REVIEW

Sequencing of high-efficacy disease-modifying therapies in multiple sclerosis: perspectives and approaches

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Abstract

Multiple sclerosis (MS) is characterized by chronic inflammation in conjunction with neurodegeneration within the central nervous system. Most individuals with MS begin with a relapsing remitting course that later transitions to secondary progressive MS. Currently available disease-modifying therapies (DMTs) for relapsing MS have been demonstrated to reduce disease activity, however most patients require a change in therapy over the course of their disease. Treatment goals include the prevention of relapses and disability accumulation and to achieve this objective requires careful planning. Sequencing of DMTs for individual patients should be designed in such a way to maximize disease control and minimize risk based on the mechanism of action, pharmacokinetic and pharmacodynamic properties of each therapy. This includes the DMT patients are being switched from to those they are being switched to. The reversibility of immune system effects should be a key consideration for DMT sequence selection. This feature varies across DMTs and should factor more prominently in decision making as newer treatments become available for the prevention of disability accumulation in patients with progressive MS. In this short review, we discuss the landscape of existing therapies with an eye to the future when planning for optimal DMT sequencing. While no cure exists for MS, efforts are being directed toward research in neuroregeneration with the hope for positive outcomes.

Key Words: *relapsing multiple sclerosis; high efficacy disease-modifying therapies; treatment optimization; treatment sequencing; therapeutic inertia; sub-optimal treatment; progressive disease; immune effects*

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Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, autoimmune disorder of the central nervous system (CNS) that damages the myelin sheath, axons, and neurons (Antel et al., 2012). The disease is categorized into different clinical courses–relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), and primary-progressive MS (PPMS; **Figure 1a**) (Lublin et al., 2014). The revised Lublin criteria considered the magnetic resonance imaging (MRI) lesion activity and progression of disability to describe MS phenotypes in addition to the clinical activity (relapses) (Lublin et al., 2014). Patients are described as (1) relapsing MS that is active (determined by clinical relapses and/or MRI activity) or inactive, with or without worsening of disability or (2) primary- or secondary-progressive disease that is active or inactive, with or without disability progression (Lublin et al., 2014). Inflammation is a hallmark of the disease that is more pronounced during the RRMS course than the SPMS and PPMS clinical courses (Lassmann et al., 2012). In the past decade, several disease-modifying therapies (DMTs) have become available, from small molecules to monoclonal antibodies, for the treatment of mild-to-moderate or moderate-to-high-disease activity in the relapsing form of MS (Martin et al., 2016). These DMTs can alter the disease course by reducing MS disease activity and the accumulation of disability. There is no cure for MS, and therapies for progressive forms are currently limited.

Due to the chronic nature of the disease, patients require long-term treatment and sub-optimal treatment response is a common concern with DMTs. Optimization of therapy is therefore a growing challenge for neurologists who must evaluate the efficacy and safety of DMTs as well as individual preferences, adherence, and characteristics. Inappropriate dosing and the timing of treatment escalation can lead to sub-optimal clinical responses. Taken together, these factors contribute to therapeutic inertia, which may lead to failure of achieving treatment goals, worsening clinical outcomes and disability (Saposnik and Montalban, 2018). Sequencing to high efficacy DMTs early in the disease course may improve the long-term prognosis.

Efficacy and Safety of DMTs in RRMS

Different DMTs have different cellular and molecular therapeutic targets in MS (Martin et al., 2016; Pardo and Jones,

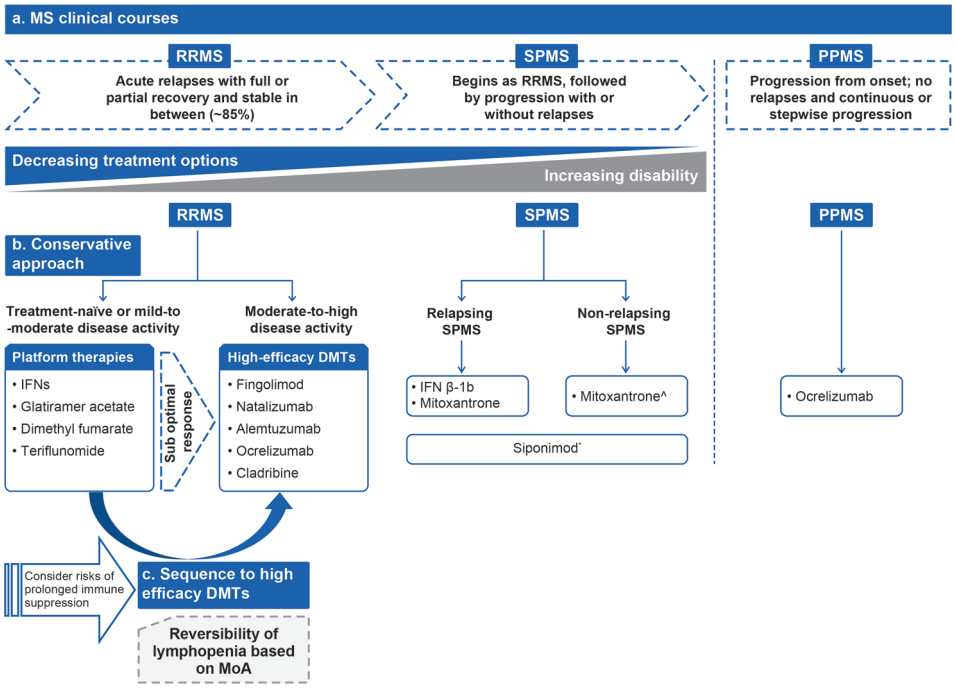

Figure 1 MS clinical courses and treatment approach.
^Approved only in few countries; *Efficacy and safety have been demonstrated in an SPMS population in the Phase III EXPAND trial (Kappos et al., 2018). IFN: Interferon; MoA: mechanism of action; MS: multiple sclerosis; RRMS: relapsing-remitting MS; SPMS: secondary-progressive MS; PPMS: primary-progressive MS; DMTs: disease-modifying therapies.

2017). Thus, the efficacy and safety of each DMT can be expected to vary widely based on the type and extent of interaction with the immune system.

In routine clinical practice, the majority of clinicians adopt a conservative approach for the treatment of RRMS (**Figure 1b**). Treatment is most often initiated with first-line therapies followed by second-line high-efficacy DMTs in patients who continue to experience on-treatment clinical or radiological disease activity. This treatment approach may have considerable consequences due to therapeutic inertia in patients who progress to high disease activity. Early or timely sequencing to high-efficacy DMTs may help to better control disease activity and achieve therapeutic goals over the long-term. A recent systematic review suggests that early initiation of high-efficacy DMTs showed better control of disease activity in some patients compared with delayed therapy (Merkel et al., 2017). Careful evaluation of the patient's condition should be performed before introducing a high-efficacy DMT in both treatment-naïve patients and suboptimal responders.

The platform therapies, such as interferon beta (IFN β) or glatiramer acetate (GA) injectables, are often used as first-line therapy in treatment-naïve patients or those with mild-to-moderate MS. These treatments are generally safe but have only modest efficacy. Injection-site reactions and flu-like symptoms are the most common adverse events (AEs). Oral DMTs, such as dimethyl fumarate (DMF) and teriflunomide, are other first-line options. The anti-inflammatory and cytoprotective aspects of DMF and teriflunomide effectively reduce relapse rates in treatment-naïve patients with MS (Martin et al., 2016; Pardo and Jones, 2017). Lymphopenia, a risk factor for rare cases of progressive multifocal leukoencephalopathy (PML) with DMF, and elevation of liver enzymes and gastrointestinal disturbances with teriflunomide are the common safety concerns experienced by patients (Martin et al., 2016; Pardo and Jones, 2017). Lateral sequencing between IFN β, GA, DMF, and teriflunomide therapies is sometimes considered to address concerns with route of administration, family planning, tolerability, adherence, and/or safety, but not for inadequate treatment response (D'Amico et al., 2016). When responses to these first-line therapies are sub-optimal, patients require escalation to high-efficacy DMTs such as fingolimod, natalizumab, alemtuzumab, ocrelizumab, and cladribine.

Fingolimod, a sphingosine-1-phosphate (S1P) receptor modulator, effectively reduces the annualized relapse rate (ARR), MRI outcomes including brain volume loss and disability progression in clinical and real-world settings. Besides its immunomodulatory function, results from preclinical and clinical studies also suggest potential neuroprotective effects of fingolimod on neural cells, either through an indirect mechanism mediated by astrocytes and oligodendrocytes, or through a direct effect on cortical neurons (Pitteri et al., 2018). Transient bradycardia is often observed with the first dose of fingolimod. A small number of serious infections, including opportunistic infections, such as PML, have been observed (Martin et al., 2016; Pardo and Jones, 2017). Natalizumab, a selective adhesion-molecule inhibitor, significantly reduces both ARR and MRI activity in clinical and observational studies. A previous study suggest that natalizumab may also exhibit secondary neuroprotective effects on brain and cortical regions owing to its strong anti-inflammatory effect (Mattioli et al., 2015). There are no major tolerability concerns with natalizumab treatment; however, it is associated with significant risk of PML in patients seropositive for John Cunningham virus (Martin et al., 2016; Pardo and Jones, 2017). Alemtuzumab, an anti-CD52 monoclonal antibody, has been shown to reduce relapse rates and MRI activity including an impact on brain atrophy in clinical studies. Currently, there are not enough data suggesting neuroprotective properties of alemtuzum-

ab in addition to its anti-inflammatory effect (Jones et al., 2010). Secondary autoimmune disorders are the major safety concerns with alemtuzumab (Martin et al., 2016; Pardo and Jones, 2017). Ocrelizumab, a humanized monoclonal antibody, selectively depletes $CD20^+$ expressing B cells. It effectively reduces relapses and MRI lesions, and slows worsening of disability progression. Infections and local and systemic infusion-related reactions are the most common AEs with ocrelizumab (Martin et al., 2016; Pardo and Jones, 2017). Lack of long-term safety data and the immune-mediated risks due to long-term B-cell depletion are key considerations with ocrelizumab treatment. Cladribine selectively depletes lymphocytes, thereby lowering the risk of disability progression and reducing MRI lesions. The preclinical data indicate that cladribine may exert direct neuroprotective effects on central neurons; however, further investigations are required to understand its mechanism (Musella et al., 2013). The risk of infection, particularly herpes virus infections, is increased with cladribine (Grand'Maison et al., 2018), and the long-term safety profile in MS is unknown.

All these DMTs reduce the immune-mediated inflammation in the CNS through their unique mode of action. Some of the DMTs have also shown effects suggestive of neuroprotection; however, these results remain to be confirmed in humans.

A recent online health survey by neurologists and patients has highlighted the challenges associated with inadequate treatment satisfaction/efficacy and safety/tolerability of treatment, cost, access to new medicines, and missed doses/compliance (Tintoré et al., 2017). More recently clinicians have started considering early intervention and timely sequencing to high-efficacy DMTs to avoid risk of disability accumulation. The benefit-risk profile of each of the high-efficacy DMTs should be carefully considered before sequencing.

Sequencing of High-Efficacy DMTs

Currently, there is no substantial evidence to guide the sequencing of high-efficacy DMTs in patients failing on second-line therapies. Data from randomized controlled and observational studies comparing the efficacy and safety of high-efficacy DMTs are lacking. There is no standard definition of treatment failure, and the lack of consensus on different outcomes that may predict the future course of disease adds to the complexity of decision-making for treatment sequencing. Selection of appropriate DMTs is therefore challenging, as it requires careful consideration of efficacy, safety, and tolerability profiles of both the previous and the new DMT of choice. When sequencing to high-efficacy DMT is considered, it is important to keep in mind the mechanism of action and lasting pharmacokinetics and pharmacodynamics of the previous DMT to avoid overlapping effects on the immune system. In addition, age, duration and severity of disease, disability status, route of administration, and family planning play important roles.

We recently discussed (Grand'Maison et al., 2018) the sequencing of DMTs for treatment optimization in RRMS patients (**Figure 1c**), highlighting the factors to be considered when switching among high-efficacy DMTs. In routine clinical practice, the questions posed are related to the appropriateness of the timing for sequencing, the duration of disease-activity and monitoring period required before switching patients to another high-efficacy DMT.

DMTs that have short, reversible immune effects and better safety profiles are attractive options for sequencing to maximize benefit and minimize carry-over risks. An adequate washout period is required to encourage recovery of the targeted immune function to 'normal' before initiating the next DMT. Fingolimod (≤ 2 months) and natalizumab (≤ 16 weeks) have reversible and shorter times to immune system reconstitution (Pardo and Jones, 2017), and could be potential options for early sequencing. Switching to fingolimod after discontinuation of natalizumab has been reported in a number of studies, but there is less data published on sequencing to other agents after fingolimod treatment. Alemtuzumab is another effective option after fingolimod or natalizumab therapy. However, the carry-over risk of PML with natalizumab and the short-term irreversible immune effects of alemtuzumab can put patients at elevated risk. A washout period after fingolimod therapy is recommended before initiating alemtuzumab to ensure that sequestered lymphocytes reappear in the peripheral circulation. Again, the short-term irreversible immune effects of alemtuzumab make it difficult to predict the clinical consequences of this DMT sequence option. If escalation is adopted as a strategy for patients with moderate-to-severe disease activity at onset, close monitoring is required to ensure that the disease is under control, especially in the early years.

Aggressive forms of RRMS disease may be managed by induction therapy that involves short-term use of a high-efficacy treatment. Clinicians generally use immunoablative chemotherapy (mitoxantrone, cyclophosphamide), and immunodepletion (alemtuzumab), to obtain rapid control of aggressive disease activity. High safety concerns, such as prolonged suppression of the immune system, leukopenia, thrombocytopenia, infections, and secondary acute myeloid leukemia are associated with these therapies (Martin et al., 2016; Pardo and Jones, 2017). The use of these therapies is therefore typically reserved as the last option for patients with an aggressive disease course.

SPMS and PPMS

Over a period of 15–20 years (Rovaris et al., 2006; Tremlett et al., 2008; Scalfari et al., 2014), more than 50% of RRMS patients progress to SPMS, with or without relapses. DMTs that are indicated for relapsing forms of MS, including RRMS and relapsing SPMS (with relapses), have not been proven to reduce disability progression in patients with non-relapsing SPMS (without relapses). Thus, there is a major unmet therapeutic need for patients with SPMS. Siponimod, an oral, selective $S1P_{1,5}$ receptor modulator, is the first DMT to demonstrate a reduction in the risk of disability progression in patients with SPMS (with and without relapses) in the Phase III EXPAND clinical trial, with a safety profile consistent with other S1P receptor modulators (Kappos et al., 2018). Ocrelizumab has been shown to reduce dis-

ability progression and MRI activity in patients with PPMS. It is currently the only DMT indicated for the treatment of PPMS (Montalban et al., 2017).

Conclusions

The chronic continuum of MS requires careful evaluation of the clinical course before and after initiation of therapy. While many neurologists accept a conservative treatment approach, patients often progress with a risk of accumulating irreversible disability. Timely monitoring and sequencing to high-efficacy DMTs, along with appropriate patient counseling, may help in managing the disease in the long-term. Included herein is one perspective on sequencing to high-efficacy DMTs for better control of disease activity. This approach requires careful consideration of benefit-risk assessment, including evaluation of the short- and long-term immunologic profiles of each DMT, sequence timing, patient preferences and compliance, family planning, access to medical care, and regular monitoring of changes after switching. Head-to-head studies that compare immunologic, safety, and efficacy data between high-efficacy DMTs in controlled clinical trials as well as in real-world settings are needed to provide evidence to support the sequencing concepts outlined above.

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