The clinical perspective: how to personalise treatment in MS and how may biomarkers including imaging contribute to this?

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Abstract

Background: MS is a highly heterogeneous disease, both in its course and in its response to treatments. Effective biomarkers may help predict disability progression and monitor patients' treatment responses.

Objective: To focus on how biomarkers may contribute to treatment individualisation in MS patients.

Methods: This review reflects the content of the presentations, polling results and discussions on the clinical perspective of MS during the first and second Pan-European MS Multi-stakeholder Colloquia in Brussels in May 2014 and May 2015.

Results: In clinical practice, MRI measures play a significant role in the diagnosis and follow-up of patients with MS. Together with clinical markers, the rate of MRI-visible lesion accrual once a person with MS has started treatment may also help to predict subsequent treatment responsiveness. In addition, several molecular (immunological, genetic) biomarkers have been established that may also play a role in predictive models of MS relapses and progression. To reach personalised treatment decisions, estimates of disability progression and likely treatment response should be carefully considered alongside the risk of serious adverse events, together with the patient's treatment expectations.

Conclusion: Although biomarkers may be very useful for individualised decision making in MS, many are still research tools and need to be validated before implementation in clinical practice.

Introduction

MS is classically regarded as an idiopathic inflammatory demyelinating and neurodegenerative disease of the CNS. Most prevalence estimates of MS in western countries vary between 25 and 200 per 100,000, with incidences peaking around 30 years of age.[1] The disease is nowadays thrice as common in women than in men and is the leading cause of non-traumatic neurological disability in young adults in western countries.[2]

Because part of the disease process in MS is clinically silent over a long period of time, for example the number of new brain lesions seen on MRI is substantially greater than the number of relapses occurring over the same period,[3] surrogate markers for disease activity and progression have been identified and have served as outcome measures in clinical trials. At present, the most important para-clinical measures predicting a patient's prognosis are changes in the CNS detected using MRI. In recent years, several prognostic molecular biomarkers have been evaluated as well. In addition, some biomarkers may assist in predicting a patient's treatment response. These markers may be useful to identify poor responders early on and to switch them to an alternative, more effective, therapy before substantial neurological damage has occurred. Alternatively, biomarkers may be used to predict a patient's risk of developing serious adverse events (SAEs) on treatment with a particular drug.[4,5] It should be noted that biomarkers that have proven valuable on a group level in clinical trials may not be suitable for the evaluation of individuals. In addition, the interval between measurements can (in part) have an impact on the sensitivity to clinically relevant changes.[6]

The current and future potential of biomarkers for predicting the disease course, treatment response and tolerability was discussed during the first and second Pan-

European MS Multi-stakeholder Colloquium, which took place on 23-24 May 2014[7] and 15-16 May 2015[8] in Brussels. The goal of these colloquia was to enhance the communication and collaboration between the different stakeholders involved in MS care, including patients and their caregivers, healthcare professionals, researchers, regulators and payers. The programmes developed by the chair and scientific committee aimed at prioritising actions needed to improve the quality of and access to care and treatment. At the first colloquium, after introductory presentations on various subjects by the different stakeholders, the audience was asked to rank priorities from a list of potential action points. The outcome of this polling was used to stimulate further discussions among the speakers, a group of experts in the field and the audience during the first and second colloquium.

This review summarises the content of the presentations, polling results and discussions related to the use of risk factors and clinical, MRI and other biomarkers in MS and their current and future utility for the individualisation of treatment.

Predicting disease progression

Clinical markers of disease progression

Relapses

Several studies have suggested an association between a higher relapse rate in the first 2-5 years after disease onset and a shorter first inter-relapse interval on the one hand and a more rapid disability progression on the other hand (Figure 1).[9-13] However, this predictive effect seems to disappear once the progressive course starts (e.g. when an Expanded Disability Status Scale (EDSS) score of 3-4 is reached) (Figure 2). Mean times from disease onset, progressive phase onset and an EDSS 3 to reaching EDSS 6, 8, and 10 are strikingly similar for patients with different relapse numbers in the relapsing-remitting (RR) phase.[10] Also in patients with progressive onset MS, superimposed relapses do not appear to affect long-term outcomes.[14] However, an important point that we should consider in evaluating these results is that the main measure of disability (EDSS) used in these studies and in daily clinical practice has significant limitations: EDSS in the 4–7 range is insensitive to change in any functional system other than ambulation. Relapses affecting upper limb or brain stem function or cognition, more prevalent in later phases of the disease, might not affect the EDSS score. These limitations might explain the limited ability of EDSS to detect a delayed impact of relapses on disability progression.[15]

MRI markers of disease progression

MRI lesions detected using conventional techniques

Conventional MRI techniques, such as spin-echo and fluid-attenuated inversion recovery (FLAIR) T2-weighted and unenhanced and contrast-enhanced T1-weighted sequences mainly detect focal lesions or plaques in the brain and spinal cord of MS patients. Classical MRI measures in MS, which can be evaluated using these techniques are the number and volume of gadolinium-enhancing (GdE) lesions, hyperintense lesions on T2-weighted scans and hypointense ‘black holes’ on T1-weighted scans. The number of GdE lesions has been found to be associated with the risk for future relapse and relapse rate.[16] However, subclinical activity detected using conventional MRI may occur at a 5 to 10 times higher rate than clinical observations would suggest.[17] Anomalies in the CNS suggestive of MS may also be identified by MRI before there is clinical evidence of the disease. This is referred to as ‘radiologically isolated syndrome’ (RIS). In a retrospective study including 451 of subjects with RIS, about one-third of these subjects had a first clinical event within 5 years of the first brain MRI study (at a mean age of 37.2 years).[18] Lesions within the cervical or thoracic spinal cord were identified as significant predictors for the development of a first clinical event (hazard ratio [HR] 3.08), together with younger age (HR 0.98, i.e. an estimated risk of developing an event decreasing by 2% for every additional year of age) and male sex (HR 1.93) (Figure 1).

The presence of GdE lesions and T2 hyperintense lesions is an important diagnostic criterion in MS, because of the established association between the number and volume of these lesions and conversion from clinically isolated syndrome (CIS) to clinically definite MS (CDMS) (Figure 1).[19-22] Despite their association with relapse rate, relatively weak correlations have been reported between conventional lesion metrics and disability progression, as measured using the EDSS.[21,23,24] In patients with relapsing-remitting MS (RRMS), early progression of T2 lesion load appears to predict progression to SPMS to some extent, but there appears to be little association between the burden of T2 lesions and future disability for EDSS values above 4.5 (Figure 2).[24,25] Chronic T1 hypointense lesions, detected on spin-echo sequences, have shown a better correlation with EDSS than GdE and T2 lesions,[26] and these lesions are believed to reflect severe and irreversible axonal damage.[27] Although potentially clinically relevant, T1-hypointese lesion assessment is still subjective and highly dependent on the type of T1-weighted sequence and field strength.[28] When considering the predictive role of MRI lesions it should be noted that the number of lesions accumulated over time may be a better predictor of future disability than the number of active (GdE) lesions at a single time point.[29] Moreover the predictive value of active lesions may be higher in the early RR phase than later in the disease evolution.[25,30]

Brain atrophy

Pathophysiological research over the past decades has shown that conventional MRI measures do not tell the full history of MS. Whereas focal inflammation and axonal demyelination in the WM seem to be mainly associated with relapses, axonal/neuronal loss is currently believed to be the main driver of irreversible disability progression. These insights have triggered interest in measuring tissue volume loss (atrophy) in the CNS as a marker of neurodegeneration. Several MRI techniques to measure brain volume loss (and in case of sustained volume loss as per definition: atrophy) such as segmentation-based or registration-based methods have been introduced in the past. Segmentation-based methods measure global or regional brain volume (e.g. brain parenchymal fraction, white matter fraction, grey matter fraction, normalized brain volume) at a single time point. Registration-based methods measure brain volume at two time points, in order to calculate the percentage brain volume change (PBVC), and are most suitable for evaluating global brain volume changes,[31] but are not usually designed to analyse regional volume changes over time.[32,33]

Studies have shown that brain atrophy affects the entire brain in MS, including white matter (WM) and grey matter (GM), and starts very early in the disease course.[34,35] Although some studies suggested that brain atrophy escalates with increasing disease stage, this was not confirmed in a large MAGNIMS (Magnetic Resonance Imaging in MS) study when data were corrected for baseline normalised brain volume.[36,37] An association between increasing early brain tissue volume loss and increasing long-term disability progression has been shown in several studies (Figure 2).[38-41] GM volume was found to be a stronger predictor of clinical disability than WM volume.[39] Measuring brain atrophy is challenging because the change in volume over time is relatively small. In MS patients, brain atrophy occurs at a rate of 0.5-1.3% per year, compared with 0.1-0.3% per year reported for healthy subjects.[34,42] Although the estimation of brain atrophy seems to be an important prognostic marker, its implementation in the clinical workflow is limited by several factors.

As brain atrophy is not necessarily linear, progression in individuals is hard to predict. Also, no common agreement on a single measurement technique to be used in clinical research or clinical practice currently exists. Differences between techniques limit direct comparison between results. Furthermore, several other confounding factors must be considered when evaluating disease progression based on brain volume loss/atrophy, including image acquisition and quality (e.g. imperfect skull extraction and outlining, imprecise registration, issues due to patient movement), the effect lesions can have on tissue segmentation (for example due to classification of T1 hypointense lesions as GM), pseudo-atrophy (reduction in inflammation due to disease-modifying treatment), change in brain water content due to hydration status or steroid use or even diurnal fluctuations, and other factors such as cardiovascular disease, smoking, high alcohol consumption, and genetic factors.[43,44] Although brain atrophy measures are very valuable for group analysis, both biological and technical variability need to be improved to make them suitable for individual analysis.

Advanced MRI measures

The introduction of new advanced imaging techniques, including sensitive techniques to quantify diffuse damage or metabolic or functional changes in tissue appearing normal on conventional MRI scans, has considerably improved the detection of pathological changes in MS.[17]

A promising new sequence for diagnostic set-up and follow-up is double-inversion recovery (DIR). DIR has considerably improved the ability to detect cortical lesions in patients with MS. Studies have shown accumulation of cortical lesions over time and correlations with clinical and cognitive dysfunction.[42] The presence of at least one cortical lesion has been found to be associated with an increased risk of conversion from CIS to CDMS.[45] Cortical lesion volume and number have also been found to independently predict future disability accumulation in RRMS, SPMS and PPMS patients (Figure 2).[46,47] However, about 80% of GM lesions still remain undetected with this technique.[48] DIR very rarely detects subpial cortical lesions,[48] which is the most abundant and specific cortical lesion type seen in histopathological work. There is no common sequence recommendation for cortical lesion detection, and DIR inter-rater reliability of cortical lesion scoring using consensus guidelines was found to be low, with a complete agreement on only ~20% of lesions between readers.[49]

Magnetisation transfer imaging (MTI) measures correlate with demyelination, remyelination and axonal loss.[50] MTI variables in GM and normal-appearing WM have been found to independently predict future disability (EDSS) progression in the long term (3-8 years) in patients with RRMS, secondary progressive MS (SPMS) and primary progressive MS (PPMS) (Figure 2).[51-53] However, MTI is time-consuming and its use in individuals is limited by the variability across sites (as the results depend on the method used) and the lack of normative values, which is a problem common to many current quantitative MRI techniques.

Proton magnetic resonance (MR) spectroscopy can provide information about metabolic changes in normal-appearing brain tissue and focal lesions. Reductions of N-acetyl-aspartate (NAA) levels (suggestive of neuroaxonal damage) are partly reversible and an association between greater increases in NAA levels after spinal relapse and greater recovery has recently been described.[54] However, MR spectroscopy is time consuming and has a greater biological variability than other structural methods, and measures are method- and scanner-specific. Therefore, this technique is currently not considered suitable for use in multi-centre studies.

Optical coherence tomography (OCT)

MS patients typically show thinning of particularly the innermost layers of the retina, even without a history of optic neuritis (ON).[55] Some studies have shown an inverse relationship between inner nuclear layer thickness and EDSS (progression).[56,57] Recently, a strong correlation between ganglion cell/inner plexiform atrophy and whole-brain, especially GM, atrophy, was established, particularly in patients with progressive MS, suggesting that it mirrors underlying disease progression.[58] Despite promising results, more large longitudinal studies are needed to evaluate the prognostic value of OCT in MS. A limitation of OCT is that measurements are affected by a history of ON, lesions elsewhere in the visual pathway and non-MS ocular conditions.[55] In addition, magnitudes of annual thinning of retinal layers are smaller than the variability between measurements.[55]

Evoked potentials (EPs)

A number of studies have suggested that multimodal EPs (nerve latencies) may be valuable for monitoring and predicting disability in MS patients.[59] Although their diagnostic value is considered poor compared with MRI,[59] several studies have shown correlations between EP measures and (future) disability.[59-61] However, its use in clinical practice requires standardisation within and between laboratories.

Molecular biomarkers

Apart from MRI, several molecular biomarkers have been identified for diagnosing MS and for monitoring and predicting disability progression.

The presence of immunoglobulin (Ig) G oligoclonal bands (OCB) and/or an elevated IgG index in the cerebrospinal fluid (CSF) support the *diagnosis of MS* in patients suspected to have demyelinating disease, but they do not contribute to proof of MS in the 2010 McDonald criteria. The best validated molecular biomarkers that predict *conversion to CDMS in patients with CIS* are the presence of IgG OCB[62,63] and the IgG index[62] in the CSF. Recently, serum auto-antibodies directed against the potassium channel KIR4.1 have been suggested as a candidate biomarker for the *diagnosis of MS*.[64] They are already detectable in the early stages of MS and have an excellent specificity but low sensitivity. However, a recent validation study could not replicate this finding in independent cohorts.[65]

Another CSF biomarker with strong evidence is Chitinase 3-like 1 (CHI3L1), which is expressed on monocytes and microglial cells and has been linked to astrocyte activation. CHI3L1 has not only been shown to predict conversion to CDMS[66,67] but also to predict more rapid disability progression.[66,67] Recently, the level of vitamin D in blood has been suggested as a candidate biomarker for *conversion to CDMS*[62,68] and *more rapid disability progression*.[68,69] In a study including patients with CIS, who were mainly treated with interferon (IFN) β-1b, low serum levels of 25-hydroxyvitamin D (a marker of vitamin D status) predicted long-term clinical and MRI activity.[68] Furthermore, lower serum 25-hydroxyvitamin D levels were also associated with lower MRI activity in RRMS patients treated with IFNβ-1b in the prospective BEYOND study.[69] However, these data should be further confirmed by other investigators before vitamin D can be used as a valid biomarker. In the future, biomarkers predicting conversion to CDMS may become useful in the decision which patients with CIS could benefit from early treatment initiation.

As mentioned above a number of molecular biomarkers for *predicting future disease activity* have been suggested as well, including CHI3L1 and vitamin D levels. In addition, the neurofilament (NF) levels in the CSF and blood have been suggested as biomarker for predicting disability progression. NFs are major axonal cytoskeleton proteins, consisting of a light chain (NFL), an intermediate chain (NFM) and a heavy chain (NFH). NFL and NFH concentrations in CSF are used in clinical practice as surrogate endpoints of neuroaxonal damage. Indeed, NFL levels seem to correlate with acute axonal damage,[70] while NFH levels may reflect chronic axonal damage and may be more strongly associated with disability progression.[71,72] Furthermore, serum NFL levels appear to correlate with MRI activity and disability scores and may present an easily accessible biomarker predicting disability progression.[73]

Although these molecular biomarkers may gain importance in the future, their integration into clinical practice requires further evaluation. Longitudinal studies in large cohorts of patients are needed to better assess the natural history of MS in relation to baseline levels of these biomarkers.

Predicting treatment response and tolerability

Initiation of the right drug at the right time is a crucial goal in MS in order to minimise further inflammation, neurodegeneration and resulting irreversible disability progression.[74] The majority of patients with RRMS will start with a first-line disease-modifying drug (DMD) with a moderate efficacy but a good safety profile (e.g. IFNβ, glatiramer acetate (GA), teriflunomide, dimethyl fumarate (DMF)).[75] In those who fail to respond to these agents, this is followed by second-, third-, fourth- or even fifth-line treatments (Figure 4). For each treatment step, drug efficacy may increase along with the associated risk of serious adverse events (SAEs). However, for patients with a high disease activity, starting therapy with highly effective but aggressive therapies such as natalizumab (NTZ) or alemtuzumab (ATZ) (also referred to as induction therapy) may be appropriate to rapidly reduce disease activity. Once disease control has been achieved, therapy can be scaled back to better tolerated −but potentially less efficacious− drugs for long-term maintenance.[75] Current experience with induction therapy is limited, particularly its immunogenic effect in the long term, and not tested against escalation strategies in randomised controlled trials.

As not all patients will sufficiently respond to first-line treatment, and conversely not all patients will develop SAEs upon treatment with highly aggressive drugs, it would be very useful to be able to predict a patient's likely treatment response and risk of SAEs. In this way, poor responders can be switched to an alternative therapy early on, before substantial neurological damage has occurred, and patients can be spared from potential SAEs associated with a particular drug, such as progressive multifocal leukoencephalopathy (PML) upon treatment with NTZ or autoimmune disorders upon treatment with ATZ.[4,5] Therefore, current research is focusing on the identification of clinical, imaging, immunological and genetic biomarkers that may help individualise treatment.

Response to first-line treatments

Response to IFNβ and GA

Regarding the injectable first-line DMDs IFNβ and GA, direct comparative studies have not shown superiority of one drug over another in terms of efficacy (BEYOND[76], REGARD[77]). Moreover, these trials do not give any indication on the most appropriate first-line treatment choice at the patient-specific level. Additionally, surrogate markers are needed to predict which patients will respond to first-line DMDs. Several studies have shown that, in patients with RRMS, high disease activity, i.e. high frequency of relapse, high rate of disability progression and/or high number of MRI lesions at baseline or in the first year of treatment, may predict (mid- and long-term) failure to IFNβ and GA.[5,78-83]

Next to these clinical and MRI measures, the titre of neutralising antibodies (NAbs) against IFNβ has been established as a clinically useful predictor of poor treatment response.[84] Indeed, NAbs reduce the therapeutic effect of IFNβ on relapse rate and MRI lesion activity.[84,85] Therefore, for patients with sustained high-titre NAbs consideration should be given to DMDs other than IFNβ[84]. In addition, other immunological biomarkers have been suggested to predict response to IFNβ in patients with RRMS, including several chemokines and cytokines.[4,72] However, for most of them, e.g. serum interleukin-17F (IL-17F), the predictive value is still highly debated.[86,87] Moreover, for those markers that have already been validated, usefulness in clinical practice still needs to be demonstrated.[72]

Furthermore, many pharmacogenomics studies have tried to identify genetic variants that may predict response to IFNβ or GA. So far, two genome-wide association studies have suggested a role for *GPC5,* glutamate receptors and *ADAR* in response to IFNβ.[88] Very few studies have evaluated the pharmacogenomics of response to GA.[88-90] To bring pharmacogenomics from academic research to clinical practice, a joint effort between academy and industry is necessary.[91] A large-scale pharmacogenomics study in GA-treated RRMS patients, including consenting patients from the FORTE (N=604) and the GALA studies (N=1,158), is currently ongoing.[92] An 11-single nucleotide polymorphisms (SNP) signature for GA response was identified in the GALA study and validated in the FORTE study. This multi-SNP signature may be able to predict which GA-naïve RRMS patients will be high responders, exhibiting annualised relapse rate (ARR) reductions significantly higher than the average response (≈33%) reported in clinical trials.[92] The predictive value of this multi-SNP signature is being validated in an independent cohort.

Response to oral first-line DMDs

Due to the development of several oral DMDs, the therapeutic landscape of MS has considerably changed over the last decade; first-line treatment choice has even become more complex. So far, there are no efficacy data showing superiority of the new oral drugs (e.g. teriflunomide, DMF) over IFNβ or GA. Indeed, the CONFIRM study was designed to show superiority or non-inferiority of DMF (twice or three times daily) vs placebo, and not vs GA, which was only added as a reference comparator.[93] Similarly, the TENERE study did not show a statistical difference in time to treatment failure between teriflunomide (7 or 14 mg) and IFNβ-1a.[94] Thus, again, these data do not facilitate the personalised treatment decision between oral and injectable first-line

DMDs and biomarkers are needed to predict the patient's treatment response to DMF or teriflunomide. However, to our knowledge, no such biomarkers have been described yet.[72,95] It remains to be investigated whether new imaging techniques such as MTI and diffusion tensor MRI, OCT or positron emission tomography may be useful for this purpose.[95]

Response to second-line treatments

A promising biomarker which objectively reflects response to second-line treatments is the level of NFs in the CSF.[72,95] NFL concentration in CSF can serve as surrogate endpoint of neuroaxonal damage[71,72] and thus as surrogate endpoint for treatment efficacy. Although NFL levels in CSF were shown to be reduced upon treatment with NTZ,[96,97] fingolimod,[98] mitoxantrone or rituximab[99], the predictive value on individual patients is very modest. A potential disadvantage of this biomarker is the need for a lumbar puncture to collect CSF. However, a recent study has shown reduced serum levels of NFL antibodies in NTZ-treated RRMS patients, suggesting that they may also serve as a biomarker of treatment efficacy as well.[100] However, their usefulness still needs to be confirmed in clinical practice.

Biomarkers that may predict response to second-line drugs, such as SNPs in the ABC transporter genes for mitoxantrone,[101] are still in the exploratory or validation phase.[72]

Tolerability

An established immunological biomarker to predict a patient's risk of SAEs is the presence of anti-John Cunningham virus (JCV) antibodies (anti-JCV-Abs) in serum.[4,72] In patients treated with NTZ, positive anti-JCV-Ab status, longer duration of treatment with NTZ and prior immunosuppressive treatment were shown to be associated with an increased risk of PML.[102] Based on these 3 parameters, a risk stratification algorithm was developed to counsel patients treated with or considering treatment with NTZ on their risk of PML. Anti-JCV-Ab positive patients with no prior use of immunosuppressants may even be further stratified according to their anti-JCV-Ab index, which is a corollary to anti-JCV-Ab titre. Patients whose anti-JCV-Ab index is more than 1.5 and whose treatment duration is longer than 24 months, have been shown to have a substantially greater risk of PML.[103] Thus they should be encouraged to switch to an alternative drug or undergo strict monitoring (including frequent MRI scanning) to detect PML if NTZ is not discontinued.[104]

Similarly, patients developing secondary autoimmunity (autoimmune thyroid disease, idiopathic thrombocytopenic purpura) following treatment with ATZ were shown to have two-fold greater pre-treatment serum levels of IL-21. The original IL-21ELISA kit, containing antibodies from ascites, has been recently withdrawn in order to switch to the more ethical cell culture-based antibody ELISA kits.[105,106] However, a recent study has shown that the currently available IL-21 kits have little or no predictive value for the risk to develop secondary autoimmunity on ATZ treatment.[106]

Finally, increased risk of developing secondary acute promyelocytic leukaemia (sAPL) after treatment with mitoxantrone was suggested to be linked to genetic variants in DNA repair and drug-metabolising enzymes (*BRCA2*, *XRCC5*, *CYP3A4*), resulting in impaired detoxification of chemotherapy or inefficient repair of drug-induced genetic damage.[107,108] More research efforts are needed to identify other biomarkers that may predict drug tolerability at the patient-specific level.

Implementation of biomarkers in clinical routine

MRI measures remain the most important biomarkers for diagnosis and routine follow-up of patients with MS in clinical practice. Brain WM and GM lesion volumes and brain atrophy measures all correlate with disability scores, and can be undertaken using images that can be acquired with all conventional clinical MRI scanners.

Beyond the role of WM lesions in the diagnosis of MS, it has yet to be determined how MRI and molecular biomarkers can be usefully integrated into patient-specific measures for routine use in clinical practice.

An important issue that hampers implementation of MRI in multifactorial decision models and their integration into the routine clinical workflow is the lack of standardised MRI protocols for monitoring disease evolution, particularly for patients receiving DMDs. A standardised basic MRI acquisition protocol should be simple and feasible, robust, fast (around 30 min), scanner vendor-independent, field strength-independent, and supported by national and international scientific societies, payers, and pharmaceutical companies. A standardised MRI acquisition protocol for the diagnosis and follow-up of MS patients has been recently developed by MAGNIMS network (Table 1).[109] European and national MS as well as neurological and (neuro)radiological societies can play an important role in the implementation of this protocol by supporting its use in clinical practice. As differences in MRI outcomes between centres may be in the same range or even exceed yearly changes due to disease progression or differences between placebo and treatment groups observed in clinical trials, ideally the same MRI machine and protocol should be used in the same patient for a many years as is feasible.

Integration of MRI into routine clinical practice also requires further automation of measurements and evaluation.[110] There is need for fully automated pipelines to perform high quality cross-sectional / longitudinal volumetric analysis, with automated detection and filling of lesions (to lessen their confounding effect on atrophy measures). These tools should be integrated in all major MR vendors' post-processing software and allow transfer of information into Picture Archiving and Communication Systems (PACS). Although outsourcing of specialised MRI analysis to dedicated companies may be a good solution for the short term, the pipelines should eventually become integrated into clinical routine allowing fast interpretation of images by (neuro)radiologists.

Not only the MRI protocols, but also the way MRI results are reported by radiologists should be standardised, and combine conventional (written) and structured reports. Dedicated teaching courses for radiologists on MRI standards in MS and interpretation of images could be conducted on a regular basis in order to deepen skills and knowledge of MRI in MS. This will facilitate and improve the communication between radiologists and clinicians and support analysis for research and decision-making. In the future, certification by e.g. European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) or European Society of Neuroradiology (ESNR) of centres and radiologists / neuroradiologists that fulfil the minimum technical requirements, have adequate quality control programmes and use standardised protocols may help to accelerate harmonisation.

One of the most important prerequisites for the successful implementation of routine MRI evaluations (e.g. including atrophy quantification) into clinical practice is that payers (patients, drug companies, private insurance) and health authorities recognise its clinical value. To achieve this, the identification of the most robust MRI biomarkers for disease evolution and treatment response in the individual patient, definitions and thresholds for MRI activity, and their integration into patient risk stratification algorithms are crucial. Today, most existing data regarding markers of treatment response are based on studies with IFNβ and may not apply to other DMDs that have different modes of action.[5,78-80] Therefore, more research is warranted. As some DMDs may take up to 6 months to become effective (e.g. GA), an additional baseline scan at 3-6 months after initiation of treatment is recommended to adequately analyse changes over time and to minimise the pseudoatrophy effect.

The current limitations of existing MRI techniques for use in clinical practice and the need for standardised protocols were confirmed by the polling results at the first Pan-European MS Multi-stakeholder Colloquium. Indeed, when attendants were asked to rank priorities in MRI research, stimulating standardisation of imaging reports and development of software was considered highest priority, followed by improvement of image acquisition and analysis techniques for patient follow-up (Figure 3(a)). The opinion of clinicians about these issues were further explored in an online questionnaire about the optimisation of imaging / MRI for use in clinical practice undertaken in preparation for the second MS Multi-stakeholder Colloquium. Among the 143 respondents of this questionnaire, mostly neuroradiologists (70%), 77.8% indicated that they already used a standardised MRI protocol for MS patients in their practice. The majority (74.1%) indicated that incorporation of measures of brain volume loss in clinical practice would be valuable. Over 80% partly or fully agreed that the development of simplified but robust techniques should be accelerated in order to allow radiologists on site to perform measurements of brain volume loss themselves and to report directly to the neurologist. In addition, 57.3% of the respondents indicated that reimbursement of MRI analysis in MS should in the first place be obtained from insurance companies and public health organisations.

How to integrate the patient's treatment expectations into individualised decision-making?

In order to take a patient-tailored treatment decision, it is not only important to predict the patient's treatment response and his/her risk of developing SAEs, but also to consider the patient's treatment expectations. Physicians' concerns and their willingness to accept SAEs in return for improved drug efficacy may differ substantially from patients' preferences.[111] In general, physicians may be more concerned about the physical manifestations of MS, while patients may be more worried about less tangible domains such as mental health, role limitations due to emotional problems and vitality. However, delaying disability progression remains the most important treatment expectation for patients, being more important than preventing SAEs and decreasing relapse rate (Figure 5).[112,113] Hence, it is not surprising that patients might be more willing to accept SAEs in return for a reduced risk of disability progression than physicians.[114] Given these differences in treatment perspectives between patients and physicians, neurologists should strongly encourage their patients to formulate their own values and preferences regarding their medical care.[115] In addition, healthcare providers have a duty to ensure patients understand the complex information given to them. Patient preferences should be carefully considered, together with the available evidence on efficacy and tolerability for each treatment option, the patient's predicted chance of treatment response and his/her predicted risk of SAEs. In this way, we can progress to personalised or patient-tailored decision making, choosing the treatment option that best matches the patient's treatment expectations, with a good balance between desired efficacy, tolerability and quality of life improvement.

The importance of tailoring treatment for MS to each individual patient also became clear from the survey among the attendants of the first Pan-European MS Multi-stakeholder Colloquium. When participants were asked to rank key issues regarding personalised treatment, evaluating the appropriateness of treatment at individual patient level turned out to be the key priority (Figure 3(b)). In contrast, further exploring and validating patient preferences was not frequently ranked among the top three priorities. This finding suggest that across stakeholders' awareness integrating of individual patient's treatment expectations into decision making in MS still needs to be improved.

Conclusions

Biomarkers may be very useful tools for individualised decision making in MS. They may assist in diagnosing MS, predicting and monitoring disability progression, and in predicting a patient's treatment response and risk of SAEs. In current clinical practice, MRI markers are still the most important biomarkers for diagnosis and routine follow-up of patients with MS, while they may also help to predict response to IFNβ or GA. In addition to clinical and MRI markers, several molecular biomarkers have been identified as well, with the level of NFs in CSF being among the most promising ones, both to predict disease progression and to monitor treatment response.

Although biomarkers can theoretically be used to individualise treatment of patients with MS, their implementation in the clinical decision model currently remains very limited. The validation of biomarkers is a long (it can take 5-15 years before a potential biomarker has been validated for use in clinical practice) and complicated process, requiring replicated evidence of correlation with clinical measures and evaluation of effectiveness, cost effectiveness, and predictive accuracy in clinical trials and real-life clinical practice.[116] In addition, implementation of biomarkers into the decision model requires regulatory approval, reimbursement agreements, ability to interpret and use the results to take decisions, acceptance in clinical guidelines and patient and clinician acceptance. The implementation of a standardised MRI protocol for monitoring disease evolution would be an important first step towards a better evaluation of MS patients in the near future. Such efforts should be accompanied by dedicated training courses on this subject to maintaining a high level of competence. In addition, further development and evaluation of automated measurements that could easily be integrated into the clinical work flow should be fostered to improve practicability of such measurements and facilitate serial analysis and comparison across centres. In addition, more research is needed to discover new clinical, imaging, genetic and immunological biomarkers, to validate new and existing biomarkers and to implement them in clinical practice. Finally, patients' preferences should be actively integrated into the decision-making process. In order to come to a patient-tailored treatment decision, the patient's predicted risks of disability progression, treatment response and SAEs with a particular treatment should be carefully considered together with his/her treatment expectations. This will ultimately help neurologists optimise to drug choices to the each individual patient at the right moment during their disease course

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Conflicts of Interest Statement

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Tables

Table 1. Standardised brain MRI acquisition protocol for an optimised follow-up of MS patients developed by MAGNIMS .[109]

Baseline evaluation

- Mandatory sequences
  - Axial proton density or T2-FLAIR/T2-weighted
  - Sagittal 2D or 3D T2-FLAIR
  - 2D or 3D contrast-enhanced T1-weighted
- Optional sequences
  - Unenhanced high-resolution isotropic 3D T1-weighted
  - 2D and/or 3D dual inversion recovery (DIR)
  - Axial diffusion-weighted imaging

Follow-up examinations

- Mandatory sequences
  - Axial proton density or T2-FLAIR/T2-weighted
- Highly recommended sequence
  - 2D or 3D contrast-enhanced T1-weighted
- Optional sequences
  - Unenhanced high-resolution isotropic 3D T1-weighted
  - 2D and/or 3D dual inversion recovery
  - Axial diffusion-weighted imaging

FLAIR, fluid attenuated inversion recovery; MS, multiple sclerosis

Figure legends

Figure 1. Schematic overview of risk factors and clinical and MRI biomarkers of progression in MS

(GdE: gadolinium-enhancing; GM: grey matter; MR: magnetic resonance; MTI: magnetic transfer imaging)

Figure 2. Median time from disease onset to reach an Expanded Disability Status Scale (EDSS) score of 6, 8 and 10 for (a) the number of relapses (1, 2, or ≥ 3) during year 1-2 after disease onset and (b) for the total number of relapses (1-2, 3-4 or ≥ 5) during the relapsing-remitting phase of 806 patients followed for 28,000 patient-years in the Canadian London Ontario cohort [10]

Figure 3. Polling results from the first Multi-stakeholder MS Colloquium showing priorities in (a) MRI research and implementation in clinical practice and (b) individualised treatment of MS. The *x*-axis shows percentages of points for each option (3 points for the first priority, 2 points for the second priority and 1 point for the third priority) versus the total number of points of all options together

(AEs: adverse events; DMDs: disease-modifying drugs; MOAs: mechanisms of action; OCT: optical coherence tomography; Tx: treatment)

Figure 4. Treatment algorithm depicting the difference between escalation and induction therapy

(BG12: dimethyl fumarate; GA: glatiramer acetate; idx: JCV antibody index; IFN: interferon; JCV: John Cunningham virus; NTZ: natalizumab; tiw: 3 times weekly)

Figure 5. Delaying disability progression is the most important treatment attribute for patients with multiple sclerosis (MS). 651 patients with MS (mean age: 47 years) with a broad range of disability levels were asked to choose between hypothetical pairs of treatment alternatives with varying levels of clinical efficacy and associated risks. From these trade-off tasks, the relative importance of each attribute was determined. Reproduced from Johnson et al, 2009[85], with kind permission from Springer Science and Business Media.