Several new medications are being investigated in late-phase studies for the treatment of patients with relapsing or progressive multiple sclerosis (MS). These agents represent a variety of mechanisms of action and provide not only lower relapse rates but also improvement in disabilities. The majority of investigational trials involve selective sphingosine-1-phosphate receptor 1 immunomodulators, such as laquinimod, ozanimod, ponesimod, and siponimod, in an effort to build on the success of fingolimod. Ocrelizumab is a CD20-positive B-cell–targeting monoclonal antibody with a promising new mechanism of action. Ofatumumab is also a CD20 inhibitor. Daclizumab, an interleukin-2 inhibitor, has evidence of good efficacy but is associated with unfavorable side effects. Masitinib is a mast-cell inhibitor that also has shown efficacy in Alzheimer’s disease and amyotrophic lateral sclerosis. Phase 3 trials for some of these agents will conclude in the next 12 months, and their manufacturers are expected to apply for US Food and Drug Administration approval soon thereafter. This review article summarizes data for newly approved and late-phase investigational agents for the treatment of patients with MS.

A chronic disease of the central nervous system, multiple sclerosis (MS) is considered an immune-mediated disorder in which the immune system attacks healthy neuronal tissue. MS affects more than 2.3 million people worldwide. Its most common symptoms include overwhelming fatigue, visual disturbances, altered sensation, and difficulties with mobility. Symptoms vary in type and severity from patient to patient.1

Research and development in the treatment of MS has been rapid and active. For this review, the Clinical Trials.gov database was searched for phase 3 studies in MS that have been updated since December 1, 2014. “Multiple sclerosis” was the sole search term. Ninety-five results were returned, which covered approved agents being studied not only to treat patients with relapsing or progressive MS but also to address the symptoms of acute disease and its comorbidities. Moreover, the pipeline includes several new agents with different mechanisms of action. In addition to relapse prevention, an important focus of the newest classes of MS agents is to prevent disability.

This article summarizes data for the agents most recently approved for treatment of patients with MS as well as data for the key investigational agents, which, if phase 3 results continue to show promise, may prove to be significant additions to the therapeutic armamentarium.

Recently Approved Agents

**Peginterferon Beta-1a**

Approved by the US Food and Drug Administration (FDA) on August 15, 2014, and marketed as Plegridy by Biogen Idec, this compound is the pegylated follow-on version of Avonex (interferon beta-1a), which received FDA approval in 1996 for relapsing-remitting multiple sclerosis (RRMS).2 Pegylation extends the half-life of the parent compound, permitting a less frequent dosing schedule than that of the unpegylated product, which requires a once-weekly injection.3 The recommended dosage of peginterferon beta-1a is 125 μg every 14 days, by subcutaneous injection, with a prefilled pen-type syringe.4

The FDA’s approval of this drug was based on results of the ADVANCE study, a 2-year, randomized, phase 3, double-blind clinical trial in which efficacy and safety were evaluated. One-year ADVANCE study results indicate that after 48 weeks of treatment with peginterferon beta-1a, patients had a “significantly reduced relapse rate compared with placebo. The drug might be an effective treatment for relapse-remitting multiple sclerosis with less frequent administration than available treatments.”5

Researchers conducted the study using a placebo-controlled design for the first 48 weeks at 183 sites in 26 countries. Patients with RRMS were randomly assigned to receive subcutaneous injection of placebo or 125 μg of peginterferon beta-1a once every 2 weeks or every 4 weeks. The primary end point was annualized relapse rate at 48 weeks. Secondary efficacy end points were the number of new or newly enlarging hyperintense lesions, the proportion of patients who experienced relapse, and the proportion of patients with disability progression at 48 weeks.

Of the 1512 patients who were randomly assigned to receive either placebo (n = 500), peginterferon beta-1a every 2 weeks (n = 512), or peginterferon beta-1a every...
4 weeks (n = 500), 1332 patients completed 48 weeks of treatment (456 [91%], 438 [88%], 439 [86%] patients, respectively).

In the first year of the study, the annualized relapse rate for patients who received peginterferon beta-1a every 2 weeks was lower than that of placebo recipients (0.256 vs 0.397; $P = .0007$). For those who took peginterferon beta-1a every 4 weeks, the annualized relapse rate was 0.288. The full results of the 2-year study were published in 2015 and affirm the clinical benefits of the pegylated product.

The most common adverse events associated with peginterferon beta-1a were injection-site reactions, flu-like symptoms, pyrexia, and headache. All adverse events registered over 1 year were published as percentages of the randomized (not completer) population (N = 1512). Adverse events, including relapse, were reported for 417 (83%) placebo recipients, 481 (94%) patients who took peginterferon beta-1a every 2 weeks, and 472 (94%) patients who took the study drug every 4 weeks.

Serious adverse events, such as relapse, pneumonia, and urinary tract infection, occurred in 76 (15%) patients who received placebo, 55 (11%) patients who received peginterferon beta-1a every 2 weeks, and 71 (14%) of those who received the study drug every 4 weeks.

**Dimethyl Fumarate**

Dimethyl fumarate (Tecfidera), also manufactured by Biogen, is an oral medication to treat relapsing forms of MS. It is taken twice daily with or without food. Tecfidera received FDA approval on March 27, 2013, based on the results of 2 global, 2-year, randomized, multicenter, double-blind, placebo-controlled, dose-comparison phase 3 clinical trials (DEFINE and CONFIRM) that demonstrated its effectiveness for long-term treatment of patients with RRMS.

In the CONFIRM trial, glatiramer 20 mg (subcutaneous daily injection) was included as a reference comparator. The trial comprised more than 1400 patients with RRMS in 28 countries. Researchers found that patients who received 240 mg of dimethyl fumarate 2 or 3 times daily had a significantly lower relapse rate (0.22 for twice-daily dimethyl fumarate, 0.20 for thrice-daily dimethyl fumarate, 0.29 for glatiramer acetate, 0.40 for placebo) and better neoradiologic outcomes than placebo recipients.

Adverse events that were more common with active treatment than with placebo included flushing and gastrointestinal reactions (with dimethyl fumarate) and injection-related effects (with glatiramer). No malignant neoplasms or opportunistic infections were reported for patients on dimethyl fumarate, but lymphocyte counts decreased with dimethyl fumarate use.

In the DEFINE study, more than 1200 patients with RRMS were enrolled at 198 sites in 28 countries. Patients were randomly assigned to receive dimethyl fumarate 240 mg or placebo 2 or 3 times daily. Compared with placebo, both regimens of dimethyl fumarate were associated with a significantly lower relapse rate (27% with twice-daily dimethyl fumarate, 26% with thrice-daily dimethyl fumarate, 46% with placebo) as well as a significantly lower annualized relapse rate, rate of disability progression, and number of lesions observed by magnetic resonance imaging (MRI). In the DEFINE trial, the adverse effects associated with dimethyl fumarate included flushing and gastrointestinal events such as diarrhea, nausea, and upper abdominal pain, as well as decreased lymphocyte counts and elevated levels of aminotransferase in the liver.

Using 2 years of pooled data from the DEFINE and CONFIRM trials, researchers affirmed that compared with placebo, dimethyl fumarate reduced the annualized relapse rate (56% reduction; $P < .0040$), the proportion of patients who experienced relapse (56% reduction; $P = .0037$), and the time to sustained 12-week progression of disability (78% reduction; $P = .0067$).

The ENDORSE trial was a 3-year extension trial of patients who participated in the DEFINE or CONFIRM studies. According to a press release from the manufacturer, the safety profile of dimethyl fumarate in the ENDORSE trial was consistent with the favorable findings of the DEFINE and CONFIRM studies and reflected a minimum of 5 years’ observation per patient. There was no increase in the overall risk for serious infections, including opportunistic infections. Dimethyl fumarate consistently showed long-term efficacy in patients with RRMS who had been treated previously with interferon.

**KEY POINTS**

- Research and development in the treatment of multiple sclerosis (MS) has been rapid and very active; 95 phase 3 trials are under way, involving a variety of agents.
- The majority of these clinical trials are being conducted with selective sphingosine-1-phosphate receptor 1 immunomodulators such as laquinimod, ozanimod, ponesimod, and siponimod.
- It appears that daclizumab, a once-monthly interleukin-2 inhibitor, is leading the race for FDA approval. A decision from the FDA may come by the middle of 2016.
- Late-phase trials are addressing not only MS treatment and relapse prevention but also the sequelae and comorbidities of the disease.
Throughout the study period, the annualized relapse rate remained low for patients who received continuous treatment with dimethyl fumarate compared with those who initially received 2 years of placebo in DEFINE and CONFIRM. The annualized relapse rate improved for patients who were switched from placebo in DEFINE and CONFIRM to dimethyl fumarate in ENDORSE, whether they were treatment-naïve or had received interferon or glatiramer acetate.11

The Phase 3 Pipeline

**Daclizumab High-Yield Process**

Biogen is also testing daclizumab (known also as daclizumab high-yield process), a once-monthly interleukin-2 inhibitor intended to reduce annualized relapse rates. The manufacturer, Biogen (and its partner AbbVie), submitted a biologic license application in April 2015 (Table),12 which means that the FDA will likely decide this product’s status in the first half of 2016.

Results from the phase 3 DECIDE clinical trial were recently published in the *New England Journal of Medicine*.13 When administered subcutaneously once monthly, daclizumab demonstrated significant reduction of disease activity in people with RRMS in comparison to injections of interferon beta-1a.13

The incidence of serious infections was higher for patients treated with daclizumab than for those who received interferon beta-1a (4% vs 2%). Daclizumab recipients had a higher incidence of cutaneous adverse events (37% vs 19%, respectively), serious cutaneous reactions (2% vs <1%), and elevations of liver transaminases greater than 5 times the upper limit of normal (6% vs 3%). There were 4 deaths in the control group and 1 in the daclizumab group, none of which were deemed related to treatment.13

Another phase 3 long-term extension study for daclizumab is under way, and is scheduled for completion in 2019.14

**Masitinib**

Masitinib, a tyrosine kinase inhibitor, is in late-stage testing for the treatment of patients with secondary and primary progressive MS (PPMS). It is a twice-daily oral medication that targets mast cells and inhibits several biochemical processes.14 Masitinib also is being tested for use in the treatment of patients with Alzheimer’s disease and amyotrophic

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**Table: Phase 3 Drug Pipeline for Multiple Sclerosis**

<table>
<thead>
<tr>
<th>Nonproprietary name</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Drug category</th>
<th>Estimated FDA submission date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclizumab high-yield process</td>
<td>Biogen Idec and AbbVie</td>
<td>RRMS</td>
<td>Interleukin-2 inhibitor</td>
<td>April 29, 2015</td>
</tr>
<tr>
<td>Masitinib</td>
<td>AB Science</td>
<td>PPMS, SPMS</td>
<td>Tyrosine kinase inhibitor</td>
<td>2017</td>
</tr>
<tr>
<td>Laquinimod</td>
<td>Teva and Active Biotech</td>
<td>RRMS</td>
<td>Immunomodulator&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2017 or beyond&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ponesimod</td>
<td>Actelion</td>
<td>RRMS</td>
<td>Sphingosine-1-phosphate receptor 1 inhibitor</td>
<td>2018</td>
</tr>
<tr>
<td>Siponimod</td>
<td>Novartis</td>
<td>RRMS, PPMS, SPMS</td>
<td>Sphingosine-1-phosphate receptors 1 and 5 inhibitor</td>
<td>2017</td>
</tr>
<tr>
<td>Ozanimod</td>
<td>Celgene</td>
<td>RRMS, PPMS, SPMS</td>
<td>Sphingosine-1-phosphate receptors 1 and 5 inhibitor</td>
<td>2018</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>Genentech</td>
<td>PPMS, SPMS</td>
<td>CD20-positive B-cell–targeting monoclonal antibody</td>
<td>2016</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mechanism of action has not been fully elucidated.

<sup>b</sup>New drug application was originally planned in February 2012, but Teva decided not to submit at that time. *FDA News*. Teva withholds NDA for MS drug laquinimod following FDA talks. February 22, 2012. www.fdanews.com/articles/144195-teva-withholds-nda-for-ms-drug-laquinimod-following-fda-talks.

PPMS indicates primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.
lateral sclerosis. A communication from the manufacturer, AB Science, indicates that phase 2B testing showed significantly improved MS Functional Composite scores for patients with PPMS and secondary progressive MS (SPMS) compared with scores of the placebo group. A phase 3 trial is currently under way in 600 patients with progressive forms of MS; it is expected to last 96 weeks. This placebo-controlled trial will test maicitinib’s effect on the MS Functional Composite test, the Expanded Disability Status Scale, and the 54-item Multiple Sclerosis Quality of Life instrument. This study is expected to conclude in 2016, with interim results currently being analyzed.

Laquinimod

Laquinimod, from Teva and Active Biotech, has demonstrated conflicting late-stage study results. In its phase 2, randomized, placebo-controlled study conducted in 209 people with RRMS, laquinimod demonstrated a 44% decrease in gadolinium (Gd)-enhancing brain lesions over 24 weeks compared with placebo. In a separate 36-week, phase 2b, randomized, placebo-controlled study of 306 patients with RRMS, laquinimod produced reductions of approximately 40% in cumulative Gd-enhancing lesions and T2 lesions compared with placebo.

Findings of the phase 3 studies of laquinimod have been difficult to interpret. The 2-year phase 3 ALLEGRO and BRAVO randomized placebo-controlled studies included a combined total of 2400 patients with RRMS. The ALLEGRO investigators found that the average annual relapse rate with laquinimod was 23% lower than with placebo. Laquinimod was also associated with a one-third reduction in the progression of disability. However, the BRAVO study provided contradictory results, demonstrating nonsignificant differences (vs placebo) in the annual relapse rate. An analysis of baseline MRI lesion characteristics for the laquinimod and placebo groups revealed that fewer members of the placebo group demonstrated significant lesions compared with that of the patients in the laquinimod group. When this bias was corrected, the annual rate of relapse was significantly lower for the laquinimod group. In the BRAVO study, it appeared that laquinimod had beneficial effects on the progression of disability.

In May 2014, the European Medicines Agency declined to approve laquinimod. Teva is moving ahead with additional studies in both RRMS and progressive MS. The CONCERTO study, a phase 3 trial of 2200 patients with RRMS is still under way and not expected to conclude in 2019.

Ponesimod

Ponesimod is an oral investigational drug of the selective sphingosine-1-phosphate receptor 1 (S1P1) immunomodulator class. Its mechanism of action involves preventing the escape of lymphocytes from lymph nodes, which results in fewer circulating blood lymphocytes and reduced infiltration of lymphocytes into organs affected by disease. Lymphocytes have been implicated in the destruction of myelin on axonal tissue. Actelion conducted a multicenter phase 2 extension study of ponesimod in which 326 patients completed at least 48 weeks of treatment. Results of the trial, published in 2013, showed that active treatment was associated with lower MRI activity and relapse rates.

The OPTIMUM phase 3 study is a multicenter, randomized, double-blind, active-controlled comparison trial of ponesimod and teriflunomide in 1100 patients with RRMS. Relapse rate is the primary end point. The 3-year study is expected to conclude in 2018.

Siponimod

Siponimod is a new drug under investigation for SPMS, manufactured by Novartis. It is a tablet taken once daily. Related to fingolimod, siponimod is an oral selective modulator of the sphingosine-1-phosphate (S1P) receptor subtypes 1 and 5. The goal of this increased selectivity is to maintain or improve the efficacy and safety profiles of fingolimod.

Like ponesimod, siponimod prevents lymphocytes from leaving lymph nodes. In a phase 2 placebo-controlled study of patients with RRMS, siponimod resulted in significantly lower relapse rates than placebo (0.20 vs 0.58, respectively) and nearly 80% fewer brain lesions as assessed by MRI. Common side effects included headache, bradycardia, dizziness, and infections of the nose and throat.

A new phase 3 study of siponimod in patients with progressive MS is ongoing. The investigators seek to determine the drug’s effect on disability progression in these patients.

Ozanimod

Like siponimod, ozanimod is an S1P receptor modulator that targets receptor subtypes 1 and 5. At the 2015 annual meeting of the American Academy of Neurology, the results of a phase 2 trial of ozanimod for relapsing forms of MS were announced. Ozanimod achieved its primary end point of reduction in MRI brain lesions (86% less activity than placebo).

In this placebo-controlled, double-blind trial comprising 258 patients, ozanimod also reduced the annualized relapse rate by 53% compared with placebo (a secondary end point for which it was not statistically powered to detect significance). The safety profile of ozanimod appears to be superior to that of other members of its class. Ninety-eight percent of the patients continued taking the drug for the course of the clinical trial (6 months), which could differentiate this agent from similar drugs.
The developing company, Receptos, was purchased by Celgene in July 2015.29 Oznanimod entered 2 phase 3 trials in December 2014 for the treatment of progressive MS. Known as RADIANCE and SUNBEAM, these trials are randomized double-blind studies designed to compare 2 doses of oznanimod with interferon beta-1a.30 These studies are scheduled to conclude in 2017,29,30

Ocrelizumab

Ocrelizumab is a CD20-positive monoclonal antibody that targets B-cells, a promising new mechanism of action. The drug is manufactured by Genentech. Results of a phase 2 study showed that 218 patients with RRMS in the intention-to-treat population were found to have 89% fewer Gd-enhancing lesions at week 24 than in the placebo group (P <.0001).31

In September 2015, Genentech announced the results of its pivotal phase 3 study (dubbed ORATORIO) to evaluate the drug’s effectiveness in patients with PPMS. ORATORIO is a multicenter, double-blind, randomized, placebo-controlled trial developed to evaluate the efficacy and safety of ocrelizumab (administered intravenously as two 300-mg infusions 2 weeks apart) in 732 patients with PPMS.32 Although study results have not yet been released, Genentech reported that ocrelizumab met its primary end point: significant reduction (vs placebo) of the patients’ clinical disability progression (ie, increase in the Expanded Disability Status Scale), which was demonstrated for 12 weeks or more. Genentech indicated that the drug’s safety profile was similar to that of placebo, with the exception of mild to moderate reactions related to the infusion and infusion site.32

Other Treatments in the Pipeline

Natalizumab (Tysabri), produced by Biogen and Elan, has been approved for use in RRMS and is being tested for progressive forms of the disease.33 Ofatumumab (Arzerra), which is approved for the treatment of patients with chronic lymphocytic leukemia, has shown promise in RMSS. In August 2015, Novartis purchased the rights to ofatumumab (entering phase 3) from GlaxoSmithKline to bolster its MS pipeline.34 Several phase 3 trials are under way for medications aimed at treating the symptoms or comorbidities of MS. For example, Acthar gel (ACTH) is being tested for its efficacy in addressing fatigue in patients with RRMS.35 MD1003, a highly concentrated form of biotin, is being tested in Europe for the treatment of patients with progressive MS as well as the optic neuritis associated with MS.36 Its manufacturer, MedDay, is currently conducting a phase 3 clinical trial for these indications. For progressive MS, interim study results indicated that 13% of the treatment group (vs 0% of the placebo group) demonstrated at least some measurable disability improvement at 12 months of treatment.37 A small pilot study had indicated a positive effect on disability, prompting the larger phase 3 investigation.38 In the optic neuritis trial, 105 patients were randomized to receive either MD1003 or placebo. The trial is expected to conclude in 2015. The clinical end points are visual clarity and retinal thickness.36

Conclusion

Several manufacturers are testing medications in late-stage clinical trials for the treatment of patients with relapsing and progressive forms of MS. The bulk of these agents are selective S1P1 immunomodulators, although other mechanisms of action are being actively investigated. An interleukin-2 agent may be the next medication facing an FDA approval decision. In any case, over the next few years, physicians should be able to choose from several additional medications for treating their patients with MS.

Author Disclosure Statement

Ms Radick and Mr Mehr have reported no conflicts of interest.

References

The Latest Innovations in the Drug Pipeline for Multiple Sclerosis


