

Novel Agents and Emerging Treatment Strategies in Multiple Sclerosis

Jodie M. Burton and Fiona Costello

Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada.
Corresponding author email: jodie.burton@albertahealthservices.ca

Abstract: In the past decade, the treatment of multiple sclerosis has undergone a significant paradigm shift. Weekly to daily self-injections of moderate benefit are making way for more effective therapies with improved relapse and disability impact with more appealing routes and frequencies of administration. Some such therapies, like natalizumab, belong to the monoclonal antibody family, while others offer novel immunomodulatory mechanisms and the much sought after oral route of administration. While novel and more powerful immune mechanisms present new issues with respect to adverse effects, these new therapies offer significant advances in the quality of patient care.

Keywords: multiple sclerosis, therapeutics, oral, monoclonal antibody, effectiveness, safety

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Introduction

Multiple Sclerosis (MS), a presumed autoimmune mediated inflammatory and degenerative disorder of the central nervous system (CNS), is the most common neurological disease of young adults in North America.¹⁻³ At present, roughly 85% of patients with MS present with the relapsing-remitting form of the disease, characterized by neurological dysfunction lasting days to weeks that at a minimum plateaus, and ideally remits.¹ A small proportion of patients who develop progressive disease may also suffer from relapses.¹ Unfortunately, no therapy has yet to demonstrate persistent and reversible impact on the progressive deficits attributable to neurodegeneration, but for almost two decades, patients with relapsing disease have had the option of choosing a first generation parenteral disease modifying therapy (DMT). These agents include the interferon beta (Betaseron[®], Extavia[®], Avonex[®] and Rebif[®]) and glatiramer acetate (Copaxone[®]) drug families. In appropriate patients, these agents reduce relapses (~30%), and the development of new T2 lesions on MRI (35%–80%).⁴⁻⁷ Side effects including skin reactions, flu-like symptoms and mild laboratory perturbations are common, but mild. While the clinical benefits of DMTs are considerable, more efficacious therapies with improved tolerability and ease of administration are needed. In 2004, the first new DMT in almost a decade, natalizumab (Tysabri[®]), was approved in North America. Natalizumab is a monoclonal antibody (mAb) that acts as an alpha-4 integrin antagonist and is given once monthly by intravenous infusion.⁸ Natalizumab has shown itself to be an extremely potent MS agent, with a 70+% reduction in relapses and a reduction in disability.⁸ Unfortunately, such benefits come with ~1/1000 risk of the often fatal progressive multifocal leukoencephalopathy (PML).⁸

Over the past decade, there has been a paradigm shift in MS therapeutics, with a renewed focus on both effectiveness and ease of administration. In this short interval, a host of new agents, including mAbs, novel parenteral, oral and “repurposed” medications have been studied. This review focuses on those agents with compelling phase II and if available, phase III trial data (see Table 1).

Table 1. New and emerging therapies in relapsing multiple sclerosis.

Medication	Mechanism of action	Route/dosing schedule	Trial phase	Results to date	Adverse events
Alemtuzumab ¹⁵⁻¹⁷	Anti-CD52	IV, OD × 5d qannum	III	– ARR 0.10 (ALEM) vs. 0.36 (Rebif [®]) at 36 mo; at 60 mo 72% relapse-free, 87% SAD-free	ITP, thyroid disease
Daclizumab ²⁵	Anti-CD25	SC, q2weeks	III	– CELs ↓ 72%/25% in HD/ LD DAC+IFN vs IFN – ARR 0.27 (HD DAC + IFN) vs 0.29 (LD DAC + IFN) vs 0.41 (IFN)	Dermatitis/rash, chest pain, headache
Rituximab ³⁰	Anti-CD20	IV, q2weeks × 2	II	– CELs absent in 80.3% on RTX vs 51.4% in placebo – ARR 0.37/0.40 (RTX) vs 0.84/0.80 (placebo) at 24/48 weeks	Infusion reactions
Ocrelizumab ^{37,39,40}	Anti-CD20	IV, q2weeks × 2	II	– CELs ↓ 96%/ 89% (OCRE HD/LD) vs placebo – ARR ↓ 80%/73% (OCRE HD/LD) vs placebo	URTI, UTI, infusion reactions, thrombotic microangiopathy



Ofatumumab ⁴⁵ Fingolimod/ Gilenya ^{®61,62}	Anti-CD20 S1P receptor agonist	IV, q2weeks × 2 Oral, OD	II III/IV	<ul style="list-style-type: none"> – CELs ↓ 99.8% vs placebo – CELs absent in 89.7%/89.8% (FTY720 HD/LD) vs 65.1% (placebo)⁶¹ – ARR 0.16/0.18 (FTY720 HD/LD) vs 0.40 (placebo), cumulative probability of SAD 16.6%/17.7% (FTY720 HD/LD) vs 24.1% (placebo)⁶¹ – CELs absent in 91.2%/90.1% (FTY720 HD/LD) vs 80.8% (placebo)⁶² – ARR (FTY720 HD/LD) 0.20/0.16 vs 0.33 (placebo)⁶² 	Infection, infusion reactions bradycardia, herpes infection, macular edema,? skin malignancy
Abatacept/ CTLA-4lg Fingolimod/ SB683699 ⁶⁴	Anti-CD80/86 α4-integrin antagonist	IV, q4weeks Oral, BID	II II	<ul style="list-style-type: none"> Not available – CELs ↓ 49% between Fingolimod and placebo groups – ARR NS – CELs ↓ 63% vs placebo 	Lymphadenopathy, URTI, UTI, headache N/V, rash, UTI, URTI
Minocycline ⁶⁷ Cladribine ⁷⁴	Reduced lymphocyte access to CNS, neuroprotective Purine nucleoside analog	Oral, BID Oral schedule	III III	<ul style="list-style-type: none"> – CELs ↓ 85–88% in both Cladribine groups vs placebo – ARR ↓ 54–58% in both Cladribine groups vs placebo 	Headache, N/V, rash, rarely serum sickness, hypersensitivity Lymphopenia, infections (viral reactivation), possible malignancy
Teriflunomide ^{79, 81}	Pyrimidine synthesis inhibitor (DHODH inhibition)	Oral, OD	III	<ul style="list-style-type: none"> – CELs absent in 38.6%/39.3% (teriflunomide HD/LD) vs 26.2% (placebo) – ARR ↓ 31% (teriflunomide HD and LD) vs placebo, SAD ↓ 29.8% 	URT, alopecia, GI distress
Laquinimod ⁹⁴ Fumarate/ BG0012 ⁹⁸	Multiple anti- inflammatory actions Multiple anti- inflammatory actions	Oral, OD Oral, TID	III III	<ul style="list-style-type: none"> – CELs ↓ 37% vs placebo – ARR ↓ 23% vs placebo – CELs ↓ 69% vs placebo – ARR ↓ 32% vs placebo 	Budd Chiari syndrome, LFT increases GI distress, flushing

Abbreviations: IV, intravenous; SC, subcutaneous; S1P, sphingosine-1-phosphate; DHODH, dihydro-orotate dehydrogenase; OD, once daily; BID, twice daily; TID, three times daily; ARR, annualized relapse rate; SAD, sustained accumulation of disability; CEL, contrast enhancing lesions; NS, not significant; ITP, immune thrombocytopenia purpura; HD, high-dose; LD, low-dose; UTI, urinary tract infection; URTI, upper respiratory tract infection; N/V, nausea and vomiting; GI, gastrointestinal; LFT, liver function tests.



Direct Interaction with T and B Lymphocytes

Alemtuzamab

Mechanism of action

Alemtuzumab (ALEM), is a humanized IgG1 κ mAb targeting CD52, which is widely expressed on T and B lymphocytes, natural killer (NK) cells, dendritic cells, monocytes and macrophages, but not on neutrophils.^{9,10} This intravenous (iv) agent is currently approved for the treatment of chronic lymphocytic leukemia. ALEM rapidly depletes cells bearing CD52, the cells mediating antibody dependent cell cytotoxicity with a consequent depletion of CD4+ and CD8+ lymphocytes, and prolonged overshooting regeneration of CD19+ B-cells.^{11,12} The immune milieu following this response may contribute to long-term efficacy, but may also contribute to the antibody mediated immune complications seen with ALEM.⁹

Early phase research

Between 1991 and 2002, Coles et al treated over 58 patients with secondary progressive MS (SPMS) or relapsing-remitting MS (RRMS) who had failed conventional treatment.¹³ Initially, patients received ALEM 20 mg/d for five consecutive days. A proportion of SPMS patients received re-treatment of 60 mg/d for three days that eventually became standard. In this uncontrolled setting, patients with active relapsing disease responded clinically, but exclusively progressive patients derived no benefit. A small proportion of patients experienced moderate to severe infections (herpes zoster, pyogenic granuloma, spirochetal gingivitis and measles).

Hirst et al reported on 39 patients with EDSS values up to 8.5 treated with ALEM in three different MS centres from 2002–2007.¹⁴ Several treatment regimens were employed (30 mg, 24 mg, 20 mg or 12 mg daily over five days). Annualized relapse rate (ARR) in year one was reduced by 87%. Those with unstable Expanded Disability Status Scale (EDSS) scores were more likely to stabilize while those with stable disability scores advanced over the two years following treatment, although by an insignificant degree. As in Coles et al, ALEM impacted active inflammatory disease, but not fixed disability. Mild to moderate infections, infusion reactions, autoimmune skin changes and positive ANA titres were reported.

Platelet abnormalities occurred, but were mild and asymptomatic. No clinical thyroid disease occurred, although two patients developed anti-thyroperoxidase antibodies.

Later phase research

The most compelling data comes from the CAMMS223 trial; a phase II randomized double-blind controlled trial of ALEM versus Rebif[®].¹⁵ In this trial, 334 RRMS patients with active and untreated disease were randomized in a 1:1:1 ratio to ALEM 12 mg or 24 mg iv daily of ALEM for five days at baseline and three consecutive days at month 12 and 24 or Rebif[®] three times weekly throughout the trial. Primary outcome measures included time to sustained accumulation of disability (SAD, confirmed for a duration \geq six months) and ARR. In 2005, the trial was suspended after three reported cases, one fatal, of immune thrombocytopenia purpura (ITP). At that time, 99% of eligible patients had received a second ALEM cycle and 25% had received a third cycle. Over the next year, three additional cases of ITP were reported in ALEM patients at both doses. Only 59% of Rebif[®] users completed the three year trial compared to 83% of ALEM users. As no significant differences in efficacy outcomes between the two ALEM dose groups occurred, the results were pooled. Compared to Rebif[®] patients, ALEM patients had a 71% reduced risk of SAD, ARR reduction in of 74% (0.10 versus 0.36 in Rebif[®] patients) (Fig. 1) ALEM patients also had reductions in brain atrophy and T2 lesion load on MRI versus patients on Rebif[®]. While infusion reactions were rare, mild to moderate infections were more common. One case of recurrent oral herpes simplex type I and tuberculosis reactivation occurred in ALEM patients.

At the 2010 European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting, it was reported that almost 60% of CAMMS223 ALEM patients were evaluable from 0–60 months with an ARR of 0.11 and SAD in 13%.¹⁶ Roughly 35% of Rebif[®] users were evaluable 0–60 months with an ARR of 0.35 and SAD in 38%. At the 2011 American Academy of Neurology (AAN) meeting, data will be presented showing that 87% of ALEM-treated patients were SAD-free and 72% were relapse-free compared to 62% and 41% of Rebif[®]

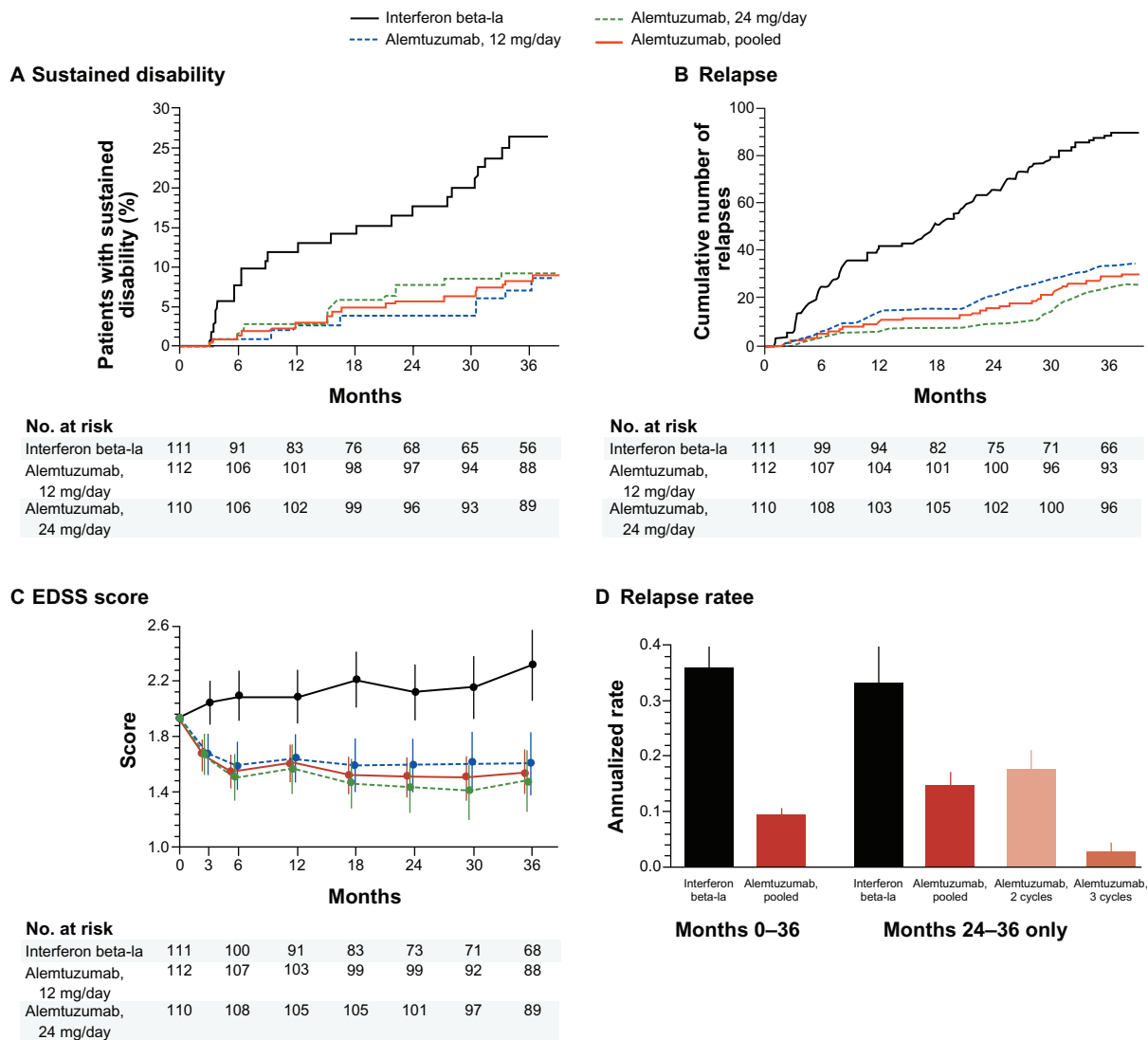


Figure 1. Efficacy outcome measures regarding disability and relapse at 36 months. Panel A shows Kaplan-Meier curves for patients who reached the criteria for sustained accumulation of disability. Panel B shows the cumulative number of relapses. Panel C shows the estimated mean score on the Expanded Disability Status Scale (EDSS, which ranges from 0 to 10, with higher scores indicating greater disability) on the basis of repeated-measures analysis of covariance. The vertical lines represent 95% confidence intervals. Panel D shows the annualized relapse rate from baseline to 36 months for 222 patients who received alemtuzumab and from month 24 to month 36 for 97 patients who received alemtuzumab for two cycles and 45 patients who received alemtuzumab for three cycles. Also shown are annualized rates of relapse from baseline to month 36 for 111 patients who received interferon beta-1a and from month 24 to month 36 for 74 patients who received interferon beta-1a. The annualized relapse rates were estimated with the use of Poisson regression analysis separately for patients who received a third cycle of therapy and for those who did not receive a third cycle. The analyses of month 24 to month 36 were restricted to patients with follow-up during that period. The vertical lines represent standard errors (reproduced with permission from the New England Journal of Medicine).

patients respectively at 60 months. Brain atrophy measures also improved significantly with ALEM.¹⁷

Ongoing and future research

The CARE-MS I trial, a phase III randomized double-blind trial of ALEM (12 mg/d for two annual cycles) versus Rebif® over two years in treatment-naïve patients with RRMS, has completed enrolment (clinicaltrials.gov NCT00530348). The CARE-MS II trial, almost identical to the CARE-MS I trial

with one additional arm of 24 mg/d ALEM, has also completed recruitment (clinicaltrials.gov NCT00548405). The endpoints in both trials are similar to those in the CAMMS223 trial. ALEM approval for MS in the U.S. and E.U. will likely occur in 2012 with fast track FDA status.

Adverse events

As with most monoclonal antibody medications, in fusion reactions and mild to moderate infections have been



reported, as has the reactivation of latent infections.^{13–15} The most concerning adverse events associated with ALEM are the immune-mediated disorders of ITP and thyroid dysfunction.¹⁵ Platelet abnormalities were seen in Hirst et al, but were transient and asymptomatic.¹⁴ Six cases of ITP, one of which was fatal, occurred in ALEM group with one case in the Rebif® group. Forty-nine cases of thyroid adverse events occurred in the ALEM group with thyroid auto-antibodies found in 96% of these patients up to 30 months after last dose of ALEM. Hyperthyroidism was most common (32 cases; three severe).¹⁵ Four patients required thyroid ablation and 25 patients did not recover thyroid function.¹⁵

Pregnancy information

ALEM has been assigned to FDA pregnancy category C. There are no animal studies or any controlled data in human pregnancy. Since human IgG crosses the placenta, ALEM might as well, potentially inducing fetal lymphocyte depletion. (http://www.accessdata.fda.gov/drugsatfda_docs/label/biologics/103948-5036_campath_lbl.pdf).

Daclizumab

Mechanism of action

Daclizumab (DAC), a subcutaneous (sc) agent already used to prevent rejection after allogenic transplantation, is a humanized IgG1 monoclonal antibody that blocks CD25, the IL-2 binding epitope of the alpha-chain of the IL-2 receptor.⁹ CD25 is found only at low levels in resting human T-cells but is significantly up-regulated on activated T-cells, allowing for the receipt of a high-affinity IL-2 signal.⁹ IL-2 is thought to play a major role in regulating expansion and contraction of lymphocytes.^{17,18} In MS, DAC leads to the profound expansion of the regulatory CD56 bright NK cells which are present in lymph nodes where they can influence T-cell priming.^{19,20} These cells also migrate into inflammatory lesions and participate in termination of the immune response by killing autologous activated T-cells.^{18–22} A recent study evaluated the effect of DAC on Tregs, believed to be protective in T-cell-mediated disorders, in 15 RRMS patients.²⁰ Despite reduction of Treg function, MRI disease activity was reduced.²⁰

Early phase research

Ali et al reviewed 55 patients in whom DAC was used for treatment failure or intolerance in a mixture

of MS phenotypes across a wide spectrum of activity and disability.²³ Treatment was stopped in 16 patients with 10 treatment failures. Serious adverse events were common including a case of eosinophilic pericarditis, psoriasis and viral meningitis.

Bielekova et al performed an uncontrolled, open-label (pre- versus post-treatment) phase II trial of DAC in 15 MS patients who failed interferon beta (IFN β).²⁴ Patients received DAC (1.0 mg/kg) while maintaining IFN β therapy. Depending on CEL count on subsequent MRIs, IFN β was either discontinued or maintained. Nine patients responded to DAC alone.

In 2010, the CHOICE study group published results of a phase II double-blind randomized placebo-controlled add-on trial in RRMS patients on IFN β for \geq six months with recent disease activity.²⁵ Two hundred and thirty patients remained on their pre-trial IFN β regimens and were randomly assigned (1:1:1) to receive high-dose (HD) DAC (IFN β and HD-DAC group) 2 mg/kg at two-week intervals for 11 doses; low-dose (LD) DAC (IFN β and LD-DAC group) 1 mg/kg every four weeks for six doses alternating with placebo every four weeks for five doses (totaling 11 doses given at 2-week intervals); or subcutaneous placebo every two weeks for 11 doses. Patients were treated for 24 weeks and assessed for 48 weeks. The primary endpoint was the total number of new or enlarged CELs on brain MRI scans done every four weeks between weeks 8 and 24. Ninety-three percent of patients completed 24 weeks of and 84% completed

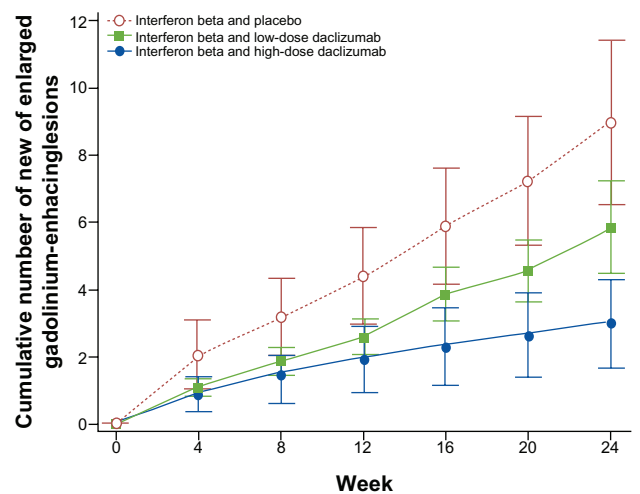


Figure 2. Change in number of new or enlarged gadolinium contrast-enhancing lesions.

Cumulative number of new or enlarged gadolinium contrast-enhancing lesions by visit. Bars=standard error. * $p < 0.05$ versus interferon beta and placebo (reproduced with permission from Lancet Neurology).



follow-up to week 72. The adjusted mean number of new or enlarged CELs was 4.75 in the IFN β and placebo group compared with 1.32 in the IFN β and HD-DAC group (72% difference, $P = 0.004$) and 3.58 in the IFN β and LD-DAC group (25% difference, NS), and the cumulative number of CELs assessed monthly was consistently lower in a dose-dependent way in the DAC-treated groups (Fig. 2). T2 lesions changed in a similar pattern. The adjusted ARR was 0.41 in the IFN β plus placebo group, compared with 0.27 in the IFN β and HD-DAC group and 0.29 in the IFN β and LD-DAC group (a 34% and 30% reduction in ARR between HD and LD-DAC plus IFN β groups versus IFN β plus placebo group respectively). After treatment discontinuation, MRI lesion formation returned to pre-treatment values in all groups.

Ongoing and future research

There are several ongoing trials examining DAC in MS. One such phase II trial is a dose-ranging trial of DAC HYP at monthly doses of 150 mg or 300 mg subcutaneously versus placebo in RRMS for 48 weeks. The primary outcome is ARR (clinicaltrials.gov NCT00390221). The DECIDE trial will evaluate if DAC HYP 150 mg sc once every four weeks is superior in relapse prevention to once weekly Avonex[®] over 96–144 weeks (clinicaltrials.gov NCT01064401).

Adverse events

In early research, cases of eosinophilic pericarditis, psoriasis and viral meningitis were reported but not seen in the larger phase II CHOICE trial.²³ In the CHOICE trial, 20 DAC patients had serious adverse infection events versus four in the IFN β and placebo, but no opportunistic infection or deaths.²⁵ Mild to moderate infections and infestations and headaches were most common in all treatment groups, not specific to DAC groups. Gastrointestinal upset was slightly more common in DAC groups. Cutaneous events such as rash occurred in 36 of 153 patients (24%) in the DAC groups and five of 77 (6%) in the placebo group, but the difference shrank over time.²⁵ Two DAC patients developed cancer—the relationship to DAC was questionable.

Pregnancy information

There is no published data on pregnancy outcomes with use of DAC in MS. DAC has been assigned to FDA pregnancy category C. Animal studies have not

been conducted. There are no controlled data in human pregnancy. Effective contraception before, during and for four months after DAC treatment is recommended. (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113486.pdf>).

Rituximab

Mechanism of action

Rituximab (RTX) is a chimeric IgG1 κ mAb targeting the CD20 antigen, expressed only on mature-B lymphocytes and not on antibody-producing plasma cells.⁹ RTX, an iv agent, is currently used in certain malignancies and illnesses such as systemic lupus erythematosus (SLE). RTX causes B-cell depletion in just two weeks that persists for \geq six months for CD27+ memory B-cells.²⁶ This B-cell depletion also occurs in secondary lymphoid tissue, but more slowly. Since plasma cells lack CD20, RTX only depletes auto-antibodies produced by memory B-cells and thus antibodies for infection and vaccinations are unaffected.⁹ Studies have also documented inhibition of innate immune responses and adaptive T-cell responses associated with the use of RTX in treatment of autoimmune diseases.⁹ The current model of long-term human B-cell memory indicates that “long-lived” plasma cells have a lifespan of only several months and therefore need to be constantly replenished by antigen-independent homeostatic activation of memory B-cells.²⁷ This suggests that long-term depletion of memory B-cells with repeated RTX administration should lead to an eventual decrease in humoral immunity.²⁷ Early repopulation of peripheral B-cells by increased output of pre-B and naïve-B-cells from bone marrow presumably contributes to clinical benefit, but may also be the mechanism by which PML can occur.⁹ PML has been reported in RTX-treated SLE patients, no such cases have occurred in MS patients.²⁸

Early phase research

Bar-Or et al performed a phase I trial of RTX in 26 RRMS patients examining safety and MRI parameters.²⁹ Patients were treated with RTX intravenous infusions twice over two weeks; then retreated at weeks 24 and 26. Adverse events were mild to moderate, none serious. In this uncontrolled safety trial, MRI and clinical parameters appeared improved versus the year prior to the trial.



The “Helping to Evaluate Rituxan in Relapsing-Remitting Multiple Sclerosis” (HERMES) trial group undertook a phase II randomized double-blind placebo-controlled trial of intravenous RTX over a 48-week monitoring period published in 2008.³⁰ Ultimately 104 RRMS patients were enrolled in a 2:1 (RTX: placebo) ratio. The primary outcome was the total number of CELs on MRI brain from scans done at weeks 12, 16, 20 and 24. Secondary outcomes included measures of relapse activity, new T2 and CELs and change in lesion volume. A total of 69 patients received intravenous RTX 1000 mg on days 1 and 15 while 35 received placebo. Despite randomization, the placebo group contained more patients with more CELs at baseline versus the RTX group. Sixty percent of RTX patients completed the 48-week trial versus 84% of placebo patients. The RTX group had a mean of 0.5 CELs versus 5.5 in the placebo group, an effect seen as early as week 12 (Fig. 3).

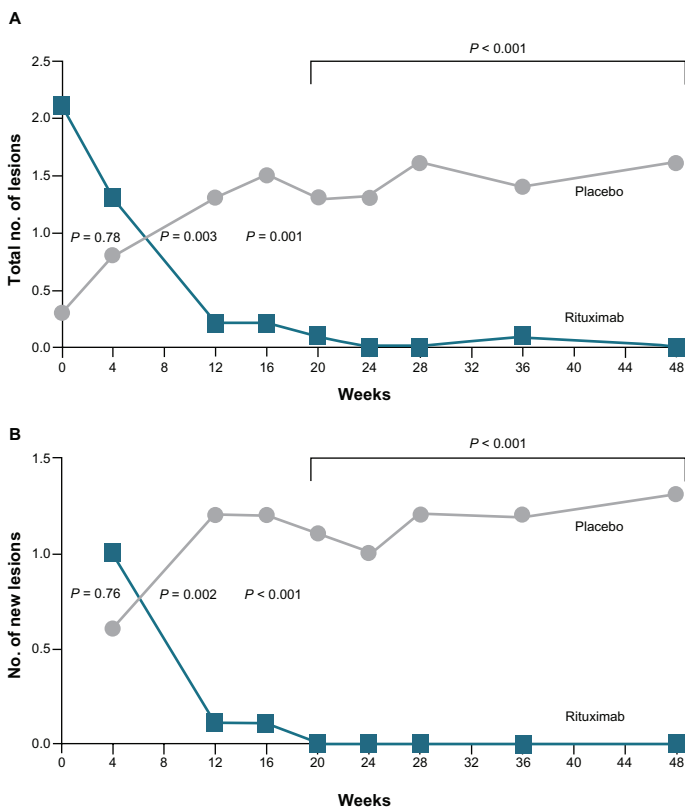


Figure 3. Gadolinium-enhancing lesions in each study group from baseline to week 48.

Panel A shows the mean total number of gadolinium-enhancing lesions by week, and Panel B shows the mean number of new gadolinium-enhancing lesions by week. Missing values were imputed by averaging the available data. The baseline MRI was obtained at week -4 (reproduced with permission from the New England Journal of Medicine).

Although not powered for clinical outcomes, the proportion of patients relapsing was 14.5% in the RTX group versus 34% in the placebo group, with ARR of 0.37 vs. 0.84 at 24 weeks respectively. Interestingly, the difference in ARR was not significant at week 48. As early as two weeks, a near complete depletion of CD19+ peripheral B-lymphocytes was noted in the treatment group, returning to roughly 30% of normal by week 48. Over 78% of RTX patients experienced infusion reactions, most of mild to moderate severity.

Another phase II trial in relapsing MS examined the benefit of add-on RTX therapy to conventional MS disease modifying medication use in RRMS patients in a single center, MRI-only blinded trial.³¹ Thirty subjects on an IFN β or Copaxone[®] received RTX (375 mg/m² iv) once weekly for four weeks. The primary endpoint was the reduction in the sum of CELs on MRI at weeks 12, 16 and 20 versus three MRIs done monthly in the three months prior to enrolment. This trial, compared to the HERMES trial, was smaller, uncontrolled and patients were relatively older and more disabled. While only 26% of the three baseline scans were free of CELs, 74% of post-treatment scans were free of such lesions. Caution should be exercised in interpretation of these results, as CELs on MRI were required for inclusion, and regression to the mean could in part explain MRI results. While clinical parameters appeared to improve post-treatment, the trial was not designed nor powered to answer such questions.

Finally, the OLYMPUS trial, a 96-week, double-blind, placebo-controlled phase II/III trial, investigating the efficacy and safety of RTX therapy in a total of 439 patients with PPMS did not result in a reduction in the proportion of those with disability progression during the trial period.³² As would be expected, those patients with superimposed inflammatory disease in the form of relapses and CELs responded with respect to these outcomes.

Ongoing and future research

Despite the promising results outlined below, RTX is presently not being further developed or trialed for MS therapy for non-medical reasons, including patent-related matters.



Adverse events

Infusion reactions were common with RTX but typically mild to moderate, including headache, back pain, depression, pruritus and rash.^{30,31} Rare grade four adverse events of coronary artery syndrome and thyroid malignancy were reported, but their relationship to RTX remains uncertain. Infection was as common in placebo patients as in RTX patients, typically of the upper respiratory (URTI) and urinary tract (UTI). No cases of PML have ever been reported in MS patients receiving RTX.

Pregnancy information

There are no reported cases of pregnancy in patients receiving RTX for multiple sclerosis. RTX is assigned to FDA pregnancy category C <http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm123013.htm>.

According to the RTX global drug safety database, 231 pregnancies associated with maternal exposure to RTX use have been identified, typically in the context of autoimmune disease or lymphoma.³³ Most cases were confounded by concomitant use of potentially teratogenic medications.³³ Of 153 pregnancies with known outcomes with 90 live births. Twenty-two infants were born prematurely with one neonatal death. Eleven neonates had hematological abnormalities; four had infection and two had congenital malformations.

Ocrelizumab

Mechanism of action

Ocrelizumab (OCRE) is a humanized monoclonal IgG1 mAb against CD20.³⁴ Compared to RTX, ocrelizumab binds to a different, but overlapping epitope of the large extracellular loop of CD20. Like RTX, OCRE acts as a B-cell depleting monoclonal antibody by way of antibody and complement dependent cell cytotoxicity.^{34,35} Infusion reactions seen with RTX are believed to be secondary to complement mediated cytotoxicity, which is reduced in OCRE.³⁶

Early phase research

At the present time, OCRE is not approved for the treatment of any disease in human subjects. There have been successful phase I/II trials of this agent in rheumatoid arthritis and non-Hodgkins lymphoma.³⁷ While having recently met its endpoint in a phase II

I trial in rheumatoid arthritis versus methotrexate, there was a higher rate of serious infections, and further phase III trials in rheumatoid and lupus were put on hold in 2009.³⁸

The results of a phase II randomized double-blind placebo controlled trial of OCRE in RRMS over 24 weeks was reported at the 2010 ECTRIMS meeting with further information to be reported at the 2011 AAN meeting.^{39,40} In this trial, 220 RRMS patients were randomized in a 1:1:1:1 ratio to receive OCRE at days 1 and 15 for total doses of 600 mg, 2000 mg, placebo, or an open-label arm receiving Avonex[®]. The primary outcome was the total number of CELs from weeks 12, 16, 20 and 24 compared between the two OCRE doses versus placebo. Both OCRE dose arms showed highly significant differences ($P < 0.0001$) in total number of CELs at all four time points versus placebo (96% for the high-dose group and 89% for the low-dose group at 24 weeks). ARR relative reduction was 80% (high-dose) and 73% (low-dose) versus placebo. In an exploratory analysis, both OCRE doses were superior to the interferon group without apparent dose-effect with respect to CEL formation.

Ongoing and future research

Two randomized double-blinded controlled phase III trials of OCRE in MS are underway, one in RRMS studying 400 mg or 600 mg total of intravenous OCRE every 24 weeks versus 44 mcg Rebif[®] for a total of 96 weeks ([clinicaltrials.gov NCT01247324](http://clinicaltrials.gov/NCT01247324)). The primary outcome is the ARR between groups. The ORATORIO trial is in PPMS will evaluate safety and efficacy with eligible patients randomized 2:1 to receive either OCRE (300 mg intravenously on days 1 and 15 of the first treatment cycle, followed by 600 mg iv every 24 weeks) or placebo ([clinicaltrials.gov NCT01194570](http://clinicaltrials.gov/NCT01194570)). The blinded treatment period is 120 weeks, followed by open label treatment phase for all patients who may benefit from further or newly initiated OCRE treatment. The primary outcome is time to sustained disability \geq three months.

Adverse events

Serious adverse events were more common in the high dose OCRE group in the above phase II trial than in the low dose arm and placebo arms. Serious infection rates were similar in all groups, but infusion reactions were more common in OCRE groups although these



decreased with repeated infusions.³⁹ Unfortunately, there was one death in the OCRE group after 12 weeks from thrombotic microangiopathy.³⁹

Pregnancy information

There is no published data on pregnancy outcomes with use of OCRE in MS, and it has not yet been categorized with respect to safety in pregnancy by the FDA.

Ofatumumab

Mechanism of action

OFA (OFA, Arzerra[®]) is a fully human IgG1 mAb against CD20.^{41,42} In contrast to RTX and OCRE it is directed against the small 7-mer loop of CD20 and binds in close proximity to the plasma membrane.³⁵ In contrast to OCRE, OFA is a weak inducer of antibody-dependent cell cytotoxicity but a strong inducer of complement dependent cell cytotoxicity.^{43,44}

Early phase research

In 2010, Soelberg Sorensen presented results from a multi-center, double-blind, randomized, placebo-controlled trial with OFA in RRMS.⁴⁵ Twenty-six patients were randomized 2:1 to increasing doses of OFA (100, 300 or 700 mg iv at baseline and week two) or placebo for an initial treatment phase of 24 weeks. MRI was performed one month prior to enrolment and then every 4 weeks over 24 weeks. Following treatment, the mean cumulative number of new CELs on monthly MRI from weeks 8 to 24 was 0.04 (0.20) in the combined OFA group compared with 9.69 (24.86) in the combined placebo group. The estimated relative reduction is 99.8% (90% confidence interval: 94.7, 100.0; $P < 0.001$). Similar reductions were estimated for all dose cohorts. All doses of OFA resulted in peripheral B-cell depletion. At week 24 a dose-dependent repletion was indicated with an observed mean CD19+ B-cell count was reduction of 78%, 95% and 98% in the 100, 300 and 700 mg cohorts. No safety issues have developed at present.

Ongoing and future research

The final results of the phase II trial above should be available in 2012–2013.

Adverse events

There is limited data on the nature of adverse events encountered in the above phase II trials. In treatment of fludarabine and ALEM resistant CLL, infusion reactions, rare neutropenia and thrombocytopenia and severe infections were seen, although this patient population is fundamentally different than an MS treatment group.⁴⁶

Pregnancy information

There are well-controlled studies of OFA in pregnancy. A reproductive study in pregnant cynomolgus monkeys that received OFA at doses up to 3.5 times the recommended human dose of OFA did not demonstrate maternal toxicity or teratogenicity. It crosses the placental barrier, and fetuses have exhibited depletion of peripheral B-cells and decreased spleen and placental weights. There are no human or animal data on the potential short-term and long-term effects of perinatal B-cell depletion in offspring following in-utero exposure to OFA. OFA does not bind normal human tissues other than B lymphocytes. The kinetics of B-lymphocyte recovery is unknown in offspring with B-cell depletion (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125326lbl.pdf).

Abatacept (CTLA-4 Ig)

Mechanism of action

Abatacept is a chimeric fusion protein that binds to the co-stimulatory molecules B7-1 (CD80) and B7-2 (CD86) on antigen presenting cells, thus preventing activation of T-cells via CD28.⁴⁷ As well, the engagement of the B7 with the receptor cytotoxic T lymphocyte-associated gene (CTLA-4) that is up-regulated leads to an inhibitory signal.⁴⁷

Early phase research

A phase I safety trial of intravenous abatacept studied 16 patients with RRMS with a mixture of pre-treatment disease activity were randomized 1:1:1:1 to dose arms of 2 mg, 10 mg, 20 mg or 35 mg/kg iv (all patients starting at 2 mg/kg for a one month safety period).⁴⁸ Patients received one dose and were followed for three months.

A double-blind placebo-controlled phase II trial of abatacept in RRMS with 2 or 10 mg/kg with a focus on CEL development was halted after patients in the 2 mg group developed worsening clinical and



radiological disease.⁴⁹ However, unblinding revealed that the low dose abatacept group had significantly more disease activity at baseline versus all other groups. From what data was available, it appeared the 10 mg/kg group had a reduction in CELs.

Ongoing and future research

The ACCLAIM study (clinicaltrials.gov NCT01116427), another phase II double-blind placebo-controlled randomized trial of abatacept in RRMS also focusing on CEL development, is currently recruiting. Patients will receive abatacept at weeks 0, 2, 4 and every 4 weeks for 24 with similar dosing for 52-week extension at doses of 500 mg; 750 mg; or 1000 mg based on weight.

Adverse events

Mild infections, headache and lymphadenopathy, and perceived worsening of MS were reported.⁴⁹

Pregnancy information

Abatacept crosses the placenta and alters immune function in animal reproductive studies. Abatacept was not teratogenic when administered to pregnant mice at doses up to 300 mg/kg and in pregnant rats and rabbits at doses up to 200 mg/kg daily representing approximately 29 times the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg. Abatacept administered to female rats every at three times the exposure associated with MRHD produced no adverse events, but doses at 11 times the MRHD exposure did alter immune function. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125118s0086lbl.pdf).

A pregnancy registry for abatacept use in rheumatoid arthritis (OTIS, AutoImmune Diseases Study Organization of Teratology Information Specialists) does exist (http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm#Specific_Medical_Products).

Prevention of Lymphocyte Transit to the CNS

Fingolimod/Gilenya® (FTY720)

Mechanism of action

Fingolimod (FTY720) is a lysophospholipid agonist and a synthetic analog of the naturally occurring

product myriocin.⁵⁰ When phosphorylated in vivo, fingolimod binds with the sphingosine-1-phosphate receptor (S1P1), which is involved in lymphocyte migration from lymphoid structures into the peripheral circulation.⁵⁰ FTY720 crosses the blood–brain barrier and may directly impact the CNS, distinguishing it from other MS immunomodulators.⁵¹ FTY720 has shown a variety of therapeutic benefits in animal models of MS.^{50–58} Prophylactic treatment with FTY720 prevented development of the clinical features of experimental autoimmune encephalomyelitis (EAE); and, therapeutic treatment with FTY720 reduced clinical manifestations at different stages of experimental disease.^{51,53,54,56–58} Further studies have demonstrated a potential neuroprotective role of fingolimod, because the agent reversed paralysis and improved electrophysiological responses in animals with EAE.^{51,59} Furthermore, FTY720 has been shown to normalize the expression of myelin proteins, and reduce brain inflammation in animal models.^{51,53} Even delayed treatment with FTY720 reduced the extent of demyelination on MRI in rats with EAE.^{51,58}

Early phase research

The benefits of FTY720 seen in animal studies were further corroborated in early clinical trials of MS. Kappos and colleagues reported the findings from a placebo-controlled, phase II clinical trial and its open-label extension.⁶⁰ This study included 281 patients with RRMS who were randomized to receive either 1.25 mg/d or 5.0 mg/d of FTY720 versus placebo for 6 months. This was followed by another 6-month phase in which treatment patients remained on their respective doses while placebo patients were randomized to one of the two FTY720 doses. In the final six-month phase, patients remained on their current treatment regimens. The study was designed to detect a 50% change in the total number of CELs on MRI at six-month intervals.⁶⁰ Secondary endpoints included MRI measured T2 lesions and CELs, ARRs, and disability progression. At six months, the cumulative number of CELs per patient was significantly lower in both treatment arms (8.4 lesions per scan; $P < 0.01$ for 1.25 mg/d and 5.7 lesions per scan; $P < 0.0006$ for 5.0 mg/d) compared with placebo (14.8 lesions per scan).⁶⁰ A significantly greater portion of patients receiving low- and high-dose FTY720



(77% and 82%, respectively) had no CELs compared with 47% of placebo patients ($P < 0.001$). MRI measured T2 lesions and CELs were significantly lower in both treatment arms as compared to placebo. The ARR decreased by 53% in the 1.25 mg/d group and 55% in the 5.0 mg/d group ($P < 0.009$ and $P < 0.01$, respectively), with a significant increase in the proportion of relapse-free patients. In the extension phase, 80% of patients using FTY720 were free of CELs at 18 months. In this phase II study, asymptomatic bradycardia occurred with FTY 720 use, but only after the first dose, and more commonly in patients in the 5.0 mg/d group.⁶⁰ In patients using high-dose FTY 720 therapy, reduction in forced expiratory volume was also observed. One case of posterior reversible encephalopathy occurred in another high-dose FTY720 patient. As therapeutic benefit was equivalent between low and high-dose FTY720 groups and most adverse events occurred in high-dose patients, subsequent phase trials employ lower dosages.

Later phase research

FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis) was phase III, double-blind, placebo-controlled study which extended our understanding regarding the safety and efficacy of FTY720 therapy in MS. This trial compared the effects of daily FTY720 treatment on ARRs, disability progression, and MRI measures of inflammation over 24 months in RRMS patients relative to placebo.⁶¹ Patients were randomly assigned (1:1:1 ratio) to receive daily oral FTY720 capsules (0.5 mg or 1.25 mg) versus matching placebo. The primary end point was the ARR, defined as the number of confirmed relapses per year. The key secondary end point was the time to confirmed disability progression. Additional secondary end points included the time to a first relapse, time to disability progression, and number of MRI measured CELs; and safety and tolerability measures after 24 months.⁶⁰ Eighty one percent of patients ($n = 1033$) completed the study. The ARR was 0.18 with 0.5 mg/d of FTY720, 0.16 with 1.25 mg/d of FTY720, and 0.40 with placebo ($P < 0.001$ for either dose versus placebo) (Fig. 4). FTY720 at doses of 0.5 mg/d and 1.25 mg/d reduced disability progression over 24-months (hazard ratio, 0.70 and 0.68, respectively; $P = 0.02$ versus placebo,

for both comparisons). The cumulative probability of disability progression was 17.7% with 0.5 mg of FTY720, 16.6% with 1.25 mg of FTY720, and 24.1% with placebo. Both FTY720 doses were superior to placebo with regard to MRI measures including T2 lesion load, CELs, and brain-volume loss, ($P < 0.001$ for all comparisons at 24 months).

The TRANSFORMS [Trial Assessing Injectable Interferon vs. FTY720 Oral in RRMS] trial was a 12-month, double blind, phase III trial involving 1292 relapsing remitting MS (RRMS) patients with at least one MS—related relapse.⁶² Patients were randomized to receive either oral FTY720 (1.25 mg/d or 0.5 mg/d) or Avonex[®] 30 μ g/week. The primary endpoint was ARR, and secondary endpoints were the number of new or enlarged lesions on T2-weighted MRI at 12 months, and disability progression. Eighty nine percent ($n = 1153$) of patients completed the trial. The ARR was lower in both groups receiving FTY720 (Fig. 5), measuring 0.20 in the 1.25 mg group and 0.16 in the 0.5 mg group versus 0.33 in Avonex[®] group 0.33 ($P < 0.001$ for both comparisons). Patients in both FTY720 treatment groups had significantly fewer T2 and CELs at 12 months than did those in the Avonex[®] group. The TRANSFORMS trial demonstrated that FTY720 was superior to Avonex[®] in reducing relapse and MRI activity in RRMS patients.

Ongoing and future research

There are several ongoing phase III studies involving FTY720. FREEDOMS II is an extension study, which will evaluate the long term safety, tolerability and efficacy of FTY720 in MS patients (clinicaltrials.gov NCT00355134). The EPOC trial (a Six-month, Randomized, Open-label, Patient Outcomes, Safety and Tolerability Study of Fingolimod (FTY720) 0.5 mg/day versus Comparator in Patients with Relapsing Forms of Multiple Sclerosis) will assess patient and physician-reported outcomes and safety/tolerability measures in patients with relapsing MS previously on DMT (clinicaltrials.gov NCT01216072). Another phase III study will evaluate the effect of treatment with FTY720 on the immune response following seasonal influenza vaccination and tetanus booster injection in patients with relapsing MS (clinicaltrials.gov NCT01199861). Because its mechanism of action may include direct

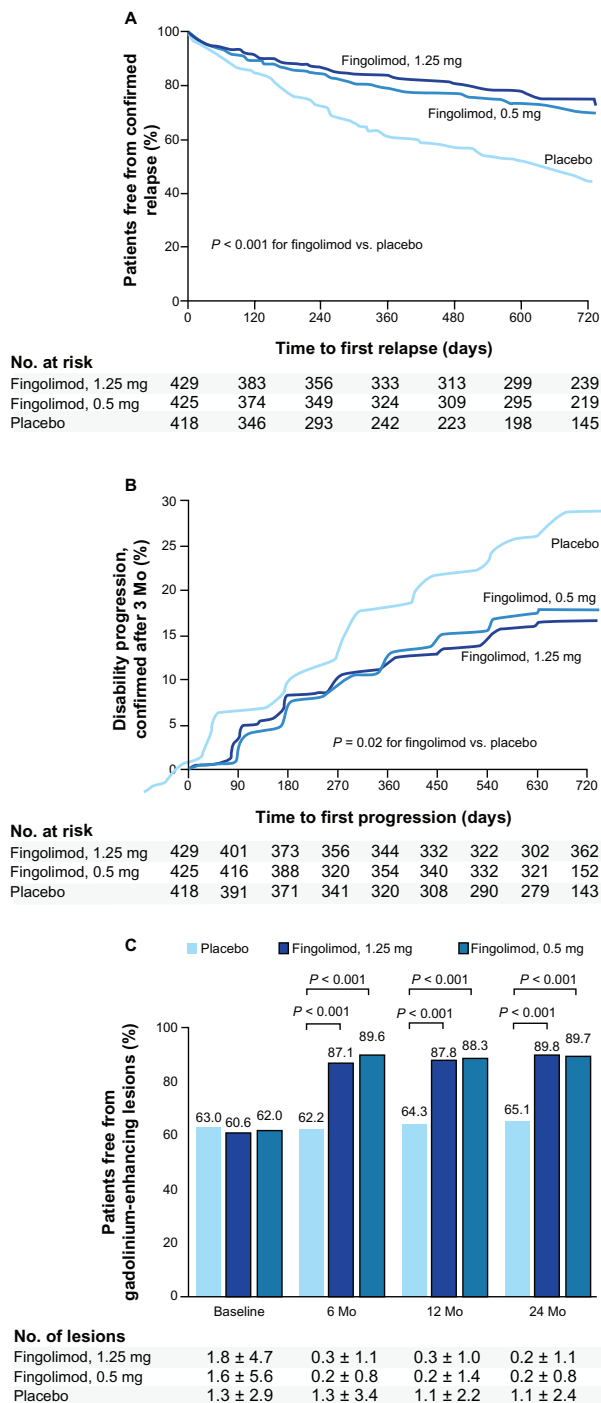


Figure 4. Study end points, according to study group. Panel A shows Kaplan–Meier estimates for the time to a first relapse, and Panel B shows Kaplan–Meier estimates for the time to disability progression, confirmed after 3 months, as measured with the Expanded Disability Status Scale (EDSS). Panel C shows the proportions of patients free from gadolinium-enhancing lesions at the mean (\pm SD) number of gadolinium-enhancing lesions at baseline and at 6, 12, and 24 months. Data on gadolinium-enhancing lesions were available for 416 patients assigned to receive placebo, 424 assigned to receive 1.25 mg of fingolimod, an 424 assigned to receive 0.5 mg of fingolimod, respectively, at baseline; 373, 388, and 403, respectively, at 6 months; 356, 376, and 394, respectively, at 12 months; and 332, 343, and 369, respectively, at 24 months. The P values for the proportions were obtained with the use of a logistic-regression model, with adjustment for study group, country, and number of lesions at baseline (reproduced with permission from the New England Journal of Medicine).

neural effects, FTY720 is also being evaluated in a multicenter phase III study in patients with primary progressive MS in the INFORMS trial, which will evaluate the impact on sustained disability progression, tolerability and MRI parameters with an enrolment goal of 654 patients (clinicaltrials.gov NCT00731692).

In September 2010, the US Food and Drug Administration (FDA) announced approval of FTY720 (Gilenya[®], Novartis) (0.5 mg/d) as the first oral treatment for relapsing forms of MS. In Canada, Health Canada announced approval in relapsing MS in March 2011. In the U.S., it is approved as first-line therapy in relapsing MS, while in Canada and Europe, it is anticipated that it will be approved for use as second-line therapy in relapsing MS patients who fail conventional DMTs (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm226755.htm>., http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/regist/reg_innov_dr-eng.php).

Adverse events

As previously mentioned, in the Phase II study by Kappos and colleagues, several cases of asymptomatic bradycardia occurred in association with FTY720, but only with the first dose and typically in the high-dose (5 mg/d) group.⁶⁰ In TRANSFORMS, two fatal infections occurred in the 1.25 mg/d FTY720 group (disseminated varicella zoster and herpes simplex encephalitis).⁶² Other adverse events associated FTY720 included: nonfatal herpes virus infections, atrioventricular block, hypertension, macular edema, skin cancer, and transaminitis. In FREEDOMS, the most common serious adverse events were bradycardia and basal-cell carcinoma, although there is much debate about a causal relationship between FTY720 and skin cancer.⁶¹ Lower respiratory tract infections were more common with FTY720 than with placebo. Macular edema was diagnosed in seven patients, all of whom received 1.25 mg/d of daily FTY720.⁶¹ Mean blood lymphocyte counts decrease by approximately 30% from baseline FTY720 use, but tended to remain stable.⁵¹

Pregnancy information

FTY720 is FDA pregnancy category C as animal studies indicate that use of this agent during pregnancy may cause potential fetal harm. For this reason it is recommended that women use effective birth control while taking FTY720 maintain effective

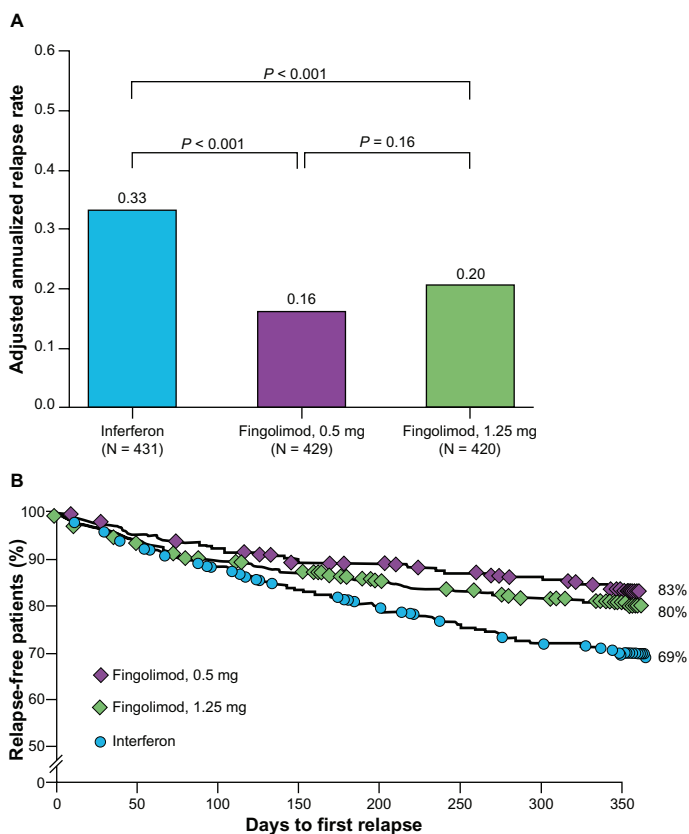


Figure 5. annualized relapse rate at 12 months and the time to the first relapse.

Panel A shows the annualized rate of relapse from baseline to 12 months, with adjustment for study group, country, number of relapses in the previous 2 years, and baseline disability score. Panel B shows Kaplan – Meier estimates of the time to the first relapse, indicating the proportion of relapse-free patients ($P < 0.001$ for both comparisons with interferon) (reproduced with permission from the New England Journal of Medicine).

contraception for two months after stopping the medication. [<http://www.multiplesclerosiscoalition.org/emergingtherapies/medications/fingolimod>]. Now that FTY720 has been approved by the FDA as a first line therapy in patients with RRMS in the United States, Novartis has initiated the Multi-National Gilenya® Pregnancy Exposure Registry in Multiple Sclerosis (MS) to monitor the frequency of major and minor teratogenic effects in the offspring of women exposed to Gilenya® before (up to 8 weeks before last menstrual period) and during pregnancy in routine clinical practice.

Firategrast (SB683699)

Mechanism of action

Firategrast (SB-683699), like natalizumab, is an $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins antagonist that interferes with the binding of $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins to ligand VCAM-1, preventing the migration of immune cells to the site

of inflammation.⁶³ Unlike natalizumab, it is a small molecule in oral form.

Early phase research

Miller et al presented the results of a phase II randomized double-blind placebo controlled dose-ranging trial of firategrast in 343 RRMS patients treated over 24 weeks and followed for 36 weeks.⁶⁴ Subjects were randomized to 1:1:1:1 to receive placebo or firategrast at doses of 150 mg, 600 mg or 900 mg (females)/1200 mg (males). The primary outcome was cumulative number of new CELs during the treatment phase. Secondary efficacy outcomes included additional MRI and clinical measures including ARR. Safety assessments included JC virology, neurological symptoms, and MRI surveillance for PML. The primary outcome was statistically significant for the 900/1200 mg firategrast group versus placebo: adjusted cumulative mean rate of CELs was 2.69 vs. 5.31 (a 49% difference). A significant decrease in new T2 lesions was also observed in the 900/1200 mg group. A non-significant trend for fewer relapses with increasing dose was also observed. Firategrast was well tolerated at all dose levels.

Ongoing and future research

Further results from the above trial are anticipated over the next one to two years.

Adverse events

Adverse events included nausea and vomiting, infection (URTIs and UTIs) and rash. At the time of presentation, there were no suspected cases of PML.⁶⁴

Pregnancy information

There is no published data on pregnancy outcomes with use of firategrast at present.

Minocycline

Mechanism of action

Minocycline (MINO) is a second generation derivative of the antibiotic, tetracycline, which has several potential mechanisms of action in modulating immune activity and neuroprotective mechanisms. Minocycline treatment provides neuroprotection against excitotoxic insults such as glutamate exposure and lipopolysaccharide-induced inflammation in a number of experimental models as shown



by preserved oligodendrocyte survival, decreased microglial activation, free-radical suppression and attenuation of apoptosis.⁶⁵ Other protective mechanisms include inhibition of inducible nitrous oxide, mitogen activated kinases. One of the major anti-inflammatory actions associated with MINO is the impact on matrix metalloproteinases (ie, inhibition of matrix metalloproteinase-9).⁶⁵

Early phase research

Metz and colleagues studied the effect of MINO on CELs in a pilot trial with 10 RRMS patients.⁶⁶ Patients received 100 mg of oral MINO twice daily for a six-month period. The mean total of CELs decreased from 1.38 to 0.22, and there were no new active scans after the second month. In another phase II, double-blind, placebo-controlled clinical study, 44 participants were randomized to either MINO 100 mg twice daily or placebo for nine months as add-on therapy to Copaxone[®].⁶⁷ Compared with Copaxone[®] plus placebo, the combination of Copaxone[®] and MINO reduced the total number of CELs by 63% (mean 1.47 versus 2.95; $P = 0.08$), the total number of new and enlarging T2 lesions by 65% (mean 1.84 versus 5.14; $P = 0.06$), and the total T2 disease burden ($P = 0.10$).

Ongoing and future research

Minocycline in Clinically Isolated Syndromes (CIS) is a phase III, double blind, randomized placebo controlled trial of MINO in CIS undertaken to determine if 100 mg of oral MINO twice daily reduces the risk of conversion to clinically definite MS by an a priori estimate of 25% versus placebo over a 6 month period (clinicaltrials.gov NCT00666887). RECYCLINE (Minocycline as add-on to IFN β -1a (Rebif[®]) in Relapsing Remitting Multiple Sclerosis) is a phase II double-blind, randomized, placebo-controlled, parallel group trial. Eligible subjects receiving IFN β -1 have been randomized for treatment with either MINO 200 mg daily as add-on therapy or placebo. The primary objective is to evaluate the possible added effect of MINO in subjects receiving treatment with IFN β -1a with the primary outcome of time to first on-trial relapse (clinicaltrials.gov NCT00203112).

The Neuroprotection and Repair in Optic Neuritis (Mino in ON) trial in an open-label, phase II pilot trial is to estimate the treatment effect of oral MINO 100 mg twice daily for 90 days within 30 days of an

optic neuritis on functional and structural optic nerve recovery (clinicaltrials.gov NCT01073813). The primary outcome measure to measure optic nerve recovery is mean retinal nerve fiber layer thickness.

Adverse events

MINO has been reported to cause serious, albeit rare, adverse events, including serum sickness-like reaction, hypersensitivity syndrome reaction, and drug-induced SLE.⁶⁵ In the combination study with MINO and Copaxone[®], 4 participants discontinued therapy due to adverse events and one participant discontinued MINO at day 17 due to moderate dizziness but continued Copaxone[®]. In this study, headache, and nausea were the most frequent adverse events.⁶⁷

Pregnancy information

MINO is a FDA pregnancy category D because there is weak evidence that tetracycline and its derivatives might increase the risk of birth defects, although it is not clear if a true risk exists. If taken when the child's teeth are forming (during the second half of pregnancy through eight years of age), MINO can cause permanent tooth discoloration. Moreover, tetracyclines might adversely affect bone formation (http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/050808lbl.pdf).

Lymphocyte/Cell Synthesis Disruption Cladribine

Mechanism of action

Cladribine, also known as 2-chlorodeoxyadenosine, is a synthetic adenosine deaminase-resistant purine nucleoside analog that preferentially depletes lymphocyte subpopulations and in some respects, is an immunosuppressant.⁶⁸ The effects of cladribine occur in both resting and proliferative lymphocytes, with the greatest effect in depleting CD4+ T-cells.⁶⁹

Early phase research

There are no phase II trials of oral cladribine in MS, but several parenteral studies have reported the efficacy of this agent in the disease.⁷⁰ Romine and colleagues performed an 18-month, double-blind, randomized, placebo-controlled trial of IV cladribine in 52 RRMS patients.⁷¹ The primary endpoints included the ARR and the number of CELs at 12 months. Treatment and placebo groups both



had reduced relapses after 6 months, but the number of relapses was significantly lower in the treatment arm ($P = 0.021$) for the remainder of the study. Beutler studied patients with both PPMS and SPMS in a double-blind, randomized crossover trial with 24 matched pairs.⁷² Treatment patients received seven consecutive doses of cladribine (0.1 mg/kg/d every 4 months), with crossover to placebo after one year. Placebo patients “crossing over” received half the dose of the original treatment group. The original treatment group had a greater delay to disability progression, but all groups worsened by 18 months. At 12 months, only two of 24 treatment patients and 12 of 24 placebo patients had CELs (versus 11 with baseline CELs). At 24 months, after the crossover period, one of the 20 remaining original treatment patients and one original placebo patients had CELs on MRI.⁷² Rice and colleagues performed a multicenter, double-blind, randomized, placebo-controlled trial with 159 progressive MS patients over 12 months.⁷³ The primary outcome was the change in EDSS over the study. Patients were assigned to two treatment arms (2.1 mg/kg or 0.7 mg/kg total) versus placebo. No significant changes were seen in EDSS between treatment and placebo groups; however, there was a significant reduction in the number of patients with CELs in both treatment groups versus placebo at 12 months. Approximately 35% of patients at baseline in each treatment and placebo group had CELs. By month 12, only 10% of patients in the 0.7 mg/kg group and 6% in the 2.1 mg/kg group had CELs ($P = 0.0080$ and $P = 0.0009$, respectively) versus 31% in the placebo group. The proportion of patients without CELs in both treatment arms remained significantly lower than placebo a 12-month of the extension phase. CEL volume was also significantly reduced in both treatment arms, whereas T2 lesion volume reduction was significant only in the 2.1 mg/kg arm.⁷³

Later phase research

CLARITY (Safety and Efficacy of Oral Cladribine in Subjects With Relapsing-remitting MS) was a phase III, randomized, double-blind, placebo-controlled, multicenter Study that aimed to evaluate the safety and efficacy of oral cladribine in subjects with RRMS.⁷⁴ The primary outcome measure was to evaluate the efficacy of cladribine versus placebo in reducing relapses over

96 weeks. In total, 1326 patients were randomized from 155 clinical centers across 32 countries (1:1:1 ratio) to receive one of two cumulative doses of cladribine tablets (3.5 mg/kg or 5.25 mg/kg) or matching placebo.⁷⁴ Patients in both cladribine dose arms had a significantly lower ARR versus the placebo group (0.14 and 0.15 vs. 0.33 respectively, $P < 0.001$), a higher relapse-free rate (79.7% and 78.9% vs. 60.9% respectively, $P < 0.001$), lower disability (3.5 mg group hazard ratio 0.67, $P = 0.02$; and 5.35 mg group hazard ratio 0.69, $P = 0.03$), and reduced MRI brain lesion count ($P < 0.001$ for all comparisons).⁷⁴

Ongoing and Future research

Other ongoing studies evaluating the role of cladribine in MS include the CLARITY (CLADribine Tablets Treating MS Orally) extension study, which will further evaluate the safety and tolerability of oral cladribine in MS patients (clinicaltrials.gov NCT00641537). The ORACLE MS (Oral Cladribine in Early MS) study is a phase III, randomized, double-blind, clinical trial designed to assess the safety and efficacy of two doses of oral cladribine relative to placebo in CIS patients (clinicaltrials.gov NCT00725985). The primary objective of this study is to evaluate the effect of two dosing regimens of oral cladribine versus placebo on time to conversion to clinically definite MS. The Phase II ONWARD (Cladribine Add-ON to Interferon-beta Therapy in MS Subjects With Active Disease) trial is evaluating the safety, tolerability, and effectiveness of oral cladribine when taken in combination with IFN β , with anticipated completion expected in 2013 (clinicaltrials.gov NCT00436826).

In March 2011 the FDA denied approval for oral cladribine as a treatment for MS as did European regulators in the preceding months, citing safety concerns and the fact that most appropriate dosage had not been well established. It was, however, approved for MS in Russia and Australia.

Adverse events

In the CLARITY study, mild to moderate infections were reported in 47.7% of the patients in the cladribine 3.5 mg group, 48.9% of those in the cladribine 5.25 mg group, and 42.5% of those in the placebo group.⁷⁴ Other common side effects were headache, nausea, upper URTIs, and lymphocytopenia. Adverse events that were more frequent in the cladribine groups included



lymphocytopenia and herpes zoster.⁷⁴ Treatment was discontinued because of adverse events in 3.5% of patients in the cladribine 3.5 mg group, 7.9% of those in the cladribine 5.25 mg group, and 2.1% of those in the placebo group.⁷⁴ There were three cases of cancer in the cladribine 3.5 mg group (melanoma and pancreatic and ovarian cancer).^{74,75} Cladribine administered intravenously to monkeys showed suppression of rapidly generating cells (testicular cells) suggesting a possible association with infertility.⁷⁵ Because cladribine may alter viral immunosurveillance, it should not be used in combination with other immunosuppressives such as natalizumab or mitoxantrone.⁷⁵

Pregnancy information

Cladribine is teratogenic in mice and rabbits and consequently has the potential to cause fetal harm when administered to a pregnant woman. It is considered FDA pregnancy category D, and therefore women of childbearing age should be advised to avoid becoming pregnant. (http://www.ppcdrugs.com/en/products/product_inserts/EN_Cladribine.pdf).

Teriflunomide

Mechanism of action

Teriflunomide, the active metabolite of leflunomide, an approved therapy for rheumatoid arthritis, has emerged as a promising new oral MS therapy.⁷⁶ This agent acts by noncompetitively and reversibly inhibiting the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH), which is needed for the de novo synthesis of pyrimidine.⁷⁶ Because it inhibits DHODH and diminishes DNA synthesis, teriflunomide has a cytostatic effect on proliferating B and T-cells.⁷⁶ Experimental autoimmune encephalomyelitis animal models have shown that teriflunomide has an ameliorating impact on the disease course and delayed disease onset and decreased disease severity in this EAE model in a dose-dependent manner.^{76–78}

Early phase research

In 2006, O'Connor and colleagues reported the findings from a phase II, randomized, double-blind, placebo-controlled trial, which was designed to examine safety, efficacy, and optimal dosing of teriflunomide in patients with relapsing forms of MS.⁷⁹ One hundred and seventy-nine (157 RRMS, 22 SPMS) patients were randomized to receive 7 mg/d

teriflunomide, 14 mg/d teriflunomide, or placebo in a 1:1:1 ratio for 36 weeks. The primary endpoint was the number of combined unique active lesions per MRI scan. Secondary MRI endpoints included the number of CELs and new or enlarging T2 lesions per MRI scan. Clinical secondary endpoints included ARR, proportion of patients with relapses requiring steroids, and disability progression as measured by EDSS. The mean number of combined unique lesions per scan was significantly reduced (approximately 61% for both treatment arms) when compared with placebo ($P < 0.005$), but with no difference between treatment groups (Fig. 6). Additionally, the number of CELs, T2 lesions per scan and the proportion with active scans were all significantly lower in both treatment arms. Both treatment arms had a trend to lower ARR, but this was not statistically significant. In the high-dose arm, there was a trend to a higher proportion of relapse-free patients and a significantly lower proportion of patients with EDSS progression (7.4% in the 14 mg/d group versus 23% in the placebo group), with a relative risk reduction of 69%.⁷⁹

Teriflunomide has also been investigated in phase II trials as an adjunctive therapy to both IFN β -1a and glatiramer acetate.⁸⁰ Results of these studies, presented in 2010 at the American Committee for Treatment and Research in Multiple Sclerosis and American Academy of Neurology meetings, suggested of a synergistic effect on MRI measured burden of disease with the addition of teriflunomide to these standard therapies.⁸⁰ Moreover, teriflunomide has shown a consistent safety profile.⁸⁰

Later phase research

The results of TEMSO (Teriflunomide in Multiple Sclerosis Oral) phase III clinical trial were recently presented at the European Committee for Treatment and Research in MS (ECTRIMS) 2010 meeting.⁸¹ This randomized, double-blind, placebo-controlled, multinational study included 1088 relapsing MS patients who were randomized to receive either 7 mg/d or 14 mg/d oral dose teriflunomide or placebo and followed for 108 weeks. The primary endpoint was the ARR. The dropout rate was about 27% in each group, with the main reasons being adverse events, perceived lack of efficacy, and withdrawal of consent. There was a 31% reduction in ARRs in both the 7 mg



and 14 mg groups. The drug significantly increased the time to first relapse in both dose groups relative to placebo. Treatment with 14 mg of teriflunomide reduced the risk of sustained disability progression by 29.8% ($P = 0.0279$). The rate of treatment-emergent adverse events and serious adverse events was the same in all groups and with no deaths.

Ongoing and future research

TENERE is a phase III study comparing two doses of teriflunomide with IFN β in 300 people over a treatment period of 48 weeks (clinicaltrials.gov NCT00883337). The aim of the study is either the time to failure defined as first occurrence of relapse, or permanent study treatment discontinuation for any cause.

In the TOPIC study (Teriflunomide Versus Placebo in Patients with First Clinical Symptom of Multiple Sclerosis) the primary objective is to demonstrate the effect of teriflunomide (14 mg/d and 7 mg/d) compared to placebo for reducing conversion to clinically-definite MS in CIS patients (clinicaltrials.gov NCT00622700). TOWER (An Efficacy Study of Teriflunomide in Patients with Relapsing Multiple Sclerosis) will evaluate the effect of two doses of teriflunomide on the frequency of relapses in patients with relapsing multiple sclerosis (clinicaltrials.gov NCT00751881). The effect on worsening of disability and fatigue will also be evaluated, as well as long term safety. The primary outcome measures will be ARR over two years. TERACLES (the Efficacy and Safety of Teriflunomide in Patients with Relapsing Multiple Sclerosis and Treated with Interferon-beta) is a phase III study that will assess the effect of Teriflunomide in comparison to placebo on frequency of relapses in patients with relapsing forms

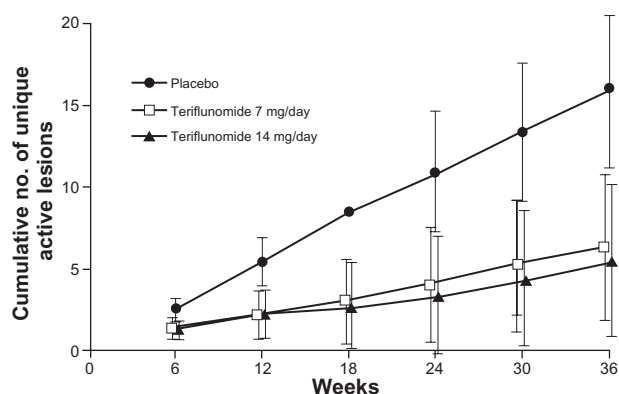


Figure 6. Cumulative mean number of combined unique active lesions adjusted for baseline (reproduced with permission from Neurology).

of MS who are treated with IFN β (clinicaltrials.gov NCT01252355). The primary outcome measure is the ARR over an estimated time frame of two years.

Adverse events

The most common adverse effects associated with leflunomide are gastrointestinal symptoms including diarrhea, dyspepsia, nausea, vomiting, abdominal pain, oral ulcers, which decline after the first two weeks of treatment.^{76,82–87} Liver toxicity seems to be one of the most serious safety issues.⁷⁶ Because of increased risk within the first six months of treatment, monthly liver enzyme checks have been recommended and if stable, to be repeated every six to eight weeks thereafter. There is also a low risk of leukopenia and pancytopenia associated with leflunomide use. In phase II MS studies, teriflunomide was associated with URIs, alopecia, and headache. Serious adverse events included hepatic dysfunction, neutropenia, and rhabdomyolysis.⁷⁹ Fifteen patients (8%) were withdrawn from the study secondary to such adverse events.⁷⁹ In the TEMSO study alanine transferase increases were observed, which were mainly mild and asymptomatic with no dose effect.⁸¹ A slight reduction in neutrophil counts was seen in the first three months of treatment and then plateaued.⁸¹

Pregnancy information

Leflunomide has shown teratogenicity when administered to rats, rabbits and mice, and both the agent and its metabolite are contraindicated in pregnancy.⁷⁶ It is considered FDA pregnancy category X (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020905s0201bl.pdf). In the TEMSO study of 11 pregnancies, 10 patients had either miscarriages or elective abortions and 1 healthy baby was born.⁸¹

Undetermined/Immune Milieu Changes Laquinimod

Mechanism of action

Laquinimod, or N-ethyl-N-phenyl-5-chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinoline-carboxamide, is a modified form of linomide.⁸⁸ The proposed mechanism of linomide (and presumably laquinimod) includes inhibition of the release of tumor necrosis factor- α (TNF- α) and NK cells and a decrease in T-cell



proliferation, antigen presentation, adhesion molecule expression, and nitrous oxide production.^{89,90} It also effects MHC-II gene transcription, stimulates neurotrophic factors.^{89,90}

Early phase research

In a phase II study, Polman and colleagues conducted a double blind, randomized, controlled trial of laquinimod in RRMS and SPMS patients, in which laquinimod doses of 0.6 mg or 0.3 mg daily were compared to placebo.⁹¹ The primary endpoint was the cumulative number of active lesions observed after 24 weeks of therapy. Dosing was based on the phase I trial that found adverse effects at 2.4 mg/d but not at 1.2 mg/d. Using the ITT method, the reduction in mean cumulative number of active lesions was 28% in the 0.1 mg/d group and 41% in the 0.3 mg/d group, both of which were not statistically significant. Patients treated with the 0.3 mg/d had a 44% reduction in mean cumulative active lesions versus placebo ($P = 0.0498$). In the subgroup of subjects who had one or more active lesions on MRI at baseline (approximately 70% of per-protocol group), the reduction in mean cumulative number of active lesions was not significant in the 0.1 mg/d group, but was 52% in the 0.3 mg/d group ($P = 0.005$).⁹⁰

The results of an open-label safety trial of laquinimod were presented by Sandberg-Wollheim in 2005, in which the primary goal was to determine the safety of higher doses of laquinimod.⁹² Inclusion criteria included a diagnosis of RRMS or SPMS, with an EDSS between 0 and 6.5. The target dose of laquinimod was 0.9 mg/d (lowered to 0.6 mg/d if needed). Twenty-two patients were enrolled, with the mean total amount of drug received by patients being 89% of the 0.9 mg/d target. Although EDSS scores decreased by only 0.27, 17 (77%) patients were relapse free; however, there was no control group with which to compare results.

Comi et al published results from the phase IIb double-blinded randomized-controlled trial of laquinimod in RRMS.⁹³ Eligible patients had McDonald confirmed RRMS, with at least one relapse in the past 12 months, EDSS 1–5 and ≥ 1 CEL on MRI. Patients received either laquinimod 0.3 mg, laquinimod 0.6 mg or a matching placebo for 36 weeks of treatment. The primary outcome was the adjusted mean CELs per scan in the last four MRIs. Based on the median CELs on the last four MRIs, the reduction in laquinimod groups versus placebo was 55%. Significant differences in favour of

0.6 mg laquinimod group were seen in the intention-to-treat cohort for almost all secondary and exploratory outcomes. Patients treated with 0.6 mg laquinimod had an ARR of 0.52 versus 0.77 in placebo group, although EDSS changes between groups were not significant. Serious adverse events occurred in 5.1% of low-dose laquinimod group, 2.8% in the high-dose group and 4.9% in placebo group. A case of Budd-Chiari syndrome occurred after one month of laquinimod in a patient with underlying heterozygosity for Factor V Leiden mutation). Additional serious adverse with laquinimod included: menometrorrhagia with a myofibroma, and two cases of transaminitis without evidence of hepatic failure, which recurred five months after drug was stopped in one of the two patients. Mild viral infections were also seen and more common in laquinimod groups.

Ongoing and future research

The two-year ALLEGRO clinical trial enrolled 1,106 MS patients, who were randomized to receive a once-daily oral dose of 0.6 mg laquinimod or placebo (clinicaltrials.gov NCT00509145). In April 2011, it was reported that treatment with laquinimod resulted in a reduction in ARR of 23% versus placebo and a 36% risk reduction of confirmed disability.⁹⁴ BRAVO (Laquinimod Double Blind Placebo Controlled Study in RRMS Patients With a Rater Blinded Reference Arm of Interferon β -1a) is a two-year, multi-center, randomized, double-blind, placebo-controlled study designed to compare the effect of daily oral treatment of laquinimod capsules 0.6 mg with the effect of placebo and Interferon β -1a) (clinicaltrials.gov NCT00605215). BRAVO study results are expected in late 2011; after which FDA submission is anticipated.

Adverse events

Various adverse events have been associated with laquinimod including transient arthralgia, myalgia, and mildly elevated erythrocyte sedimentation rate and liver enzymes. Viral infections were also more common but typically mild.⁹³ As mentioned above, one patient in the phase IIb trial on laquinimod developed Budd-Chiari syndrome.⁹³

Pregnancy information

There is no published information on the safety of laquinimod in pregnancy.



BG00012/Fumarate

Mechanism of action

Fumarate (also known as BG00012) is a second-generation fumaric acid derivative that was originally developed and approved for oral treatment of psoriasis.^{95,96} Although the precise mechanisms of action for fumarate remains unclear, *in vitro* studies demonstrate that dimethyl fumarate and related FAEs increase the production and induce the expression of anti-inflammatory cytokines, such as IL-10, IL-4 and IL-5.^{95,96} Other *in vitro* studies demonstrated that dimethyl fumarate and its primary metabolite, monomethyl fumarate, can both inhibit expression of proinflammatory cytokines such as IL-6, IL-1 β and tumour necrosis factor (TNF)- α and inhibit the secondary effects of inflammatory cytokines such as IL-1 β and TNF- α .^{95,96} Hence, it is thought that dimethyl fumarate can induce a shift from a Th1 (pro-inflammatory) response to a Th-2 (anti-inflammatory) T-cell response.^{95,96} BG00012 may also modulate metabolic homeostasis and cellular response to oxidative stress, a possible cause of cell and tissue damage in persistent inflammation.^{95,96}

Early phase research

Schimrigk et al performed a phase II open-label study to assess the safety and effectiveness of fumaric acid esters in 10 patients with RRMS.⁹⁷ Outcomes included safety and tolerability, the number and volume of CELs, ARR, and EDSS. Patients were included if they had one or more active lesions on baseline MRI and a relapse in the year prior to enrolment. There was initially a six-week baseline monitoring phase, followed by an 18-week treatment phase. After a four-week washout period, there was a second treatment phase lasting 48 weeks. Patients were titrated to a maximum of 720 mg/d in the first treatment phase and 360 mg/d in the second phase of the trial. It was observed that from 18 to 70 weeks, the mean number of CELs per scan decreased from 11.28 to 0.28 ($P < 0.02$).

Kappos and colleagues reported the results of a phase II, multicenter, double-blind, placebo-controlled, dose-ranging fumaric acid study of 257 patients from 10 countries.⁹⁸ Patients were randomized to receive placebo or fumaric acid at 120, 360, or 720 mg/d for six months, and followed for an additional six months as part of a dose-blinded safety extension study.⁹⁷ Patients treated with 720 mg/d had a 69% reduction in the mean number of CELs as compared to placebo as

measured monthly from weeks 12 to 24 of the study (4.5 versus 1.4, $P < 0.0001$). Fumarate 240 mg three times daily reduced new or enlarging T2 ($P = 0.0006$) and T1 ($P = 0.014$) lesions and ARRs by 32% (0.44 versus 0.65 for placebo; $P = 0.272$) compared to placebo. The 720 mg/d group had a 48% reduction in new/enlarging T2 lesions. Outcomes in the 120 mg/d and 360 mg/d dose arms were not significant.

Ongoing and future research

BG00012 Phase II Combination Study in Subjects with Multiple Sclerosis (EXPLORE) is an open-label, multicenter, study (clinicaltrials.gov NCT01156311). Subjects receiving IFN β or Copaxone[®] as monotherapy are being enrolled. The primary objective of the study is to evaluate the safety and tolerability of BG00012 administered in combination with IFN β or Copaxone[®] in subjects with RRMS. The phase III randomized, multicenter, double-blind, placebo-controlled, dose-comparison “Efficacy and Safety of Oral BG00012 in Relapsing-Remitting Multiple Sclerosis” or DEFINE trial will determine if BG00012 is effective in reducing the proportion of relapsing subjects at two years in RRMS patients (clinicaltrials.gov NCT00420212). The CONFIRM trial is a phase III randomized double-blind dose comparison trial of BG00012 versus both a placebo and Copaxone[®] arm in RRMS (clinicaltrials.gov NCT00451451).

Adverse events

In the phase II study reported by Kappos, headache, adverse events that were higher in all fumarate groups included flushing, abdominal pain, headache, and fatigue.^{98,99} Overall BG00012 appears to have a promising short-term efficacy and safety profile.¹⁰⁰

Pregnancy information

In psoriasis, there have been no data indicating that fumaric acid esters are teratogenic or mutagenic. However, experts advise that they should be avoided with pregnancy or lactation because of limited data on use in these conditions.¹⁰¹

Discussion

The landscape of disease modifying medications in MS, specifically RRMS, continues to evolve. While the choice of such medications has changed little in the past twenty years, novel oral and parenteral therapies are fast on their way to entering the treatment



arsenal. The first of these medications, the oral agent FTY720 (Gilenya®), has just been approved in RRMS in North America, and we anticipate the approval of teriflunomide and alemtuzumab will soon follow.

These emerging agents are likely to meet the most common needs raised by patients with relapsing disease over the past two decades, namely greater ease of administration, as well as improved efficacy for relapse and progressive disease activity. However, with greater efficacy comes greater potential risk; a sobering lesson learned with the release of natalizumab and the consequences of associated PML, and given the impact of other mAbs on B-cells, PML and other immune-mediated complications can and do occur. Recently, concern for the incidence of serious infections and malignancies in the phase III oral cladribine trial have stymied its approval in MS. Even the approved agent Gilenya® has the potential to impact respiratory, cardiac and visual systems. Despite these risks, these therapies have the potential to provide better efficacy, tolerability and ease of administration and improve quality of life for MS patients. And while MS may be a very different disease for relapsing patients in this era, the hope remains that one day, a therapy for the degenerative and progressive aspects of the disease will be found.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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