**Is NEDA a clinically relevant endpoint for therapeutic decisions? No**

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With the advent of more efficacious MS therapies in recent years, a mere reduction of relapse rate is no longer considered a satisfactory therapeutic goal (1,2). Moreover, recent data on MS disease course suggest that probably only relapse rates in the first few years from onset are associated with long-term disability and prognosis, thus underscoring the necessity for additional measures of disease activity and progression that could help guide treatment decisions (3). Therefore, the concept of “no evidence of disease activity” (NEDA) which roots in the field of rheumatology were disease-free status is an accepted goal for clinical trials and patient care was transferred to MS and first applied in 2009 to the AFFIRM trial (“disease activity free status”), one of the pivotal natalizumab trials (4,5). NEDA was defined as a composite score comprising the criteria “No EDSS worsening”, “Freedom from relapses”, “No new/enlarging T2 lesions” and “No gadolinium-enhancing lesions”. 37% of study participants who received natalizumab in the AFFIRM trial were “disease activity free” over 2 years according to this definition. Subsequent analyses for dimethyl-fumarate, fingolimod, cladribine and the combination of glatiramer acetate / interferon beta-1a reported NEDA rates ranging from 28 to 44% (6). However, despite the beneficial promotional aspect of such a composite score for pharmaceutical companies, the clinical relevance for individual patient management and treatment decisions has not been proved. Moreover, NEDA has been criticized because it heavily relies on radiographic measures whose correlation with clinical measures is only moderate and whose relevance for long term prognosis is equivocal. Most NEDA data are derived from very short follow-up periods and lack comparability between studies which questions the long term importance and predictive value of this measure.

Moreover, the NEDA concept disregards relevant features of disease pathology (diffuse tissue damage, grey matter atrophy, retinal atrophy etc.) that are probably more relevant for disease prognosis and long term disability than focal T2/gadolinium-enhancing lesions (7-11). Even more serious is the fact that it is totally unclear what the clinical meaningfulness of NEDA is from the patients’ perspective as it does not entirely reflect the clinical need by not taking “intangible” but often severely debilitating symptoms like fatigue, depression, cognitive impairment, pain and sleep disorders into account (12-18). Moreover, a recent study from the US has shown that NEDA is hardly an achievable goal in clinical practice as only 7.9% of more than 200 RRMS patients retained NEDA status after a period of observation of 7 years (19). Recent attempts to overcome some of the criticism by including brain atrophy measurements into the concept (NEDA-4) fall short as standardized brain volume assessments in clinical routine are probably not feasible in the nearer future. In sum, NEDA is currently not relevant for therapeutic decisions.

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