

Magnetic Resonance Imaging as a Major Milestone in Multiple Sclerosis Diagnosis and Treatment

Magnetik Rezonans Görüntüleme Multipl Skleroz Tanı ve Tedavisinde Temel Bir Kilometre Taşdır

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ABSTRACT

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system. Magnetic resonance imaging (MRI) has played a unique role in the diagnosis and management of patients with MS. In recent years, there have been considerable changes in the diagnostic criteria for MS as MRI-based studies have demonstrated their power in the earlier and more accurate diagnosis of the disease. Moreover, MRI metrics have become key supportive outcome measures for evaluating the efficacy of experimental treatments in randomized controlled trials. MRI can also be used as a prognostic tool in patients with clinically isolated syndrome (CIS). Conventional MR techniques including proton density, T1/T2-weighted images, and FLAIR sequences are now accepted in standard protocols for diagnostic and treatment outcome measures in clinical trials for MS. Radiological features may show a similarity between radiologically isolated syndrome and MS. Approximately two-thirds of individuals with RIS exhibit radiological progression and one-third develop neurological symptoms during mean follow-up times of up to five years. However, a current challenge in the global application of established criteria for RIS involves the accurate classification of subjects

with incidentally identified anomalies that are highly characteristic of MS, in comparison to those categorized in medical parlance as possessing "unidentified bright objects" or nonspecific T2-hyperintensities, which are commonly identified in patients with migraine headache who fulfill the spatial dissemination requirements for MS. The need for systematically acquired data for improvements in the classification of radiologically isolated syndrome (RIS) and the generation of risk algorithms are critically important, providing a basis for scientifically supported management and most importantly, minimizing the number of improperly classified subjects exposed to unnecessary medical testing, MS treatments, and psychological harm. In addition, brain atrophy is a common finding that can now be quantitatively assessed by MR volumetric measures. Further, integrated strategies that combine MRI and clinical markers in scoring systems have provided a potentially useful approach for the management of patients with MS.

Keywords: Multiple sclerosis, magnetic resonance imaging, diagnostic criteria

ÖZET

Multipl skleroz (MS), merkezi sinir sisteminin inflamatuvar demiyelizan bir hastalığıdır. Magnetik Rezonans Görüntüleme (MRG), MS hastalarının tanı ve tedavisinde eşsiz bir role sahiptir. Son yıllarda yapılan MRG bazı çalışmaları hastalığın daha erken ve kesin tanısında MRG'nin gücünü gösterirken, MS'in tanı kriterlerinde önemli değişiklikler olmuştur. Randomize, kontrollü çalışmalarda deneysel tedavilerin etkinliğini değerlendirmede MRG, temel destekleyici sonuç ölçüsü olmuştur. MRG, klinik izole sendromlu hastalarda da prognostik araç olarak kullanılabilir. Proton yoğunluğu, T1/T2-ağırlıklı imajlar ve FLAIR sekansı dahil geleneksel MR teknikleri MS klinik çalışmalarında tanı ve tedavi sonuç ölçümleri için standart protokol olarak kabul edilmektedir. Radyolojik özellikler RIS ve multipl skleroz arasında benzerlik gösterebilir. RIS'li hastaların yaklaşık üçte ikisi radyolojik progresyon gösterirken, üçte birinde beş yıllık takip süresinde nörolojik semptomlar gelişir. Ancak oluşturulan RIS kriterlerinin global uygulamasındaki mevcut sorun, medikal olarak "tanımlanmamış parlak objeler" olarak

adlandırılan veya yaygın olarak migren hastalarında tanımlanan MS'te alana göre dağılımı karşılayan spesifik olmayan T2-hiperintensitelere kıyasla MS için son derece karakteristik olan anomalilerin kazara tanımlanmasıyla kesin bir sınıflandırma yapılmasıdır. RIS sınıflandırmasını iyileştirmek için sistematik veriler ve risk algoritmalarının oluşturulması son derece önemlidir. Böylelikle bilimsel olarak desteklenen tedavi temeli sağlanır ve en önemlisi hatalı sınıflandırma nedeniyle gereksiz medikal testlere, MS tedavilerine ve psikolojik hasara maruz kalan hasta sayısı en aza indirilmiştir. Bunlara ek olarak, beyin atrofi MR volumetrik ölçümleriyle kuantitatif olarak değerlendirilebilen yaygın bir bulgudur. MRG ve skorlama sistemlerindeki klinik markörleri birleştiren entegre stratejiler MS hastalarının tedavisinde potansiyel olarak kullanışlı bir yaklaşım sağlamıştır.

Anahtar kelimeler: Multipl skleroz, magnetik rezonans görüntüleme, tanı kriterleri

INTRODUCTION

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease of the central nervous system that affects young adults.

Magnetic resonance imaging (MRI) has played an expanding and unique role in the diagnosis and management of MS since the beginning of its application by Young (1981) in this field. Sagittal fluid-attenuated inversion-recovery (FLAIR), axial T2A, FLAIR or double ecoT2A, axial T1A, gadolinium (Gd) sequences (0.1 mmol/kg, timing is important), axial and coronal T1A sequences are currently the standard methods for assessing clinical diagnosis in MS (1,2). MRI is also used as a prognostic tool at first presentation in patients with clinically isolated syndrome (CIS) (2).



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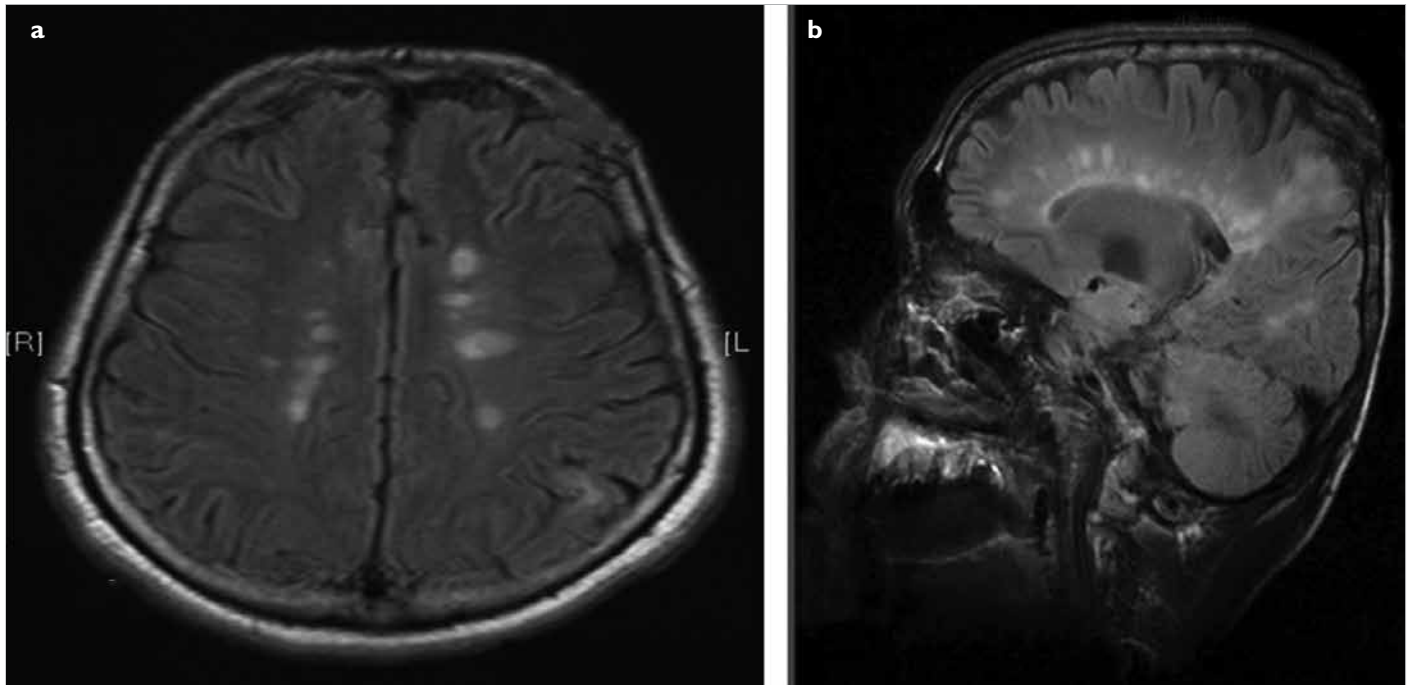


Figure 1. a, b. Axial T1-weighted and proton density images of patients with RRMS demonstrate multiple hyperintense lesions, mainly around the ventricles. Some of the lesions are enhanced in T1-weighted images with contrast. Note that all enhanced lesions have corresponding T2 hyperintensity. (b) Dawson's finger

MS LESIONS IN T2-WEIGHTED IMAGES

T2-weighted images are highly sensitive for the detection of MS lesions. The characteristic MR appearance of MS is multiple hyperintense lesions on this sequence. Typical lesions are usually round or oval and may occur in any part of the central nervous system where myelin is present. These lesions are more frequent in the periventricular area, but the juxtacortical and infratentorial regions are other common sites of involvement (Figure 1) (2).

Although MS is predominantly a disease of white matter, initially, 5–10% of the lesions may involve the gray matter (GM), including the cerebral cortex and basal ganglia. GM lesions are usually small with intermediate to high signal intensity and a less severe degree of inflammation, which may cause the appearance of GM lesions on MRI to be obscure compared with that of white matter lesions. MS lesions tend to have an ovoid configuration with the major axis perpendicular to the corpus callosum (Dawson's fingers) (2).

Conventional MR sequences, such as dual-echo, FLAIR, and T1-weighted imaging, both with and without the administration of a gadolinium-based contrast agent, provide important pieces of information for diagnosing MS, understanding its natural history, and assessing the treatment efficacy. Dual-echo and FLAIR imaging have high sensitivity for the detection of MS lesions, which appear as focal areas of hyperintensity on these types of images. However, there is a lack of specificity to the heterogeneous pathologic substrates of individual lesions (1).

MS LESIONS IN T1-WEIGHTED IMAGES WITH CONTRAST

Gadolinium-enhanced T1-weighted MR images enable active lesions to be distinguished from inactive ones because enhancement occurs as a result of increased permeability of the blood–brain barrier and corresponds to areas of ongoing inflammation (1).

The enhancement of MS plaques can precede new T2 lesions by hours or days. Most new lesions go through a phase of enhancement that usually persists for 2–6 weeks. It is extremely unusual for a lesion to exhibit

gadolinium enhancement beyond 6 months. The natural history of contrast-enhancing lesions is highly variable and unpredictable. Approximately 65–80% of contrast-enhancing lesions display corresponding hypointensity on native T1-weighted images. These acute hypointense lesions may become isointense or develop into persistent black holes. Some lesions may be visible for a relatively short period of time, some shrink or disappear, and others may eventually become permanent. It is generally believed that longer-lasting, ring-shaped, and larger lesions are more likely to form chronic black holes than a nodular enhancing lesion of shorter duration (2).

Further, enhancing lesions may vary in size, shape, or enhancement pattern. Most of them are small and display a homogeneous nodular pattern (68%), whereas 23% exhibit ring-like enhancement and 9% have other enhancement patterns (Figure 2). Ring enhancing lesions display higher levels of tissue destruction and therefore tend to resolve more slowly. None of these patterns are characteristic of MS. The only exception might be the “open-ring” sign for differentiating large tumor-like demyelinating lesions from actual tumors and infections. These lesions create an incomplete ring, and typically, the open section is oriented toward GM or is adjacent to it. An open-ring pattern can be seen in 66–90% of ring enhancements in demyelinating lesions compared with 6–17% in abscesses or tumors (2).

COMPARISON OF CURRENT MRI CRITERIA

Multiple sclerosis is ultimately a histopathological diagnosis. Till date, to increase sensitivity in diagnosing a patient, several clinical as well as radiological criteria have been developed. Clinical criteria essentially require the fulfillment of two prerequisites, i.e., the dissemination of the disease progress in both time and space (3). In 1983, Poser suggested that paraclinical evidence is used for diagnosis as clinically definite or laboratory-supported definite MS. The paraclinical support for MS consists of abnormalities that are detected via evoked potentials, cerebrospinal fluid analysis, or imaging techniques. The most sensitive paraclinical test is MRI, which shows abnormalities in approximately 95% of the patients with clinically definite MS (4), but MRI is not included in the Poser criteria. Individual MRI criteria, including gadolinium enhancement, are assessed in patients who are monitored

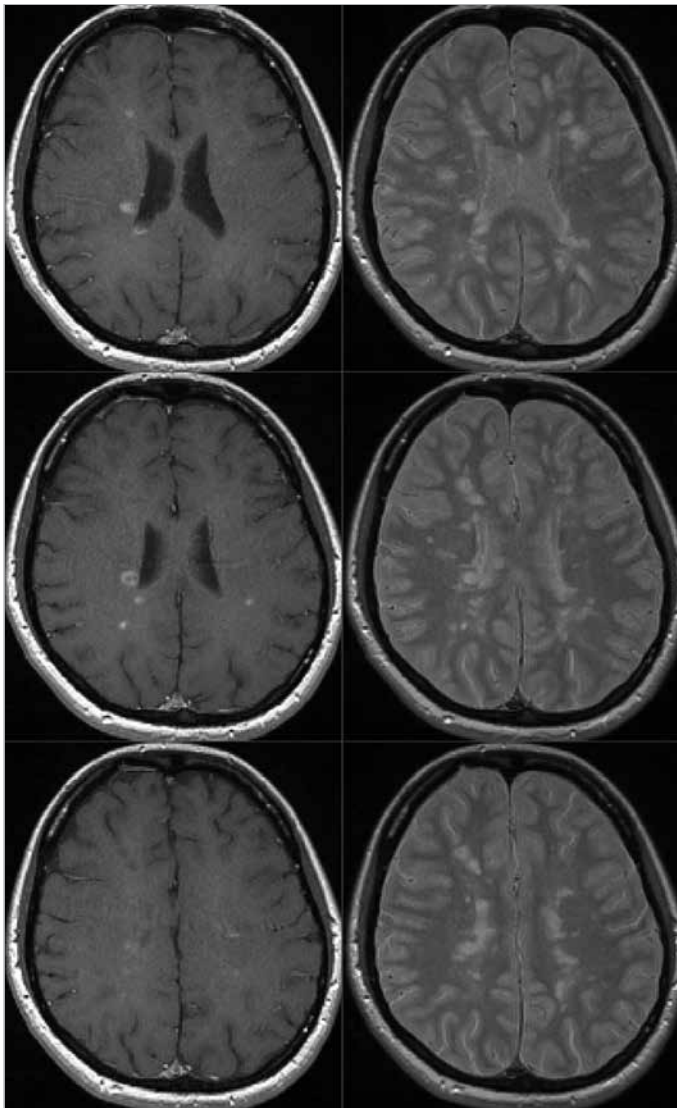


Figure 2. a-d. Axial T1-weighted and proton density images of a patient with RRMS demonstrate multiple hyperintense lesions, mainly around the ventricles. Some of the lesions are enhanced in T1-weighted images with contrast. Note that all enhanced lesions have corresponding T2 hyperintensity (2)

starting from the onset of symptoms and are used to determine up-to-date criteria with high predictive value for conversion to clinically definite MS. Moreover, a four-parameter dichotomized MRI model that includes gadolinium enhancement and juxtacortical, infratentorial, and periventricular lesions best predicts conversion to clinically definite MS (5).

In 2001, MRI was formally included in the diagnostic work-up for patients suspected of having MS by an international panel of MS experts who convened in London. This panel sought to reassess existing diagnostic criteria and recommend, if necessary, appropriate changes. The definition of MRI criteria for the diagnosis of MS is based on the demonstration of lesion dissemination in space (DIS) and dissemination in time (DIT) on dual-echo and post-contrast T1-weighted MR studies of the brain and on the exclusion of alternative neurological conditions (1).

In 2005, the original criteria from the International Panel on the Diagnosis of Multiple Sclerosis were revised in an attempt to simplify the approach while maintaining adequate sensitivity and specificity. The main changes that were introduced relate to the demonstration of the disease DIT, which can also be achieved via the detection of a new lesion with high

signal intensity on T2-weighted MRIs (hereafter, a T2-hyperintense lesion), if identified at any time since a reference MR study was performed at least 30 days after the onset of the first clinical event. The revised criteria also clarified the use of spinal cord MRI to demonstrate the disease DIS (1).

In 2010, the International Panel on the Diagnosis of MS met for a third time to examine requirements for demonstrating DIS and DIT and focusing on the application of the McDonald criteria in pediatric, Asian, and Latin American populations. The Panel found that the underlying concepts of the original (2001) and revised (2005) McDonald criteria are still valid, including the possibility of establishing a diagnosis of MS based on the objective demonstration of the dissemination of lesions in both space and time on clinical grounds alone or by the careful and standardized integration of clinical and MRI findings. However, the Panel now recommends key changes in the McDonald criteria that are related to the use and interpretation of imaging criteria for DIS and DIT as emphasized by the recently published work from the MAGNIMS research group (6).

The Panel accepted these MAGNIMS DIS Criteria, which can simplify the diagnostic process for MS while preserving specificity and improving sensitivity. The Panel recommends revisions to the McDonald criteria for the diagnosis of MS, focusing specifically on requirements to demonstrate DIS and DIT and on the diagnosis of primary progressive MS (6).

In summary, the 2010 revisions to the McDonald criteria will in some instances enable a more rapid diagnosis of MS, with equivalent or improved specificity and/or sensitivity compared with those of past criteria and will in many instances clarify and simplify the diagnostic process with fewer MRI examinations required. Moreover, the role and importance of RIS were discussed during the last revision of the McDonald Criteria (7).

RIS

Magnetic resonance imaging findings suggestive of MS in individuals without typical symptoms of MS and with normal neurological findings are defined as having RIS. Half the individuals with RIS have their initial MRI performed because of headache, and some have a subclinical cognitive impairment similar to that seen in MS. Radiological measurements also show a similarity between RIS and MS. Approximately two-thirds of individuals with RIS exhibit radiological progression and one-third develop neurological symptoms during mean follow-up times of up to five years. Cervical cord lesions are important predictors of clinical conversion (7).

Magnetic resonance imaging has become increasingly available since its clinical introduction in the early 1980s. Over 200 million MRI examinations had been performed by 2006, and the number of examinations continues to rapidly increase. With its increasing availability, there has also been an increase in the number abnormal incidental findings and an increased awareness of MRI findings suggestive of MS in patients without typical MS symptoms (7). In 2009, Okuda et al. defined this entity as RIS (8). Since then, studies have been published that describe the prognosis of small RIS cohorts and show that persons with RIS are at a high risk of developing MS. The prevalence of RIS ranges from 0.06% to 0.7% (7).

According to the published RIS cohorts, headache was by far the most common reason for performing MRI, and it seems to be the indication in about half the cases. Other less common indications were trauma and endocrinological and psychiatric disorders. The possibility of headaches in RIS being an early and/or atypical onset of demyelinating disease can therefore not be ruled out. A summary of the most common indications is presented in Figure 3 (7).

The following predictors increase the risk of clinical progression: cervical spine lesions, infratentorial lesions, a higher lesion number, pathological visual evoked potential, younger age, oligoclonal bands, and/or a pathological IgG index in combination with more than nine T2-lesions on the initial MR examination, and pregnancy shortened the time to clinical conversion in those who developed MS. Of these predictors, cervical spinal cord lesions were identified as important because of their high sensitivity, specificity, and positive predictive value for clinical conversion (7).

In the study by De Stefano et al. (9), non-conventional MRI methods in the form of magnetization transfer measurements and volumetric measurements were used to improve the characterization of RIS. This showed that patients with RIS and relapsing–remitting MS (RRMS) not only have a similar lesion volume and distribution but also have similar low brain volumes in comparison with those healthy controls (9). These results strengthen the association of RIS and MS and show that this kind of radiological data might be useful in classifying which individuals with RIS are at risk of developing MS (7).

Approximately two-thirds exhibit radiological progression on subsequent MRI examination, and from a clinical perspective, roughly one-third exhibit clinical conversion to CIS and/or MS in cohorts with a range of mean follow-up times of 2–5 years. Cervical spine lesions have been identified as important predictors for clinical conversion. Management is still a matter of debate, but there are two generally accepted approaches: wait and follow. This has to be individualized depending on available resources and the physician's and patient's views, as well as the presence of prognostic factors for clinical progression, with spinal cord lesions being an important finding (7).

IMPROVE STUDY

A new formulation of subcutaneous (sc) interferon (IFN)-beta 1a has been developed with the aim of improving tolerability of injection and reducing immunogenicity in the treatment of RRMS. A 96-week single-arm open-label study has assessed the safety and immunogenicity of this new formulation. The aim of the IMPROVE (Investigating MRI Parameters with Rebif imprOVEd formulation) study was to evaluate the short-term efficacy of this new sc IFN-beta 1a formulation compared with placebo in patients with relatively active RRMS (10).

Patients (n=180) were randomized (2:1) to IFN-beta 1a or placebo for 16 weeks; all patients then received IFN-beta 1a for 24 weeks. A monthly brain MRI scan was performed. The primary endpoint was the number of combined unique active (CUA) brain lesions on MRI at week 16 in the IFN-beta 1a group compared with the placebo group, using a baseline MRI scan as reference. The secondary endpoint was the number of CUA lesions/patient/scan during the double-blind phase (weeks 1–16) versus the rater-blinded phase (weeks 17–40) in patients who were originally randomized to placebo. Safety was assessed at weeks 16 and 40 (10).

At week 16, the mean number of CUA lesions was lower with IFN-beta 1a than with placebo ($p<0.001$; 69% fewer lesions). The mean cumulative number of CUA lesions was already lower with IFN-beta 1a by week 4 (post hoc analysis; $p=0.015$). The new formulation of sc IFN-beta 1a has rapid beneficial effects on MRI outcomes in RRMS (Figure 4) (10).

This study demonstrates the beneficial early impact of the new formulation of sc IFN-beta 1a on MRI efficacy outcomes in patients with RRMS and shows that, as with the previous formulation, this new formulation has a prompt, favorable effect on disease activity. Safety results during both phases were consistent with those in a previous 96-week safety study

(data not shown) and no unexpected events occurred. In summary, the results of this study demonstrate the beneficial early impact of the new formulation of sc IFN-beta 1a on MRI efficacy outcomes in patients with RRMS and show that, as with the previous formulation, this new formulation has a prompt, favorable effect on disease activity (10).

BRAIN ATROPHY

In patients with MS, brain atrophy is a common finding that can now be quantitatively assessed by volumetric MR measures. Total brain atrophy was significantly greater in patients with MS than in control subjects. In addition, the annual rate of loss of brain tissue was similar between patients with RRMS and those with secondary progressive MS (SPMS). There was a significant correlation between brain atrophy and Expanded Disability Status Scale (EDSS) score in patients with SPMS (11).

Quantification of the degree of atrophy that is seen using T1-weighted MRI sequences provides an estimate of the magnitude of the most destructive aspects of MS. In MS patients with different disease phenotypes, brain volume decreases by about 0.7–1% per year, on average. Although brain atrophy appears to be more pathologically specific than T2 lesion load measurements, it is at best only moderately correlated with disability in RRMS and SPMS (1).

Fisher (12) compared atrophy rates over 4 years across the main MS clinical phenotypes and found that the rate of atrophy of GM increases with the disease stage from 3.4 times the normal rate in patients with CIS converting to RRMS to 14 times the normal rate in patients with SPMS (12). Atrophy appears to vary in different brain structures in different phases of the disease, as suggested by several voxel-based morphometry studies. In patients with CIS, GM atrophy mainly involves the thalamus, hypothalamus, putamen, and caudate nucleus. In patients with RRMS, cortical atrophy, which preferentially affects the fronto-temporal area, is typically detected. In patients with SPMS, atrophy of deep GM structures, the brainstem, the cerebellum, and several cortical regions (in virtually all lobes) is observed (Figure 5). Compared with control subjects, benign MS (BMS) patients have a reduced volume of GM in the subcortical and frontoparietal regions. In comparison with patients with BMS, those with SPMS have a significant ($p<0.05$) loss of GM in the cerebellum. The assessment of atrophy in key GM structures could help explain deficits in selected cognitive domains or specific disease-related symptoms. For example, atrophy of the hippocampus has been associated with deficits in memory encoding and retrieval, whereas atrophy of the frontal and parietal lobes has been correlated with the presence and severity of fatigue. A few longitudinal studies have suggested a relationship between the accumulation of T2 hyperintense lesions over time and the progression of atrophy in spatially related cortical areas (1).

IMAGING OF THE SPINAL CORD

In patients with CIS who present with spinal cord symptoms, spinal cord MRI is highly recommended to rule out other conditions, such as compressive lesions, that may mimic MS (1). In patients with established MS, repeated MRI examinations of the spinal cord are advisable only if there is a suspicion that a new condition such as mechanical compression has developed or if atypical symptoms arise. Dual-echo spin-echo MRI can depict spinal cord abnormalities with high sensitivity in MS patients. Spinal cord MS lesions, which are more frequently observed in the cervical spine than in other regions, are usually in the peripheral white matter, are limited to two vertebral segments in length or less, occupy less than half the cross-sectional area of the cord, and are typically not T1-hypointense (Figure 6). Asymptomatic spinal cord lesions have been described in 30–40% of patients with CIS at presentation and in up to 90% of patients with definite MS. More recently, the use of S19

T1-weighted inversion–recovery MRI has resulted in increased contrast between lesions and normal-appearing spinal cord, as compared with that from short-inversion-time inversion–recovery and fast-spin echo sequences (1).

MRI PREDICTORS OF CLINICAL OUTCOMES IN MS

Magnetic resonance imaging markers have not been formally accepted by drug regulatory agencies as surrogate endpoints for assessing the effect of new drugs and monitoring the response of individual patients to treatments for MS. Findings from a meta-analysis of randomized trials that assessed different drugs for MS showed a strong correlation between the effect of treatment on conventional MRI markers and relapses, i.e., those MRI markers can be good surrogate markers for assessing the effect of treatments on relapses in clinical trials. Further support for a role of MRI endpoints as reliable surrogates for clinical relapses, at least in patients with relapsing–remitting disease treated with immunomodulatory drugs, comes from findings from validation studies that were based on individual patient data from trials of IFN-beta and glatiramer acetate (13).

Sormani and Bruzzi (13) identified 31 eligible trials, which provided data for 18901 patients with RRMS. The regression equation that was derived

using data from these studies showed a relation between the concurrent effects of treatment on MRI lesions and relapses that was much the same as was previously estimated ($p_{\text{interaction}}=0.45$) (Figure 7). Analysis of trials that tested the same drugs in phase 2 and phase 3 studies showed that the effects on MRI lesions over short follow-up periods (6–9 months) can also predict the effects on relapses over longer follow-up periods (12–24 months), with reported effects on relapses that were within a 95% prediction interval in eight out of nine trials (13).

The dependence of the regression line on characteristics of the trial (interaction analysis) is reported in Figure 8. The correlation between effects on MRI and effects on relapses seemed to be similar in phase 2 (6–9 month trials with frequent MRI) and phase 3 (12–36 month trials with 6-monthly or annual MRI; p (interaction)=0.20) and in placebo-controlled compared with active-controlled trials (p (interaction)=0.48). A sensitivity analysis (see appendix) showed good stability of the regression equation according to different weighting systems and different mathematical assumptions and across trials run over different time periods (13).

Sormani and Bruzzi (13) determined the correlation between the reported effects on relapses and those that were predicted by the effects on MRI lesions within the same study in trials of IFN-beta and glatiramer acetate. Twelve trials were selected: nine trials with comparisons of different preparations of IFN-beta or glatiramer acetate with placebo, one trial that compared different doses of IFN-beta 1a, and two trials that compared different doses of glatiramer acetate were included in this analysis. As shown in Figure 9, all the effects on relapses for IFN-beta and glatiramer acetate were close to those that were predicted by the corresponding effects on MRI (as estimated by excluding these 12 trials from the regression equation) and well within the 95% prediction intervals. The χ^2 goodness-of-fit test showed no difference between the observed and predicted effects ($\chi^2[9 \text{ DF}]=4.35$; $p=0.88$) (13).

This analysis, which is based on an independent set of randomized clinical trials in RRMS, reproduces the results of our previous meta-analysis, which was based on earlier placebo-controlled studies, validating the role of MRI parameters as surrogate endpoints for relapses in efficacy trials in MS. Firstly, they found that a strong association was established between the effect of a treatment on MRI lesions and its effect on the relapse rate. Secondly, the accurate prediction of the effect of a treatment on relapses on the basis of the effect seen on MRI lesions is possible by means of a simple regression equation. The newly derived equation is almost identical to that derived in the previous analysis, which indicates that the quantitative association be-

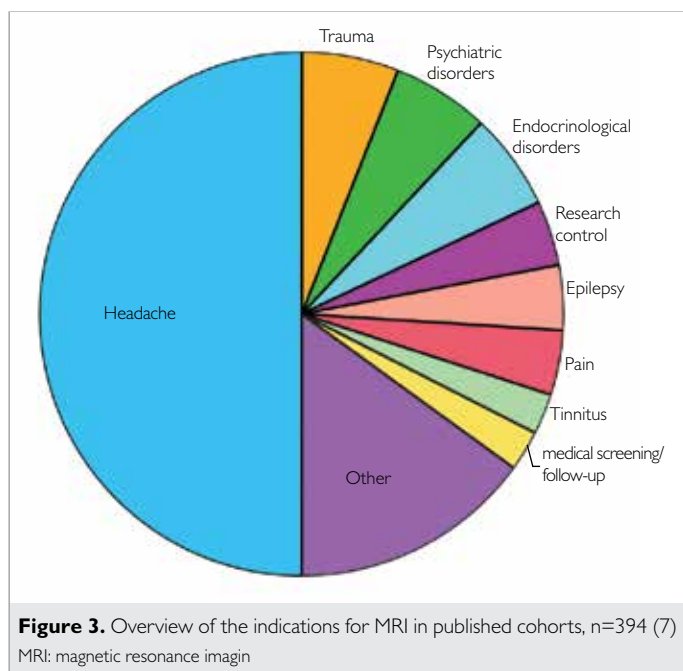


Figure 3. Overview of the indications for MRI in published cohorts, n=394 (7)
MRI: magnetic resonance imagin

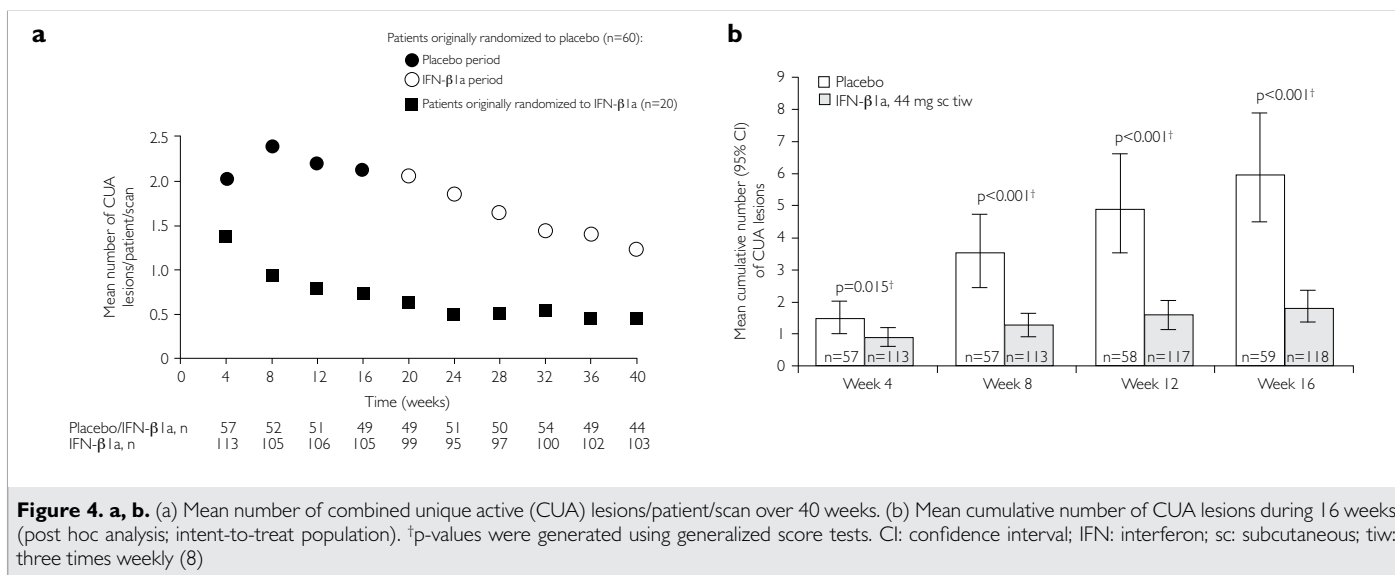


Figure 4. a, b. (a) Mean number of combined unique active (CUA) lesions/patient/scan over 40 weeks. (b) Mean cumulative number of CUA lesions during 16 weeks (post hoc analysis; intent-to-treat population). †p-values were generated using generalized score tests. CI: confidence interval; IFN: interferon; sc: subcutaneous; tiw: three times weekly (8)

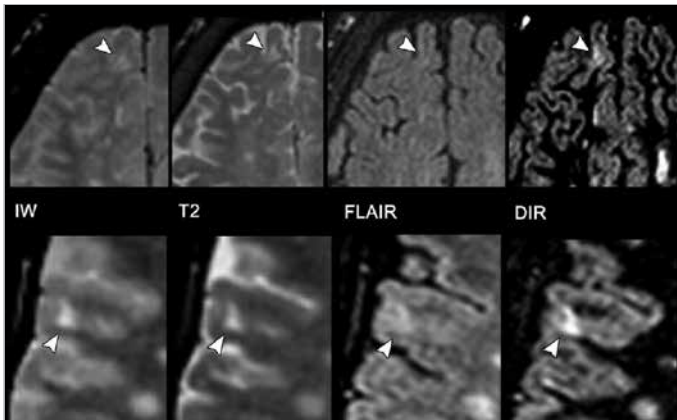


Figure 5. Axial dual-echo (intermediate-weighted [IW] and T2-weighted) (2690/45, 90), three-dimensional fluid-attenuated inversion–recovery (FLAIR; repetition time (ms)/echo time (ms)/inversion time (ms), 6500/119/2200; turbo factor, 37), and three-dimensional double inversion–recovery (DIR; 7100/99/330, 3480; turbo factor, 37) images of intracortical lesions. Top row: A lesion (arrowhead) in cortical gray matter with a possible juxtacortical component is shown. The intracortical lesion is particularly poorly visible on intermediate-weighted and T2-weighted images, as well as on the FLAIR image, whereas it is depicted clearly on the double inversion–recovery image. Bottom row: In a different patient, a double inversion–recovery image shows very good delineation of an intracortical lesion (arrowhead), which may be mistaken for a juxtacortical lesion or partial volume artifact on the T2-weighted image and may even be missed on the FLAIR image (1)

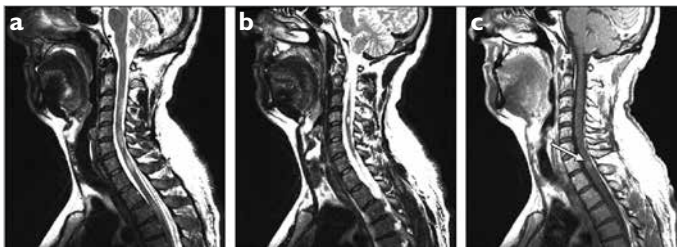


Figure 6. a-c. Sagittal (a, b) T2-weighted (4130/104; echo train length, 25) and (c) contrast-enhanced T1-weighted (700/15; two signals acquired) spin-echo MR images of the cervical spinal cord in a 46-year-old patient with RRMS. Multiple hyperintense lesions are visible in (a) and (b), which suggest multifocal disease. In (c), one of these lesions (arrow) is contrast-enhancing (1)

tween the effects on MRI lesions and those on relapses, and also across different types of treatments, can be generalized. This confirmation of the previous results should inform the scientific community and encourage the regulatory agencies to accept MRI markers formally as surrogate outcomes in clinical trials in MS, at least in specific situations. Moreover, the role of MRI as a surrogate in treatments that have different mechanisms of action (e.g., neuroprotection and repair) is not addressed by this analysis. Also, a global statistical approach (i.e., weighted regression analysis) is not the most efficient in the case of trials with multiple groups, for which more sophisticated statistical methods (e.g., network meta-analyses) are recommended when the effects of treatment are to be assessed. Finally, there are some limitations to the use of MRI as an outcome measure in efficacy trials. The assessment of active T2 lesions (which is usually visual) does not have optimal inter-rater and intra-rater concordance. Concordance and accuracy can be improved by the visual assessment of not only T2-weighted images but also contrast-enhanced T1-weighted and T2-weighted images in combination, especially in trials of 6 months' duration (13).

MARKERS OF RESPONSE TO TREATMENT

According to Sormani and De Stefano (14), integrated strategies that combine MRI and clinical markers in scoring systems have provided a po-

tentially useful approach for the management of patients with MS. Although no cure currently exists, the range of available treatments is rapidly broadening, at least for the relapsing–remitting form of the disease. The use of injectable therapies with various formulations of IFN- β and glatiramer acetate has changed the course of the disease by reducing the relapse rate, as well as the development of new lesions as detected by MRI. The long-term experience with these drugs confirms their safety over the long term, combined with an efficacy, in terms of reducing relapses, of about 30% (14).

The detection of early markers of response to any treatment is very challenging in MS, which is possibly due at least in part to the inherent complexity of the definition of response and non-response to therapy in this chronic disease. The trial referred to by Sormani and De Stefano (14) focused predominantly on the response to treatment by IFN- β . Also, it has shown the many definitions of clinical response to IFN- β that have been provided to date and investigated the markers that can predict such a response. The definition of a “marker of response” to a therapy encompasses two classes of factors. The first class, which is termed treatment effect modifiers, includes baseline variables that can identify subgroups of patients who display different effects of treatment. The second class includes variables that can be measured earlier or more conveniently than the actual clinical endpoint of interest once treatment has commenced. The latter factors, which are also known as surrogate markers, can predict the effects of therapy on the relevant clinical endpoint and thereby identify patients who are responding to therapy. The assessment of both effect modifiers and surrogate markers requires the presence of a control group for comparison with the treatment group so as to rule out the effects of variables that are simply prognostic factors (14).

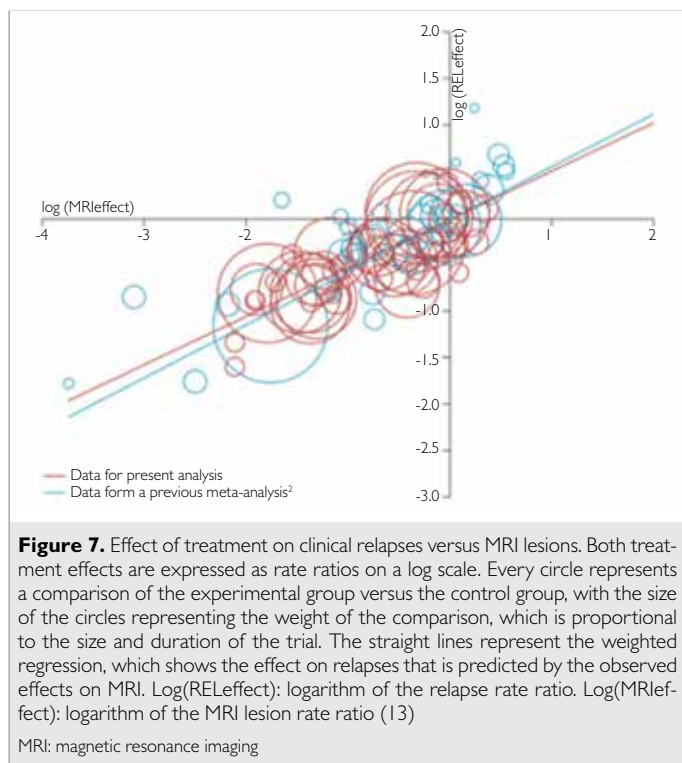
The combined use of parameters of disease activity to predict the response to therapy is the basis of the Treatment Optimization Recommendations that were published by the Canadian MS Working Group (CMSWG) and subsequently tested on the PRISMS (Prevention of Relapses and disability by IFN- β 1a Subcutaneously in Multiple Sclerosis) trial data. The CMSWG described a model, which was derived from an expert consensus, that is based on different levels of progression of disability, relapse, and MRI activity during treatment. PRISMS data have been shown to be able to identify a group of suboptimal responders, 89% of whom experienced a continued breakthrough in terms of relapses and progression (14).

In a study published in 2008, Río et al. (15) analyzed a clinical data set of 222 patients with RRMS, each of whom had been treated with one of several formulations of IFN- β for more than 1 year. On the basis of their findings, the authors proposed a more quantitative version of a composite score. The new scoring system involved the combined assessment at 1 year from the start of treatment of the presence of clinical relapses, progression of disability (as measured by an increase of 1 EDSS point confirmed at 6 months), and active MRI lesions (that is, more than two new T2- or gadolinium-enhancing lesions) to identify patients with poor outcomes during the subsequent 2 years (Table 1). Patients who were positive for at least two of the three criteria that were measured after the first year of IFN- β therapy were found to have a higher probability of experiencing progression of disability or displaying relapse activity at follow-up. These individuals would, therefore, be strong candidates for a switch in treatment. Notably, the isolated presence of relapses or MRI activity after 1 year of treatment did not significantly predict the risk of new clinical activity or progression of disease in the ensuing 2 years. In addition, an increase in disability alone during the first year of treatment was a poor predictor of the subsequent progression of disability (14).

Table 1. The Rio and Modified Rio Scores (15).

Rio Score		Modified Rio Score	
Criterion	Change over the first year	Criterion	Change over the first year
MRI criterion=0	≤2 active* T2 lesions	MRI criterion=0	≤4(5) [‡] new T2 lesions
MRI criterion=1	>2 active T2 lesions	MRI criterion=1	>4(5) [‡] new T2 lesions
Relapse criterion=0	No relapses	Relapse criterion=0	No relapses
Relapse criterion=1	≥1 relapse	Relapse criterion=1	1 relapse
		Relapse criterion=2	≥2 relapses
EDSS criterion=0	Increase in EDSS score of <1 point	Not included	Not included
EDSS criterion=1	Increase in EDSS score of >1 point sustained over at least 6 months		
Rio Score=MRI criterion+relapse criterion+EDSS criterion		Modified Rio Score=MRI criterion+relapse criterion	

*Active lesions defined as new or enlarging T2-weighted lesions plus gadolinium-enhancing lesions over the first year. [‡]The cut-off point at four lesions was in the validation set; the cut-off point at five lesions was in the training set. EDSS: Expanded Disability Status Scale.



A recent study proposed a simplified version of the Rio Score (the so-called Modified Rio Score). The new score was based on an analysis of the treatment arms of the PRISMS study that included 365 patients with RRMS who were treated with two doses of subcutaneous IFN-beta 1a (training set). The Modified Rio Score groups patients into three risk groups (Table 1). The validation exercise established that the probability of the progression of disability was 24% in the low-risk group, 33% in the medium-risk group, and 65% in the high-risk group (14).

Patients who are classified as medium risk by the Modified Rio Score are the most difficult to classify in terms of response to treatment and planning. A study has shown that further evaluation by an MRI scan and clinical visit 6 months after the first year of therapy could enable better classification of these patients. On the basis of these findings, an evidence-based quantitative algorithm for monitoring response to IFN-beta can be proposed (Figure 10) (14).

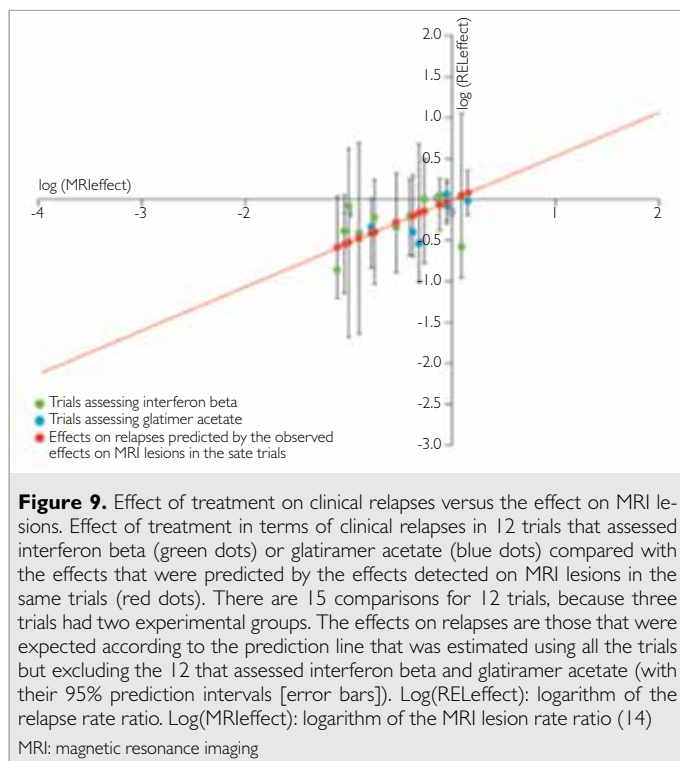
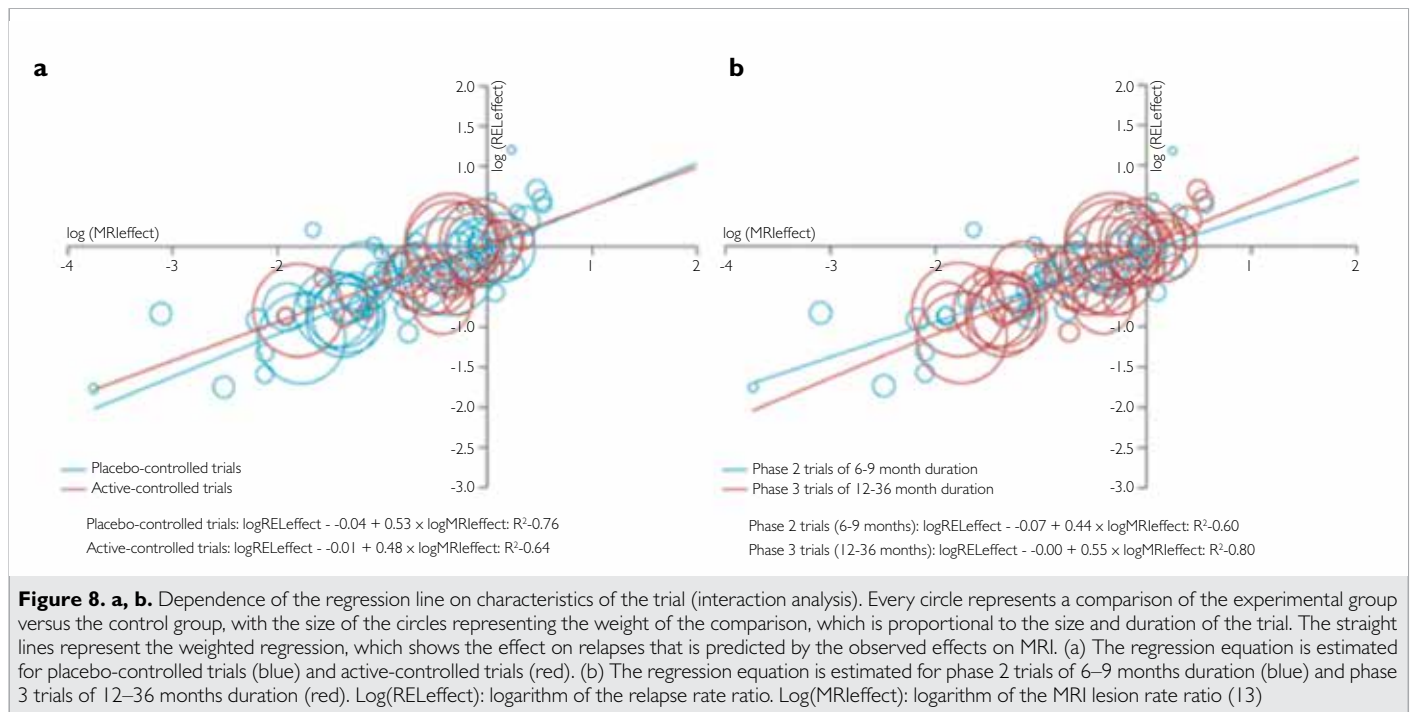
In a preliminary study, both the Rio and Modified Rio Scores were further validated in an independent large data set of 516 patients who were treated with IFN-beta with at least 5 years of follow-up in a clinical setting. Both score systems were confirmed to provide good discrimination of patients at risk of progression of disease at 1 year from initiation of treatment (14).

The advent of a large number of new therapies for MS warrants the development of tools to select the best treatment for each new patient and to identify factors that can predict whether that patient will respond to the selected therapy. Such tools would enable early, evidence-based, and individualized decisions to be made about this crucial clinical issue. A large number of imaging studies have provided evidence that the measurement of focal T2 lesions that accumulate during the course of the disease is not sufficient to properly profile the clinical heterogeneity of MS and monitor its progression. Recent data have shown that, among the different MRI measurements, that of brain atrophy is the one that many investigators deem to be the most promising for the future (14).

CONCLUSION

Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system. MRI has played a unique role in the diagnosis and management of patients with MS. In recent years, there have been considerable changes in the diagnostic criteria for MS as MRI-based studies have demonstrated their power in the earlier and more accurate diagnosis of the disease (16).

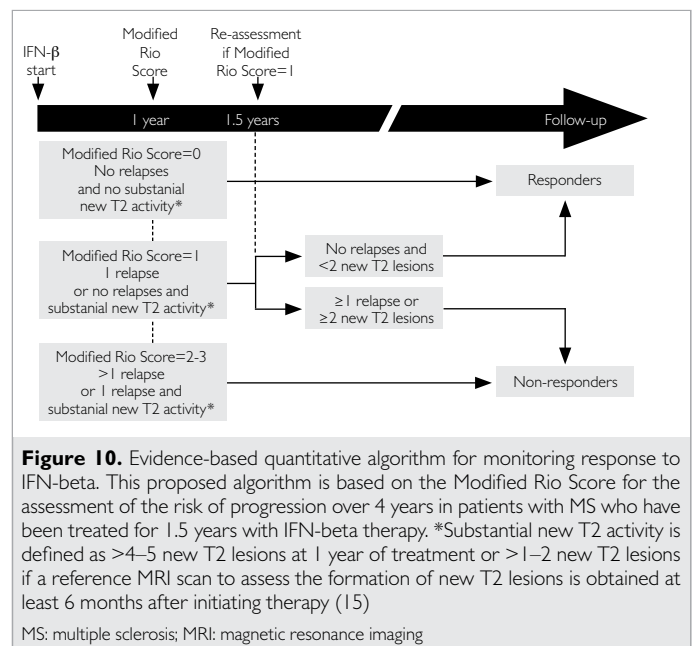
Conventional and advanced MR methods have been extensively applied to the study of MS and have greatly contributed to improving our ability to diagnose and monitor the disease as well as to our understanding of its pathophysiology. Nevertheless, there are still many challenges ahead. At present, conventional MR sequences remain the reference standard for the diagnosis and monitoring of disease progression in patients who present with CIS suggestive of MS. MRI has improved the understanding of the pathophysiology of the disease and of the mechanisms responsible for the development of irreversible neurologic disability. At present, these quantitative techniques demonstrate differences at the group level but do not allow inferences to be made about an individual. Furthermore, none of the available MRI techniques used in isolation are able to provide a complete picture of the MS disease process in all its complexity. This calls



for the creation of aggregate MRI measurements that reflect the different aspects of MS pathology to improve our ability to monitor the evolution of the disease, particularly in the context of clinical trials (1).

Future studies should also try to establish the prevalence and long-term prognosis of RIS and its impact on the quality of life and define the role of disease-modifying therapy in RIS (7).

The availability of multiple agents for RRMS and the increasingly solid evidence in support of the validity of MRI endpoints as surrogate endpoints in this setting are radically changing the ethical, scientific, and methodolog-



ical perspectives of clinical trials in MS. This new scenario warrants the development of more flexible and efficient designs of trials in which MRI outcomes can play a pivotal part, thanks to the fact that they are objective, statistically efficient, and enable early (e.g., 6 months) predictions of long-term (e.g., 2 years) effects of treatment on clinical endpoints. These properties could prove useful in dose-finding studies, in studies of associations of multiple drugs, and most importantly, in fostering the wider use of adaptive designs in efficacy trials (13).

Future challenges for a personalized approach to the treatment of MS based on combined scores will be three fold. First, more precise and meaningful measures of disease progression together with standardized definitions of response to therapies must be defined and acknowledged by the MS community. Second, new studies are needed to determine the value of new and promising biomarkers that can be integrated to-

gether with paraclinical and clinical variables into predictive scores. Finally, the applicability to clinical practice should be taken into account to generate scoring systems simple enough to be implemented in any clinical setting (14).

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Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

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