My MRI worsened but I didn't. Should I change my disease-modifying treatment?

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Abstract

It is imperative to recognize multiple sclerosis (MS) patients with high risk of disability progression as soon as possible and offer them more potent treatment.

Data about the influence of early conventional MRI parameter worsening (without clinical progression or relapses) on early or late disability in treated MS patients are available mainly for interferons beta. Some of the studies showed that the development of new T2 or Gd enhancing lesions in the first year of interferon beta treatment predicted second and third year disease activity or worse late clinical outcome, but some of the studies were negative. The first-year MRI activity was not associated with clinical worsening of the disease in the next two years in patients treated with glatiramer acetate. There are no data which would indicate that the MRI-only worsening in patients treated with the oral drugs or monoclonal antibodies predicts poor outcome.

There are many caveats which also need to be taken into account when considering an individual patient with the MRI-only worsening for escalation of therapy such as adherence to the injectables, presence of neutralizing antibodies, large interrater variability for comparative MRI data and adverse effects of the second-line drugs. Therefore a close clinical and MRI follow-up of patients with the MRI-only worsening is appropriate but escalation should be given only to those with more realistic risk of a poor prognosis.

Keywords: Multiple sclerosis, Treatment, Prognosis, MRI

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**Introduction**

Modern multiple sclerosis (MS) therapy includes more than 10 drugs which affect the disease course. More powerful drugs have a more severe adverse effects profile than moderately effective ones. For example, there is a risk of progressive multifocal leukoencephalopathy in patients treated with natalizumab, cardiac effects of fingolimod and increased risk of autoimmune reactions such as thyroid disorders, immune thrombocytopenia or glomerulonephritis with alemtuzumab. Clinicians most often start treatment in an MS patient with safer, moderately effective agents and escalate when clinical activity occurs. Approximately 70% of patients will be stable on first-line agents and others will progress [1, 2].

It is imperative to recognize the disease worsening as soon as possible and offer more potent drugs to patients who need them. But who are those in need for more potent drugs, the ones with clinical disease worsening, relapses, MS progression or also patients with MRI only worsening?

**Does MRI worsening predict poor early or late prognosis?**

There were some studies performed in patients treated with interferons beta which showed that early MRI worsening predicted worse early and late future outcome, but the evidence is far from conclusive [1-4].

Prosperini and colleagues included more that 400 patients treated with interferons beta and followed them for 4 years [1]. Patients who had MRI worsening with new T2 lesions at year 1 were more likely to progress according to the EDSS score than patients without MRI activity. The effect of MRI lesions on late prognosis was augmented with approximately 10-fold increase for each T2 lesion [1]. Yet, the included patients were only mildly disabled. The patients with no disease activity had mean EDSS score 1.6 and the ones who worsened mean EDSS score 2.3. We are very well aware that there is a large interrater scoring variability for low EDSS scores. For example, in patients with additional purely subjective complaints such as fatigue and some sensory loss increased EDSS score would be found and they would fall into the "worsening" category. Furthermore, nearly 20% of patients with new T2 lesions on MRI had stable clinical course [1].

Bermel and colleagues analyzed data from the pivotal interferon beta-1a clinical trial [3]. Patients were treated with either intramuscular interferon beta-1a once weekly or placebo for 2 years and after that the treatment was not regulated by study protocol. Authors managed to found nearly 80% of patients after 15 years. The analysis of the data showed that the presence of at least 2 Gd enhancing lesions (HR nearly 9) or relapses (HR over 4) at year 2 was a strong predictor of late disability (EDSS scores from 4.5 to 8) but not the presence of T2 lesions [3].

The study from Barcelona showed different results [2]. Rio et al included more than 200 interferon beta treated patients and followed them for 3 years. They found that the clinical or clinical and radiological activity at year 1 was associated with relapses or worsening disability within the three years which was not seen with the MRI-only activity [2].

Dobson and colleagues performed a systematic review of studies examining long and short term prognosis in patients defined as responders and nonresponders to interferon beta [4]. They found, for example that a presence of Gd enhancing lesions at year one predicted more than 2 relapses in 5 years. On the other hand, presence of >1 T2 lesion at year 1 was not associated with worsening disability in the interferon treated MS patients over 2 years [4].

To summarize, there is some evidence that MRI activity predicts unfavorable early and late outcome in interferon beta treated patients, especially the presence of Gd enhancing lesions, but there were also many negative studies. It has to be said that the number of novel T2 or Gd lesions on the reference scans was different from study to study: from 1 T2 lesion, 2 or 3 T2 lesions and also from 1 to more than 2 Gd lesions which make the results of the studies even more difficult to interpret [1-4]. Some of the experts suggest that the appearance of additional 2–5 T2 lesions or 1–2 Gd enhancing lesions represents a threshold of concern for future relapses and disability [5].

There was only one study, again from Barcelona, in which the effect of clinical or radiological worsening on late disability in glatiramer acetate treated MS patients was investigated [6]. More than 150 patients were included in the study with a reference scan at year 1 and a follow-up for 3 years. The study revealed that the presence of clinical or clinical and radiological worsening at year one predicted future relapses or EDSS worsening which was not seen with the MRI only worsening [6].

So far there are no data which would indicate that the radiological only worsening in patients treated with the oral drugs or monoclonal antibodies is a poor long-term prognostic sign.

**Practical problems**

In order to interpret MRI worsening as a bad prognostic sign we have to be sure that the immunomodulatory drug-effect has begun. Some drugs, especially glatiramer acetate have a delayed mode of action, therefore the reference control scan should be obtained at a proper time which means at least after a half year for interferons and after 1 year for glatiramer acetate.

It is also known that compliance to the injectables can be very poor. The results of a recent study from Germany which included more than 50,000 patients treated with injectables showed that less than 40% of them were adherent to the therapy [7]. The data from our center (N=299) are not so discouraging with about 80% adherence rate [8].
We also need to have diligent radiologists with uniform MRI protocols for a proper interpretation of comparative MRI data. A recent study from the US showed that inter-rater variability can be very high among specialists when enlisting T2 lesions are compared and moderate when novel T2 and fortunately low when Gd enhancing lesions are analyzed [9].

The problem of neutralizing antibodies to interferons beta on early development of MRI lesions is not very high because antibodies usually appear by the end of a first year of treatment and have a delayed clinical and radiological effect [10].

The gathered data will probably further lose their importance because of a rapidly changing landscape of MS treatment. For example, in 2013 there were over 1300 patients in the MS Centre in Ljubljana, Slovenia, Approximately 50% of them were treated with immunomodulators, 90% of those with interferons or glatiramer acetate [11]. Dimethyl fumarate and teriflunomide became available in autumn 2014 and in just over a year 25% of patients switched from the injectables to the orals. Among patients who started with the first-line agents in our center in 2015 less than 15% started with the interferons or glatiramer acetate. Thus far there is no evidence that the MRI only worsening is associated with a bad future outcome in patients treated with the oral drugs.

**Unconventional MR parameters**

Brain volumetric MRI studies are not very useful and cannot guide physician in the early treatment decision making. The results of various studies showed that the effect of disease-modifying agents on brain volume is small and inconclusive [12]. There is also a problem of pseudo-atrophy which is usually seen during the first year of treatment with potent immunomodulators, such as natalizumab, where shrinking of the brain (instead of expected preservation) is observed because of a resolution of edema and antiinflammatory activity of the drugs [12].

**Conclusion**

There is some evidence that the MRI-only worsening predicts future relapses and poor late prognosis in interferon beta treated MS patients, yet the results of the studies are far from conclusive. Considering the side effects profile of more potent drugs, poor adherence to the injectables and difficulties with the MRI data comparison in the rapidly changing landscape of MS treatment I would not recommend escalation of therapy in patients with the MRI-only worsening. Common clinical reasoning with a closer follow-up is appropriate in patients with additional MRI lesions but more potent and riskier therapy should be given to the patients with clinical or clinical and radiological signs of activity.

**Abbreviations**

EDSS: Expanded Disability Status Scale; HR: Hazard ratio; MS: Multiple sclerosis

**Competing interests**

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**References**


