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The Clinical Course of Multiple Sclerosis Needs to be Redefined in the Treatment Era of MS

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Results of key natural history of studies from carefully managed data sets have unfortunately lead some leading experts in the field of multiple sclerosis to conclude that the most severe cases of multiple sclerosis are causally connected to degenerative processes as the primary driver of disability [1,2]. A strong relationship between age and disability bolsters this thinking. The epidemiologic facts derived from these and other important studies are sometimes combined with the shortcomings of treatment trials to formulate legitimate questions concerning the long-term impact of our therapies, which are felt to principally impact relapses and inflammation mediated injury (having unknown effects on long term degeneration) [3]. However, not only are most MS clinical specialists confident that they are positively impacting many of their patients through disease modifying therapies (DMTs), they also embrace "switch therapy" when initial therapies fail. Gradually accumulated evidence concerning the dangers of treatment failure [4,5] and our vast personal experience with switching among DMTs, have lead us to feel we are well justified in searching for a treatment response through treatment changes. Indeed some recent treatment trials involving patients randomized to stay on a "failed" treatment versus a new therapy have shown that patients in general did better with "switch therapy" in this scenario [6,7]. Considering these studies and our personal experience we are now ready to discuss the concept of remission of multiple sclerosis [8]. What will the language describing remission look like? The prior language describing the course of multiple sclerosis seems woefully inadequate [9]. This editorial proposes some of the language which might be used soon to describe the course of multiple sclerosis.

"Benign MS": No evidence of disease or very low disability, further defined by the presence or absence of immune modulating therapies, and the number of years on treatment. Modifying the definition with the quality of treatment duration takes into account the increasing likelihood that a patient is a true "responder" to immune modulation over time. A definition of benign MS could also be modified by subcategories of benign disease [10].

"Active MS, with or without relapses": Again, a temporal modifier for cadence is needed. Has the relapse occurred within the last six months, with or without recovery? Has a significant change in neurological exam or function occurred within the last 6 to 12 months? Clinicians monitor for disease activity because they are willing to change medications in patients who appear to be "failing." Clinicians are not waiting, nor should they, for clear class I evidence of every possible scenario for switch therapy being efficacious, but are rather forging ahead with common sense based in strong biological plausibility suggested by treatment trials. Certainly, we are urged to consider changes in therapy in patients with ongoing clinical and radiographic evidence of disease activity given the known efficacy of each of the approved drugs as standalone therapies in the various scenarios wherein they were approved for use.

"MS in apparent therapy induced remission": If a patient with at least moderate disability accumulation stabilizes within 6 months of a new treatment and maintains stabilization for a year or more, we are certainly tempted to conclude that our change in therapy has induced a remission.

"Late stage slow progressive MS:" A precise definition for the age-related slow decline which seems inevitable in all patients with MS remains lacking, but the concept is ever present and undeniable. Certainly, we are less enthusiastic about our abilities to impact the later stages of MS. Any definition for this stage of MS will likely include a lack of clinical relapses as well as lack of active inflammation by MRI measures, with progression being similar to that seen in primary progressive MS [11].

It is beyond the scope of this editorial to provide precise definitions for ongoing disease activity and remission of multiple sclerosis, yet I hope to foreshadow the spirit of such an endeavor occurring in the future. For research purposes more precise language and definitions can and should be developed, but in practice neurologists already are thinking in terms of inducing remission. It is a testament to the apparent efficacy of our new and old armamentarium of therapeutic agents for multiple sclerosis that we have now begun to think this way.

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