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The pitfalls of natalizumab discontinuation in patients with multiple sclerosis and their abatement by minimizing washout duration: The results of four clinical studies

Multiple sclerosis is a leading cause of serious disability of young and middle-aged people in western nations. Natalizumab, a high efficacy medication for control of multiple sclerosis disease activity, increases risk of progressive multifocal leukoencephalopathy in patients harboring JC virus and may necessitate discontinuing natalizumab. Because discontinuing natalizumab may increase the risk of multiple sclerosis reactivation by 30% or more, strategies to transition patients off natalizumab are needed. These reported studies purposes was to demonstrate that multiple sclerosis reactivation was related to duration of post-natalizumab drug-free washout interval, and by reducing washout duration, risk of multiple sclerosis reactivation could be significantly reduced. These studies employed different methodologies and medications: a retrospective analysis of multiple sclerosis patients treated with dimethyl fumarate after discontinuing natalizumab, 2 prospective studies utilizing washouts of 6, 8, 12 and 16 weeks since last natalizumab before initiating fingolimod therapy, and lastly, 4 weeks since last natalizumab dose prior to initiation of teriflunomide.

Results: There was 51% (p=0.0216) relapse risk reduction when starting dimethyl fumarate 90 days or less after the last natalizumab dose compared to waiting more than 90 days. Patients starting fingolimod 8-12 weeks post-natalizumab had a lower risk of clinical disease activity than after 16 weeks washout, and compared to a washout of 6 weeks or less, patients with a washout of more than 8 weeks had an odds ratio of 6.8 (95% CI 1.4, 32.8) for return of disease activity. Utilizing 4-week natalizumab washout, 94% patients remained relapse-free after one year of teriflunomide treatment (95% CI 0.83, 0.98). These studies, utilizing different medications and designs, each demonstrated that minimizing post natalizumab washout was associated with reduced multiple sclerosis reactivation and conform with anticipated results when considering the pharmacodynamics of natalizumab receptor desaturation, and efficacy onset time of these 3 different therapeutic agents.

Recent Publications

1. Polman CH, O'Connor PW, Havrdova E, *et al.* A randomized, placebo-controlled tral of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006; 354:899-910
2. Bloomgren G, Richman S, Hotermans C, *et al.* Risk of antalizumab-associated progressive mutifocal leukoencephalopathy. N Engl J Med 2012; 366:1870-1880
3. West TW, Cree BA. Natalizumab dosage suspension: are we helping or hurting? Ann Neurol 2010; 68:395-399

4. Cohan SL, Moses H, Calkwood J, *et al.* Clinical outcomes in patients with relapsing-remitting multiple sclerosis who switch from natalizumab to dimethyl fumarate: A multicenter retrospective observational study. Mult Scler Relat Disord 2018; 22:27-34
5. Kappos L, Radue E-W, Comi G, *et al.* Switching from natalizumab to Fingolimod. A randomized, placebo-controlled study in RRMS. Neurology 2015; 85:29-39
6. Leurs CE, Van Kempen ZL, Dekker I, *et al.* Switching natalizumab to fingolimod within 6 weeks reduces recurrence of disease activity in MS patients. Mult Scler 2018; 24:1453-1460
7. Cohan SL, Edwards K, Lucas L, *et al.* Reducing return of disease activity in Patients with relapsing multiple sclerosis transitioned from natalizumab to teriflunomide: 12 month interim results of teriflunomide therapy. Mult Scler J Exp Transl Clin 2019; doi: 10.1177/2055217318824618.
8. Derfuss T, Kovarik JM, Kappos L, *et al.* α4-integrin receptor desaturation and disease activity return after natalizumab cessation. Neurol Neuroimmunol Neuroinflamm 2017; doi: 10.1212/NXI.0000000000000388.

Biography

Stanley Cohan is past Professor and Chairman, Department of Neurology, Georgetown University School of Medicine, the Founding Director of the Providence Multiple Sclerosis Center, Co-Founder of the Pacific Northwest Multiple Sclerosis Registry and Director of the Providence Neuroimmunology Translational Research Program. He has been an active multiple sclerosis clinical investigator since the early 1990's. His primary interests are in the development of new therapeutic agents for the treatment of multiple sclerosis, mechanisms of multiple sclerosis pathogenesis and development of web and I cloud-based technology for multiple sclerosis patient monitoring and treatment.

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