**DEBATE: CAN WE AIM FOR A "DISEASE-FREE STATUS" WITH CONTEMPORARY MS THERAPIES? NO**

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We can certainly "**aim**" for **disease-free status** in patients with relapsing remitting MS. But is it a realistic aim or ever achievable? Is it even measurable? If it is achieved, can it be distinguished from the natural history of MS and tendency of the disease to remit in some patients? What are the potential toxicities of escalating therapy in MS based on very limited evidence that this goal would be achievable?

1. Is it measurable? There are many aspects of MS that are not measurable, some of which might be eventually measurable with better technology, but many of which will not feasibly be measurable even with foreseeable technical advances. Cortical inflammatory pathology is thought to be an important generator of pathology in MS, and is grossly underestimated by current MRI capabilities and likely even by high field MRI. Neurodegeneration is only partially measurable with neuroimaging (volume measurements and MR spectroscopy) and is a critical aspect of the disease from an early point in the illness. It is certainly not measurable in the contemporary routine patient care settings.
2. Is it achievable? Recently, contemporary clinical trials are exploring the frequency of "no evident disease activity" (NEDA), a construct that generally refers to no relapses, no MRI T2 or gadolinium enhancing lesions and no EDSS progression. This is a pragmatic strategy recognizing the realities inherent in point #1 (i.e. disease free status is not measurable). Even so, no agent has been shown to have NEDA in all patients, although in a variety of studies compared to placebo, NEDA has been achieved in a significantly greater proportion of patients on active drug rather than on placebo…not surprisingly. NEDA offers a "triple opportunity" at counting overlapping outcome events and enhances the power of clinical trial outcome measures, an attractive strategy for a clinical trialist or a trial sponsor searching for a sensitive outcome. Predictably, the concept has "caught on". However, NEDA was NOT seen in 55-75% of patients in clinical trials. Hence, it is clear that NEDA is not achievable even with the most effective therapy, and not achievable in the majority of patients even using this pragmatic but incomplete surrogate for "disease-free status".
3. Is it distinguishable from the natural history of MS? It is well established that some patients with MS can be free of evident disease activity for years. Typically, this occurs after a period of active disease, but some patients may have prolonged remissions after a first attack. Does NEDA tell us anything more in clinical trials than we have learned by using attack frequency and MRI lesion frequency as outcome measures?
4. What are the consequences of "NEDA"? There is a tacit assumption that if a patient does not achieve NEDA status in the context of clinical follow-up that the treatment has "failed" the patient and treatment should be escalated. Would a new treatment be more effective than the first "failing" treatment? Might it be less effective? Would the toxicity be greater? Will this result in ongoing constant switching of treatments to achieve an unrealistic objective?

The concept of NEDA is attractive. It has positive aspects. It forces the clinician to be aware of the need to monitor patients who are on (or who are not on) treatment, and to consider changes of treatment in the face of treatment failure. But what are the "actionable" thresholds that will optimize this concept? This must be established in the context of development of algorithms for escalation of treatment in a logical way, and move MS clinical studies from clinical trials evaluating the efficacy of individual agents to effectiveness studies evaluating the effectiveness of a treatment algorithm. We are just at the threshold of considering such algorithms, which are a prerequisite for implementation of "Aiming for NEDA".