DEBATE: CLINICALLY ISOLATED SYNDROMES (CIS): TO TREAT OR NOT TO TREAT START EARLY:

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Numerous findings about early events in multiple sclerosis (MS) demonstrate how seriously the onset of MS has to be taken and that early treatment initiation is in the patients' best interest.

From a pathological angle, one can argue that axonal damage starts very early in the course of the disease. Likewise, inflammatory activity in relapsing-remitting MS is not restricted to episodes of clinical impairment, but typically starts before an initial clinical relapse which has let to the concept of "clinically absent syndrome" and generally continuous during remission. Moreover,

the immune-mediated processes that underlie MS become more compartmentalised in the CNS and thus more difficult to control as the disease progress.

Patients with a first event suggestive of MS (also called: clinically isolated syndrome (CIS)) and an abnormal MRI scan have a high risk of developing MS. According to findings from CHAMPS and ETOMS clinical trials and epidemiological studies, the risk depends on the number of lesions on the initial MRI. Patients with a high number of lesions at first presentation have a very high risk of developing a second attack shortly after the first attack. Baseline MRI features in patients with a first event seem not only to determine the risk of conversion to definite MS but also correlate with disability at 5 years.

Further evidence for the importance of early treatment derives from the demonstration that vast majority of patients with CIS and positive brain MRI develops new brain MRI lesions allowing the diagnosis of MS according to the McDonald criteria (McDonald 2001). For example in the BENEFIT clinical trial it has been shown that 85% of patients on placebo developed McDonald MS within 2 years, the majority of them within one year (Kappos et al., 2006). The 2005 revision of the criteria might even have allowed for a quicker diagnosis in many of these patients.

All three clinical trials conducted in patients with CIS – BENEFIT, CHAMPS and ETOMS (Kappos et al., 2006, Jacobs et al., 2000, Comi et al., 2001) – have shown that treatment with IFNB can slow down the rate of conversion to clinically definite MS (CDMS), prolong the time to CDMS and reduce MRI activity. The three years extension of the BENEFIT trials shows that IFNB-1b treatment right after a first clinical event suggestive of MS can significantly reduce the risk of permanent increase of disability as measured by the Expanded Disability Status Scale (EDSS) compared to delayed treatment. Delayed treatment is treatment initiation after the second clinical event of after 2 years whichever came first. This is a truly novel finding and another convincing argument in favour of a paradigm shift towards earlier treatment initiation.

From studies in relapsing-remitting MS, we already have evidence that late treatment initiation or low-dose regimens do not seem to match the benefit of early, high-dose therapy, at least over an observation period of four years (PRISMS Study, 2001). However, now it has been shown that this concept is already applicable at the stage when patients display the first signs of MS, which underscore the urgent need to treat patients rather early than wait for further MS signs to develop.

In summary, all these findings convincingly indicate that treatment with IFNB should be started as early as possible in the course of MS. Clearly, what is lost in delaying MS treatment is not regained, and with the BENEFIT 3-year data we see that time lost means loss of brain function, even in the early stages. Physicians and patients should carefully consider these observations in deciding when to initiate treatment.