Journal of the Neurological Sciences 361 (2016) 158–167

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review article

Short-term suboptimal response criteria for predicting long-term non-response to first-line disease modifying therapies in multiple sclerosis: A systematic review and meta-analysis

Jordi Río [a,*], Juan Luís Ruiz-Peña [b]

[a] Centre d'Esclerosi Múltiple de Catalunya (CEM-Cat), Servei de Neurologia-Neuroimmunologia, Hospital Universitari Vall d'Hebron, Psg. Vall d'Hebron 119–120, Barcelona 08035, Spain
[b] Unidad de Esclerosis Múltiple, Hospital Universitario Virgen Macarena, Avd. Dr Fedriani, 3, Sevilla 41071, Spain

ARTICLE INFO

Article history:
Received 27 July 2015
Received in revised form 7 December 2015
Accepted 28 December 2015
Available online 29 December 2015

Keywords:
Multiple sclerosis
Interferon beta
Glatiramer acetate
Suboptimal response
Disability
Prediction

ABSTRACT

Introduction: There is no consensus about short-term suboptimal response to first-line treatments in relapsing-remitting multiple sclerosis.
Methods: We searched studies with interferon beta or glatiramer acetate in which a long-term (≥2 years (y)) outcome could be predicted using short-term (≤1 y) suboptimal response criteria (EDSS-, imaging- and/or relapse-based). We obtained pooled diagnostic accuracy parameters for the 1-y criteria used to predict disability progression between 2–5 y.
Results: We selected 45 articles. Eight studies allowed calculating pooled estimates of 16 criteria. The three criteria with best accuracy were: new or enlarging T2-weighted lesions (newT2) ≥ 1 (pooled sensitivity: 85.5%; specificity:70.2%; positive predictive value:48.0%; negative predictive value:93.8%), newT2 ≥ 2 (62.4%, 83.6%, 55.0% and 87.3%, respectively) and RIO score ≥ 2 (55.8%, 84.4%, 47.8% and 88.2%). Pooled percentages of suboptimal responders were 43.3%, 27.6% and 23.7%, respectively. Pooled diagnostic odds ratios were 14.6 (95% confidence interval: 1.4–155), 9.2 (1.4–59.0) and 8.2 (3.5–19.2).
Conclusions: All criteria had a limited predictive value. RIO score ≥ 2 at 1-y combined fair accuracy and consistency, limiting the probability of disability progression in the next years to 1 in 8 optimal responders. NewT2 ≥ 1 at 1-y had similar positive predictive value, but diminished the false negatives to 1 in 16 patients. More sensitive measures of treatment failure at short term are needed.

Contents

* Corresponding author at: Unitat de Neuroimmunología Clínica, 2ª planta antiga EUI, Hospital Universitari Vall d'Hebron, Psg. Vall d'Hebron 119–120, Barcelona 08035, Spain.
E-mail address: jrio@cem-cat.org (J. Río).

http://dx.doi.org/10.1016/j.jns.2015.12.043
0022-510X/

1. Introduction

Multiple Sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by inflammation and destruction of myelin and axons [1,2]. In most patients, the disease has a relapsing-remitting course during the first years, with repeated episodes of relapses. Within 10 years, approximately 50% of patients progress to secondary progressive MS (SPMS). Due to the variability in the clinical presentation and the heterogeneity in the response to disease-modifying therapies (DMTs), the long-term individual prognosis of disease is not yet feasible in an accurate manner.

Several DMTs have demonstrated sustained reduction of relapse rate and delayed disability progression versus placebo in relapsing–remitting multiple sclerosis (RRMS) [3–6]. Currently, authorized first-line treatments are considered equally effective, and include interferon beta (IFN-β) and glatiramer acetate (GA). In clinical trials with these therapies, outcomes of non-response (24 months after treatment initiation) have been defined based on several criteria, such as disability progression, relapse rate, increased burden or activity detected by magnetic resonance imaging (MRI), or further neurologic or cognitive impairment [3–6].

Within the first months after DMT initiation, most patients already show persistent clinical activity, which may be considered as a suboptimal response. In these cases, possible strategies include switching to another first-line DMT or to a second-line DMT [7]. Natalizumab and fingolimod have demonstrated high efficacy and effectiveness in patients previously non-responding to IFN-β or GA. An accurate and timely assessment of suboptimal response in this period would allow an early switch before neurological damage progresses too much.

Since the commercialization of the first IFN-β in 1993, many different criteria based on relapses, disability progression, MRI or combinations of these have been proposed for defining suboptimal response. In 2004, the Canadian Multiple Sclerosis Working Group developed recommendations based on monitoring relapses, neurological progression and MRI activity [8], which were subsequently evaluated in several cohorts [9,10]. The Rio score has been recently proposed. This score is based on disability progression, relapses and MRI [11], which was tested (and further modified and refined) in other cohorts [12–14]. Other criteria have also been defined by the European Medicines Agency in the label specifications of second-line drugs [15] or by the drug agencies of several countries, such as Italy [16]. The absence of an international consensus definition is probably due to several causes: the lack of a criterion with high predictive value and/or validated in sufficient number of patients, different follow-up procedures among centers, different regulatory criteria among countries, etc.

In the selection of an optimal predictive criterion, there is usually a trade-off between the measures of performance. The best criterion should be characterized by the lowest possible number of "false positives" (i.e. patients in whom treatment is unnecessarily switched) and by the lowest possible number of "false negatives" (i.e. patients in whom treatment is not switched despite having suboptimal response). Since both categories are inversely correlated and strongly associated to the degree of restriction imposed by the selected definition (Fig. 1), the more restrictive criteria fail to detect a significant number of suboptimal responders, whereas the less restrictive ones lead to an unacceptable rate of false positives.

The objectives of the present systematic review were: to describe all criteria that have been used in the literature to define long-term (≥2 years since treatment initiation) and short-term (≤2 years since treatment initiation) non-response to IFN-β or GA; to describe the predictive value of the short-term suboptimal response criteria for long-term non-response and to calculate the pooled diagnostic accuracy parameters in those criteria used in more than one cohort with similar definition of long-term non-response (increase in EDSS ≥ 1 between 2 and 5 years after treatment initiation).

2. Methods

See extended version in Annex 1 (online).

2.1. Literature search and eligibility criteria

Studies were searched in Pubmed, SCOPUS (MEDLINE, EMBASE), Web of SCIENCE and the lists of references of articles. The search was done on July 2nd, 2014 (Fig. 2).

We limited the search to articles published between 1993 and 2014 and written in English language (see Annex 2 for detailed search strategy). The retrieved manuscripts were further selected according to the additional criteria: adults aged 18 years and over; RRMS diagnosis; treatment with IFN-ß or glatiramer; one or more short-term suboptimal response criteria (including at least EDSS and/or MRI parameters and/or relapse rate) measured post-treatment initiation (at a maximum of

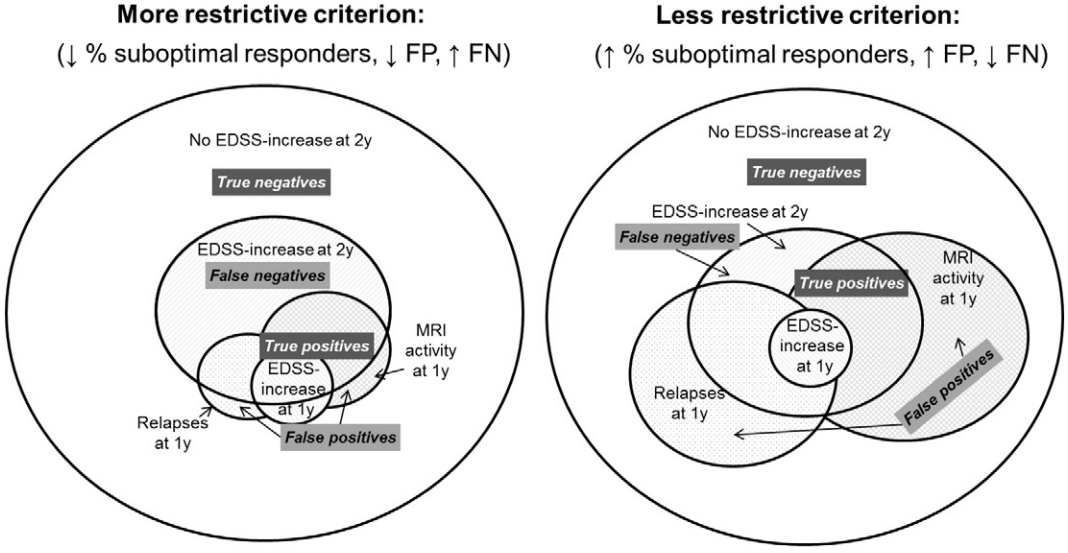

Fig. 1. Relationship between restrictiveness and predictive value of the clinical and radiological suboptimal response criteria used to predict long term non-response to first-line DMTs in RRMS (FN = false negatives; FP = false positives; y = year).