Natalizumab to fingolimod

Questions answered, unanswered, and unasked

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For 2 decades, it has been a high priority to develop effective therapies for patients with relapsing-remitting multiple sclerosis (RRMS). This effort has been tremendously successful, and there are currently 13 anti-inflammatory agents approved for the treatment of RRMS. These treatments vary in mechanism of action, route and frequency of administration, side-effect profiles, and efficacy. The availability of this palette of treatments creates the opportunity to control disease activity in most people with RRMS. They also demand a new level of sophistication from neurologists using these agents to treat RRMS.

One area in which there is much discussion, but few good data, is how to transition patients from one multiple sclerosis (MS) disease-modifying therapy to another. Do you need to have a washout period between the 2 treatments, and if so, how long should it last? This has particularly been a concern when transitioning from the monoclonal antibody natalizumab to one of the oral drugs, such as fingolimod. This has gained particular importance because patients on natalizumab are at risk of developing progressive multifocal leukoencephalopathy (PML), especially if they are positive for antibodies against the causative agent JC virus.[1] The concerns about transitioning from natalizumab to an oral agent are twofold. If the washout period is too long, the patient's MS will become reactivated. If the washout period is too short, patients may be put at risk of side effects, particularly PML, by overlapping the new drug with the lingering effects of natalizumab.

In this issue of *Neurology*®, Kappos et al.[2] report on a randomized trial assessing washout periods of 8, 12, and 16 weeks during the transition of patients from natalizumab to fingolimod. The trial was originally powered to determine differences among the 3 washout periods with respect to reactivation of disease, as assessed by the number of new T2 lesions on brain MRI during washout through the first 8 weeks of fingolimod therapy. There were a number of secondary outcome measures, including assessment of safety. The sponsor, Novartis, terminated the clinical trial early, after 142 of the originally planned 600 participants were enrolled, thereby limiting some conclusions (see below). Despite this, the study clearly showed that participants undergoing a 16-week washout had greater reactivation of disease as measured by brain MRI activity than those undergoing 8- and 12-week washout periods. Differences in the 2 groups undergoing the shorter washouts were not so obvious. There was no difference in the 2 shorter groups as assessed by the primary outcome measure, but some secondary measures favored the 8-week washout period. There was a suggestion of a slight increase in infections in the group undergoing the 8-week washout, but none of these infections was serious. This study confirms other studies that indicate a 16-week or longer washout period of natalizumab risks increased disease activity and support washout periods of no longer than 8–12 weeks to avoid disease reactivation.[3,4] It is unfortunate that the study was stopped prematurely as the larger trial would have provided more definitive data on differences between 8- and 12-week washout periods, both with regards to risk of disease reactivation and infections once fingolimod was started.

Does this study give us information useful in transitioning patients from natalizumab to other agents? Any new agent should probably be started before 16 weeks to avoid MS disease reactivation. How early one can safely start a new agent depends on speed of action, effects on the immune system, and side effect profile of the new treatment. But there is little research to guide us and we are left to use our best judgment.

There is a critical question that the study by Kappos et al. did not seek to answer. Is a washout period needed at all? The biological rationale for a washout has been unclear to many clinical neuroimmunologists,[5] and it is not evidence-based. The requirement for a natalizumab washout before starting fingolimod appears based on an expert opinion that is summarized in a fingolimod product description by the European Medicines Agency (EMA), which recommends a

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washout period of 2–3 months when transitioning from natalizumab to fingolimod.[6] The concern seems mainly to be over the risk of PML developing during the transition period, given the long half-lives and clinical effects of antibodies. Some individuals have developed PML several months after stopping natalizumab,[7] and the current prescribing information for natalizumab suggests monitoring patients for PML for 6 months after stopping the medication.[8] In addition, the immunologic effects of natalizumab may last much longer than 6 months.[9] Given these prolonged effects, it is questionable that much is being accomplished by having a washout lasting 8–12 weeks.

Does delaying starting fingolimod or the other oral agents dimethyl fumarate and teriflunomide (which is possible in some, but not all, countries) alter the risk of PML after stopping natalizumab? By themselves, none of these agents appears to have a high risk of causing PML. The manufacturer of fingolimod recently alerted prescribers that there has been 1 case of PML under fingolimod monotherapy. The single case of PML associated with the Food and Drug Administration–approved formulation of dimethyl fumarate occurred after prolonged lymphocytopenia. There are no cases reported of PML with teriflunomide. In addition, PML has occurred in patients previously treated with natalizumab and then started on fingolimod after a washout period.[10] Given that MS disease activity occurs after stopping natalizumab, are we doing more harm than good in having washout periods of any length? A question that is not being asked is whether we can safely switch patients on natalizumab to another agent without a delay, especially if their brain MRI shows no evidence of PML.

As we seek to personalize the treatment of RRMS using the array of medications now available, we need accurate information not only about the individual medication, but also about how to transition from one medication to another. It is not good enough to rely on guessing and expert opinion.

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