Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: informahealthcare.com/journals/iern20

MRI for monitoring response to preventive treatment in multiple sclerosis

Carlo Pozzilli, Nikolaos Petsas & Luca Prosperini

To cite this article: Carlo Pozzilli, Nikolaos Petsas & Luca Prosperini (2009) MRI for monitoring response to preventive treatment in multiple sclerosis, Expert Review of Neurotherapeutics, 9:3, 305-307, DOI: 10.1586/14737175.9.3.305

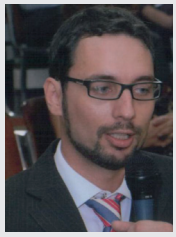
To link to this article: https://doi.org/10.1586/14737175.9.3.305

Published online: 09 Jan 2014.

MRI for monitoring response to preventive treatment in multiple sclerosis

Expert Rev. Neurother. 9(3), 305–307 (2009)

Carlo Pozzilli
Author for correspondence
Multiple Sclerosis Centre, S. Andrea Hospital, Department of Neurological Sciences, 'La Sapienza' University, Via di Grottarossa, 1035-00189, Rome, Italy
Tel.: +39 063 377 5686
Fax: +39 063 377 5900
carlo.pozzilli@uniroma1.it



Nikolaos Petsas
Multiple Sclerosis Centre, S. Andrea Hospital, Department of Neurological Sciences, 'La Sapienza' University, Rome, Italy
Tel.: +39 063 377 5686
Fax: +39 063 377 5900
petsas@gmail.com

Luca Prosperini
Multiple Sclerosis Centre, S. Andrea Hospital, Department of Neurological Sciences, 'La Sapienza' University, Rome, Italy
Tel.: +39 063 377 5686
Fax: +39 063 377 5900
luca.prosperini@uniroma1.it

> "...early identification of patients with a poor response to first-line therapy may represent a crucial point to lead a different therapeutic approach."

Treatment options in multiple sclerosis (MS) have dramatically broadened over the past decade: immunomodulatory drugs, such as IFN-β and glatiramer acetate (GA), are currently applied as first-line therapies to prevent disease activity in relapsing–remitting MS (RR-MS) patients [1–4]. A recent observational study based on data from a large cohort of RR-MS Italian patients suggested that IFN-β treatment was associated with a significant reduction in the incidence of secondary progression and reaching Expanded Disability Status Scale (EDSS) scores 4.0 and 6.0 [5], two important milestones in the history of the disease, corresponding to limited walking ability and the need for unilateral support when walking, respectively. Nevertheless, a high degree of variability is present in terms of disease activity among patients during treatment and a relevant number of subjects treated with IFN-β or GA continue to experience clinical bouts and disease progression.

Since alternative drugs more active against MS are currently available (i.e., mitoxantrone [6] or natalizumab [7]) and some current Phase III investigational therapies, in particular oral drugs (cladribine, teriflunomide, fumarate, fingolimod and laquinomid), are going to be available within a few years [8], early identification of patients with a poor response to first-line therapy may represent a crucial point to lead a different therapeutic approach. There are some difficulties in detecting those patients, because a clear and shared definition for the lack of response to immunomodulating therapies in RR-MS patients does not exist. Moreover, the majority of data were obtained in subjects under IFN-β treatment, while there are no data available on patients treated with GA.

It has been suggested that criteria based on disability progression are more sensitive and more specific than criteria based on relapse rate in patients on IFN-β therapy [9]. Moreover, the potential variables predictive of 'good' or 'poor' response to IFN-β closely depend on the *a priori* criterion assumed [10]. Some clinical markers, such as disease duration, disability level and relapse rate prior to IFN-β, have been suggested as predictors of poor therapeutic response [11–13]. However, the studies investigating the predictive value of the aforementioned variables are conflicting in terms of results and overall based on short-term follow-up (2–4 years).

> "...conventional MRI represents a useful and accurate tool to detect signs of subclinical disease activity."

Therefore, since clinical data were unsuitable to judge response to treatment, several studies have been performed in order to clarify the use of conventional MRI in detecting the disease activity during therapy [14–18]. It has already been well established that conventional MRI represents a useful and accurate tool to detect signs of subclinical disease activity. The occurrence of new active lesions (i.e., gadolinium-enhancing lesions on T1-weighted postcontrast sequences) was five- to tenfold more frequent than a clinical relapse, although with a great variability among individuals [19]. In addition, it has been shown that histopathology findings better correlate with MRI than clinical signs [20]. Finally, since it gives highly reproducible measures on ordinals scales and allows a higher level of blinding, MRI represents a powerful

EXPERT REVIEWS

 10.1586/14737175.9.3.305 ISSN 1473-7175

surrogate marker of latent disease activity adopted in randomized controlled trials [19]. At present, MRI variables are used as primary outcome measures of treatment efficacy in Phase II studies and as a supportive secondary outcome in Phase III trials.

As it is noninvasive and increasingly available, the use of conventional MRI to evaluate response to treatment in daily clinical practice may provide an important index of long-term first-line therapy effectiveness. Since the mechanism of action of immunomodulating drugs encompasses the suppression of the inflammatory component of the disease [21], detecting persistent signs of subclinical activity during IFN-β or GA use may induce a high level of concern in the treating neurologist.

> **"…the use of conventional MRI to evaluate response to treatment in daily clinical practice may provide an important index of long-term first-line therapy effectiveness."**

Some studies suggested that MRI parameters considered during treatment (i.e., the accumulation of new hyperintense lesions in T2-weighted sequences, the occurrence of enhancing areas in T1-weighted postcontrast sequences, the presence of T1-hypontense lesions ['black holes'] and the development of brain atrophy) might be useful to define the patient response status to IFN-β [14–18].

Natural history studies indicate that the presence of enhancing lesions, even on a single MRI scan, is associated with an increased risk of clinical relapses and forecasts subclinical demyelination in untreated patients with a clinically isolated syndrome (CIS) suggestive of MS or a RR-MS course [22,23]. In addition, detecting gadolinium-enhancing lesions on a single MRI scan is an easier procedure in evaluating the efficacy of the ongoing therapy and does not require a baseline assessment.

Nevertheless, it has been demonstrated that the appearance of new hyperintense areas on T2-weigthed sequences after 6–12 months of treatment is a more sensitive method for identifying a suboptimal therapeutic response, representing the disease activity accrued over time [16,18]. The lesion burden as seen on T2-weighted sequences than gadolinium-enhancing lesions at the time of the clinical presentation is more predictive of the clinical course of the disease and the extent of disability in CIS [24]. Also, there is evidence that IFN-β exerts a beneficial effect in reducing new T2 lesion formation over at least 4 years [25]. Therefore, an increase in T2 lesion burden in patients receiving therapy may represent an important marker of suboptimal response, as demonstrated by some independent, postmarketing surveys.

A *post hoc* analysis of the pivotal trial on intramuscular IFN-β-1a indicated that patients with significant disease activity, as measured by new T2 lesions during therapy with IFN-β, had outcomes very similar to placebo-treated patients [16], not only in terms of disability outcome (mean change in EDSS score and in Multiple Sclerosis Functional Composite [MSFC] score), but also in terms of development of brain atrophy, which was shown to be more significantly related to disability compared with conventional MRI measures. More recently, Rio and colleagues confirmed these findings, demonstrating that the occurrence of two or more active lesions (i.e., the new or enlarging T2-weighted lesions plus gadolinium-enhancing T1-weighted lesions) on the 12-month MRI scan had a prognostic value for identifying patients with a confirmed increase in disability after 2 years of therapy [18].

The main problem for the use of new T2-hyperintense lesions is that their detection is resolution- and slice thickness-dependent and, therefore, an approach based on the comparison between baseline and follow-up images requires a careful accuracy in repositioning the patient.

In conclusion, we are entering the second era of MS treatment, since biological and oral drugs will be available in the next few years for the prevention of MS attacks and disability progression. Nevertheless, it is likely that immunomodulating treatment will continue to be the first-line therapy in CIS and RR-MS patients, mainly owing to the important safety concerns of the novel therapeutic agents. The identification of potential candidates to different therapeutic approaches represents a key point in improving MS management. Therefore, MRI variables, especially the early accumulation of new T2-hyperintense lesions during immunomodulating therapy, may represent more accurate and useful markers in detecting suboptimal response to treatment.

Financial & competing interests disclosure

Carlo Pozzilli has received honoraria for consultancy or speaking from Sanofi Aventis, Biogen, Bayer Schering and Novartis, and research grants from Merck Serono and Sanofi Aventis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

• of interest

1 The IFN β Study Group. Interferon β-1b is effective in relapsing–remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFN β Multiple Sclerosis Study Group. *Neurology* 43, 655–661 (1993).

2 Jacobs LD, Cookfair DL, Rudick RA *et al.* Intramuscular interferon β-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann. Neurol.* 39, 285–294 (1996).

3 PRISMS (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) study group. Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. *Lancet* 352, 1498–1504 (1998).

4 Johnson KP, Brooks BR, Cohen JA *et al.* Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a Phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. *Neurology* 45, 1268–1276 (1995).

5 Trojano M, Pellegrini F, Fuiani A *et al.* New natural history of interferon-β-treated relapsing multiple sclerosis. *Ann. Neurol.* 61, 300–306 (2007).

6 Hartung HP, Gonsette R, König N *et al.* Mitoxantrone in Multiple Sclerosis Study Group (MIMS). Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 360, 2018–2025 (2002).

7 Polman CH, O'Connor PW, Havrdova E *et al.* A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N. Engl. J. Med.* 354, 899–910 (2006).

8 Gasperini C, Ausili Cefaro L, Borriello G *et al.* Emerging oral drugs for multiple sclerosis. *Expert Opin. Emerg. Drugs* 13, 465–477 (2008).

9 Rio J, Nos C, Tintoré M *et al.* Defining the response to interferon β in relapsing–remitting multiple sclerosis patients. *Ann. Neurol.* 59, 344–352 (2006).

- **Shows that the proportion of patients defined as IFN-β responders changes according to predefined criteria of suboptimal response to therapy.**

10 Portaccio E, Zipoli V, Siracusa G *et al.* Response to interferon-β therapy in relapsing-remitting multiple sclerosis: a comparison of different clinical criteria. *Mult. Scler.* 12, 281–286 (2006).

- **Shows that the clinical characteristics able to predict clinical response change according to predefined criteria of suboptimal response to therapy.**

11 Trojano M, Liguori M, Paolicelli D *et al.* Interferon β in relapsing-remitting multiple sclerosis: an independent post-marketing study in southern Italy. *Mult. Scler.* 9, 451–457 (2003).

12 Waubant E, Vukusic S, Gignoux L *et al.* Clinical characteristics of responders to interferon therapy for relapsing MS. *Neurology* 61, 184–189 (2003).

13 O'Rourke K, Walsh C, Antonelli G *et al.* Predicting β-interferon failure in relapsing–remitting multiple sclerosis. *Mult. Scler.* 13, 336–342 (2007).

14 Koudriavtseva T, Pozzilli C, Fiorelli M *et al.* Determinants of Gd-enhanced MRI response to IFN β-1a treatment in relapsing-remitting multiple sclerosis. *Mult. Scler.* 4, 403–407 (1998).

15 Tomassini V, Paolillo A, Russo P *et al.* Predictors of long-term clinical response to interferon β therapy in relapsing multiple sclerosis. *J. Neurol.* 253, 287–293 (2006).

16 Rudick R, Lee J, Simon J. Defining interferon β response status in multiple sclerosis patients. *Ann. Neurol.* 56, 548–555 (2004).

- **A *post hoc* analysis showing that the occurrence of new MRI lesions during therapy correlates with a lack of response to IFN-β.**

17 Durelli L, Berbero P, Bergui M *et al.* MRI activity and neutralizing antibody as predictor of response to IFNB treatment in MS. *J. Neurol. Neurosurg. Psychiatry* 79, 646–651 (2008).

18 Rio J, Rovira A, Tintoré M *et al.* Relationship between MRI lesion activity and response to IFN-β in relapsing–remitting multiple sclerosis patients. *Mult. Scler.* 14, 479–484 (2008).

19 Miller DH, Albert PS, Barkhof F *et al.* Guidelines for the use of magnetic resonance techniques in monitoring the treatment of multiple sclerosis. US National MS Society Task Force. *Ann. Neurol.* 39, 6–16 (1996).

20 Traboulsee A. MRI relapses have significant pathologic and clinical implications in multiple sclerosis. *J. Neurol. Sci.* 256, 19–22 (2007).

21 Yong VW. Differential mechanisms of action of interferon-β and glatiramer acetate in MS. *Neurology* 59, 802–808 (2002).

22 Barkhof F, Filippi M, Miller DH *et al.* Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 120, 2059–2069 (1997).

23 Koudriavtseva T, Thompson AJ, Fiorelli M *et al.* Gadolinium enhanced MRI predicts clinical and MRI disease activity in relapsing-remitting multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry* 62, 285–287 (1997).

24 Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N. Engl. J. Med.* 346, 158–64 (2002).

25 PRISMS (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) Study Group and UBC MS/MRI Analysis Group. PRISMS-4: long-term efficacy of interferon β-1a in relapsing MS. *Neurology* 56, 1628–36 (2001).