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Review

Optimizing therapy early in multiple sclerosis: An evidence-based view

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ABSTRACT

Therapies that target the underlying pathology of multiple sclerosis (MS), including focal and diffuse damage, may improve long-term disease control. Focal damage (inflammatory lesions) manifests clinically mainly as relapses, whereas diffuse damage (neurodegeneration and brain volume loss) has been more closely associated with disability progression and cognitive decline. Given that first-line therapies such as beta-interferon and glatiramer acetate, which are primarily directed against inflammation, might fail to adequately control disease activity in some patients, it has been recommended to switch these patients early to a therapy of higher efficacy, possibly targeting both components of MS pathology more rigorously. This review provides an overview of the efficacy of EU-approved disease-modifying therapies on conventional MS outcome measures (relapses, disability progression and paraclinical magnetic resonance imaging endpoints) in addition to brain volume loss, a measure of diffuse damage in the brain. In addition, the evidence supporting early treatment optimization in patients with high disease activity despite first-line therapy will be reviewed and an algorithm for optimal disease control will be presented.

Contents

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1. Changing the course of multiple sclerosis: the need for early treatment optimization

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease with complex underlying pathological processes, including focal and diffuse damage (Filippi et al., 2012; Markovic-Plese and McFarland, 2001). Focal white matter (WM) lesions are considered the classic hallmark of MS, but recent imaging and histopathological studies have shown that focal lesions are also present in the gray matter and play a crucial role in MS pathogenesis (Filippi et al., 2012; Markovic-Plese and McFarland, 2001; Lucchinetti et al., 2011; Kutzelnigg and Lassmann, 2014; Smirniotopoulos et al., 2007). Diffuse damage can occur independently of focal lesions and is frequently observed in normal-appearing tissue (Kutzelnigg et al., 2005; Filippi and Rocca, 2005). Neurodegeneration, which is part of the diffuse pathology of MS, begins early in the disease course and contributes to ongoing disease activity, but may not always be clinically evident (Filippi et al., 2012; Kutzelnigg and Lassmann, 2014; Filippi and Rocca, 2005). Whereas axonal and neuronal damage in the early stages of the disease are likely to be driven by inflammation, neurodegeneration observed in the later, progressive stages may primarily be explained by intrinsic, inflammatory-independent mechanisms (Dutta and Trapp, 2011; Lassmann and van Horssen, 2011). Profound alterations in the gray matter and normal-appearing WM have been associated with progressive loss of brain volume (Kutzelnigg and Lassmann, 2014). While focal damage (inflammatory lesions) may manifest clinically as relapses (Brück, 2005), diffuse damage (neurodegeneration and brain volume loss [BVL]) has been associated with disability progression (Kutzelnigg et al., 2005; Sanfilipo et al., 2005; De Stefano et al., 2014). Targeting both focal inflammatory and diffuse neurodegenerative damage in relapsing–remitting MS (RRMS) earlier may prevent the accumulation of irreversible neurological damage and reduce the risk of disability progression.

The widely used first-line therapies beta-interferon (IFN β) and glatiramer acetate (GA) have only demonstrated partial efficacy in the treatment of MS (Shirani et al., 2012; Kremenchutzky et al., 2007; Johnson et al., 1995; Gajofatto et al., 2009). Some patients experience significant disease activity despite IFN β or GA treatment (Gajofatto et al., 2009; Río et al., 2002; Killestein and Polman, 2011; Bermel et al., 2013), indicating the need for an alternative therapeutic strategy. Thus, it seems crucial to identify non-responders to first-line therapies early on, in order to switch patients to a more potent therapy early in their disease course. Magnetic resonance imaging (MRI) measures, including BVL, have been found to play an important role in predicting long-term disability, and may, thus, help to identify treatment non-response early (Río et al., 2009; Popescu et al., 2013; Sormani and De Stefano 2013; Sormani et al., 2014; Sormani et al., 2013). It has been suggested previously that the clinical course of MS consists of two major phases: one early, inflammatory phase and one later, progressive, inflammatory-independent phase (Leray et al., 2010). Irreversible, pathological damage occurs in the early phase of MS and significantly contributes to disability progression (Freedman, 2011; Gold et al., 2010). Once patients enter the progressive phase, permanent damage has already accumulated and it becomes difficult to improve outcomes (Freedman, 2011). Considering the early window of opportunity to influence the accumulation of irreversible long-term damage (Leray et al., 2010; Freedman, 2011), early switching to a high-efficacy therapy that targets both focal and diffuse pathology may impact favorably on long-term outcomes (Bermel et al., 2013; Río et al., 2009). Early treatment has been shown to be associated with a reduction in disability progression in patients with RRMS and a reduction in the risk of developing clinically defined MS in patients with clinically isolated syndrome (Jacobs et al., 2000; Comi et al., 2001; Comi et al., 2009; Kappos et al., 2006). Thus, optimizing therapy early by addressing key aspects of disease activity and worsening, including relapses, disability progression, MRI lesions and BVL, may most effectively delay disease progression and modify the course of this disabling disease.

The expansion of the treatment landscape in MS over the last few years has increased the complexity of treatment decisions. Recommendations and algorithms can help to maximize the benefit of each available therapy; however, there is currently no consensus algorithm available, with most of the recently published recommendations being regional (Multiple Sclerosis Therapy Consensus Group (MSTCG) et al., 2008; Correale et al., 2014; Freedman et al., 2013; Río et al., 2011). Most guidelines currently used in clinical practice are driven by the labels of the therapies. Current disease-modifying therapies (DMTs) approved in the EU for the treatment of RRMS include IFN β, GA, teriflunomide, dimethyl fumarate (DMF), fingolimod, natalizumab, and alemtuzumab.

In this review, we will discuss the therapies used for treatment-naive patients and patients with active disease despite first-line treatment, based on their use in current clinical practice (Fig. 1). To collect the available data for each of the therapies and evidence for early treatment optimization, we searched PubMed (the US National Library of Medicine [NLM]'s medline and pre-medline database by the National Institutes of Health [NIH] and National Center for Biotechnology Information [NCBI]) as well as a number of congress libraries (e.g, the American Academy of Neurology [AAN] and the European Committee for Treatment and Research in Multiple Sclerosis [ECTRIMS]) using search terms such as 'Phase III trials', 'real-world evidence' and 'early treatment optimization' along with the individual drug names. In addition, we retrieved the most recent versions of the summaries of product characteristics of the individual therapies from the European Medicines Agency (EMA) website. We will review here the efficacy of the different therapies in terms of four key measures of disease activity (relapses, disability progression, MRI lesions, and BVL) as well as their safety, and we will discuss the current evidence that might help in the process of treatment optimization in MS, focusing on switching early to a high-efficacy therapy in patients with breakthrough disease activity.

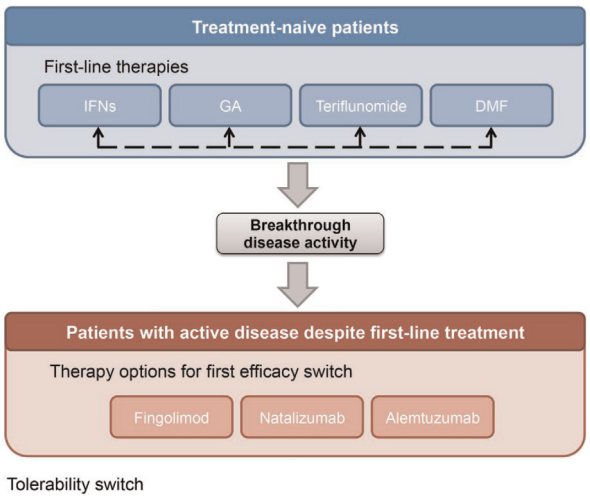

Fig. 1. Treatment algorithm for first- and second-line therapies based on their use in current clinical practice. DMF, dimethyl fumarate; EMA, European Medicines Agency; GA, glatiramer acetate; IFN, interferon.

Table 1
Overview of evidence supporting the treatment positioning of the more recently approved DMTs[a].

	Teriflunomide (Sanofi-Aventis Groupe, 2014; Vermersch et al., 2014; O'Connor et al., 2011; Confavreux et al., 2014; Wolinsky et al., 2013; Olsson et al., 2014; Leist et al., 2014)	**DMF** (Gold et al., 2012; Fox et al., 2012; Arnold et al., 2014; Miller et al., 2012; Gold et al., 2015; Hutchinson et al., 2013; Hutchinson et al., 2013; Bar-Or et al., 2013; Tan and Koralnik, 2010; Multiple Sclerosis Society News, 2014; Biogen Idec, 2015)	**Fingolimod** (Novartis Pharma GmbH, 2014; Calabresi et al., 2014; Cohen et al., 2010; Bergvall et al., 2014; Khatri et al., 2011; He et al., 2015; Ziemssen et al., 2014; Novartis International AG, 2014; Havrdová et al., 2011)	**Natalizumab** (Biogen Idec, 2015; Biogen Idec Ltd, 2014; Polman et al., 2006; Rudick et al., 2006; Miller et al., 2007; Butzkueven et al., 2014; Río et al., 2012; Belachew et al., 2011; Castillo-Trivino et al., 2011; Prosperini et al., 2012; Putzki et al., 2010; Putzki et al., 2009; Putzki et al., 2010; Bloomgren et al., 2012)	**Alemtuzumab** (Genzyme Therapeutics Ltd, 2014; Cohen et al., 2012; Coles et al., 2012; Coles, 2013; Miller et al., 2014)
Positioning Efficacy	For treatment-naive patients and mild/moderate disease activity		For patients with (highly) active disease (despite first-line treatment)		
	• Mild to moderate efficacy • Homogenous efficacy on clinical disease activity across subgroups stratified by baseline demographics, clinical, and MRI characteristics • No proven efficacy vs. active comparator • No significant reduction in global BVL	• High efficacy in newly diagnosed patients • More effective in treatment-naive patients than in patients previously treated with ≥ 1 DMT • No proven efficacy vs. active comparator • Inconsistent effect on BVL across clinical trials	• High efficacy in patients with disease activity despite prior DMT use • High efficacy in patients who switched from IFNs or GA to fingolimod (RCT, RWE) • Proven efficacy against active comparator (IFN β-1a IM) • Early and consistent effect on BVL	• High efficacy in patients with suboptimal treatment response on IFN β or GA (RWE) • No proven efficacy vs. active comparator (as monotherapy) • No early and consistent effect on BVL	• High efficacy in patients with ≥ 1 relapse on IFN β or GA • Proven efficacy vs. active comparator (IFN β-1a SC) • Effect on BVL vs. active comparator (IFN β-1a SC)
Total number of patients treated worldwide (estimate)	• 30,000(data cut-off August 2014)	• 138,535(data cut-off December 2014)	• ~104,700(data cut-off August 2014)	• 138,043(data cut-off December 2014)	• 1486(data cut-off October 2014, clinical trials only[b])
Total patient-years of exposure (estimate)	• > 6800(data cut-off August 2014, clinical trials only[b])	• 112,096(data cut-off December 2014)	• 172,500(data cut-off August 2014)	• 404,299(data cut-off December 2014)	• 6483(data cut-off October 2013, clinical trials only[b])
Primary safety/tolerability concerns and monitoring required	• Generally well tolerated, with routine monitoring of liver function required due to a risk of hepatotoxicity • Should be avoided during pregnancy as it may cause major birth defects • Hair thinning is a commonly reported side effect that may influence patient preference	• Most common AEs include flushing and GI events, which tend to begin early in the course of treatment • DMF has been associated with prolonged lymphopenia, which may increase the risk of PML	• Fingolimod has been associated with a transient, mostly asymptomatic decrease in heart rate treatment initiation, requiring monitoring over the first 6 h following the first dose • Vigilance for symptoms and signs of infection	• Natalizumab has been associated with an increased risk of PML in patients who are JCV antibody-positive, requiringmonitoring for early signs and symptoms of PML	• Alemtuzumab has been associated with an increased risk in secondary autoimmunity (especially thyroid disease, idiopathic thrombocytopenic purpura, and, seldom, Good pasture syndrome), requiringextensive monitoring for early signs of autoimmune disease
Convenience/ ease of use	• Convenient oral administration, once-daily	• Convenient oral administration, but twice-daily dosing may pose adherence issues	• Convenient oral administration, once-daily	• Intravenous infusion over approximately 1 h every 4 weeks	• Intravenous infusion over 2 treatment courses (5 consecutive days initially and 3 consecutive days 1 year later)

AE, adverse event; BVL, brain volume loss; DMF, dimethyl fumarate; DMT, disease-modifying therapy; GA, glatiramer acetate; GI, gastrointestinal; IFN, interferon; IM, intramuscular; JCV, John Cunningham virus; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; RCT, randomized controlled trial; RWE, real-world evidence; SC, subcutaneous.

[a] IFNs and GA, whose treatment positioning has been well established, have not been included here;
[b] Post-marketing data not available.

1.1. Treatment options for treatment-naive patients

1.1.1. IFN β and GA

IFN β and GA are first-line therapies for the treatment of RRMS based on their established efficacy and safety profiles (Kremenchutzky et al., 2007; Johnson et al., 1995; Reder et al., 2010; Ford et al., 2010). It is evident that in some patients IFN β and GA do not adequately control MS disease activity (Johnson et al., 1995; Río et al., 2002; Killestein and Polman 2011; Bermel et al., 2013; Pereira et al., 2012). Given the limited evidence supporting switching between different IFNs and/or GA (Gajofatto et al., 2009; Prosperini et al., 2011; Carrá and Onaha, 2008; Caon et al., 2006) and the lack of consistent disability reduction with long-term treatment with IFNs (Katrych et al., 2009; Ebers et al., 2010; Shirani et al., 2013), cycling between IFNs and GA may not be advisable. Thus, patients with breakthrough disease activity on first-line therapies seem to benefit more from a switch to a therapy with higher efficacy. Cycling among IFNs or GA seems primarily plausible for safety or tolerability reasons. In addition, switching therapy from IFN to GA should also be considered in cases where neutralizing antibodies to IFN develop, which may impact the efficacy of the drug (Kappos et al., 2005; Sorensen et al., 2003).

1.1.2. Teriflunomide

Teriflunomide, a once-daily oral agent, is approved (14 mg/day) in the EU for the treatment of adult patients with RRMS (Sanofi-Aventis Groupe, 2014). Teriflunomide primarily targets the inflammatory component of the disease through selective inhibition of dihydroorotate dehydrogenase, a key mitochondrial enzyme required for *de novo* pyrimidine synthesis, leading to a reduction in proliferation of activated T and B lymphocytes (Bar-Or et al., 2014).

The efficacy of teriflunomide was assessed in two placebo-controlled Phase III trials, TEMSO (Teriflunomide **M**ultiple **S**clerosis **O**ral) and TOWER (**T**eriflunomide **O**ral in people **W**ith relapsing multipl**E** scle**R**osis) (O'Connor et al., 2011,Confavreux et al., 2014), and in the active comparator Phase III trial, TENERE (**TE**riflu**N**omid**E** and **RE**bif®) (Vermersch et al., 2014). Teriflunomide resulted in a significant reduction in annualized relapse rates (ARRs) and the risk of 3-month confirmed disability progression compared with placebo in TEMSO and TOWER (O'Connor et al., 2011; Confavreux et al., 2014). Teriflunomide's effect on 6-month confirmed disability progression was not significant in TEMSO and not reported in TOWER (O'Connor et al., 2011; Confavreux et al., 2014; US Food and Drug Administration (FDA), 2012). In the 2-year TEMSO trial, teriflunomide significantly reduced the number of gadolinium-enhancing (Gd+) T1 lesions and unique active lesions (i.e. Gd+ T1 and new or enlarging T2 lesions) (O'Connor et al., 2011; Wolinsky et al., 2013). Neither T1 nor T2 lesions were reported in TOWER (Confavreux et al., 2014). In TEMSO, teriflunomide was associated with a beneficial effect on WM loss, whereas global BVL was not significantly reduced (O'Connor et al., 2011; Wolinsky et al., 2013). In the 2-year TENERE trial, treatment with teriflunomide did not result in a significant reduction in relapse rates compared with subcutaneous (SC) IFN β-1a (Vermersch et al., 2014). Relapse rate was, however, not the primary endpoint in this trial (Vermersch et al., 2014). Disability and MRI outcomes have not been reported for TENERE (Vermersch et al., 2014).

Subgroup analyzes of pooled data from TEMSO and TOWER have demonstrated consistent efficacy with teriflunomide across a number of subgroups, stratified by baseline demographics, clinical, and MRI disease characteristics (Olsson et al., 2014), confirming the suitability of teriflunomide as first-line treatment for MS, irrespective of baseline characteristics.

Treatment with teriflunomide is generally well tolerated, with predominantly mild to moderate adverse events (AEs) and only rare serious AEs (Sanofi-Aventis Groupe, 2014). Common AEs include hair thinning, diarrhea, alanine aminotransferase elevation, nausea, and headache (Sanofi-Aventis Groupe, 2014; Bar-Or et al., 2014). Hair thinning may influence the patient's preference, in particular that of women, who might be reluctant to use teriflunomide. Due to an increased risk of hepatotoxicity with teriflunomide, routine monitoring of liver function is required (Sanofi-Aventis Groupe, 2014). Also, blood pressure measurements and complete blood cell counts should be performed before and during treatment (Sanofi-Aventis Groupe, 2014). In addition, it should be noted that teriflunomide should not be given to patients who wish to become pregnant, as it has been associated with an increased risk of major birth defects when administered during pregnancy (Sanofi-Aventis Groupe, 2014). Teriflunomide is labeled as 'Pregnancy Category X' by the US Food and Drug Administration (FDA), which means that women of childbearing age must have a negative pregnancy test before starting the drug and must use effective birth control during treatment (Genzyme Corporation, 2014). Overall, teriflunomide has demonstrated a manageable safety and tolerability profile in clinical trials, which is, however, based on relatively small patient numbers and limited long-term data (Bar-Or et al., 2014; Leist et al., 2014). A good long-term safety profile has been established for the parent compound leflunomide in the treatment of rheumatoid arthritis (van Riel et al., 2004). It can be assumed that teriflunomide may exhibit a similar profile to leflunomide; however, at present such data have not been established in relevant numbers for this drug.

Based on the Phase III trial data, including the subgroup analyzes, teriflunomide is used as a first-line treatment option (see also Table 1). Given its convenient oral route of administration and once daily application, patients may prefer teriflunomide over injectables, which may further influence treatment decisions.

1.1.3. Dimethyl fumarate

DMF, an orally administered agent, is approved (240 mg twice daily) in the EU for the treatment of adult patients with RRMS (Biogen Idec Ltd, 2014). The mechanism of action (MoA) of DMF has not been fully elucidated, but may include anti-inflammatory and cytoprotective aspects reported to be mediated via the nuclear factor (erythroid-derived 2)-like 2 transcriptional pathway, which is involved in the cellular response to oxidative stress (Burness and Deeks, 2014).

The efficacy and safety of DMF was assessed in the 2-year, placebo-controlled, Phase III trials, DEFINE (**D**etermination of the **E**fficacy and safety of oral **F**umarate **IN** r**E**lapsing–remitting MS) and CONFIRM (**CO**mparator and a**N** oral **F**umarate **I**n **R**elapsing–remitting **M**ultiple sclerosis) (Gold et al., 2012; Fox et al., 2012). In both trials, DMF resulted in a significant reduction in ARR, the number of Gd+ T1 lesions, and the number of new or enlarging T2 lesions vs. placebo (Gold et al., 2012; Fox et al., 2012). A significant effect on 3-month confirmed disability and BVL was observed in DEFINE but not in CONFIRM (Gold et al., 2012; Fox et al., 2012; Arnold et al., 2014; Miller et al., 2012). DMF did not significantly reduce 6-month confirmed disability progression in either trial (Gold et al., 2012; Fox et al., 2012).

Although GA was included as a reference comparator in CONFIRM, the trial was not designed or powered to demonstrate statistical superiority or non-inferiority of DMF vs. GA (Fox et al., 2012). A *post-hoc* analysis of the CONFIRM study comparing the efficacy of DMF and GA did not demonstrate the superiority of DMF (Fox et al., 2012. (supplementary appendix)) A *post-hoc* analysis of DEFINE and CONFIRM demonstrated higher efficacy of DMF in newly diagnosed patients compared with the placebo group (Gold et al., 2015), and in treatment-naive patients compared with patients previously treated

with DMTs (Hutchinson et al., 2013). Subgroup analyzes of DEFINE and CONFIRM have also shown that treatment with DMF is effective on relapse rates across a broad range of patients with RRMS, stratified by various baseline demographics and disease characteristics (Hutchinson et al., 2013; Bar-Or et al., 2013).

DMF is generally well tolerated in patients with RRMS; the most frequently reported AEs include flushing and gastrointestinal events, which tend to start early in the course of treatment (Biogen Idec Ltd, 2014). The use of DMF has also been associated with lymphopenia, a potential risk factor of progressive multifocal leukoencephalopathy (PML), a rare but in some cases fatal disease, caused by reactivation of the polyomavirus John Cunningham virus (JCV) (Tan and Koralnik, 2010; Multiple Sclerosis Society News, 2014; Calabrese et al., 2015). Especially persistent lymphopenia may increase the risk for PML in patients treated with DMF (Bomprezzi, 2015), but the real MoA by which PML occurs in these patients is not yet fully understood. Two cases of fatal PML in patients receiving DMF have recently been reported; one with and one without severe lymphopenia (Multiple Sclerosis Society News, 2014; Sheremata et al., 2015; Nieuwkamp et al., 2015; Rosenkranz et al., 2015). Thus, regular monitoring of lymphocyte levels may be advisable for early identification of patients treated with DMF who may be at risk of PML (Biogen Idec Ltd, 2014). In addition, complete blood count assessments of renal and hepatic function before and during treatment are also recommended (Biogen Idec Ltd., 2014). Although more than 100,000 patients have already been treated with DMF (Biogen Idec, 2015), its clinical use is limited to shorter-term application; clearly, more long-term experience is needed to confirm and further characterize its safety profile.

Overall, DMF may be recommended as a first-line treatment that can be used as an alternative treatment to injectable DMTs and teriflunomide (see also Table 1). Patients may prefer DMF over injectables due to its oral administration; however, the twice-daily dosing may pose adherence issues that may impact real-life efficacy in the long term (CMEcorner.com).

1.2. Guidance on when to switch therapy in patients with breakthrough disease activity

Making decisions on when to switch therapy is challenging, due to the lack of a standardized definition of treatment non-response (Sormani and De Stefano, 2013; Coyle 2013; Prosperini et al., 2014). Given that relapse activity is a key clinical parameter, a switch in therapy may be recommended at the earliest sign of relapse activity, irrespective of its severity. However, as current DMTs are unable to fully suppress relapse activity, it may not be advisable to switch therapy based on relapse criteria only. MRI activity has increasingly been proposed as a surrogate marker to provide early information on the likelihood of future treatment failure, which can inform treatment decisions before clinical relapses or disability progression occur (Dobson et al., 2014). New, active, clinically silent lesions on MRI are 5–10-times more frequently observed than clinical relapses (Miller et al., 1998). Several studies have shown that MRI performed after 6–12 months of treatment is able to predict a subsequent lack of response to IFN β, even in the absence of clinical activity (Prosperini et al., 2009; Durelli et al., 2008; Tomassini et al., 2006), and MRI disease activity has also been reported as a valid surrogate marker for clinical activity in relapsing MS (Río et al., 2009; Sormani et al., 2011; Sormani et al., 2009; Sormani and Bruzzi, 2013). Scoring systems combining MRI and clinical markers have been shown to predict long-term treatment non-response (Río et al., 2009; Sormani and De Stefano, 2013; Sormani et al., 2013; Sormani, 2013) and may be suitable for the early identification of treatment non-responders in clinical practice in the future.

Other biomarkers, such as the presence of neutralizing antibodies, may also help in identifying treatment non-responders early. High and persistent neutralizing antibody titers have been shown to reduce the efficacy of IFN β (Kappos et al., 2005; Sorensen et al., 2003).

1.3. Treatment options for patients with active disease despite first-line treatment

1.3.1. Fingolimod

Fingolimod, a once-daily oral agent, is approved (0.5 mg/day) in the EU for adult patients with RRMS who experience high disease activity despite treatment with at least one DMT, or have rapidly evolving severe RRMS (Novartis Pharma GmbH, 2014). Fingolimod is a sphingosine 1-phosphate receptor modulator that prevents the egress of autoreactive lymphocytes from lymph nodes, thereby reducing their infiltration into the central nervous system (CNS) (Chun and Hartung, 2010). Preclinical evidence suggests that fingolimod may also have direct effects on the CNS (Chun and Hartung, 2010).

The efficacy and safety of fingolimod was assessed in three Phase III trials, including the 2-year placebo-controlled trials, FREEDOMS (**F**TY720 **R**esearch **E**valuating **E**ffects of **D**aily **O**ral therapy in **M**ultiple **S**clerosis) and FREEDOMS II, and the 1-year active-comparator trial, TRANSFORMS (**TR**ial **A**ssessing injectable interfero**N** versu**S** **F**TY720 **O**ral in **R**elapsing–remitting **M**ultiple **S**clerosis) (Kappos et al., 2010; Calabresi et al., 2014; Cohen et al., 2010). Fingolimod significantly reduced ARRs compared with placebo in FREEDOMS and FREEDOMS II (Kappos et al., 2010; Calabresi et al., 2014) and IFN β-1a intramuscular (IM) in TRANSFORMS (Cohen et al., 2010). A significant effect on 3- and 6-month confirmed disability progression vs. placebo was only observed in FREEDOMS (Kappos et al., 2010; Calabresi et al., 2014; Cohen et al., 2010). MRI lesion activity, including Gd+ T1 lesions and new or enlarging T2 lesions, was significantly reduced across all three trials (Kappos et al., 2010; Calabresi et al., 2014; Cohen et al., 2010). Fingolimod also demonstrated a significant and consistent effect on BVL across the Phase III trials (Kappos et al., 2010; Calabresi et al., 2014; Cohen et al., 2010).

In addition, *post-hoc* analyzes of the Phase III trials demonstrated that fingolimod is also highly effective in patients with high disease activity despite first-line treatment, in line with its EU label indication (Cohen et al., 2013; Devonshire et al., 2012; Khatri et al., 2014; Bergvall et al., 2014; Comi, 2014).

The TRANSFORMS extension trial provided evidence for the use of fingolimod as an early efficacy switch therapy: switching treatment from IFN β-1a IM to fingolimod was associated with a beneficial effect on relapse rate, MRI lesion activity, and BVL (Khatri et al., 2011). The benefit of switching therapy to fingolimod in patients with high disease activity despite first-line treatment has been further confirmed by real-world evidence (RWE). Data obtained from the ongoing, international MSBase (Multiple Sclerosis dataBase) Registry showed a significant reduction in relapse rates and more favorable disability outcomes when patients switched from an injectable DMT to fingolimod rather than to another injectable (Jokubaitis et al., 2014; He et al., 2015). In the ongoing observational study, PANGAEA (**P**ost-**A**uthorization **N**on-interventional **G**erman s**A**fety of Gil**E**ny**A** in RRMS patients), switching to fingolimod from previous DMTs in routine clinical practice in Germany resulted in a beneficial effect on relapse rates and disability progression (Ziemssen et al., 2014).

Fingolimod has demonstrated a consistent and well-characterized safety and tolerability profile in clinical trials, which has been confirmed in the real world (Novartis Pharma GmbH, 2014; Ziemssen et al., 2014; Cohen et al., 2014; Kappos et al., 2014; Singer, 2013; Sanford, 2014). The main safety observations with

fingolimod treatment are its short-term effects on the heart following the first dose, including a transient, and mostly asymptomatic, reduction in heart rate and the risk of atrioventricular conduction delays (Novartis Pharma GmbH, 2014; DiMarco et al., 2014). In pooled data from the Phase III trials, these effects were found to be transient and mostly benign, with < 1% of patients reporting symptomatic bradycardia,(DiMarco et al., 2014) which has been further confirmed by RWE (Ziemssen et al., 2014; Hughes et al., 2014). Administration of fingolimod therefore requires first-dose blood pressure and electrocardiogram (ECG) monitoring for a period of 6 h (Novartis Pharma GmbH, 2014). Further monitoring procedures of complete blood counts, assessments of hepatic function, and ophthalmological evaluations, are required before and/or during treatment with fingolimod (Novartis Pharma GmbH, 2014). Recently, a case of PML was reported in a clinically asymptomatic patient treated with fingolimod for more than 4 years without previous exposure to immunosuppressive drugs, including natalizumab (Multiple Sclerosis Society of Canada, 2015). Given the current understanding of the MoA of fingolimod and the overall experience with fingolimod (> 114,000 patients treated for more than 195,000 patient-years (Novartis International AG, 2014), the causal relationship between fingolimod and the occurrence of PML in this patient remains unclear at this present stage, but raises the possibility that in rare cases PML may occur in patients treated with fingolimod.

In summary, the well-established safety profile of fingolimod along with the extensive clinical experience in both clinical trial and real-world settings make it an attractive efficacy switch option. Its convenient oral route of administration and once-daily application may also influence patient preference and treatment decisions.

1.3.2. Natalizumab

Natalizumab is approved (300 mg, administered intravenously every 4 weeks) in the EU for adult patients with RRMS who experience high disease activity despite treatment with IFN β or GA, or who have rapidly evolving RRMS (Biogen Idec Ltd, 2014). Natalizumab is a monoclonal antibody that targets the α4-integrin component of adhesion molecules found on immune cells, which has been suggested to interfere with their migration into the CNS (Coyle, 2010). Thus, natalizumab's MoA is mainly based on its anti-inflammatory properties (Biogen Idec Ltd, 2014; Coyle, 2010).

The efficacy of natalizumab was assessed in the 2-year placebo-controlled Phase III trial, AFFIRM (N**A**talizumab Safety and E**FFI**-cacy in **R**elapsing–Remitting **M**ultiple Sclerosis), and the combination Phase III trial, SENTINEL (**S**afety and **E**fficacy of **Nat**alizumab in Combination with **In**terferon Beta-1a in Patients with R**el**apsing Remitting Multiple Sclerosis) (Polman et al., 2006; Rudick et al., 2006). In AFFIRM, natalizumab significantly reduced relapse rates, 3- and 6-month confirmed disability progression, and the number of Gd+ T1 and new or enlarging T2 lesions on MRI (Polman et al., 2006). However, no early and consistent reduction in BVL over 2 years was observed with natalizumab treatment compared with placebo; BVL was only reduced from Year 1 to Year 2 (Miller et al., 2007). While the 2-year trial, SENTINEL, demonstrated that natalizumab added to IFN β-1a IM resulted in a significant reduction in relapse rates compared with IFN β-1a IM treatment alone (Rudick et al., 2006), there are, so far, no prospective, randomized clinical trials comparing natalizumab monotherapy with any other DMT.

The 5-year interim data of the 10-year ongoing TOP (**T**YSABRI **O**bservational **P**rogram) study further confirmed natalizumab's robust effect on ARR and disability progression in a post-marketing setting (Butzkueven et al., 2014). A number of observational studies provide evidence for the beneficial effect of natalizumab in patients with suboptimal response to IFN β or GA (Río et al., 2012; Belachew et al., 2011; Castillo-Trivino et al., 2011; Prosperini et al., 2012; Putzki et al., 2010; Putzki et al., 2009; Putzki et al., 2010), suggesting that natalizumab may be an effective efficacy switch option.

Natalizumab has a well-established safety profile (Planas et al., 2014; Rudick et al., 2013), but post-marketing data for patients with more than 6 years of exposure are limited (O'Connor et al., 2014). One major safety concern associated with natalizumab treatment is the risk of PML and thus, patients need to be instructed together with their caregivers on early signs and symptoms of PML (Biogen Idec Ltd, 2014). Risk factors for developing PML include anti-JCV antibody-positivity, prior immunosuppressant use, and prolonged natalizumab exposure (> 24 months) (Bloomgren et al., 2012).

Natalizumab may be recommended as an efficacy switch option for JCV antibody-negative patients. It is recommended that anti-JCV antibody-negative patients should be retested, given the false-negative rate of about 2–3% and the potential of seroconversion (Outteryck et al., 2013; Gorelik et al., 2010). When making treatment decisions, the long-term use of therapies also needs to be taken into consideration. Thus, in JCV antibody-positive patients (~40 – 60% of patients (Berger et al., 2013)), prolonged use of natalizumab for more than 24 months should be considered carefully, due to the increased risk of PML (Planas et al., 2014). As of December 2014, 517 cases of natalizumab-associated PML have been reported in > 132,600 patients, with a mortality of 23% (Multiple Sclerosis Research, 2014). Frequent MRI assessments are recommended in order to detect early subclinical signs of PML, which might be associated with a better clinical outcome (Nicholas et al., 2014). Some studies have reported that the discontinuation of natalizumab is associated with rebound of disease activity, which may complicate patient management when switching therapy from natalizumab (Planas et al., 2014); these observations remain controversial, since rebound was not seen in other cohorts (Fernández, 2013). More data are clearly warranted on how to switch over from natalizumab to other therapies, and over what periods of time (Planas et al., 2014).

Overall, natalizumab can be recommended as an efficacy switch option dependent on clinical practice, e.g. the patient's JCV-antibody status might influence treatment decisions. In an observational study that used JCV serology to determine therapy, natalizumab was found to have increased efficacy on time to relapse or Gd+ lesions compared with fingolimod (Carruthers et al., 2014). Additional RWE demonstrated that, in patients with active MS during treatment with first-line therapies, switching to natalizumab is more effective than switching to fingolimod in reducing relapse rate and short-term disability burden (Kalincik et al., 2015).

1.3.3. Alemtuzumab

Alemtuzumab is approved (12 mg/day administered by intravenous infusion for 5 consecutive days initially and for 3 consecutive days 1 year later) in the EU for adult patients with RRMS with active disease defined by clinical or imaging features (Genzyme Therapeutics Ltd, 2014). Alemtuzumab is a humanized monoclonal antibody directed against CD52, a cell-surface protein highly expressed on T and B lymphocytes (Freedman et al., 2013). The binding of alemtuzumab to CD52 results in the depletion of T and B lymphocytes from the circulation through antibody-dependent cell-mediated cytolysis, complement-dependent cytolysis and induction of apoptosis (Freedman et al., 2013).

The efficacy of alemtuzumab was assessed in the 2-year, active comparator Phase III trials CARE-MS I (**C**omparison of **A**lemtuzumab and **R**ebif® **E**fficacy in **M**ultiple **S**clerosis, Study One) and CARE-MS II (Study Two) (Cohen et al., 2012; Coles et al., 2012). Alemtuzumab was compared with IFN β-1a SC in treatment-naive patients in CARE-MS I and in patients with ≥ 1 relapse on IFN β or

GA in CARE-MS II (Cohen et al., 2012; Coles et al., 2012). Both trials demonstrated superiority for alemtuzumab over IFN β-1a SC regarding reductions in relapse rate, MRI lesion activity (including the number of Gd+ T1 and new or enlarging T2 lesions) and BVL (Cohen et al., 2012; Coles et al., 2012). An improvement in 6-month confirmed disability progression was observed in CARE-MS II but not in CARE-MS I, and 3-month confirmed disability progression was not reported for either trial (Cohen et al., 2012; Coles et al., 2012). Alemtuzumab's beneficial effect observed in patients with suboptimal response to IFN β or GA in CARE-MS II suggests that alemtuzumab may be a suitable efficacy switch option.

The most common side effects reported with alemtuzumab treatment are infusion-associated symptoms including rash, headache, influenza-like symptoms, and, less frequently, transient recurrence of previous MS symptoms (Genzyme Therapeutics Ltd, 2014; Coles 2013). Alemtuzumab has also been associated with serious AEs, in particular secondary autoimmune disorders, such as thyroid disease and immune thrombocytopenia, arising months or years following treatment (Genzyme Therapeutics Ltd, 2014; Coles 2013). Thus, treatment with alemtuzumab requires extensive monitoring, including complete blood counts and thyroid function tests, and a high level of vigilance from the patient and physician (Genzyme Therapeutics Ltd, 2014; Coles 2013). The ongoing, open-label extension studies of CARE-MS I and CARE-MS II revealed no unexpected AEs 4 years after initiation of alemtuzumab treatment (Hartung et al., 2014; Coles et al., 2014); however, the long-term safety profile needs to be characterized in clinical trials as well as in a post-marketing setting.

Overall, the efficacy data from clinical trials, in particular CARE-MS II, suggest that alemtuzumab may be a suitable switch option for patients with suboptimal treatment response on first-line therapies. Even though alemtuzumab has been indicated as first-line therapy for patients with active MS according to the EMA label (Genzyme Therapeutics Ltd, 2014), it is commonly used as a second- or third-line therapy in clinical practice. When discussing treatment options with patients, the risk of secondary autoimmunity with alemtuzumab needs to be considered.

2. Improving treatment decision-making

2.1. Four key measures of disease activity

Considering the complex pathological processes underlying MS and the heterogeneity of the disease, composite measures may be able to provide a more complete assessment of disease activity. In the previous sections, we reviewed the efficacy of MS therapies based on the four key measures of disease activity that reflect the focal and diffuse damage occurring in MS. A direct comparison of efficacy endpoints among different trials would not be valid due to different study designs (e.g. different study populations or different time points), and has therefore been avoided. Currently, only clinical relapses, disability progression and MRI lesion activity, but not BVL, are commonly used outcome measures in routine clinical practice in MS. The current clinical and MRI assessments have been associated with various limitations and may not be able to detect all aspects of disease activity (Lavery et al., 2014; Lublin et al., 2014; Balcer, 2001), e.g. disability progression, measured using the Expanded Disability Status Scale (EDSS), is not very sensitive in the mid and upper range of scores, mainly focuses on ambulation status, and lacks adequate cognitive and visual components (Balcer, 2001) Measurements of BVL are able to detect subtle pathological changes that are not captured by the other three measures. BVL begins early in MS and has been shown to correlate with measures of disability and cognitive impairment (De Stefano et al., 2014; Amato et al., 2012; Zivadinov et al., 2013; Deloire et al., 2011; Bermel and Bakshi 2006; De Stefano et al., 2010). It is also considered an overall marker of neurodegeneration and has been shown to predict long-term disability progression and cognitive decline (Popescu et al., 2013; Deloire et al., 2011; Minneboo et al., 2008; Horakova et al., 2009; Filippi et al., 2013). It has recently been reported that treatment effects on disability progression correlate with treatment effects on BVL (Sormani et al., 2014), supporting the use of BVL, alone or in combination with MRI lesions, as a surrogate marker of disability progression in MS. While the clinical relevance of BVL in MS has been widely accepted, BVL measurements have not yet been integrated into routine clinical practice, due to lack of standardization, software availability, and lack of reimbursement for post-image acquisition processing (Projects in Knowledge, 2013) However, some effort has recently been made towards the definition of pathological cut-offs of BVL rates that could be used in clinical practice (De Stefano et al., 2015).

Composite measures that have been used in MS in the past are based on the conventional outcome measures. The composite measure 'freedom from disease activity', also known as 'no evidence of disease activity' (NEDA) is defined as no relapse activity, no EDSS disability progression, and no new MRI lesions (T1 Gd+ and/or active T2 lesions) (Havrdová et al., 2009; Giovannoni et al., 2011). These outcome measures may not be able to provide a complete assessment of the underlying pathology in MS; thus, the inclusion of additional measures in the definition of NEDA, such as BVL, could potentially provide a more comprehensive and balanced assessment of the focal and diffuse damage occurring in MS (De Stefano et al., 2014; Bevan and Cree 2014). The routine assessment of additional outcome measures, such as cognitive impairment and patient-reported outcomes (e.g. health-related quality of life), may provide further information on the ongoing disease activity in MS. Inclusion of these measures in NEDA may further enhance our understanding of disease progression and may help to identify treatment non-response to allow physicians to switch to more effective therapies earlier.

3. Conclusion

Optimizing treatment early in MS may prevent the accumulation of irreversible neurological damage and reduce the risk of disease progression. When optimizing treatment and defining a treatment regimen, it is important to consider the four key measures of disease activity: relapses, MRI lesions, disability progression, and BVL. In addition, the MoA, benefit:risk profiles, real-world effectiveness, specific safety concerns, risks associated with long-term use, and the overall perceived burden of the therapies should also be taken into account when making treatment decisions.

Based on the evidence-based considerations, IFN β, GA, teriflunomide, and DMF have been suggested for use in treatment-naive patients, and fingolimod, natalizumab, and alemtuzumab in patients with active disease despite first-line treatment. The proposed treatment algorithm (Fig. 1) may help to guide treatment decisions when considering optimizing therapy early in patients with breakthrough disease activity despite first-line treatment. Switching patients early to a high-efficacy therapy that targets both focal and diffuse damage may impact the course of the disease and achieve long-term disease control. Additional measures of disease activity may enable physicians to gain a more accurate view of disease progression and give them the opportunity to make treatment decisions earlier.

Disclosures

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