INADEQUATE RESPONDERS: IDENTIFICATION AND TREATMENT MODIFICATION*

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ABSTRACT

Many patients with multiple sclerosis (MS) experience significant breakthrough disease despite ongoing treatment with first-line disease-modifying agents. The management of breakthrough disease requires consideration of the potential causes of new MS exacerbations and the selection of an appropriate therapy. Poor treatment adherence is an important barrier for many patients, and may occur as a result of numerous patient-related, physician-related, or medication-related factors. Strategies to enhance treatment adherence include effective patient education about the likely benefits of therapy and the importance of using medications as prescribed, as well as the use of specific measures to help patients overcome adverse effects of disease-modifying drugs. Some patients who are treated with interferon (IFN) β experience treatment failure as a result of the formation of neutralizing antibodies to IFN. There is little information about the effectiveness of switching between first-line treatments for patients with MS who are not responding adequately to therapy. Switching to natalizumab is an option for patients with continued disease activity, although the potential for progressive multifocal leukoencephalopathy is a significant cause for concern.

Patients with breakthrough disease may benefit from the addition of a second medication to the treatment regimen, although combination therapy for MS has not been extensively studied in controlled clinical trials. Immunomodulatory therapy with pulsed corticosteroids is often added to the initial disease-modifying agent. Intravenous immunoglobulin (IVIG) is used by some clinicians, although there is little evidence that IVIG reduces long-term disability. Several cytotoxic agents have been used to treat breakthrough disease, including mitoxantrone, azathioprine, mycophenolate, and methotrexate. The oral lymphocytotoxic agent cladribine is currently being evaluated in late-phase clinical trials for the treatment of MS. Alemtuzumab, a monoclonal antibody against the CD52 cell-surface marker, has produced promising results in early clinical studies. All of these treatment options require careful consideration of the potential for significant adverse events.

Breakthrough disease may be defined as the presence of clinical or radiologic evidence of disease activity that is considered unacceptable on the basis of the patient’s individual condition and history, and that is not sufficiently controlled by a current treatment intervention. The management of breakthrough disease requires consideration of several factors, including the possibility of patient nonadherence to treatment, other possible causes of continued disease activity, and therapeutic options for patients with suboptimal response to therapy.

**Assessing and Improving Treatment Adherence**

Before concluding that a patient is exhibiting breakthrough disease, it is important to assess adherence to prescribed therapy. Poor treatment adherence is a complex issue that may reflect a number of patient-related factors, including unrealistic expectations about the benefits of therapy, depression, anxiety, fear of self-injections, medication side effects, fatigue, cognitive status, the patient’s lifestyle, and the patient-physician relationship. In one study of factors that were related to poor treatment adherence in MS, forgetting to inject medication was the most common reason for treatment nonadherence.11

Several strategies may help to improve medication adherence, including frequent assessment of patient outcomes, effective patient education about the rationale for disease-modifying therapy, and setting realistic expectations. To the extent possible, the regimen should be matched to the goals and interests of the patient. For example, it may be best to avoid an agent that is administered by frequent self-injection if the patient has expressed a fear of needles. Patients should be educated about the importance of consistent medication administration and how the medication should be taken. Patient instructions should include written materials summarizing medication use. It is also helpful to test the patient’s recall of this information by asking them to explain how they plan to take the medication. If possible, the patient’s caregiver should be included in the education about MS and instructions for correct medication use.

Treatment adherence may also be improved by the use of strategies to help manage adverse effects of disease-modifying therapy. Flu-like symptoms (fever, chills, aching) with IFN therapy generally diminish after the first few months. These adverse reactions may be avoided by gradually escalating the dose when starting treatment; by premedication with pain relievers, such as acetaminophen, ibuprofen, or naproxen; and by evening administration. Some patients develop depression during IFN therapy, although it is not clear whether the depression is causally linked to IFN. Regardless of the relationship between depression and IFNβ, treating depression has been shown to improve adherence in patients receiving IFNβ therapy for MS. Patients who are taking GA or IFNβ should be counseled about the likelihood of injection-site reactions. With IFNs, injection-site reactions are very common with subcutaneous (SC) injection, and are less of a problem when administered by the intramuscular (IM) route. Tissue atrophy and lipoatrophy can occur in some patients, especially at high IFN doses. GA can cause injection-site reactions, including lipoatrophy. GA may also cause an immediate post-injection reaction that is characterized by flushing, chest pain, palpitations, anxiety, shortness of breath, and nausea. Patients should be counseled about the possibility of this reaction and instructed to remain calm and comfortable until the reaction has passed (usually within 15 minutes). Patients who have significant fear of needles or self-injection may benefit from referral to a behavioral therapist.

**Options for Managing Breakthrough Disease**

There is little information regarding the effectiveness of switching from one first-line therapy to another in patients with an inadequate response. One large, retrospective, open-label study found that switching from one IFNβ to another for poor treatment response did not result in better treatment outcomes. Some studies have suggested greater clinical benefit for patients who were treated with higher-dose IFNβ regimens (eg, IFNβ-1a 44 µg by SC injection 3 times weekly or IFNβ-1b 250 µg every other day) than lower-dose regimens (eg, IFNβ-1a 30 µg by IM injection once weekly). Increasing the IFN dose is therefore a reasonable option for a patient with breakthrough disease on low-dose IFN. It is also reasonable to attempt a switch from IFN to GA or vice versa, although there are no prospective clinical trial results documenting the efficacy of this approach.

Switching to natalizumab is another option for patients with breakthrough disease despite first-line therapy. Natalizumab has been shown to reduce clinical
and MRI evidence of disease activity in patients with inadequate response to IFNβ. However, natalizumab has also been associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a potentially life-threatening opportunistic viral infection of the central nervous system. Overall, evidence from pivotal randomized-clinical trials suggests that PML occurs in approximately 1 out of every 1000 patients who are treated with natalizumab. However, risks associated with continued long-term natalizumab therapy or with the combination of natalizumab and other immunosuppressive drugs have not been studied.

Neutralizing antibodies (NAbs) may also contribute to poor treatment response in patients who are being treated with IFNβ. The incidence of NAbs is lower with IFNβ-1a IM than with IFNβ-1a SC or IFNβ-1b. NAbs usually develop after 6 to 18 months of therapy, and may occur earlier in patients who are treated with IFNβ-1b (6–12 months) than with IFNβ-1a (12–24 months). Sustained high-titer NAbs to IFN are associated with increased MRI lesion load within 1 to 2 years and increased clinical disease burden within 3 to 4 years. NAbs spontaneously revert to negative in some cases, which has been associated with a restoration of the beneficial effects of IFN therapy. In addition, not all cases of treatment failure are related to NAbs: many patients who are treated with IFNs are antibody negative but still fail to respond to therapy, whereas other antibody-positive patients remain clinically stable for long periods of time. Testing for NAbs may be reasonable for patients who are failing to respond adequately to IFN therapy, but is expensive to perform and often has little impact on clinical decision making. Antibodies may also form to natalizumab, although the incidence of persistent antibodies is low (approximately 6%).

**COMBINATION THERAPY FOR BREAKTHROUGH DISEASE**

Combination therapy is a potential option for patients with breakthrough disease, but it has not been extensively studied. One approach to combination therapy is shown in Figure 1. During the first stage of management, patients are treated with an immunomodulator (IFNβ, GA, or natalizumab) as a platform therapy. Patients with breakthrough disease may be switched from one platform therapy to another, or the platform therapy may be combined with another medication. After managing breakthrough disease, occasionally patients may step back down to the platform drug alone.

Several options are available for combination therapy with a platform disease-modifying agent. Immunomodulatory therapy with pulsed corticosteroids is a common adjunctive therapy to reduce the duration of acute exacerbations in patients with MS. Some clinicians use intravenous immunoglobulin (IVIG), although this therapy is expensive, is often not reimbursed by insurance companies, and appears to have little effect on the progression of long-term disability. A randomized-clinical trial is currently evaluating the efficacy and safety of combination therapy with GA and IFNβ-1a.

Several cytotoxic agents have been shown to improve the clinical course of MS, and may be added to platform therapy for patients with continued breakthrough disease. Mitoxantrone causes DNA cross-linking and strand breaks, and can be administered by

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**Figure 1. Management of Breakthrough Disease**

Patients are initially treated with a platform immunomodulator (Stage I). Patients with breakthrough disease activity despite Stage I therapy may be treated with pulsed corticosteroids as needed (Stage II). Patients with continued disease activity may receive additional therapy with an oral immunosuppressant (Stage IIIA) or an IV immunosuppressant (Stage IIIB). After successful management of breakthrough disease, patients may return to monotherapy with a platform drug.

- **Stage I**: Maintenance
  - Platform drug (immunomodulator)
    - IFNβ-1a IM
    - IFNβ-1a SC
    - IFNβ-1b
    - GA
    - Natalizumab

- **Stage II**: Breakthrough disease
  - Platform drug (immunomodulator) plus Pulsed corticosteroids as needed

- **Stage III**: Continued breakthrough disease
  - Platform drug (immunomodulator) plus Maintenance pulsed corticosteroids
  - Stage IIIA: Oral immunosuppressant (Stage IIIB: IV immunosuppressant

GA = glatiramer acetate; IFN = interferon; IM = intramuscular; IV = intravenous; SC = subcutaneous.

intravenous (IV) infusion monthly or once every 3 months. Randomized placebo-controlled clinical trials have demonstrated reduced relapse rate and disease progression with mitoxantrone in patients with relapsing/remitting MS and secondary progressive MS (SPMS; Figure 2). Mitoxantrone is approved for worsening relapsing forms of MS, including SPMS. Its use is limited by concerns about cardiac toxicity, infections, infertility, and leukemia. Patients require extensive evaluation before each course of therapy, including assessment of cardiac function, complete blood count, liver function tests, and pregnancy test. There is a lifetime maximum dose of 120 mg/m², which translates into 2 to 3 years of therapy if administered at the dose of 12 mg/m² every 3 months. Some researchers have reported good results with the combination of mitoxantrone and GA, including the use of mitoxantrone as induction therapy followed by maintenance with GA (Figure 3).

Other cytotoxic agents are used to treat patients with MS who have breakthrough disease, although they are not specifically approved for this indication. Azathioprine, a nucleoside analogue that inhibits DNA and RNA synthesis, has been used as monotherapy or in combination with IFN. Although some studies have demonstrated reduced relapse rates with oral azathioprine (Figure 4), it has been associated with several adverse effects, including allergic reactions, liver toxicity, alopecia, lymphopenia, and anemia. Mycophenolate is similar to azathioprine in terms of its mechanism of action and may have a more favorable adverse effect profile. However, gastrointestinal adverse effects are still common, and approximately 9% of patients with MS experienced diarrhea in one clinical trial. Cyclophosphamide, an alkylating agent that causes immune suppression, has been evaluated in a regimen consisting of an IV induction phase of 400 to 500 mg/m² per day for 5 days, followed by booster doses of 700 to 1000 mg/m² every 1 to 2 months. Cyclophosphamide can induce rapid suppression of MS disease activity, but is associated with several potentially significant adverse events, including hematologic toxicity, hemorrhagic cystitis, malignancy, nausea, vomiting, alopecia, and infertility. Methotrexate is an anti-inflammatory and immunomodulating agent that suppresses the activity of several inflammatory cytokines, including interleukin-1, interleukin-2, and interleukin-6. It may be used once per week, supplemented with folic acid.

![Figure 2. Time to First Treated Relapse](image)

In a placebo-controlled clinical trial of patients with worsening RRMS or SPMS, IV infusion of mitoxantrone once every 3 months for up to 2 years (a total of 8 treatments) significantly increased the time to first relapse at the FDA-approved dose of 12 mg/m² ($P = .0004$). A lower dose (5 mg/m²) that was included for exploratory purposes tended to increase the time to first relapse compared with placebo, but this difference was not statistically significant.

![Figure 3. Mean (±SE) Total Number of T1 Gd-Enhancing Lesions](image)

An induction regimen of mitoxantrone plus GA produced a significantly more rapid reduction in Gd-enhancing lesion number than GA alone over a 15-month period. GA = glatiramer acetate; Gd = gadolinium; M-GA = mitoxantrone and glatiramer acetate. Reprinted with permission from Vollmer et al. Mult Scler. 2008;14:663-670.
and has some benefit in patients with MS, including improvement in upper extremity function in patients with SPMS.51

Cladribine is a lymphocytotoxic agent that induces apoptosis in resting and dividing lymphocytes, especially in CD4+ T cells.52,53 An oral formulation of cladribine is in late-phase clinical testing for the treatment of MS. Initial clinical studies demonstrated a robust effect on MRI lesions, including the complete suppression of gadolinium-enhancing lesions and a 58% reduction in relapse rate compared with placebo.54

Alemtuzumab, a monoclonal antibody against the CD52 cell-surface marker, triggers the rapid complement-mediated lysis of B and T lymphocytes.55 Initial clinical studies have suggested that alemtuzumab is a very promising alternative for MS therapy. In a 2-year, randomized, phase II clinical trial, alemtuzumab produced a 75% reduction in relapse rate compared with IFNβ-1a SC.56 Although these results are promising, alemtuzumab was associated with several potentially serious adverse events, including immune thrombocytopenia purpura (including 1 fatality), autoimmune thyroid disorder, and other secondary autoimmune effects.

**Figure 4. Effects of Combination Therapy with IFNβ-1a and AZA on Relapse Rate**

![Graph showing effects of combination therapy on relapse rate](image)

The effects of combination therapy with IFNβ-1a and AZA on relapse rate were examined in 3 groups of patients with MS: those who were not previously treated, those who had continued disease activity despite prior treatment with AZA, and those who had continued disease activity despite prior treatment with IFNβ-1a. In the AZA and IFNβ-1a groups, patients had previously been treated for at least 2 years. In all 3 groups, the mean number of relapses during combined therapy (white bars) was significantly lower than the relapse rate during the 2-year period before initiation of combined therapy (gray bars).

AZA = azathioprine; IFN = interferon.

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**Conclusions**

Many patients with MS experience unacceptable disease activity despite disease-modifying therapy. Treatment adherence should be assessed before the regimen is modified. In patients who are being treated with IFNβ, NABs may contribute to inadequate response to therapy. Several options are available for unacceptable breakthrough activity, including pulsed corticosteroids, IVIG, switching to an alternative disease-modifying agent, and the adjunctive use of immunosuppressive agents, such as azathioprine, methotrexate, or mycophenolate. Chemotherapy with mitoxantrone or cyclophosphamide may be considered for patients with recurrent, severe exacerbations that are not controlled by more conservative measures. Natalizumab is also an option, although the risk of PML remains a significant concern.

**References**

10. Ross AP. Strategies for optimal disease management, adher-


