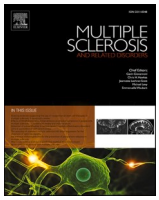
Multiple Sclerosis and Related Disorders 65 (2022) 103995

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Review article

Use of natalizumab in persons with multiple sclerosis: 2022 update

Sarah A. Morrow [a,*], Fraser Clift [b], Virginia Devonshire [c], Emmanuelle Lapointe [d], Raphael Schneider [e], Mark Stefanelli [b], Reza Vosoughi [e]

[a] Department of Clinical Neurological Sciences, Western University, London, ON, Canada
[b] Department of Neurology, Memorial University of Newfoundland, St. John's, NL, Canada
[c] Department of Medicine, Division of Neurology, University of British Columbia, Vancouver, BC, Canada
[d] Department of Medicine, Division of Neurology, University of Sherbrooke, QC, Canada
[e] Department of Medicine, Division of Neurology, University of Toronto, ON, Canada

ARTICLE INFO

Keywords:
Multiple sclerosis
Natalizumab
Clinical practice
Disease-modifying therapy

ABSTRACT

Background: Natalizumab is a humanized monoclonal antibody used for treatment of highly active relapsing-remitting multiple sclerosis (MS). With more than 15 years of post-marketing experience with natalizumab in Canada, several real-world studies have shown the long-term efficacy and safety of natalizumab. In addition, risk stratification/mitigation strategies for progressive leukoencephalopathy (PML), an adverse effect associated with natalizumab based on the John Cunningham virus (JCV) index; treatment duration beyond 24 months; and prior exposure to immunosuppressant drugs have been developed.
Methods: A group of neurologists from various MS clinics across Canada met in September 2021 to update the 2015 Canadian practice recommendations for the use of natalizumab in persons with MS (PwMS).
Results: The recommendations focused on the long-term efficacy and safety data from real-world studies, patient selection according to JCV index criteria, risk management strategies for PML (including extended interval dosing), and options for switching to currently available disease-modifying therapies for MS.
Conclusions: The recommendations of clinical neurologists seek to optimize the management of PwMS who may benefit from treatment with natalizumab.

1. Introduction

Natalizumab, a recombinant humanized IgG4κ monoclonal antibody selective for α4-integrin, is indicated as monotherapy for the treatment of persons with the relapsing-remitting form of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations, to decrease the number and volume of active brain lesions identified on magnetic resonance imaging (MRI) scans, and to delay the progression of physical disability (Biogen Canada Inc, 2017).

Since the last Canadian practice recommendations relating to the use of natalizumab in persons with MS (PwMS) (O'Connor and Kremenchutzky, 2015), there have been considerable strides toward improving clinical risk management, although many of the recommendations still hold and constitute standard care for PwMS who are either candidates for treatment or currently being treated with natalizumab. The authors, a group of neurologists representing MS clinics across Canada, convened in September 2021 to review the 2015 recommendations and determine key areas for updating.

Although many real-world, international studies have added evidence that natalizumab is a highly effective treatment for relapsing MS, reports of strategies for minimizing the risk of progressive multifocal leukoencephalopathy (PML) have provided clinicians with options for optimizing the benefits of natalizumab treatment. The risk of PML is the most common reason for discontinuation of treatment with natalizumab (Chisari et al., 2021). Patient selection, switching protocols minimizing washout periods, managing PwMS after discontinuation of natalizumab, treatment-withholding procedures, risk-management strategies involving anti-John Cunningham virus (JCV) antibody testing, education, and extended-interval dosing (EID) are key strategies for optimizing the management of PwMS receiving natalizumab. These updates will be the focus of this article.

2. Methods

A group of neurologists from various MS clinics across Canada met in September 2021 to update the 2015 Canadian practice

* Corresponding author.
E-mail address: Sarah.Morrow@lhsc.on.ca (S.A. Morrow).

https://doi.org/10.1016/j.msard.2022.103995
Received 26 April 2022; Received in revised form 4 May 2022; Accepted 23 June 2022
Available online 26 June 2022

recommendations for the use of natalizumab in persons with MS (PwMS) (O'Connor and Kremenchutzky, 2015) A PubMed literature search (2014–2021) for natalizumab-related topics was performed, which informed the focus of the clinical practice updates — i.e., real-world, long-term efficacy and safety of natalizumab, patient selection, switching to other disease-modifying therapies (DMTs), protection against opportunistic infections, managing PwMS after discontinuation of natalizumab, treatment-withholding procedures (including management of PwMS around pregnancy), risk-management strategies involving JCV antibody testing, and EID. An initial draft of the updated practice recommendations for the use of natalizumab was prepared and sent to the members of the group and revised after an online meeting. A second draft was revised based on additional feedback and the final draft was approved.

3. Efficacy and safety of natalizumab in MS

3.1. Long-term efficacy and safety of natalizumab

Natalizumab has been a treatment option for persons with relapsing forms of MS for more than a decade. The short-term efficacy and safety of natalizumab treatment has been well-documented in pivotal (Polman et al., 2006; Rudick et al., 2006) and observational studies (Horga and Tintoré, 2011; Kappos et al., 2013; Krysko and O'Connor, 2011; Outteryck et al., 2014). However, longer duration of therapy with natalizumab ($\geq$ 24 months) increases the risk of PML. There is increasing evidence of long-term efficacy and safety of natalizumab, including on the use of EID, in persons with relapsing forms of MS, mainly from real-world studies. The Tysabri Observational Programme (TOP) is a real-world, open-label, multinational, prospective, observational study that aims to evaluate the long-term safety and effectiveness of natalizumab in persons with relapsing-remitting MS (RRMS). A 10-year interim analysis ($N = 6148$) (Butzkueven et al., 2020a), with a median time on natalizumab of 3.3 (range 0–11.6) years and a median follow-up time of 5.2 (range: 0–10.8) years confirmed the long-term safety of natalizumab, including the comparable safety of EID with standard interval dosing (SID) (Butzkueven et al., 2021a). A subset of TOP data of propensity score-matched EID and SID PwMS ($n = 219$ pairs) was used to compare clinical outcomes between the two dosing regimens for natalizumab. Participants were either treated with natalizumab on a SID schedule or transitioned from SID to EID schedule after $\geq$ 1 year on the SID treatment regimen. Annualized relapse rates were similar for EID (0.150) and SID (0.157) groups. The probability of remaining relapse free did not differ significantly between EID and SID groups. TOP participants on EID and SID dosing had similar incidence of all serious adverse events (SAEs) as well as SAEs related to treatment based on a qualitative assessment. Two cases of PML were observed in this study, both in the EID dosing group; notably, both PML cases were characterized by the presence of known risk factors for PML and were, therefore, in the highest PML risk category (Butzkueven et al., 2021a). The study showed that natalizumab effectiveness is maintained in those PwMS who switch to EID after $\geq$1 year on SID treatment regimen (Butzkueven et al., 2021a).

Overall, in the 10-year analysis of TOP, 13.5% ($n = 829$) experienced $\geq$ 1 SAE; 53 participants (0.9%) had confirmed PML. A total of 3210 participants (52.2%) discontinued natalizumab; 2117 (34.4%) withdrew from TOP (Butzkueven et al., 2020a). The 10-year analysis of TOP confirmed long-term effectiveness of natalizumab. The on-natalizumab annualized relapse rate was 0.15, a 92.5% reduction from the year before initiation (Butzkueven et al., 2020a). Of 5384 PwMS, 1287 (23.9%) had confirmed disability improvement (CDI); 51.8% experienced CDI in the first treatment year (Wiendl et al., 2021). When initiated early in the disease course, natalizumab was associated with fewer relapses and reduced disability worsening (Butzkueven et al., 2020a; Wiendl et al., 2021). The long-term effectiveness of natalizumab was also described in other real-world studies (Boziki et al., 2021; Davidescu et al., 2021; Efthimios et al., 2021; Guger et al., 2021; Horakova et al., 2020; Prosperini et al., 2017). Results from these studies indicate that, when administered long-term, natalizumab is effective and has an adequate safety profile, provided subjects are closely monitored.

3.2. First-line treatment using natalizumab

The efficacy of natalizumab as a first-line therapy for persons with relapsing MS was effectively demonstrated in the pivotal placebo-controlled, Phase 3 trial, AFFIRM, since most (90%) of the participants randomized were naive to DMT (Polman et al., 2006). Subsequent analysis of DMT-naive participants with highly active relapsing MS in the AFFIRM trial demonstrated substantial beneficial effects of first-line natalizumab in this subpopulation. Persons with highly active relapsing MS treated with natalizumab ($n = 148$) experienced significant 53% reduction in 12-week sustained disability progression and 64% reduction in 24-week sustained disability progression at 2 years versus placebo ($n = 81$). The annualized relapse rate (ARR) during the 2 years was significantly lower for natalizumab than placebo (0.28 vs. 1.46, respectively; $p < 0.001$), representing an 81% decrease with natalizumab treatment (Hutchinson et al., 2009). The rapid and sustained effect of natalizumab on ARR was also shown in the overall population in AFFIRM and has been corroborated in real-world clinical practice, where analysis of the TOP registry has shown ARR to be significantly reduced from 1.99 at baseline to 0.26 after 3 months of natalizumab treatment and maintained at that rate for 4 years (Kappos et al., 2013). Clinical and other real-world data described in the following section provide a robust argument for first-line use of natalizumab in PwMS for whom natalizumab is acceptable based on the risk profile of PML.

3.3. Comparative effectiveness of natalizumab versus other DMTs

The TOP and MSBase registries have been used to compare the effectiveness of first-line natalizumab against standard first-line therapies, interferon (IFN)-beta or glatiramer acetate, in PwMS with active disease. Comparisons were made between 732 propensity score-matched PwMS who initiated natalizumab or interferon-beta/glatiramer acetate. There was a statistically significant relative reduction of 68% in ARR for PwMS treated with natalizumab versus interferon-beta/glatiramer acetate (0.2 vs. 0.63; $p > 0.0001$). A lower proportion of PwMS discontinued natalizumab (29.5%; 108/366) than interferon-beta/glatiramer acetate (62.6%; 229/366), representing a 27% decrease in discontinuation rate with natalizumab (Spelman et al., 2016). Treatment with first-line natalizumab compares favorably with its use in second line or even third-plus line in terms of disability improvement. In an analysis of participants from the TOP registry, PwMS initially treated with natalizumab were significantly more likely to experience CDI than those who had been treated with one prior DMT by 20% and two or more prior DMTs by 40%. Moreover, subgroup analysis of treatment-naive participants showed that PwMS who initiated natalizumab $\leq$ 1 year after symptom onset had a significantly greater decrease in Expanded Disability Status Scale (EDSS) score and a significantly higher likelihood of achieving CDI than those who initiated more than one treatment after symptom onset (Wiendl et al., 2021). These data demonstrate the positive impact that early initiation of natalizumab has on disability improvement.

Real-world cohorts of persons with RRMS from single centers, multicenters, and national and international registries have been well utilized to explore the comparative effectiveness of natalizumab with another highly effective DMT, fingolimod, across clinical, radiological, disability, and disease activity outcomes (Barbin et al., 2016; Baroncini et al., 2016; Boziki et al., 2021; Braune et al., 2013; Curti et al., 2019; Guerra et al., 2021; Kalincik et al., 2015; Koch-Henriksen et al., 2017; Prosperini et al., 2017). The majority of these studies have shown natalizumab to be superior to fingolimod with regard to ARR, proportion of PwMS relapsing at 1 and 2 years and over longer time periods,

short-term disability improvement, and proportions of PwMS with gadolinium (Gd)-enhancing lesions or new T2 lesions at 1 and 2 years (Barbin et al., 2016; Baroncini et al., 2016; Boziki et al., 2021; Kalincik et al., 2015). Several studies use the metric of "no evidence of disease activity (NEDA) encompassing the absence of three clinical/imaging markers (NEDA-3)" — i.e., absence of relapses, no new radiological activity, and no confirmed disability progression (Wong et al., 2018) — have shown a significantly higher proportion of PwMS treated with natalizumab than fingolimod achieved NEDA-3 at 2 years, with one study extending this observation to 4 years (Baroncini et al., 2016; Curti et al., 2019; Guerra et al., 2021; Prosperini et al., 2017).

Data from prospective, head-to-head clinical trials have been published providing further supportive evidence that natalizumab is more efficacious that fingolimod, at least in the short-term (Butzkueven et al., 2020b; Cohen et al., 2021). REVEAL was a Phase 4, randomized, international study comparing natalizumab and fingolimod, which terminated early due to slow enrollment. In the subsequent exploratory analysis of the data from 108 PwMS (54 in each treatment group) who were enrolled, the mean number of new T1 Gd-enhancing lesions was ≥ 70% lower at 12 weeks ($p = 0.030$) following natalizumab treatment versus fingolimod treatment, with this difference still apparent through 24 weeks, even with reduced participant numbers. The difference between the on-treatment reduction from baseline in ARR was significant in favor of natalizumab ($p = 0.023$) (Butzkueven et al., 2020b). In the Best-MS head-to-head study, treatment choice was at the discretion of physician, with 109 PwMS receiving natalizumab and 114 receiving fingolimod. At the end of the 12-month study, 47.8% of PwMS treated with natalizumab and 30.4% treated with fingolimod had NEDA ($p = 0.015$) (Cohen et al., 2021).

There is some conflicting evidence from retrospective, observational studies where differences between natalizumab and fingolimod were not found (Braune et al., 2013; Koch-Henriksen et al., 2017).

A comparison of natalizumab versus other high-efficacy DMTs with limited reproducible findings is beyond the scope of this paper.

3.4. Extended interval dosing

The first step in exploring the utility of EID with natalizumab to reduce the risk of PML is establishing that there is no loss of clinical effectiveness. As described earlier, long-term data from the TOP registry indicate that the effectiveness of natalizumab is maintained with an EID schedule in comparison with SID, with no change to the safety profile (Butzkueven et al., 2021a). A number of real-world studies further support the findings that EID maintains the efficacy of natalizumab in cohorts that include anti-JCV antibody-positive and antibody-negative PwMS (Butzkueven et al., 2020a; Chisari et al., 2020; De Mercanti et al., 2021; Riancho et al., 2021). The effect of switching PwMS who were clinically stable on a once every 4 weeks (Q4W) SID to a once every 6 weeks (Q6W) EID versus maintaining the SID schedule was explored in NOVA, the first randomized trial to assess the efficacy of natalizumab Q6W dosing. The estimated mean number of new/newly enlarged T2 (N/NET2) lesions at week 72 (primary endpoint) was 0.20 (95% CI: 0.07 0.63) in the Q6W group ($n = 247$) and 0.05 (95% CI, 0.01–0.22) in the Q4W group ($n = 242$). However, the mean lesion values in the Q6W dosing group were strongly influenced by the two participants with extreme values. There were no significant or clinically meaningful differences between the dosing schedules on secondary efficacy endpoints of ARR, time to first relapse, and time to 24-week confirmed disability worsening. Safety was also consistent between the dosing schedules (Foley et al., 2021). An analysis of published pharmacokinetic/-pharmacodynamic models to simulate distribution of natalizumab saturations for different body weight categories and dosing intervals indicated that every-5-week or every-6-week dosing is likely to maintain the efficacy of natalizumab, particularly at body weights < 80 kg, in PwMS who switch from SID after a period of stability (Chang et al., 2021). Together the real-world and clinical trial data indicate that EID could be considered for both PwMS who are anti-JCV antibody-positive and anti-JCV antibody-negative. Further clinical research is required to define applicability of EID based on patient factors and at this time the decision is at the discretion of the clinical provider on a case-by-case basis.

With evidence of comparable effectiveness of EID and SID schedules accruing, the next step in exploring the utility of EID with natalizumab is to examine PML risk. A retrospective cohort study ($N = 35,521$) using the large dataset from the Tysabri Outreach Unified Commitment to Health (TOUCH) program was undertaken to compare natalizumab-associated PML risk between EID versus SID in anti-JCV antibody-positive PwMS. The effect of EID on PML risk was evaluated with three analyses, with PwMS being stratified by prior immunosuppressant use. The mean average dosing intervals were 35–43 days for the EID cohort, and 30–31 days for the SID cohorts. For each of the three different analyses, there was a substantial reduction in PML risk with natalizumab EID compared with SID as shown in Table 1 (Zhovtis Ryerson et al., 2019).

4. Patient selection

Therapies such as IFN and glatiramer acetate, that are traditionally used as first-line treatment for persons with RRMS, either through clinician choice or, as in Canada, through health authority stipulation, are selected based on their well-known safety profile rather than superior efficacy (Freedman et al., 2020; Nicholas et al., 2014). These agents offer only partial protection against relapse and disease progression and with the availability of new highly effective DMTs, the bar for treatment success has shifted to complete freedom of disease activity.

For persons with RRMS who are DMT-naive, there is compelling evidence for natalizumab to be considered as a first-line treatment option for those in whom natalizumab is acceptable based on the risk profile of PML (Freedman et al., 2020). As described earlier, first-line natalizumab treatment has been shown to be highly effective against disability progression and relapse in comparison with placebo, including PwMS with highly active disease and with a rapid and sustained beneficial effect (Hutchinson et al., 2009; Kappos et al., 2013; Polman et al., 2006). Although not demonstrated in a head-to-head study, using registry data from propensity score-matched subjects, first-line natalizumab was more effective than standard first-line DMTs at protecting against relapse (Spelman et al., 2016). Data showing PwMS have better disability outcomes when treated with natalizumab first-line versus second or third-plus, or early on in their disease course, versus those treated later (Wiendl et al., 2021) have important implications on the treatment sequence that clinicians should be considering for DMT-naive PwMS.

Natalizumab should be considered as a second-line option for persons with RRMS with failure or insufficient response to an adequate course (i.e., at least 6 months) of one or more conventional DMTs, such as IFN, glatiramer acetate, or oral agents (Kappos et al., 2011; O'Connor and Kremenchutzky, 2015). The Canadian MS working group have recommended criteria for switching therapy based on relapse rate, the clinical presentation of relapse severity and recovery and MRI scans (Freedman et al., 2020). Major criteria indicative of a suboptimal treatment response requiring treatment optimization are (1) two or more relapses in the first year of treatment, (2) a severe relapse with functional impairment and bowel bladder, cerebellar, pyramidal, and brain stem involvement; (3) incomplete recovery from relapse with functional impairment and EDSS change > 1 point at 6 months; and (4) three or more new/newly enlarging lesions on MRI. Regarding the

Table 1
Estimates of PML risk over successive epochs of natalizumab treatment for three different test conditions for PwMS on an EID or SID treatment schedule (Zhovtis Ryerson et al., 2019).

		Estimated risk of PML per 1,000 PwMS (No. of cases per adjusted No. of subjects)					
		Primary analysis (*Effect of the last 18 months of dosing history on PML risk*)		Secondary analysis (*Effect of any prolonged periods of EID on PML risk*)		Tertiary analysis (*Effect of dosing history consisting primarily of EID on PML risk*)	
Natalizumab exposure epoch[a]	No. of infusions	EID-1° Group	SID-1° group	EID-2° group	SID-2° group	EID-3° group	SID-3° group
1	1–12	0 (0/1,806)	0 (0/11,890)	0 (0/2,980)	0 (0/13,049)	0 (0/662)	0 (0/18,364)
2	13–24	0 (0/1,659)	0.28 (3/10,907)	0 (0/2,722)	0.60 (6/9,921)	0 (0/510)	0.52 (7/13,425)
3	25–36	0 (0/1,366)	0.46 (4/8,608)	0.44 (1/2,292)	0.46 (3/6,514)	0 (0/371)	0.42 (4/9,603)
4	37–48	0 (0/1,080)	2.02 (13/6,439)	0 (0/1,841)	2.58 (12/4,650)	0 (0/265)	1.79 (13/7,254)
5	49–60	1.23 (1/810)	3.96 (19/4,801)	1.45 (2/1,380)	4.14 (14/3,385)	0 (0/169)	3.67 (20/5,443
6	61–72	1.70 (1/589)	4.46 (15/3,363)	2.04 (2/980)	4.74 (11/2,323	0 (0/104)	4.16 (16/3,848)

EID: extended-interval dosing, PML: progressive multifocal leukoencephalopathy, PwMS: persons with MS, SID: standard interval dosing.
Primary analysis was conducted to test the effect of the last 18 months of dosing history on PML risk. EID-1° was defined as ≤ 15 infusions in the last 18 months. SID-1° as > 15 infusions in the last 18 months.
Secondary analysis was conducted to test the effect of any prolonged periods of EID on PML risk. EID-2° was defined as any infusion preceded by ≤ 10 doses in the prior 365 days; PwMS received consecutive EID-2° infusions for ≥ 6 months. SID-2° was defined as > 10 doses over 365 days prior to any infusion; participants received consecutive SID-2° infusions for ≥ 6 months
Tertiary analysis was conducted to test the effect of dosing history consisting primarily of EID on PML risk. EID-3° was defined as ≤ 10 infusions/year over the entire treatment duration. SID-3° was defined as > 10 infusions/year over the entire treatment duration.
PML risk is shown as the incidence rate per 1,000 subjects (number of cases of PML per adjusted number of subjects at risk) in anti-JC virus antibody-positive PwMS without prior immunosuppressant use for the primary and secondary definitions. PwMS with prior immunosuppressant use could not be analyzed due to the insufficient number of subjects.
The adjusted number of subjects at risk was 95 in the EID-1° group, 689 in the SID-1° group, 171 in the EID-2° group, and 747 in the SID-2° group. PML risk could not be calculated in the tertiary analysis of EID because no cases of PML occurred in this analysis.
Reproduced from Zhovtis Ryerson et al, Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. Neurology. 2019;93(15): e1452-e1462.
[a] Data beyond 6 years are not shown.

timing of MRI, a reference MRI should be obtained after initiating or changing treatment, which is 3–6 months for IFN, glatiramer acetate and oral agents and annually for the first few years (Freedman et al., 2020).

Other scenarios for use of natalizumab include:

- Those who have intolerability to first-line DMT and evidence of inflammatory disease activity (O'Connor and Kremenchutzky, 2015)
- PwMS who are at risk of an aggressive clinical course, worse outcomes, and/or a poorer response to DMT, for example males, individuals of non-White ethnicity, and those with high-risk clinical/radiological disease factors. Natalizumab is a particularly suitable option for such PwMS given its rapidity of response in preventing the development of lesions and reducing ARR (Kappos et al., 2013; Miller et al., 2003).
- PwMS younger than 18 years of age who meet the criteria for treatment.

Scenarios where natalizumab should not be considered include:

- Older PwMS (> 55 years), as there are insufficient data regarding use of natalizumab in this population.
- Currently, there is no evidence that natalizumab is effective in PwMS with worsening secondary progressive MS (SPMS). An open-label, extension study (ASCEND) comparing natalizumab versus placebo treatment in persons with SPMS did not meet the primary or secondary endpoints, although a statistically significant treatment effect was observed in delaying disability progression in upper limb function (Kapoor et al., 2018).

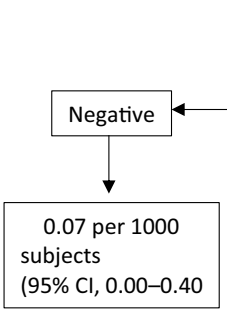
5. Recommendations

5.1. PML risk stratification incorporating the JCV index

Three major factors have been associated with increased risk of the development of PML in PwMS treated with natalizumab: (1) the presence of JCV antibodies, (2) prior immunosuppression, and (3) duration of therapy (Bloomgren et al., 2012; Ho et al., 2017). The risk of natalizumab-associated PML is low in PwMS who are JCV antibody-negative at initiation of natalizumab (Mason, 2019). It is advisable to monitor JCV-serostatus every 3–6 months in JCV antibody-negative PwMS (Freedman et al., 2020). For those PwMS who are JCV antibody-positive monitoring strategies, such as the anti-JCV antibody index, are available to manage risk through an individualized patient management approach. PML risk estimates are available to support benefit-risk discussions. Fig. 1 provides the current PML risk estimates for JCV-antibody-positive PwMS based on anti-JCV antibody index, natalizumab exposure in months based in a once-monthly infusion SID schedule and previous immunosuppressant use. Evidence is starting to accrue to support EID as a strategy to manage the risk of PML. Table 1 provides the PML risk estimates for EID and SID schedules for JCV-antibody-positive PwMS, not previously exposed to immunosuppressants (Zhovtis Ryerson et al., 2019). JCV-antibody-positive PwMS should be monitored on a regular basis for signs and symptoms of PML, through clinical vigilance, neurologic assessment, and periodic MRI scans (Carillo-Infante et al., 2016; Kappos et al., 2011). Fig. 2 is an algorithm for MRI-based PML safety monitoring during natalizumab therapy. As a result of patient education and monitoring strategies, the incidence of natalizumab-associated PML has decreased in recent years (Vivekanandan et al., 2021; Vukusic et al., 2020).

5.2. Switching to natalizumab from other DMTs

Formal guidelines on switching DMTs are not clearly defined. The decision on the appropriate between-treatment duration when switching to natalizumab should be individualized, taking into consideration



Natalizumab exposure (months)†	PwMS without previous immunosuppressant use, per 1000 subjects (95% CI)			PwMS with previous immunosuppressant use, per 1000 subjects (95% CI)
	Index ≤ 0·9	Index > 0·9 to ≤ 1·5	Index > 1·5	
1–12	0·01 (0·00–0·03)‡	0·1 (0·0–0·2)	0·2 (0·0–0·5)	0·3 (0·0–1·9)
13–24	0·05 (0·00–0·14)‡	0·3 (0·0–0·6)	0·9 (0·3–1·6)	0·4 (0·0–2·3)
25–36	0·2 (0·0–0·4)	0·8 (0·1–1·5)	2·6 (1·4–3·9)	3·6 (1·4–7·4)
37–48	0·4 (0·0–1·0)	2·0 (0·2–3·8)	6·8 (4·4–9·1)	8·3 (4·3–14·5)
49–60	0·5 (0·0–1·2)	2·4 (0·2–4·5)	7·9 (4·9–10·9)	8·4 (3·7–16·6)
61–72	0·6 (0·0–1·5)	3·0 (0·2–5·8)	10·0 (5·6–14·4)	5·5 (1·1–16·0)§

Fig. 1. Updated PML risk estimate based on natalizumab exposure, previous immunosuppressant use, and anti-JCV antibody index (Ho et al., 2017).
Abbreviations: JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy; PwMS = persons with multiple sclerosis. *PML risk estimates were calculated using a life table method in the pooled cohort of anti-JCV antibody-positive PwMS who participated in the STRATIFY-2 (Campagnolo et al., 2016), TOP (Butzkueven et al., 2014), TYGRIS (Foley et al., 2019), and STRATA (O'Connor et al., 2014) clinical studies. †Data beyond 6 years of treatment are scarce. ‡Although estimates below 0·1 per 1000 subjects were rounded up to 0·1 per 1000 subjects for regulatory documents and management guidelines (2016), these estimates are shown with greater precision in this manuscript. §Variability might be due to small sample size. Reprinted from The Lancet, 16(11), Ho PR, et al, Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies, pages 925-933, Copyright (2017), with permission from Elsevier.

medication history, disease activity, goals of treatment, and personal preferences. The use of natalizumab following immunosuppressive therapy should be considered with extreme caution and only in expert hands because of the increased risk of PML in JCV antibody-positive PwMS (Freedman et al., 2020; Rae-Grant et al., 2018). A treatment-free period during treatment transition to natalizumab may not be in the best interest of the PwMS, particularly those with rapidly worsening disease and/or high disease activity. Whether a washout period is required prior to switching to natalizumab is dependent on the treatment being discontinued (Bigaut et al., 2021). For PwMS who have failed IFN or glatiramer acetate therapy, escalating treatment by switching to natalizumab has been shown to be more effective than lateral switching between IFN and glatiramer acetate (Prosperini et al., 2012). Transitioning to natalizumab from IFN or glatiramer acetate has been shown to be more effective than switching to fingolimod in reducing relapses and promoting reduction of disability (Kalincik et al., 2015).

5.3. *Monitoring during natalizumab treatment*

Evaluation should occur at a minimum of every 6 months, and more frequently if there are any concerns such as hypersensitivity reactions, infusion reactions, new neurological symptoms, or disease worsening (O'Connor and Kremenchutzky, 2015). In the context of PML, there can be progressive worsening of multifocal neurological symptoms due to involvement of supratentorial or infratentorial structures in the brain. Clinical manifestations of spinal cord and optical nerves are rare (Cortese et al., 2021).

The following evaluations should form part of routine follow-up visits:

- History of any new neurological symptoms and complete neurological examination.
  - Symptoms indicative of PML most commonly include cognitive and behavioral abnormalities, sensory and motor deficits, ataxia, aphasia, and cortical visual changes (Cortese et al., 2021).
- Updated medical history with a physical examination looking particularly for signs of opportunistic infection, malignancy (skin or otherwise), and liver disease.
- Liver function tests in those PwMS at risk for hepatotoxicity.
- Neutralizing antibodies (NAbs). Although in clinical trials only approximately 6% of participants developed persistent anti-natalizumab antibodies, their development was associated with loss of efficacy (Calabresi et al., 2007).
  - Testing should be conducted in those who experience persistent infusion reaction or any hypersensitivity reaction. PwMS testing positive for NAbs should be retested 3 months later to confirm persistence (Calabresi et al., 2007).
  - Routine testing for NAbs can be considered at 3 and 6 months in the absence of infusion reactions to prevent unnecessary continuation of a therapy rendered ineffective by NAbs
  - Testing for NAbs should be done immediately in the case of breakthrough disease, unless a PwMS is treated promptly with an alternative DMT.
- Anti-JCV index, at least every 6 months, and potentially more frequently (e.g., 3 months) for those with higher risk of PML (Calabresi et al., 2007).
- Active evaluation of PwMS (clinically and radiologically) for any indications of PML (see the following section) or disease worsening. Those presenting with new neurological symptoms should be referred for MRI scans.
  - The recommended MRI sequences include two- or three-dimensional axial FLAIR and axial diffusion-weighted imaging; a contrast agent is not required (Igra et al., 2017).

5.4. *Identification and management of possible PML cases*

PwMS should be instructed to promptly report any new neurological symptoms to their clinician; reminder should occur at each visit. Follow the algorithm for evaluating possible PML cases proposed by the International Multiple Sclerosis Expert Forum (adapted by this panel). PML can be fatal; cases that are identified and treated early may have a more

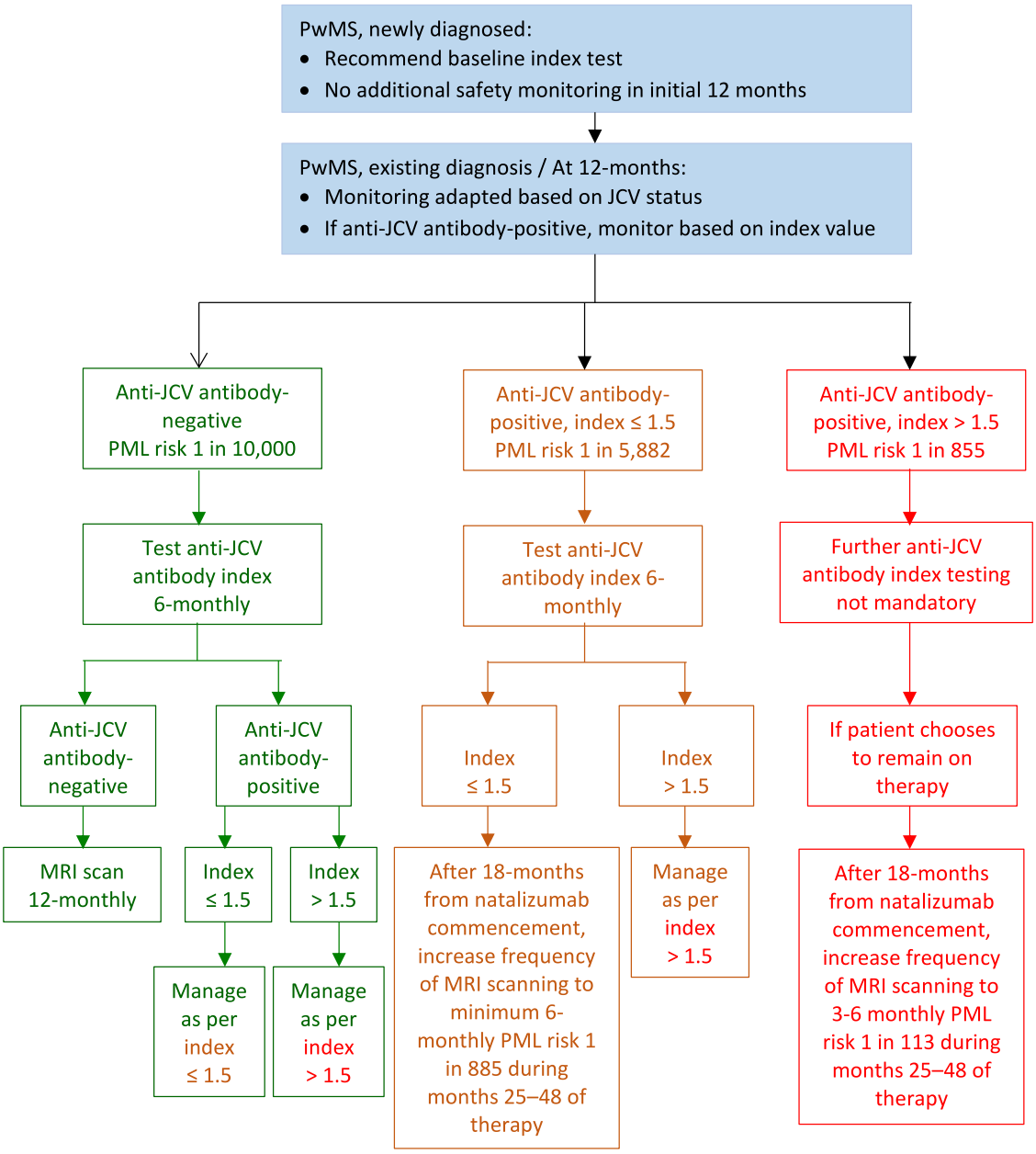


Fig. 2. Algorithm for MRI-based PML safety monitoring during natalizumab therapy, utilizing anti-JCV antibody status and anti-JCV antibody index level (McGuigan et al., 2016). [color figure]

favorable outcome. After 24 infusions (18–24 months depending on SID or EID schedule) inform PwMS, particularly those with a high JCV antibody index, about the risks of natalizumab, including that the risk of PML increases with longer treatment duration; obtain consent for continuation of treatment.

If there is uncertainty about whether a PwMS on natalizumab is showing signs of PML versus a relapse, then assume PML and do not treat with steroids until proven otherwise. If there is suspicion of PML: (1) dosing should be suspended, (2) perform MRI with Gd enhancement and diffusion-weighted imaging as soon as possible, and (3) contact the drug manufacturer. Re-dose natalizumab only if PML is excluded and if deemed appropriate. If the MRI shows features suggestive of PML, a cerebrospinal fluid sample should be obtained and tested (by polymerase chain reaction [PCR]) for the presence of JCV DNA. Suspend natalizumab dosing if PML is confirmed, and instruct PwMS and caregivers to be vigilant for any new signs or symptoms that may be suggestive of PML for approximately 6 months following discontinuation of natalizumab.

In natalizumab-treated PwMS who developed PML, immune reconstitution inflammatory syndrome (IRIS) has been described within 1–3 months of discontinuation. Immunoadsorption and plasma exchange may increase the probability/hasten onset of IRIS (Khoy et al., 2020). There have been no large-scale studies defining best practice in management of IRIS; cautious use of steroids may be helpful. Avoid prophylactic steroids in the absence of IRIS. Maraviroc is a potential treatment of PML-IRIS in PwMS who were treated with natalizumab.

Natalizumab is not recommended for PML survivors because JCV is not always cleared from the CNS but can instead return to a state of latency or persistent infection (Cortese et al., 2021).

5.5. *Other opportunistic infections and malignancies*

Infections and infestations were the most common SAEs in the 10-year interim analysis of natalizumab safety and effectiveness in TOP,

with an incidence of 4.1%. PML, pneumonia, urinary tract infection, and herpes zoster were the most commonly reported infections. The rates of development of malignancies and opportunistic infections in this long-term study (with the exception of PML) remained very low. The median time to onset for opportunistic infections was 14 months from natalizumab initiation, with a range of 3 months to 5 years (Butzkueven et al., 2020a).

Of note:

- No statistically significant differences in incidence rates of opportunistic infections and malignancies in PwMS treated with natalizumab compared with placebo in randomized trials were found.
- There were no unexpected SAEs, and the incidence of SAEs (including infections and hypersensitivity reactions) has been similar to that observed in clinical trials.
- Malignancy has been a theoretical concern with monoclonal antibodies.
- There were no observed differences in incidence rates or the nature of malignancies between natalizumab- and placebo-treated groups in clinical trials.

5.5.1. Vaccination and DMT treatment efficacy

Although some opportunistic infections can be prevented by vaccines, vaccine efficacy may be reduced in PwMS who are immunosuppressed. Vaccine responses have been shown to be reduced to varying degrees in those treated with glatiramer acetate, teriflunomide, sphingosine-1-phosphate receptor modulators, and natalizumab (Ciotti et al., 2020). When considering DMT for a PwMS, the benefits of a treatment to the individual should be considered against the expected response to future vaccinations that may be needed (Ciotti et al., 2020). For seasonal influenza, vaccination is recommended for PwMS who are treated with immunosuppressive drugs unless there is a specific contraindication. Natalizumab-treated PwMS may benefit from a second dose of the influenza vaccine, in cases of insufficient protection (Olberg et al., 2018). PwMS should be vaccinated against COVID-19 (National Multiple Sclerosis Society, 2021; Yamout et al., 2021). It has been determined that the risks of COVID-19 disease outweigh any potential risks from the vaccine. PwMS who are about to start natalizumab need not delay treatment for vaccination.

5.6. Possible considerations for withholding natalizumab therapy

5.6.1. Infection

Withhold natalizumab in PwMS with systemic infections. Natalizumab can be administered with viral cold or influenza in the absence of fever; withhold until resolution for febrile cold or infections. For those who develop shingles, withhold natalizumab until the condition is resolved.

5.6.2. PML

Suspend natalizumab treatment if new neurological symptoms and positive/high index MRI findings suggest an unfavorable risk of PML versus benefit ratio.

5.6.3. Pregnancy and lactation

Data from the natalizumab global safety database, clinical trials, and post-marketing cases do not suggest an effect of natalizumab exposure on pregnancy outcomes (Demortiere et al., 2021; Friend et al., 2016; Portaccio et al., 2018). Ongoing analysis of the Tysabri Pregnancy Exposure registry data showed no specific pattern of malformations that would suggest a teratogenic effect of natalizumab, and the spontaneous abortion rate was consistent with that of the general population (Friend et al., 2016). Another study showed that exposure to natalizumab in early pregnancy does not appear to increase the risk of adverse pregnancy outcomes in comparison to a disease-matched group not exposed to natalizumab (Ebrahimi et al., 2015). Natalizumab continuation into pregnancy has been shown to reduce the odds of relapse during pregnancy. In women considered to be at high relapse risk, use of natalizumab before pregnancy and continued up to 34 weeks gestation with early re-initiation after delivery may be an effective option to minimize fetal exposure in the third trimester while minimizing the risk of relapse (Yeh et al., 2021). In a case series, 10 out of 13 infants exposed to natalizumab in the third trimester were found to have hematologic abnormalities of thrombocytopenia, anemia, and leukocytosis. None required specific treatment, and in most cases, the abnormalities resolved during the 4 months after birth (Haghikia et al., 2014). The transfer of natalizumab into breastmilk appears to be at a relative infant dose (a metric comparing the infant with maternal drug) far below the threshold of concern of 10% (Proschmann et al., 2021). Biological plausibility of harm is low with the use of monoclonal antibodies in pregnancy and breastfeeding (Mahadevan et al., 2019; Puchner et al., 2019). Due to the risk of relapse and rebound disease activity, it may be detrimental to stop natalizumab before pregnancy. Any change to medication use when pregnancy planning should be in consultation with the clinical provider.

5.7. Possible considerations for discontinuation of therapy

5.7.1. Hypersensitivity

Natalizumab should be immediately and permanently discontinued in PwMS who experience hypersensitivity.

5.7.2. PML and JCV index

Anti-JCV antibody seropositivity and increased risk for PML is the most common reason for natalizumab discontinuation (Boziki et al., 2021; Chisari et al., 2021; Coerver et al., 2021; Guger et al., 2021; Hersh et al., 2020; Karanasios et al., 2021). If JCV index is > 1.5, management options include extending the dosing interval of natalizumab or switching to an alternative DMT.

5.7.3. Neutralizing antibodies

NAbs testing should be repeated soon after obtaining a positive result. Suspend natalizumab treatment while awaiting the results of the second NAbs test. Discontinue natalizumab treatment if positive NAbs persist (i.e., $\geq$2 separate tests). There is no indication for routine testing beyond 6 months, unless indicated (e.g., development of hives or radiologic evidence of loss of response) (O'Connor and Kremenchutzky, 2015).

5.7.4. Secondary progressive MS

There is no evidence that natalizumab can prevent or slow the sustained progressive disability experienced by persons with SPMS, although there may be a positive effect on the progression of upper limb disability (Kapoor et al., 2018).

5.7.5. Return of disease

Continuous natalizumab treatment is required for maximization of clinical benefit. Increased disease activity (i.e., relapse, rebound) following natalizumab discontinuation has been well-documented (Butzkueven et al., 2021b; Guger et al., 2019; Hersh et al., 2020; Papeix et al., 2016; Sellner and Rommer, 2019). A large-scale, multicenter, post-marketing assessment of disease activity within 12 months after natalizumab discontinuation showed that the probability of relapse within the year after natalizumab discontinuation was about 45% (Papeix et al., 2016). A meta-analysis of data from six articles identified via systematic review, with a total population of 1183 PwMS found that younger age, higher number of relapses and Gd-enhanced lesions before treatment start, and fewer natalizumab infusions were associated with increased risk for disease reactivation after treatment discontinuation ($p \leq 0.05$) (Prosperini et al., 2019). PwMS who stop natalizumab treatment after only two infusions and subsequently reinfused are more prone to

Table 2
Recommendations for the management of PwMS after discontinuation of natalizumab.

1	Treatment for PwMS who have discontinued natalizumab should be individualized — taking into consideration disease and treatment history, and the magnitude of and attitude to PML risk
2	Treatment options for PwMS considering discontinuation from natalizumab may include (Hersh et al., 2020; Sellner and Rommer, 2019) (1) Continuing natalizumab therapy with increased monitoring and vigilance for PML (2) Extending the dosing interval of natalizumab (3) Switching to moderate- or high-efficacy DMT
3	Start on another DMT as soon as possible to prevent the return of disease activity
4	When starting a new DMT minimize the washout period (i.e., no more than 4 weeks)
5	The use of immunosuppressant therapy immediately following natalizumab discontinuation should only be considered with extreme caution and only in expert hands
6	MRI should be done within 4 to 6 months of natalizumab discontinuation to assess for the return of disease activity
7	To rule out PML, lumbar puncture for JCV PCR is recommended for PwMS who are anti-JCV antibody-positive prior to switching to another DMT with a risk of PML
8	Monitor for PML for up to 6 months

DMT: disease-modifying therapy, JCV: John Cunningham virus, MRI: magnetic resonance imaging, MS: multiple sclerosis, PCR: polymerase chain reaction, PML: progressive multifocal leukoencephalopathy, PwMS: persons with multiple sclerosis.

developing infusion reactions and NAbs and are more susceptible to a rebound in T2 disease activity following discontinuation (O'Connor and Kremenchutzky, 2015). Hence, clinicians should monitor infusion reactions in PwMS who had short-term natalizumab treatment and manifests a return of disease activity.

In the TOP study (Butzkueven et al., 2020a), PwMS were encouraged to remain in the study after discontinuing natalizumab. Risk of relapse, ARR, and EDSS scores were analyzed in 3221 TOP participants, some of whom, after $\geq$ 2 years on natalizumab, were switched to an oral DMT (fingolimod, dimethyl fumarate, or teriflunomide; $n = 660$) or injectable DMT (IFN beta formulation or glatiramer acetate; $n = 95$). PwMS who persisted on natalizumab had better clinical outcomes than those who switched to oral or injectable therapies after $\geq$ 2 years on natalizumab (Butzkueven et al., 2021b).

5.8. Management of PwMS who are considering natalizumab discontinuation

Careful management of PwMS is required after discontinuation of natalizumab to prevent return of disease activity. Management recommendations are provided in Table 2.

6. Conclusions

Since the 2015 Canadian recommendation for the use of natalizumab in PwMS, data on long-term efficacy and safety, EID, DMT switching, and risk management strategies have emerged to inform improvements in the clinical management of those receiving natalizumab treatment for RRMS. Much of the previous recommendations still hold, as these have become standard of care in MS.

The long-term studies (Boziki et al., 2021; Butzkueven et al., 2020a; Guger et al., 2021; Prosperini et al., 2017) confirm that natalizumab is a highly effective treatment option for PwMS. Risk stratification for PML and risk management strategies that include patient education and close monitoring have improved outcomes and reduced the number of natalizumab-associated PML incidences (Vivekanandan et al., 2021; Vukusic et al., 2020). With close monitoring, PwMS at high risk for PML may be kept on natalizumab treatment instead of discontinuing.

EID (Q6W) of natalizumab has been shown to have comparable efficacy as the standard interval dosing (Q4W), while minimizing the risk of PML (Butzkueven et al., 2020a; Chisari et al., 2020; De Mercanti et al., 2021; Riancho et al., 2021; Ryerson et al., 2019). For PwMS who have to be switched from natalizumab to another DMT, minimizing the length of the washout period can reduce the likelihood of disease activation.

An individualized approach to patient selection and subsequent monitoring of natalizumab treatment outcomes and risk factors for PML is key to optimizing the benefit-risk ratio of this highly effective therapy for relapsing forms of MS.

Study funding

Biogen (Canada) provided funding for medical writing support for manuscript development and reviewed medical accuracy. The authors had full editorial control of the manuscript and provided their final approval of all content.

CRediT authorship contribution statement

Sarah A. Morrow: Writing – original draft, Writing – review & editing, Validation, Supervision. **Fraser Clift:** Writing – original draft, Writing – review & editing, Validation, Supervision. **Virginia Devonshire:** Writing – original draft, Writing – review & editing, Validation, Supervision. **Emmanuelle Lapointe:** Writing – original draft, Writing – review & editing, Validation, Supervision. **Raphael Schneider:** Writing – original draft, Writing – review & editing, Validation, Supervision. **Mark Stefanelli:** Writing – original draft, Writing – review & editing, Validation, Supervision. **Reza Vosoughi:** Writing – original draft, Writing – review & editing, Validation, Supervision.

Declaration of Competing Interest

SAM has received research funding from Biogen, Celgene, EMD Serono, Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, Novartis, Roche, and Sanofi-Genzyme; has received honoraria from Biogen, Celgene, EMD Serono, Novartis, Roche, Sanofi-Genzyme, and Teva Neurosciences. FC has received honoraria from Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Novartis, Roche, and Sanofi. VD has received honoraria from Biogen, EMD Serono, Novartis, Roche, Sanofi-Genzyme, and Teva Neurosciences. EL has received honoraria from Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Novartis, Roche, and Sanofi-Genzyme. RS has received honoraria from Biogen, Bristol Myers Squibb, EMD-Serono, Novartis, and Sanofi-Genzyme. MS has nothing to declare. RV has received educational support and honoraria from Biogen.

Acknowledgment

Bess Reinoso, PhD, of Excel Scientific Solutions (Fairfield, CT, USA) provided initial editing support based on a draft from authors and incorporated author comments during revisions, and Cara Dickinson from Excel Scientific Solutions copyedited and styled the manuscript per journal requirements.

References

Biogen Canada Inc, 2017. TYSABRI (natalizumab) product monograph. Biogen Canada Inc, Mississauga ON.

Barbin, L., Rousseau, C., Jousset, N., Casey, R., Debouverie, M., Vukusic, S., et al., 2016. Comparative efficacy of fingolimod vs natalizumab: a French multicenter observational study. Neurology 86 (8), 771–778. https://doi.org/10.1212/wnl.0000000000002395.

Baroncini, D., Ghezzi, A., Annovazzi, P.O., Colombo, B., Martinelli, V., Minonzio, G., et al., 2016. Natalizumab versus fingolimod in patients with relapsing-remitting multiple sclerosis non-responding to first-line injectable therapies. Mult. Scler. 22 (10), 1315–1326. https://doi.org/10.1177/1352458516650736.

Bigaut, K., Fabacher, T., Kremer, L., Ongagna, J.C., Kwiatkowski, A., Sellal, F., et al., 2021. Long-term effect of natalizumab in patients with RRMS: TYSTEN cohort. Mult. Scler. 27 (5), 729–741. https://doi.org/10.1177/1352458520936239.

Bloomgren, G., Richman, S., Hotermans, C., Subramanyam, M., Goelz, S., Natarajan, A., et al., 2012. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N. Engl. J. Med. 366 (20), 1870–1880. https://doi.org/10.1056/nejmoa1107829.

Boziki, M., Bakirtzis, C., Giantzi, V., Sintila, S.A., Kallivoulos, S., Afrantou, T., et al., 2021. Long-term efficacy outcomes of natalizumab vs. fingolimod in patients with highly active relapsing-remitting multiple sclerosis: real-world data from a multiple sclerosis reference center. Front. Neurol. 12, 699844 https://doi.org/10.3389/fneur.2021.699844.

Braune, S., Lang, M., Bergmann, A., 2013. Second line use of fingolimod is as effective as natalizumab in a German out-patient RRMS-cohort. J. Neurol. 260 (12), 2981–2985. https://doi.org/10.1007/s00415-013-7082-0.

Butzkueven, H., Kappos, L., Pellegrini, F., Trojano, M., Wiendl, H., Patel, R.N., et al., 2014. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results. J. Neurol. Neurosurg. Psychiatry 85 (11), 1190–1197. https://doi.org/10.1136/jnnp-2013-306936.

Butzkueven, H., Kappos, L., Spelman, T., Trojano, M., Wiendl, H., Su, R., et al., 2021a. No evidence for loss of natalizumab effectiveness with every-6-week dosing: a propensity score-matched comparison with every-4-week dosing in patients enrolled in the Tysabri Observational Program (TOP). Ther. Adv. Neurol. Disord. 14, 17562864211042458 https://doi.org/10.1177/17562864211042458.

Butzkueven, H., Kappos, L., Wiendl, H., Trojano, M., Spelman, T., Chang, I., et al., 2020a. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). J. Neurol. Neurosurg. Psychiatry 91 (6), 660–668. https://doi.org/10.1136/jnnp-2019-322326.

Butzkueven, H., Licata, S., Jeffery, D., Arnold, D.L., Filippi, M., Geurts, J.J., et al., 2020b. Natalizumab versus fingolimod for patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a prospective, randomised head-to-head study. BMJ Open 10 (10), e038861. https://doi.org/10.1136/bmjopen-2020-038861.

Butzkueven, H., Trojano, M., Kappos, L., Spelman, T., Wiendl, H., Rosales, K., et al., 2021b. Clinical outcomes in patients who discontinue natalizumab therapy after 2 years in the Tysabri(®) Observational Program (TOP). Mult. Scler. 27 (3), 410–419. https://doi.org/10.1177/1352458520917925.

Calabresi, P.A., Giovannoni, G., Confavreux, C., Galetta, S.L., Havrdova, E., Hutchinson, M., et al., 2007. The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. Neurology 69 (14), 1391–1403. https://doi.org/10.1007/s40262-017-0614-5.

Campagnolo, D., Ho, P.R., Patel, R.N., Chang, I., Subramanyam, M., Koendgen, H., et al., 2016. Four-year longitudinal index stability data from the STRATIFY-2 study. EAN, Copenhagen, Denmark. May 28-31.

Carillo-Infante, C., Richman, S., Yu, B., 2016. Functional and survival outcomes of asymptomatic progressive multifocal leukoencephalopathy in natalizumab-treated multiple sclerosis patients. ECTRIMS, London, UK, September 14-17 P1528.

Chang, I., Muralidharan, K.K., Campbell, N., Ho, P.R., 2021. Modeling the efficacy of natalizumab in multiple sclerosis patients who switch from every-4-week dosing to extended-interval dosing. J. Clin. Pharmacol. 61 (3), 339–348. https://doi.org/10.1002/jcph.1737.

Chisari, C.G., Comi, G., Filippi, M., Paolicelli, D., Iaffaldano, P., Zaffaroni, M., et al., 2021. PML risk is the main factor driving the choice of discontinuing natalizumab in a large multiple sclerosis population: results from an Italian multicenter retrospective study. J. Neurol. https://doi.org/10.1007/s00415-021-10676-6.

Chisari, C.G., Grimaldi, L.M., Salemi, G., Ragonese, P., Iaffaldano, P., Bonavita, S., et al., 2020. Clinical effectiveness of different natalizumab interval dosing schedules in a large Italian population of patients with multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 91 (12), 1297–1303. https://doi.org/10.1136/jnnp-2020-323472.

Ciotti, J.R., Valtcheva, M.V., Cross, A.H., 2020. Effects of MS disease-modifying therapies on responses to vaccinations: a review. Mult. Scler. Relat. Disord. 45, 102439 https://doi.org/10.1016/j.msard.2020.102439.

Coerver, E.M.E., Wessels, M.H.J., van Lierop, Z.Y.G., van Kempen, Z.L.E., Killestein, J., Strijbis, E.M.M., 2021. Natalizumab discontinuation in a Dutch real-world cohort. Mult. Scler. Relat. Disord. 52, 102974 https://doi.org/10.1016/j.msard.2021.102974.

Cohen, M., Mondot, L., Bucciarelli, F., Pignolet, B., Laplaud, D.A., Wiertlewski, S., et al., 2021. BEST-MS: a prospective head-to-head comparative study of natalizumab and fingolimod in active relapsing MS. Mult. Scler. 27 (10), 1556–1563. https://doi.org/10.1177/1352458520969145.

Cortese, I., Reich, D.S., Nath, A., 2021. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. Nat. Rev. Neurol. 17 (1), 37–51. https://doi.org/10.1038/s41582-020-00427-y.

Curti, E., Tsantes, E., Baldi, E., Caniatti, L.M., Ferraro, D., Sola, P., et al., 2019. The real-world effectiveness of natalizumab and fingolimod in relapsing-remitting multiple sclerosis. An Italian multicentre study. Mult. Scler. Relat. Disord. 33, 146–152. https://doi.org/10.1016/j.msard.2019.05.026.

Davidescu, E.I., Odajiu, I., Sandu, C.D., Ghergu, A., Luca, D., Mureşanu, D.F., et al., 2021. Real-world data regarding long-term administration of natalizumab from a neurology department along literature review. CNS Neurol. Disord. Drug Targets. https://doi.org/10.2174/1871527320666210827113733.

De Mercanti, S.F., Signori, A., Cordioli, C., Signoriello, E., Lus, G., Bonavita, S., et al., 2021. MRI activity and extended interval of natalizumab dosing regimen: a multicentre Italian study. J. Neurol. Sci. 424, 117385 https://doi.org/10.1016/j.jns.2021.117385.

Demortiere, S., Rico, A., Maarouf, A., Boutiere, C., Pelletier, J., Audoin, B., 2021. Maintenance of natalizumab during the first trimester of pregnancy in active multiple sclerosis. Mult. Scler. 27 (5), 712–718. https://doi.org/10.1177/1352458520912637.

Ebrahimi, N., Herbstritt, S., Gold, R., Amezcua, L., Koren, G., Hellwig, K., 2015. Pregnancy and fetal outcomes following natalizumab exposure in pregnancy. A prospective, controlled observational study. Mult. Scler. 21 (2), 198–205. https://doi.org/10.1177/1352458514546790.

Efthimios, D., Georgios, K., Antonia, A., Rania, G., Maria-Eleutheria, E., 2021. Long-term effectiveness of natalizumab in patients with relapsing-remitting multiple sclerosis treated in the routine care in greece: results from the multicenter, observational 5-year prospective study 'TOPICS Greece'. Clin. Drug Investig. 41 (10), 865–874. https://doi.org/10.1007/s40261-021-01073-y.

Foley, J., Carrillo-Infante, C., Smith, J., Evans, K., Ho, P.R., Lee, L., et al., 2019. The 5-year Tysabri global observational program in safety (TYGRIS) study confirms the long-term safety profile of natalizumab treatment in multiple sclerosis. Mult. Scler. Relat. Disord. 39, 101863 https://doi.org/10.1016/j.msard.2019.101863.

Foley, J., Defer, G., Zhovtis Ryerson, L., Cohen, J.A., Arnold, D.L., Butzhueven, H., et al., 2021. Primary results of NOVA: a randomised controlled study of the efficacy of 6-week dosing of natalizumab versus continued 4-week treatment for multiple sclerosis. In: ECTRIMS. October 13-15. Virtual. P970.

Freedman, M.S., Devonshire, V., Duquette, P., Giacomini, P.S., Giuliani, F., Levin, M.C., et al., 2020. Treatment optimization in multiple sclerosis: Canadian MS working group recommendations. Can. J. Neurol. Sci. 47 (4), 437–455. https://doi.org/10.1017/cjn.2020.66.

Friend, S., Richman, S., Bloomgren, G., Cristiano, L.M., Wenten, M., 2016. Evaluation of pregnancy outcomes from the Tysabri® (natalizumab) pregnancy exposure registry: a global, observational, follow-up study. BMC Neurol. 16 (1), 150. https://doi.org/10.1186/s12883-016-0674-4.

Guerra, T., Caputo, F., Orlando, B., Paolicelli, D., Trojano, M., Iaffaldano, P., 2021. Long-term comparative analysis of no evidence of disease activity (NEDA-3) status between multiple sclerosis patients treated with natalizumab and fingolimod for up to 4 years. Neurol Sci. 42 (11), 4647–4655. https://doi.org/10.1007/s10072-021-05127-z.

Guger, M., Enzinger, C., Leutmezer, F., Di Pauli, F., Kraus, J., Kalcher, S., et al., 2021. Long-term outcome and predictors of long-term disease activity in natalizumab-treated patients with multiple sclerosis: real life data from the Austrian MS treatment registry. J. Neurol. 268 (11), 4303–4310. https://doi.org/10.1007/s00415-021-10559-w.

Guger, M., Enzinger, C., Leutmezer, F., Kraus, J., Kalcher, S., Kvas, E., et al., 2019. Switching from natalizumab to fingolimod treatment in multiple sclerosis: real life data from the Austrian MS treatment registry. J. Neurol. 266 (11), 2672–2677. https://doi.org/10.1007/s00415-019-09464-0.

Haghikia, A., Langer-Gould, A., Rellensmann, G., Schneider, H., Tenenbaum, T., Elias-Hamp, B., et al., 2014. Natalizumab use during the third trimester of pregnancy. JAMA Neurol. 71 (7), 891–895. https://doi.org/10.1001/jamaneurol.2014.209.

Hersh, C.M., Harris, H., Conway, D., Hua, L.H., 2020. Effect of switching from natalizumab to moderate- vs high-efficacy DMT in clinical practice. Neurol. Clin. Pract. 10 (6), e53–e65. https://doi.org/10.1212/cpj.0000000000000809.

Ho, P.R., Koendgen, H., Campbell, N., Haddock, B., Richman, S., Chang, I., 2017. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. Lancet Neurol. 16 (11), 925–933. https://doi.org/10.1016/s1474-4422(17)30282-x.

Horakova, D., Uher, T., Krasensky, J., Seidl, Z., Ribbens, A., Van Hecke, W., et al., 2020. Long-term effectiveness of natalizumab on MRI outcomes and no evidence of disease activity in relapsing-remitting multiple sclerosis patients treated in a Czech Republic real-world setting: a longitudinal, retrospective study. Mult. Scler. Relat. Disord. 46, 102543 https://doi.org/10.1016/j.msard.2020.102543.

Horga, A., Tintoré, M., 2011. Natalizumab for relapsing-remitting multiple sclerosis. Neurologia 26 (6), 357–368. https://doi.org/10.1016/j.nrl.2010.10.004.

Hutchinson, M., Kappos, L., Calabresi, P.A., Confavreux, C., Giovannoni, G., Galetta, S.L., et al., 2009. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. J. Neurol. 256 (3), 405–415. https://doi.org/10.1007/s00415-009-0093-1.

Igra, M.S., Paling, D., Wattjes, M.P., Connolly, D.J.A., Hoggard, N., 2017. Multiple sclerosis update: use of MRI for early diagnosis, disease monitoring and assessment of treatment related complications. Br. J. Radiol. 90 (1074), 20160721 https://doi.org/10.1259/bjr.20160721.

Kalincik, T., Horakova, D., Spelman, T., Jokubaitis, V., Trojano, M., Lugaresi, A., et al., 2015. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. Ann. Neurol. 77 (3), 425–435. https://doi.org/10.1002/ana.24339.

Kapoor, R., Ho, P.R., Campbell, N., Chang, I., Deykin, A., Forrestal, F., et al., 2018. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. Lancet Neurol. 17 (5), 405–415. https://doi.org/10.1016/s1474-4422(18)30069-3.

Kappos, L., Bates, D., Edan, G., Eraksoy, M., Garcia-Merino, A., Grigoriadis, N., et al., 2011. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. Lancet Neurol. 10 (8), 745–758. https://doi.org/10.1016/s1474-4422(11)70149-1.

Kappos, L., O'Connor, P.W., Polman, C.H., Vermersch, P., Wiendl, H., Pace, A., et al., 2013. Clinical effects of natalizumab on multiple sclerosis appear early in treatment course. J. Neurol. 260 (5), 1388–1395. https://doi.org/10.1007/s00415-012-6809-7.

Karanasios, P., Karachalios, G., Gourgioti, R., Alexopoulou, A., Mastorodemos, V., 2021. Patient and treatment characteristics and safety outcomes of patients with relapsing-remitting multiple sclerosis treated with natalizumab in Greece: results from the multicenter, 5-year prospective observational study 'TOPICS Greece'. Mult. Scler. J.

Exp. Transl. Clin. 7 (3), 20552173211035803 https://doi.org/10.1177/20552173211035803.
Khoy, K., Mariotte, D., Defer, G., Petit, G., Toutirais, O., Le Mauff, B., 2020. Natalizumab in multiple sclerosis treatment: from biological effects to immune monitoring. Front. Immunol. 11, 549842 https://doi.org/10.3389/fimmu.2020.549842.
Koch-Henriksen, N., Magyari, M., Sellebjerg, F., Soelberg Sørensen, P., 2017. A comparison of multiple sclerosis clinical disease activity between patients treated with natalizumab and fingolimod. Mult. Scler. 23 (2), 234–241. https://doi.org/10.1177/1352458516643393.
Krysko, K.M., O'Connor, P.W., 2011. The Toronto observational study of natalizumab in multiple sclerosis. Can. J. Neurol. Sci. 38 (3), 422–428. https://doi.org/10.1017/s0317167100011811.
Mahadevan, U., Robinson, C., Bernasko, N., Boland, B., Chambers, C., Dubinsky, M., et al., 2019. Inflammatory bowel disease in pregnancy clinical care pathway: a report from the american gastroenterological association IBD parenthood project working group. Gastroenterology 156 (5), 1508–1524. https://doi.org/10.1053/j.gastro.2018.12.022.
Mason, L., 2019. Low risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients who were anti-JC virus antibody negative at baseline. ECTRIMS, Stockholm, Sweden. September 11-13. P673.
McGuigan, C., Craner, M., Guadagno, J., Kapoor, R., Mazibrada, G., Molyneux, P., et al., 2016. Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. J. Neurol. Neurosurg. Psychiatry 87 (2), 117–125. https://doi.org/10.1136/jnnp-2015-311100.
Miller, D.H., Khan, O.A., Sheremata, W.A., Blumhardt, L.D., Rice, G.P., Libonati, M.A., et al., 2003. A controlled trial of natalizumab for relapsing multiple sclerosis. N. Engl. J. Med. 348 (1), 15–23. https://doi.org/10.1056/nejmoa020696.
National Multiple Sclerosis Society, 2021. COVID-19 vaccine guidance for people living with MS. National Multiple Sclerosis Society. https://www.nationalmssociety.org/coronavirus-covid-19-information/multiple-sclerosis-and-coronavirus/covid-19-vaccine-guidance (Accessed Nov 17 2021).
Nicholas, J.A., Racke, M.K., Imitola, J., Boster, A.L., 2014. First-line natalizumab in multiple sclerosis: rationale, patient selection, benefits and risks. Ther. Adv. Chronic Dis. 5 (2), 62–68. https://doi.org/10.1177/2040622313514790.
O'Connor, P., Goodman, A., Kappos, L., Lublin, F., Polman, C., Rudick, R.A., et al., 2014. Long-term safety and effectiveness of natalizumab redosing and treatment in the STRATA MS Study. Neurology 83 (1), 78–86. https://doi.org/10.1212/wnl.0000000000000541.
O'Connor, P.W., Kremenchutzky, M., 2015. Use of natalizumab in patients with multiple sclerosis: 2015 update. Can. J. Neurol. Sci. 42 (6), 372–380. https://doi.org/10.1017/cjn.2015.296.
Olberg, H.K., Eide, G.E., Cox, R.J., Jul-Larsen, Å., Lartey, S.L., Vedeler, C.A., Myhr, K.M., 2018. Antibody response to seasonal influenza vaccination in patients with multiple sclerosis receiving immunomodulatory therapy. Eur J Neurol 25 (3), 527–534. https://doi.org/10.1111/ene.13537.
Outteryck, O., Ongagna, J.C., Brochet, B., Rumbach, L., Lebrun-Frenay, C., Debouverie, M., et al., 2014. A prospective observational post-marketing study of natalizumab-treated multiple sclerosis patients: clinical, radiological and biological features and adverse events. The BIONAT cohort. Eur. J. Neurol. 21 (1), 40–48. https://doi.org/10.1111/ene.12204.
Papeix, C., Vukusic, S., Casey, R., Debard, N., Stankoff, B., Mrejen, S., et al., 2016. Risk of relapse after natalizumab withdrawal: results from the French TYSEDMUS cohort. Neurol. Neuroimmunol. Neuroinflamm. 3 (6), e297. https://doi.org/10.1212/nxi.0000000000000297.
Polman, C.H., O'Connor, P.W., Havrdova, E., Hutchinson, M., Kappos, L., Miller, D.H., et al., 2006. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N. Engl. J. Med. 354 (9), 899–910. https://doi.org/10.1056/nejmoa044397.
Portaccio, E., Annovazzi, P., Ghezzi, A., Zaffaroni, M., Moiola, L., Martinelli, V., et al., 2018. Pregnancy decision-making in women with multiple sclerosis treated with natalizumab: I: fetal risks. Neurology 90 (10), e823–e831. https://doi.org/10.1212/wnl.0000000000005067.
Proschmann, U., Haase, R., Inojosa, H., Akgün, K., Ziemssen, T., 2021. Drug and neurofilament levels in serum and breastmilk of women with multiple sclerosis exposed to natalizumab during pregnancy and lactation. Front. Immunol. 12, 715195 https://doi.org/10.3389/fimmu.2021.715195.
Prosperini, L., Giannì, C., Leonardi, L., De Giglio, L., Borriello, G., Galgani, S., et al., 2012. Escalation to natalizumab or switching among immunomodulators in relapsing multiple sclerosis. Mult. Scler. 18 (1), 64–71. https://doi.org/10.1177/1352458511417481.
Prosperini, L., Kinkel, R.P., Miravalle, A.A., Iaffaldano, P., Fantaccini, S., 2019. Post-natalizumab disease reactivation in multiple sclerosis: systematic review and meta-analysis. Ther. Adv. Neurol. Disord. 12, 1756286419837809 https://doi.org/10.1177/1756286419837809.
Prosperini, L., Saccà, F., Cordioli, C., Cortese, A., Buttari, F., Pontecorvo, S., et al., 2017. Real-world effectiveness of natalizumab and fingolimod compared with self-injectable drugs in non-responders and in treatment-naïve patients with multiple sclerosis. J. Neurol. 264 (2), 284–294. https://doi.org/10.1007/s00415-016-8343-5.
Puchner, A., Gröchenig, H.P., Sautner, J., Helmy-Bader, Y., Juch, H., Reinisch, S., et al., 2019. Immunosuppressives and biologics during pregnancy and lactation: a consensus report issued by the Austrian societies of gastroenterology and hepatology and rheumatology and rehabilitation. Wien. Klin. Wochenschr. 131 (1-2), 29–44. https://doi.org/10.1007/s00508-019-1448-y.
Rae-Grant, A., Day, G.S., Marrie, R.A., Rabinstein, A., Cree, B.A.C., Gronseth, G.S., et al., 2018. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the guideline development, dissemination, and implementation subcommittee of the American academy of neurology. Neurology 90 (17), 777–788. https://doi.org/10.1212/wnl.0000000000005347.
Riancho, J., Setien, S., Sánchez de la Torre, J.R., Torres-Barquin, M., Misiego, M., Pérez, J.L., et al., 2021. Does extended interval dosing natalizumab preserve effectiveness in multiple sclerosis? A 7 year-retrospective observational study. Front. Immunol. 12, 614715 https://doi.org/10.3389/fimmu.2021.614715.
Rudick, R.A., Stuart, W.H., Calabresi, P.A., Confavreux, C., Galetta, S.L., Radue, E.W., et al., 2006. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N. Engl. J. Med. 354 (9), 911–923. https://doi.org/10.1056/nejmoa044396.
Ryerson, L.Z., Foley, J., Chang, I., Kister, I., Cutter, G., Metzger, R.R., et al., 2019. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. Neurology 93 (15), e1452–e1462. https://doi.org/10.1212/wnl.0000000000008243.
Sellner, J., Rommer, P.S., 2019. A review of the evidence for a natalizumab exit strategy for patients with multiple sclerosis. Autoimmun. Rev. 18 (3), 255–261. https://doi.org/10.1016/j.autrev.2018.09.012.
Spelman, T., Kalincik, T., Jokubaitis, V., Zhang, A., Pellegrini, F., Wiendl, H., et al., 2016. Comparative efficacy of first-line natalizumab vs IFN-β or glatiramer acetate in relapsing MS. Neurol. Clin. Pract. 6 (2), 102–115. https://doi.org/10.1212/cpj.0000000000000227.
Vivekanandan, G., Abubacker, A.P., Myneni, R., Chawla, H.V., Iqbal, A., Grewal, A., et al., 2021. Risk of progressive multifocal leukoencephalopathy in multiple sclerosis patient treated with natalizumab: a systematic review. Cureus 13 (4), e14764. https://doi.org/10.7759/cureus.14764.
Vukusic, S., Rollot, F., Casey, R., Pique, J., Marignier, R., Mathey, G., et al., 2020. Progressive multifocal leukoencephalopathy incidence and risk stratification among natalizumab users in france. JAMA Neurol. 77 (1), 94–102. https://doi.org/10.1001/jamaneurol.2019.2670.
Wiendl, H., Spelman, T., Butzkueven, H., Kappos, L., Trojano, M., Su, R., et al., 2021. Real-world disability improvement in patients with relapsing-remitting multiple sclerosis treated with natalizumab in the Tysabri Observational Program. Mult. Scler. 27 (5), 719–728. https://doi.org/10.1177/1352458520926869.
Wong, B., Cahill, J., Rizvi, S., 2018. Moving Towards a Cure for MS: Increased Immunosuppression and Striving for no evidence of disease activity (NEDA). R. I. Med. J. 101 (2), 26–29 (2013).
Yamout, B.I., Zakaria, M., Inshasi, J., Al-Jumah, M., Zeineddine, M., Dahdaleh, M., et al., 2021. MENACTRIMS practice guideline for COVID-19 vaccination in patients with multiple sclerosis. Mult. Scler. Relat. Disord. 56, 103225 https://doi.org/10.1016/j.msard.2021.103225.
Yeh, W.Z., Widyastuti, P.A., Van der Walt, A., Stankovich, J., Havrdova, E., Horakova, D., et al., 2021. Natalizumab, fingolimod and dimethyl fumarate use and pregnancy-related relapse and disability in women with multiple sclerosis. Neurology 96 (24), e2989–e3002. https://doi.org/10.1212/wnl.0000000000012084.
Zhovtis Ryerson, L., Foley, J., Chang, I., Kister, I., Cutter, G., Metzger, R.R., et al., 2019. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. Neurology 93 (15), e1452–e1462. https://doi.org/10.1212/wnl.0000000000008243.