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Do not treat from CIS onset: evaluate disease course and prognosis first - No (treat!)

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Rebuttal

When patients present with a first clinical event consistent with central demyelination or clinically isolated syndrome (CIS)[1] and have lesions consistent with multiple sclerosis (MS) on magnetic resonance imaging (MRI) or cerebrospinal fluid (CSF)-specific oligoclonal bands,[2] the chances they will go on to develop either more MRI lesions or further clinical attacks in the imminent coming years is probably >90%. The group we call 'CIS' has probably been further halved by the new diagnostic criteria,[3] which have established that even the first MRI can be used to satisfy both dissemination in space and time, thus making many of the patients previously thought to have CIS, now 'MS'. If we adopt the new criteria, then the natural history of this 'new CIS' cohort has yet to be carefully defined, although recent studies suggest that their risk of developing new lesions or attacks is probably the same as those satisfying the new criteria. Therefore, it is the first event that critically defines whether a person has, or is highly likely to imminently display the signs and symptoms of MS. The debate as to whether or not to treat patients with CIS can be reduced to simply 'should we be treating MS or not?'. Suggesting we wait until the course defines itself before initiating therapy that could significantly reduce further events, ignores the most important evidence we have gained from nearly two decades of treatment with disease-modifying therapies (DMT): that therapies are at best modestly effective at reducing events, but their greatest efficacy is observed when used as early as possible after the disease reveals itself.

One of the most important and somewhat startling messages we learned around the same time we started using DMT, and has been reiterated most recently in further elegant pathological studies, was that the greatest amount of inflammation associated with axonal transaction[4] or cortical demyelination[5] occurs early in the disease course and is often silent, preceding clinical presentation. DMT target inflammation, which as it wanes, yields to a slow progressive axonopathy that is at the present time not treatable. Loss of neurons and axons appear irreversible and is probably the substrate of disability in ambulation and cognition. Therefore, does it not make sense to 'strike when the iron is hot' to get the most out of our DMT? What is the 'down side' of doing so? If we follow the recommended work-up for patients presenting with CIS[1] then it is highly unlikely we will be treating patients that do not have MS. Are the DMT harmful if taken long term? At least with respect to interferon-beta or glatiramer acetate, there is no real danger signal in over 25 years of experienced treatment, and treatment with interferon-beta has even been associated with reduced mortality.[6] It is possible that DMT might be needlessly given to a patient destined to have a 'benign' disease course: something one can only be certain of after many decades of having the disease. If there was some way of knowing who would and would not have a 'benign' course then it might be possible to selectively not treat certain patients, but there is no sure way of predicting disease course at any point in time.

Some data have emerged from studying MS soon after it presents regarding the prognostic capability of MRI: with the disease burden on the first MRI predicting earlier onset of disability,[7] but that is not to say that patients with lower brain disease loads will not sustain permanent disability from lesions throughout their spinal cord. If the argument is to wait for MS to declare itself before treating with DMT, then how much 'declaration' is required? How many new lesions need to develop or how many attacks need to occur before it is clear that the course warrants treatment? If the answer is a single new lesion or a single attack, then studies have shown us that nearly 90% of untreated CIS patients will have new MRI activity within the next 2 years and at

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least 40% will experience at least one new attack. With every new lesion or attack comes more irreversible damage, so what is the purpose of sustaining more permanent brain injury before trying to prevent it, especially with the odds of having it so high?

We now have evidence that every first-line agent proven to alter the natural history of relapsing MS is also effective when given to CIS patients, and in virtually all of the cases, the efficacy was greater than that observed in later established relapsing disease.[8] In addition, there were no added safety concerns regarding administering interferon-beta or glatiramer acetate to patients with CIS than were not already known from the years of treating relapsing disease.

In summary, a diagnosis of CIS implies that there is no other condition that can better explain the new onset of signs and symptoms suggestive of MS[1] and most CIS patients meet full diagnostic criteria[3] if left untreated within a couple of years of presenting. Damage in MS is irreversible, builds silently and is associated early on with inflammation that is amenable to treatment with DMT. All first-line DMT are highly efficacious at CIS (even perhaps more so than at the established relapsing MS stage) and are safe thereby maximizing the benefit-to-risk ratio. It makes absolute sense therefore to offer treatment when patients first 'declare' their disease.

References

1. Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Mult Scler* 2008; 14: 1157–1174.
2. Tintore M, Rovira A, Rio J, et al. Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis? *Neurology* 2008; 70: 1079–1083.
3. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292–302.
4. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S and Bo L. Axonal transection in the lesions of multiple sclerosis. *N Engl J Med* 1998; 338: 278–285.
5. Lucchinetti CF, Popescu BF, Bunyan RF, et al. Inflammatory cortical demyelination in early multiple sclerosis. *N Engl J Med* 2012; 365: 2188–2197.
6. Reder AT, Ebers GC, Traboulsee A, et al. Cross-sectional study assessing long-term safety of interferon-beta-1b for relapsing-remitting MS. *Neurology* 2010; 74: 1877–1885.
7. Filippi M, Horsfield MA, Morrissey SP, et al. Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. *Neurology* 1994; 44: 635–641.
8. Goodin DS and Bates D. Treatment of early multiple sclerosis: the value of treatment initiation after a first clinical episode. *Mult Scler* 2009; 15: 1175–1182.