

Switching patients at high risk of PML from natalizumab to another disease-modifying therapy

Gavin Giovannoni,^{1,2} Monica Marta,^{1,2} Angharad Davis,^{1,2}
Benjamin Turner,^{1,2} Sharmilee Gnanapavan,^{1,2} Klaus Schmierer^{1,2}

¹Department of Neurosciences, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK

²Department of Neurology, Royal London Hospital, Barts Health NHS Trust, London, UK

Correspondence to
Professor Gavin Giovannoni,
Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University London, 4 Newark Street, London E1 2AT, UK;
g.giovannoni@qmul.ac.uk

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ABSTRACT

There are several options for switching people with multiple sclerosis (MS) who are at high risk of developing progressive multifocal leukoencephalopathy (PML) from natalizumab to alemtuzumab. However, some of these have risks that need to be managed, for example, the risks of carrying over asymptomatic PML from natalizumab on to the new therapy, and the risk of rebound disease activity associated with a prolonged washout after starting natalizumab. We propose a pragmatic bridging strategy, using another disease-modifying therapy (DMT), to reduce the risk of switching from natalizumab to alemtuzumab. We also discuss the caveats and subtleties associated with sequencing DMTs in MS and the complex decision making involved.

People with multiple sclerosis (MS) on natalizumab who are JC virus seropositive are at high risk of developing progressive multifocal leukoencephalopathy (PML).^{1,2} The risk is particularly high in those who have (i) been on the drug for longer than 12 months, (ii) had previous exposure to immunosuppressive therapies and/or (iii) have a high anti-JC virus antibody index.^{1,2}

With the recent licensing of several other MS disease-modifying therapies, it is now possible to lower the risk of PML in people with MS who are JC virus seropositive and on natalizumab by switching them to another disease-modifying treatment (DMT). One caveat of this strategy is so called 'carryover PML':^{3,4} PML that develops a few months after stopping natalizumab and starting a different DMT. In these cases, PML had probably developed already without causing symptoms while the patient was still on natalizumab, or shortly after stopping natalizumab.

Carryover PML can be explained by the complex pathogenesis of PML, which

develops over months to years.¹ First, wild-type JC virus has to acquire several mutations in its genome that presumably make the virus neurotropic and pathogenic; these mutations typically occur in the viral capsid protein and regulatory region of the JC viral genome.⁵ We do not know in which body compartment the JC virus resides and acquires these pathogenic mutations. However, once the virus becomes pathogenic and migrates to the brain (if not already resident in the brain), it infects glial cells, causes lytic infection and spreads locally and to other areas of the brain to cause PML. As most cases of carryover PML identified to date occurred within 6 months of switching treatments,³ with only one reported case presenting at 8 months,³ the at-risk period for carryover PML is probably less than 12 months after switching from natalizumab to another DMT.

It is very difficult to quantify the risk of carryover PML as we do not know the denominator. We are aware of 15 cases of carryover PML from natalizumab,³ that is, 15 JC virus-positive patients developing PML within 12 months after changing from natalizumab. Also, five people with MS have developed PML on fingolimod with no prior natalizumab exposure (Novartis, personal communication). These 20 cases have occurred on a denominator of over 125 000 patients treated with fingolimod worldwide.⁶ However, we do not know the proportion of those with prior natalizumab exposure, making it difficult to calculate specific risks and to draw any firm conclusions, except to say that carryover PML after natalizumab is much more likely to occur on fingolimod than non-carryover (*de novo*) PML.

Most people with MS treated with natalizumab in the UK have had rapidly



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evolving severe MS and are at increased risk of rebound MS disease activity typically occurring 3–4 months after stopping natalizumab.^{7 8} Rebound activity coincides with the drop in plasma blood concentrations of natalizumab and the desaturation of the $\alpha 4\beta 1$ -integrin antigen, natalizumab's target, on the surface of lymphocytes.⁹ The $\alpha 4\beta 1$ -integrin binds to vascular cell adhesion molecule-1, expressed on the endothelium, and assists in the trafficking of lymphocytes across the blood–brain barrier.

To prevent rebound disease activity, we recommend starting a different DMT as soon as possible after the last infusion of natalizumab, preferably within 4 weeks of the last dose.¹⁰ Natalizumab washout periods of longer than 4 weeks are associated with higher recrudescence of disease activity in the form of relapses and/or gadolinium-enhancing MRI activity. We tend to use fingolimod as the follow-on agent given the evidence that it prevents rebound disease activity, provided it is started within 4 weeks of the last natalizumab infusion.^{11 12} Published data on the use of pulsed corticosteroids, interferon- β and glatiramer acetate show that these agents cannot prevent rebound activity.¹³ Similarly, real-life data presented at recent meetings indicate that breakthrough disease activity occurs in a proportion of people with MS treated with either dimethyl fumarate¹⁴ or teriflunomide.¹⁵

If a person with MS does develop carryover PML on fingolimod (a once-daily oral DMT), simply stopping it allows immune reconstitution and trafficking of cytotoxic T cells into the central nervous system to counteract and clear JC virus.¹⁶ A problem arises, however, if considering alemtuzumab (an anti-CD52 antibody) or other induction therapies (cladribine, mitoxantrone, haemopoietic stem cell transplant) as the next DMT after stopping natalizumab. These drugs induce long-term immunosuppression (induction) with delayed immune reconstitution. The effects of induction DMTs cannot be reversed quickly. Therefore, if a person with MS at risk of PML switches from natalizumab to, for example, alemtuzumab and develops carryover PML, they have very high risk of succumbing to PML due to their significantly compromised immune system following induction. Reconstitution of the T-cell compartment after giving alemtuzumab takes over 6 months and both CD4+ and CD8+ cell counts rarely return to normal.¹⁷ Therefore, these patients cannot mount the early cytotoxic CD8+ T-cell response required to clear the JC virus infection. Survival from PML is strongly linked to the cytotoxic CD8+ T-cell response against JC virus.¹⁸

Genzyme, the company that markets alemtuzumab, has reported one fatal case of carryover PML, in a patient who switched from natalizumab to alemtuzumab (personal communication). Should such a circumstance arise in the future, which is likely, an

immune stimulant such as interleukin 2 and/or G-cerebrospinal fluid (CSF), or peripheral-blood progenitor cell transplantation from an human leukocyte antigen-identical JC virus-seropositive donor might be tried. The aim is to stimulate the proliferation of autologous, or provide allogeneic, anti-JC virus CD8+ cytotoxic cells that would then need to traffic to the brain to clear the JC virus infection. Should carry-over PML develop within 3 months of the last natalizumab infusion, we would also recommend plasma exchange to lower residual circulating levels of natalizumab below 1 ng/mL, thereby avoiding the block due to remnant natalizumab of trafficking donor (and self) T cells into the central nervous system.⁹

A safer option with regard to carryover PML risk would be to wash out natalizumab for 6 months, thereby allowing immune reconstitution of the central nervous system. Doing this relies on the immune system detecting subclinical PML, which could then trigger an immune reconstitution inflammatory syndrome.¹⁶ An obvious downside of this strategy is that it also allows MS disease activity to return, and possibly rebound above the levels of activity seen before starting natalizumab treatment.⁷

Our preferred option is therefore to bridge patients with a maintenance therapy for a period of time to lower the risk of carryover PML. We currently use fingolimod as the bridging DMT, based on its proven efficacy after natalizumab. Before starting fingolimod, we perform (i) an MRI scan of the brain and (ii) CSF analysis to rule out the presence of JC virus DNA and thereby exclude asymptomatic PML. As a note of caution when interpreting the results, there are significant numbers of false-negative JC virus DNA results.^{19–21} These depend on the sensitivity of the diagnostic assay used. We then start fingolimod, usually 2–4 weeks after the last natalizumab infusion. At present we propose a bridging period of 6–12 months; the longer the bridge the lower the risk of carryover PML.

One could argue that a person uses natalizumab because they have rapidly evolving severe, or aggressive, MS, and thus switching them to a lower efficacy drug such as fingolimod for 6–12 months may delay their access to the potential benefits of a potentially more effective induction therapy. We do not think that this is a major issue as several studies have now shown that fingolimod prevents rebound in most people who switch from natalizumab to fingolimod, provided they start fingolimod within 4 weeks after the last dose of natalizumab.^{11 12} Our practice and advice is meant to pragmatic and will need to be personalised based on the circumstances of the individual with MS. As a centre, we have no problem with a well-informed patient not wanting to bridge with fingolimod, choosing and consenting to be treated with an induction therapy without a natalizumab washout. The shared decision is all about risks and benefits; if

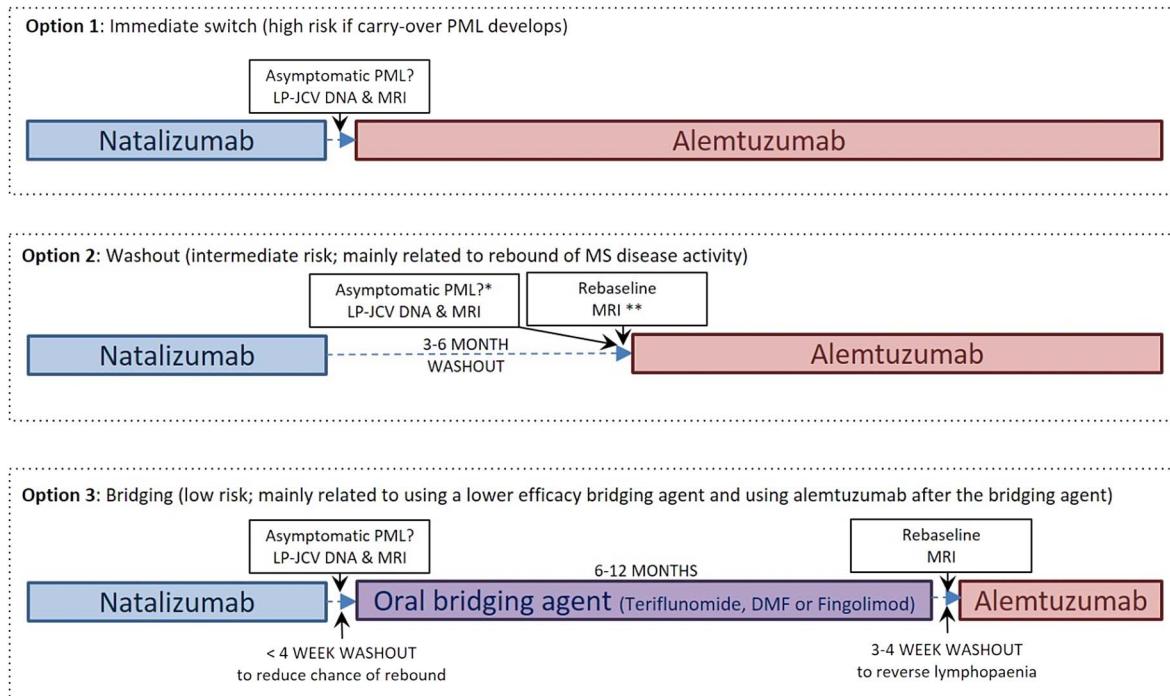


Figure 1 Options available when switching people with multiple sclerosis (MS) who are at high risk of developing PML from natalizumab to alemtuzumab. Option 1: an immediate switch without a washout is potentially the most risky; the risk being a small chance of carrying over asymptomatic PML and not being able to respond to the JC virus due to alemtuzumab-induced immunosuppression. Option 2: a switch after a 3–6 month washout of natalizumab; this allows time for asymptomatic carryover PML to manifest and for reconstitution of immune surveillance to mount a response to fight PML. This strategy is risky as the immune reconstitution of the central nervous system potentially allows rebound of MS activity. Option 3: a bridging strategy in which there is a switch to a maintenance oral agent, such as teriflunomide, dimethyl fumarate or fingolimod. The bridging agent will hopefully prevent rebound MS activity but provide time to detect PML. The important point here is that if PML should develop, these oral bridging therapies can be stopped to allow reconstitution of immune surveillance to occur to fight PML. DMF, dimethyl fumarate; LP, lumbar puncture; PML, progressive multifocal leukoencephalopathy.

induction therapies had a reversible mode of action, this discussion would be superfluous. However, it is very difficult to quantify the precise risk of carryover PML and so the decision is likely to be based on perceived risk and the consequences of carryover PML in a person who has been treated with an irreversible induction therapy.

It is important to be aware that the risk of PML after stopping natalizumab is unlikely to disappear completely, despite a bridge. As mentioned above the pathogenesis of PML is complex, and if JC virus has started to acquire pathogenic mutations these are unlikely to be reversed by simply stopping natalizumab. Therefore, before switching, we counsel people with MS who are JC virus seropositive and have been on natalizumab that their risk of getting PML in the future may be higher than in someone who has not been exposed to natalizumab.

In addition to testing for JC virus DNA in the CSF, there is a test for people with MS who are on natalizumab to detect to predict their future risk of PML, using the level of L-selectin (CD62L) expressing CD4+ T cells. CD62L is involved with $\alpha 4\beta 1$ -integrin

in the rolling and transmigration of lymphocytes across the blood-brain barrier; it falls below a threshold level in patients with asymptomatic PML.^{22,23} Levels of L-selectin below a certain threshold increase the risk of PML almost 55-fold.²³ The protocol to detect L-selectin is rather complex, and its role in the risk management of people with MS has yet to be determined. Also, not all studies have confirmed L-selectin as a reliable biomarker for predicting PML risk in natalizumab-treated patients.²⁴

There are several caveats when switching from fingolimod to alemtuzumab after the bridging period (figure 1). First, fingolimod is a sphingosine-1-phosphate (S1P) receptor modulator that traps lymphocytes in lymph nodes; it works by internalising the S1P receptor and preventing it from being recycled to the lymphocyte membrane. Without the surface expression of S1P receptors, lymphocytes cannot egress from lymph nodes.²⁵ Data from animal studies suggest that intravenous alemtuzumab targets circulating lymphocytes and is less effective at depleting lymphocytes in lymph nodes.²⁶ Therefore, we recommend stopping fingolimod, waiting 4 weeks,

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checking peripheral lymphocyte counts to ensure that they are returning towards normal, and then giving the first course of alemtuzumab. We do not recommend a prolonged washout after fingolimod as rebound MS activity can develop after stopping fingolimod.^{27 28} Another reason for a short fingolimod washout is to exclude the remote possibility of persistent postfingolimod lymphopenia. There have been a few cases of persistent lymphopenia in people with MS treated with fingolimod for many years.²⁹ We do not know if persistent lymphopenia can occur after as little as 12 months of fingolimod exposure. However, the lymphocyte count should recover towards the normal range after stopping fingolimod and before starting alemtuzumab. We suggest a total lymphocyte count of at least $0.8 \times 10^9/L$ (WHO grade 2 lymphopenia cut-off).

In conclusion, as the complexity of MS disease-modifying therapy increases, the decision making around sequencing and switching of therapies becomes more difficult. In an ideal world, this decision making should be evidence based. However, as long as there is no available evidence, we need a pragmatic approach to help other clinicians make decisions when there is only limited evidence. Our motivation is to reduce the risk of using the highly effective drug natalizumab in people with MS who are JC virus seropositive, and to prevent unnecessary morbidity and mortality from PML.

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