have a risk management plan …In Europe, it is mostly based on clinical vigilance. In Europe, it is clearly working because both patients were diagnosed by physicians based on new signs and symptoms and appropriately tested by MRI and CSF." Another official said, "In the U.S., there is also intensive education on heightened vigilance for PML, and if a physician is concerned, he should stop the drug and evaluate the patient by MRI and CSF…Both programs have that in common."

PML Patient #1 required more than one CSF test for JCV DNA. Asked if that means some PML cases may be missed in the first CSF check, a Biogen Idec official said, "There is no serial testing in TOUCH…We educate physicians that if there is a clinical suspicion, then MRI and CSF testing is highly recommended. If the clinical suspicion remains, even if there is a negative lumbar puncture, we recommend a second

lumbar puncture…That is what we tell physicians, and that is exactly what happened in this case."

Dr. Sandrock said the companies recommend that Tysabri use be suspended if there is a clinical suspicion of PML until a workup is done. Dr. Bozic added, "In both (these) cases, the doctors stopped the drug as soon as they were concerned with PML, which is consistent with our teaching."

Asked what can be done when someone has PML and how successful plasma exchange (plasmapheresis) is, Dr. Sandrock replied, "In both cases…the use of plasma exchange appears to be working. That removes Tysabri from the serum. And we showed at the American Academy of Neurology (AAN) in the spring that it restores the migration of leukocytes through the extracellular matrix." Dr. Bozic said, "Doctors do perform plasma exchange when they suspect PML even without confirmation by CSF…Some physicians thought it was the right thing to do for suspected PML." Dr. Michael Panzara, chief medical officer of Biogen Idec, added, "The methodology of plasma exchange is really at the discretion of the treating physician. We don't require that they initiate the procedure. When they ask us for information, we provide them with the methodology that has been used and presented at AAN…How they treat the patient is left to their discretion."

Asked if there have been other opportunistic infections of the brain in Tysabri patients, Dr. Bozic said, "In the U.S. label, we do have one case of herpes encephalitis and one case of herpes meningitis…Other than that, that's it…The herpes can occur in the general population."

Asked about the FDA's reaction to the new cases, Dr. Bozic would say only, "We reported these cases to all relevant regulatory authorities, including the FDA. It is premature to speculate on label changes…We can say that the (PML) rate is well within what is in the label (1 in 1,000)."

Asked if the company is suggesting that PML is treatable, Dr. Sandrock said, "We have not ever said that CSF results are prognostic. They are certainly helpful in diagnosis, but it is difficult to say if they are prognostic…We've highlighted the risk of PML. We have not said it is treatable. Our label says that it is potentially fatal. We are just reporting the facts of these cases."

Asked what Biogen Idec is doing to communicate with the patient and physician community, an official said, "We have four additional calls planned…And our medical science liaison team throughout Europe and the U.S. have been fully updated, and they will go talk to their physicians. We have a patient services line that is prepared to deal with the calls we may get. We have updated our website. We are using all the channels we normally use to educate physicians and patients about any of our drugs." Dr. Bozic added, "Our commercial goal is to reach all 3,000 prescribers in the U.S., and a similar effort is underway in Europe."

Asked what feedback the company is getting from neurologists about the PML cases, Dr. Sandrock said, "The first thing I heard was that they were grateful we called, talked to them, and shared the cases, and that they were notified in a timely fashion. They pointed out to me that there is no drug that carries no risk, and it is always a benefit:risk analysis…Those were the two themes in my conversations."

PHYSICIAN REACTION

Six physicians were interviewed after the Biogen Idec announcement. None of them was surprised by the PML cases, but they indicated some physicians and patients may have become complacent about the PML risk, and these cases are a reminder that the risk of a potentially fatal side effect is real. They predicted that some Tysabri patients – but not significant numbers – are likely to stop taking the drug.

The initial reaction to the news was disappointment:

- **Dr. Syed Rizvi**, a neurologist with the Neurology Foundation in Providence RI, called the PML news "discouraging" but said, "This is not a total surprise. Most of us were expecting more cases of PML."
- **Dr. Jerry Wolinsky** of the University of Texas Health Science Center at Houston Medical School said that these cases were "unfortunate," adding, "I would have been delighted if we never had another case of PML, but that would have been unlikely. That would have made me more comfortable about using the drug in those settings where patients need something more than what they are on because they're not very good responders."
- **Dr. Brian Silver** of Michigan said that he hasn't prescribed Tysabri for any of his MS patients yet and now he may not start, "I am aware of some others in my practice who have (prescribed it)…I would be very hesitant about prescribing the medication given these reports."
- **Dr. Frederick Munschauer** – a neurologist at the State University of New York at Buffalo School of Medicine, chief of the Jacobs Neurological Institute, and a board member of the National MS Society – said that the PML news was not unexpected, "This was not a surprise. We are disappointed that it happened, but it was not an unexpected finding. We were hoping that we would never see (PML) again, but we now can say that the risk is somewhere around one in 3,000, whereas up to now we've been telling our patients that the risk was one in 1,000…I think that we will increase our vigilance."
- **Dr. Hillel Panitch**, a Vermont neurologist, said that he has about 20 patients on Tysabri for second- or third-line therapy because they did not respond to, or did not tolerate, at least one and usually two of the other MS drugs, "The two new (PML) cases were not unexpected and do not change the estimate we have been using of one case of PML per 1,000 treated patients."

- **Dr. Richard Ransohoff**, director of the Center for Neuroinflammation Research at the Cleveland Clinic, said, "I was keeping an open mind. I think that you have to pay attention to the fact that the people who got PML in the clinical trial were also on interferon, but there have been no cases of PML in the MS literature…until Tysabri came along. I was hoping for the best and prepared for the worst. I don't think we know anything for sure except that monotherapy can be associated with PML. That is the real new information. There is a strong impression so far that susceptibility or the occurrence of disease is somehow related to time of exposure. There have been no cases with less than 12 months (of exposure), so that's something to look at."

What do the new PML cases mean for use of Tysabri in existing patients or for starting new patients on Tysabri?

- Dr. Rizvi said, "Obviously, all of these patients have accepted the risk of PML. They all know the possibility, and I would predict that some of them would want to continue, and some of them, given the additional information, will want to come off it and try other drugs…If we start seeing more and more (PML), that will be a fairly negative thing for most of these patients. But I would predict that patients already on it who feel good on it and whose disease is stable might want to continue."

- Dr. Wolinsky said that the news will affect his hospital "some, but perhaps not as much as some other centers." He explained, "The reason is that we've been very cautious and very discriminating in our use of Tysabri up until now, and at the moment there are certain aspects in terms of the risk that are perhaps a little bit better defined…When something's rare, it's hard to say it's well-defined, but these two cases will give us a little bit more caution for patients…but not a lot. I think that's because of the way we generally worried about the potential problems with this drug to begin with. We have somewhere around 2,500 patients that I and my colleagues follow actively, and we have about 40 patients on the drug. So, it's not a really large cohort of patients, and that's basically because we all took the point of view that the earlier developed drugs, where we had a better safety protocol, for most people are the right first choice until they start to fail that, and we reserve Tysabri until they've shown that they need something more."

Dr. Wolinsky said he is planning to get his whole group together to discuss the situation, "We all have to come to a consensus on this and begin contacting the patients on Tysabri to let them know what our position is, given the news...I'd rather try to contact them before it's disseminated out…What we're discussing is not a whole lot different than what we considered (at the beginning), but the majority of patients who needed something different are on Tysabri because it made a difference for them. And then there's a group of patients who pushed us hard to put them on it because of the perception that this was a substantially better drug, and for those, if we're not sure that it made a difference, then the discussions will be longer and in a different direction, so that they fully understand that this is not a risk that was only associated with concomitant use of Tysabri with Avonex (Biogen Idec's beta-interferon) – that it certainly can happen in others…If the second case is what I think it was – a patient who was neither on combined therapy nor who had seen important immuno-suppressive drugs in the past – that means that anyone is at risk for this who is on this particular drug."

- Dr. Munschauer said that he won't take patients off Tysabri unless they want to be off the drug, and he hopes the news won't persuade other doctors and patients to stop using Tysabri, "My concern is that you'll throw the baby out with the bathwater. The most important thing is treating MS but doing so in a way that you've done an appropriate balancing of the risks of the disease compared to the risk of the treatment …The only way you can really evaluate this new information is to view it through the lens of the underlying disease you're trying to treat, and for those patients who have failed the first line of therapy, those are the people where you take a little bit more risk. You ask if the risk is appropriate for the severity of the disease." He suggested that PML may, in fact, be "a very treatable disease in this setting. It is so different because we can get rid of the drug."

- Dr. Panitch said, "I plan to continue using it conservatively, as I have before."

- Dr. Ransohoff said the news "is going to change my life in a lot of ways because for people that I contemplated putting on Tysabri, I now have to think about it six or seven more times. I also have to re-evaluate the people I have on it. Until the other shoe falls, you don't know what to do…The things that we need to know now are: What is the real risk on a year-by-year basis? Maybe it's zero during the first year, maybe 1 in 5,000 or 10,000 during the second year. We certainly need to know if it goes up, down, or doesn't change in subsequent years. We need to know what the real-world efficacy is. And we need to know whether PML, in the context of Tysabri or other similar drugs, with plasma exchange to bring about immune reconstitution, is going to be manageable."

Asked if there may be a risk of MS progression if a patient goes off of Tysabri, Dr. Ransohoff said, "There are data showing that if a person gets just a few infusions of Tysabri, a small number like two to four, and then stops, there may be a liability for rebound. There are also data suggesting that a typical longer treatment of a year or so is not associated with risk of rebound."

The Role of Plasmapheresis

While Biogen Idec officials indicated that some doctors are doing plasmapheresis on patients with suspected PML, none of the U.S. doctors interviewed would do it unless the PML was confirmed. Dr. Munschauer said, "PML is caused by the JC virus, and normally our immune system keeps it suppressed. If the white blood cells are coated with an antibody (Tysabri), they may not suppress the infection of the brain

with the JC virus. The potential antidote for Tysabri is to get rid of those antibodies, and you do that by plasmapheresis. If we thought a patient had suspicion of PML, you have to get rid of the drug, and the only way to do that is plasmapheresis – throw it away. Therefore, we restore the body's own native immunity quickly, which is already pre-programmed to attack the JC virus…We have more than 250 patients on Tysabri, which is a lot, and we haven't seen anything resembling PML in any of those patients for the past five years. It would take 10 to 15 centers our size to see one patient. The only PML cases since the reintroduction are in Europe. To the best of my knowledge, there is ***not even a suspicion*** of any patient in the U.S. having PML. I would be floored if any patient got plasma exchange because that would only be done after PML is confirmed."

Dr. Rizvi pointed out that plasmapheresis is not just for Tysabri, "We do plasmapheresis for other reasons. Typically, a patient taking Tysabri who starts developing cognitive problems – that would be a red flag (for PML). If they start developing relapses which don't get better, and they don't respond to steroids, that's not a good sign. You can do an MRI and a lot of times the MRI can help diagnose PML. Confirmation is typically from a spinal tap. You would do plasmapheresis if you did a confirmation for PML."

Dr. Wolinksy said, "That (plasmapheresis) makes no sense to me. I know they did a study. I know how quickly they can get the antibody down with plasma exchange, and once you have PML, you can get the antibody out a little faster. But if the data from Dr. (Olaf) Stuve at Southwestern (University of Texas Southwestern Medical Center in Dallas) is correct, once you have significant exposure to the drug – when you have re-established fairly typical immune surveillance – is probably, at least for cytoxic T-cells, the most important thing in containing the JC virus. The notion that maybe you can use it (Tysabri) for only 12 months or 14 months or 16 months (may not be correct). I'm not sure why PML activates in these patients, but my suspicion is that it's activating randomly, unless there is something about Tysabri that activates it. But when it activates in you or me, we contain it, and it doesn't activate (into PML). But when you're immunocompromised, you can't contain it as well, so the other events may not happen. It may not matter if it's 14 or 17 doses, it may be the luck of the draw. Are you on this drug when you happen to activate? We won't know about what cumulative incidence might be with exposures to the drug – which might be in excess of what we've seen so far. More experience is going to be necessary. So, I'd love to know that this drug could be used increasingly – as perhaps it has at some centers, but now we understand that the estimates that were made for what the range of incidence of PML could be – from the original trial articles – it ain't on the low side. It could be on the high side, and it could be in the middle."

Dr. Panitch added, "I have not needed to do plasmapheresis in any patient because none of them has developed PML or other complications that require immediate lowering of the drug level. There has been a small study of pheresis, and it seems to be effective in removing the drug from circulation, and perhaps in permitting cells to regain their ability to enter the CNS (central nervous system). However, the effect on PML is unknown."

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