Individualizing therapy for multiple sclerosis: a focus on disease-modifying drugs

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Practice points

- Patients with multiple sclerosis (MS) have various backgrounds and lifestyles. Individualizing therapy should always be pursued in clinical practice.

- Recent progress in disease-modifying drugs (DMDs) for MS is remarkable, and the available DMD options are increasing.

- Some molecules and genetic factors have been studied as potential predictors of treatment response to DMDs, such as IFN-β. However, it is currently impossible to predict the DMD response and adverse events of each MS patient.

- Pharmacogenetic data will provide invaluable information on DMDs and improved therapeutic regimens for MS patients.

SUMMARY Remarkable progress has recently been made regarding new therapies for multiple sclerosis, especially in the form of disease-modifying drugs that can be administered either intravenously or orally. However, responses to drugs, including efficacy and adverse reactions, vary considerably between individuals. Although it is preferable to predict these responses prior to commencing therapy, biomarkers and genetic factors for disease-modifying drugs are not available for routine clinical use. Newer techniques and methods of analysis will result in improved screening of individual benefit/risk balances for multiple sclerosis treatments.

Multiple sclerosis (MS) is considered to have a complex etiology in which environmental and genetic factors are implicated. Although MS is not a curable disease, there are currently several disease-modifying drugs (DMDs), which are effective for reducing the clinical relapses, slowing the progression of physical disability and reducing brain atrophy as shown by MRI. The effects and risks of DMDs vary between individuals, so identification of the most appropriate

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drug for each patient prior to commencing therapy is preferable.

Previously, the MHC region on chromosome 6 encoding the HLA genes was the only confirmed susceptibility region to MS. However, recent technological advances in genetic approaches including genome-wide association studies (GWAS) will hopefully help identify non-HLA genetic risk factors of MS. If susceptibility genes for MS can be identified, this will provide direct information about the relevant biological causes of MS. It might also be possible to identify interacting genetic traits that provide the basis to predict disease characteristics and risks, such as age of onset, disease course and severity. Moreover, patients will be able to receive optimal and individualized therapies.

Pharmacogenetics refers to the study of inherited differences in drug metabolism and response. Although some studies have investigated the pharmacogenetics of drugs for MS, such as IFN-β, current pharmacogenetic data are far from being available for clinical applications. This article reviews the currently available DMDs and the predictive factors for DMD response prior to starting therapy, including pharmacogenetics. It also discusses individualizing MS therapy and future perspectives.

Current DMDs for MS
■ IFN-β
IFN-β-1b for MS was first launched in 1993, and since then several types of IFN-β therapy have been used as DMDs for MS. The effectiveness of IFN-β has already been demonstrated in relapsing–remitting MS (RRMS) in reducing the rate of clinical relapses and and suppressing the development of brain lesions on MRI. Neurological damage occurs at the time of relapse in MS, even in its early stages, and some damage may be irreversible. However, clinical trials evaluating IFN-βs (IFN-β-1b subcutaneously [sc.], IFN-β-1a intramuscular and IFN-β-1a sc.) for the treatment of clinically isolated syndrome suggest that early treatment with DMDs can delay the time to a second demyelinating event and the development of MS [1–3].

Treatment with IFN-β-1b sc. for secondary progressive MS (SPMS) is controversial. In a European study, IFN-β-1b sc. significantly delayed the progression of disability in patients with SPMS [4]. However, the efficacy of IFN-β-1b sc. in SPMS could not be confirmed in a similar pilot study in North America [5]. Some possible reasons for this include differences in the period of time to be diagnosed with SPMS and differences in patient disease activities between the two studies [6]. Nevertheless, these results suggest that the effects of IFN-β are limited and less effective for SPMS compared with RRMS. IFN-β is classified as a first-line DMD for RRMS [7].

■ Glatiramer acetate
Glatiramer acetate (GA), composed of a mixture of synthetic polypeptides derived from four amino acids (L-glutamic acid, L-alanine, L-lysine and L-tyrosine), reduces relapses and disease activity as monitored by MRI [8], and was launched in 1996 for the treatment of RRMS. A Phase III study demonstrated that early GA treatment was efficacious in delaying conversion to clinically definite MS in patients presenting with clinically isolated syndrome and brain lesions detected by MRI [9]. The most common adverse events of GA are injection-site reactions and immediate postinjection reactions but it is generally considered to be safe [9]. GA is classified as a first-line DMD for RRMS [7].

■ Mitoxantrone
Mitoxantrone is an anthracycline-based antineoplastic drug that inhibits the proliferation of T cells, B cells and macrophages, and suppresses production of proinflammatory cytokines. Mitoxantrone particularly decreases the population of B cells, especially memory B cells, and suppresses production of proinflammatory cytokines from B cells [10]. Its clinical efficacy was confirmed in the MIMS trial [11], and it is currently used for the treatment of several forms of advanced MS including SPMS, progressive relapsing MS and advanced RRMS. However, mitoxantrone is currently falling into disuse or becoming a third-line treatment in MS owing to its serious side effects, such as cardiac toxicity and leukemia.

■ Natalizumab
Natalizumab is a humanized monoclonal antibody, and an antagonist of the α4-subunit (CD49d), which consists of VLA-4 with β1-integrin (CD29). Various immune cells such as T and B cells and monocytes, express VLA-4 that binds to VCAM-1 on endothelial

cells. The binding of VLA-4 and VCAM-1 is an important step in immune cell transmigration through the blood–brain barrier and into the CNS, and natalizumab inhibits the binding of immune cells and endothelial cells.

Two large Phase III clinical trials demonstrated the significant clinical effects of natalizumab [12,13], and intravenous natalizumab infusion for MS therapy was launched in 2004. The most critical risk for natalizumab treatment is progressive multifocal leukoencephalopathy (PML), which is an opportunistic brain infection caused by the John Cunningham (JC) virus. PML is progressive and usually fatal, and there are currently no approved or proven therapies for the disease. Based on this adverse event, natalizumab is used as a second-line DMD [7]. Recent studies showed that the risk of PML following natalizumab treatment varied according to anti-JC virus antibody status, immunosuppressant use prior to natalizumab treatment and duration of natalizumab treatment [14]. The highest PML incidence was 11.1 (95% CI: 8.3–14.5) per 1000 patients in those with a positive anti-JC virus status, prior to immunosuppressant use and natalizumab exposure over 24 months. The lowest incidence was <0.1 (95% CI: 0–0.48) per 1000 patients in those with no anti-JC virus [14]. Despite this, most MS patients appear willing to accept risks in exchange for clinical efficacy [15]. It is, therefore, important for medical staff to discuss the risks and benefits of natalizumab therapy with each patient. The Committee for Medicinal Products for Human Use in Europe recommended that natalizumab should only be used in patients who have a real need for the medicine either because they have failed to respond to a IFN-β or GA, or because their disease is severe and getting rapidly worse, owing to its safety profile. There have been no established data on effects of natalizumab for SPMS or primary progressive MS, however, there is a possibility that natalizumab may have efficacy in disabled SPMS subjects [16].

■ Fingolimod (FTY720)

Fingolimod (FTY720) is the first US FDA-approved oral agent for RRMS that has been available for oral administration during the last 3 years. Fingolimod is phosphorylated by sphingosine kinase-1 or -2 into an active form, which binds to specific sphingosine 1-phosphate receptors and induces the internalization of the sphingosine 1-phosphate receptor, thereby blocking the migration of lymphocytes out of secondary lymphoid structures. A Phase III clinical trial demonstrated that fingolimod improved the relapse rate, the risk of disability progression and reduced new or enlarged lesions on T2-weighted images, gadolinium-enhancing lesions and brain-volume loss in MRI [17]. Causes of study discontinuation and adverse events related to fingolimod included bradycardia and atrioventricular conduction block at the time of fingolimod initiation, as well as macular edema, elevated liver enzyme levels and mild hypertension. Another study reported sustained bradycardia and asystole 21 h after the first dose of fingolimod treatment for MS, suggesting that careful monitoring of patients is needed at this stage [18].

A second Phase III clinical trial of fingolimod-versus IFN-β-1a intramuscular demonstrated that the annualized relapse rate was significantly lower in the fingolimod group than in the IFN-only group; however, it should be noted that about half of these patients had received IFN-β prior to participation [19]. In this trial, there were two different dosages of fingolimod (1.25 and 0.5 mg), and two fatal infections occurred during this study in patients who received a 1.25 mg dose of fingolimod, which were caused by disseminated primary varicella zoster and herpes simplex encephalitis. Even though these cases received fingolimod at a dose more than twice as high as the currently approved dose (0.5 mg), careful attention should be paid to infection during treatment with fingolimod.

Although 0.5 mg fingolimod was approved as a first-line drug for MS treatment in 2010 in the USA, only restricted approval was granted in the EU in 2011 for fingolimod as first-line therapy for highly active MS or second-line therapy in patients not tolerating or not responding to first-line DMDs.

■ Teriflunomide

Teriflunomide is a dihydro-orotate dehydrogenase inhibitor and the active metabolite of leflunomide, an oral disease-modifying anti-rheumatic drug. The Phase III clinical TEMSO trial compared three placebo arms, 7 mg of teriflunomide and 14 mg of teriflunomide once daily. It demonstrated that teriflunomide reduced the annualized relapse rate with relative risk reductions of 31.2% (7 mg dose) and 31.5% (14 mg dose) in comparison with placebo [20].

Both teriflunomide doses were also superior to placebo at reducing disability progression, and teriflunomide was well tolerated [20]. Diarrhea, nausea and hair thinning were the more common adverse events of teriflunomide, and alanine aminotransferase levels were also higher in the teriflunomide-treatment group [20]. Teriflunomide was approved as a once-daily, oral DMD by the FDA in September 2012, and also in the EU in August 2013.

■ Dimethyl fumarate

Fumaric acid is an unsaturated dicarbonic acid, and, in 1994, Fumaderm® (Biogen Idec Inc., MA, USA), an enteric-coated tablet containing dimethyl fumarate was approved for the treatment of moderate to severe psoriasis in Germany. After oral administration, dimethyl fumarate is rapidly hydrolyzed by esterases to the bioactive metabolite monomethyl fumarate. Dimethyl fumarate is thought to interfere with the cellular redox system by modulating intracellular thiols, thereby increasing the level of reduced glutathione, although the mechanism of action is not fully understood [21]. Two Phase III clinical trials of oral BG-12 (dimethyl fumarate) demonstrated that BG-12 treatment significantly reduced relapse rates as well as progression of disability compared with placebo, and the adverse effects that occurred most frequently in patients who received BG-12 were flushing and gastrointestinal events [22,23]. BG12 was approved by the FDA in March 2013.

■ Alemtuzumab

Alemtuzumab (Campath-1H) is a humanized monoclonal antibody that binds to the CD52 antigen on lymphocytes and monocytes. Although the function of CD52 is unknown, this protein is expressed on a number of cell populations, including thymocytes, B and T lymphocytes and monocytes but not on plasma cells or haematological precursors [24]. Administration of alemtuzumab causes antibody-dependent cell-mediated lysis, producing a profound lymphopenia [25]. The two Phase III trials of CARE-MSI and CARE-MSII demonstrated that alemtuzumab reduces relapse rate compared with IFN-β-1a sc. three times a week: a reduction of 55 and 49% in the CARE-MSI and the CARE-MSII, respectively [26,27]. Concerns regarding safety were raised when three cases of immune thrombocytopenic purpura

were reported during treatment with alemtuzumab, one resulting in death. In addition, immune thrombocytopenic purpura occurs in 1–3% of patients receiving alemtuzumab. The main adverse effect of alemtuzumab is secondary autoimmunity, and most commonly, 30% of patients develop autoimmune thyroid disease, both Graves' disease and hypothyroidism after alemtuzumab. Other autoimmune diseases have occurred in lower frequencies after alemtuzumab, most notably antiglomerular basement membrane disease [24]. Alemtuzumab was approved in the EU in September 2013.

Genetic biomarkers for treatment monitoring for MS

The genetic contribution to the susceptibility of developing MS is thought to be approximately 25%, which is largely based on the concordance rates of monozygotic twins [28]. With methodological improvements, including GWASs that use statistics to identify the cosegregation of polymorphic markers and disease states to identify genomic regions containing susceptibility loci, many reports have recently been published on studies of large population sizes. Although GWASs are theoretically capable of detecting susceptibility genes of modest effects in multifactorial complex genetic disorders such as MS [29], only 20–30% of the perceived heritability of MS can be explained even from large GWASs [30–32].

The most consistent and strongest evidence for the genetic linkage of MS has been shown at *HLA-DRB1*1501* on chromosome 6p21 [33]. The International Multiple Sclerosis Genetics Consortium performed a GWAS including 9722 cases and 17,376 controls, which refined the identity of the *HLA-DRB1* risk alleles and confirmed that variation in the *HLA-A* gene underlies the independent protective effect attributable to the class I region within the MHC. Furthermore, the study detected over 50 loci associated with MS outside the HLA region including 29 novel susceptible loci [33]. Immunologically relevant genes are significantly over-represented, particularly those with a role in T-cell activation and proliferation. This suggests that immune mechanisms mediated mainly by T cells are associated with the pathogenesis of MS.

In the consideration of genetic and environmental associations as risk factors of MS,

CYP27B1, a gene associated with vitamin D metabolism, has an important impact. This is because mapping the distribution of MS reveals a high prevalence of the disease in high-latitude areas, indicating an involvement for UV-radiation/vitamin D in MS. *CYP27B1* encodes a protein that converts 25-hydroxyvitamin D to the active hormone 1,25-dihydroxyvitamin D [33,34]. Genetic mutations of *CYP27B1* are suggested to affect circulating levels of 1,25-dihydroxyvitamin D [35,36]. Furthermore, vitamin D is reported to specifically interact with *HLA-DRB1*1501* to influence its expression [37], indicating a potential interaction between environmental and genetic factors in the pathogenesis of MS. Currently, clinical trials of vitamin D for MS are ongoing, and it is likely that more focus will be placed on *CYP27B1* if vitamin D becomes a treatment option for MS.

From current evidence, the genetic analysis of MS is considered to be further complicated owing to its racial heterogeneity. When multiple ethnic groups were tested for disease-susceptibility genes, the results were not always uniform. It is conceivable that variants responsible for disease-susceptibility genes could be heterogenous, which renders it difficult to identify disease-associated genetic markers owing to the existence of rare, multiple susceptibility variants. The location of SNPs and their frequencies vary between different populations; thus, when interpreting any of the associations presented, genetic variation between racial and ethnic groups should be considered.

Candidate genes could be associated with clinical characteristics such as severity or disease course [38,39], and this issue is relevant in the evaluation of responsiveness to treatments. Pharmacogenetic studies have established the importance of genetic polymorphisms in receptors or drug targets that mediate interindividual differences in the efficacy and toxicity of many medications because response to drugs is, to some extent, determined by genetic factors. Pharmacogenetics could shed light on inherited differences in drug metabolism and response, which would make individualizing therapy possible in MS. Susceptible gene studies and pharmacogenetic studies will provide invaluable information concerning new drugs for the treatment of MS and improved therapy plans for MS patients. Among the DMDs, the most extended pharmacogenetic research for

individualizing therapy has been conducted on IFN-β, with some studies on GA reported. Few pharmacogenetic investigations have been carried out on more recent DMDs.

■ Glatiramer acetate

The mechanism of GA is thought to involve its binding to HLA class II molecules. Two studies demonstrated that *HLA-DRB1*1501* is associated with an improved response to GA [40,41]. However, these findings could not be replicated in another study, which instead demonstrated that the two genes *TRB@*, rs71878 and *CTSS* rs2275235 were associated with GA response [42].

■ IFN-β

IFN-β exerts its biological effects via binding a heterodimeric IFN-α/β receptor (IFN-AR) consisting of IFN-AR1 and IFN-AR2 subunits. This then triggers the JAK-signal transducer and activator of transcription signaling pathway. STAT1–STAT2–IRF9 complexes, known as ISGF-3 complexes, translocate to the nucleus and bind interferon-stimulated response elements in DNA to initiate gene transcription.

Genes associated with IFN-signaling are considered candidates to respond to IFN-β treatment. It was reported that the increased expression levels of a specific set of 15 IFN-response genes in the peripheral blood mononuclear cells of MS patients prior to treatment were associated with the absence of a pharmacological effect of IFN-β-treatment in RRMS [43]. Other studies demonstrated similar findings [44,45], and IFN-β nonresponsiveness may be predicted by the differential expression of a small number of type I IFN-inducible genes prior to the start of IFN-β therapy. In these studies identifying IFN-β responders and nonresponders, monocytes are considered the main players in determining the response outcome of MS patients [44,45].

Cunningham *et al.* screened 100 IFN-stimulated response element-containing genes using a pooled DNA-sequencing approach and identified four containing polymorphisms associated with response to IFN-β treatment: *IFN-AR1*, *LMP7*, *CTSS* and *MXA* [46]. On the other hand, there was no significant association between the *MXA* genotype and clinical response in MS patients treated with IFN-β in another study [47], while a third study found no significant differences in genotype distributions of *IFN-AR1* between IFN responders and nonresponders [48,49].

IRF-5 is a transcription factor that is important in the regulation of type I IFN-induced gene activity as well as in the production of type I IFN. In 2011, two studies reported the *IRF5* polymorphisms rs3807306, rs4728142 [50], rs2004640 and rs47281420 [51], which are related to clinical response to IFN-β treatment in MS. In the former study, a nonsignificant trend for association was observed between the SNP rs3807306 and response to IFN-β treatment [50]. On the other hand, in the latter study, rs2004640 and rs47281420 genotypes were associated with pharmacological response to IFN-β treatment in MS [51].

ApoE is a ligand for lipid transport that contributes to myelin repair and axonal regeneration in the CNS. The *e4* allele of the *APOE* gene is known to be a risk factor for Alzheimer's disease, and some studies report an association between *APOE* polymorphisms and response to IFN-β treatment in MS. One study reported that the *e2* allele may be associated with improved response to IFN-β treatment [52], although a second showed that both alleles were not associated with IFN-β treatment response [53].

The development of neutralizing antibodies (NAbs) to IFN-β is associated with decreases in the effects of IFN-β treatment [54]. In a study on genetic polymorphisms and NAbs, an association was reported between the rs5743810 polymorphism of *TLR6* and development of IFN-β-specific NAbs in men but not women [55]. In addition, a genome-wide SNP genotyping study identified rs9272105 within HLA and rs4961252 in an intergenic region on chromosome 8q24.3 as predictors of NAb titers in IFN-β-treated MS patients [56].

The TRAIL/TRAILR system participates in crucial steps in immune cell activation or differentiation, and is also able to induce the apoptosis of neurons and oligodendrocytes. In a study of 54 SNPs in *TRAIL*, *TRAILR-1*, *TRAILR-2*, *TRAILR-3* and *TRAILR-4* genes, it was suggested that the rs20576 SNP of *TRAILR-1* was associated with clinical response to IFN-β treatment [57].

A genome-wide pharmacogenomic approach is currently underway to identify SNP allelic differences associated with IFN-β treatment response. However, as with earlier pharmacogenetic studies on IFN-β treatment, data using this approach are not consistent [58,59] and it is too early to use them in routine clinical practice.

This may support the underlying polygenic and complex responses to IFN-β treatment in MS. Some reasons for inconsistent results include differences in backgrounds of participating patients such as clinical type, gender, ethnicity and differences of environment. In particular, determining the method to use in the evaluation of drug efficacy across different trials is a key issue. The definition of 'responder' is also highly variable: it may be based on clinical criteria or both clinical and MRI criteria. Taken together, a consistent and reproducible definition of drug efficacy and 'responder' across studies is extremely important for study design and data interpretation [60].

Predictive factors of responders & nonresponders to IFN-β treatment

MRI markers and clinical relapses have been the most widely studied short-term factors to predict long-term response to IFN-β, however, the results are conflicting [61]. On the other hand, predictive factors before starting IFN-β treatment are still unclear. Since MS physiopathology is heterogeneous, it may mean that a drug with '*a priori* lower efficacy' is very effective in a determined group of patients. Bosca *et al.* reported that lipid-specific oligoclonal IgM bands (LS-OCMB) of which intrathecal synthesis is related to a worse disease course in MS patients, may have an influence on the response to IFN-β treatment in RRMS patients [62]. This study demonstrated that the reduction of relapses was lower in RRMS patients with LS-OCMB compared with patients without LS-OCMB [62].

IL-17, a cytokine produced by Th17 cells, participates in the pathogenesis of experimental autoimmune encephalomyelitis (EAE), an animal model of MS [63], and IFN-β exacerbates EAE induced by Th17 cells [64]. In RRMS, it was reported that nonresponders to IFN-β treatment had high serum concentrations of IL-17F prior to the initiation of IFN-β therapy [64]. A recent study also demonstrated that RRMS patients with high serum IL-17A levels had a worse response to IFN-β than those patients with low IL-17A serum levels, although the sample size of this study was low [65]. Moreover, large clinical trials did not confirm serum IL-17F concentration as a predicting factor for IFN-β-treatment response [66] or IFN-β-1b therapy in patients with RRMS [67].

Sema4A, a transmembrane-type semaphorin, is expressed in human dendritic cells where it

is upregulated on the surface in MS patients. Sema4A plays critical roles in helper T-cell activation and Th1 differentiation during the course of EAE [68], and is also involved in Th17- and Th1-mediated pathogenesis in experimental models [69]. Furthermore, patients with high serum Sema4A levels show Th17 skewing, and high Sema4A levels are associated with severe disabilities and nonresponsiveness to IFN-β therapy [69]. As IL-17 is of interest in the response to IFN-β treatment, further studies are necessary to confirm these associations.

Approach to individualizing therapy for MS in DMDs

National or regional guidelines about treatment for MS can be useful to determine which DMD is appropriate for each patient. However, guidelines are not sufficient for individualizing therapy, and many studies have been conducted to detect predictive factors of responders and nonresponders using genetic and molecular approaches prior to starting DMD therapy. It is also important to consider drug efficacy in relapse reduction, which is reported as 30% for IFN-β, GA and teriflunomide treatment, 50% for fingolimod and dimethyl fumarate and 70% for natalizumab [70].

Pharmacogenomics can be applied for the pretreatment assessment of whether a patient will have effects from a specific drug and/or reduce adverse drug reaction. However, DMD pharmacogenetics for MS are poorly studied, not least owing to the shortage of established data on the precise mechanism of drug action, which genetic polymorphisms should be assessed and whether haplotypes provide more information than the individual genotype for a given gene–drug interaction.

How do we approach individualized therapy in MS? Unfortunately, data on individualized therapies for clinical use are currently limited. Medical staff should, therefore, provide information about available DMDs including current guidelines, and risks/benefits such as PML risk following natalizumab treatment. Furthermore, several factors should be considered for individualization of MS treatment including economic factors, treatment strategy, treatment goals, disease profile and disease characteristics [71]. Morgante *et al.* recommended the following approaches to enable patients to make more informed decisions [72]:

- Establish a collaborative, trusting relationship based on mutual respect;

- Be nonjudgmental (understand the patient's perspective);

- Explore the patient's health beliefs and values, focusing on ethnic/cultural differences (e.g., ask about previous experiences);

- Assess the level of patient support (family, employment and finances);

- Identify obstacles to patient participation in decision-making (e.g., cognitive limitations);

- Clarify treatment options by explaining risks and benefits of each therapy;

- Identify patient priorities;

- Listen to patient concerns;

- Help patients recognize and achieve personal comfort with decision-making;

- Advocate for patients if a decision goes against team consensus;

- Help patients implement decisions (e.g., navigate insurance hurdles);

- Evaluate outcomes of decision;

- Realize that decision-making is a continuous process.

Patients require up-to-date evidence-based information and decision support systems to make informed decisions as they face increasingly complex decisions over the choice of DMD [73]. They also need the support of their physicians, as a strong relationship between patients and medical staff together with good availability of information on MS has been shown to be important factors affecting patient quality of life [74].

Other key factors in choosing DMDs is the region or country of patient residence as guidelines for MS treatment and insurance systems differ between nations. Insurance systems are particularly important because high costs of DMDs may limit a patient's available options. Governments, regulators, funding agencies, clinicians, pharmaceutical industries and patient groups need to work together to develop strategies that deliver more cost-effective medicines, and need to widen the focus of research to ensure the continuous development of better therapy

options with improved efficacy, safety and tolerability profiles [75].

Conclusion

Individualized therapies are required for all types of MS, which means that new approaches should be developed to incorporate a wide range of pharmacological and nonpharmacological strategies that focus on the needs of people living with the disease as individuals. These should aim to reduce disease activity, slow disability progression and improve management of MS symptoms such as depression, immobility and fatigue [75]. We need to provide patients with evidence-based information about the risks and benefits of each DMD, as it is notable that the majority of patients want to be more involved in decisions about their treatment [71].

Future perspective

Limited data are currently available on the pharmacogenetics of novel DMDs such as fingolimod, teriflunomide and BG12. Moreover, although many pharmacogenetic studies on IFN-β have been reported, the data have not been applied in routine clinical practice. However, clinical trials of several different types of agents are ongoing or have recently been undertaken, so these results will be included in the choice of DMDs in the near future. This will further increase the complexity of deciding which DMD should be used in each patient.

MS displays a great deal of clinical heterogeneity that reflects its diverse etiology. Promising technologies such as proteomics, metabolomics or immunological studies may be applied for individualizing therapy. Individual genetic characteristics are thought to play an important role in the treatment response, and genetic polymorphisms in drug receptors, metabolizing enzymes, transporters and targets are considered to be linked to interindividual differences in the efficacy and toxicity of many medications. In the near future, whole-genome SNP profiling would help to determine those predisposing genetic factors involved in adverse drug reactions, and, for patients with MS, its application could give us great clinical benefit. Future techniques may assess an individual's probability of benefiting from and/or developing adverse reactions to a specific drug although we require more information before applying pharmacogenomics to day-to-day clinical practice. In addition, the frequencies of polymorphisms that affect drug metabolism are very different between different ethnic groups. Similarly, susceptibility genes for MS may also differ between such groups. With this in mind, studies that further improve individualizing therapy for MS should be continued. This can be combined with progressive research into molecular medicine to more readily identify markers of responders or nonresponders in the future.

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