ABSTRACT

This article addresses the management of patients with multiple sclerosis (MS) who are refractory to first-line therapies. Evidence from clinical studies, in addition to practical issues related to switching and combining therapies, are discussed. Challenges to successful outcomes, including the appearance of neutralizing antibodies, and complications from promising therapies such as natalizumab are also addressed. Updates on second-line therapies are provided, including what may be in the pipeline for relapsing and remitting and secondary progressive MS.


PROCEEDINGS

WHAT NOW? WHEN FIRST-LINE THERAPY FAILS*

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ALTHOUGH some patients with multiple sclerosis (MS) respond well to disease-modifying therapy, clinicians are often faced with the challenge of frequent relapses, worsening neurological examinations, and/or magnetic resonance imaging (MRI) studies with new lesions or progressive brain atrophy. This article discusses various options, including switching first-line therapies (eg, from interferon to glatiramer acetate or vice versa) or combining agents. The role of neutralizing antibodies in treatment failure is also reviewed, as is the use of chemotherapeutic agents and other second-line drugs.

INTERFERON VERSUS GLATIRAMER ACETATE

Traditional first-line therapy for MS has focused on the use of immunomodulatory drugs, such as interferon (Avonex, Biogen Idec, Cambridge, Mass; Rebif, Serono, Geneva, Switzerland; Betaseron, Berlex, Montville, NJ) or glatiramer acetate (Copaxone, Teva Neuroscience, Kansas City, Mo), and there are several main distinguishing features between these 2 classes. Interferons have a robust and rapid effect on inflammation, as evidenced by MRI studies that demonstrate a 50% to 80% reduction in the appearance of new gadolinium-enhancing lesions. Interferons also reduce T2 lesion volume. Clinically, interferon treatment results in an approximately 30% reduction in relapse rates. However, the interferons have issues related to safety, tolerability, and the development of neutralizing antibodies, some of which are dose related.

By contrast, the onset of action on inflammatory activity of glatiramer acetate may be delayed, and it does not appear to bring about as large a reduction in the number of new gadolinium-enhancing lesions, which is a measure of inflammatory activity (generally, there is only a 35%–40% decrease). Glatiramer acetate...
is similar to the interferons in its ability to reduce clinical relapse rates by approximately 30%. It is also a safer and better-tolerated alternative to interferon, with fewer adverse effects. Furthermore, there is an emerging body of literature about glatiramer acetate, indicating that it may have some neuroprotective properties. Because interferons and glatiramer acetate each have their pros and cons, 1 option for patients who do not respond to a particular regimen is to switch therapies.

**Switching Therapies**

Within the interferons as a class, there are several differences that must be taken into consideration when switching therapies. First, there are chemical differences between these molecules. Specifically, Avonex and Rebif are both interferon beta-1a molecules, whereas the interferon beta-1b molecule is manufactured as Betaseron. Betaseron is less potent; however, this is compensated for by a higher dosage, and thus larger amounts of the protein. In terms of biological activity, 1 µg of Avonex or Rebif is equivalent to 14 µg of Betaseron.

The route of administration is also different, although all interferons require an injection. The pharmacokinetics and pharmacodynamics are essentially equivalent between Avonex (administered intramuscularly) and Rebif (administered via a subcutaneous route). Avonex is administered once weekly, whereas Rebif is injected 3 times per week, and the frequency of injection does seem to have a pharmacodynamic impact. Administering the same total dose in 3 injections per week improves biological activity by 2 to 3 times over giving the dose in a single injection.

**Combination Therapy**

Another possibility for refractory patients, rather than changing therapies, is to initiate combination therapy. Although there is a host of available agents and combinations that have been attempted, supporting data for these are scarce and/or anecdotal. The standard therapies (interferon and glatiramer acetate) can be combined with one another, with scheduled pulses of intravenous methylprednisolone, with chemotherapeutic agents (eg, mitoxantrone, cyclophosphamide, or methotrexate), or immunosuppressive drugs such as azathioprine and mycophenolate mofetil. Thus far, combining these treatments has not led to major safety concerns or serious adverse effects.

**Neutralizing and Binding Antibodies**

One common reason for considering switching MS therapies has been the development in some patients of neutralizing or binding antibodies that may decrease the efficacy of a particular drug. Technically, there is a distinction between so-called “binding antibodies” and “neutralizing antibodies.” Binding antibodies (BABs) bind to the interferon molecule at various antigenic sites and may or may not interfere with its interaction with the interferon receptor. Neutralizing antibodies (NABs) attach specifically to the receptor-binding portion of the interferon molecule, preventing interaction with the receptor. Therefore, neutralizing antibodies have the potential to inhibit interferon function, particularly in patients with persistently high titers.

After 6 to 18 months of treatment, NABs may develop in patients taking any of the available interferons, albeit the risk of antibody formation varies with each specific medication. Betaseron is most likely to induce NAB formation (in 30%–35% of patients), followed by Rebif (15%–20%), and Avonex (5%). The development of NABs may be related to the purity and dose of the compound, protein aggregation properties, and host factors, and is less likely to depend on the drug’s route of administration.

Sustained, high titers of NABs are likely to decrease interferon efficacy, but this is neither an “all or none” phenomenon, nor is it necessarily permanent. Furthermore, there have been patients who develop NABs but who remain clinically stable; conversely, interferon treatment failures may occur in patients who are NAB negative.

Several assays are available to test for the presence of both binding and neutralizing antibodies. For BABs, an enzyme-linked immunosorbent assay test is commercially available that is inexpensive and provides quick results. Although the assay is an adequate screening tool, the finding of BABs does not necessarily imply that they are diminishing the biological activity of the interferon molecule. Assays to test for the presence of NABs include a viral cytopathic effect (CPE) test and a myxovirus protein A (MxA) induction assay. MxA appears to be more sensitive and more accurate, but is not currently commercially available. The CPE and MxA tests...
are expensive and time consuming at the present time. In addition, there are certain questions about the results of NAB tests, including assay standardization, the interpretation of a titer in terms of actual clinical effect, and the persistence of antibody levels. Neutralizing antibodies can resolve spontaneously, and it is not always clear when and how often patients should be tested for them.9-14

In terms of clinical strategies for minimizing the risk of this complication, some studies have shown a 50% reduction in the development of NABs when interferons are administered along with pulsed steroids.15 Immunosuppressant drugs also may be useful for preventing NAB formation or reducing antibody titers. Additionally, the dose of interferon may play a role. One study noted that patients on higher doses of Rebif (44 µg vs 22 µg) actually had a lower incidence of developing antibodies.4,5 Similar studies are ongoing to evaluate this phenomenon for Betaseron. Finally, in patients who are NAB positive and who appear to be failing therapy, clinicians may consider switching to a less immunogenic compound, such as Copaxone and/or other non-interferon–based drugs. One of these alternatives may be natalizumab (Tysabri, Biogen Idec, Cambridge, Mass, and Elan, New York, NY) in the future.

NATALIZUMAB

Tysabri is a recombinant, humanized immunoglobulin G monoclonal antibody that had been approved by the US Food and Drug Administration (FDA) in November 2004 for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS). The drug had been evaluated in 2 randomized, double-blind, placebo-controlled studies. Study 1 (AFFIRM trial) was a monotherapy study, enrolling patients who had not received interferon or glatiramer acetate for 6 or more months.16 Study 2 was a combination therapy trial for patients who had experienced relapses while taking Avonex (SENTINEL trial).17 One-year data from these then ongoing trials resulted in fast-track approval by the US FDA. However, 3 months after Tysabri first became available, the development of 3 cases of progressive multifocal leukoencephalopathy (PML) in patients who had been treated with Tysabri came to the attention of researchers and the US FDA. Two of these cases occurred in patients with MS, and 1 of these was fatal. Both patients had received more than 2 years of therapy with natalizumab in combination with Avonex. In February 2005, Tysabri was withdrawn from the market. The US FDA is currently debating the return of Tysabri, but only as monotherapy. These decisions will be based, in part, on positive data from the AFFIRM trial.

The AFFIRM Trial

The AFFIRM trial followed 627 patients on Tysabri monotherapy and demonstrated a 68% reduction (P < .0001) in the number of annual relapses compared to the number experienced by the 315 patients randomized to placebo (Figure 1). There was a 59% reduction in risk of relapse (hazard ratio = 0.41), and 67% of patients remained relapse-free on natalizumab (vs 41% on placebo) over the 2 years of the study. Other significant findings from the AFFIRM trial included a reduction in the risk of sustained disability progression (by 42% compared to placebo over 2 years [P = .0002]), and a reduction in disability progression as determined by change in the Multiple Sclerosis Functional Capacity scale (P < .0001). In terms of MRI endpoints, there was a 92% reduction in gadolinium-enhancing lesions at 2 years (Figure 2), along with an 83% reduction in new or enlarging T2 lesions by the second year and a 76% reduction in T1 hypointense (“black hole”) lesions.
In terms of the production of antibodies to natalizumab, 91% of patients were antibody negative (9% were positive at any given point, with 3% “transiently positive” and 6% “persistently positive”). Persistently positive patients experienced loss of Tysabri efficacy and an increase in infusion-related reactions. As monotherapy, Tysabri was safe and well tolerated. The most common adverse effects included headache, fatigue, and arthralgias. There was no significant difference in the incidence of serious adverse events, infections, or malignancies between the Tysabri-treated and placebo groups. There were no cases of PML identified in the AFFIRM trial. However, infusion-related reactions did occur (18% in the placebo group vs 24% in the treated group), and 1.3% of patients experienced a serious hypersensitivity reaction.

**WHAT THE FUTURE HOLDS FOR NATALIZUMAB**

At the present time, the US FDA is considering whether Tysabri should be made available again and, if so, what label changes may accompany its re-release. Combination therapy and/or its use in immunocompromised patients may be discouraged, and it will also be important to obtain informed consent from patients. Despite the risks, many patients are interested in starting or restarting Tysabri, and the US FDA has approved the initiation of a 2-year follow-up safety trial. Subjects in this study will undergo blood polymerase chain reaction (PCR) monitoring for the JC virus, annual MRI, and cognitive screening tests. If Tysabri were to become commercially available as a result of these follow-up safety trials, safety monitoring no doubt would be ongoing at a heightened vigilance, perhaps including the performance of MRI and lumbar puncture in suspected cases, with PCR analysis of the cerebrospinal fluid (CSF) for the JC virus in patients with suspicious CSF results.18

Several unanswered questions remain. Currently available data indicate that the risk of PML associated with Tysabri treatment is approximately 1 in 1000. It is unclear if the risk for monotherapy is any different than the risk for combination therapy; it is possible that the presence of another immunosuppressant/immunomodulator drug may play a role. A patient who was taking Tysabri for Crohn’s disease also died of PML; this patient was not on interferon therapy, but had taken immunosuppressant drugs in the past. Other questions arise as to which patients would be appropriate candidates for Tysabri (eg, patients who are refractory to other treatments vs newly diagnosed patients), and what specific treatment algorithms should be developed. If patients had been on other therapies, should there be a washout period? Is there a method of detecting potential cases of PML early enough to prevent irreversible damage? All of this remains to be answered as clinicians and scientists continue to examine the potential role of Tysabri in treating MS. In the meantime, other nontraditional therapies (primarily chemotherapeutic or immunosuppressive agents) are being examined in patients with MS when first-line therapies fail.

**CHEMOTHERAPEUTIC AND IMMUNOSUPPRESSIVE AGENTS**

**Mitoxantrone**

Mitoxantrone, an antineoplastic medication, is also indicated for worsening RRMS, including secondary progressive multiple sclerosis (SPMS). The drug is administered intravenously every 3 months, but its lifetime use is limited to 2 to 3 years due to the potential of cardiac toxicity. Other side effects that need close monitoring include infections, infertility, and leukemia. Patients treated with mitoxantrone must...
undergo careful monitoring, including regular multiple gated acquisition scans or echocardiography; complete blood counts, including platelets; liver function tests; a pregnancy test; and urinalysis; all to be performed before each course of therapy. Adverse effects from the medication include nausea and alopecia.

**AZATHIOPRINE AND MYCOPHENOLATE**

Azathioprine is an immunosuppressive agent generally used to prevent organ rejection in transplant recipients. It is a nucleoside analogue that inhibits DNA and RNA synthesis, and has demonstrated mixed results in MS clinical trials, but does appear to have some efficacy in terms of relapse rate reduction.19

Azathioprine is administered orally, and has multiple potential adverse effects, including allergic reactions, liver toxicity, alopecia, lymphopenia, anemia, and lymphoma in long-term users.

Mycophenolate is also an immunosuppressive agent, and appears to have some efficacy in MS. This drug is better tolerated than azathioprine, but does have gastrointestinal side effects, including nausea and diarrhea.20 Mycophenolate and azathioprine may be most useful in combination with other MS therapies, rather than as monotherapy.

**METHOTREXATE**

Methotrexate is an anti-inflammatory and immunomodulatory agent that inhibits dihydrofolate reductase and the activity of interleukins (IL)-1, IL-2, and IL-6. It is generally well tolerated, but has the potential to cause liver toxicity, gastrointestinal upset, and interstitial pneumonitis. Methotrexate has been shown to have some benefits in upper extremity function in SPMS and is currently being evaluated in combination with Avonex and steroids.

**CYCLOPHOSPHAMIDE**

This drug is an antineoplastic alkylating agent that causes immune suppression, decreases levels of gamma-interferon, and increases levels of various interleukins (IL-4 and IL-10). It is administered intravenously, initially on a daily basis for 5 days and then in booster doses every 1 to 2 months. Cyclophosphamide is a potent and potentially dangerous drug that may cause hematologic toxicity, hemorrhagic cystitis, malignancy, nausea, vomiting, alopecia, and infertility. These toxicities limit its use to patients with aggressive MS and SPMS with or without relapses.

**ALEMTUZUMAB**

Alemtuzumab is a monoclonal antibody that is currently used to treat patients with B-cell chronic lymphocytic leukemia. In studies of patients with MS, the drug decreased risk of relapse by 75% compared to Rebif, but it is on clinical hold by the US FDA due to adverse effects, including the occurrence of idiopathic thrombocytopenic purpura and some deaths currently under investigation.21

**CLADRIBINE**

Another cancer chemotherapeutic agent, cladribine, is lymphocytotoxic (induces apoptosis in resting and dividing lymphocytes) and, in pilot studies in patients with MS, demonstrated a reduction in relapses and a robust effect on MRI with complete suppression of gadolinium-enhancing lesions.22,23 Unfortunately, the drug did not appear to slow progression as measured by Expanded Disability Status Scale. An oral formulation of cladribine is currently undergoing further studies to determine its potential utility in MS.

**CLINICAL TRIALS: AGENTS CURRENTLY UNDER INVESTIGATION**

Several other agents are currently undergoing phase II and III studies as potential treatments for MS. These agents include: FTY720, daclizumab, rituximab, laquinimod, and teriflunomide. FTY720 is an oral agent administered once daily, for which phase II data showed a 62% reduction in gadolinium-enhancing lesions and a 55% reduction in relapses. (Phase III placebo-controlled studies have been initiated.) Daclizumab, administered as a weekly subcutaneous injection for patients with RRMS, reduced MRI lesions in combination with interferon (as an add-on therapy for patients on interferon who had breakthrough relapses) during phase II and III studies. Rituximab, administered by intravenous infusion every 6 months, depletes B cells and is currently in phase II studies for RRMS. This drug is the only treatment currently undergoing phase III investigation for primary progressive disease. Laquinimod is an oral agent that has various immune regulatory effects. Phase II data for patients with RRMS demonstrated a 44% reduction of new lesions on MRI scans. Finally, another oral agent being evaluated for use in RRMS is teriflunomide. Phase II data showed a 64% reduction in new MRI lesions, and current studies are evaluating this drug as monotherapy and in combination with interferon or glatiramer acetate.24
CONCLUSIONS

In the future, treatment of MS will likely involve combination therapies, possibly in a stepwise fashion similar to algorithms for other chronic conditions or replacing one therapy with another after efficacy wanes or adverse effects appear. In addition, antibody testing will likely be routine in the future with standardized assays. As for new and returning therapies, Tysabri will likely return as a treatment for MS, but under careful scrutiny. In addition, chemotherapies will continue to emerge for more aggressive RRMS cases and SPMS, providing hope for a better future for patients with MS refractory to the first-line therapies in our current armamentarium.

REFERENCES