According to Dr. Weinshenker, NMO should not be automatically diagnosed in AQP4+ patients, as false positive results very rarely may occur. However, AQP4 autoantibodies are highly specific, and a positive test should lead to careful consideration of the diagnosis. Physicians should be aware that the spectrum of NMO is broader than previously thought, and some patients clinically diagnosed as having CIS, MS or opticospinal MS may, in fact, have NMO.

Another Perspective

Joab Chapman, MD, PhD, Tel Aviv University, Tel Aviv, Israel, argued that NMO and MS do overlap. He presented a case study of a 15-year-old girl with rapidly progressing paraplegia, who clinically recovered on corticosteroids. Virology, lupus, and other autoimmune workups were negative, including presence of NMO. A clinical diagnosis of MS was made based on neurologic deficits (subacute dissemination in time and space, retrobulbar neuritis, and myelitis), typical MRI lesions, evoked potentials, and oligoclonal bands in cerebrospinal fluid.

NMO disturbs MS dogma because antibody-producing cells and astrocytes (AQP4 is on astrocyte foot plates) play a major role, indicating that the MS complex comprises several diseases of which NMO is the first to be extracted. Prof. Chapman has treated several patients with NMO who also had systemic lupus erythematosus (SLE). This coexistence of autoimmune diseases, especially with SLE, is common, suggesting that NMO may be a manifestation of SLE.

MS also overlaps with antiphospholipid syndrome (APS). Both affect white matter, cause motor disability, cognitive dysfunction, epilepsy, myelitis, are autoimmune disorders, and sometimes have similar magnetic resonance images. The two conditions can be differentiated with electrophysiologic tests; evoked potentials have 78% sensitivity and 90% specificity for differentiating MS from APS. ELISA studies found significantly high ($p<0.001$) levels of antiphospholipid antibodies in MS patients.

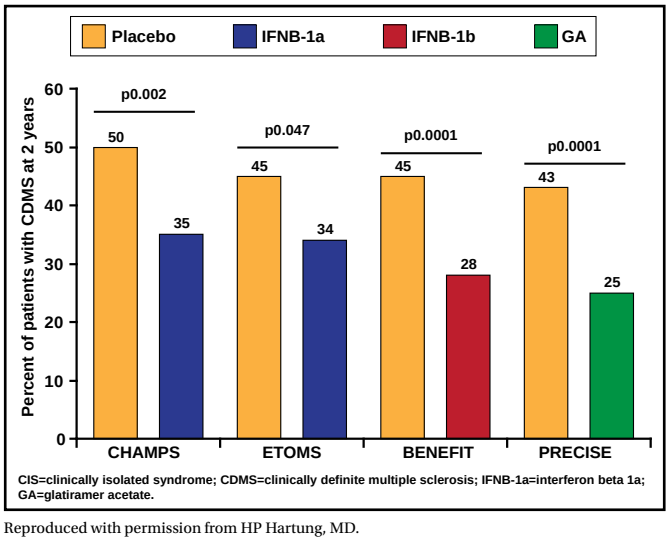
The "New" Clinically Isolated Syndrome: To Treat or Not to Treat?

Clinically isolated syndrome (CIS) refers to the first neurologic episode in which a person experiences multiple sclerosis (MS)-related symptoms. According to the McDonalds 2010 criteria, MS can be diagnosed in patients with only one clinical episode. The diagnosis of CIS is reserved for patients who do not meet the criterion of dissemination in space and/or dissemination in time clinically and in the first magnetic resonance image (MRI). In this session, presenters debated whether or not patients with CIS should be treated.

Hans-Peter Hartung, MD, Heinrich Heine University, Düsseldorf, Germany, presented the case that patients with CIS should be treated. In the MAGNIMS study [Filippi M et al. *Arch Neurol* 2009;], patients had a first MRI at 1.3 months and a second one at 5.0 months. With regard to conversion to clinically definite MS (CDMS), the two MRIs demonstrated 47% and 43% sensitivity, 88% and 87% specificity, and 76.5% and 75% accuracy, respectively. The investigators concluded that a single MRI may suffice to identify a subset of CIS patients with a high risk of developing CDMS, even when it is performed within the first three months after the onset of symptoms.

Studies have shown that a shorter first inter-attack interval and incomplete recovery from the first attack are predictors of long-term disability in patients with relapsing-remitting MS (RRMS). A 20-year study found that an early high rate of MRI disease activity is associated with long-term disease progression. Numerous studies show that axonal damage occurs early in MS and is irreversible. Several Phase 3 trials of early therapy for CIS have been completed. The CHAMPS, ETOMS, BENEFIT, and PRECISE trials demonstrated that significantly fewer treated CIS patients versus placebo patients had CDMS at 2 years (Figure 1) [Jacobs LD et al. *N Engl J Med* 2000; Comi G et al. *Lancet* 2001; Kappos et al. *Neurology* 2006; Comi G et al. *Lancet* 2009].

Figure 1. Studies in CIS Populations.



CIS=clinically isolated syndrome; CDMS=clinically definite multiple sclerosis; IFNB-1a=interferon beta 1a; GA=glatiramer acetate.

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Prof. Hartung concluded that irreversible axonal damage occurs early and has an impact on the development of disability. Disease-modifying therapy seems to be more effective if used earlier.

Karl Vass, MD, University of Vienna, Vienna, Austria, argued that patients with CIS should not be treated early for the following reasons: the definition of CIS is vague; not every patient with CIS will develop MS; many patients will develop only mild disease; and many patients will not accept immediate treatment. In a long-term follow-up of patients with CIS, among those with an abnormal MRI at baseline, 83% had converted to CDMS at 10 years. Only 50% of patients had developed CDMS within 2 years. Further, it takes a long time for significant disability to occur, which usually is preceded by additional relapses or more MRI activity [Confavreux C. *N Engl J Med* 2000].

In the CIS studies, ETOMS, CHAMPS, REFLEX, BENEFIT, and PRECISE [Comi G et al. *Lancet* 2001; Jacobs LD et al. *N Engl J Med* 2000; Kappos L et al. *Neurology* 2006; Kappos L et al. *Lancet* 2007; Comi G et al. *Lancet* 2009], 30% to 60% of the patients already had MS according to the McDonald 2010 Criteria. These study results provide insufficient evidence for efficacy of disease-modifying therapy in "new" CIS patients. Finally, clinical experience shows that many patients are not ready to begin therapy after a diagnosis of CIS.

Prof. Vass concluded that not every patient with CIS should be treated; more than 50% do not need disease-modifying therapy, which is insufficiently effective and expensive.

Risk Management of New DMTs

Adequately Assessing Risk Management of New Disease Modifying Therapies (DMT) is Difficult

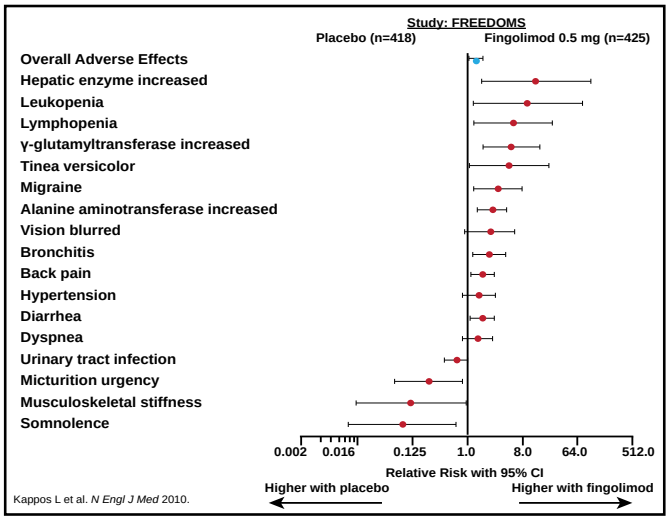
DMTs for multiple sclerosis (MS) carry potentially serious risks, including opportunistic infections, altered response to vaccinations, development of cancer, and the appearance of autoimmune disorders. Jacek Losy, MD, PhD, Poznań University School of Medical Sciences, Poznań, Poland, reviewed safety data from clinical studies and post-marketing surveillance of DMTs for MS.

Phase 3 safety data from the AFFIRM [Polman CH et al. *N Engl J Med* 2006] and SENTINEL [Rudick RA et al. *N Engl J Med* 2006] studies of natalizumab show that the most common adverse events (AEs)—headache, fatigue, urinary tract infection, and arthralgia—were mild. Serious AEs were comparable to those observed with placebo. The rate of hypersensitivity reactions was 4% (0.8% serious reactions), and 6% of patients were persistently positive for antibodies to natalizumab. There was no increased risk of malignancies or depression. Two cases of progressive multifocal leukoencephalopathy (PML) and other opportunistic infections were reported. The risk of PML was 1/1000 over 18 months. Among all patients treated with natalizumab through January 2012 (n=96,582), 201 cases of PML have been reported. These data show that the key safety issues with natalizumab are hypersensitivity, immunogenicity, and PML and other opportunistic infections.

AEs associated with alemtuzumab include infusion reactions, infections, and malignancies. Autoimmune diseases have developed with long-term use in patients with diseases other than MS. Rituximab treatment in MS patients is associated with infusion reactions, infections, and grade IV ischemic coronary artery syndrome, malignant thyroid neoplasm, and symptoms of acute and progressive MS. Increased risk of PML and enteroviral infections is possible.

AEs reported with fingolimod are shown in Figure 1. ECG abnormalities were reported in more patients treated with fingolimod versus placebo or interferon beta-1a. Other potential complications of fingolimod therapy are latent DNA virus activation, bacterial infections, reversible posterior encephalopathy, and macular edema.

Figure 1. AEs: Fingolimod 0.5 mg Compared with Placebo.



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Prof. Losy concluded that clinical trials are of limited value for evaluating the safety of these drugs because