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LONG-TERM ASSESSMENT OF NO EVIDENCE OF DISEASE ACTIVITY IN RELAPSING-REMITTING MS

The advent of new effective therapies for relapsing-remitting (RR) multiple sclerosis (MS) has increased the expectations for disease control. This has made it crucial to use measures able to accurately evaluate the impact of therapeutic intervention, shifting the treatment paradigm of MS from partial response to remission.¹

Measures combining both clinical and MRI activity are increasingly used in MS to assess patients' disease status and capture the beneficial effect of disease-modifying therapies (DMTs). In particular, the concept of no evidence of disease activity (NEDA) has become an appealing new outcome measure in clinical trials and a conceivable goal for the treatment of MS.^{1,2} NEDA is currently defined by incorporating absence of activity due to new/enlarging MRI lesions and clinical relapses as well as absence of sustained disability progression as measured by the Expanded Disability Status Scale (EDSS). Since this definition is heavily weighted towards focal inflammatory disease activity, the addition of measures of brain volume loss (BVL) to the NEDA definition (NEDA-4) has been proposed recently for a more comprehensive assessment of both disease activity and worsening.³

Most of the current NEDA assessments in patients with MS have been done as exploratory analyses of clinical trials²⁻⁴ and therefore have a limited time frame (e.g., 2-3 years). Recently, a longer study from a real-world cohort of patients with RRMS under mixed drug therapies has been performed,⁵ showing that NEDA can be found over 7 years in a minimal proportion of patients with MS (7.9%). To provide new insights into the long-term persistence of NEDA, we performed a study assessing NEDA and NEDA-4 in a cohort of patients with RRMS with 10-year clinical and MRI follow-up.

Methods. Ninety-one patients with RRMS (mean \pm SD age 34.2 ± 8.4 years, disease duration 5.3 ± 6 years, median EDSS 1.5, 71% female) were recruited between January 2000 and May 2001 among those who were referred to the MS Clinics of the Universities of Siena and Florence, and the Hospital of Empoli, Tuscany, Italy. During an average follow-up of 10.2 years (range 9.3-12.5), patients underwent yearly

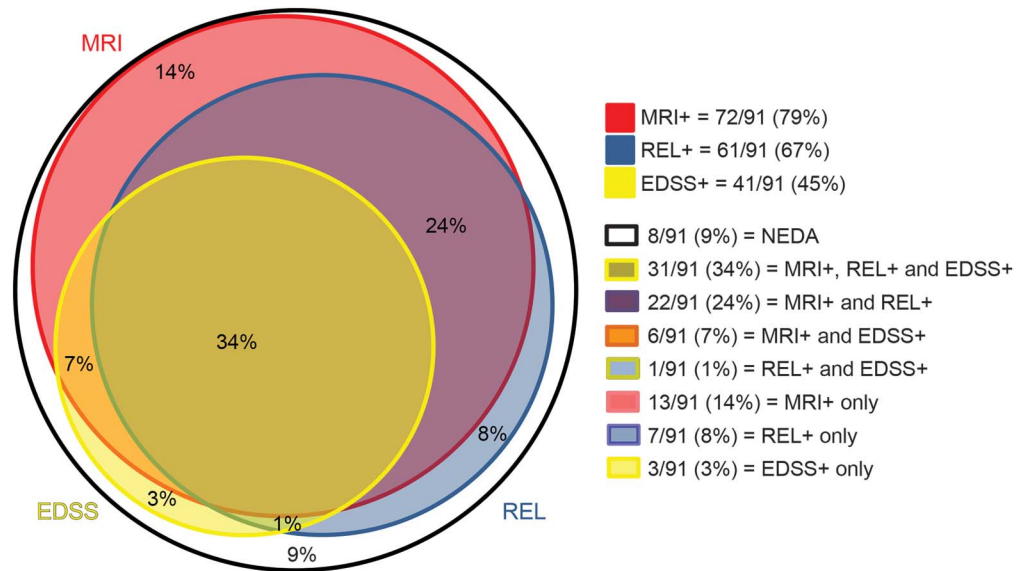
clinical assessment, which included relapse recording and EDSS scoring, and 2 identical brain MRI examinations (at start and end of study). Brain MRIs were acquired using the same 1.5T Philips Gyroscan (Philips Medical Systems, Best, the Netherlands) and an identical protocol consisting of a dual-echo, turbo spin-echo sequence yielding proton density and T2-weighted images for assessment of brain lesions and T1-weighted images for measurement of BVL (quantified using the SIENA method⁶). During the follow-up, 83/91 patients were under treatment: 79 with injectable, first-line drugs (i.e., interferons or glatiramer acetate) and 4 with immunosuppressants; 13 patients were unresponsive to first-line drugs and were thus switched to second-line therapies. NEDA was defined as absence of new/enlarging T2 lesions on MRI, clinical relapses, and sustained EDSS progression (defined as an EDSS increase of at least 1 point confirmed 6 months apart). NEDA-4 was also assessed, keeping the annualized value of -0.4% as the cutoff for no evidence of BVL as previously described.⁷

The Ethics Committee of the Azienda Ospedaliera Universitaria Senese approved this study.

Results. At follow-up, 19/91 patients with RRMS were free from MRI activity (21%), 30/91 were free from relapses (33%), and 50/91 were without sustained EDSS progression (55%) (figure). Also, 34/91 patients (37%) showed BVL below the defined annualized value of -0.4% . There were no clear differences in NEDA between treated and untreated patients, likely due to the small sample size of the latter group.

Discussion. NEDA can represent the benchmark in the management of patients with MS, but a recent study has shown difficulties in sustaining this target in the long term even with treatment. The present study extends previous work, providing compelling evidence that NEDA, although it is known to occur more in patients with treated vs untreated MS in the short term,³ rarely persists after 10 years in a real-world cohort of patients with RRMS. Interestingly, NEDA is even more difficult to sustain when a marker of diffuse brain tissue damage and potentially of neurodegeneration, such as BVL, is included in the definition (i.e., NEDA-4). In this respect, it needs to

Figure Detailed description of disease activity in the 3 main no evidence of disease activity (NEDA) components in our patients with relapsing-remitting multiple sclerosis



Red, blue, and yellow circles represent, respectively, patients with evidence of new MRI lesions (MRI+), clinical relapses (REL+), or sustained disability progression (Expanded Disability Status Scale [EDSS]+). Circles with mixed colors represent patients with evidence of disease activity in more than one outcome measure. The white circle represents the remaining NEDA patients.

be stressed that, although most patients were under treatment with DMTs, the study was started at a time when only injectable DMTs were available, and so it is likely that more patients could reach NEDA-4 with modern DMTs.³

Results of the study suggest that NEDA remains an interesting outcome for clinical trials, but might not be an easy goal in the clinical setting with current DMTs.

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