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Review article

Is there a change of paradigm towards more effective treatment early in the course of apparent high-risk MS?

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ABSTRACT

Background: Aggressive, highly active, or rapidly evolving severe relapsing-remitting multiple sclerosis (RRMS) is characterized by frequent relapses and active disease on magnetic resonance imaging, ultimately leading to a high risk for rapid disability accumulation. The treatment approach for high-risk patients is evolving into a model of individualized therapy in which early initiation of high-efficacy disease-modifying therapy (DMT), which I refer to as "early and strong" therapy, is viewed as a rational strategy to prevent the irreversible damage that occurs at disease onset and early in the disease course. This approach uses an individualized benefit-risk assessment to match the level of DMT efficacy with the patient's risk of disease progression and balances it against the risk of drug-related adverse events. It also includes consideration of the patient's risk tolerance and desire for a high-efficacy treatment. This paper discusses the rationale for early treatment, and summarizes the available clinical data on high-efficacy and moderately-high efficacy DMTs in patients with high-risk RRMS.
Methods: Literature searches were conducted using search terms "aggressive RRMS", "highly active RRMS", and "severe RRMS" alone and in conjunction with the terms "natalizumab", "fingolimod", "alemtuzumab", "mitoxantrone", and "cyclophosphamide". Studies of drug efficacy in these high-risk populations were reviewed.
Results: Subgroup analyses of pivotal trials of natalizumab, fingolimod, and alemtuzumab were available, as well as an independent study of mitoxantrone and a pilot study of cyclophosphamide. In each study, DMT reduced relapses versus either placebo, active comparator, or baseline relapse rate.
Conclusion: Data for the high-efficacy DMTs natalizumab and alemtuzumab, and the moderately high-efficacy DMT fingolimod, suggest they are effective in this patient population. Further studies are warranted, and clinical trial data to inform treatment decisions for this high-risk group represent a significant unmet need.

1. Introduction

The clinical course of multiple sclerosis (MS) is highly variable among individuals with the disease, with differences in clinical manifestations, rates of progression, accumulation of disability, and the degree of underlying pathology (i.e., demyelination and neurodegeneration). "Aggressive" or "high-risk" MS is typically characterized by frequent relapses, rapid disability worsening, and high magnetic resonance imaging (MRI) activity (Menon et al., 2013; Rush et al., 2015). Treatment for patients with high-risk relapsing-remitting MS (RRMS) is evolving from a traditional "one-size-fits-all" approach, in which all patients are initiated on first-line therapy with interferon beta (IFNB), glatiramer acetate, teriflunomide, or dimethyl fumarate, to a more individualized approach, in which patients with high-risk disease can be treated with "early and strong" therapy with high-efficacy disease-modifying agents (DMTs) from the start. This approach takes into consideration disease severity and risk within the heterogeneous spectrum of MS and affords particular benefit over the traditional treatment approach for patients with high-risk RRMS, as it provides a model of individualized treatment. This article explores the hypothesis that early use of highly effective therapies in patients with high-risk RRMS is the best opportunity for preventing the irreversible damage that can begin from disease onset (Freedman et al., 2014; Rush et al., 2015; Ziemssen et al., 2015).

An individualized benefit-risk assessment ensures that the level of DMT efficacy is appropriate for the MS patient's likely disease course, and that the risk associated with the drug is balanced against the risk of untreated or undertreated disease. This article reviews the available literature on high-risk RRMS, as it relates to patient identification and current treatment options, and discusses the implications of emerging data on clinical practice.

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Table 1
Terminology and definitions used to describe a more high-risk disease course.

Term	Definition	
Aggressive disease	≥1 of the following: ● EDSS ≥6 within 5 years of MS onset ● EDSS ≥6 by age 40 ● SPMS within 3 years of a relapsing-onset course	(Menon et al., 2013)
	≥1 of the following: ● EDSS score of 4 within 5 years of onset ● Multiple (≥2) relapses with incomplete resolution in the past year ● ≥2 MRI studies showing new/enlarging T_2 lesions or Gd-enhancing lesions despite treatment ● No response to therapy with ≥1 DMTs for ≤1 year	(Rush et al., 2015)
Highly active disease	≥2 relapses in the year before study entry/randomization and ≥1 Gd-enhancing lesion at study entry/BL	(Hutchinson et al., 2009; Krieger et al., 2013, 2014, 2016)
	Any prior DMT during year before study enrollment, ≥1 relapse within the previous year, plus ≥1 Gd-enhancing lesion or 9 T2 lesions at BL	(Devonshire et al., 2012)
	Any prior DMT during year before study enrollment and ≥1 of the following: ● ≥1 relapse in the previous year and either ≥1 Gd-enhancing T1 lesion or ≥9 T2 lesions at BL ● As many, or more relapses, in the year before BL as in the previous year	(Derfuss et al., 2015)
Rapidly evolving severe disease	≥2 relapses in the year before BL and ≥1 Gd-enhancing lesion at BL	(Devonshire et al., 2012)

BL, baseline; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd, gadolinium; MRI, magnetic resonance imaging; MS, multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

2. Identifying patients with high-risk RRMS

2.1. Defining high-risk RRMS

At present, there is no consensus definition or accepted terminology for high-risk RRMS in the literature. Current concepts incorporate several components, including multiple relapses within given time frames, insufficient or suboptimal recovery from relapses, multiple active/enlarging lesions on MRI, suboptimal response to DMTs within given periods, and measures of worsening disability (Table 1). The term “aggressive” MS is often used in the literature. The definition of this term is largely descriptive, which limits its utility in identifying at-risk patients in the clinic (Menon et al., 2013; Rush et al., 2015).

A retrospective analysis of data from a prospective population database in British Columbia explored three definitions of “aggressive” MS (Menon et al., 2013). These definitions varied in terms of clinical threshold (e.g., Expanded Disability Status Scale [EDSS] score of 6.0, or conversion to secondary progressive MS) and time frame for reaching this threshold (Menon et al., 2013). Depending on the definition used, the estimated prevalence of “aggressive disease” ranged from 4% to 14%. However, these definitions are limited, because they do not allow for the diagnosis of aggressive MS early in the disease course. A more recent article has attempted to define “aggressive” MS in a manner that would aid earlier identification of at-risk individuals. The proposed definition includes one or more of the following features: multiple relapses with incomplete recovery in the past year, EDSS score of 4.0 within 5 years of onset, more than two MRI scans showing new/enlarging T2 lesions or gadolinium (Gd)-enhancing lesions despite therapy, or no response to DMT for up to 1 year (Rush et al., 2015).

The terms “highly active” and “rapidly evolving severe” MS have been used in subgroup analyses of large clinical trials to identify patients who might benefit from early treatment with moderately high or highly effective drugs. Some regulatory agencies have also defined these terms in prescribing recommendations. Although there are some minor variations across trials in the definitions of “highly active” and “rapidly evolving severe”, in general, their use is fairly consistent. In subgroup analyses of clinical trials, 10–34% of enrolled RRMS patients met criteria for highly active or rapidly evolving severe MS at baseline (Derfuss et al., 2015; Devonshire et al., 2012; Hutchinson et al., 2009; Krieger et al., 2013, 2014). These prevalence rates are influenced not only by each trial's definition of “highly active” or “rapidly evolving severe”, but also by the inclusion criteria. The incidence of highly active or rapidly evolving severe MS in the overall MS population is more difficult to estimate.

2.2. Identifying patients with high-risk RRMS in the clinic

Recognizing prognostic factors at disease onset or during follow-up evaluation is an important step in identifying patients with high-risk RRMS. Findings from natural history studies suggest that several factors predict a poor prognosis, including time from MS onset to the second neurological episode, number of relapses during the first several years, time from MS onset to an EDSS score of 4.0, age of MS onset (≥40 years), motor system involvement at onset including weakness of the extremities or ataxia, at least four T2-weighted lesions suggestive of MS, and incomplete recovery from the initial two relapses (Confavreux et al., 2003; Scott et al., 2000). MRI indicators of more active disease early in the clinical course (including in patients with clinically isolated syndrome) also correlate with a higher risk of disability worsening (O'Riordan et al., 1998; Rudick et al., 2006a; Tintore et al., 2015). Taken together, these results suggest that, by identifying patients at greater risk of disability worsening, clinicians may be able to determine which patients may benefit from early initiation of more highly active therapies.

3. A critical window of opportunity exists early in the MS disease course

MS is a complex, heterogeneous disease (Fig. 1). Recurring relapses generally coincide with inflammation of the central nervous system (CNS) and demyelination, and disability accumulates as recovery from relapse decreases (Dendrou et al., 2015). Myelin-reactive inflammatory T cells enter the CNS to initiate inflammation. Activation of the innate immune system may result in a self-sustaining inflammatory environment within the CNS parenchyma that drives the progressive phase of the disease (Weiner, 2009). Considerable disease activity may also occur within the CNS in the absence of clinical symptoms.

Tissue damage and atrophy begin early in the disease process and

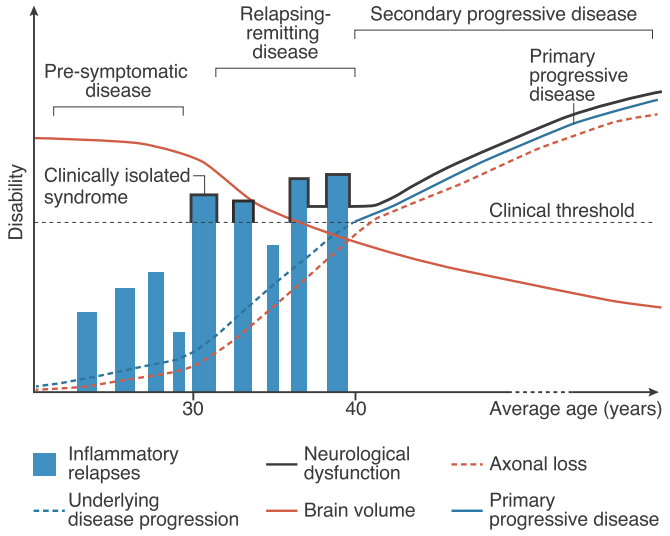

Fig. 1. The heterogeneity of MS (Dendrou et al., 2015).

ultimately lead to loss of function. Pathological and MRI studies show that irreversible axonal damage is already detectable before the clinical signs of MS become apparent (Freedman et al., 2014). Furthermore, DMT efficacy is maximal in the early, inflammatory stage of disease. In patients with high-risk RRMS, the window of treatment opportunity may be quite short (Rush et al., 2015). Thus, it is hypothesized that potent treatment early in the disease course may be necessary to help protect high-risk patients from accumulating irreversible damage.

Before the availability of high-efficacy DMTs, most RRMS patients received "platform" agents (i.e., IFNB or glatiramer acetate) as first-line therapy. Although these medications are generally well-tolerated (Subei and Ontaneda, 2015), their efficacy is mild to moderate in many patients. However, an increasing number of oral therapies and high-efficacy DMTs available for RRMS allows greater individualization of therapy according to the benefit-risk profiles of each drug and the patient's risk for disease progression, and can potentially offer superior control of disease.

4. Higher-efficacy DMTs in high-risk RRMS

Properties of the moderately high-efficacy DMT, fingolimod, and the three high-efficacy DMTs—mitoxantrone, natalizumab, and alemtuzumab—as well as efficacy, safety, and patient-reported outcomes from pivotal trials of each of these agents have been reviewed elsewhere (Chataway and Miller, 2013; Hartung et al., 2015; Khatri, 2016; Martinelli Boneschi et al., 2013). All are approved for treatment of RRMS in the US, Canada, and Europe and licensed for use in other countries. They are regarded as high-efficacy agents primarily owing to their superior ability to reduce relapse activity compared with interferons or glatiramer acetate. Fingolimod and alemtuzumab have been shown to be superior to intramuscular and subcutaneous (SC) IFNB-1a, respectively, in head-to-head trials (Cohen et al., 2010, 2012; Coles et al., 2008, 2012). Despite the pitfalls of cross-trial comparison, mitoxantrone and natalizumab are widely perceived as high-efficacy therapies given that relapse reduction versus placebo approaches 70% for each drug (Sorensen, 2014). Unfortunately, few blinded, head-to-head trials exist for RRMS treatments to definitively establish their comparative efficacy. Such trials are acutely needed given the large number of available therapies.

Data from large prospective trials on early use of these agents in patients with high-risk MS are also lacking. Pivotal trials of fingolimod, natalizumab, and alemtuzumab did not specifically recruit patients who were high-risk, or those who were early in their disease course. However, pre-planned or post hoc subgroup analyses of these trials are informative on treatment response in patients with high-risk disease (Table 2). Additionally, several observational studies on natalizumab, alemtuzumab, mitoxantrone, and cyclophosphamide recruited RRMS patients with high-risk disease, further adding to our knowledge of outcomes in these patients (Table 3). However, variability among studies in inclusion criteria and the definition of "high-risk", and the paucity of head-to-head studies, complicate accurate efficacy assessment in this patient population. Furthermore, the designation of "high-risk" status may rely on historical data; the degree to which such data are verifiable may vary among studies.

4.1. Fingolimod

Fingolimod is an oral sphingosine-1-phosphate receptor modulator that is believed to exert therapeutic effects in MS by preventing the egress of lymphocytes from lymph nodes, thereby reducing recirculation of autoreactive lymphocytes to the CNS (Brinkmann et al., 2002; Mandala et al., 2002; Matloubian et al., 2004). In many countries, fingolimod 0.5 mg once daily is approved for the treatment of relapsing MS; in the European Union, it is approved in patients with high disease activity despite treatment with IFNB or those with rapidly evolving severe RRMS (Novartis Europharm Ltd, 2015; Novartis Pharmaceuticals Corporation, 2016). Fingolimod has shown improved efficacy on clinical and MRI outcomes compared with intramuscular IFNB-1a and placebo (Calabresi et al., 2014; Cohen et al., 2010; Kappos et al., 2010).

Most common adverse events (AEs) that occurred more frequently with fingolimod than comparators included infections, hypertension, elevated liver enzymes, lymphopenia/leukopenia, macular edema, and cardiac effects. Reactivation of latent herpes is a potential risk with fingolimod. Two fatal herpes infections occurred in the TRANSFORMS study with the 1.25-mg dose of fingolimod (Cohen et al., 2010), and herpes zoster incidence was increased versus placebo in FREEDOMS II (Calabresi et al., 2014), but there were no differences in herpes virus infections with fingolimod compared with placebo in the FREEDOMS study (Kappos et al., 2010). Several cases of progressive multifocal leukoencephalopathy (PML) have emerged with fingolimod in the postmarketing period: 3 confirmed in patients with no prior natalizumab exposure and 17 suspected cases in patients with prior natalizumab (Medicines and Healthcare Products Regulatory Agency, 2016). Dose-dependent cardiac effects of fingolimod, including bradycardia and atrioventricular conduction block, are of concern at the time of the first dose (Calabresi et al., 2014; Cohen et al., 2010; Kappos et al., 2010). First-dose cardiac monitoring is required so that these may be appropriately managed (Novartis Europharm Ltd, 2015; Novartis Pharmaceuticals Corporation, 2016).

The efficacy of fingolimod in patients with highly active disease has been studied in a post hoc analysis of the FREEDOMS I study. In this analysis, highly active disease was defined as patients who received any DMT during the previous year and had at least one relapse in this time plus at least either one Gd-enhancing T1 lesion or nine T2 lesions at baseline (Devonshire et al., 2012). Annualized relapse rate (ARR) was significantly reduced by 51% ($p = 0.0028$) and risk of 3-month disability worsening was numerically lower by 46% ($p = 0.092$) over 24 months with fingolimod 0.5 mg versus placebo in this patient group. In a second post hoc analysis from the FREEDOMS I study in patients with treatment-naive, rapidly evolving severe RRMS, defined as at least two relapses within the year before baseline and at least one Gd-enhancing lesion at baseline, ARR was significantly reduced by 67% ($p = 0.0006$) and the risk of 3-month disability worsening was numerically lower by 27% ($p = 0.55$) over 24 months with fingolimod 0.5 mg versus placebo (Devonshire et al., 2012).

A post hoc analysis on pooled data from FREEDOMS I and II was performed in patients (n = 249 for fingolimod; n = 257 for placebo) with previous DMT treatment and highly active disease, defined as at least one relapse in the previous year plus at least either one Gd-enhancing T1 lesion or nine T2 lesions at baseline; or as many or more

Table 2
Summary of subgroup analyses (primary and key secondary endpoints) of randomized trials of approved drugs in patients with rapidly evolving, severe MS, or highly active RRMS.

Study	Study duration, years	Endpoint	Treatment (n)	Patient characteristics	Clinical efficacy
AFFIRM (Hutchinson et al., 2009)	2	Post hoc	• Natalizumab (148) • PBO (61)	Highly active MS (≥2 relapses in the year before study entry, ≥1 Gd-enhancing lesion at study entry)	• ARR ratio (natalizumab vs PBO): 0.19; $p < 0.001$ • 6-month CDW (natalizumab 12 mg vs PBO): HR: 0.36; $p = 0.008$
CARE-MS I (Krieger et al., 2014)	2	Pre-specified	• Alemtuzumab (105) • SC IFNB−1a (61)	Highly active MS (≥2 relapses in the year before randomization, ≥1 Gd-enhancing lesion at BL)	• ARR ratio (alemtuzumab 12 mg vs. SC IFNB-1a): 0.49; $p = 0.0068$ • 6-month CDW (alemtuzumab 12 mg vs. SC IFNB-1a): HR: 0.87; $p = 0.7873$
CARE-MS II (Krieger et al., 2013)	2	Pre-specified	• Alemtuzumab (101) • SC IFNB−1a (42)	Highly active MS (≥2 relapses in the year before randomization, ≥1 Gd-enhancing lesion at BL)	• ARR ratio (alemtuzumab 12 mg vs. SC IFNB-1a): 0.49; $p = 0.0044$ • 6-month CDW (alemtuzumab 12 mg vs. SC IFNB-1a): HR: 0.49; $p = 0.1516$ (Sanofi Genzyme, 2013)
FREEDOMS I (Devonshire et al., 2012)	2	Post hoc	• Fingolimod 0.5 mg (48) • PBO (37)	Rapidly evolving severe MS (treatment-naive, ≥2 relapses within the year before BL, ≥1 Gd-enhancing lesion at BL)	• ARR ratio (fingolimod 0.5 mg vs. PBO): 0.33; $p = 0.0006$ • 3-month CDW (fingolimod 0.5 mg vs. PBO): HR: 0.73; $p = 0.55$
FREEDOMS I (Devonshire et al., 2012)	2	Post hoc	• Fingolimod 0.5 mg (84) • PBO (80)	Highly active MS (any prior DMT during year before study enrollment, ≥1 relapse within the previous year, plus ≥1 Gd-enhancing lesion or 9 T2 lesions at BL)	• ARR ratio (fingolimod 0.5 mg vs. PBO): 0.49; $p = 0.0028$ • 3-month CDW (fingolimod 0.5 mg vs. PBO): HR: 0.54; $p = 0.092$
FREEDOMS I and II (Derfuss et al., 2015)	2	Post hoc	• Fingolimod 0.5 mg (249) • PBO (257)	Highly active MS (any prior DMT during year before study enrollment, ≥1 relapse in the previous year, plus either ≥1 Gd-enhancing T1 lesion or ≥9 T2 lesions at BL; or as many or more relapses in the year before BL as in the previous year)	• ARR ratio (fingolimod 0.5 mg vs. PBO): 0.52; $p < 0.001$ • 6-month CDW (fingolimod 0.5 mg vs. PBO): HR: 0.55; $p = 0.016$

ARR, annualized relapse rate; BL, baseline; CDW, confirmed disability worsening; DMT, disease-modifying therapy; Gd, gadolinium; HR, hazard ratio; IFNB, interferon beta; MS, multiple sclerosis, PBO, placebo; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous.

Table 3
Summary of studies in patients with aggressive MS.

Study	Study design (n)	Definition of aggressive disease	Treatment	Follow-up	Efficacy
(Krishnan et al., 2008)	Open-label (9)	1 clinical exacerbation between 6 and 12 mo of treatment or a sustained increase in > 1 EDSS point in the past year and ≥2 Gd-enhancing lesions on each of 2 pretreatment MRI scans	**Cyclophosphamide** 50 mg/kg/d for 4 consecutive days, followed by 5 μg/kg/d of G-CSF 6 days until the absolute neutrophil count exceeded 1.0 × 10^9 cells/L for 2 consecutive days	2 y	• Sustained remission of all detectable disease activity in some patients • Statistically significant reduction in EDSS of 39.4% (from 5.17 at BL to 3.06 at follow-up; $p = 0.02$) • 81.4% reduction in Gd-enhancing lesions ($p = 0.01$) • Rescue therapy due to relapse: n = 2
(Le Page et al., 2008)	Observational, open-label (100)	≥2 relapses with sequelae or a ≥2-point increase in EDSS during last 12 mo; ≥1 Gd-enhancing lesion on MRI in last 3 mo	**Mitoxantrone** 20 mg once monthly for 6 mo	1 y	• ARR: 91% reduction vs BL • 78% of patients relapse-free • Mean EDSS: improvement of 1.2 points from BL • Gd-enhancing MRI lesions: 89.5% reduction from BL
				2–5 y	• ARR: 0.39 at 2 y, 0.42 at 3 y, 0.38 at 4 y, 0.39 at 5 y • Proportion of patients relapse free: 62% at 2 y, 42.5% at 3 y, 39% at 4 y, 32% at 5 y • Mean EDSS score: 3.1 at 2 y, 3.3 at 3 y, 3.5 at 4 y, 3.6 at 5 y ($p < 0.008$)
(Capobianco et al., 2012)	Prospective, observational (5)	Patients in whom autologous HSCT failed to control disease	**Natalizumab**	Mean 31.2 mo (range, 18–40)	• No clinical disease activity or Gd-enhancing lesions after starting natalizumab in 3 patients • 1 patient had a relapse after the first natalizumab infusion, and then no clinical disease activity or Gd-enhancing lesions • 1 patient had Gd-enhancing lesions 2 mo after natalizumab initiation, and then no clinical disease activity or Gd-enhancing lesions thereafter
(Le Page et al., 2015)	Observational, Rennes EDMUS database (16 [8 SPMS, 8 RRMS])	• Suboptimal response to mitoxantrone (≥1 new relapse and 1 new Gd-enhancing lesion during 3 mo mitoxantrone) plus pre-mitoxantrone disease activity; or late reactivation of disease after mitoxantrone use • Active MS (sustained increase of EDSS ≥1 point for scores ≤5.5 or 0.5 points for scores > 5.5 and new Gd-enhancing lesions)	• **Alemtuzumab** 20 mg/d (n = 13) • **Alemtuzumab** 12 mg/d (n = 3) • Both given for 5 days	6.2 y	• SPMS: mean EDSS improved within 6 mo after alemtuzumab by 0.37 points (0–1) • RRMS: mean EDSS improved significantly within 6 mo after alemtuzumab by 1.9 points (0–4)
(Hirst et al., 2008)	Retrospective analysis of patients from 3 regional MS units (39)	• Relapsing disease course • Disease duration: ≤6 y • Aggressive disease: high relapse rate, rapidly accumulating disability, or early motor, cerebellar or cognitive dysfunction	• **Alemtuzumab**: • 30 mg/d for 5 days (n = 2) • 24 mg/d for 5 days (n = 11) • 20 mg/d for 5 days (n = 12) • 12 mg/d for 5 days (n = 13) • Retreatment as-needed at 12- to 18-mo intervals with alemtuzumab 60 or 36 mg over 3 days • Total courses: 1 course (n = 23); 2 courses (n = 13); 3 courses (n = 3)		• Mean ARR: 0.19 post-treatment vs 2.48 pre-treatment ($p < 0.0001$) • 14 relapses in 39 pts over 73.8 patient-years of follow-up; 4 (29%) occurred within 12 wk of initial infusion • Mean change in EDSS was –0.36 overall and –0.15 in pts completing ≥1 y of follow-up • Stable or improved disability: 83%

ARR, annualized relapse rate; BL, baseline; EDSS, Expanded Disability Status Scale; G-CSF, granulocyte-colony stimulating factor; Gd, gadolinium; HSCT, hematopoietic stem cell transplant; MRI, magnetic resonance imaging; MS, multiple sclerosis; pt = patient; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

relapses in the year before baseline as in the previous year (Derfuss et al., 2015). At 2 years, ARR was reduced by 48% with fingolimod compared with placebo ($p < 0.001$), and the risk of 3- and 6-month confirmed disability worsening was reduced by 35% ($p = 0.031$) and 45% ($p = 0.016$), respectively. MRI endpoint analysis showed that mean percent brain volume change was reduced by 46% ($p < 0.001$). At Month 24, the number of Gd-enhancing lesions was reduced by 65% ($p < 0.001$), and new/enlarging T2 lesions were reduced by 69% ($p < 0.001$).

4.2. Mitoxantrone

Mitoxantrone inhibits proliferation of B and T cells and suppresses cytokine production via cytocidal effects of DNA intercalation. It is approved for use in several European countries in patients with worsening RRMS, secondary progressive MS (SPMS), and relapsing-progressive MS (RPMS) in doses of 12 mg/m^2 of body surface area every 3 months (EMD Serono Inc, 2008, 2016). Mitoxantrone is also approved in the US for use in SPMS, in RPMS, and for patients with worsening RRMS (EMD Serono Inc, 2008, 2016). Because of toxicity concerns, mitoxantrone is usually reserved for severe cases or when other treatment options have been exhausted (Goodin et al., 2003). In a meta-analysis of randomized, controlled trials, mitoxantrone reduced relapses and disability worsening at 2 years of follow-up and reduced the number of patients with active MRI lesions (Martinelli Boneschi et al., 2013).

In trials with 2-year follow-up, AEs most commonly reported with mitoxantrone were nausea and vomiting, alopecia, urinary tract infections, transitory leukopenia, and amenorrhea (Martinelli Boneschi et al., 2013). Concerns have been raised about secondary acute leukemias, which have been reported to occur in approximately 0.8% of mitoxantrone-treated patients in randomized, controlled trials (Martinelli Boneschi et al., 2013); however, this may be an underestimate based on the potentially long latency period of secondary leukemia and the relatively short duration of the trials. The incidence in two observational cohorts of Mediterranean patients with RRMS and SPMS was as high as 2.8% (Pascual et al., 2009). Cardiotoxicity is another area of concern, occurring in approximately 12% of patients. Cardiovascular effects are cumulative dose-dependent and, thus, retreatment may not be possible (Martinelli Boneschi et al., 2013). Risk mitigation includes baseline cardiac assessments before each infusion and limited dosing (Subei and Ontaneda, 2015).

Induction therapy with mitoxantrone 20 mg once monthly for 6 months was prospectively evaluated in 100 consecutive patients with aggressive MS, defined as at least two relapses with sequelae or an increase in EDSS score of ≥2 points in 12 months and the presence of at least one Gd-enhancing lesion (Le Page et al., 2008). Within 6 months after induction, 73 patients received maintenance therapy: mitoxantrone every 3 months (n = 21); IFNB (n = 25); azathioprine (n = 15); methotrexate (n = 7); and glatiramer acetate (n = 5). Compared with the 12 months before mitoxantrone initiation, the 12 months following initiation showed an ARR reduced by 91% ($p < 10^{-6}$), the proportion of patients with Gd lesions was reduced by 90%, mean EDSS score decreased by 1.2 points ($p < 10^{-5}$), and 64% of patients had a ≥1-point EDSS score improvement. Over 5 years of follow-up, 60% of patients had not worsened on EDSS and a reduced ARR was sustained. Larger prospective studies on mitoxantrone in high-risk patients are needed to further characterize its efficacy in this subgroup.

4.3. Natalizumab

Natalizumab is a selective adhesion molecule inhibitor that attenuates lymphocyte migration into the CNS. It is approved for use in the US as monotherapy for patients with relapsing forms of MS, and in several European countries in patients with highly active RRMS despite DMT or those with rapidly evolving severe RRMS defined by ≥2 relapses in 1 year and ≥1 Gd-enhancing lesion or significant increase in T2 lesion load. The approved dose of 300 mg is infused intravenously for 1 h every 4 weeks (Biogen Idec, 2013; Biogen Idec Limited, 2016). In the AFFIRM study in adult patients with relapsing MS, natalizumab significantly improved clinical and MRI outcomes over 2 years compared with placebo (Polman et al., 2006).

Most common AEs that were higher with natalizumab than placebo were fatigue and allergic reaction. Serious infections occurred in 3.2% of patients receiving natalizumab monotherapy compared with 2.6% of patients on placebo (Polman et al., 2006). The greatest safety concern with natalizumab is PML (Polman et al., 2006; Rudick et al., 2006b). As of June 2015, the overall incidence of PML in 138,800 natalizumab-treated patients in the postmarketing setting was 3.96 cases per 1000; the highest risk occurred in patients positive for John Cunningham virus who had received prior immunosuppression and exceeded treatment duration of 24 months (25–48 months: 11/1000; 49–72 months: 9/1000) (McGuigan et al., 2016). Patients should be monitored for signs and symptoms of PML for ≥6 months after natalizumab discontinuation (Biogen Idec, 2013; Biogen Idec Limited).

The efficacy of natalizumab versus placebo in treatment-naive patients with highly active disease (n = 148 and n = 61, respectively) was evaluated in a post hoc analysis of patients enrolled in the AFFIRM study (Hutchinson et al., 2009). Highly active disease was defined as at least two relapses in the year before study entry and at least one Gd-enhancing T1 lesion at study entry. Natalizumab reduced the ARR over 2 years by 81% compared with placebo (0.28 vs 1.46; $p < 0.001$) and reduced the risk of 3-month and 6-month confirmed disability worsening by 53% ($p = 0.029$ vs placebo) and 64% ($p = 0.008$ vs placebo), respectively. Significant improvements versus placebo in other relapse-related endpoints, such as relapses requiring steroid therapy ($p < 0.001$) and rate of hospitalization ($p = 0.048$), along with MRI endpoints (number of new or enlarging T2 hyperintense lesions [$p < 0.001$], number of Gd-enhancing lesions at 2 years [$p < 0.001$], and number of new T1 hypointense lesions [$p = 0.003$]) were observed with natalizumab compared with placebo in this subgroup.

In addition, natalizumab has been studied prospectively in five female patients with aggressive RRMS who had incomplete response to autologous hematopoietic stem cell transplantation (Capobianco et al., 2012). Treated patients showed no evidence of disease activity (NEDA; assessed on MRI and clinical endpoints) through a mean follow-up duration of 31.2 (range, 18–40) months.

4.4. Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody that targets CD52 on T and B lymphocytes, thereby achieving rapid lymphocyte depletion, followed by a distinct pattern of repopulation which is believed to be associated with a rebalancing of the immune system (Hu et al., 2009; Rao et al., 2012). After 3 months, B-cell counts return to baseline levels (Thompson et al., 2010). By approximately 20 months and 35 months respectively, CD8+ and CD4+ T-lymphocyte levels repopulate to the lower limit of normal (Hill-Cawthorne et al., 2012). Repopulation is associated with relative increases in the proportions of regulatory and memory T cells and a decrease in T-helper 1 and T-helper 17 cells (Zhang et al., 2013). Additionally, serum cytokines shift to a less inflammatory profile (Cox et al., 2005).

Alemtuzumab is approved in Europe for the treatment of patients with RRMS with active disease defined by clinical or MRI parameters and in the US, generally for patients who have had an inadequate response to at least two therapies (Genzyme Corporation, 2014; Genzyme Therapeutics Ltd., 2015). It is administered as a 12-mg/day intravenous (IV) infusion for two treatment courses, with an initial course of 12 mg/day on 5 consecutive days, and a second course 12 months later of 12 mg/day on 3 consecutive days (96 mg total dose). Unlike other therapies, alemtuzumab is not dosed continuously, and most patients do not receive retreatment following the initial 2 courses through 6

years (Coles et al., 2016; Fox et al., 2016). Alemtuzumab has demonstrated superior clinical and MRI efficacy over the active comparator SC IFNB-1a in two phase 3 studies: CARE-MS I in treatment-naive patients with RRMS (Cohen et al., 2012), and CARE-MS II in RRMS patients with an inadequate response to prior therapy (Coles et al., 2012).

Infusion-associated reactions were the most common AE with alemtuzumab. Mild to moderate infections occurred more often with alemtuzumab than with SC IFNB-1a, with more instances of herpes infections in the alemtuzumab group (predominantly oral infections and herpes zoster) (Cohen et al., 2012; Coles et al., 2012). Autoimmune AEs were predominantly mild to moderate thyroid disorders including hyperthyroidism, hypothyroidism, and Graves' disease. Incidence of thyroid AEs was 34% in pivotal trials, peaking in Year 3 and declining thereafter. Immune thrombocytopenia (2%) and glomerulonephritis (0.3%) were associated with alemtuzumab, but less frequently. Patients treated with alemtuzumab undergo monthly monitoring until 48 months after the last dose, which allows for early detection and treatment of autoimmune AEs associated with alemtuzumab treatment (Genzyme Corporation, 2014; Genzyme Therapeutics Ltd., 2015).

The efficacy of alemtuzumab in patients with highly active disease was evaluated in prespecified subgroup analyses of CARE-MS I (Krieger et al., 2014) and CARE-MS II (Krieger et al., 2013). Highly active disease was defined as at least two relapses in the year before randomization and at least one Gd-enhancing lesion at baseline. Data from CARE-MS I showed a 51% reduction in ARR with alemtuzumab compared with SC IFNB-1a over 2 years ($p = 0.0068$), with the proportion of patients with relapses at 24% versus 50% ($p = 0.0007$), respectively. Alemtuzumab-treated patients with highly active disease were also significantly more likely to have no evidence of clinical disease activity over 2 years (71% vs 48%; $p = 0.0025$), no evidence of MRI disease activity (i.e., Gd-enhancing lesions or new or enlarging T2 hyperintense lesions; 72% vs 46%; $p = 0.0009$), had 32% lower median brain volume loss from baseline at Year 2 ($p = 0.0089$), and were more likely to achieve NEDA at Year 2 compared with patients treated with SC IFNB-1a (26% vs 20%; $p = 0.0002$) (Krieger et al., 2014). In CARE-MS II, ARR was reduced by 51% with alemtuzumab in previously treated patients with highly active disease at baseline versus SC IFNB-1a over 2 years ($p < 0.0001$), and the proportion of patients with relapse was reduced by 56% versus SC IFNB-1a ($p = 0.0018$) (Confavreux et al., 2012; Krieger et al., 2013). Alemtuzumab-treated patients with highly active disease were significantly more likely to have no evidence of clinical disease activity over 2 years (61% vs 33%; $p = 0.0027$), to be free of MRI disease activity (40% vs 8%; $p = 0.0007$), and to achieve NEDA at Year 2 compared with patients treated with SC IFNB-1a (24% vs 0%; $p = 0.0002$). Median brain volume loss was reduced at 2 years by 28% (Callegaro et al., 2014; Comi et al., 2016). Longer-term follow-up of the highly active subgroups demonstrated ARRs of 0.16 (89% of patients free of relapse) in CARE-MS I patients and 0.23 (81% free of relapse) in CARE-MS II patients at Year 5, in the absence of continuous treatment, and with most patients not receiving alemtuzumab retreatment (Krieger et al., 2016; Singer et al., 2016).

In a prospective observational study, 8 patients with aggressive RRMS and suboptimal response to mitoxantrone treatment received alemtuzumab 12 or 20 mg/day for 5 days (Le Page et al., 2015). This dosing does not represent the full treatment regimen of two alemtuzumab courses; however, within 6 months after alemtuzumab treatment, mean EDSS improved by 1.9 points (range, 0–4). One patient remained stable up to last visit (8.7 years), and 7 patients improved. Four of these remained disease free up to last visit (12, 24, and 38 months and 7 years).

Another study pooled experience of three regional MS units using alemtuzumab at varying doses (30 mg, 24 mg, 20 mg, or 12 mg daily on 5 consecutive days) as a treatment in aggressive relapsing MS over 4 years (Hirst et al., 2008). This study also did not administer the full treatment of two courses. The mean ARR fell from 2.48 before treatment to 0.19 after treatment, with a mean improvement of 0.36 in EDSS score. Overall, EDSS scores improved in 14 patients, remained stable in 12, and worsened in 6.

5. Evaluation of other therapies in RRMS patients with high-risk disease

5.1. Cyclophosphamide

Cyclophosphamide is a wide-spectrum alkylating compound that exerts its effects on B and T cells, suppressing both humoral and cell-mediated immunity (Awad and Stüve, 2009). It has been used off-label in the treatment of MS. Cyclophosphamide treatment for MS most commonly consists of monthly IV pulses at a dose of $250-1500\ mg/m^2$ of body surface area for 1 year followed by bimonthly pulses for the second year, with or without prior infusion of corticosteroids (Perini et al., 2007; Rinaldi et al., 2009).

The most common AEs with this protocol are mild alopecia, nausea and vomiting, and cystitis, which are dose-dependent, transient, and reversible. Definitive amenorrhea is observed in female patients aged > 40 years (Perini et al., 2007; Rinaldi et al., 2009). Increased risk of malignancy, hemorrhagic cystitis, and gonadotoxicity are AEs of concern, and cyclophosphamide has limitations on lifetime cumulative dose around 80–100 g (Awad and Stüve, 2009).

Few data exist on the efficacy of cyclophosphamide in high-risk patients. High-dose cyclophosphamide was evaluated in a pilot study of nine patients with severe MS who were followed up for 23 months (Krishnan et al., 2008). Inclusion criteria were failure or refusal of conventional therapy, one relapse between 6 and 12 months prior to treatment, or a sustained > 1-point EDSS score increase in the past year and ≥2 Gd-enhancing lesions on each of two pretreatment MRI scans. Patients received 50 mg/kg/day of IV cyclophosphamide for 4 consecutive days, followed by granulocyte colony-stimulating factor 6 days later. High-dose cyclophosphamide induced a 39% reduction in disability, from a mean EDSS score of 5.17 at baseline to 3.06 at follow-up ($p = 0.02$), and an 81% reduction in the number of Gd-enhancing lesions ($p = 0.01$). Larger, prospective studies with narrower inclusion criteria are needed.

6. Conclusions

Increasing evidence suggests that early, optimal intervention is needed to prevent inflammatory events that ultimately lead to a progressive disease course. Because patients with high-risk MS accumulate irreversible neurologic damage more rapidly than other patients, they have a limited opportunity in which to change the disease trajectory (Rush et al., 2015). In the author's opinion, these patients are the best candidates for early treatment with strong, high-efficacy DMTs, either as initial treatment or in response to the earliest sign of suboptimal DMT response. Although the available data on high-efficacy DMTs in high-risk patients are imperfect, results of subgroup analyses and smaller studies are promising. With the growing understanding that our ability to modify disease in an individual patient diminishes with time, clinicians are faced with balancing the risk of inaction with that of acting on the basis of encouraging, yet incomplete, information.

An individualized benefit-risk assessment ensures that the level of DMT efficacy is appropriate for the patient's likely disease course, and that the risk of serious drug-related AEs is considered in relation to the risk of disease progression. DMT-related risks also need to be balanced against considerations of treatment duration and the potential need for the use of sequential therapies (Kornek, 2015). Such considerations are important for cyclophosphamide and mitoxantrone, which are limited by restrictions on lifetime cumulative dose (Rush et al., 2015), and natalizumab, which is limited by increasing PML risk over time and potential rebound activity after treatment cessation (Giovannoni et al., 2016; Kornek, 2015).

Subgroup analyses of pivotal clinical trial data have demonstrated

the ability of agents of high efficacy (i.e., natalizumab, alemtuzumab) and moderately high efficacy (i.e., fingolimod) to significantly reduce relapses in patients with highly active or rapidly evolving severe MS. A limitation of these data is that subgroup analyses of studies with overall positive treatment effects also tend to be positive. Additional data from smaller studies of natalizumab and alemtuzumab that prospectively recruited high-risk patients help support results of the phase 3 subgroup analyses; however, more prospective studies are needed to strengthen the evidence base for the treatment effects of these therapies in patients with high-risk RRMS. Data supporting the use of mitoxantrone in patients with "aggressive" MS come from a study in which high-risk patients were prospectively recruited, but there was no comparator arm. Evidence of cyclophosphamide efficacy in patients with high-risk RRMS is limited. The field would benefit from studies specifically designed to evaluate high-risk patients, using a set of consensus inclusion criteria to better define this population. Furthermore, formalized testing of the hypothesis that early therapeutic intervention can delay or reduce disease progression in these patients is needed.

Although they reflect clinical practice, these studies vary considerably in their definitions of "aggressive" disease, the timing of treatment, and the dosages of therapies used, with some studies conducted in patients receiving induction regimens. Furthermore, although the prospective studies and post hoc analyses focused on patients with high-risk RRMS, none required patients to be early in the disease course. More studies are needed to evaluate the early use of existing treatment options to prevent the accumulation of neurologic damage and disability in high-risk patients. Studies of new therapies and those currently in development for the treatment of RRMS (cladribine, ocrelizumab, ofatumumab, etc.) will also add to our understanding of early treatment in these patients.

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Conflicts of interest

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References

Awad, A., Stüve, O., 2009. Cyclophosphamide in multiple sclerosis: scientific rationale, history and novel treatment paradigms. Ther. Adv. Neurol. Disord. 2, 50–61.

Idec Biogen, 2013. TYSABRI (natalizumab) injection, for intravenous use. Prescribing Information. Available at: 〈http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125104s033lbl.pdf〉. (Accessed 8 June 2016).

Biogen Idec Limited. TYSABRI SmPC. Available at:〈http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000603/WC500044686.pdf〉. (Accessed 8 June 2016).

Brinkmann, V., Davis, M.D., Heise, C.E., Albert, R., Cottens, S., Hof, R., et al., 2002. The immune modulator FTY720 targets sphingosine 1-phosphate receptors. J. Biol. Chem. 277, 21453–21457.

Calabresi, P.A., Radue, E.W., Goodin, D., Jeffery, D., Rammohan, K.W., Reder, A.T., et al., 2014. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 13, 545–556.

Callegaro D., Krieger S., Arnold D.L., Coles A.J., Hartung H.P., Havrdova E. et al. 2014. Superior efficacy with alemtuzumab compared with subcutaneous interferon beta-1a in highly active relapsing-remitting multiple sclerosis patients who relapsed on a prior therapy. In: Proceedings of the 8th Latin American Committee for Treatment and Research in Multiple Sclerosis (LACTRIMS) Meeting. Lima, Peru.

Capobianco, M., Motuzova, Y., Frau, J., Cocco, E., Mamusa, E., Marrosu, M.G., et al., 2012. Natalizumab in aggressive multiple sclerosis after haematopoietic stem cell transplantation. Neurol. Sci. 33, 863–867.

Chataway, J., Miller, D.H., 2013. Natalizumab therapy for multiple sclerosis. Neurotherapeutics 10, 19–28.

Cohen, J.A., Barkhof, F., Comi, G., Hartung, H.P., Khatri, B.O., Montalban, X., et al., 2010. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N. Engl. J. Med. 362, 402–415.

Cohen, J.A., Coles, A.J., Arnold, D.L., Confavreux, C., Fox, E.J., Hartung, H.P., et al., 2012. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 380, 1819–1828.

Coles, A.J., Boyko, A.N., Cohen, J.A., de Seze, J., Fox, E.J., Havrdova, E., et al., 2016. Alemtuzumab provides durable improvements in clinical outcomes in treatment-naive patients with active relapsing-remitting multiple sclerosis over 6 years in the absence of continuous treatment (care-MS I). Mult. Scler. J. 22, P213.

Coles, A.J., Compston, D.A., Selmaj, K.W., Lake, S.L., Moran, S., Margolin, D.H., et al., 2008. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N. Engl. J. Med. 359, 1786–1801.

Coles, A.J., Twyman, C.L., Arnold, D.L., Cohen, J.A., Confavreux, C., Fox, E.J., et al., 2012. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 380, 1829–1839.

Comi, G., Berkovich, R., Rovira, A., Pelletier, D., Schippling, S., Traboulsee, A., et al., 2016. Durable effect of alemtuzumab on MRI lesion outcomes over 5 years in patients with highly active relapsing-remitting multiple sclerosis who had an inadequate response to prior therapy (care-MS II). Mult. Scler. J. 22, P613.

Confavreux, C., Twyman, C., Arnold, D.L., Cohen, J., Coles, A.J., Fox, E., et al., 2012. Efficacy of alemtuzumab in relapsing-remitting multiple sclerosis (RRMS) patients with highly active disease despite therapy. Eur. J. Neurol. 19, Suppl 1.

Confavreux, C., Vukusic, S., Adeleine, P., 2003. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 126, 770–782.

Cox, A.L., Thompson, S.A., Jones, J.L., Robertson, V.H., Hale, G., Waldmann, H., et al., 2005. Lymphocyte homeostasis following therapeutic lymphocyte depletion in multiple sclerosis. Eur. J. Immunol. 35, 3332–3342.

Dendrou, C.A., Fugger, L., Friese, M.A., 2015. Immunopathology of multiple sclerosis. Nat. Rev. Immunol. 15, 545–558.

Derfuss, T., Bergvall, N.K., Sfikas, N., Tomic, D.L., 2015. Efficacy of fingolimod in patients with highly active relapsing-remitting multiple sclerosis. Curr. Med. Res. Opin. 31, 1687–1691.

Devonshire, V., Havrdova, E., Radue, E.W., O'Connor, P., Zhang-Auberson, L., Agoropoulou, C., et al., 2012. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol. 11, 420–428.

EMD Serono Inc, 2008. NOVANTRONE Prescribing Information. Available at: 〈http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019297s030s031lbl.pdf〉. (Accessed 30 September 2016).

EMD Serono Inc, 2016. NOVANTRONE SmPC. Available at: 〈http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Novantrone_30/WC500205489.pdf〉. (Accessed 30 September 2016).

Fox, E.J., Alroughani, R., Brassat, D., Broadley, S., Cohen, J.A., Hartung, H.P., et al., 2016. Efficacy of alemtuzumab is durable over 6 years in patients with active relapsing-remitting multiple sclerosis and an inadequate response to prior therapy in the absence of continuous treatment (care-MS II). Mult. Scler. J. 22, P1150.

Freedman, M.S., Comi, G., De Stefano, N., Barkhof, F., Polman, C.H., Uitdehaag, B.M., et al., 2014. Moving toward earlier treatment of multiple sclerosis: findings from a decade of clinical trials and implications for clinical practice. Mult. Scler. Relat. Disord. 3, 147–155.

Genzyme Corporation, 2014. November 2014. LEMTRADA (alemtuzumab), for intravenous injection. Prescribing Information. Available at: 〈http://www.fda.gov/downloads/drugs/drugsafety/ucm426512.pdf〉. (Accessed 11 February 2016).

Genzyme Therapeutics Ltd, 2015. LEMTRADA (alemtuzumab) SmPC. Available at: 〈http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003718/WC500150521.pdf〉. (Accessed 2 September 2015).

Giovannoni, G., Marta, M., Davis, A., Turner, B., Gnanapavan, S., Schmierer, K., 2016. Switching patients at high risk of PML from natalizumab to another disease-modifying therapy. Pract. Neurol. 16, 389–393.

Goodin, D.S., Arnason, B.G., Coyle, P.K., Frohman, E.M., Paty, D.W., Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, 2003. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 61, pp. 1332–1338.

Hartung, H.P., Aktas, O., Boyko, A.N., 2015. Alemtuzumab: a new therapy for active relapsing-remitting multiple sclerosis. Mult. Scler. 21, 22–34.

Hill-Cawthorne, G.A., Button, T., Tuohy, O., Jones, J.L., May, K., Somerfield, J., et al., 2012. Long term lymphocyte reconstitution after alemtuzumab treatment of multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 83, 298–304.

Hirst, C.L., Pace, A., Pickersgill, T.P., Jones, R., McLean, B.N., Zajicek, J.P., et al., 2008. Campath 1-H treatment in patients with aggressive relapsing remitting multiple sclerosis. J. Neurol. 255, 231–238.

Hu, Y., Turner, M.J., Shields, J., Gale, M.S., Hutto, E., Roberts, B.L., et al., 2009. Investigation of the mechanism of action of alemtuzumab in a human CD52 transgenic mouse model. Immunology 128, 260–270.
Hutchinson, M., Kappos, L., Calabresi, P.A., Confavreux, C., Giovannoni, G., Galetta, S.L., et al., 2009. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. J. Neurol. 256, 405–415.
Kappos, L., Radue, E.W., O'Connor, P., Polman, C., Hohlfeld, R., Calabresi, P., et al., 2010. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N. Engl. J. Med. 362, 387–401.
Khatri, B.O., 2016. Fingolimod in the treatment of relapsing-remitting multiple sclerosis: long-term experience and an update on the clinical evidence. Ther. Adv. Neurol. Disord. 9, 130–147.
Kornek, B., 2015. An update on the use of natalizumab in the treatment of multiple sclerosis: appropriate patient selection and special considerations. Patient Prefer Adherence 9, 675–684.
Krieger S., Arnold D.L., Cohen J., Coles A.J., Fox E.J., Hartung H.P., et al. 2013. Alemtuzumab is efficacious in highly active RRMS patients in CARE-MS II. Joint Consortium of Multiple Sclerosis Centers (CMSC)/Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Meeting. Orlando, FL. May 29-June 1.
Krieger S., Lubetzki C., Arnold D.L., Fisher E., Palmer J., Margolin D.H., 2014. Alemtuzumab reduces disease activity in treatment-naive patients with highly active relapsing-remitting multiple sclerosis. In: Proceedings of the Joint Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS)–European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Meeting. Boston, MA. September 10–13.
Krieger, S., Singer, B., Freedman, M.S., Lycke, J., Berkovich, R., Margolin, D.H., et al., 2016. Treatment-naive patients with highly active RRMS demonstrated durable efficacy with alemtuzumab over 5 years. Neurology 86 (S51.003).
Krishnan, C., Kaplin, A.I., Brodsky, R.A., Drachman, D.B., Jones, R.J., Pham, D.L., et al., 2008. Reduction of disease activity and disability with high-dose cyclophosphamide in patients with aggressive multiple sclerosis. Arch. Neurol. 65, 1044–1051.
Le Page, E., Deburghgraeve, V., Lester, M.A., Cardiet, I., Leray, E., Edan, G., 2015. Alemtuzumab as rescue therapy in a cohort of 16 aggressive multiple sclerosis patients previously treated by Mitoxantrone: an observational study. J. Neurol. 262, 1024–1034.
Le Page, E., Leray, E., Taurin, G., Coustans, M., Chaperon, J., Morrissey, S.P., et al., 2008. Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients. J. Neurol. Neurosurg. Psychiatry 79, 52–56.
Mandala, S., Hajdu, R., Bergstrom, J., Quackenbush, E., Xie, J., Milligan, J., et al., 2002. Alteration of lymphocyte trafficking by sphingosine-1-phosphate receptor agonists. Science 296, 346–349.
Martinelli Boneschi, F., Vacchi, L., Rovaris, M., Capra, R., Comi, G., 2013. Mitoxantrone for multiple sclerosis. Cochrane Database Syst. Rev. 5, CD002127.
Matloubian, M., Lo, C.G., Cinamon, G., Lesneski, M.J., Xu, Y., Brinkmann, V., et al., 2004. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature 427, 355–360.
McGuigan, C., Craner, M., Guadagno, J., Kapoor, R., Mazibrada, G., Molyneux, P., et al., 2016. Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. J. Neurol. Neurosurg. Psychiatry 87, 117–125.
Medicines and Healthcare Products Regulatory Agency, 2016. Fingolimod (Gilenya): risks of progressive multifocal leukoencephalopathy, basal-cell carcinoma, and opportunistic infections. Available at: ⟨https://www.gov.uk/drug-safety-update/fingolimod-gilenya-risks-of-progressive-multifocal-leukoencephalopathy-basal-cell-carcinoma-and-opportunistic-infections⟩. (Accessed 20 September 2016).
Menon, S., Shirani, A., Zhao, Y., Oger, J., Traboulsee, A., Freedman, M.S., et al., 2013. Characterising aggressive multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 84, 1192–1198.
Novartis Europharm Ltd, 2015. GILENYA Summary of Product Characteristics. Available at: ⟨http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf⟩. (Accessed 5 October 2016).
Novartis Pharmaceuticals Corporation, 2016. GILENYA (fingolimod). Prescribing information. Available at: ⟨https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/gilenya.pdf⟩. (Accessed 30 September 2016).
O'Riordan, J.I., Thompson, A.J., Kingsley, D.P., MacManus, D.G., Kendall, B.E., Rudge, P., et al., 1998. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain 121 (Pt 3), 495–503.
Pascual, A.M., Tellez, N., Bosca, I., Mallada, J., Belenguer, A., Abellan, I., et al., 2009. Revision of the risk of secondary leukaemia after mitoxantrone in multiple sclerosis populations is required. Mult. Scler. 15, 1303–1310.
Perini, P., Calabrese, M., Rinaldi, L., Gallo, P., 2007. The safety profile of cyclophosphamide in multiple sclerosis therapy. Expert Opin. Drug Saf. 6, 183–190.
Polman, C.H., O'Connor, P.W., Havrdova, E., Hutchinson, M., Kappos, L., Miller, D.H., et al., 2006. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N. Engl. J. Med. 354, 899–910.
Rao, S.P., Sancho, J., Campos-Rivera, J., Boutin, P.M., Severy, P.B., Weeden, T., et al., 2012. Human peripheral blood mononuclear cells exhibit heterogeneous CD52 expression levels and show differential sensitivity to alemtuzumab mediated cytolysis. PLoS One 7, e39416.
Rinaldi, L., Perini, P., Calabrese, M., Gallo, P., 2009. Cyclophosphamide as second-line therapy in multiple sclerosis: benefits and risks. Neurol. Sci. 30 (Suppl 2), S171–S173.
Rudick, R.A., Lee, J.C., Simon, J., Fisher, E., 2006a. Significance of T2 lesions in multiple sclerosis: a 13-year longitudinal study. Ann. Neurol. 60, 236–242.
Rudick, R.A., Stuart, W.H., Calabresi, P.A., Confavreux, C., Galetta, S.L., Radue, E.W., et al., 2006b. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N. Engl. J. Med. 354, 911–923.
Rush, C.A., MacLean, H.J., Freedman, M.S., 2015. Aggressive multiple sclerosis: proposed definition and treatment algorithm. Nat. Rev. Neurol. 11, 379–389.
Sanofi Genzyme, 2013. Data on File.
Scott, T.F., Schramke, C.J., Novero, J., Chieffe, C., 2000. Short-term prognosis in early relapsing-remitting multiple sclerosis. Neurology 55, 689–693.
Singer, B., Krieger, S., Berkovich, R., Freedman, M.S., Lycke, J., Margolin, D.H., et al., 2016. Patients who had highly active RRMS and an inadequate response to prior therapy demonstrated durable efficacy with alemtuzumab: 5-year follow-up of the care-MS II study. Neurology 86 (P6.164).
Sorensen, P.S., 2014. New management algorithms in multiple sclerosis. Curr. Opin. Neurol. 27, 246–259.
Subei, A.M., Ontaneda, D., 2015. Risk mitigation strategies for adverse reactions associated with the disease-modifying drugs in multiple sclerosis. CNS Drugs 29, 759–771.
Thompson, S.A., Jones, J.L., Cox, A.L., Compston, D.A., Coles, A.J., 2010. B-cell reconstitution and BAFF after alemtuzumab (Campath-1H) treatment of multiple sclerosis. J. Clin. Immunol. 30, 99–105.
Tintore, M., Rovira, A., Rio, J., Otero-Romero, S., Arrambide, G., Tur, C., et al., 2015. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 138, 1863–1874.
Weiner, H.L., 2009. The challenge of multiple sclerosis: how do we cure a chronic heterogeneous disease? Ann. Neurol. 65, 239–248.
Zhang, X., Tao, Y., Chopra, M., Ahn, M., Marcus, K.L., Choudhary, N., et al., 2013. Differential reconstitution of T cell subsets following immunodepleting treatment with alemtuzumab (anti-CD52 monoclonal antibody) in patients with relapsing-remitting multiple sclerosis. J. Immunol. 191, 5867–5874.
Ziemssen, T., De Stefano, N., Pia Sormani, M., Van Wijmeersch, B., Wiendl, H., Kieseier, B.C., 2015. Optimizing therapy early in multiple sclerosis: an evidence-based view. Mult. Scler. Relat. Disord. 4, 460–469.