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Review

A review of the evidence for a natalizumab exit strategy for patients with multiple sclerosis

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ABSTRACT

Natalizumab is an effective treatment for relapsing-remitting multiple sclerosis (RRMS), but treatment for > 2 years is associated with an increased risk of opportunistic infection and progressive multifocal leukoencephalopathy (PML). For this reason, patients and physicians may consider discontinuing natalizumab therapy. This article reviews the evidence for the various therapeutic approaches that may be taken in such patients. Stopping therapy altogether is unlikely to be appropriate for most patients, as it is associated with a high rate of relapse or rebound. Continuing natalizumab therapy with increased monitoring and vigilance for PML may be an acceptable option for some patients, while the data on extending the dosing interval of natalizumab look promising. In some patients whose pre-natalizumab disease activity was not very high and who did not relapse while on natalizumab, switching to a first-line treatment may be an option. In this case, dimethyl fumarate may carry a lower risk of relapse than interferon beta or glatiramer acetate. Fingolimod is the most studied post-natalizumab therapy, and the relapse rate appears to be higher than on natalizumab but lower than was seen before initiation of natalizumab. The evidence suggests that the washout period between natalizumab and fingolimod should not exceed 12 weeks. Finally, the limited evidence available for rituximab and alemtuzumab is promising, and further data on these and other newer therapies for RRMS are awaited.

1. Introduction

1.1. Background and rationale

Multiple sclerosis (MS) is a chronic demyelinating disorder of the central nervous system (CNS), which follows a relapsing course in most patients [1]. The causes and mechanisms of MS relapses have not been completely elucidated, but stress has been shown to be associated with disease onset and exacerbations [2], and increased RNA polymerase 1 pathway activity in acute MS relapse suggests a possible molecular mechanism [3]. Older disease-modifying therapies (DMT) such as interferon beta-1a and glatiramer acetate can reduce relapse rates by about 30% and have an uncertain long-term benefit [1]. Active MS management with high-efficacy DMTs such as fingolimod, natalizumab or alemtuzumab reduces relapse activity, disability accrual and irreversible brain atrophy to a greater extent than the older drugs, and there is some evidence that earlier treatment with these high-efficacy, but higher-risk, therapies leads to better control of relapse activity than their later initiation [4].

Natalizumab has been available since 2004 for the treatment of highly active relapsing-remitting multiple sclerosis (RRMS) despite treatment with interferon beta or glatiramer acetate, or those patients with rapidly evolving severe RRMS, although it was withdrawn from the market for safety reasons in 2005 and reintroduced in 2006 [5]. The clinical trial program, as well as a substantial body of real-world evidence, has shown natalizumab to be very effective in terms of reducing MS relapses and improving other MS outcomes. The AFFIRM and SENTINEL trials showed that natalizumab, as monotherapy or in combination with interferon beta-1a, significantly reduced annualized relapse rate (ARR), disability progression and accumulation of new or enlarging hyperintense lesions on MRI compared with placebo [6,7]. In observational studies, around 60% of natalizumab-treated patients have been shown to be free from disease activity [8–10].

However, natalizumab treatment is associated with an increased risk of opportunistic infection and progressive multifocal leukoencephalopathy (PML) caused by JC virus (JCV). The risk of developing PML increases with seropositivity for anti-JCV antibodies, previous use of immunosuppressant therapy and duration of natalizumab treatment, especially beyond 2 years of treatment [11]. The risk is 0.1 per 1000 in natalizumab-treated patients negative for anti-JCV antibodies, as well

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Table 1
Relapse rates before, during and after natalizumab therapy.

Study	No of patients	Age, years[a]	MS duration[a]	Relapse rate (follow-up) or ARR[a]		
				Before NTZ	During NTZ	On new drug
Beta interferon						
Gobbi [18]	9	39 (24–48)	12 (2 − 13)	1 (range 0.5–2.5)	0 (range 0)	22% (1 yr)
Rossi [27]	25	36.1 ± 9.0	10.1 ± 5.8	2.4 ± 0.8	–	24% relapse-free (6 mo)
Glatiramer acetate						
Havla [19]	7	35.8 ± 7.7 (pre-NTZ)	8.6 ± 5.0	2.2 ± 1.5	0.3	1.8 ± 1.6
Magraner [20]	18	35.3 (23–54)	10.9 (3 − 20)	2.1	0.1	0.3
Rossi [21]	40	37.3 ± 9.1	9.1 ± 5.5	2.3 ± 0.9	0.06 ± 0.2	0.6 ± 0.8
Rossi [27]	40	36.1 ± 9.0	10.1 ± 5.8	2.4 ± 0.8	–	65% relapse-free (6 mo)
Interferon beta or glatiramer acetate						
Laroni (2012)	4	44.5 ± 9.0	14.8 ± 3.3	2.25 ± 1.89	0.15 ± 0.30	2/4 (13–34 wks)
Villaverde-González [22]	21[b]	44.2 ± 7.8	11.3 ± 5.1	1.6	0.1	0.3
Dimethyl fumarate						
Calabrese [29]	39	34.8 ± 8.6	6	100% (32 mo)	7.7% (28 mo)	13% (24 mo)
Cohen (2018)	506	47.0 ± 10.9	12.7 ± 7.2	0.49 (95% CI 0.43–0.56)	0.11 (95% CI 0.08–0.14)	0.25 (95% CI 0.20–0.30)
Zurawski [28]	30	44.9 ± 1.9	13.5 ± 1.5	0.624 ± 0.073	0.325 ± 0.035	27% (> 12 mo)
Fingolimod						
Alping (2006)	142	40.8 (33.7–47.7)	9.8 (5.8–16.6)	–	–	18% (1.5 yr)
Cohen [39]	333	Mean 41 (range 18–67)	–	–	–	20% (6 mo)
Diem [37]	43	46.2 ± 11.3	15.8 ± 9.2	0.55	0.07	0.09
Evangelopoulos [43]	20	34 ± 4	11.1 ± 2.9	7.2 ± 2.7	0	1/20 (20 mo)
Havla [33]	26	34 (IQR 15.5) (pre-NTZ)	37 (IQR 12.5)	2.0 (2.0)	0.0 (0.2)	0.0 (0.9)
Hoepner [36]	33	35.6 ± 10.5	7.5 ± 6.1	2.0 (1.62)	0 (0.1)	0 (1.0)
Jokubaitis [31]	89	43.2 ± 9.7	Age 29.9 ± 9.7 at MS onset	1.54	0.26	0.38
Kappos [38]	142	41.6 ± 8.8	Median 12 (range 3–28)	–	0.42 ± 0.64	0.33–0.65 (dep. on washout)
Laroni (2012)	11	38 ± 8.5	13.7 ± 10.5	2.60 ± 1.71	0.57 ± 0.59	1/11 (13–34 wks)
Leurs [40]	52	40.5 ± 8.9	–	1.5 ± 1.0	0.05 ± 0.1	39% disease activity (6 mo)
Rinaldi [34]	22	35 ± 7	10.7 ± 5.7	2.4	1 relapse	36% (9 mo)
Sempere (2014)	8	Mean 34	Mean 11.1	–	88% relapse-free	63% (9 mo)
Rituximab						
Alping [44]	114	40.2 (33.7–50.4)	10.4 (7.2–14.9)	–	–	2% (1.5 yr)

ARR, annualized relapse rate; MS, multiple sclerosis; NTZ, natalizumab.
[a] Mean ± SD or median (interquartile range) at time of switch.
[b] Only 1 patient switched to interferon beta.

as in antibody-positive patients with no prior immunosuppressant use, a treatment duration of 1–12 months and an antibody index ≤1.5 [12]. The risk is ≤0.6 per 1000 up to 72 months' treatment in patients with an antibody index ≤0.9, but increases to 10 per 1000 after 61 months' treatment in those with an index > 1.5. The latest data indicates that, as of 1 March 2018, there had been 766 confirmed PML cases in natalizumab-treated patients, giving an overall incidence of 4.16 per 1000 patients (Biogen, data on file).

In the light of the increased risk of PML after 2 years of treatment or for other reasons, some patients or physicians may wish to consider discontinuation of natalizumab and initiation of another MS treatment or adoption of a "wait and see" approach. However, discontinuation of an effective MS treatment may increase the risk of MS relapses. Patients stopping natalizumab treatment may experience a return to pre-treatment levels disease activity or occasionally a severe rebound with a marked clinical and radiological worsening [13]. In a prospective observational study of 124 MS patients with no clinical or MRI activity after 24 doses of natalizumab, MS activity was significantly lower in those who continued natalizumab than in those who stopped natalizumab or switched to an alternative therapy. A protective effect of natalizumab on the risk of relapse was seen in natalizumab continuers compared with natalizumab quitters (odds ratio 4.40, 95% CI 1.72–11.23) and natalizumab switchers (3.28, 0.99–10.79) [14].

In addition, information on the carry-over risk of PML, post-natalizumab discontinuation, is relative limited. Neurological deterioration due to PML can manifest during the 6 months following natalizumab withdrawal in MS patients who discontinue the drug for unrelated reasons [15]. This means that clinicians need to consider new-onset PML, immune reconstitution inflammatory syndrome (IRIS) and relapsed MS activity when evaluating MS patients with progressive neurological decline following discontinuation of natalizumab.

The new ECTRIMS/EAN guideline on the pharmacological treatment of people with MS recommends that "When treatment with a highly efficacious drug is stopped, either due to inefficacy or safety concerns, consider starting another highly efficacious drug… In treatment decisions, consider the possibility of resumed disease activity or even rebound when stopping treatment, particularly with natalizumab" [16].

Recommendations on patient selection and monitoring for natalizumab treatment to reduce the risk of PML, as well as on the diagnosis and management of PML, were made by Kappos et al. in 2011 [11]. Further recommendations on risk stratification using the anti-JCV antibody index were made by McGuigan et al. in 2016 [17]. However, practical guidance for neurologists on how best to manage discontinuation of natalizumab treatment and selection of appropriate MS treatment options post-natalizumab is currently lacking. This article is intended to review the available data and propose a rational approach to dealing with these real clinical dilemmas.

1.2. Objective

This review article is intended to provide practical guidance for neurologists treating people with RRMS who may be considering discontinuation of natalizumab treatment.

2. Methods

A search was conducted in PubMed for published reports of studies that examined alternative MS treatment approaches post-natalizumab, and current national guidelines were checked. Studies reported in English and of any study design were included. The details of the included studies have been summarized and the information reviewed to identify themes in terms of timing of initiation of new treatment post-natalizumab discontinuation, key outcomes and any complications.

3. Results

Among the 27 studies included, most of which were prospective observational studies, only one looked at switching from natalizumab to rituximab, three looked at switching to dimethyl fumarate (DMF), nine looked at switching to interferon beta or glatiramer acetate, and 18 looked at switching to fingolimod. Several of the fingolimod studies examined different durations of washout period between therapies and a few considered use of pulsed methylprednisolone during the washout or transition period. Table 1 summarizes MS relapse rates before, during and after natalizumab therapy, where available in the study reports. Details of the study designs, participants and outcomes are in Supplementary Tables 1 and 2.

3.1. Interferon beta and glatiramer acetate

A small randomized pilot trial compared nine patients free of disease activity on natalizumab who were switched to interferon beta-1b with 10 who continued on natalizumab [18]. After 1 year, seven (78%) interferon patients and all natalizumab patients remained relapse-free, and 25% versus 63% had no new T2 lesions. In one of the three prospective observational studies looking at switching to glatiramer acetate, 5/7 (71%) patients relapsed within 12 months [19]. Patient numbers were small, but those who relapsed on glatiramer acetate had slightly higher disease activity before natalizumab initiation than those who did not relapse. In the second study, 3/18 (17%) patients had relapsed by 6 months and 10 (56%) had gadolinium-enhancing lesions; another six (33%) patients relapsed after 6 months (mean follow-up 10 months) [20]. The third study reported that 25/40 (63%) patients were relapse-free after 12 months, while 18/32 (56%) had MRI activity; 35% experienced neither clinical nor radiological evidence of disease activity up to 6 months after natalizumab discontinuation, and 57% of these (20% overall) continued to be in complete remission up to the end of the 12-month protocol [21]. Notably, the frequency of relapses was 50%y lower among patients who had experienced two or fewer relapses the year before initiation of natalizumab, compared with those who had had three or more relapses ($p = 0.04$).

A further six studies (1 retrospective, 5 prospective) assessed patients switched from natalizumab to either interferon beta or glatiramer acetate (usually whichever they had not been treated with prior to natalizumab). One study reported relapses in 6/21 (29%) patients within 12 months, with MRI activity in 38%; in this study, patients who relapsed after natalizumab did not have significantly higher disease activity before natalizumab than patients who did not (ARR 1.7 vs 1.3; $p = 0.302$), but they did have higher EDSS scores (5.7 ± 1.1 vs 3.4 ± 1.2; $p = 0.001$) [22]. Two studies compared interferon beta or glatiramer acetate with fingolimod post-natalizumab, both reporting higher relapse rates with the former [23,24]. In one of these ($n = 613$), switching to fingolimod was associated with a 64% reduction in the risk of relapse compared with interferon/glatiramer acetate ($p < 0.0001$) [24]. The strongest risk factors for relapse after starting the new therapy were washout duration > 3 months (incidence rate ratio [IRR] 1.78; $p < 0.0001$), number of relapses before (IRR 1.13; $p = 0.018$) and during (IRR 1.61; $p < .0001$) natalizumab treatment, and the presence of comorbidities (IRR 1.4; $p = 0.0097$) [24]. Two other studies included interferon beta and glatiramer acetate among a variety of post-natalizumab treatment options (including fingolimod), none of which provided adequate protection from disease reactivation [25,26]. In one of these studies, patients defined as “high activity” in the year before natalizumab initiation had a higher risk of disease reactivation ($p = 0.004$) [25]. The sixth study compared patients who were switched to interferon beta-1b ($n = 25$) or glatiramer acetate with ($n = 40$) or without ($n = 40$) pulsed methylprednisolone for up to 6 months [27]. A significantly higher proportion of patients remained relapse-free after switching to glatiramer acetate than interferon beta (65% vs 24%, $p < 0.05$); surprisingly, those who also received methylprednisolone were more likely to relapse than those who received glatiramer acetate alone (40% vs 65% relapse-free, $p < 0.05$).

Overall, it seems that neither interferon beta nor glatiramer acetate is likely to prevent reactivation of MS in the majority of patients stopping natalizumab, particularly if pre-natalizumab disease activity was high.

3.2. Dimethyl fumarate

Two of the three studies of use of DMF after natalizumab were small. A retrospective study of 30 patients with a washout period of < 12 weeks between drugs reported that eight (27%) patients had a clinical relapse on DMF, of which five (17%) had a severe relapse, and new MRI lesions were observed in 8/23 (35%) patients. The mean time to relapse was 3.5 ± 0.6 months after natalizumab withdrawal, and patient age and elevated ARR prior to natalizumab use were significantly associated with risk of relapse following a switch to DMF [28]. The second study was prospective and included 39 patients with a mean washout period of 34 days [29]. Over a follow-up period of 2 years, two (5%) patients discontinued DMF, five (13%) relapsed, eight (21%) had MRI activity and three (8%) had disability progression. No evidence of disease activity was seen in 80% of patients, compared with 85% during natalizumab treatment. The number of relapses and MRI parameters before and during natalizumab treatment were good predictors of disease activity during treatment with DMF.

A larger retrospective study in 506 patients reported an ARR in the first year after initiation of DMF that was higher than in the first year of natalizumab therapy (rate ratio 2.32, 95% CI 1.69–3.18) but lower than before natalizumab initiation (rate ratio 0.51, 95% CI 0.40–0.64) [30]. The risk of relapse 1 year after DMF initiation was 19.6%; 82% of patients had no relapses, 15% had one relapse, 3% had two relapses and 0.6% had three relapses. The risk of relapse was 14.4% for patients without relapse during natalizumab treatment compared with 37.6% for patients who relapsed during natalizumab treatment (hazard ratio 0.35, 95% CI 0.23–0.5). Among patients without relapse during the first year of natalizumab treatment ($n = 387$), the ARR 1 year after DMF initiation was significantly lower in those with a washout duration ≤ 90 days versus > 90 days (rate ratio 0.49, 95% CI 0.26–0.90) [30].

These findings suggest that DMF may be an appropriate post-natalizumab therapy in some patients, particularly those without high disease activity before starting natalizumab or relapses during natalizumab therapy, but it is not completely protective.

3.3. Fingolimod

Fingolimod was the most commonly used post-natalizumab therapy in the studies. Most of the studies were small, but one included 536 patients from the MSBase Registry starting fingolimod treatment [31]. Of these 97 were treatment-naïve, 350 had switched from interferon beta or glatiramer acetate and 89 had switched from natalizumab. Over

a median follow-up of 10.3 months, the overall relapse rate on fingolimod was 20.7%, with very little difference between the groups. The ARR increased from 0.26 on natalizumab to 0.38 on fingolimod ($p = 0.002$), compared with 1.54 before natalizumab. No correlation was seen between relapse activity before natalizumab initiation and relapse activity on fingolimod.

Among the prospective observational studies, one reported no change in EDSS and no relapses or new/enlarged lesions a median of 13 months after a switch to fingolimod in 25 patients [32]. A study in 36 patients stopping natalizumab found that 11/26 (42%) patients who switched to fingolimod relapsed over a median follow-up of 55 weeks from natalizumab discontinuation, compared with 7/10 (70%) who remained therapy-free ($p < 0.05$) [33]. Gadolinium-enhancing lesions were seen in 1/11 (9%) and 6/9 (67%), respectively. There was no correlation between the ARR before and after natalizumab. Two other studies with a mean follow-up of 9 months reported relapse rates of 8/22 (36%) and 5/8 (63%) on fingolimod [34,35]. No relationship with pre-natalizumab disease activity was observed. In a retrospective study, 20/33 (61%) patients had relapses after cessation of natalizumab and 16/33 (48%) during ≥12 months' fingolimod therapy, of whom 10 (63%) had been relapse-free while on natalizumab and 14 (88%) during the switching period (mean 15 weeks) [36]. ARR before or during natalizumab or during the switching period did not predict relapses on fingolimod; only the last EDSS during the switching period was a predictor ($p = 0.04$). Another retrospective study reported that, while most patients remain clinically stable after switching from natalizumab to fingolimod, a considerable proportion show disease reactivation in terms of the “no evidence of disease activity” (NEDA)-3 criteria [37]. Among patients who continued natalizumab treatment, 90% fulfilled NEDA-3 criteria throughout the study, compared with 77% among those who switched to fingolimod or other therapies.

Several studies examined the effect of duration of washout period (and/or use of methylprednisolone during washout) between natalizumab and fingolimod. A randomized controlled trial ($n = 142$) compared washout periods of 8, 12 or 16 weeks, followed by fingolimod treatment for 24, 20 or 16 weeks, respectively [38]. The ARR during the 24 weeks since the last natalizumab infusion was 0.36 for an 8-week washout, 0.33 for 12 weeks and 0.65 for 16 weeks; the mean number of active T2 lesions at week 24 was 3.2, 4.4 and 7.7, respectively. Among prospective cohort studies, one ($n = 333$) found a relapse rate of 19.9% during the washout period in patients with a washout period < 3 months, 31.3% for 3–6 months, and 59.1% for > 6 months [39]. A washout period < 3 months was associated with a significantly lower risk of relapse (odds ratio 0.23, 95% CI 0.10–0.65; $p = 0.001$), while stopping natalizumab because of a lack of tolerance or efficacy was associated with a significantly higher risk of relapse (odds ratio 3.20, 95%CI 1.44–5.10; $p = 0.004$). In this study, 20% of patients relapsed during the first 6 months of fingolimod therapy; the occurrence of relapse during washout was the only statistically significant prognostic factor for relapse during fingolimod therapy (odds ratio, 3.80; 95% CI, 1.26–7.58; $p = 0.05$) [39]. Two other studies (one prospective and one retrospective) also reported higher relapse rates with longer washout periods [40,41]. The ARR before natalizumab treatment did not correlate with disease activity 6 months after natalizumab discontinuation in the prospective study [40]. In another study, the relapse rate after 10–11 months of fingolimod treatment was 5% among 38 patients who had a short washout period (4–8 weeks) and 10% among 58 who had a longer washout period with monthly pulses of methylprednisolone [42]. Finally, in patients with a washout period of 6 months, pulsed methylprednisolone significantly reduced the number of relapses ($p < 0.03$) during this period [43]. Of the 20 patients who received methylprednisolone, 19 went on to receive fingolimod for a mean of 20 months; one had a relapse 1 month after starting fingolimod and improved after treatment with methylprednisolone.

As with the other drugs considered above, fingolimod seems to be a suitable post-natalizumab therapy in some but not all patients. It appears that the washout period between natalizumab and fingolimod should be kept below 6 months, and possibly not exceeding 3 months. There is some suggestion that pulsed methylprednisolone may be helpful if the washout period is more prolonged, but the evidence on this is contradictory. Unlike switches to first-line therapies (interferon beta/glatiramer acetate or DMF), the success of switches to fingolimod does not appear to be influenced by the patient's previous disease activity.

3.4. Rituximab and other drugs

The single study that assessed patients switching from natalizumab to rituximab ($n = 114$) reported relapses within 1.5 years of natalizumab discontinuation in 1.8% of patients compared with 17.6% of those who switched to fingolimod ($n = 142$). The rates of adverse events (5.3% vs 21.1%) and treatment discontinuation (1.8% vs 28.2%) also favored rituximab, as did the proportion of patients with gadolinium-enhancing lesions (0.9% vs 16.2%) [44]. In addition, a case has been reported in which a patient who developed PML followed by IRIS after 5 years' natalizumab treatment went on to relapse while taking fingolimod but then achieved freedom from disease activity with rituximab treatment [45]. Thus, the limited evidence available suggests that rituximab is a promising option for post-natalizumab therapy.

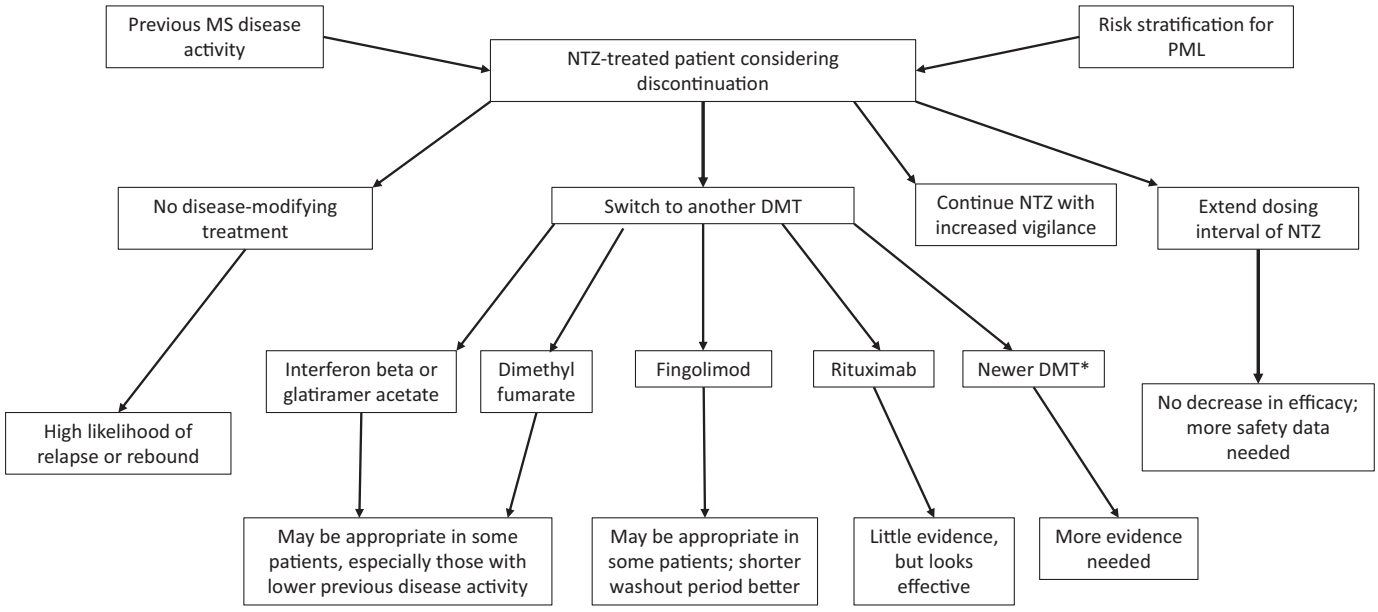
Data in patients switching from natalizumab to newer therapies such as alemtuzumab, ocrelizumab or teriflunomide are scarce. However, one small observational study of 16 patients switched to alemtuzumab (median washout 70 days) reported on 6-month results in eight patients. No MRI activity, relapses or increase in EDSS were seen [46]. A poster presented at the American Academy of Neurology Annual Meeting in April 2018 showed continued control of disease activity in the 14 patients in this cohort with > 12 months' follow-up on alemtuzumab [47]. There are also two case reports relating to alemtuzumab. One patient experienced severe clinical and radiological disease reactivation after switching from natalizumab to daclizumab (withdrawn from market in March 2018) due to PML safety concerns; control was subsequently established with methylprednisolone and alemtuzumab [48]. The second patient also experienced a dramatic course with severe CNS inflammation after discontinuation of natalizumab and treatment initiation with daclizumab; methylprednisolone and 10 courses of plasmapheresis did not control the inflammation, but the disease course was stabilized by use of alemtuzumab [49].

3.5. Extended interval dosing of natalizumab

An alternative approach to reducing the risk of PML in natalizumab-treated patients is use of an extended dosing interval. One retrospective review of 361 patients who received natalizumab for ≥6 months found no difference in relapse rates or MRI activity between patients receiving monthly dosing (mean 22 ± 13 months) and the 96 who opted to extend the dosing interval to 6–8 weeks (mean 20 ± 11 months) [50]. Another retrospective review of 1998 natalizumab-treated patients found no decrease in effectiveness with dosing intervals of up to 8 weeks and 5 days. No cases of PML were observed in 905 patients with extended dosing compared with four cases among 1093 patients using standard dosing, despite a higher rate of anti-JCV antibody positivity and higher antibody index in the former group [51]. The latest data from this study confirm a statistically significantly and clinically meaningful lower risk of PML in the patients with a history of extended interval dosing in the previous 18 months ($p < 0.0001$) [52].

4. Discussion

Natalizumab is a highly effective treatment for RRMS, but the increased risk of PML after 2 years' therapy and in patients with other risk factors means that discontinuation may be considered in some patients. The decision-making process will be individual to the patient and



*Such as alemtuzumab, ocrelizumab or teriflunomide
DMT, disease-modifying therapy; MS, multiple sclerosis; NTZ, natalizumab; PML, progressive multifocal leukoencephalopathy

Fig. 1. Decision-making in patients considering discontinuation of natalizumab.

influenced by several factors such as disease and treatment history, and magnitude of and attitude to PML risk. Fig. 1 illustrates the options available to physicians and patients considering natalizumab discontinuation. For some patients, continuing natalizumab therapy with increased monitoring and vigilance for PML may represent the best option. In others, extending the dosing interval of natalizumab may be a suitable approach; the data on this so far look very promising [50–52]. Stopping MS treatment altogether is unlikely to be appropriate for most patients, given the high risk of relapse or rebound [13,14]. Thus, for some patients, the decision may be made to consider switching to another therapy.

As natalizumab is usually a second-line therapy, many patients will already have been treated with first-line drugs such as interferon beta or glatiramer acetate before starting natalizumab. Returning to a previously used therapy is unlikely to be either acceptable or successful, and the evidence suggests that the use of either of these agents after natalizumab carries a high risk of clinical relapse, MRI activity and disability progression [18–22]. Data on switching to DMF are slightly more favorable, but again the chance of disease reactivation is not negligible [28–30]. For all these therapies, the evidence suggests that the likelihood of relapse is greater in patients whose disease activity was high before they started natalizumab or who relapsed during natalizumab treatment [19,21,25,28–30].

The most studied post-natalizumab therapy is fingolimod, for which the risk of relapse appears to lower than for interferon beta or glatiramer acetate [23,24]. Several studies show a relapse rate on fingolimod that is higher than on natalizumab but lower than was seen before initiation of natalizumab [31,33,36,43]. The evidence suggests that the washout period between natalizumab and fingolimod should not be too long – preferably no longer than 12 weeks [38,39]. The use of pulsed methylprednisolone during longer washout periods may be beneficial [43], but the evidence is not very strong [42]. The risk of relapse on fingolimod does not appear to be correlated with previous disease activity [31,33,34,36,40].

The newer second-line DMTs may in time be shown to represent a good option for patients switching from natalizumab. The limited data available for rituximab and alemtuzumab look promising [44,46,47]. Ongoing clinical trials will provide more data on these options. The SUPPRESS study is looking at open-label treatment with alemtuzumab after natalizumab in 40 RRMS patients [53], another trial is examining switching from natalizumab to teriflunomide in 70 patients [54], and a prospective cohort study is following 70 patients transitioning from natalizumab to ocrelizumab [55]. Data from MS registries would also be useful in this context.

While the results of the ongoing studies are awaited, physicians and patients considering natalizumab discontinuation need to reach a joint decision on what is likely to be the most appropriate option for each individual. We hope that the algorithm in Fig. 1 will be of some assistance in making this decision.

5. Conclusions

This article has considered the various options for natalizumab-treated patients at high risk of PML. These include continuing treatment with increased monitoring/vigilance and possibly an extended dosing interval; stopping MS treatment, which is not advisable for most patients; or switching to an alternative treatment. In the latter case, fingolimod appears to be a better choice than interferon beta, glatiramer acetate or DMF, particularly in patients with previous high disease activity. A long washout period between therapies should be avoided. Limited data suggest that rituximab and alemtuzumab may be appropriate options, and further data on these and other newer therapies are awaited.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2018.09.012.

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