Trends-in-Medicine

October 2008

by Lynne Peterson

SUMMARY

The 2 new PML cases with Biogen Idec/Elan's Tysabri have not impacted physician or patient willingness to use Tysabri, but questions have been raised about the use of plasma exchange in suspected or confirmed PML patients because both these patients developed immune reconstitution inflammatory syndrome (IRIS). ♦ Neurologists are still very excited about Genzyme/Bayer's alemtuzumab. Though ITP and Grave's disease are more manageable than PML, alemtuzumab is expected to have a strict risk management program. ♦ Merck Serono's cladribine is likely to be the first oral agent, but the side effect to watch is shingles. ♦ Novartis's oral fingolimod continues to show excellent efficacy but numerous side effects, and experts predicted it also will require a serious risk management program. ♦ Acorda Therapeutics' fampridine showed good data in its second Phase III trial, and doctors predicted 1 in 5 MS patients are likely to take it long term.

Trends-in-Medicine
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
TrendsInMedicine@aol.com

WORLD CONGRESS ON TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS (WCTRIMS)

Montreal, Canada
September 16-20, 2008

An estimated 2.5 million people have multiple sclerosis (MS): 40% with relapsing-remitting (RRMS), 40% with secondary progressive (SPMS), 10% with primary progressive (PPMS), and 10% with benign MS. Experts emphasized the need for agents that promote neurodegenerative repair. Dr. Mark Freedman of the University of Ottawa, Canada, said, "We have good treatments for inflammation control, but what we lack is a repair agent."

Just after WCTRIMS, an article published in ***Neurology*** (the medical journal of the American Academy of Neurology) on October 8, 2008, was released in which French researchers reported that the majority of children vaccinated against hepatitis B are ***not*** at increased risk of developing MS. However, they found that the children with MS were 1.74 times more likely to have received a certain type of hepatitis B vaccine. The increased risk was only found for this one specific type of hepatitis B vaccine – GlaxoSmithKline's Engerix B – and not for all vaccines against hepatitis B.

The researchers studied 349 children <age 16 with MS and 2,941 children <age 16 without the disease. In the three years before the study, 24% of the MS children had been vaccinated for hepatitis B vs. 27.3% of the children without MS.

The researchers concluded that the association between the Engerix B hepatitis vaccine and MS cannot be viewed as confirmation that the vaccine caused MS. They insisted that further studies are needed to determine whether this is a causal relationship.

At WCTRIMS, most of the focus was on new therapies to treat MS. Neurologists were particularly excited about oral medications, especially Novartis's fingolimod, and Genzyme/Bayer's monoclonal antibody alemtuzumab, but there are a host of other agents in development. However, new data from three separate studies on a possible link between sunlight/vitamin D and MS also got a lot of attention. The question is whether exposure to sunlight (and the higher levels of vitamin D the body makes from sunlight) can explain the higher incidence of MS in regions farther away from the equator.

Australian researchers studying this issue presented early evidence from the Ausimmune Study in which they collected cases of people with a clinically isolated syndrome (CIS), considered a risk factor for development of MS, and followed them over time. They found early evidence that patients with CIS

had less cumulative skin damage caused by the sun than the control cases, suggesting they had had less sun exposure. The investigators also reported that the incidence of CIS increased by 9.2% with each higher degree of latitude.

Canadian researchers from the Hospital for Sick Children in Toronto reviewed the records of 35 Canadian children with MS whose serum levels of vitamin D had been tested. They reported that 34% of the kids had vitamin D serum levels considered "adequate" (>70 nmol/L), while 65% had levels deemed "insufficient" (31-69 nmol/L) or "deficient" (0-30 nmol/L).

A researcher from the University of Toronto and colleagues from the Canadian National Pediatric Demyelinating Disease Network looked at 117 children at high risk for MS because of a single neurologic episode. They took blood samples and followed the children for ~1 year, finding that vitamin D levels were significantly lower in the 16% of the children who developed MS.

Does this mean that adults and children should take vitamin D supplements – or get out in direct sunlight more often – to prevent MS? John Richert, executive vice president of research for the National Multiple Sclerosis Society, warned, "It is premature to know what the potential benefits and the potential risks are of vitamin D supplementation in people with MS or at risk of developing MS. But a number of studies are either ongoing or in the planning stage to answer those questions. In the meantime, there is no strong information at this point to say it is either beneficial or safe."

MONOCLONAL ANTIBODIES

Dr. Ludwig Kappos of University Hospital in Basel, Switzerland, called the monoclonal antibodies "smart missiles" but "not as effective as we would hope." He added, "Ideally, they should be followed by oral compounds that mimic their specific mode of action and that are, perhaps, easier to handle and modify."

There was considerable discussion at WCTRIMS about the method of action of anti-CD-20 monoclonal antibodies in MS. Dr. Stephen Hauser of the University of California, San Francisco, suggested that Genentech's Rituxan (rituximab) may block formation of new lesions rather than preventing reactivation of old lesions, "I would argue that it makes it unlikely that autoantibody production is significantly affected by a single cycle of treatment (with Rituxan)…Only 2% of B-cells are in the peripheral blood…Monoclonal antibodies like Rituxan are relatively poor at depleting moving B-cells…How could B-cell depletion work? It is very clear…that the B-cell receptor bears the mark of an antigen-driven T-cell process…The reduction of pathogenic autoantibodies is unlikely the method of action of B-cell depletion in MS…Anti-CD-20 trials have demonstrated that B-cells are central players in the pathogenesis of focal inflammatory lesions, especially new lesions, in MS. This, for me, represents a real paradigm shift. The method of action of other therapies, including glatiramer acetate and the interferons, need to be reconsidered in light of this new data. Many new questions have been raised:

- Phenotype of pathogenic B-cells entering the central nervous system (CNS) needs to be nailed down.
- Relationship between cerebrospinal fluid (CSF) and CNS B-cells and IgG.
- B-cell egress pathways.
- Possible distinctions between new and reactivated inflammatory lesions."

Dr. Hauser added, "Therapies that selectively target defined subsets of B-cells or their interacting network should have considerable promise for MS. The biggest message here for me over the last five years is: The rubber hits the road when we take ideas from the lab and move them into patients."

Monoclonal Antibodies in Development to Treat MS

Company	Monoclonal antibody	Status
	Anti-CD-20	
Genentech	Rituxan (rituximab)	Approved in non-Hodgkin's lymphoma (NHL) and rheumatoid arthritis (RA); Phase II/III in MS
Genentech	Ocrelizumab	Phase II in MS
GlaxoSmithKline/ Genmab	Fully-humanized ofatumumab	Phase II/III in NHL, Phase II in MS, Phase II in RA
N/A	TRU-815	Phase III in RA, Phase I in systemic lupus erythrematosus (SLE)
	Anti-CD-22	
UCB/Immunomedics	LymphoCide (epratuzumab)	Phase II in SLE, Phase II in Sjogren's
	Anti-CD-25	
Roche	Zenapax (daclizumab)	Phase IIb/III in MS
	Anti-CD-52	
Genzyme/Bayer	Alemtuzumab	Phase II/III in MS
	BAFF-BlyS	
Bristol-Myers Squibb	Orencia (abatacept)	FDA approved in RA, Phase II in MS and SLE
Human Genome Sciences	LymphoStat-B (belimumab)	Phase II in RA and SLE, Phase I in RA
Merck Serono/ ZymoGenetics	Atacicept	Phase I in RA and SLE
	Anti-VLA-4	
Antisense Therapeutics/ Isis Pharmaceuticals	ATL-1102	Phase II in MS

ANTISENSE THERAPEUTICS/ISIS PHARMACEUTICALS' ATL-1102

Dr. Volker Limmroth of Germany presented the results at WCTRIMS of a double-blind, placebo-controlled, multicenter, randomized study of ATL-1102 in 80 RRMS patients that was conducted in Europe. He concluded that the antibody showed activity in RRMS with only 8 weeks of treatment, reduced new T1 lesions, and was generally safe and well tolerated. He said, "We think these are promising results that warrant further investigation of this drug."

12-Week Results of ATL-1102 in RRMS

Measurement	Placebo n=41	ATL-1102 n=36	p-value
Baseline EDSS	2.83	2.49	---
Primary endpoint: Number of new active lesions (either T1 Gd+ or non-enhancing, new, or enlarging T2 lesions)	---	Down 54.4%	0.01
Secondary endpoint: Cumulative volume of T1 Gd+ lesions	---	---	Nss, 0.1068
New T1 Gd+ lesions	---	Down 66.7%	0.002
Annualized relapse rate	---	---	Nss
MS relapses	19.5%	16.7%	---
Safety			
Serious adverse events	15%	8%	---
Deaths	0	0	---
Adverse events leading to discontinuation	2%	8% *	---
Injection site reactions	0	25% **	---
ALT elevation	7.3%	19.4%	Nss
Headache	7.3%	11.1%	---
Platelet count reduction	0	4 patients	---
Thrombocytopenia	0	4 patients	---

* 2 patients due to thrombocytopenia, and one of these also had leukopenia and neutropenia but returned to normal following drug discontinuation; one for edema and dizziness.

** lasting a few hours a day.

BIOGEN IDEC/ELAN'S Tysabri (natalizumab)

A little more was learned at WCTRIMS about the 2 new PML cases, and several doctors said this information has made them a little ***more worried*** about Tysabri safety. The new issue is something called immune reconstitution inflammatory syndrome (IRIS). IRIS has been seen in AIDS patients: The immune system begins to recover but then responds to a previously acquired opportunistic infection with an overwhelming inflammatory response that, paradoxically, makes the symptoms of the infection worse.

After plasma exchange, IRIS was seen in ***both*** of the new PML patients, causing some experts to question whether plasma exchange is a good idea after all. Plasma exchange, which once looked as a possible rescue for PML patients, now is understood to have its own complications in PML patients. An expert said, "Immune reconstitution means some damage. Immune reconstitution always has a negative effect on the brain (whether major or minor)." Another said, "I'm not sure I agree that plasma exchange is the way to treat (PML) patients because with PML there is a lot of JC virus in the brain. If the plasma exchange takes the natalizumab away, you uncloak the T-cells, and you have IRIS. Taking away Tysabri may not necessarily be the way. You need an anti-viral strategy. I think the plasma exchange could be dangerous."

The status of the PML patients is:

1. **Patient #1 (Scandinavia):** This Tysabri monotherapy patient was caught early and is still recovering, with a good recovery expected. He was described as a "clinically stable and ambulatory outpatient with mild CSF inflammation – presently, clinically stable. The patient remains an outpatient and was an outpatient throughout the evaluation, workup, and plasma exchange…The latest update is the person is still an outpatient, ambulatory, and recovering as far as we are aware of. The last data we received is they did have some evidence for immune reconstitution…The person is basically stable and doing well at this time." Another expert familiar with this patient's case said, "This patient has completely normal cognition. He was ambulatory, deteriorated, and is now in rehab. The suspicion now is that it is an MS relapse and not PML. Everything in that patient looks like it is just MS now."

2. **Patient #2 (Germany):** This 52-year-old male patient, if he lives, will have some brain damage, according to Dr. Ralf Gold of City Hospital in Offenburg, Germany, who presented the details on the patient at WCTRIMS. Dr. Gold said the patient is "somnolent" and "cognitive function is not good." The patient's titer had climbed every week and is currently ~2,000 (compared to 50 for Patient #1). This patient was on azathioprine for ~4 years before going on Tysabri, with a ~3-4 month washout. The patient is currently on nasogastric tube feeding.

   There are two contributing factors to the patient's poor outcome that are of interest:

   a. The patient's family noted mood changes months before anything was picked up by the doctor.

   b. The patient continued to be treated with Tysabri after developing PML. This led to experts strongly emphasizing at WCTRIMS that vigilant oversight is needed and that the guidelines for Tysabri use must be followed.

Dr. Gold estimated that the PML rate is currently 1:7,000, far less than the 1:1,000 on which the FDA based its decision to allow Tysabri back on the U.S. market. He wondered if perhaps doctors should start thinking about even more heightened vigilance for PML and, perhaps, drug holidays.

Despite the new PML cases, none of the doctors questioned is trimming use of Tysabri, and all of them insisted none of their patients (existing or new) has been frightened away, although several sources knew of some colleagues who have gotten a

little more conservative in their use of Tysabri. Over and over, sources pointed out that they are using Tysabri for refractory RRMS patients, patients with no other real options who are willing to take the risk – provided that risk doesn't worsen. Experts estimated that <5% of European patients going on Tysabri are naïve to immunomodulatory agents. Among doctor comments were:

- *U.S. #1:* "I haven't changed my Tysabri use, and patients are still willing to take it. Tysabri use overall is increasing ***slowly***."
- *U.S. #2:* "I will still put patients on Tysabri, but it is too early to say if patients will become more reluctant to take it."
- *U.S. #3:* "Patients haven't had much reaction to the PML cases. Before I heard about the IRIS, the PML cases had no effect on my Tysabri use. Now, I don't know. The IRIS is confusing us."
- *U.S. #4:* "The question is whether long-term use could induce longer immune suppression so that it takes time for the immune response to swing back."
- *U.S. #5:* "For me, Tysabri has been a second-line agent, and the patients on it know why they are using it. But we contacted each and every one of them to discuss the new cases (of PML)…I never thought PML was a combination (drug) issue. It's an inherent issue. These cases put more emphasis on monitoring."
- *U.S. #6:* "The PML cases are worrisome. If there are more atypical cases like that, it could be threatening…but most of us are trying Tysabri in patients who failed the other therapies. The new cases put emphasis on trying other drugs first, which you are supposed to do."
- *U.S. #7:* "IRIS doesn't dictate against plasma exchange, but you need to be aware that it will happen…It is unrealistic not to expect PML cases to happen…Both (of the new PML) cases had an atypical clinical syndrome and atypical MRI lesions, so the clinical vigilance worked…I've heard some doctors say it will impact their use, but not much."
- *U.K. #1:* "I'm not changing my use of Tysabri, though it is very limited already, because the incidence of PML is still no more than 1 in 1,000. But I monitor Tysabri patients every three months."
- *Germany #1:* "I still use Tysabri, but I'm informing patients more (about the risk of PML). So far, patients are still willing to take it. I think Europe should have a tougher risk management program, like TOUCH in the U.S. Perhaps centers will have to be licensed to infuse Tysabri in Germany."
- *U.K. #2:* "I haven't changed my Tysabri use, but I don't use it a lot. You need to be careful in getting consent. Patients haven't gotten less willing to take Tysabri since the PML deaths. Many would take a risk of death to feel better."
- *France:* "I don't use Tysabri, and I'm not planning to start. I feel justified in that decision after these (PML) cases. It confirms my reason for not using Tysabri."
- *Belgium:* "I'm not changing my use. These patients are willing to accept the risk. The oral agents have their own side effects. Everything has a price."
- *Germany #2:* "Patients are asking about PML more, but most still are going ahead with Tysabri."

Drug holidays were discussed, but more in the context of IFNs/Copaxone than Tysabri, and there does not appear to be any real movement to giving Tysabri patients a drug holiday.

There was a case report of a brain hemorrhage in a Tysabri patient caused by a pulmonary embolism. German researchers reported on a 41-year-old woman with acute right-sided hemiparesis due to an atypical intracerebral hemorrhage located in a previously incomplete ring-enhancing demyelinating lesion. Spontaneous intracerebral hemorrhage occurred 22 days after the third infusion of Tysabri. They noted that the association of Tysabri and hemorrhage could be chance, but that intracerebral hemorrhage is "very rare" in MS. Their conclusions: In MS patients with tumefactive lesions, early imaging may be warranted in case of new neurological symptoms under natalizumab treatment." Without more hemorrhage cases, most sources found the report "interesting" but not very concerning.

There was also a case report on a patient who developed thrombocytopenia with Tysabri. The presenters recommended that "clinicians should be aware of this potential adverse event." Again, this report did not appear to generate much concern about new Tysabri safety issues.

Researchers from the University of Minnesota and from Greece reported on an observational study of five children <age 11 who had a "dramatic clinical improvement" with Tysabri and no adverse events. They concluded: "Tysabri seems an effective, well tolerated, and safe therapy in children with an aggressive form of RRMS unresponsive to disease modifying therapies."

Biogen researchers presented a poster suggesting that mefloquine, an antimalarial drug, may be an effective therapy for PML. There is no animal model for PML, so the Biogen researchers used *in vitro* studies to confirm that mefloquine has anti-JCV activity at non-toxic concentrations. They also found it inhibits JCV DNA replication.

No new data from the TOUCH program were presented at WCTRIMS, but Biogen provided an update on the TYGRIS program, the voluntary global observational safety study. As of May 23, 2008, 3,062 patients were enrolled in TYGRIS (1,170 patients from Germany, 750 patients from the U.S., 569 from France, and 573 from other countries). Of the TYGRIS patients, 93% had received prior immunomodulatory therapy. The overall serious adverse event (SAE) incidence was 2.4%, with the most common SAEs hypersensitivity reactions

(0.5%) and urinary tract infections (0.2%) – rates similar to that in clinical trials. No unexpected SAEs or PML were reported (the 2 new PML cases were outside of TYGRIS).

Among the other Tysabri data presented in posters at WCTRIMS:

- **Tysabri increases disease-free patients.** Dr. Eva Havrdova of the Czech Republic and colleagues performed a Biogen-funded post hoc analysis of data from the AFFIRM study, and they found Tysabri significantly increased the proportion of disease-free patients vs. placebo over two years, whether assessed by clinical or MRI criteria (or by both combined).
- **It is safe to switch patients to Tysabri from other therapies.** Preliminary data from the open-label, multi-national, single-arm STRATA extension study found no immediate safety or tolerability concerns for patients switching to Tysabri. The risk of hypersensitivity and immunogenicity upon re-dosing in prior Tysabri patients was low, but patients with a history of 1-2 doses of prior exposure have a higher risk of experiencing these events upon re-exposure.
- **Tysabri patients might benefit from 6-month CSF and plasma testing for JCV.** Researchers from the Multiple Sclerosis Research Center of New York independently studied 200 MS patients on Tysabri. They found that after 18 months of Tysabri, 4% of patients had detectable JCV/BKV in plasma/CSF. When Tysabri was stopped, 7 patients reverted to normal values within 6 months. No patient developed clinical or radiological symptoms of PML. They concluded, "It is not known whether discontinuation of natalizumab aborted the development of impending PML in our patients and whether such testing would have prevented PML in the two recent European cases. It may be prudent to test for plasma and CSF JCV/BKV DNA in all patients undergoing natalizumab treatment at 6-month intervals."
- **Tysabri patients might benefit from regular monitoring for BK virus reactivation and for renal dysfunction.** An independent study by Irish researchers of 48 MS patients found BKV reactivation in 28% of patients after a mean of 11.6 Tysabri doses. They suggested that MS alone does not account for the high rate of BKV reactivation in these patients. They concluded, "BKV reactivation can occur during treatment with natalizumab. In the absence of renal impairment, its significance is unclear. We propose regular monitoring for BKV reactivation and also for renal dysfunction."
- **Tysabri costs more than interferon therapy.** A study sponsored by EMD Serono and Pfizer found – not surprisingly – that, despite adjustments for baseline characteristics, total medical and pharmacy costs were considerably greater for patients started on Tysabri vs. those started on Rebif: an average of $60,221 for Tysabri vs. $32,772 for Rebif.
- **Tysabri efficacy was confirmed in Danish patients.** A Danish study, supported by grants from the Danish MS Society, found that Tysabri is effective in patients with high disease activity, decreasing the relapse rate from 2.40 to 0.76 (68%). But the Tysabri relapse rate was higher than the 0.26 reported in the AFFIRM study after the first treatment year, which the researchers speculated could be due to differences in baseline disease activity and disability.
- **EDSS improvement is sustained with Tysabri.** In a Biogen-sponsored post hoc analysis of AFFIRM patients, Dr. Frederick Munschauer of the Jacobs Neurological Institute in Buffalo NY and colleagues found that Tysabri significantly increased the probability of an improvement ≥1 point in the EDSS score sustained for 36 and 48 weeks. They said that this is the "first evidence that natalizumab is associated with a significant improvement in functional outcome, rather than only slowing or preventing progression of disability" in RRMS patients.

Sustained EDSS Improvement with Tysabri

Sustained improvement in EDSS	Placebo n=203	Tysabri n=417	p-value
Week 12	17.7%	28.8%	0.003
Week 24	14.8%	20.9%	Nss, 0.069
Week 36	10.3%	17.5%	0.020
Week 48	8.4%	15.1%	0.019

- **Tysabri reduces relapse activity.** U.K. researchers, sponsored by Biogen, analyzed data from the AFFIRM and SENTINEL studies looking at subgroups of patients with ≥1 Gd+ lesion over 2 years of treatment. They found that Tysabri patients derived marked clinical benefit despite the presence of Gd+ lesions. They noted that the efficacy of Tysabri on relapses was further increased when patients who developed persistent antibodies to Tysabri were excluded. They also speculated that Tysabri may shift the course of disease activity to a less active or less severe state and may induce a state of remission.

Relapse Activity with Tysabri

Measurement	Placebo Gd+ n=126	Tysabri Gd+ n=417	Tysabri Gd+/Ab- n=18
Patients with ≥1 Gd+ lesion over 2 years (AFFIRM)	43%	5%	
Patients with ≥1 Gd+ lesion over 2 years (SENTINEL)	42%	8%	
Among patients with ≥1 Gd+ lesion in AFFIRM			
Relapse-free patients	37%	60% (p=0.019)	78% (p<0.001)
Annualized relapse rate	0.66	0.28 (p=0.004)	0.14 (p=0.002)
Among patients with ≥1 Gd+ lesion in SENTINEL			
Relapse-free patients	25%	51% (p<0.001)	64% (p<0.001)
Annualized relapse rate	0.74	0.41 (p=0.008)	0.22 (p=0.001)

GENENTECH's Rituxan (rituximab)

After Phase I/II trials showed efficacy of Rituxan in RRMS, the randomized, double-blind, placebo-controlled, multicenter, 96-week OLYMPUS trial in 439 PPMS patients was undertaken. The top-line data on Rituxan in PPMS were released before WCTRIMS, and the trial failed to meet the primary endpoint. More data from OLYMPUS were presented at WCTRIMS, and there was no reprieve in that data. The results on the secondary endpoints were mixed – a benefit in T2 lesion volume but no difference on brain volume.

The only real hint of efficacy came from a subgroup analysis, which suggested that the drug worked better in younger patients (under age 55) with more baseline lesions than in older patients with fewer baseline lesions. This subgroup analysis suggested that age and baseline Gd lesions may be predictive of response to Rituxan, but the value of such a subgroup analysis in a failed trial is questionable.

While there were more serious infections with Rituxan than placebo, overall adverse events and serious adverse events were fairly comparable to placebo. Infusion reactions decreased with each infusion and were described as mostly mild-to-moderate in severity.

Why did Rituxan fail in PPMS? Probably because nothing works in PPMS, experts speculated. Dr. Robert Naismith of Washington University in St. Louis MO said, "They have to get PPMS patients with enhancing lesions, but it is not easy to do that. Neither drug (Rituxan or ocrelizumab) will have an indication for PPMS."

96-Week Results of Rituxan in PPMS in the OLYMPUS Trial

Measurement	Placebo n=147	Rituxan n=292	p-value
Completers	84.4%	82.5%	---
Median EDSS	4.5	5.0	---
Prior IFN/Copaxone therapy	65.3%	64.7%	---
Primary endpoint: Confirmed disease progression *	38.5%	30.2%	Nss, 0.1442
Secondary endpoint #1: Change in T2 lesion volume	---	Less	<0.008 favoring Rituxan
Secondary endpoint #2: Change in brain volume	-9.9	-10.8	Nss, 0.62
EDSS progression	38%	30%	N/A
Post hoc subgroup analysis of confirmed disease progression based on:			
Age <51	44.9%	27.5%	0.0101
Gd+ lesions at baseline	52.8%	27.4%	0.0069
Age <51 and Gd+ lesions at baseline	51.6%	24.6%	0.0088
Age <55 and Gd+ lesions at baseline	49.5%	29.1%	0.0126
Adverse events			
Any adverse events	100%	99%	---
Drug-related adverse events	45%	75%	---
Serious adverse events	13.6%	16.1%	---
Adverse events leading to drug discontinuation	<1.0%	3.1%	---
Grade 5 adverse event	1.4%	<1.0%	---
Grade 4 adverse event	2%	4.1%	---
Serious infections	<1.0%	4.5%	---

* required 12-week confirmation

Interestingly, neurologists did not appear overly concerned with the PML reports with Rituxan in other autoimmune diseases (lupus and rheumatoid arthritis). A U.S. neurologist said, "It is still a high risk, high yield treatment. It is very effective but with tremendous risks."

Researchers said there are no plans to take Rituxan forward in MS, that it is being replaced by ocrelizumab, a humanized anti-CD-20.

GENENTECH's ocrelizumab, a humanized anti-CD-20

This is the replacement for Rituxan in MS, but experts did not see any reason that this would perform better than Rituxan. A Phase II study in RRMS is ongoing, but it reportedly "hasn't gone far yet." Dr. Naismith said, "If Rituxan doesn't work in PPMS, ocrelizumab probably won't either."

GENZYME/BAYER SCHERING PHARMA AG (Bayer HealthCare in the U.S.)'s alemtuzumab – *sold in oncology for chronic lymphocytic leukemia (CLL) as Campath*

Alemtuzumab was the hot topic at last year's European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting in Prague, and doctors were still very, very excited about it this year. Bayer appears to be putting considerable marketing effort behind alemtuzumab, and neurologists described the efficacy as "stunning," "fantastic," and "powerful." But they also expressed concerned about the side effects, including a new one – lymphoma.

The serious side effects with alemtuzumab that have gotten the most attention up until now have been thyroid problems (Graves disease) and idiopathic thrombocytopenic purpura (ITP), but both of these were described as manageable. Doctors insisted – and the companies admitted – alemtuzumab will require a careful risk management program in MS if it is approved for MS. Another concern is Goodpasture's syndrome (in which the immune system makes antibodies that attack the lungs and kidneys), which has been reported in one alemtuzumab patient.

Another big question is how long to give alemtuzumab or how early in the disease. Should it be used as induction therapy? How many courses can a patient take? A U.S. neurologist said, "The appeal is to use it for one or two years as induction therapy."

There were no indications that the Phase III trials will be stopped early due to toxicity. But doctors want to see the Phase II data on this drug. An investigator pointed out that ITP development can occur over a broad time span – with anywhere from 1 to 5 years of

alemtuzumab use. Another expert said that he wants to see the brain atrophy and MRI data on it.

How would doctors choose between Tysabri and alemtuzumab? An investigator said, "It depends on the FDA, but it is being designed as a first-line therapy." Other doctors said it is too early to say; they need to see the Phase III safety data on alemtuzumab first. A U.K. doctor said, "Alemtuzumab will wipe the floor, but I think the company will change the protocol to a lower dose once every three months." A German neurologist said, "Campath looks great, but the side effects are enormous. I doubt it can be used widely. Now, we have lymphoma cases. I would not choose Campath over Tysabri now."

New and updated data were presented at WCTRIMS from the CAMMS-223 Phase II trial, and these data are expected to be published soon in a major medical journal.

Ongoing and planned trials include:

- **CARE-MS-1.** This trial is testing only the 12 mg dose, given for five days in Year 1 and three days in Year 2 vs. Rebif 44 µg TIW. Recruitment is ongoing in Australia, Europe, North America, and Latin America. About 250 patients have been enrolled so far, and investigators hope that it will be fully enrolled in 2009.
- **CARE-MS-2.** This is a superiority trial comparing alemtuzumab to Rebif. There are three arms: (a) 12 mg for five days in Year 1 and then 12 mg for three days in Year 2; (b) 24 mg for five days in Year 1 and 24 mg for three days in Year 2; (c) Rebif 44 µg TIW. An investigator said this is enrolling slower than CARE-MS-1.

Alemtuzumab Results in CAMMS-223 Trial

Measurement	Rebif n=111	Alemtuzumab 12 mg n=113	Alemtuzumab 24 mg n=110
Reduction in annual relapse rate			
At 1 year	---	78% vs. Rebif (p<0.001)	Down significantly
At 2 years	0.35	0.11 72% vs. Rebif (p<0.001)	0.05 87% vs. Rebif (p<0.0001)
NNT at 2 years to prevent a relapse	---	4.1	3.3
NNT at 3 years to prevent a relapse	~ 3.25	~ 1.0	~ 1.6
		73% vs. Rebif (p<0.001)	
Patients relapse free at Month 12	69.3%	91.l% (p<0.0001)	
Patients relapse free at Month 24	58.5%	88.2% (p<0.0001)	
Patients relapse free at Month 36	~ 50%	80.2% (p<0.0001)	
Other findings			
Serious adverse events	23 patients	21 patients	19 patients
Grade 3 infections	48 infections	1 infection	
T2 lesion load at 2 years by MRI	Down 11	Down 22 (p<0.05 vs. Rebif)	Down 20 (p<0.05 vs. Rebif)
MSFC Z-score	Up ~ 3.5	Up ~ 4.5 (p<0.0001 vs. Rebif)	Up ~ 6.0 (p<0.0027 vs. Rebif)
Time to sustained accumulation of disability (SAD failure rate)			
At 1 year	---	Down 83%	
At 2 years	~ 20%	~ 4% Down 66%	~ 8% Down 88%
At 3 years	---	Down 71%	
Mean EDSS score			
Baseline EDSS	1.9	1.9	2.0
EDSS	Worsens	Stable or improved	
Delay in confirmed disability progression	N/A	Down 88% (p<0.0008)	Down 66% (p<0.0098)
EDSS change at 2 years	Up 0.22	Down 0.35	Down 0.51 (p<0.0005)
EDSS change at 3 years	Up 0.39	Down 0.39	N/A

MERCK SERONO/ZYMOGENETICS' ATACICEPT

The design of the ongoing Phase II ATAMS study was outlined in a poster at WCTRIMS. This is a 4-arm, randomized, placebo-controlled, 36-week, dose-finding study of atacicept monotherapy in RRMS. About 300 patients will be enrolled and randomized to one of three doses of atacicept (initial loading dose of 25 mg, 75 mg, or 150 mg subcutaneous BIW for 4 weeks, followed by weekly subcutaneous injections of 25 mg, 75 mg, or 150 mg) vs. placebo. The primary endpoint is the mean number of T1 Gd+ lesions from Weeks 12-36.

Another poster described the design of the ongoing Phase II ATON study which will explore the neuroprotective potential of atacicept in patients with optic neuritis. This 36-week study will assess the safety and tolerability of atacicept in optic neuritis patients and explore its ability to preserve the retinal nerve fiber layer (RNFL) thickness as assessed by optical coherence tomography (OCT). The primary endpoint is the change in RNFL thickness in the affected eye at Week 36.

A third poster reported on a study of atacicept in mouse models of experimental autoimmune encephalomyelitis (EAE). The ZymoGenetics researchers reported that atacicept significantly delayed disease onset, incidence, and/or severity vs. placebo-treated mice. They also demonstrated that atacicept acts on both the cellular and the humoral effector arms of the immune response in the murine EAE models, which may represent a new mechanism of action for MS treatment.

ROCHE's Zenapax (daclizumab)

There were no new data on daclizumab at WCTRIMS. A Phase IIb/III study, SELECT, is ongoing to assess the safety and efficacy of daclizumab monotherapy.

An independent poster by researchers in New York and Utah reported on a case of granuloma annulare (a self-limited, chronic, benign dermatosis) in an MS patient receiving daclizumab. They noted that it was unclear as to why the patient developed the condition but suggested it raises questions over possible long-term complications with prolonged IL-2 receptor blockage.

ORAL AGENTS

BIOGEN IDEC's BG-00012 (fumaric acid)

Safety is less an issue with BG-12 (as it is called), but it also does not appear to have terrific efficacy. A Belgian doctor said, "BG-12 is not as effective as the other orals. It will be a last resort before a big gun like Tysabri."

At WCTRIMS, Biogen laid groundwork for the drug, but there were little really new data. A poster reviewed the safety profile of BG-12 from a randomized, single-center, Phase I QTc study in 54 healthy volunteers as well as a double-blind, dose-ranging, 24-week Phase IIb safety extension study in MS patients.

- **Phase I cardiac study:** There was a -2 ms reduction with BG-12 vs. placebo. No risk observed.
- **Phase IIb safety extension study:** The most common adverse events were flushing, MS relapse, and headache. Flushing and GI events decreased after the first month. No concerning serious adverse events were noted.

Two Phase III trials of BG-12 are ongoing:

- **DEFINE** – a 3-arm, 1,101-patient trial with the primary endpoint the percentage of patients relapsing.
- **CONFIRM** – a 4-arm, 1,232-patient trial with the primary endpoint annualized relapse rate.

In a 10-patient Phase I study, BG-12 decreased the number of Gd+ lesions. In a 24-week, placebo-controlled, Phase II study to be published soon in ***The Lancet***, BG-12 significantly decreased the imaging endpoints only with highest dose tested (240 mg TID). Although this trial was not powered to show an effect on annualized relapse rate, Dr. Kappos said there was a "suggestion of a trend in the correct direction." Serious adverse events included: one pelvic inflammation, one upper respiratory tract infection, and one breast cancer – all at the 120 mg TID dose – and one uterine leiomyoma (benign fibroid) with placebo. ALTs were elevated ≥3xULN in 6.8% of patients, but none of these patients had bilirubin ≥2xULN.

MERCK SERONO's cladribine

The company was emphasizing that this is likely to be the first oral agent, and they were educating physicians about it. The issue to watch may be shingles. An expert said there has been no safety signal in terms of leukemia, secondary cancer, or infections, but a long-term registry is needed or a program like the European TYGRIS program for Tysabri.

Merck Serono appears confident that the FDA will approve cladribine on the basis of a single Phase III trial – the CLARITY trial – provided the results are robust, because this is a known drug, approved for another indication (hairy cell leukemia), and the parenteral administration data for that indication will be used as supporting data for the MS application.

Oral Agents in Development to Treat MS

Company	Agent	Dosing	Method of action
Biogen Idec	BG-00012 (fumaric acid)	TID	May promote Th2 shift, and it does activate the Nrf2 pathway
BioMS Medical	MBP-8298	---	---
Eisai	Perampanel (E-2007)	---	---
Merck Serono	Cladribine	QD for 1 week per month for 2-4 months per year	Preferential depletion of CD4+ T-cells, not CD8+ T-cells; crosses the BBB
Novartis	Fingolimod (FTY-720)	QD	Modulation of S1P1 receptors on lymphocytes and on neural cells; possibly segregation of lymphocytes into secondary lymphatic organs; crosses the BBB
Novartis	Myfortic (mycophenolic acid)	---	---
Sanofi-Aventis	Teriflunomide	QD	May block lymphocyte proliferation by inhibiting a key enzyme needed for *de novo* pyrimidine synthesis. Probably more effect on B-cells than T-cells.
Teva Pharmaceuticals/ Active Biotech	Laquinimod	QD	Promotes a shift toward Th2 immunity. Immunomodulation achieved by changing dendritic cell response; crosses the BBB
Various	Statins	QD	---
Wyeth	Torisel (temsirolimus)	---	---

Posters presented at WCTRIMS examined:

- Design of the Phase IIIb CLARITY trial.
- MRI and clinical data from a Phase II RRMS trial which found that parenteral cladribine significantly reduced MRI disease activity in RRMS patients who did not require ambulatory assistance.
- Preferential and sustained depletion of CD4+ T-cells with cladribine, a less pronounced dose-dependent reduction in CD8+ T-cells, and smaller dose-dependent reductions in CD19+ and CD16+/CD56+ lymphocytes.
- A cell-line study that showed cladribine markedly inhibits *in vitro* T-cell effector functions and promotes the survival of a discrete T-cell population. The conclusion was that cladribine seems to directly influence and shape the T-cell response through mechanisms that are distinct from those of adenosine.

Ongoing cladribine trials include:

- **CLARITY** – a 1,327-patient Phase IIIb trial in RRMS. The trial is completed, and the patients are transitioning to an extension study. The results are expected by the end of 2008 or in January 2009.
- **CLARITY Extension** – a two-year extension in ~1,000 of the CLARITY patients.
- **ONWARD** – a double-blind, randomized, multicenter, placebo-controlled, three-arm, 96-week, Phase IIb study in 260 patients of the safety and efficacy of cladribine added to Rebif after 1 relapse.
- **ORACLE-MS** – a randomized, placebo-controlled, three-arm, double-blind, multicenter, two-year study in 642 patients with a first attack (CIS) to evaluate the effect of cladribine on subsequent treatment responses.

NOVARTIS's fingolimod (FTY-720)

Novartis officials and speakers were cleverly emphasizing the oral dosing with fingolimod by calling it not just fingolimod but "oral fingolimod" every time it was mentioned – orally or on a slide. This wouldn't be so unusual if there were also an IV version, but there isn't.

The efficacy of this drug looks as good – and perhaps better – than Tysabri, but safety issues continue to haunt it. And those safety issues are not going away with time. There have been two fatal infections in the Phase III trials, but a Novartis official insisted that both of these were "not properly treated" and that the DSMB decided to continue the trial. Experts said the most concerning side effects – and the ones they are watching most closely – are: skin cancer, herpes encephalitis, varicella zoster virus (VZV), and cardiac side effects (blood pressure and heart rate increases as well as syncope). Dr. Kappos, a leading fingolimod investigator, said, "We have to observe the skin cancer incidence and the risk of zoster reactivation during the ongoing Phase III program." Another expert said, "Two patients died, and this is concerning. The pulmonary, ophthalmic, and dermatologic side effects don't seem like a big deal."

Dr. Kappos summarized the fingolimod safety issues this way, emphasizing that there is no evidence that the adverse events increase over time:

- Transient reduction in **heart rate** upon treatment initiation, which is "well tolerated" and showed no evidence of effects with chronic therapy.
- Higher **blood pressure** (4-6 mmHg) over placebo, but he said this remained stable over time in the extension studies.
- Dose-dependent decrease in **FEV_1**, mainly with the 5 mg dose, but this did not worsen over time.
- Asymptomatic elevation of **liver enzymes** (>2xULN) in ~16% of patients.
- Increase in mild **infections**, mainly nasopharyngitis, but there has also been a herpes zoster reactivation rate of ~15/10,000. Two fatal infections occurred in the Phase III program, both with the 1.25 mg dose. One of these was a primary disseminated VZV infection, and one was a herpes simplex virus (HSV) type 1 encephalitis. Dr. Kappos said, "While a role for fingolimod cannot be ruled out, both cases had confounders that may have contributed to the final outcome. The VZV was after a nursery exposure and subsequent to high dose steroids for treatment of MS relapse. The other was a patient treated with acyclovir for HSV encephalitis one week after initial presentation of symptoms."
- 2 skin **cancers** initially observed with the 5 mg dose – 1 squamous cell and 1 basal cell – so regular skin exams are now being conducted. Those exams found 5 additional cases of localized skin cancer (2 basal cell, 1 squamous cell, 2 melanoma), all of which were successfully excised.
- One case of **psoriasis**.
- One case of **PRES (posterior reversible encephalopathy syndrome)** in the first six months of a Phase II trial, but no additional cases have been observed.
- There were cases of **macular edema** when fingolimod was tested in transplant patients, so ophthalmic screening is a part of the MS trials, and there haven't been any confirmed cases in MS patients.

Is fingolimod likely to be approved by the FDA? Sources were mixed. Some think it is approvable, and others think a risk-averse FDA may not be willing to approve it. Sources – doctors and Novartis officials – generally agreed that, if it is approved, the FDA will require a risk management program for fingolimod, and just how restrictive this will be probably will be determined by the safety findings in the Phase III program. How to design a risk management program for an oral agent could also be tricky. U.S. patients, at least, couldn't

be required to come to the doctor's office to get their pill because doctors don't dispense medications. It was also considered unlikely that patients would get only a 30-day prescription and then have to return to the doctor once a month to get a refill prescription. Sources doubted that a specialty distributor would limit access. One expert suggested the answer may simply be education and a patient registry.

How will doctors choose between oral fingolimod and the IFNs/Copaxone or even Tysabri? Bayer, Bigoen Idec, Merck Serono, and Teva were all defending their existing franchises by emphasizing the long-term data available with the injectables, and doctors agreed that oral agents, while expected to be very popular with patients, will not immediately and entirely replace injectables – especially if the orals have as many side effects as fingolimod does. But the decision really is likely to be made by patients.

How long does fingolimod stay on board? Experts agreed that the drug remains in the system about 4 weeks after administration is stopped.

Fingolimod data presented in posters at WCTRIMS included:

- **Cardiac and pulmonary effects.** A single-center, randomized, parallel-group, placebo-controlled, multiple-dose,double-blind, Phase I study in 38 healthy volunteers found fingolimod did not appear to have any impact on cardiac or lung function. There was no significant change from baseline in cardiac output, stroke volume, or systemic vascular resistance with any of the doses tested (0.5 mg and 1.25 mg). On Day 1, heart rate was significantly reduced vs. placebo (p=0.0001). Fingolimod did not appear to affect pulmonary function over the course of the study.

3-Year Results of Fingolimod Phase II Extension Study

Measurement	Placebo/ fingolimod n=93	Fingolimod 1.25 mg n=94	Fingolimod 5.0 mg/1.25 mg n=94
Mean number of Gd+ lesions	0.1	0.2	0.3
Patients free of Gd+ lesions	89.3%	87.5%	89.1%
Mean number of new T2 lesions	0.5	0.7	1.1
Annualized relapse rate	0.31	0.20	0.21
Relapse-free patients	51%	68%	73%
Safety			
Any adverse event	95.7%	96.8%	98.9%
Any severe adverse event	21.5%	17.0%	21.3%
Any drug-related adverse event	67.7%	72.3%	79.8%
Any serious adverse event	16.1%	10.6%	22.3%
Any infection	64.5%	68.1%	76.6%
Serious infection	4.3%	0	1.1%
ALT increase	16.1%	12.8%	16.0%
Basal cell carcinom	1 patient	0	2 patients
Squamous cell carcinoma	1 patient	1 patient	0
Malignant melanoma	1 patient	1 patient	0
Low white cell count	34%		
Elevated ALT	16%		
Elevated creatinine	14%		

- **Asians.** A PK/PD study in healthy volunteers found no clinically relevant differences between Caucasian and Asian subjects given fingolimod.
- **Disease progression.** A rat study suggested that fingolimod may have protective effects during the progressive stages of MS. In the rat model of EAE, treatment with fingolimod after the onset of pronounced demyelination significantly reduced disease severity, blocked disease progression, and reduced inflammation, demyelination, and axonal loss.
- **3-year results.** The results of a 36-month extension of an exploratory Phase II study showed that low MRI and clinical disease activity were maintained for up to 36 months with both the 1.25 mg/day and 5.0 mg/day doses.

Three Phase III trials in RRMS are ongoing:

- **FREEDOMS-I.** This ~1200-patient, 2-year (plus extension), non-U.S. trial compares fingolimod (0.5 mg and 1.25 mg) to placebo in RRMS. There are no planned interim data analyses. The primary endpoint is reduction in relapses. The results are expected in early 2009.
- **FREEDOMS-II.** This ~950-patient, 2-year (plus extension), U.S.-only trial compares fingolimod to placebo in RRMS. There are no planned interim data analyses. The primary endpoint is reduction in relapses. The results are expected in mid-2010.
- **TRANSFORMS.** This is a 1,292-patient, global, double-dummy, 1-year (plus extension) comparison of fingolimod to Biogen Idec's Avonex QW in RRMS. Fingolimod patients will get sham injections. Asked why Avonex was chosen as the comparator, an investigator said, "The differences between the interferons are not so important, and we wanted to provide patients with the option with the lowest number of injections." There will be an interim data analysis.

Other fingolimod studies underway in MS include:

- **Study 1201** in Japan.
- **INFORMS** – testing 1.25 mg fingolimod QD vs. placebo in ~650 PPMS patients worldwide (~75% from North America and 25% from Europe) over 3 years. This trial is expected to start shortly. Dr. Alan Thompson of University College in London said, "The unique method of action of fingolimod provides a rationale for evaluating it in PPMS." However, studying PPMS is difficult for several reasons, especially (1) limited experience with the validity of diagnostic criteria for identify PPMS patients, and (2) measuring progression by EDSS alone may not provide sufficient sensitivity. The primary endpoint in INFORMS was designed to address these problems by using an "innovative clinical endpoint" – time to confirmed disability progression on any of these: EDSS, timed 25-foot walk test (T25FW), or 9-hole peg test.

SANOFI-AVENTIS's teriflunomide

Dr. Kappos explained that this active metabolite of Sanofi-Aventis's Ariva (leflunomide) works by inhibiting the proliferation and function of activated, but not resting, lymphocytes. Although the primary endpoint was met in a clinical trial over 36 weeks with both the 7 mg/day and 14 mg/day doses, he called the clinical results "less convincing," noting there is "some effect on the relapse rate but it was not significant (30%). The safety was quite encouraging – some lab changes but no real side effects."

Sanofi reported that:

- Randomization is complete in the Phase III TEMSO trial of 1,088 patients, with results expected in mid-2010.
- Phase II MRI results were positive.
- A head-to-head vs. Rebif will start in RRMS patients in 2009.
- A CIS study is ongoing.
- More than 90 patients have >5 year follow-up so far.
- The key advantage of this agent may be its tolerability, but it is too early to compare oral agents.
- Only one patient has discontinued for neutropenia.

TEVA PHARMACEUTICALS/ACTIVE BIOTECH's laquinimod

Dr. Kappos said the method of action is not fully understood. It appears there is no increased infection risk. The results of a second Phase II trial were published recently in ***The Lancet***, with a trend to a reduction in annualized relapse rate and no major or minor serious adverse events. Two large studies have been initiated and are ongoing (one vs. placebo and one vs. an interferon).

APPROVED INJECTABLE THERAPIES

- **BIOGEN IDEC's Avonex (interferon-β-1a)**
- **BAYER SCHERING PHARMA's Betaseron/Betaferon (interferon-β-1b)**
- **MERCK SERONO's Rebif and Rebif New Formulation (interferon-β-1a)**
- **TEVA PHARMACEUTICALS' Copaxone (glatiramer acetate, copolymer-1)**

Doctors questioned at WCTRIMS reported no significant share shifts among the currently approved injectable MS drugs:

- The failure of the Copaxone 40 mg dose (vs. the 20 mg dose) in the FORTE trial may have been disappointing, but it doesn't appear to be affecting Copaxone use because none of these doctors was using 40 mg anyway.
- Novartis has not yet started marketing Betaseron, so that has not had any impact on overall Betaseron use – yet.
- Data on Rebif New Formulation appear to have reassured Rebif users but not generated much change in prescribing practices (not even vs. Avonex).
- There was no information on what to expect over the next year in terms of price increases for these agents.

A study presented by researchers at the Marshfield Clinic in Wisconsin found that there is no rebound worsening of MS after stopping disease modifying therapy. They looked at 573 RRMS patients in their database and found 103 who discontinued treatment or had treatment interrupted, usually because of side effects, and the relapse rate for these patients was 0.37/year. Of these 103 patients, 19 had a relapse in the first year of treatment (0.18 attacks/year). There was no difference in attack rates by drug (Copaxone or any of the interferons), and no genotype was associated with worsening of MS after stopping therapy. The researchers concluded that prophylactic MS therapy with Copaxone or the interferons can be interrupted without precipitating any rebound worsening.

Effect of Discontinuing Injectable Therapy

Measurement	Number of patients	Number of patients stopping therapy	Number of relapses within 1 year
Copaxone	254	13%	6
Betaseron	113	25%	6
Avonex	228	16%	7
Rebif	21	14%	0

BAYER SCHERING PHARMA's Betaseron/Betaferon

Bayer announced it is introducing a new needle (30 gauge) for Betaseron during WCTRIMS, and it is the smallest needle for one of these approved disease-modifying therapies. The new needle – which will come with an optional new autoinjector called the Betaject Lite – is as thin as the needle commonly used for insulin and pediatric injections.

MERCK SERONO's Rebif New Formulation (RNF)

Dr. Nicola De Stefano presented new data at WCTRIMS from the 16-week, double-blind, placebo-controlled, Phase IIIb IMPROVE study in RRMS patients in Europe and Canada, showing a 69% decrease in new MRI lesions and a significant decrease in T2 lesion volume. He said, "This is the first

16-Week Results with Rebif New Formulation

Measurement	Placebo n=60	RNF n=120	p-value
Primary endpoint: Combined unique active (CUA) MRI lesions	2.2	0.7 (69% reduction)	<0.001
Mean new Gd+ lesions	3.4	0.8	---
No new Gd+ lesions	20.0%	60.8%	<0.001
Mean T2 lesion volume	+1.11	-0.11	<0.001
No new T2 lesions	50%	78%	---
Patients with ***no*** CUA lesions at Week 16	N/A	53%	N/A

double-blind, placebo-controlled study to demonstrate the rapid and beneficial treatment effects of Rebif New Formulation in RRMS patients…53% of patients receiving Rebif New Formulation had no CUA (combined unique active) lesions at Week 16."

TEVA PHARMACEUTICALS' Copaxone (glatiramer acetate, copolymer-1)

Data presented at WCTRIMS showed that doubling the dose of Copaxone does not improve the efficacy. Dr. Giancarlo Comi of Milan, Italy, presented the results of the FORTE trial, which was funded by Teva. This was a 1-year, double-blind, multicenter, parallel-group, open-label, extension study in 1,155 RRMS patients comparing two different doses (the standard 20 mg/day and 40 mg/day dose) of Copaxone. The trial was powered to detect a 30% difference in the annualized relapse rate.

Dr. Comi said that the only interesting observation came from the subgroup of patients who got frequent MRIs (n=234), "In this group there was an imbalance between the high and the low dose at baseline, with the high dose having more baseline activity…And we see an interesting phenomenon…There was a trend for an earlier effect of high dose on MRI activity – an advantage for the high dose in accelerating the response to treatment…This is probably the only positive aspect coming from this trial…The curious thing is that when the glatiramer dose was selected, those who made the choice were absolutely right."

1-Year Results of FORTE Trial of Double-Dose Copaxone

Measurement	Copaxone 20 mg n=586	Copaxone 40 mg n=569	p-value
Completers	91.1%	86.1%	---
Primary endpoint: Annualized relapse rate	0.33	0.35	Nss, 0.4859
ARR in completers	0.27	0.27	Nss
Relapse-free patients	77.6%	77.0%	Nss
T1 Gd+ lesions at Month 12	0.68	0.54	Nss
New T2 lesions at Month 12	2.87	2.72	Nss
Change in brain atrophy	- 0.58	- 0.53	Nss
Serious adverse events	4.3%	4.3%	---
Injection site reactions	55.6%	58%	---

SYMPTOMATIC THERAPY

ACORDA THERAPEUTICS' fampridine sustained release (SR)

The results of the second Phase III trial, which were presented at WCTRIMS, confirmed the findings of the first Phase III trial, and experts were predicting that the FDA will approve this drug. Acorda officials said they plan to submit fampridine to the FDA in 1Q09 and are hoping for priority review. Both Phase III trials were done under a Special Protocol Assessment (SPA) with the FDA, which indicates the FDA has accepted the primary endpoint as sufficient for approval.

The patients who didn't respond to fampridine showed a walking speed comparable to placebo, while responders had a dramatic improvement.

The efficacy data from this double-blind, parallel-group, randomized, Phase III trial were considered clinically meaningful by every doctor asked. There was an absolute 32.4% improvement over placebo, and a 15% delta was described as clinically important. Dr. Andrew Goodman, director of the MS Center at the University of Rochester School of Medicine and Dentistry and a fampridine researcher, said the consistent response criteria used in the trial was validated against the MSWS-12, which is a recognized and validated scale. He explained that MSWS-12 was not used in the trial because "we wanted an objective measure in addition to a subjective measure…There has never been a therapy that has consistently and reliably improved patients' ability to walk. And we have two Phase III studies in which a significant percentage of patients vs. placebo could consistently walk better…People who show consistent improvement – which in most studies is ~25% vs. baseline – also experience improvement that is meaningful to them." An Acorda official said, "The MSWS-12 gets to that issue. We showed that responders had a much greater response than non-responders. Responders improved by about 7 points on a 100-point scale. We incorporated that (MSWS-12) in this study, but it was not an FDA requirement (in this trial) because that was an FDA requirement in the first Phase III trial."

The most common side effects were insomnia, dizziness, and nausea. Seizures, which had been a question, were not seen with fampridine in this trial. Dr. Goodman said, "It has been a concern in the course of development of the drug. We did dose-ranging studies and saw an increase in frequency and severity of side effects with considerably higher doses than we are using currently, and among the most serious adverse events were several seizures. In this (current Phase III) study, however – at a much lower dose (10 mg BID) – there was only 1 seizure, and it was in a placebo patient." An Acorda official said, "We need to show the seizure rate is not higher than the background rate, but the background rate is not that well documented (about 1:200 patient-years). Our rate is in that region…we will need some form of risk management program, probably mostly education." Safety extension studies are ongoing, but they are open-label, not placebo-controlled.

Fampridine also appears to reduce fatigue. A source said, "The difficulty in walking is a tremendous drain on energy, leading to fatigue, so the side benefit of fampridine is the reduction of fatigue." Dr. Goodman added, "That is called 'fatigability,' meaning you can just walk so far and can't go any more – or stamina. Anecdotally, stamina improvement is what people report with fampridine."

Only one doctor questioned at WCTRIMS currently compounds 4AP (the base ingredients of fampridine), and all said they probably will use fampridine if it gets approved by regulators (FDA and EMEA). Dr. Goodman said, "My sense is there are pockets of (compounded 4AP) use…I think it is popularly used in certain parts of the country more than others, but that is not an FDA-approved use."

Experts agreed that more than half of all MS patients have issues with mobility and walking. Dr. Goodman said, "In my experience, more than half of MS patients develop impairment (of mobility)…Fampridine could be a novel way of improving a function that is lost in progressive MS in a high proportion of patients. It is a novel way of treating an important problem in MS, the difficulty with walking that so many people develop."

On average, doctors questioned estimated that they would prescribe fampridine for 40% of their MS patients, but many warned that perhaps half of these either would not have a satisfactory response or would stop taking it for other reasons. That leaves about 20% of all MS patients likely to take this long term. Dr. Goodman noted that 33%-42% of patients given fampridine are responders. A German neurologist said, "It will be good for a few, selected cases, probably <10% of MS patients." A U.K. doctor said, "If it really works in a very good trial with appropriate outcome measures, ~50% of patients would try it." A U.S. neurologist said, "If the FDA approves fampridine, I'll use it, and I expect approval. From 40%-50% of my patients will try it, but many will be disappointed with the results, so about 20%-25% may get good value from it."

Fampridine Phase III Results

Measurement	Placebo n=119	Fampridine 10 mg BID n=120
Primary endpoint: Patients with improvement in T25FW	9.3%	42.9% (p<0.001)
Change in lower extremity muscle strength	~ +0.04	~ +0.05 in non-responders (Nss, p=0.68) ~ +0.13 in responders (p=0.028)
T25FW by MS type		
RRMS	---	~ 38%
SPMS	---	~ 46%
PPMS	---	~ 50%
PRMS	---	~ 40%
Safety		
Any treatment-emergent adverse event	66.4%	85.8%
Any treatment-emergent serious adverse event	2.5%	4.2%
Urinary tract infection	8.4%	17.5%
Insomnia	1.7%	10.0%
Headache	0.8%	9.2%
Asthenia	4.2%	8.3%
Dizziness	0.8%	8.3%
Nausea	0.8%	8.3%
Balance disorder	1.7%	5.8%

How long would patients continue on the drug? As long as they get a benefit, doctors said. Although the drug does not alter the natural course of MS – meaning that patients will continue to deteriorate in terms of EDSS – fampridine does improve their mobility over what it would be without the drug. So what patients are likely to do, experts explained, was occasionally stop the drug and see if they deteriorate, then re-start it, and see if they improve. There is a quick response to this drug, so patients could self-test frequently if they wished. Thus, even if patients decline in status while taking fampridine, they may continue to take the drug if, when they stop it, they worsen even further.

Dr. Goodman emphasized that fampridine is not a disease modifying therapy; it just improves disability, so there is no reason to think it would have any prophylactic effect. However, it can be given on top of standard therapies. Asked what happens over time, he explained, "Our sense is that where the patient is, there is incremental improvement. There may be a time when the progression of MS is so severe that fampridine won't be able to improve the patient. Studies have been for 8 and 14 weeks, and for that period, there is a consistent effect …The data show patients go back to baseline upon discontinuation…The approach would be equivalent to other symptomatic therapies – continue it as long as the patient and the physician perceive that it is helping…It is likely that during the course of the day the effect will wear off, and then the patient will take the next pill and feel better again."

Asked about the mechanism of action, Dr. Goodman said, "It is a potassium channel blocker, and the presumed mechanism of action is improvement of induction in axons that are demyelinated…If someone progressed to the point where there were not sufficient viable axons, then presumably that is when someone wouldn't or couldn't respond. Presumably that is why only a percentage of patients respond to this drug."

Other Agents to Watch

Naltrexone (generic)

Several posters investigated the use of this drug – which is FDA approved to treat alcoholism and drug addiction – to prevent MS relapses and attenuate the severity of other symptoms. Researchers at Penn State/Hershey Medical Center are leading the way, but they are looking for funding for a large trial, and they are hoping for support from the National Institutes of Health (NIH), the Multiple Sclerosis Society, or private funding. Dr. Gary Thomas said, "Naltrexone is given in addition to current standard of care, so it doesn't step on anyone's toes." Ian Zagon PhD said, "This is very promising. Off-label use has mushroomed. The problem is no company cares…Low dose naltrexone (rather than the higher dose used for alcohol/drug addiction) works for 4-6 hours, then there is a rebound effect for the next 6-18 hours which is beneficial because if you continuously block the receptors, the effect is bad." A pilot study reportedly showed no problems with adding naltrexone to Copaxone or an interferon.

Other neurologists questioned about naltrexone were less optimistic. A U.K. doctor called it "quack medicine."

Simvastatin (generic)

The results from an ongoing trial of the effect of 80 mg simvastatin on the rate of brain atrophy in SPMS patients is ongoing. So far 34 of the planned 140 patients have been enrolled. Results are expected in 2011. The primary endpoint is T1 weighted volumetric MRI, and a variety of secondary endpoints will be measured.

TORAY INDUSTRIES' Peg-rIFN-β

A poster presented the results of PK and EAE studies in mice of this daily subcutaneous injected pegylated interferon-β. The company claims to have developed a proprietary technology that allows successful large-scale production. The researchers concluded that pegylation of rIFN-β "markedly alters its pharmacokinetic properties, which results in greatly ameliorated disease symptoms of EAE. Therefore, pegylation of human rIFN-β could provide an efficient therapy for MS with low dose or infrequent administration." A Phase I trial is expected to start in Japan this year.

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