COMMENTARY

Multiple Sclerosis: Switching from Natalizumab to Other High-Efficacy Treatments to Mitigate Progressive Multifocal Leukoencephalopathy Risk

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With the approval of the injectables interferon-β and glatiramer acetate a quarter of a century ago, the new era of multiple sclerosis (MS) treatment started [1]. A decade passed until the first representative of the second generation of immunomodulatory drugs for MS emerged: natalizumab. The evolution from unravelling the mechanisms of lymphocyte homing and migration during inflammatory processes, identification of critical molecular checkpoints, experimental blockade of decisive molecular interactions in vitro and in the animal model of experimental autoimmune encephalomyelitis by a monoclonal antibody, and translation into therapeutic trials in people with MS can serve as a case study of successful rational drug development [2, 3]. The recombinant humanized monoclonal antibody natalizumab recognizes the alpha4 subunit of integrins that is expressed predominantly on T lymphocytes but also by B lymphocytes and neutrophils. Natalizumab disrupts the interaction between alpha4 integrin and very late antigen VLA-4 displayed on the surface of endothelial cells. Consequently, invasion of the CNS through the blood–brain barrier by potentially autoaggressive T cells is diminished or blocked [2, 4]. Phase 2 and 3 clinical trials and extensive real-world experience underscored the high efficacy of natalizumab, which compared to the first-generation treatments had the additional advantage of requiring less frequent administration and exhibiting overall good tolerability and safety [3].

The most dreaded complication is progressive multifocal leukoencephalopathy (PML) [5]. Approximately 25% of patients developing PML following natalizumab therapy die and a large proportion are left with marked disability. A risk stratification scheme has been implemented accounting for JC virus antibody index, treatment duration, and prior exposure to immunosuppressant drugs [5, 6]. Strict adherence has apparently reduced the number of natalizumab users who have come down with PML [7, 8]. The main reason driving the decision to discontinue the highly effective immunomodulator natalizumab is the potential risk to develop PML as signified by a high JC virus antibody index and reaching a critical threshold of 18 months of continued natalizumab administration [9, 10]. Stopping natalizumab treatment has been associated with disease reactivation, which cannot be sufficiently prevented by subsequent use of lower efficacy drugs [11, 12]. Avoiding disease recrudescence clearly is of fundamental clinical importance. It requires appropriate timing of the interval between stop and commencement of a new disease modifying treatment, taking into account pharmacokinetics and pharmacodynamics of natalizumab, in particular saturation of alpha4 integrin on lymphocytes, and the choice of a high-efficacy drug that can contain pathobiological and clinical MS activity with an acceptable safety profile. Based on the results of pivotal trials and real-world experience, the anti-CD20 monoclonal antibodies ocrelizumab and rituximab [13–19] and oral cladribine [20–22], a synthetic purine analogue, are accepted as highly efficacious and overall safe treatments for relapsing MS [13–22].

As published in the April 2021 issue of *Neurotherapeutics*, a retrospective observational study representing a joint effort of 11 Italian MS centers compared effectiveness, tolerability, and safety of switching disease-modifying treatment in relapsing MS patients with a high JCV antibody index and at least 24 infusions (administered monthly for at least 1 year and then with standard or extended interval) from natalizumab to ocrelizumab, rituximab, or cladribine [23]. The

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primary outcome was the annualized relapse rate with additional outcome MRI activity after 12 months and 12 weeks confirmed disability progression. The investigators applied a generalized regression model using treatment as independent variable and age, sex, EDSS in the year before treatment switch, number of natalizumab infusions, and EDSS during natalizumab treatments as covariates. Of 120 patients fulfilling inclusion criteria, 64 switched to ocrelizumab, 36 to rituximab, and 20 to cladribine. The mean annualized relapse rates in these groups were 0.001, 0.308, and 0.5000, respectively. Patients who switched to ocrelizumab had a lower risk for MRI activity. There was no difference in confirmed disability progression. No PML occurred. Severe infections were reported in 3 patients on ocrelizumab, one on rituximab, and one on cladribine. A recent smaller study from one Italian center similarly looked at efficacy and safety of switching natalizumab users deemed to carry an elevated risk of developing PML (duration of exposure and JCV antibody index) to ocrelizumab [24]. In the first 3 months, in one of 42 patients a relapse and in 4 individuals MRI activity were recorded, whereas in the subsequent 3 months, no relapse occurred. Similar control of disease activity was reported in 2 retrospective studies from the USA and Germany involving 28 and 20 patients, respectively [25, 26].

A recent observational study from Amsterdam analyzing 42 patients who stopped natalizumab and switched directly or indirectly to ocrelizumab obtained no evidence of disease activity (NEDA)-3 in 83% or 50%, respectively [27]. Two patients who received ocrelizumab directly had carry-over mild PML [28], an infrequent event in general, observed also with fingolimod.

In a multicenter Swedish study of 256 relapsing MS patients who discontinued natalizumab because of JCV antibody positivity, rituximab was markedly superior to fingolimod in keeping clinical and MRI activity at bay over a period of 18 months [29]. One single small study of 17 patients stopping natalizumab because of high JCV antibody index ($n=13$), continued disease activity ($n=6$), presence of MRI disease activity ($n=4$), and a switch to oral cladribine demonstrated effective disease suppression over a mean period of 9.7 months and no serious adverse events other than the expected lymphopenia [30].

In aggregate, these observational studies provide evidence that high-efficacy drugs are effective and generally safe in a critical situation of MS management when treatment with natalizumab is discontinued. The results of an ongoing multicenter prospective open-label phase IV study examining the transition from natalizumab to ocrelizumab (interval 4–6 weeks) are expected by mid-2022 (Clinicaltrial.gov identifier NCT03157830) and will yield further data on which to base the important therapeutic decision.

Finally, pilot studies reported abolition or marked diminution of PML risk in individuals receiving natalizumab at extended dosing intervals [31, 32]. These findings prompted a number of ongoing observational and controlled randomized trials investigating feasibility, effectiveness, and safety of such an approach, with the particular goal to further minimize the risk of PML (Clinicaltrial.gov identifier: NCT04225312; NCT04580381; NCT0368992; NCT03516526). Results are eagerly awaited and will undoubtedly be implemented in current treatment algorithms.

References

1. Tintore M, Vidal-Jordana A, Sastre-Garriga J. Treatment of multiple sclerosis – success from bench to bedside. Nat Rev Neurol 2019; 15: 53-58.
2. Steinman L. Blocking adhesion molecules as therapy for multiple sclerosis: natalizumab. Nat Rev Drug Disc 2005; 510–518.
3. Rudick R, Polman C, Clifford D et al. Natalizumab. Bench to bedside and beyond. JAMA Neurol 2013; 70: 172–182.

4. Rice GPA, Hartung HP, Calabresi PA. Anti-alpha4 integrin therapy for multiple sclerosis. mechanisms and rationale. Neurol 2005; 64: 1336–1342.

5. Major EO, Yousry TA, Clifford DB. Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned. Lancet Neurol 2018; 17: 467-480.

6. Ho PR, Koendgen H, Campbell N et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. Lancet Neurol 2017; 16: 925-933.

7. Vukusic S, Rollot F, Casey R, et al. Progressive multifocal leukoencephalopathy incidence and risk stratification among natalizumab users in France. JAMA Neurol 2020; 77: 94-102

8. Kagstrom S, Fält A, Berglund A, et al. Reduction of the risk of natalizumab treated MS patients in Sweden: An effect of improved PML risk surveillance. Mult Scl Rel Disord 2021; 50: 102842.

9. Chisari CG, Comi G, Filippi M , et al. 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 2021 https://doi.org/10.1007/s00415-021-10676-6

10. Coerver EME, Wessels MHJ, van Lierop ZYG, et al. Natalizumab discontinuation in a Dutch real-world cohort. Mult Scler Rel Disord 2021; 52: 102974.

11. Papeix C, Vukusic S, Casey R, et al. Risk of relapse after natalizumab withdrawal. Results from the French TYSEDMUS cohort. Neurol Neuroimmunol Neuroinflamm 2016; 3:e297.

12. Prosperini L, Kinkel RP, Miravalle AA, et al. Post-natalizumab disease reactivation in multiple sclerosis: systematic review and meta-analysis. Ther Adv Neurol Disord 2019;

13. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferonß-1a in relapsing multiple sclerosis. N Engl J Med 2017; 376: 221-234.

14. Ng HS, Rosenbult CL, Tremlett H. Safety profile of ocrelizumab for the treatment of multiple sclerosis: a systematic review. Expt Opin Drug Saf 2020; 19: 1069-1094.

15. Graf J, Mares J, Barnett M, et al. Targeting B cells to modify MS, NMOSD, and MOGAD. Neuro Neuroimmunol Neuroinflamm 2021; 8: e918.

16. Cotchett KR, Dittel BN, Obeidat AZ. Comparison of the efficacy and safety of anti-CD20 B cells depleting drugs. Mult Scler Rel Disord 2021; 49: 1027887.

17. Torgauthen HM, Myhr KM, Wergeland S, et al. Safety and efficacy of rituximab as first- and second line treatment in multiple sclerosis – a cohort study. Mult Scler Exp Transl Clin 2021. https://doi.org/10.1177/2055217320973049.

18. Vollmer BL, Wallach AJ, Corboy JR, et al. Serious safety events in rituximab-treated multiple sclerosis and related disorders. Ann Clin Transl Neurol 2020; 7: 1477-1487.

19. Focosi D, Tuccori M, Maggi F. Progressive multifocal leukoencephalopathy and anti-CD20 monoclonal antibodies: What do we know after 20 years of rituximab. Rev Med Virol 2019; e2077.

20. Giovannoni G, Comi G, Cook S et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med 2010; 362: 416-426.

21. Giovannoni G, Soelberg Sorensen P, Cook S et al. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study: Mult Scler 2018; 24: 1594-1604.

22. Pfeuffer S, Rolfes L, Hackert J et al. Effectiveness and safety of cladribine in MS: real world experience from two tertiary centers. Mult Scler 2021. https://doi.org/10.1177/113524585211012227.

23. Zanghi A, Gallo A, Avolio C et al. Exit strategies in natalizumab-treated RRMS at high risk of progressive multifocal leukoencephalopathy: a multicentre comparison study. Neurother 2021. https://doi.org/10.1007/s13311-021-01037-2.

24. Mancinelli CR, Scarpazza C, Cordioli C, et al. Switching to ocrelizumab in RRMS patients with extended interval dosing of natalizumab. Mult Scler 2021; 27: 790-794.

25. Levine S N, Ezuma C, Levine L, et al. Switching from natalizumab to ocrelizumab in patients with multiple sclerosis. Mult Scler 2020; 26: 1964-1965.

26. Ellwardt E, Rolfes L, Klein J et al. Ocrelizumab initiation in patients with MS. A multicenter observational study. Neurol Neuroimmunol Neuroinflamm 2020; 7:e719.

27. Van Lierop ZYGJ, Toorop AA, Coerver EME et al. Ocrelizumab after natalizumab in JC-virus positive relapsing remitting multiple sclerosis patients. Mult SclerExp Transl Clin 2021. https://doi.org/10.1177/20552173211013831.

28. Toorop AA, van Lierop ZYG, Strijbis EEM et al. Mild progressive multifocal leukoencephalopathy after switching from natalizumab to ocrelizumab. Neuro Neuroimmunol Neuroinflamm 2021; 8:e904.

29. Alping P, Friselli T, Novakova L et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann Neurol 2016; 79: 950-958.

30. Moehn N, Skripuletz T, Sühs KW, et al. Therapy with cladribine is efficient and safe in patients previously treated with natalizumab. Ther Adv Neurol Disord 2019; 12: 1-8.

31. Ryerson LZ, Foley J, Chang I, et al. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. Neurol 2019; 93e1452-e1462.

32. Clerico M, De Mercanti SF, Signori A et al. Extending the interval of natalizumab dosing: is efficacy preserved? Neurother 2020; 17: 200-207.