Sustained reduction of MS disability

New player in comparing disease-modifying treatments

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Neurology® 2016;87:1966–1967

As our choice of treatments for relapsing-remitting multiple sclerosis (RRMS) grows, clinicians are faced with complex decisions about selecting the best drug for an individual patient. The proportional effectiveness among drugs cannot be easily gleaned from comparing drugs' efficacy against placebo. This is not only because the effectiveness of multiple sclerosis (MS) drugs is population-dependent (i.e., decreases with age and level of disability), but also because clinical trial designs and outcomes continuously evolve.

In this issue of *Neurology*®, Giovannoni et al.[1] demonstrate that comparing 2 drugs for their efficacy on disability progression omits a crucial aspect of the MS disease process: sustained reduction in disability (SRD). The Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS) II trial[2] compared efficacy of alemtuzumab (12 mg/d IV ×5 days at baseline and ×3 days at 12 months) against interferon-β-1a (IFN-β-1a [Rebif], 44 μg subcutaneously ×3/wk). Figure 1 from the presented reanalysis of CARE-MS II data shows distributions of patients in relationship to measured Expanded Disability Status Scale (EDSS) change after 2-year treatment with alemtuzumab (n = 426) vs IFN-β-1a (n = 202). The Gaussian distributions of these 2 histograms are centered on zero, showing that approximately a third of patients in each treatment group did not change their disability. Clear benefit of alemtuzumab is visible on the side of disability progression, where approximately 40% of IFN-β-1a–treated patients finished the trial with higher EDSS than when they entered, compared to approximately 25% of alemtuzumab-treated patients. (Note that the proportion of patients with sustained disability progression, verified at follow-up visit, was much lower: 21% in the IFN-β-1a arm and 13% in the alemtuzumab arm[1]). Analogous benefit of alemtuzumab was noted on the side of disability reduction, where approximately 29% of IFN-β-1a–treated and 45% of alemtuzumab-treated patients ended the trial with improved EDSS. Again, considering only SRD (verified at follow-up visit), the proportions of patients are smaller: 12.9% of IFN-β-1a–treated and 28.8% of alemtuzumab-treated patients. Thus, comparing both sides of the disability changes between the 2 drugs doubles the amount of clinically useful information. Alemtuzumab's benefit on disability was observed in each functional system, with the strongest treatment effect noted in the cerebral, cerebellar, sensory, pyramidal, and visual systems. This consistency across multiple domains supports clinical relevance of SRD as an outcome measure. However, the CARE-MS II design may artificially overestimate the benefit of alemtuzumab over IFN-β-1a, because more than 50% of enrolled patients were previously treated with IFN-β-1a and the inclusion criteria required presence of relapses while on such therapy,[2] which technically excluded patients who had optimal therapeutic response to IFN-β-1a. Nevertheless, a similar observation was seen in treatment-naive patients with RRMS in the CAMMS223 phase 2 trial.[3]

What is the biological basis of the SRD? The authors explored, and to some degree ruled out, the possibility that the measured improvements are due solely to reversal of exacerbation-related disability. Because the results on multiple outcomes consistently favored alemtuzumab, it is also unlikely that SRD simply reflects measurement variance, even though imprecision of the measurement plays some role. For example, note that measurements of sustained reductions or progressions of disability are always considerably smaller than reductions or progressions of disability measured at a single timepoint. Instead, observed data indicate that SRD is mediated by biological mechanisms that are consistently stronger in alemtuzumab in comparison to IFN-β-1a–treated participants. One can only speculate whether the SRD is due to structural repair (i.e., remyelination) or functional repair (i.e., plasticity, such as formation of new synapses). We favor the latter idea, based on the early experience with CD52-depleting antibody, where virtually all 36 patients with mean EDSS of 5.8 and mean disease duration of 11.2 years demonstrated either temporal arrest or steady disability progression, but no disability improvements.[4] Indeed, if SRD is caused by plasticity, it should not be observed in patients with more advanced

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disability, where the extent of CNS tissue destruction precludes functional recovery because of the lack of neuronal reserves. However, one can also make an argument that remyelination may be less efficient in advanced disease.

Even though cumulative evidence[2,5–7] indicates that alemtuzumab is one of the strongest MS-modifying treatments currently available, it is not curative, even when applied as early in the disease process as phase II/III trials of alemtuzumab wisely targeted (i.e., mean age ~33 years, mean disease duration ~2 years and mean EDSS ~2).[5] Even though a minority of alemtuzumab-treated patients in these trials progressed on EDSS,[2,6,7] EDSS is too insensitive to demonstrate subtle disease progression in 2-year trials. Twenty-five feet walk is more informative in this regard, and slow, but sustained progression on this measure (surprisingly equal for both drugs) suggests that with longer follow-up, progression of disability will likely affect a larger proportion of alemtuzumab-treated patients. This residual disease will need to be targeted by combination therapies if our goal is to arrest disability progression in all patients.

The ability of alemtuzumab to nearly abrogate formation of new MS lesions has been interpreted as evidence that neurodegeneration, rather than inflammation, drives progression of disability postalemtuzumab.[5] However, this interpretation may not be entirely correct: patients with progressive MS have quantitatively comparable amounts of intrathecal inflammation to untreated patients with RRMS,[8] but their inflammation is qualitatively different, corresponding to compartmentalized inflammation visualized on pathology outside of MS lesions[9,10] and in the meninges.[11] Compartmentalization makes CNS inflammation inaccessible to systemically administered treatments. Furthermore, compartmentalization is a continuous process that starts at disease onset and evolves over time.[8] As such, even patients with RRMS differ in the proportion of CNS-compartmentalized inflammation[8]; those who have little or none may achieve lasting benefit from alemtuzumab or other immune system-resetting strategies such as bone marrow transplant, whereas those with higher levels of compartmentalization may benefit to a comparatively lesser degree. It is only if we successfully abolish compartmentalized inflammation and observe no arrest of disability progression that we could rule out its role in MS progression and focus entirely on neurodegenerative aspects of MS. Thus, despite unarguable progress in MS therapeutics, there is still a long road ahead until we can eliminate disease progression for all patients.

STUDY FUNDING

The work of Dr. Bielekova was supported by the intramural research program of the National Institute of Neurologic Disorders and Stroke.

DISCLOSURE

The authors report no disclosures related to this work. Go to Neurology.org for full disclosures.

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