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Letter

Disease modification in advanced MS: Focus on upper limb function

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Pivotal disease-modifying treatment (DMT) trials for people with multiple sclerosis (pwMS) commonly employ the Expanded Disability Status Scale (EDSS) as the primary outcome.[1] The upper EDSS limit set by sponsors for trial eligibility almost invariably excludes patients who have become dependent on wheelchairs. As a result, successful trial data may not support an application for licensing of new DMTs to treat people with advanced MS (pwAMS; EDSS $\geqslant$6.5).

However, the positive effect on upper limb (UL) function of several immunomodulatory DMTs in pwAMS indicates the potential for disease modification at higher EDSS scores. For example, results from the ASCEND (A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Participants with Secondary Progressive Multiple Sclerosis, NCT01416181) and ORATORIO (NCT01194570) trials suggest that pwAMS may indeed benefit from immunotherapy.[2] However, the major effects in these trials were detected using secondary, non-ambulatory, outcome measures suggesting that in pwAMS variables should be employed that reflect functions independent of ambulation.[3] We explored attitudes on the importance of UL function among pwMS as well as neurologists with a special interest in MS (MS neurologists) practising in the United Kingdom. Using an infographic and the Barts-MS blog (www.ms-res.org), we asked pwMS to rate the importance of UL function and whether wheelchair users should be excluded from DMT trials. MS neurologists were contacted by email to complete a related survey.

Of 360 pwMS who responded, 93% felt that pwMS in wheelchairs should not be excluded from DMT trials. In addition, 88% of pwMS considered UL more important than lower limb (LL) function, which is perhaps not surprising, since UL function is closely linked to completing daily tasks independently.[4] And while there are several ways to compensate for ambulatory impairments, there are fewer options once both UL and LL functions are compromised.[5]

In contrast, only 49% of 43 MS neurologists were in favor of including pwMS who are wheelchair users in DMT trials. MS neurologists are more aware of LL function in people with MS compared to UL function, which is perhaps not surprising given that the most commonly used outcome measures are biased toward LL function; in particular the EDSS, the most common primary outcome to assess disease progression phase III DMT trials.

This focus on the EDSS as the key outcome in DMT trials likely affects perceptions in relation to disability and likelihood of successful disease modification in pwAMS. Further research into the evidence underpinning these views is needed. A higher degree of awareness of the importance of UL function for pwMS may lead to a shift in practice such that investigators and sponsors become more prepared to consider DMT trials for pwAMS and EDSS scores in the range of 6–8.5.

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