Benefits versus risks of latest therapies in multiple sclerosis: a perspective review

Daniel Ontaneda and Daniela Di Capua

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Abstract: Disease-modifying treatments for multiple sclerosis (MS) have now been available for almost 20 years. Interferon β (IFN- β) products and glatiramer acetate (GA) were the first available options and are now considered first-line agents for the treatment of MS. These medications have several years of favorable safety data, but are not effective in completely controlling disease activity in all patients. Alternate medications with increased efficacy have been developed and identified; however, these newer medications have known or potential safety concerns which have prompted clinicians to view them as second-line agents. Highly efficacious and safe medications are continuously being searched for and developed; however, time is needed to establish the long-term safety of any new therapeutic agent. MS practitioners are faced with the clinical dilemma of treating patients with very safe modestly effective medications or using more efficacious and potentially riskier agents. The risk–benefit profile of every medication will have to be weighed carefully and clinicians will need to gage the risk tolerance of each patient in order to tailor treatment. This review will summarize benefits and risks of recently approved therapies in MS and will provide a perspective view on the placement of these medications within the MS treatment algorithm in the near future.

Keywords: disease-modifying agents, multiple sclerosis, risk/benefit, safety, toxicity

Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system (CNS). The current aim of disease-modifying treatment in MS is the reduction of magnetic resonance imaging (MRI) activity and clinical relapses to prevent the accrual of disability over time. Interferon- β (IFN- β) and glatiramer acetate (GA) are well-established MS therapies which are safe and well tolerated, but are not sufficient to control disease activity in a large proportion of patients. IFN- β and GA reduce relapse rate by approximately one third, however all formulations are administered through frequent injections [Goodin, 2004]. Long-term safety data for IFN- β and GA are available and it appears these medications are safe although some minor adverse effects do occur [Ann Marrie and Rudick, 2006; Miller *et al.* 2008]. Patients frequently experience breakthrough disease activity on first-line agents and tolerability to these agents may be suboptimal [Rudick and Polman, 2009]. This has prompted the search for more efficacious

therapies in MS, which has led to the successful approval of several new medications. The safety and tolerability of these new agents have prompted physicians to view these medications as ‘second-line agents’ [Marriott and O’Connor, 2011]. Mitoxantrone is an example of a second-line agent that is now seldom used due to malignancy potential and cardiac adverse effects [Martinelli *et al.* 2009]. The mechanism(s) of action of first-line MS medications is not entirely clear but it appears to be mediated at several levels [Kala *et al.* 2011; Kieseier, 2011]. Newer MS therapies have been designed with clearer mechanisms of action with the intent of regulating the immune system through more specific pathways. In many cases this has resulted in clear and at times predictable immune regulation responses, which may also underlie potential foreseeable adverse effects. Alternatively, several new MS therapies have been developed *de novo* and human experimentation is somewhat limited, which makes adverse effects difficult to predict, especially when mechanisms of action affect multiple body systems.

Correspondence to:

Daniel Ontaneda, MD, MS
Mellen Center for Multiple
Sclerosis Treatment and
Research, Cleveland Clinic
Foundation, 9500 Euclid
Avenue, U-10, Cleveland,
OH 44195, USA
ontaneda@ccf.org

Daniela Di Capua, MD
Neurology Service,
Hospital Clínico
Universitario San Carlos,
Madrid, Spain

The risk–benefit profile of new medications will have to be evaluated critically by patients and physicians in order to tailor a treatment that is both efficacious and safe in keeping with the risk aversion profile and clinical situation of individual patients. However, before a given medication reaches a patient or physician, a rigorous process of estimating the risk–benefit ratio of new medications is conducted by regulatory agencies. It is the duty of regulatory agencies to accept medications that have a certain minimum standard of net benefit to patients and ensure that product labeling is accurate. This minimum standard however is likely a moving target, and will change depending greatly on the safety and efficacy of established MS therapies, as well MS disease severity. Once a minimum net benefit is established and after medication approval by regulatory agencies, physicians and patients must ensure that the medication is well suited to the individual's risk aversion and clinical scenario. The goals of disease-modifying agents are also changing with the availability of new therapies. The possibility of attaining a disease-free state (absence of new brain MRI lesions and clinical relapses) may now be feasible through the use of highly effective disease modifying agents. Clinicians will have to develop an algorithm of medications in a step-wise approach. This will likely involve switching patients to more effective and potentially riskier medications after treatment failure. For this reason, an understanding of the risk–benefit profile of all MS therapies and a focus on outcomes that measure disease-free status, such as the proportion of relapse-free patients, will become increasingly important. This review is intended to highlight recent developments in the risk–benefit profile of approved and emerging MS therapies. We also provide a perspective view on the place of new therapies within the MS treatment algorithm. Summary data is presented in Table 1 and a comparison of adverse effects with placebo or active comparators is presented in Table 2.

Natalizumab

Natalizumab is a humanized monoclonal antibody directed at the alpha 4-integrin receptor and acts by preventing cellular adhesion and subsequent leukocyte migration across the blood–brain barrier [Rudick and Sandrock, 2004]. Natalizumab is highly effective at reducing gadolinium-enhanced lesions and clinical relapses in patients with relapsing MS when compared with placebo and intramuscular (IM) interferon β -1a

(IFN β -1a) [Polman *et al.* 2006; Rudick *et al.* 2006]. Natalizumab was associated with a two-thirds relative reduction of annualized relapse rate (ARR) in phase III clinical trials. A total of 54–67% of patients from natalizumab treated remained relapse free at 2 years in phase III trials. Natalizumab reduced sustained Expanded Disability Status Scale (EDSS) scores by 42% over 2 years when compared with placebo. No major safety concerns were detected after completion of phase III clinical trials; however, after regulatory approval three cases of progressive multifocal leukoencephalopathy (PML) were identified and the medication was temporarily removed from the market in 2005 [Kleinschmidt-DeMasters and Tyler, 2005; Langer-Gould *et al.* 2005; Van Assche *et al.* 2005]. PML results from the reactivation of latent John Cunningham virus (JCV), and is thought to be a direct consequence of decreased CNS immune surveillance [Monaco and Major, 2012]. The medication was reintroduced in 2006 with a specific risk management program. A retrospective review showed that the risk of PML infection in patients treated with natalizumab was close to 1 per 1000 at that time [Yousry *et al.* 2006]. Outcomes after PML infection have been typically described as poor; however, a more recent review of natalizumab-associated PML indicates that mortality might be slightly lower and that there is a range in disability outcomes [Vermersch *et al.* 2011].

Several additional cases of PML have been identified and described with ongoing natalizumab use in MS [Clifford *et al.* 2010]. The use of previous immunosuppressive medications and duration of therapy are related to the overall risk of PML and natalizumab [Sorensen *et al.* 2012]. The use of JCV serology has been studied as a risk stratification tool for development of PML in natalizumab-treated patients. It appears that all patients with natalizumab-associated PML who had serum available for testing, had serological evidence of prior JCV exposure, and approximately half of MS patients had tested positive for anti-JCV antibodies [Gorelik *et al.* 2010]. A model of risk stratification for natalizumab-associated PML has been proposed that incorporates treatment duration, JCV antibody status and prior immunosuppression use [Sorensen *et al.* 2012]. Among patients with positive JCV serology the risk of PML appears to be greatest in patients with treatment duration beyond 24 months along with prior immunosuppressive medication use (11/1000), and lowest in patients who have been treated for

Table 1. Risks and benefits of medications for treatment of multiple sclerosis.

Name	Route	Mechanism of action	Efficacy data	Adverse effects	Regulatory status/ Monitoring studies
Natalizumab [Polman <i>et al.</i> 2006; Rudick <i>et al.</i> 2006]	IV	Monoclonal antibody directed at $\alpha 4$ -integrin, inhibits leukocyte migration across the blood-brain barrier.	Phase III AFFIRM (<i>versus</i> placebo): ARR reduction 68%, 54–67% relapse free at 2 years, disability reduction 42%, new or enlarging T2 lesions decreased by 83%.	PML, allergic reactions. JCV serology is a predictor of PML risk. Treatment duration and previous immunosuppressant use are also risk factors for PML development.	Currently approved. JCV serology yearly; natalizumab antibodies at 6 months; LFTs every 6 months.
Fingolimod [Cohen <i>et al.</i> 2010; Cohen and Chun, 2011; Kappos <i>et al.</i> 2010]	PO	Sphingosine 1-phosphate modulator, sequesters T lymphocytes in secondary lymphoid organs.	Phase III <i>versus</i> placebo (FREEDOMS): reduction of ARR by 54–60%, positive effect on brain volume and gadolinium-enhancing lesions, 70% relapse-free at 2 years, disability reduction (HR 0.70), 33% reduction in brain volume. Phase III trial <i>versus</i> IM IFN β -1a: reduction of ARR by 38–52%.	Bradycardia/slowing of AV conduction with first dose, macular edema, disseminated herpes infections, skin malignancies, lymphopenia, hypertension.	Currently approved. First dose observation, CBC, LFT, OCT, ophthalmology exam at 3 months and then every 6 months.
Teriflunomide [Confavreux <i>et al.</i> 2012; O'Connor <i>et al.</i> 2011]	PO	Metabolite of leflunomide, reversible noncompetitive inhibitor of the mitochondrial enzyme dihydroorotate dehydrogenase. It inhibits pyrimidine synthesis and has cytostatic effects on T and B cells. Inhibition of tyrosine kinases results in reduced T-cell activation and cytokine production).	Phase III TEMSO (<i>versus</i> placebo): ARR by 31%, sustained disability reduction 29.8% (14 mg dose), 53.7–56.5% relapse free at 2 years, positive effects on MRI lesional measures, effects on brain parenchymal fraction were not statistically significant.	Diarrhea, nausea, hair density loss, elevation of liver function tests, upper respiratory tract infections, paresthesias. Leflunomide is pregnancy category X.	Submitted to FDA in October of 2011.
Laquinimod [Comi <i>et al.</i> 2012; Vollmer <i>et al.</i> 2012]	PO	Modulates cytokine expression with an effect on antigen presentation, T cells, B cells, and microglia.	Phase III ALLEGRO (<i>versus</i> placebo): ARR reduction: 23%, sustained disability reduction 36%, 63% relapse-free at 2 years. Phase III BRAVO (<i>versus</i> placebo): ARR reduction did not reach significance, pooled reduction in brain atrophy of 30% <i>versus</i> placebo.	Elevation in liver function enzymes. Pro-inflammatory effects. Increased CRP, ESR.	FDA submission on hold. EMA submission planned for 2012.
Dimethylfumarate [Fox <i>et al.</i> 2012; Gold <i>et al.</i> 2011; Phillips <i>et al.</i> 2012]	PO	Fumaric acid acts on nuclear factor-E2-related factor, has immunomodulatory properties and neuroprotective effects.	Phase III DECIDE (<i>versus</i> placebo): ARR reduction (48–53%), disability reduction (34–38%). Phase III CONFIRM (<i>versus</i> placebo): ARR reduction (44–51%), disability reduction (21–24%).	Flushing, headache, gastrointestinal upset. Safety partly established by long-term use of dimethylfumarate for psoriasis in Germany.	Submitted to FDA in February of 2012.

(Continued)

Table 1. (Continued)

Name	Route	Mechanism of action	Efficacy data	Adverse effects	Regulatory status/ Monitoring studies
Alemtuzumab [Cohen <i>et al.</i> 2012; Coles <i>et al.</i> 2012a; Costelloe <i>et al.</i> 2012]	IV	Humanized monoclonal antibody directed at CD52.	Phase III CARE-MS I (<i>versus</i> subcutaneous IFN β 1-a in treatment naïve): ARR reduction: 55%, sustained disability reduction did not reach significance. Phase III CARE-MS II (<i>versus</i> subcutaneous IFN β 1-a in treatment failure): ARR reduction: 49%, disability reduction: 42%.	Infusion-related reactions, mild/ moderate respiratory infections. Autoimmune reactions including hyperthyroidism, immune thrombocytopenic purpura, and Goodpasture's syndrome.	Submitted to FDA in June 2012.
IFN β 1-a, Interferon β 1-a; IV, intravenous; PO, oral; ARR, annualized relapse rate ; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; JCV, John Cunningham virus; CBC, complete blood count; LFT, liver function test; OCT, optical coherence tomography; HR, hazard ratio; FDA, Food and Drug Administration; EMA, European Medicines Agency; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.					

less than 24 months with no prior immunosuppression (0.56/1000). Patients with negative JCV serology are felt to be at a very low risk for PML (<0.09/1000) [Bloomgren *et al.* 2012]. An algorithm to estimate more precise risk estimates using the three different factors has also been made available as an online tool [Fox and Rudick, 2012]. Although these tools have significantly improved our risk estimates of PML there are still some unanswered questions. Although the rate of JCV seroconversion is felt to be only 2–3% yearly [Gorelik *et al.* 2010], the ramifications of developing a primary JCV infection while on natalizumab are not clear. Other than the risk of PML natalizumab is a well-tolerated medication. Antibodies to natalizumab are seen in approximately 10% of treated patients, are associated with decreased efficacy, and may be associated with allergic reactions to the medication [Calabresi *et al.* 2007].

Perspective view

Currently natalizumab is used primarily as a second-line agent for treatment of patients who have had breakthrough disease on one of the first-line agents. However, the use of the medication as a first-line agent in JCV antibody-negative patients, and in patients with an aggressive early disease course is becoming more widely accepted. The use of natalizumab as a first- and second-line agent will likely increase in patients with negative JCV serology as more safety data become available in this group of patients. The use of natalizumab

in JCV-positive patients will likely depend on the availability of safe and efficacious alternative treatment options. Monitoring of JCV serology for those patients with an initial negative serology should be conducted yearly given the possibility of seroconversion during treatment.

Fingolimod

Fingolimod is a sphingosine 1-phosphate (S1P) analog that produces S1P type 1 (S1P₁) receptor internalization and downregulation [Brinkmann, 2007]. The downregulation of S1P₁ receptors on lymphocytes results in an inhibition of S1P mediated egress of these cells from lymph nodes and is thought to be the principal mechanism of action through which fingolimod is effective in MS [Chun and Hartung, 2010]. S1P₁ are not only responsible for lymphocyte egress but are ubiquitously expressed and carry out vital roles in the control of endothelial permeability [Ishii *et al.* 2004]. It is important to note that a variety of S1P receptors with pleiotropic roles in several body systems exist [Hla, 2003] and fingolimod binds not only to S1P₁ but also to receptor types 3, 4, and 5 [Brinkmann *et al.* 2002]. The widespread distribution of S1P receptors and the limited experience with S1P receptor modulation in the past makes the safety of fingolimod somewhat difficult to predict, and the widespread use of the medication might reveal unknown and unexpected adverse effects [Ontaneda and Cohen, 2011].

Table 2. Selected adverse effects of disease-modifying treatments in multiple sclerosis.

Therapy/adverse events	Treatment arms (%)	Placebo/active comparator arm (%)
Natalizumab [Bloomgren <i>et al.</i> 2012; Polman <i>et al.</i> 2006; Rudick <i>et al.</i> 2006]		
PML	JCV negative: <0.01% (estimated) JCV positive, <24 months, no IS: 0.06% JCV positive, >24 months, with IS: 1.1%	No reported cases
Fingolimod [Cohen <i>et al.</i> 2010; Cohen and Chun, 2011; Kappos <i>et al.</i> 2006]		
Headache	25%	23%
LFT elevation	14%	5%
Back pain	12%	7%
Herpes infections	9%	8%
Bradycardia	4%	1%
Macular edema	0.4%	0.1%
Teriflunomide [O'Connor <i>et al.</i> 2011]		
Diarrhea	16.3%	8.9%
LFT elevation	13.1%	6.7%
Hair thinning	11.7%	3.3%
Nausea	11.3%	7.2%
Laquinimod [Comi <i>et al.</i> 2012]		
LFT elevation	34.7%	19.2%
Back pain	16.4%	9.0%
Cough	7.5%	4.5%
Abdominal pain	5.8%	2.9%
Appendicitis	0.9%	0.2%
Dimethylfumarate (BG-12) [Gold <i>et al.</i> 2011]		
Flushing	35%	5%
Diarrhea	17%	13%
Nausea	13%	9%
Upper abdominal pain	10%	5%
Alemtuzumab [Cossburn <i>et al.</i> 2011; Selmaj <i>et al.</i> 2012]		
Autoimmune thyroid disease	18%	6.4% (IFN β 1-a)
Immune thrombocytopenic purpura	0.8%	1.6% (IFN β 1-a, by platelet count)
Goodpasture's syndrome	3 cases reported to date, none from phase III MS trials	0% (IFN β 1-a)
IFN β 1-a, interferon β 1-a; IS, immune suppression; JCV, John Cunningham virus; LFT, liver function tests; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.		

The efficacy of fingolimod in MS has been established by two large phase III trials, which studied both 0.5 and 1.25 mg daily doses of fingolimod. Fingolimod was tested against placebo in the FTY721 Research Evaluating Effects of Daily Oral therapy in MS (FREEDOMS) trial [Kappos *et al.* 2010]. In that study fingolimod showed a relative reduction between 54% and 60% in ARR

and the proportion of relapse-free patients was higher than placebo at 2 years (74.7–70.4%). A 3-month sustained EDSS progression was also reduced by fingolimod when compared with placebo (hazard ratio 0.70). Fingolimod also significantly reduced brain atrophy when compared with placebo (32–36% reduction). The Trial Assessing Injectable Interferon *versus* FTY720

Oral in Relapsing Remitting Multiple Sclerosis (TRANSFORMS) [Cohen *et al.* 2010] was a 1 year active comparator trial. Fingolimod reduced ARR between 38% and 52% and was also effective on similar MRI outcome measures.

Several safety concerns have been identified with the use of fingolimod in phase II and phase III trials [Collins *et al.* 2010]. A reduction in resting heart rate between 8 and 11 beats/minute (bpm) was observed within the first 6 hours of first treatment along with slowing of AV conduction in phase III trials [DiMarco *et al.* 2010]. A small increase in blood pressure over time was also observed in patients receiving fingolimod, but was modest. Macular edema, likely related to a vascular leak phenomenon also occurred in 0.3–1% of patients in phase III trials and risk of macular edema has been associated with diabetes and advanced age [Hoitsma *et al.* 2011; Salvadori *et al.* 2006; Tedesco-Silva *et al.* 2007]. Elevation of liver function enzymes was reported in fingolimod arms as well, but these were mostly transient and did not result in liver failure. Infections occurred more frequently in patients treated with fingolimod and were typically respiratory and self-limited; however, cases of disseminated herpes zoster and herpes simplex infection resulted in two fatalities in the 1.25 mg arm of TRANSFORMS [Cohen *et al.* 2010]. Fingolimod was approved by the United States Federal Drug Administration (FDA) in October of 2010; several screening tests were recommended including baseline liver function tests, complete blood counts, varicella zoster serology, 12 lead EKG and screening OCT for macular edema. A revision of the initial guidelines for first dose monitoring was made in 2012 [Food and Drug Administration, 2012] and includes a 6-hour observation period with hourly blood pressure and pulse checks and EKG, prior to starting, and at completion of first dose observation. Prolonged cardiac monitoring is recommended if the 6-hour post-dose pulse is below 45, the heart rate post-dose is at its lowest post-dose value, or post-dose EKG shows new onset second-degree or higher AV block. In addition, patients with cardiac risk factors (ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, history of symptomatic bradycardia, history of recurrent syncope, severe untreated sleep apnea, AV block, sino-atrial heart block), patients with prolonged QT interval (or using medications that prolong QT interval), or patients receiving medications

that slow AV conduction are recommended to be monitored for 24 hours post-first dose. It is estimated fingolimod is currently being used by approximately 40,000 individuals with MS and 11 reported deaths in patients treated with fingolimod have been reported [European Medicines Agency, 2012]. It is still not clear how or if the deaths are related to fingolimod. A report of a patient who developed asystole with concomitant use of fingolimod and risperidone raises safety concerns in patients using fingolimod and other pro-arrhythmic medications [Espinosa and Berger, 2011]. The safe use of fingolimod will require patients to have monitoring of liver function enzymes, complete blood counts, and OCT at 3 months and every 6 months thereafter.

Perspective view

Fingolimod was the first orally available approved medication for MS and as such has been welcomed by many patients as an alternative to frequent injection or infused medications. The medication also appears to be more effective than first-line medications showing a relative relapse reduction of approximately 50%. However, the lack of clinical experimentation with S1P modulation and the limited long-term safety data with fingolimod has prevented widespread use of the medication. Owing to these issues fingolimod has been used mostly as a second-line agent and recent reports of possible fingolimod-associated fatalities are likely to make some clinicians wary of using this medication as a first-line agent in the near future. The need for complicated pretreatment screening and first-dose observation is a further deterrent to the use of fingolimod. The safety/efficacy of newer oral agents for MS will also determine the placement of this medication in the treatment algorithm.

Emerging therapies

Several new therapeutic compounds have completed or are in the process of completing phase III trials. Phase III trials have been completed for teriflunomide, laquinimod, dimethylfumarate (BG-12) and alemtuzumab, and the risk–benefit profile of these medications will be reviewed.

Teriflunomide

Teriflunomide (2-hydroxyethylidene-cyanoacetic acid-4-trifluoromethyl anilide) is an active metabolite of leflunomide and is a reversible noncompetitive inhibitor of the mitochondrial enzyme

dihydroorotate dehydrogenase [Greene *et al.* 1995]. This enzyme is crucial in the *de novo* synthesis of pyrimidine nucleotides for DNA replication and mediates a cytostatic effect on proliferating B and T cells. Teriflunomide also reduces T-cell activation as well as cytokine production by inhibiting tyrosine-kinases [Xu *et al.* 1997], and interferes with the interaction between T cells and antigen-presenting cells [Zeyda *et al.* 2005].

The efficacy and safety of teriflunomide has been evaluated in phase II [O'Connor *et al.* 2006] and phase III trials [O'Connor *et al.* 2011]. In both trials teriflunomide at doses of 7 and 14 mg once daily was tested against placebo. The Teriflunomide Multiple Sclerosis Oral (TEMISO) phase III trial showed a reduction of the ARR by 31% for both doses and the higher dose reduced EDSS progression by 29.8% compared with placebo. The percentage of patients who remained relapse-free at the completion of the study (108 weeks) was significantly different between teriflunomide (53.7% for 7 mg, 56.5% for 14 mg) and placebo (45.6%). Teriflunomide was effective in several measures of disease activity as well as on MRI measures, including total lesion volume, gadolinium-enhanced lesions and unique active lesions. Teriflunomide reduced brain parenchymal fraction by 25% when compared with placebo but this change was not statistically significant. A safety extension for this trial is ongoing. In addition to the TEMISO trial, additional phase III trials include: a Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon B-1a in Patients with Relapsing (TENERE), the Efficacy and Safety of Teriflunomide in Patients with Relapsing Multiple Sclerosis and Treated with Interferon- β (ClinicalTrials.gov, 2012a), and an Efficacy Study of Teriflunomide in Patients with Relapsing Multiple Sclerosis (TOWER). Top-line results from TENERE failed to show nonsuperiority for teriflunomide when compared with subcutaneous IFN β -1a [Genzyme Corporation, 2011], while top-line results from TOWER showed that teriflunomide decreased ARR by 36.3% with a 31.5% reduction in 12-week EDSS sustained disability [Genzyme Corporation, 2012]. A phase III Study of Teriflunomide *versus* Placebo in Patients with First Clinical Symptom of Multiple Sclerosis (ClinicalTrials.gov, 2012b) is also underway.

Teriflunomide has a good safety profile and in clinical trials adverse events were mild or moderate in severity and it has been shown to be well

tolerated over 8.5 years of follow up [Confavreux *et al.* 2012]. The most frequent adverse events include: gastrointestinal symptoms (diarrhea and nausea), decreased hair density, mild upper respiratory tract infections, nonclinically relevant liver function enzyme increases, sensory disturbances and headaches. Most of these adverse events were transitory and rarely led to treatment discontinuation. No serious opportunistic infection or PML has been reported. Transient rashes were reported in 22 % in the 7 mg group and in 16.7% in the 14 mg group. Fatigue was frequently reported (30%) in both treatment arms. Leflunomide is a FDA category X medication and it is likely teriflunomide may have similar risks on fetal/embryonic health; a wash out with cholestyramine however can rapidly eliminate teriflunomide [O'Connor *et al.* 2011].

Perspective view. Teriflunomide is one of the five oral agents tested in phase III clinical trials and was submitted for licensing to the FDA in October 2011. The magnitude of efficacy with teriflunomide is similar to the approved injectable disease-modifying therapies and its main advantage is its attractive oral route of administration along with a good safety profile. In addition, the favorable safety experience of the prodrug leflunomide, approved since 1998 for the treatment of rheumatoid arthritis, can be extrapolated to teriflunomide. Potential risks in women of child-bearing age will have to be weighed carefully given the potential for fetal/embryonic adverse effects. The potential for an increase in PML risk for patients who switch from teriflunomide to natalizumab should also be considered when using this medication. The addition of a safe orally available agent may have a role in the treatment algorithm in the future, but this will have to be weighed against medications of superior efficacy and comparable safety. Ongoing trials comparing teriflunomide with other disease-modifying treatments and combination therapy as an add-on are underway.

Laquinimod

Laquinimod (N-ethyl-N-phenyl-5-chloro-1,2-dihydroxy-1-methyl-2-oxo-quinoline-3-carboxamide) is a novel oral agent structurally similar to linomide (roquinimex). Linomide was evaluated in phase III trials of MS but development was halted due to serious cardiovascular events [Tan *et al.* 2000]. The immunomodulatory mechanisms of laquinimod are not completely

understood and a well-defined target has not been identified. Laquinimod induces Th1 to Th2/3 shift, suppresses Th17 responses, downregulates secretion of pro-inflammatory cytokines, enhances production of anti-inflammatory cytokines and decreases lymphocyte migration into the CNS [Jonsson *et al.* 2004; Yang *et al.* 2004]. In addition, an increase in serum brain-derived neurotrophic factor levels was detected in laquinimod-treated MS patients; this finding has suggested a neuroprotective effect [Thone *et al.* 2012].

The safety, tolerability and efficacy of laquinimod have been assessed in two phase II and two phase III clinical trials. In the first phase II trial a dose of 0.3 mg of laquinimod was effective on MRI outcome measures, including number of gadolinium-enhanced lesions and new T2 lesions [Polman *et al.* 2005]. In the second phase II trial only the 0.6 mg dose of laquinimod showed evidence of efficacy, with a reduction of 40% in active lesions and a 51% reduction in T1 hypointense lesions [Comi *et al.* 2008].

The Assessment of Oral Laquinimod in Preventing the Progression in Multiple Sclerosis trial (ALLEGRO) studied the efficacy of oral laquinimod 0.6 mg against placebo [Comi *et al.* 2012]. Laquinimod treatment reduced the ARR by 23% with a 36% reduction in the EDSS progression. The proportion of patients who were relapse-free during the study also favored laquinimod (63% *versus* 52%). Brain atrophy was reduced in the laquinimod arm by 33% when compared with placebo. The mean cumulative number of gadolinium-enhanced lesions and new or enlarging T2 lesions was also lower in patients receiving laquinimod. The Benefit–Risk Assessment of Avonex and Laquinimod (BRAVO) trial was a parallel group study that compared laquinimod 0.6 mg with placebo and with intramuscular IFN β -1a. The BRAVO study did not achieve its primary endpoint of reducing the annualized relapse rate, but led to significant reduction in EDSS progression (34%) and brain volume loss (27%) [Teva Pharmaceutical Industries, 2011]. Pooled results from both trials were recently presented at the American Academy of Neurology, and showed that laquinimod had beneficial effects on ARR (21.4% reduction), disability progression (34.2% reduction), and brain volume (30% reduction) when compared with placebo [Vollmer *et al.* 2012].

Laquinimod has good tolerability and the safety concerns previously reported with linomide have

not emerged in clinical trials. The most frequent adverse events reported with laquinimod were: back pain, abdominal pain, cough, and reversible elevations in alanine transaminase (ALT) levels [Comi *et al.* 2012]. These adverse events rarely led to discontinuation of laquinimod. In the laquinimod arms there were five cases of appendicitis and one case of Budd–Chiari syndrome in a genetically predisposed individual [Comi *et al.* 2008, 2012]. A higher incidence of cancer or serious infections was not seen in the laquinimod arms.

Perspective view. The FDA considered that data from laquinimod phase III trials was not sufficient for approval and submission to that agency was voluntarily withheld. Submission to the European Medicines Agency (EMA) is planned for the second half of 2012. The efficacy of laquinimod is modest, but it has a favorable tolerability and safety profile. In addition, laquinimod may have a neuroprotective effect from what is known about its effects in animal models and the positive effect in brain atrophy and disability progression in clinical trials.

BG-12

BG-12 (dimethylfumarate) is a fumaric acid ester which has immunomodulatory properties and neuroprotective effects through its action on nuclear factor-E2-related factor 2 [Linker *et al.* 2011]. Dimethylfumarate has been used as part of a compound named FumadermTM in German-speaking countries to treat psoriasis for several years and has a favorable safety profile [Hoefnagel *et al.* 2003]. BG-12 has been examined in two phase III clinical trials. The DEFINE trial studied two regimens of BG-12 (240 mg BID, 240 mg TID) against placebo [Gold *et al.* 2011] and showed a reduction of the ARR by 53–48% when compared with placebo, with a decrease in confirmed disability progression by 34–38%. A second phase III trial compared BG-12 against placebo and a registration arm treated with GA (CONFIRM Trial). Significant effects were observed for both a reduction in ARR (44–51%) and confirmed EDSS progression (21–24%) in BG-12 arms [Fox *et al.* 2012]. No new safety concerns were reported, however flushing and gastrointestinal events were the most common adverse effects. More efficacy and safety data will be available once the results from phase III trials are published. A new drug application was submitted to the FDA in February of 2012. It is still

unclear what dose/scheduling will be used for the medication as it was studied in both two and three times daily dosing [Biogen Idec, 2012].

Perspective view. BG-12 is an orally administered therapy showing an advantage in a phase III clinical trials over a first-line MS drug and has shown a favorable safety profile to date. The medication is currently under FDA review and, if approved, is likely to be used both as a first- and second-line agent in the future; however, a review of the complete results from phase III trials is still needed.

Alemtuzumab. Alemtuzumab (Campath 1-H) is a humanized monoclonal antibody which targets the CD52 antigen expressed on the surface of T and B lymphocytes, dendritic cells, natural killer cells and most monocytes [Coles *et al.* 2006]. Alemtuzumab lyses target cells through antibody-dependent cellular and complement-dependent cytotoxicity. It induces a rapid and sustained depletion of B and T lymphocytes [Lutterotti and Martin, 2008].

Alemtuzumab was first studied in several open-label studies where it showed robust effects on new gadolinium-enhanced lesions, relapse rate, and even improvement in the EDSS [Fox *et al.* 2012b; Hirst *et al.* 2008; Jones and Coles, 2008]. CAMMS223 was the first phase II clinical trial that evaluated the efficacy and safety of alemtuzumab against subcutaneous IFN β -1a in previously untreated patients [Coles *et al.* 2008]. The initial study was intended to last 36 months, but in September 2005 alemtuzumab therapy was suspended after three patients developed immune thrombocytopenia, one of whom died with a fatal brain hemorrhage. Alemtuzumab reduced the ARR by 74% and reduced sustained disability by 71% with an improvement in mean disability scores. T2 lesion volume was decreased and an increase in brain volume was observed. The improvement in disability was sustained after 5 years [Coles *et al.* 2012b]. The Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis (CARE-MS) I and II studies are phase III clinical trials which have been completed and reported but not yet published. CARE-MS I showed a reduction in ARR of 55% when compared with subcutaneous IFN β -1a in treatment-naïve patients, but did not meet significance for disability progression [Coles *et al.* 2012a]. CARE-MS II showed a significant reduction relapses (49%) and disability progression (42%)

when compared with subcutaneous IFN β -1a in patients who relapsed on prior treatment [Cohen *et al.* 2012]. CARE-MS I showed that alemtuzumab also reduced measures of brain atrophy (−0.9% for alemtuzumab, −1.5% for IFN β -1a) and T1 hole volume (−21.6% for alemtuzumab, −0.1% for IFN β -1a) [Arnold *et al.* 2012].

The most notable adverse event in the alemtuzumab groups was the occurrence of novel autoimmunity. Approximately 25% of patients treated with alemtuzumab will develop thyroid autoimmunity over time. Idiopathic thrombocytopenic purpura was also seen in both phase II and III trials of alemtuzumab and occurred in approximately 1% of patients [Selmaj *et al.* 2012]. Three cases of antglomerular basement membrane disease (Goodpasture's syndrome) have been identified in patients treated with alemtuzumab. Infections occurred more frequently in alemtuzumab arms, but were mostly mild or moderate with no cases of life-threatening or fatal infectious events. A large proportion of patients (approximately 90%) from alemtuzumab arms experienced infusion-associated reactions.

Perspective view. The efficacy on relapse rate and sustained disability seen in clinical trials with alemtuzumab makes it an attractive therapeutic option especially for aggressive forms of relapsing–remitting MS (RRMS). It has been suggested that alemtuzumab may have neuroprotective effects [Jones *et al.* 2010] due to an improvement in EDSS scores as well as favorable atrophy and T1 black hole metrics. The major limitation of alemtuzumab is the development of autoimmunity; this adverse event is likely related to abnormal reconstitution of lymphocytes. However, since not all lymphopenic patients developed autoimmunity, it has been proposed that other external and internal cofactors are also required [Cossburn *et al.* 2011]. In the future, biomarkers might be able to detect, prior to treatment with alemtuzumab, which patients are at a higher risk to develop autoimmunity [Klotz *et al.* 2012]. Surveillance testing for thyroid function, platelet count and renal function will likely be needed if the medication is approved. Alemtuzumab was submitted to the FDA in June of 2012. Owing to the occurrence of autoimmunity it is likely alemtuzumab will be used as a second-line agent. The long-term safety concerns and need of ongoing surveillance several years after its use will be a further deterrent of alemtuzumab in clinical practice.

Conclusion

Significant advances have been made in the development of therapies for MS in the last two decades. Increasingly effective therapies, which target the immune system, may carry concomitant risks of opportunistic infections and malignancies. Additional adverse effects that are not directly mediated by immunosuppressive effects have also been noted and are of particular concern in medications that target ubiquitous physiologic processes. The number of available treatments will expand significantly in the future and treatment selection will have to take in to consideration the risk–benefit profile of these new medications. Tailored approaches at the individual patient level will have to incorporate not only considerations of efficacy but also toxicity and safety. This will certainly be complicated when considering new therapies where potential unknown risks will have to be incorporated into the risk–benefit profile. The introduction of new therapies, when combined with well-informed and risk-adjusted choices, will result in net benefits for patients and will promote the goal of disease-free status.

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Conflict of interest statement

Dr Ontaneda has received speaking fees in the last year from Biogen Idec. Dr Di Capua has no disclosures.

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