Minimal or No Evidence of Disease Activity: which target to prevent long-term disability in multiple sclerosis?

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INTRODUCTION

The No Evidence of Disease Activity (NEDA) is a desirable outcome measure for the treatment of relapsing-remitting multiple sclerosis (RRMS) [1].

However, NEDA represents a stringent goal to achieve, especially with platform therapies [2]. Therefore, Minimal Evidence of Disease Activity (MEDA) has been proposed as a more realistic target that can be tolerated without any significantly increased risk of future disability worsening [3].

Aim of our study is to investigate the effect of early NEDA or MEDA status on long-term disability outcome in RRMS patients who started a standard platform treatment with Interferon Beta (IFNB) or Glatiramer Acetate (GA).

METHODS

We collected data of patients with RRMS regularly attending 3 Italian MS Centres. Patients were considered eligible if they started IFNB or GA as first treatment, had an Expanded Disability Status Scale (EDSS) score ≤4.0 and were followed for ≥5 years. They were classified in subgroups according to level of disease activity after the first year of treatment:

(i) NEDA, i.e. absence of relapses, of confirmed EDSS worsening and of magnetic resonance imaging (MRI) activity;

(ii) MEDA (different definitions were tested, see **TABLE 1**);

(iii) Evidence of disease activity (EDA), i.e. the counterpart of NEDA and MEDA status.

We ran multivariable Cox regression models (stratified by Centre) to explore the long-term risk of reaching the disability milestone of EDSS≥6.0 according to one-year status (NEDA, MEDA or EDA) by exploring different definition of disease activity as shown in TABLE 1). Baseline variables such as sex, age, MS duration, EDSS score, no. of relapses in previous year, no. of GD+ lesions, were inserted in models as covariates of no interest. Treatment escalation or lateral switching during the follow-up was also inserted in models as time-dependent covariate to account for the effect of monoclonal antibodies on disability. [Phillips JT et al 2013].

RESULTS

We analyzed 1,195 patients (822 F, 373 M) with mean age of 33.9±9.6 years, median MS duration of 3 years (range: <1 to 35) and median EDSS score of 1.5 (range: 0 to 4.0). Of them, 1,061 (89%) and 134 (11%) were treated with IFNB and GA, respectively.

Overall, 209 (17.5%) patients reached EDSS≥6.0 after a median time of 9 years (range 2-22).

The risk of reaching EDSS≥6.0 was higher in the event of one-year EDA (HRs from 1.77 to 1.88, p≤0.001) regardless of the adopted definition (see **TABLE 2**).

We found no significant difference bewteen NEDA and MEDA when definition 'A' and 'B' were adopted (p>0.3). On the other hand, patients with MEDA (according to definition 'C') were at higher risk of reaching the disability milestone of EDSS ≥6.0 when compared with those who had NEDA at 1-year visit (p=0.017).

The risk of reaching the disability milestone was approximately 2.5% per year in the event of EDA (regardless of definition adopted), 1.5% per year in the event of MEDA (according to definition 'A' and 'B') and 2.0% in the event of MEDA according to 'C' definition (see **FIG. 1**).

CONCLUSIONS

Our findings suggest that we should treat patients with RRMS to target the NEDA status as early as possible to prevent the risk of future irreversible disability. However, we could tolerate even a MEDA, defined as no more than 1 GD+ lesion and 1-2 new T2 lesions at one-year MRI scan. We should not tolerate the occurrence of a single relapse in the first treatment year, even if accompanied by minimal MRI activity.

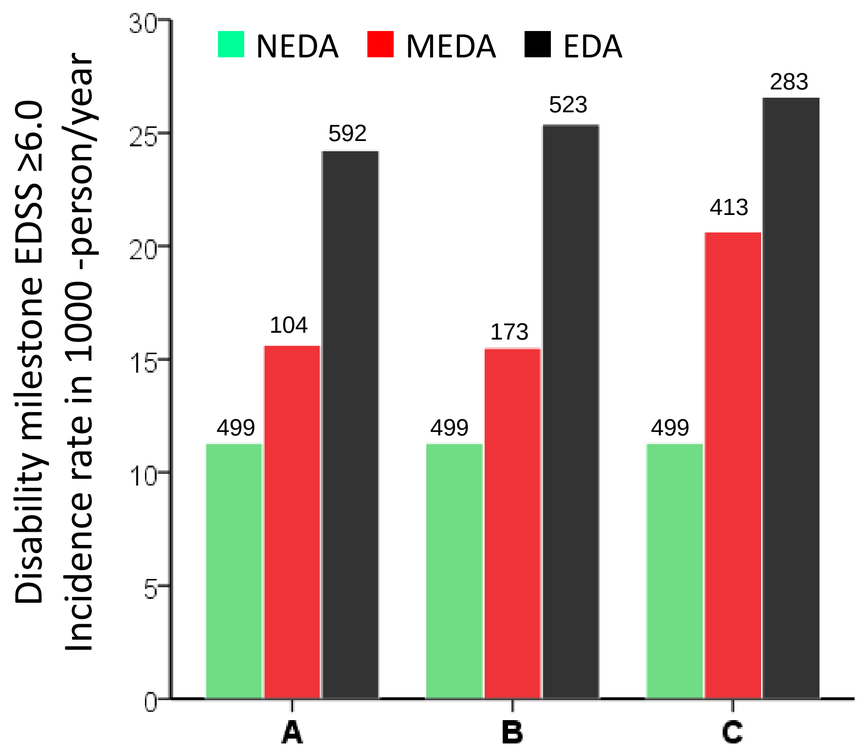
TABLE 1. Different definition of Minimal Disease Activity (MEDA) based on occurrence of relapses and MRI features in the first treatment year.

	Relapses		GD+ lesions		New T2 lesions
A	**0**	*and*	**0**	*and*	**1-2**
B	**0**	*and*	**1**	*and/or*	**1-2**
C	**1**	*and/or*	**1**	*and/or*	**1-2**

TABLE 2. Hazard ratios and their relative 95% confidence intervals for the risk of reaching the disability milestone of EDSS ≥6.0, according to different definition of MEDA.

	NEDA	MEDA	EDA
A	1.00	1.10 (0.61-2.00)	**1.77 (1.26-2.49)**
B	1.00	1.30 (0.79-2.15)	**1.78 (1.25-2.48)**
C	1.00	**1.55 (1.08-2.22)**	**1.88 (1.27-2.80)**

FIG. 1. Risk per year of reaching the disability milestone of EDSS ≥6.0 according to different definition of MEDA.



REFERENCES

[1] Giovannoni G et al. Mult Scler 2017
[2] Rotstein DL et al. JAMA Neurol 2015
[3] Río J et al. Mult Scler 2017
[4] Phillips JT et al. Mult Scler 2011