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by Lynne Peterson

Quick Pulse

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Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA Advisory Panel Recommends Restricted Approval of Tysabri for Crohn's Disease

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The FDA's Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee recommended approval of Biogen Idec/Elan Pharmaceuticals' Tysabri (natalizumab), a multiple sclerosis drug, for moderate-to-severe Crohn's disease (CD), an inflammatory bowel disorder. The panel voted 12-3, with two abstentions. Two committee members left before the final vote. The panel said that Tysabri's use should be limited to patients for whom other therapies have failed, and it also said that Biogen Idec and Elan must implement strict post-marketing surveillance to monitor for possible deadly side effects.

The 20-member panel (with 19 voting members) included: four gastroenterologists, two neurologists, two epidemiologists, two pharmacologists, a toxicologist, an infectious disease specialist, a biostatistician, a family practice doctor, a patient advocate, a consumer advocate, an industry representative, and three other experts.

The panel generally concluded that:

- Tysabri's benefits for patients with CD outweigh the risks for patients with moderately to severely active CD with inflammation.
- Tysabri should be restricted to patients who have failed all other available therapies, including steroids and anti-TNF agents.
- The risk management program should be very strong, perhaps even stronger than the one the companies proposed.
- There should be more post-marketing randomized clinical trials (RCTs), in addition to the already planned registry.

The FDA offered its take on the joint panel's actions:

- The committee approved Tysabri for patients with moderate-to-severe Crohn's disease with very strict post-marketing surveillance.
- The committee required a strict risk management program for Tysabri, for the FDA to put clearly defined endpoints to protect patients, and to remove it from the market if needed.

FDA officials said that they would take the panel information and discuss it internally and with Biogen and Elan. Dr. Joyce Korvick, deputy director of the FDA's Division of Gastrointestinal Drug Products, CDER, said, "We heard loud and clear from the advisory committee to expand it (Tysabri) in a very restricted population – and that a very effective risk management program needed to be

developed." Dr. Gerald Dal Pan, director of the Office of Surveillance and Epidemiology, added, "That is the basic message…We need to look at the proposed CD-TOUCH program and see how to modify it, to see what needs to be changed."

The FDA action date (the PDUFA date) is in October. Beyond saying that, FDA officials would not indicate how quickly they are likely to act on the panel recommendations.

The proposed label for Tysabri in CD is:

> *Tysabri is indicated for* ***inducing and maintaining*** *sustained response and remission, and* ***eliminating corticosteroid use*** *in patients with moderately to severely active Crohn's disease with inflammation as evidenced by* ***elevated CRP level or another objective marker****…Because Tysabri increases the risk of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability, Tysabri is* ***generally recommended for patients who have had an inadequate response to or are unable to tolerate, conventional Crohn's disease therapies.***

The panel vote came even after a critical FDA staff report questioned Tysabri's effectiveness for treating the disease. The report said that Tysabri "isn't distinguished" from current Crohn's disease treatments. FDA staff members also expressed concern that patients taking the drug could develop a rare and deadly nervous system disease. The drug, which was originally approved for multiple sclerosis (MS), was pulled in February 2005, after only a few months on the market, because two patients developed a usually deadly disorder called progressive multifocal leukoencephalopathy (PML). A third case was later reported. 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 risk management program (RiskMAP), and in June 2006 the FDA agreed, and ~11,500 U.S. patients have taken Tysabri for MS since then. In December 2006, Biogen submitted Tysabri to the FDA for the treatment of Crohn's disease. Two months ago, European regulators rejected the use of Tysabri for CD.

Background on Crohn's Disease

In the U.S. and Canada, more than 630,000 people have Crohn's disease, with 10,000-47,000 new cases diagnosed each year. CD is an inflammatory bowel disease (IBD) that involves chronic inflammation of all layers of the bowel and may affect any segment of the GI tract, but most commonly the small intestine and colon. Symptoms include diarrhea, abdominal pain, weight loss, fever, and rectal bleeding. Morbidity can be high, and some patients have chronic poor health due to active bowel inflammation, fistulas, or other disease-related events.

CD is a waxing and waning disease, but it is a lifelong, debilitating disease.

- Median time to the most common complication, strictures, is five years.
- Median time to fistulas or abscesses is eight years.
- Median age of onset is 30, with peak age of onset 15-25 years, so patients will often have the disease for 30-50 years.
- 70%-90% of patients will undergo surgery within 20 years, many getting two or three CD surgeries in their lifetime.

Treatment guidelines call for patients to be treated step-wise, generally starting with an aminosalicylate (5-ASA), then progression in order to: oral steroids, an immunosuppressant, and/or a biologic (anti-TNF). Surgery is used to treat complications such as bowel obstructions or abscesses or to control the patient's symptoms when medical therapy fails.

Dr. William Sandborn, a gastroenterologist at the Mayo Clinic speaking on behalf of Elan, explained, "We are still very much in the step-up progressive strategy. The clinical trials to investigate a top-down approach are just beginning…so we are a number of years away from changing our treatment paradigm in CD…There is a big unmet need in CD. About 30% of patients won't respond to anti-TNFs, and some responders eventually lose response. We need new treatments with a different mechanism of action that will treat some fraction of those patients."

Dr. Sandborn argued that Tysabri is both safe and effective in CD. He said, "I think there is robust evidence of efficacy for both induction and maintenance with Tysabri…We have an advantage over neurologists in the way we will practice with this drug. With neurology, you are waiting for patients to relapse, and it will take a year or so to see if patients are benefiting from Tysabri. In CD, patients will get infusions at Week 0, Week 4, and Week 8, and by 12 weeks, if they are not improved, you will stop the drug. So, it is a short-time to see if you have responders…Also, the absolute response rate approaches 60%...Those who don't respond, go off the drug, so that is a real advantage for this patient population to help tip the scales in favor of Tysabri in CD."

Tysabri Efficacy in CD

Dr. Sandborn pointed to two CD patients he recently saw who could benefit from Tysabri:

- A 22-year-old woman diagnosed at age 16 with CD who has already had one surgery and is now facing another resection. She has osteoporosis, is a non-responder to a TNF, and got pancreatitis from azathioprine. He said, "She needs some other therapy."

- A 59-year-old woman who "has been through everything," with only 80 cm of small bowel left – and that is now inflamed. Dr. Sandborn said, "If Tysabri is not approved, her next stop is a small bowel transplant, and we are preparing for that."

Stephen Jones, director of clinical development at Elan, summarized the efficacy of Tysabri for CD:

➢ **Induction:**

- Demonstrated response and remission in patients with objective markers of inflammation.
- Demonstrated efficacy in patients who failed therapy with corticosteroids, immunosuppressants, and who failed therapy with TNF inhibitors.

➢ **Maintenance:**

- Demonstrated sustained response and remission.
- Significant improvement in quality of life that was maintained.
- Significant steroid sparing.
- Concomitant immunosuppressants not required to maintain long-term efficacy.

Dr. Anil Rajpal, a medical officer in the FDA's Division of Gastroenterology Products, also reviewed the efficacy of Tysabri in CD.

Induction. He said that for induction therapy, the clinical response treatment effects "are relatively modest" – 8%-16%. For clinical remissions, he said, "None of the effects was particularly large" – 7%-12%. A retrospective analysis in one study of patients with elevated CRP found a treatment effect of 12.8%, but there was no confirmation in the other induction that elevated CRP predicts response.

The FDA also found no CD subgroup in which there is a particular benefit with Tysabri. Dr. Rajpal said, "The treatment effect in each subgroup was generally similar to the overall effect. We could not find any subgroup with substantially increased or reduced efficacy." The subgroups examined were:

- Baseline CDAI.
- Prior meds.
- Inadequate response to prior medications.
- Concomitant medications.

Tysabri Development Program in CD

Measurement	Trial #1	Trial #2	Trial #3
Phase II			
Study	Study CD201	Study CD202	None
Type	Pilot	Induction	---
Phase III			
Study	Study CD301 ENACT-1	Study CD303 ENACT-2	Study CD307 ENCORE
Number of patients	905	428	509
Type	Induction	Maintenance	Induction
Primary outcome	Not effective	Effective	Effective
Efficacy in patients with elevated CRP	Effective in post hoc analysis	Effective	Effective in primary analysis
Efficacy in patients who failed other CD therapies	Effective in post hoc analysis	N/A	Effective in primary analysis
Patients who failed prior anti-TNFs	N/A	N/A	Significant benefit

FDA View of Efficacy of Tysabri in CD *(by ITT)*

Measurement	Tysabri	Placebo	p-value
ENACT-1 – Study CD301 (induction) Results at Week 10			
Number of patients	724	181	---
Primary endpoint: Clinical response (CDAI reduction ≥70 from baseline)	56.4%	48.6%	Nss, 0.051
Clinical remission (CDAI ≤150)	36.9%	30.4%	Nss, 0.124
Clinical response in **patients on immunosuppressants** at baseline *(post hoc analysis)*	61.9%	45.3%	0.027
Clinical response in **patients with elevated CRP** *(post hoc analysis)*	57.6%	44.8%	0.007
Clinical remission in **patients with elevated CRP** *(post hoc analysis)*	39.5%	27.6%	0.014
Clinical response in patients with **elevated CRP *and* on immunosuppressants** at baseline *(post hoc analysis)*	62.0%	36.8%	0.005
ENCORE – Study CD307 (induction in patients with elevated CRP) Results at both Week 8 and Week 12			
Number of patients	259	250	---
Primary endpoint: Clinical response	47.9%	32.4%	<.001
Clinical remission	26.3%	16.0%	0.002
Clinical response in patients who had taken prior anti-TNF agents	37.4%	21.2%	0.007
ENACT-2 – Study CD303 (maintenance in CD301 responders) Results at Month 9			
Number of patients	168	170	--
Primary endpoint: Clinical response	61.3%	28.2%	<.001
Patients in clinical remission at Month 3 who maintained clinical remission	43.8%	25.8%	0.003
Patients **with elevated CRP** who had clinical response at Month 3 and maintained it *(post hoc analysis)*	46.9%	24.5%	0.002
Patients **with elevated CRP** in clinical remission at Month 3 who maintained it *(post hoc analysis)*	60.5%	25.8%	<.001
Patients taking steroids able to be withdrawn from steroids and maintain remission	44.8%	22.4%	0.014

Maintenance: Dr. Rajpal said the maintenance findings were consistent with the induction findings, with a treatment effect of 33%. However, the subset of patients with elevated CRP at baseline had a similar response. He said this questions whether elevated CRP should be a criteria for use of Tysabri in CD.

SAFETY IN CD

The FDA considered the safety data on Tysabri in MS as well as all the CD data, finding: "Conclusions regarding safety concerns have not changed." The four safety concerns raised were:

1. PML. No new cases of PML have been reported. FDA officials expressed concern that cases of PML, which often present with neurological signs and symptoms, might be less readily identified by gastroenterologists than neurologists. However, they acknowledged that the background rate of neurological signs and symptoms would be considerably less in a CD patient than in an MS patient, allowing for easier detection of PML cases in CD patients. Dr. Margo Smith, an infectious disease expert from the Washington Hospital Center, gave an overview of PML. She said that there are no tests for screening or monitoring PML and no real treatment. She said, "In HIV and AIDS, highly active antiviral treatment is a mixed bag…It is a 50/50 response; 50% of people stabilize – and I emphasize stabilize; the disease does not go away – and 50% rapidly progress." Survival with PML in AIDS is measured in weeks to months and in non-AIDS patients it is measured in months to one year.

Dr. Smith posed several unanswered questions about PML:

- Does prior immune suppression really increase the risk?
- If so, does the length of time of immunosuppression increase the risk?
- Is there a role in monitoring antigen-specific CD-8 cells?
- Is a risk of 1:1000 reasonable?

There have been no new cases of PML reported since Tysabri was re-introduced for MS in June 2006. The biggest safety concern with Tysabri is PML, a rare disorder associated with progressive demyelination of the central nervous system (CNS), caused by JC virus infection, and typically only seen in patients that are immunocompromised. It generally causes a progressive neurological decline – dementia and progressive motor deterioration – and is usually fatal within six months of diagnosis. There is no accepted method for early detection and currently no adequate treatment. So far, there have been three cases of PML with Tysabri – two in MS patients and one in a CD patient. Elan's senior vice president, Dr. David Feigal, said, "We don't know if PML is a random event for any patient who gets any amount of drug or whether it is a cumulative (issue). The number of cases so far are too few to comment on that."

Adverse Events with Tysabri

Measurement	Tysabri	Placebo
Serious adverse events (SAEs)		
Any SAE	14.9%	14.0%
Any SAE with monotherapy	8.6%	8.4%
Malignancies	0.6%	0.2%
SAE in patients on concomitant immunosuppressants	13.7%	6.7%
SAE in patients with concomitant steroids	15.9%	15.6%
SAE in patients with immunosuppressants and steroids	23.5%	25.7%
GI SAE	9.8%	9.9%
CD	5.9%	8.7%
Serious infections and infestations	2.4%	2.4%
Herpes infections	1.7%	1.2%
Perianal abscess	0.6%	0.6%
Viral meningitis	0.2%	0
Adverse events		
Any adverse event	87.4%	85.6%
Infections	1.67 per person-year	1.45 per person-year
Any infection	40.4%	36.2%
Upper respiratory tract infection	26.6%	21.5%
Pneumonia	0.3%	0.2%
Lower respiratory tract infection	3.1%	3.4%

The PML patient in CD was a 60-year-old man who got Tysabri for three months, then placebo for nine months, and then Tysabri for another five months. He died and was diagnosed with astrocytoma. PML was determined on a retrospective pathology review. Analysis of banked samples showed that serum JC virus samples were positive two months before his death. The man had intermittent signs of deficient hematopoiesis for approximately six years, and he was on azathioprine (75-150 mg/day) for >4 years but had discontinued it eight months before his death. He also had taken Johnson & Johnson's Remicade (infliximab) in the past, but not for at least 20 months before his death.

Dr. Sandborn insisted that Tysabri is safe in CD. He said, "If not for PML, we would be looking for a label like that for an anti-TNF…For us, I think the PML issue tips it a bit…I would look at this (Tysabri) for patients who fail azathioprine or an anti-TNF…That is where the real unmet need is…For me, that is where the benefit outweighs the risk."

Can gastroenterologists handle treating CD patients with Tysabri, given the PML risk? Dr. Sandborn thinks so. He said, "We were first trained as internists…We've dealt with organ transplantation. And in GI training, we get liver transplantation training…We also have nine years of experience with infliximab, and we are used to dealing with opportunistic infections and assembling multidisciplinary teams…We can pull together the teams and successfully treat patients…As a specialty we need this drug, our patients need this drug… There is an important unmet need, and I think we can handle the safety with the TOUCH program."

2. Infections other than PML, including herpes infections, lower respiratory tract infections (especially atypical pathogens), and viral meningitides. Pneumonia was the most common serious infection reported for patients who received Tysabri in the post-marketing setting (0.11% of patients), but none of these were due to atypical organisms. FDA reviewers concluded that Tysabri appears to be "associated with an increased incidence of atypical and serious infections; these included viral meningitis, herpes infections, and atypical pulmonary and gastrointestinal infections."

The FDA reviewers reported 14 deaths in Tysabri-treated patients: 6 in MS studies, 6 in CD trials, and 2 in rheumatoid arthritis (RA) studies. Five of the Tysabri deaths were due to infections. A reviewer said, "Potential safety signals raised by a review of deaths in the natalizumab development program and in the post-marketing setting are for ***infections*** and ***mood disorders***."

Stephen Jones, Elan's director of clinical development, responded, "There are no data to suggest there is an increasing risk of infection with more infusions over time." The companies are recommending ***against*** concomitant medication use with Tysabri, but Jones said they looked at the safety of Tysabri during concomitant therapy since during the first three months of Tysabri use other medications may not be fully washed out of a patient's system.

Dr. Gordon Francis, senior vice president of clinical development at Elan, said there is a slight (1%-2%) increase in the rate of serious infections vs. monotherapy, "So, physicians need to be aware there is a potential for an increase in serious infections, but this is with concomitant therapy, not wash out therapy." He also admitted there is a slightly higher rate of herpes infections with Tysabri (1.7% vs. 1.2%), but he said the majority of that was "driven by herpes simplex…and the finding was similar in the MS population." The rate of opportunistic infections was 0.6 per 1,000 patient-years (PYs), which compares to a rate of 0.3%-0.5% for conventional therapies or TNF inhibitors.

3. Hypersensitivity reactions. FDA reviewers noted that Tysabri is associated with an increased risk for hypersensitivity reactions in both MS and CD trials, most often during or immediately after the second infusion.

An Elan official explained that hypersensitivity reactions are more common in patients previously dosed with Tysabri than in patients naïve to Tysabri therapy, and he said the company is making a change in the Tysabri label for MS to highlight this. Elan's Dr. Francis said hypersensitivity reactions occurred in 3.5% of CD patients in the two induction studies, generally on the second or third infusions, "This is quite comparable to what was seen in MS (4%) and not unexpected in an IV infusion of a biologic therapy. Serious systemic hypersensitivity reactions were quite infrequent – 0.1% – in both short-term and long-term studies."

4. Carcinogenicity. While the FDA found no clear increase in risk, overall malignancies were higher with Tysabri than placebo in CD (but not in MS), and the reviewers noted that longer-term follow-up data are needed on this issue. A reviewer said the one case of metastatic melanoma may not be related to Tysabri but, given the mechanism of action of Tysabri, raises a concern.

New Liver Safety Issue

No liver injury "signal" was identified in the clinical trials of Tysabri, either in MS or CD, but the FDA has noticed some spontaneous reports of Tysabri-associated liver injury. An official said, "At this point the FDA has not reached any conclusions, and the issue is under further evaluation."

- 28 cases were reported between November 2004 and June 22, 2007.
- 4 of these were potentially serious hepatocellular injury (3 in the U.S.).
- 24 of these were reports of "mild liver abnormalities" (e.g., increased liver enzymes or increased LFTs).
- No deaths or liver transplants.

Risk Management

The companies' proposed PML risk management plan for Tysabri for CD, CD-TOUCH, is essentially the same as the original TOUCH program for MS, with a few minor differences:

- Patients on steroids at initiation of Tysabri are to taper those steroids after response to Tysabri. If they are not tapered off by six months, Tysabri must be stopped.
- Use must be discontinued if there is no response to Tysabri by three months.
- Specific education materials will be prepared for CD.

Dr. William Maier, senior director of epidemiology at Elan, said, "We expect it (Tysabri) to be prescribed by gastroenterologists who specialize in CD and who are familiar with serious complications, including CNS demyelination. Our education plan will build on this practice pattern. Gastroenterologists should have no expectation of having a role in PML, so they should routinely refer patients (with any symptoms) to specialty physicians for further evaluation."

Elan's Dr. Feigal said, "Patients on corticosteroids can't stop those abruptly, but what we've seen is that responses (to Tysabri) can occur within four weeks, and our TOUCH and education program will recommend that as soon as a patient achieves a Tysabri response, steroid tapering should begin immediately, so it could begin as early as four weeks…In one study, 70% of patients were off steroids at eight weeks…One would hope that physicians would try to get patients off steroids as quickly as possible." Another Elan official said, "We do not want this drug used in combination with immuno-

suppressants or steroids…We don't want combination use to happen. Of course, we recognize you can't stop steroids abruptly, and that is the reason for the initial taper period for six months."

Elan and Biogen also plan a risk assessment observational cohort study in CD similar to the one being conducted in MS (Tigris). The CD study would voluntarily enroll 4,000 patients and follow them for five years. The study would be powered to detect rare events with a rate of 0.2 per 1,000 PYs, collecting all serious adverse events. An Elan official said that the observational study in MS didn't get started until this year, and only about 800 patients are enrolled so far.

Claudia Karwoski, a PharmD and Risk Management Team Leader in the FDA's Office of Surveillance and Epidemiology (OSE), said the Tysabri RiskMAP, MS-TOUCH, has been working well, "At this time the Tysabri RiskMAP appears to be satisfactorily working in the MS population. There has been good compliance with RiskMAP processes by prescribers and infusion site staff. The surveys of prescribers and nurses indicate a high level of understanding of the risks and requirements of the RiskMAP. To date, there have been no reports of PML or other serious opportunistic infections reported to the Agency since the reintroduction of Tysabri into the marketplace (clinical trials and in the post-marketing setting)."

FDA and Elan officials offered some statistics on the commercial experience with Tysabri in MS:

- 16,900 patients worldwide, including 13,745 U.S. patients, have been exposed to Tysabri.
- 8,313 TOUCH patients have been infused with Tysabri (71% women):
  - 6,245 infused for the first time.
  - 38,898 total infusions given.
  - A median of 4 infusions per patient.
- The median duration of patient exposure to the drug is 3.8 months.
- ~2,100 patients have received Tysabri continuously for ≥6 months, but none has taken Tysabri for more than 12 months continuously.
- Overall, more women have been treated with Tysabri than men, at a ratio of ~2.4:1.
- ~3% of Tysabri use is among patients aged ≥65.
- As of the end of the third reporting period, 1,405 prescribers have registered with the program, and 1,124 of these have prescribed Tysabri to at least one patient.
- 1,504 infusion sites have been trained and authorized, and 808 of these have administered Tysabri to at least one patient.
- 584 central pharmacies have been trained and authorized to dispense Tysabri to authorized infusion sites.

Karwoski cited several special considerations in CD:

- The appropriate patient and how these patients would be identified in clinical practice.
- The best way to monitor the CD population for PML.
- Whether concomitant immunosuppressive and immunomodulatory therapy will be permitted.
- Whether the concurrent use of chronic steroids for six months is acceptable.
- How flares of CD will be treated.

Risk:Benefit Profile

Tysabri's original approval for MS was based on what an FDA reviewer termed "an unprecedented treatment effect" in MS patients, which "appeared to be considerably greater than that of existing MS therapies." PML changed the risk:benefit profile of the drug, but the FDA determined that the benefit still outweighed the risk, though only as monotherapy, and allowed Tysabri back on the market.

Elan's Dr. Francis argued that there is a favorable risk:benefit profile for Tysabri in CD. FDA reviewers contended that risk:benefit in the CD population is considerably different from that in MS, "The treatment effect in the CD population (13%-16% in induction, 33%-35% in maintenance) was not as high as that in the MS population…nor is it clearly distinguished from approved CD therapies…(And) CD patients are more likely to be on chronic immunosuppressant and/or steroid therapy than MS patients…There remains the concern that the risk of infections and of PML might be higher with concomitant therapies."

Public Speakers

Four gastroenterologists who treat patients with CD urged the panel to recommend approval of Tysabri for Crohn's disease. Their comments included:

- "There is an unmet need in CD for an agent that can benefit this population…There are 125,000-250,000 CD patients in the U.S. and North America who might benefit from agents such as this."
- "It is my opinion that strong consideration has to be given to the wishes of patients themselves…Patients are willing to take a surprising amount of risk."
- "These patients are willing to take risks…Patients are willing to gamble 20% of their life to achieve remission and a normal quality of life."
- "Where do I see this falling in our armamentarium? I see this for patients with persistent moderate-to-severe symptoms with confirmed active inflammation (either elevated CRP or lesions on endoscopy) who are not responders to conventional drugs and anti-TNF biologics

…The prescribers are most likely to be experienced gastroenterologists and tertiary centers with the ability to pursue active safety/efficacy monitoring."

- "I don't think this (Tysabri) will entail a radically different skill set (for gastroenterologists)."
- "I have very little doubt that when presented with a side effect of death (with Tysabri), that we will get their attention and that they will understand what that risk is."

Patients and patient advocates urging approval of Tysabri included:

- A 29-year-old woman who has had CD since age 7. She did well on Tysabri but required surgery when Tysabri was withdrawn from the market. She said, "If you bring Tysabri back on market, are the risks severe? Yes…Risk can never be eliminated; it can only be managed. And we deserve the right to assume that risk in exchange for the benefits we can get…Would I take Tysabri if it came back on the market? Probably not right now…but I have to think about the rest of my life. And there may be a time when the risks of Tysabri are worth it. What I fear most is going through my therapeutic options one at a time until there is nothing more to do but cut out my intestine, a piece at a time."
- An official of the Foundation for Research in IBD said, "Patients who received Tysabri were thrilled with the results and heartbroken when it was withdrawn…I am relieved the FDA has agreed to revisit its release."

PANEL DISCUSSION

The panel chair, Dr. David Sacher, director emeritus of Mt. Sinai School of Medicine's division of gastroenterology, set the tone for the panel discussion, suggesting that the panel would vote to approve Tysabri for CD. He said that there were essentially four issues for the panel:

1. **How great is the need for Tysabri?** The panel chair said there is a need for another drug "because only about 30% of CD patients have what we as gastroenterologists and patients would consider satisfactory."
2. **What percentage of people who might need it will benefit?** The chair said that patients "who are refractory to everything else ***or*** those who are responsive only to steroids and cyclosporine – that is, only to drugs that can't be maintained at high doses for long term. It looks like about 50%-60% of patients with a therapeutic delta of about 10%-12%. And we have to decide if that is a real benefit."
3. **What factors will help identify patients most likely to benefit?** The chair said that they should have some manifestation of active inflammation.
4. **Is the benefit clinically significant in terms of disease control and quality of life vs. statistically significant (just a p-value)?** The panel chair said, "Yes, I think we heard from patients and practicing doctors, and we have seen quantitative quality of life data and objective risk acceptance data…that I think would suggest the benefits we are talking about transcend simple p-values."

These were Dr. Sacher's own opinions, and initially, at least, he did not encourage discussion. He announced what he thought, apparently thinking that the panel members would simply and quietly go along with him. However, Dr. Judith Kramer, an internist and associate professor at Duke University Medical Center, boldly spoke up and challenged him, asking, "Can we express our opinion, not just hear yours?" After the exchange, Dr. Sacher allowed panel members who didn't agree with him to have their say, though he still seemed to be bullying the panel a bit.

Dr. Kramer was the most outspoken critic. She said, "I take issue (with the statement) that we have clear evidence of efficacy. My reading of the data is that there is a single study for induction. The first study failed…There does not appear to be any evidence that the sponsor went back to the drawing board after withdrawal (of Tysabri from the market) to see how to change its development program to address the population they requested approval for (in CD)…We don't actually have a population that they want for their label that has been studied…There is a single trial that is statistically significant …but 30% of those patients were also on immunosuppressants concomitantly…They randomized all-comers."

Instead of recommending approval of Tysabri for CD, Dr. Kramer suggested the drug be made available under a compassionate use program until and unless there are more data proving the efficacy. Dr. Margo Smith of Washington Hospital Center also thought approval should be delayed, but she was more concerned with obtaining more safety, not efficacy, data before approval.

Arthur Levin MPH, director of the Center for Medical Consumers in New York, said he found Dr. Kramer's arguments persuasive, agreeing, "There may be other ways for patients in dire need of this drug to get it (other than full FDA approval)."

Before the panel voted on the FDA's formal questions, each panel member was given an opportunity to bring up areas of concern. Among their concerns were:

- *The consumer representative* – was concerned with the vagueness of the proposed labeling.
- *Ruth Day, PhD, director of the medical cognition lab at Duke* – wanted more time to discuss risk management. She didn't really get it.
- *A pharmacist* – was concerned whether the MS-TOUCH risk management plan needed more modifications than were being proposed for CD-TOUCH.

- *A neurologist* – wanted to know more about patient selection.
- *Dr. Richard Platt, an epidemiologist from Harvard Medical School* – wanted to see written guidelines for patient selection.
- *Dr. James Couch, a neurologist at the University of Oklahoma Health Sciences Center* – wanted to know more about risk management training for infusion center personnel.
- *Timothy Lesar, PharmD* – wanted to know more about how well MS-TOUCH has been implemented.
- *James Neaton, PhD, a biostatistician from the University of Minnesota School of Public Health* – thought long-term safety issues needed to be more reliably monitored.

FDA Questions for the Panel

After a long day of FDA and Elan presentations as well as the public witnesses, panel members were a little rushed in their discussion of the long list of specific questions the FDA had posed. However, by combining some and eliminating one, they were able to convey their thinking and opinions. And a formal vote was taken on the key issue: Should Tysabri be approved for Crohn's disease? The answer was yes – but with strict conditions.

Question 1 – CRP. Do the available data support the efficacy of Tysabri in patients with moderately to severely active CD with inflammation, as evidenced by elevated CRP level or another objective marker: (a) For the induction of sustained response and remission? (b) For the maintenance of sustained response and remission? (c) In eliminating corticosteroid use? (d) Is elected CRP level a logical or clinically meaningful restriction?

By a vote of 15 Yes to 3 No, the panel agreed elevated CRP – but not just elevated CRP – should be a criteria for Tysabri use. *(One member left before this informal vote.)*

Panel member comments included:

- *Panel chair:* "I would be reluctant to restrict (Tysabri) only to patients with elevated CRP because there are so many other clinical markers available for active inflammation, including endoscopy imaging, MRI, radionucleotide techniques, fecal markers, etc."
- *Dr. Robert Levine, a toxicologist at NYU's School of Medicine:* "I don't think we should stick with CRP completely, but it was a good estimate…I think we (gastroenterologists) have enough clinical judgment."
- *Elan's Dr. Feigal:* "We are not trying to say CRP is a predictor of treatment response…but patients without elevated CRP probably don't have as much inflammation and probably should not be exposed to the risk of the drug."
- *Elan's expert, Dr. Sandborn:* "If it took elevated CRP to get the drug to patients, I could accept it, but it is probably not the best thing."

Question 2a – Efficacy. Do the available data support the efficacy of Tysabri (in Crohn's disease)?

The panel agreed by a vote of 16 to 1 that Tysabri has shown at least *modest* efficacy in CD for induction.
(Two members left before this informal vote.)

Panel member comments included:

- *Dr. Pankaj Jay Pasricha, a gastroenterologist from the University of Texas Medical Branch, Galveston:* He estimated that the number needed to treat (NNT) with Tysabri is 6-7 and compared this to 2-3 for Remicade, but the chair pointed out that physicians might be willing to accept a higher NNT in patients unresponsive to other medications.
- *Dr. Lin Chang, a gastroenterologist and co-director of the Center for Neurovisceral Sciences and Women's Health in Los Angeles:* "I personally believe it looks efficacious…Overall, it probably has efficacy, but it is not definitive at all."
- *Dr. Day:* "I think there is some demonstrated efficacy."
- *Dr. Carol Lee Koski, a retired professor of neurology from Pennsylvania:* "There is some evidence of efficacy …(but) I am concerned about what the label will say."
- *Jacqueline Gardner, PhD, an epidemiologist from the University of Washington:* "Based on the data presented, I would say efficacy has been shown, but clearly there is more work needed to be done in conjunction with the Agency."
- *Dr. Platt:* "I'm persuaded that there is efficacy in some people…The potential risk for long-term therapy is the greatest unknown, so I hope we come to quite restricted availability until there are more data on use beyond 18 months…The notion of 1:1000 risk doesn't really apply …We don't know that the risk is greater, but it could be much greater…I would put much more restrictive language (in the label) than the agency put out…Until there is sub-stantially more data, especially on long-term exposure, it makes sense to be restrictive."

Question 2b – Subgroups. Is there a subset of the CD population in which the increased risk of PML in patients taking Tysabri might be acceptable – e.g., inadequate responders, patients with a specific level of disease severity, other disease characteristics? Have any subgroups been adequately described and studied in clinical studies? Is the currently available exploratory subgroup analysis sufficient?

Other than elevated CRP, no specific subgroup was identified that might respond better.

QUESTION 3 – Maintenance therapy. Are there sufficient data to support maintenance therapy for CD with monotherapy vs. combined treatment with corticosteroids and/or immunosuppressants?

Most of the panel said efficacy looks better for maintenance than for induction, but a few felt there wasn't sufficient monotherapy data.

Panel member comments included:

- *Dr. Levine:* "For maintenance, the data are strongest but modest. I don't think the induction data are good, but the maintenance (effect) is good."
- *Panel chair:* "The maintenance data to me looked even stronger than the induction data."

QUESTION 4 – Risks. What risks associated with the use of Tysabri in CD are important for a risk:benefit assessment (e.g., PML, hypersensitivity, infection, malignancy, other)? How might these risks be impacted by current CD treatment strategies for induction and maintenance (e.g., 'step-up,' 'top-down,' steroid sparing)?

Opportunistic infections, malignancy, liver toxicity, and long-term safety.

Panel member comments included:

- *Sean Hennessey, PharmD, an epidemiologist from the University of Pennsylvania School of Medicine:* "I would restrict (the label) further than even the sponsor is proposing."
- *Dr. Alexander Krist, family practitioner from Fairfax, VA:* "I think we need to allow this drug out there for the indicated populations with strong caveats and a risk management program."
- *Dr. Neaton:* "I think we need more controlled data not just observational data…I want a randomized controlled trial."
- *Dr. Smith:* "You simply don't know what will happen in the long-term. The intent is to use this drug for years. We are now seeing secondary malignancies at a higher rate in HIV patients even after anti-viral therapy. There is a higher rate of lung cancer, lymphoproliferative diseases, etc. This is something that has to be heavily weighed, and right now we don't have the data." The chair then asked, "Your vote is that the risk is so high you would rather not let the drug out there yet?" Dr. Smith said that was correct.
- *Consumer advocate Levin:* "This is no blockbuster…We won't know about safety, so I am on the fence…but for the sake of having a drug with a new mechanism that possibly may work in some patients, I might go forward."
- *Elan's Dr. Feigal:* "The label has to be discussed with the FDA after further evaluation of the hepatotoxicity… and cancer also is not in the current label."

QUESTION 5 – Additional studies. Considering the currently available data, and taking into account the preceding discussion of specific populations, proposed use, and anticipated risk, **are there additional efficacy or safety data (studies) that should be obtained *prior* to approval of Tysabri for Crohn's disease?**

Some panel members wanted more pre-approval studies, but most wanted more post-approval studies only.

Panel member comments included:

- *Dr. Smith:* "I want more RCTs first. It is safety, not efficacy that I want studied. I want to follow current patients longer and study a new group."
- *Dr. Kramer:* "I am arguing that the responsible thing is to study this longer and make it available through a treatment IND and a compassionate use program."
- *Dr. Chang:* "I'd like more data on liver toxicity."
- *Dr. Platt:* I'd say that before widening the indications, a full randomized clinical trial should be conducted."

QUESTION 6 – Concomitant medications. Commonly used therapies for CD include corticosteroids, immunosuppressants, and/or biological agents (e.g., TNF-α blockers). **If Tysabri were to be approved for CD, should treatment with Tysabri be prohibited based on duration of prior use and/or total doses of these therapies?** What should the washout period be for prior use? For each therapy, what should the period of concomitant use of steroids be? Is 6 months for steroid tapering acceptable? What should the maximum period of concomitant steroid use be for CD flares? Do you recommend use of any other concomitant therapy besides steroids for CD flares (e.g., immunosuppressants or anti-TNF agents)?

Concomitant therapy should be minimal was the consensus, but the panel never got to a formal discussion of this question or its sub-parts.

QUESTION 7 – Patient monitoring. If Tysabri were to be approved for CD, **what specific requirements, if any, would you recommend for CD patients, either upon initiation of Tysabri or for ongoing monitoring** – MRI of the brain, general physical exam, full neurological exam (by a neurologist), brief physical function questionnaire, cognitive testing, JC virus assay in serum and/or cerebrospinal fluid."

The panel agreed strict labeling is necessary, and some thought patients should get a neurological exam before taking Tysabri.

Panel comments included:

- *Dr. Levine, gastroenterologist:* "I'd be as restrictive as possible…so they can't slip patients in outside the restrictions."

- *Dr. Pasricha*, *gastroenterologist:* "Why not test patient urine for JC virus and eliminate those patients?"
- *Dr. Platt*, *epidemiologist:* "It should be: individuals who are not adequately controlled on ***all*** available classes of therapy…and that includes not satisfactorily controlled on chronic steroid therapy." He said patients also should have to fail a TNF inhibitor first.
- *Hennessey, epidemiologist:* "The right thing is to make the drug available clinically on a restricted basis and to do the best studies we can to characterize it."
- *Dr. Koski*, *neurologist:* "If you are going to put these patients into a program with the potential for opportunistic infections that may be very subtle in presentation, then at least you should have a baseline neurological exam."
- *Dr. Smith*, *infectious disease specialist:* "An MRI simply won't help. It is expensive, and it doesn't given any information, but a good physician exam and a neurological examination would be helpful."

QUESTION 8 – Approval. Based on currently available efficacy and safety data, **should Tysabri be approved for the treatment of Crohn's disease**, assuming that an effective risk management plan is in place? Specify for which CD patient population Tysabri should be indicated.

Approval by a vote of 12 Yes, 3 No, 2 Abstentions – but only with strict limitations.
(Two members left early and didn't vote.)

Panel comments included:

- *Dr. Lewis Nelson, a toxicologist from New York University School of Medicine:* "I really have a lot of concerns about the quality of most post-marketing surveillance performed in our country, and I would request that the FDA try to create a system even stronger than that proposed by the sponsor…and if the endpoints are not met, it would allow the FDA to remove it from the market…Something very strong has to be in place."
- *Marilyn Eichner, a patient representative:* "I think a very strong risk management program needs to be in place… Patients are more concerned about opportunistic infections than anything else."
- *The FDA's Dr. Dal Pan:* "I heard (a recommendation for) restricted distribution as TOUCH currently exists… but I also heard the need for a lot more research data. Some people called for (post-market) controlled studies …but I think what I'm hearing is that the committee as a whole wants more information than the CD-TOUCH program would provide, which would be information on PML and other opportunistic infections as they occur...I think the committee wants more than that."

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