REPORT

Emerging oral therapies for Multiple Sclerosis. Report of the 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)

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*I*ntroduction

Multiple sclerosis (MS) is a demyelinating autoimmune disease of the central nervous system (CNS). A continuous deposition of sclerotic plaques leads to progressive physical disability. Etiological, exacerbating or remitting agents and curative treatments have not been firmly established.

The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) is a representative European organization that facilitates communication and creates synergies among clinicians and scientists to promote and enhance research and improve clinical outcomes in multiple sclerosis.

ECTRIMS hosts the world's largest annual international conference devoted to basic and clinical research in multiple sclerosis. This year the 25th ECTRIMS Congress was held in Düsseldorf, Germany, 9–12 September 2009.

ECTRIMS congresses have over the years evolved into the largest and most important annual international meeting devoted to multiple sclerosis. International experts in MS research, both scientists and clinicians, shared and discussed recent advances in this fast moving field. Clearly, the ultimate goal of all these efforts is to combat and eventually cure this disabling disease which affects some two million individuals throughout the world. A better understanding of the immunopathological processes underlying MS has in recent years led to the design of numerous novel therapeutical approaches. At the ECTRIMS special attention was paid to oral therapies, a topic which we would like to comment for you in this report.

Multiple sclerosis (MS) represents the prototypic inflammatory autoimmune disorder of the CNS and the most common cause of neurological disability in young adults, exhibiting considerable clinical, radiological and pathological heterogeneity.

In 1868, the French neurologist Jean-Martin Charcot was the first to describe MS as a distinct disease, calling it "sclerose en plaques". Charcot's MS triad refers to nystagmus, intention tremor and telegraphic speech. He was one of the foremost neurologists of his day, and many other medical terms also bear his name: Charcot's joint, Charcot-Marie-Tooth disease, Charcot-Leyden crystals, and others.

MS is much more common among white persons living in northern latitudes, but individuals who move to northern climates before the age of 15 also have an increased risk. Females are twice as likely as males to develop MS, and it most commonly affects adults aged 18-50. In some MS natural-history studies, overall life expectancy has been shown to be only 5-7 years shorter, but patients usually die from complications associated with MS and not from the disease itself.

The disease can present several different phenotypic forms: progressive relapsing, secondary progressive, primary progressive and relapsing remitting. Early during the course of the disease, patients may be able to remyelinate and repair some of the damage caused by the MS plaques. However, as the disease progresses, the body cannot successfully compensate the demyelination burden, and changes become permanent.

MS may be protean in symptoms, depending on the exact location and duration of lesions, and the physical findings may change over the course of the disease. A thorough physical examination with neurologic assessment must be undertaken to determine the extent of disease burden. Common findings include localized weakness, focal sensory disturbances, hyperreflexia, stiffness, ocular findings and gait disturbances. Secondary problems include infections, skin breakdown, and musculoskeletal complaints. The 10-point Kurtzke Expanded Disability Status Scale allows for the accurate rating of disease sign and symptom severity.

Although blood work and cerebrospinal fluid analysis are valuable to rule out other etiologies of a patient's neurologic symptoms, MRI remains as the imaging procedure of choice to help confirm diagnosis and for monitoring disease progression when correlated with symptomatic findings. MS plaques have increased signal intensity on T2, contrasted T1, and FLAIR MRI procedures. Non contrasted T1-weighted imaging is less sensitive for the detection of MS lesions but can give an excellent assessment of the global cerebral atrophy present in advanced, chronic MS. Demyelinating lesions may sometimes mimic brain tumors because of associated edema and inflammation.

Symptomatic management is a major component of the disease treatment. Because disease-modifying drugs have poor efficacy in overall disease progression, a patient's well-being relies on symptom relief. Treatment must be individualized by the physician for each type of symptom. It should be noted that the medications listed are not FDA approved for use in MS; rather, they represent a summary of recommendations from clinicians who treat MS-associated symptoms.

Medications used to treat MS are classified as either disease-modifying or symptomatic management. No currently approved medications offer any hope for cure. For acute exacerbations, methylprednisolone is given to shorten the flare duration. For patients

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with relapsing MS, interferon beta (1a or 1b), natalizumab, glatiramer acetate, and mitoxantrone are FDA approved. Mitoxantrone is also approved for secondary-progressive and progressive-relapsing MS. No approved treatments are available for primary-progressive MS.

Currently, licensed disease-modifying agents for MS all share the need for parenteral administration. Oral therapies would have the advantage of convenience and greater acceptability. Several pivotal reports have provided promising results for new oral therapies evaluating the safety and efficacy of new agents including fingolimod, fumaric acid, cladribine, teriflu-nomide and laquinomid.

This report deals with interesting aspects that were highlighted in ECTRIMS Congress concerning emerging oral therapies for MS.

Oral therapies in multiple sclerosis inspire excitement and concern

Effects of new oral treatment options now in the pipeline for multiple sclerosis have caught the attention of physicians and patients. The new therapies promise an end to injections for many, but although their reported efficacy rates have been excellent, emerging details on adverse events are troubling.

At the 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, the new therapies, and how clinicians might incorporate them, were hot topics.

"Several oral drugs are in the final stage of evaluation," Kris Selmaj, MD, from the Medical University of Lodz in Poland, said during a session on future treatments. "They appear to provide higher efficacy, but also the risk of serious side effects" he noted.

"Many questions remain on how we will handle these new agents," Dr. Selmaj added. Although adverse events appear to be rare, they can have a devastating effect on those experiencing them. Reports of progressive multifocal leukoencephalopathy, malignancies, infertility, bradycardia, atrioventricular block, and infections such as herpes have been worrisome. Will the new agents have a long-term effect on immune response?

"The stakes are definitely high" Paul O'Connor, MD, from the University of Toronto in Ontario, Canada, said; "We are expecting several oral agents to enter the market in the next few years - this could be as many as 5." Dr. O'Connor says that adding these to the existing 4 drugs already on the market for multiple sclerosis will give neurologists a record 9 possible agents to choose from.

"Patients definitely like pills more than injections" said the ECTRIMS incoming president Michel Clanet, MD, from the Hôpital Purpan in Toulouse, France. "But they also have a more severe safety profile and it will present challenges in managing patients".

Current president Hans-Peter Hartung, MD, from Heinrich-Heine University in Düsseldorf, Germany, added,"It is a very exciting time in multiple sclerosis therapy research. This is the most active therapeutic field in all of neurology" Dr. Hartung said that the new potent drugs are prompting neurologists to consult with their oncology and rheumatology colleagues on how to best manage immunosuppressive and cytotoxic agents.

During a talk on treatment paradigms, Thomas Berger, MD, from Innsbruck University in Austria, told attendees that evidence-based medicine is now more important than ever. "What are you basing your medical decisions on?" he asked. "Do you accept recommendations and guidelines from experts without question or doubt? Are you reading studies including the methodology or merely scanning abstracts?". Clinicians are more overwhelmed with information today than ever before, he noted, but it is important that they take the time to carefully weigh the evidence.

ECTRIMS executive committee member Maria Trojano, MD, from the University of Bari in Italy, said the group is developing a plan for an independent risk management program to assess new oral agents. "We want to make sure we have a clear understanding of the risks such as infections and cancer" she said.

"Most patients with multiple sclerosis are especially sophisticated" Dr. Hartung pointed out at the meeting. "They are members of our team, and we have to be advocates for them"

Oral fingolimod appears to reduce inflammation in multiple sclerosis

One of the most important oral drugs in development for MS is Fingolimod. It is a derivative of the naturally occurring immunosuppressive substance myriocin, with a structural similarity to sphingosine, a ubiquitous sphingolipid. Fingolimod is a sphingosine 1-phosphate receptor modulator; it acts as an immunomodulator interfering with the egress of T and B lymphocytes from secondary lymph organs, which results in lymphopenia. A phase II study in patients with multiple sclerosis showed a significant reduction in annual relapse rate and lesions in magnetic resonance imaging with an acceptable rate of side effects. An advantage of fingolimod compared to interferon beta, glatirameracetate and natalizumab is its oral availability.

New magnetic resonance imaging data suggest that oral fingolimod decreases inflammation in MS. The investigational drug, also known as FTY720, is being developed by Novartis. Researchers at the ECTRIMS showed that treatment reduced the number of T2 lesions (Table 1) and gadolinium-enhancing T1 (Table 2).

"Oral fingolimod demonstrated its superiority over interferon beta1-a in relapse-remitting disease at 12 months" lead investigator Frederik Barkhof, MD, from the VU University Amsterdam in the Netherlands, said at the meeting (Table 1).

Dr. Barkhof was speaking on behalf of the TRANSFORMS study group. The acronym refers to the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapse-Remitting Multiple Sclerosis. The phase 3 study of over 1200 patients showed an advantage of oral fingolimod over the interferon product (Avonex, Biogen) (Table 2).

Table 1. New and enlarging T2 lesions at 12 months

T2 Lesions	Interferon Beta1-a	Fingolimod	Fingolimod
n	365	380	356
Dose	-	0.5 mg	1.25 mg
Mean number	2.1	1.5	1.4

"The results are exciting because they compare oral fingolimod against interferon — not placebo — and we know that interferon is active" study coauthor Giancarlo Comi, MD, from the University Vita-Salute San Raffaele in Milan, Italy, added during a talk at the meeting on new oral agents.

Researchers reported that the relapse rate was reduced by 52% in the fingolimod low-dose group and 38% in the high-dose group.

The trial did, however, raise some safety concerns. Researchers reported that serious adverse events were more common with the new treatment (Table 3). Events included bradycardia, atrioventricular block, and infections such as cases of herpes that resulted in 2 deaths. Localized skin cancers and breast cancers were also more likely with the oral agent.

Dr. Comi pointed out at the meeting that all of the oral agents in development for multiple sclerosis are showing increased risks.

Presenting new results, Dr. Barkhof showed that brain volume reductions were significantly less with fingolimod -0.31% for the lower dose, -0.30% for the higher dose, and -0.45% for interferon; P <.001).

"All other MRI endpoints either significantly favored fingolimod over interferon or were similar across treatment groups", he said. "TRANSFORMS is demonstrating a consistent clinical effect, and it is very promising", according to session co-chair Paul O'Connor, MD, from the University of Toronto in Ontario, Canada. "We are going to have to carefully weigh the benefit and risks", he said, "but this is certainly an interesting time in multiple sclerosis research".

New safety data presented on oral cladribine for multiple sclerosis

Investigators released new safety data on oral cladribine, a purine nucleoside analog in development for the treatment of MS.

Cladribine, which is a preferential lymphocyte-depleting therapy, has the potential to be the first oral agent available for the treatment of relapsing forms of MS. This oral formulation is administered through intermittent, once-daily dosing to treat relapsing forms of MS. Cladribine as a parenteral formulation has an extensive clinical experience for other disease conditions including hematologic malignancies and relapsing and progressive forms of MS. Cladribine tablets now are undergoing phase III development for the treatment of relapsing forms of MS.

Results from the CLAdRIbine Tablets Treating MS OrallY (CLARITY) study were presented at the Annual Meeting of the American Academy of Neurology in April. The phase 3 trial showed a greater-than-50% reduction in annualized relapse rates with both low- and high-dose regimens.

ECTRIMS presenters detailed the potential risks of therapy. "We observed no major differences between the 2 groups", lead investigator Stuart Cook, MD, from the New Jersey Medical School in Newark, said at the meeting. "Lymphopenia was more frequent with cladribine tablets", he noted, "as expected, based on its mechanism of action".

Table 2. Mean number of gadolinium-enhancing T1

T1 Lesions	Interferon Beta 1-a	Fingolimod	Fingolimod
n	365	380	356
Dose (mg)	-	0.5	1.25
Mean number	0.51	0.23	0.14

Table 3. Serious adverse events

CULTIVAR	Direct shoots (%)	Rooting	Indirect shoots	Regeneration frequency
JEWEL	85.00	+ + +	100	0.85
CEMSA-78354	27.50	+ + +	12.00	0.27

Rooting: + Moderated; + + Good; + + + High.

Dr. Cook reported that the incidence of infections was comparable across treatment groups, with the exception of herpes zoster. Patients on cladribine had about 2 times more zoster events. They were also more likely to have malignancies. One patient had melanoma, another had ovarian cancer, a third had a metastatic pancreatic carcinoma, and a fourth had choriocarcinoma.

During a talk on new oral agents, Giancarlo Comi, MD, from the University Vita-Salute San Raffaele in Milan, Italy, pointed out that agents such as cladribine may help patients move away from injections. The drugs also appear to be highly effective. However, along with improved efficacy come new, more virulent safety concerns, he said.

"Dr. Comi raised an important point,» session co-chair Paul O'Connor, MD, from the University of Toronto in Ontario, Canada, said. "It does appear that the more efficacious an agent is, the greater the likelihood of adverse events".

Dr. Cook reported that cladribine is activated in lymphocyte subtypes, resulting in targeted and sustained immunomodulation. Researchers propose that the oral formulation will be appropriate as a short-course annual treatment.

The CLARITY study was a 2-year randomized, double-blind, placebo-controlled, international trial. It included more than 1300 patients with relapsing-remitting MS.

Participants were randomly assigned to 1 of 3 different treatment groups consisting of placebo and different dose regimens of cladribine. All primary and secondary endpoints for the trial were met.

Dr. Cook reported that 5.8% of the patients in the cladribine groups discontinued the treatment because of adverse events compared to 2.1% of the patients in the placebo group.

Dr. Cook reported that a CLARITY extension study will provide long-term safety and efficacy data. "I'm pleased to note that a cladribine safety registry is being implemented to further characterize the long-term safety profile of the treatment", he said. This will include patients who participated in the sponsored trials; information will be collected for up to 8 years.

Teriflunomide and Laquinimod are other two new oral therapies for MS in development.

Teriflunomide is one of several oral agents currently undergoing Phase III studies. Its mode of action largely depends on the inhibition of pyrimidine synthesis. There is now evidence on the efficacy of teriflunomide in animal models and Phase II human studies. In view of the favorable safety profile of teriflunomides it appears to be a promising oral alternative to interferon beta and glatiramer acetate. The ongoing Phase III stud-

ies of teriflunomide as mono- and combination therapies were discussed.

Laquinimod is a new quinolonecarboxamide that has demonstrated efficacy in animal models of several autoimmune diseases, including MS. It shows immunomodulatory effects, probably through Th1/Th2 shift, but does not lead to immunosuppression. Laqui-nimod is metabolized in the liver, primarily by the CYP3A4 enzyme. Phase II studies in relapsing MS demonstrate a dose-response effect on disease activity, measured by the number of active lesions observed on brain magnetic resonance imaging, and show favorable tolerability and safety based on clinical and laboratory indicators. Two Phase III studies currently in progress are evaluating the efficacy of laquinimod 0.6 mg/day in relapsing MS. The drug was granted a fast track review by the FDA in 2009. Laquinimod is a novel, orally administered immunomodulator that has advanced to the pre-submission stage and may become an alternative to the current injectable first-line treatments for relapsing MS

Conclusions

It is unknown whether these oral drugs could be used as a first-line treatment for MS; this will depend mostly on their safety profile. Alternatively, these drugs could be used as add-on treatments for failed first-line therapy, or as effective induction agents.

Developing an evidence-based approach to their differential indication and the combination of an increasing number of therapeutic options, will be a challenge in the forthcoming.