SciMedCentral

Journal of Immunology & Clinical Research

Case Report

Special Issue on
Multiple Sclerosis

Switching from Natalizumab to Fingolimod: Case Report and Review of Literature

Sarah J. Clark, Qin Wang, and Yang Mao-Draayer*

Department of Neurology, University of Michigan, USA

***Corresponding author**
Yang Mao-Draayer, Department of Neurology, University of Michigan Medical School, 4015 A. Alfred Taubman Biomedical Sciences Research Building, 109 Zina Pitcher Place, Ann Arbor, Michigan 48109-2200, Tel: 734-763-3630; Fax: 734-615-7300; Email: maodraay@umich.edu

Submitted: 10 September 2016

Accepted: 01 November 2016

Published: 23 November 2016

ISSN: 2333-6714

Keywords

- Natalizumab
- Multiple sclerosis
- Progressive multifocal leukencephalopathy
- Fingolimod

Abstract

For multiple sclerosis (MS) patients, discontinuing natalizumab and starting another disease modifying therapy (DMT) is complicated by two paradoxical considerations: 1) too short of a drug holiday might increase the risk of Progressive Multifocal Leukencephalopathy (PML) due to drug overlap; 2) too long of a drug holiday may increase the risk of disease activity while the patient is without drug modulation. In this case report, a 50 year-old male with relapsing remitting MS (RRMS) showed no signs of increased disease activity or PML during a nine month drug holiday after natalizumab treatment and for 24 months after beginning fingolimod therapy and remained relapse free. This suggests that a nine month break between natalizumab and fingolimod treatment may be an appropriate time length in patients with stable RRMS disease activity. While further analysis is required to determine the most appropriate drug holiday after natalizumab, this case report may help clinicians make such treatment decisions for patients with less aggressive disease.

ABBREVIATIONS

MS: Multiple Sclerosis; CNS: Central Nervous System; RRMS: Relapsing Remitting MS; DMT: Disease Modifying Therapy; MRI: Magnetic Resonance Imaging; PML: Progressive Multifocal Leukencephalopathy; JC Virus: John Cunningham Virus; S1P1: Sphingosine 1-Phosphate Receptor 1; TOUCH: Tysabri Outreach: Unified Commitment To Health; ARR: Annualized Relapse Rate

INTRODUCTION

Multiple sclerosis (MS) is a chronic, debilitating disease of the central nervous system (CNS) that commonly develops during young adulthood. Relapsing remitting MS (RRMS) is a subtype that occurs in approximately 85% of MS patients and is defined by distinct attacks of acute worsening of neurological function followed by partial or complete recovery [1]. MS patients do not always recover from their relapses [2].

Natalizumab (Tysabri®, Biogen Idec and Elan Pharmaceuticals) is a humanized monoclonal antibody which binds to the alpha 4 integrin that is approved for treatment of RRMS patients. Phase III trials and post-marketing studies have consistently shown a significantly greater efficacy of natalizumab than other established disease modifying therapies (DMTs) for multiple measures, including annualized relapse rate (ARR), risk of progression of disability, and magnetic resonance imaging (MRI) activities [3-7]. Natalizumab is also associated with increased risk of progressive multifocal leukencephalopathy (PML), a frequently fatal viral infection of the brain caused by John Cunningham virus (JC virus), for which there is currently no approved treatment. As of the end of September 2016, there have been 685 confirmed PML cases reported in ~156,500 natalizumab-treated patients worldwide, resulting in a PML risk estimate of 4.22 per 1,000 patients (95% confidence interval: 3.91–4.55 per 1,000 patients) [natalizumab prescribing information]. Such risk has been estimated to increase with longer treatment duration, positive anti-JC virus antibody, and prior immunosuppressant use [8]. These risks are currently being addressed by risk stratifications, such as the one proposed by Sørensen et al. [9]. Based on the algorithm, risk of PML is lower for all patients during the first two years of treatment, even if they are positive for the JC virus antibody and have a history of prior immunosuppressant use (<1/1,000 patients). Beyond two years of use, the risk increases almost three fold. Although PML poses a serious risk, the significant clinical efficacy of natalizumab is becoming increasingly more obtainable due to the guiding risk stratifications and the rigorous drug monitoring program, TOUCH.

Approved in September 2010 [10], fingolimod became the first oral MS therapy for the treatment of RRMS patients. Due to its clinical efficacy, fingolimod has become a common treatment choice after natalizumab discontinuation. Most MS patients initiate natalizumab after breakthrough disease on first-line therapies such as interferon-beta and glatiramer acetate; therefore, it is unlikely that patients will have a positive

treatment response to these medications after natalizumab treatment [11,12]. Unfortunately, short washout of natalizumab to fingolimod has been shown to increase risk of PML. As of October 2016, 26 cases of PML have been reported in fingolimod-treated patients with MS: 17 of these cases had prior history of natalizumab use. This presents a heightened concern in relation to immunomodulatory effects of drug overlap. The therapeutic effect of fingolimod is due to sphingosine 1-phosphate receptor 1 (S1P1) modulation, which causes insensitivity of lymphocytes to migration signals and thus their accumulation in secondary lymphoid tissues. This results in a significant reduction of circulating lymphocytes [12]. Natalizumab inhibits migration of autoreactive leukocytes out of blood vessels into the central nerve system (CNS) by blocking α4-integrin, a component of adhesion molecules, thereby blocking adhesion to endothelial cells and extravasation into the CNS [13]. The exact mechanisms of how natalizumab results in decreased immunosurveillance in the CNS that is conducive to PML are not entirely clear at the current time. In addition, pharmacokinetic data suggest that at least 3 months are required for serum concentrations of natalizumab to drop to levels that allow desaturation of α4-integrin (1μg/ml) [14].

In addition, patients relapsed within six months after natalizumab withdrawal [7,15,16], emphasizing the importance of timely initiation of a DMT following natalizumab cessation. Thus there are conflicting concerns requiring a washout period after cessation of natalizumab in order to diminish serum drug concentration before initiating another DMT and to minimize time spent treatment-free. An appropriate washout length has yet to be established. We report a positive outcome after a nine month drug holiday between natalizumab and fingolimod treatment. We propose that this longer wash out is possible through consideration on an individual basis.

CASE PRESENTATION

A 50 year-old caucasian man presented with RRMS for ten years. He was initially treated with interferon-beta 1a (Rebif®) but developed neutralizing antibodies after six years and was switched to glatiramer acetate (Copaxone®). While on glatiramer acetate, magnetic resonance imaging (MRI) showed three new lesions, one enhanced with gadolinium, suggesting possible an increase of radiological activity. In addition, he developed increased spasticity in the lower extremities. Due to possible relapse, glatiramer acetate was stopped after 6 months of treatment and natalizumab (300 mg intravenous, every four weeks) was started. All TOUCH questions were answered negatively, and there was no evidence either by history or examination of development of an infection such as PML, suggesting no contraindications to natalizumab.

At this time, exam findings included a partial internuclear opthalmoplegia (INO) on the right lateral gaze and mild action tremor when touching finger to nose. He had spastic paraparesis (left worse than right) and bilateral hip flexor power was 4+. Reflexes were 3+ with bilateral upgoing toes. He had a wide-based ataxic spastic gait and was unable to heel, tandem or toe walk. He also suffered from depression, insomnia, fatigue, numbness/tingling, urinary urgency and frequency, weight loss, and loss of appetite. All were noted previously.

After two doses of natalizumab, the patient developed severe psoriasis on his extremities. The patient had no previous history of psoriasis. Initial treatment with topical clobetasol (Temovate®) and mupirocin (Bactroban®) showed no improvement. After six doses of natalizumab, the patient continued to have psoriasis and felt pain in his feet that made walking more difficult. He was treated with three-day intravenous Solumedrol with some improvement. Due to psoriasis, natalizumab was discontinued after the sixth dose. The anti-JC viral antibody was tested to be negative. At this time, exam findings were unchanged from natalizumab treatment initiated six months ago. The patient remained treatment-free for nine months with no signs of disease progression or relapse by physical exam or MRI. Comparison of MRI for a time frame within the drug holiday showed no new enhancing or T2 FLAIR lesions (Figure 1). Psoriasis severity peaked less than a month after natalizumab cessation.

The patient was started on fingolimod (Gilenya®; 0.5 mg orally, daily) after a nine month drug holiday from natalizumab. After 24 months of fingolimod treatment, the patient showed no signs of progression or relapse. A 25-foot timed walk was completed in 5.3 seconds without the use of a cane, which extended the continual improvement from 7.5 seconds measured ten months earlier during the drug holiday. Gait and strength tests improved and Romberg sign returned to negative. Although the patient was still unable to heel or tandem walk, he regained the ability to toe walk. Psoriasis was almost completely resolved, with minimal scarring. All other exam findings remained unchanged.

DISCUSSION

Natalizumab treatment for MS has proven to be a complex treatment paradigm. The presented case supports the feasibility of safely stopping natalizumab treatment and starting fingolimod

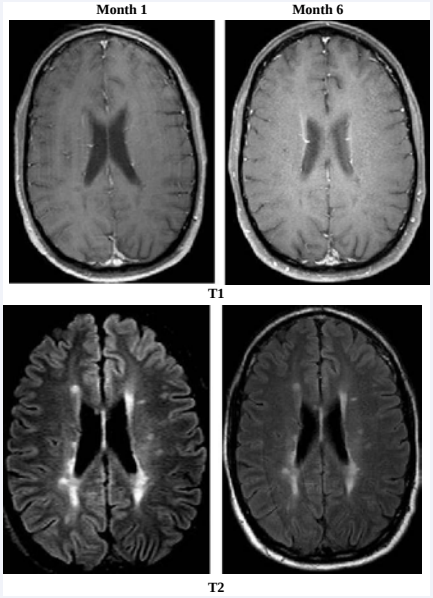

Figure 1 The MRI of brain of the reported patient. The brain MRI showed no enhancing or new T2 FLAIR lesions between drug holiday month 1 and month 6 after discontinuation of natalizumab. Axial T1 with contrast showed no new enhancing lesions. Axial T2 FLAIR showed no new lesions.

after a nine-month drug holiday. The patient even experienced some clinical improvement, especially in mobility and strength, during the drug holiday and continuing into fingolimod treatment. This positive treatment outcome suggests that nine months wash-out period from natalizumab to fingolimod may be feasible in patients without high disease activity. The drug holiday appears to be long enough to avoid the risk of PML due to drug overlap causing potential additive immunocompromise. Conversely, in this case the nine month time length between the two drugs appears to be short enough to avoid return of disease activity thought to occur after DMT termination. These conflicting risks need to be considered on an individual patient basis, as well as on the mechanism of action of the specific DMT utilized after natalizumab treatment. For example, for a patient with a higher rate of relapse than the presented patient, a shorter drug holiday should be considered. Our patient may provide a starting point for treatment decisions, especially for fingolimod treatment following natalizumab.

Previous case studies have reported increased disease activity after natalizumab discontinuation, as well as shortly after fingolimod initiation (Table 1) [17-21]. There were three published case reports presenting a total of five patients with disease reactivation within seven months after natalizumab discontinuation (range: 6-7 months). All disease activity occurred within two months after fingolimod initiation (range: 6-60 days). Halva et al (2012) [21] retrospectively determined that 42% (11/26) of patients had a documented clinical relapse and/or radiological evidence of disease activity after natalizumab discontinuation. Five of the 19 total relapses occurred before fingolimod initiation, and six occurred during the first eight weeks of fingolimod treatment. In a subgroup that remained treatment-free after natalizumab, 70% (7/10) of patients reported relapse (median follow up: 55.1 weeks; range: 31-109 weeks) [21]. One patient had an additional relapse one month after natalizumab discontinuation. In the only prospective study, Rinaldi et al. (2012) employed a three-month drug holiday and found signs of clinical and/or radiological disease reactivation in 50% (11/22) of patients after fingolimod initiation, with 7/11 within the first month (mean follow up: 9 months) [20].

There are multiple factors that could contribute to the different outcomes between our reported case and the published literature. Our patient had lower disease activity, with an ARR of one the year before natalizumab and no relapses for approximately ten years prior, compared to the high disease activity mentioned in the cited case reports. All patients were treated with natalizumab for greater than 24 months (range 24-46 months), except Halva's study which had a range of 6-57 months (median 27 months). Due to the onset of severe psoriasis, our patient was treated with natalizumab for only 7 months. In addition, the published literature reported all drug holidays to be less than 6 months (range: 2-6 months), and all authors concluded either that shorter drug holidays should be employed to possibly minimize the risk of disease reactivation or that the safety of fingolimod should be assessed. Although there were some relapses during the drug holiday (5/19 relapses in Havla's study and 1/2 relapses in one case report), most occurred shortly after fingolimod initiation [17,21]. Our patient remained treatment-free for 9 months and initiated fingolimod without signs of disease activity.

In addition, our patient's previous treatment failure was not only due to breakthrough disease, but he was unable to continue interferon-beta 1a due to neutralizing antibodies. The treatment failures presented in the literature were due to breakthrough disease specifically. Of note, MRI was only available for 20/36 patients (11 patients treated with fingolimod and 9 untreated) in Halva et al. (2012), and 7/22 patients in Rinaldi et al. (2012), [20,21]. Therefore, subclinical disease reactivation in the remaining asymptomatic patients cannot be excluded.

The differences between the present case report and the reviewed studies suggest that the current literature represents a very specific patient cohort and is not necessarily representative of the entirety of the MS population. Outcomes following a switch from natalizumab to fingolimod were assessed for patients with high disease activity and treatment failure due to breakthrough disease prior to natalizumab treatment, long treatment durations, and short drug holidays. High disease activity pre-natalizumab is predictive of reactivation following treatment discontinuation, especially going from a higher to a lower efficacy treatment. Therefore breakthrough disease after natalizumab could be due to lack of treatment effect with a lower efficacy treatment or an inevitable more aggressive disease course. The duration of natalizumab treatment may have an influence on disease activity following treatment cessation. In addition, disease reactivation appears to be independent of treatment, as glatiramer acetate treatment following natalizumab also could not prevent disease activity within the first year [22]. Taken together, these issues suggest that a positive outcome while switching from natalizumab to fingolimod is more likely than is represented by the current literature and can possibly be enhanced by assessment of these factors on an individual basis. Despite that natalizumab treatment did not significantly alter peripheral lymphocyte counts, there were significant lower rates of CD4, CD8, and CD19 cells in the CSF [20], which is consistent with its proposed mechanism of action. Furthermore, the lower rate of these cells persisted for 6 months after stopping natalizumab, and the normal level was not regained until 14 months after natalizumab cessation [23,24]. Therefore, considering all these concerns, a longer washout in stable patients could be achieved without disease exacerbation. Similarly, switching from natalizumab to dimethyl fumarate or teriflunomide raises the same concerns.

Additionally, the coincidence of psoriasis with natalizumab treatment is an interesting aspect of this case report. In pivotal clinical trials of natalizumab in treating MS patients, no significant difference was found between the incidence of skin disturbances between treatment and placebo groups [5]. The only report of psoriasis occurrence with natalizumab treatment was in a woman with RRMS and a history of mild, stable psoriasis [25]. Although our patient had no history of psoriasis, he does report a family history of autoimmune disease, including a parent with MS and a first cousin with psoriasis. It is more likely that these reported patients have a hereditary predisposition to autoimmune disturbances, exacerbated by the immune-modulating effects of natalizumab, than a natalizumab-induced side effect, due to the low incidence of the reaction.

Obviously, a single case report does not provide definite

Table 1: Previous reports suggested increased disease activity after natalizumab discontinuation.

References	Patients with disease reactivation after natalizumab cessation	Time to relapse after fingolimod initiation	Drug holiday length (months)	ARR pre-natalizumab
Daelman et al. 2012 [14].	1/1 (100%)	11 days	3.5	2
Centonze et al. 2012, [15].	3/3 (100%)	16 days; 19 days; 6 days	3; 3; 4	1; 2; 2
Jander et al. 2012, [16]	1/1 (100%)	2 months	2	6
Rinaldi et al. 2012, [17]	11/ 22 (50%)	Within 8 months	3	Mean: 2.4
Halva et al. 2013, [18]	11/ 26 (42%) treated with fingolimod; 7/10 (70%) untreated	Within 6 months (median: 3.2 months)	Less than 6 (median: 3); greater than 6	Median: 2

assessment of these treatment issues. Until more thorough analysis is completed, this case report can only provide some information for clinical decisions regarding the transition between natalizumab and fingolimod and possible interpretation of autoimmune reactions to natalizumab treatment. Larger studies are needed to further analyze safety for the transition between natalizumab and fingolimod or other DMT treatment, as well as to elucidate the possible relationship between autoimmune disturbances, such as new-onset psoriasis and natalizumab treatment response. Future studies will help to determine optimal washout periods for natalizumab based on individual patient disease courses.

DISCLOSURE

Sarah Clark and Qin Wang have nothing to disclose. Yang Mao-Draayer has served as a consultant and/or received grant support from: Acorda, Bayer Pharmaceutical, Biogen Idec, EMD Serono, Genzyme, Novartis, Questor, Chugai, and Teva Neuroscience and is currently supported by grants from NIH NIAID Autoimmune Center of Excellence: UM1-AI110557; NIH NINDS R01-NS080821 and the University of Michigan Neurology Department.

REFERENCES

1. Smith KJ, McDonald WI. The pathophysiology of multiple sclerosis: The mechanisms underlying the production of symptoms and the natural history of the disease. Philos Trans R Soc Lond B Biol Sci. 1999; 354: 1649 -1673.
2. De Stefano N, Matthews PM, Narayanan S, Francis GS, Antel JP, Arnold DL. Axonal dysfunction and disability in a relapse of multiple sclerosis: Longitudinal study of a patient. Neurology. 1997; 49: 1138-1141.
3. Castillo-Trivino T, Mowry EM, Gajofatto A, Chabas D, Crabtree-Hartman E, Cree BA, et al. Switching multiple sclerosis patients with breakthrough disease to second-line therapy. PLoS One. 2011; 6: 16664.
4. Lanzillo R, Bonavita S, Quarantelli M, Vacca G, Lus G, Amato L, et al. Natalizumab is effective in multiple sclerosis patients switching from other disease modifying therapies in clinical practice. Neurol Sci. 2013; 34: 521-528.
5. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006; 354: 899-910.
6. Hutchinson M, Kappos L, Calabresi PA, Confavreux C, Giovannoni G, Galetta SL, et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. J Neurol. 2009; 256: 405-415.
7. Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2003; 348: 15-23.
8. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012; 366: 1870-1880.
9. Sørensen PS, Bertolotto A, Edan G, Giovannoni G, Gold R, Havrdova E, et al. Risk stratification for progressive multifocal leukoencephalopathy in patients treated with natalizumab. Mult Scler. 2012; 18: 143-152.
10. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010; 362: 402-415.
11. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010; 362: 387-401.
12. Fazekas F, Berger T, Fabjan TH, Ledinek AH, Jakab G, Komoly S, et al. Fingolimod in the treatment algorithm of relapsing remitting multiple sclerosis: a statement of the Central and East European (CEE) MS Expert Group. Wien Med Wochenschr. 2012; 162: 354-366.
13. Selewski DT, Shah GV, Segal BM, Rajdev PA, Mukherji SK. Natalizumab (Tysabri). AJNR Am J Neuroradiol. 2010; 31: 1588-1590.
14. Khatri BO, Man S, Giovannoni G, Koo AP, Lee JC, Tucky B, et al. Fox, Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. Neurology. 2009; 72: 402-409.
15. Miravalle A, Jensen R, Kinkel RP. Immune reconstitution inflammatory syndrome in patients with multiple sclerosis following cessation of natalizumab therapy. Arch Neurol. 2011; 68: 186-191.
16. Cohen M, Maillart E, Tourbah A, De Sèze J, Vukusic S, Brassat D, et al. Switching from natalizumab to fingolimod in multiple sclerosis: a French prospective study. JAMA Neurol. 2014; 71: 436-441.
17. Daelman L, Maitrot A, Maarouf A, Chaunu MP, Papeix C, Tourbah A. Severe multiple sclerosis reactivation under fingolimod 3 months after natalizumab withdrawal. Mult Scler. 2012; 18: 1647-1649.
18. Centonze D, Rossi S, Rinaldi F, Gallo P. Severe relapses under fingolimod treatment prescribed after natalizumab. Neurology. 2012; 79: 2004-2005.
19. Jander S, Turowski B, Kieseier BC, Hartung HP. Emerging tumefactive multiple sclerosis after switching therapy from natalizumab to fingolimod. Mult Scler. 2012; 18: 1650-1652.
20. Rinaldi F, Seppi D, Calabrese M, Perini P, Gallo P. Switching therapy from natalizumab to fingolimod in relapsing-remitting multiple sclerosis: clinical and magnetic resonance imaging findings. Mult Scler. 2012; 18: 1640-1643.
21. Havla J, Tackenberg B, Hellwig K, Meinl I, Krumbholz M, Seitz F, et al. Fingolimod reduces recurrence of disease activity after natalizumab

withdrawal in multiple sclerosis. J Neurol. 2013; 260: 1382-1387.

22. Havla J, Gerdes LA, Meinl I, Krumbholz M, Faber H, Weber F, et al. De-escalation from natalizumab in multiple sclerosis: recurrence of disease activity despite switching to glatiramer acetate. J Neurol. 2011; 258: 1665-1669.

23. Stüve O, Cravens PD, Frohman EM, Phillips JT, Remington GM, von Geldern G, et al. Immunologic, clinical, and radiologic status 14 months after cessation of natalizumab therapy. Neurology. 2009; 72: 396-401.

24. Stüve O, Marra CM, Jerome KR, Cook L, Cravens PD, Cepok S, et al. Immune surveillance in multiple sclerosis patients treated with natalizumab. Ann Neurol. 2006; 59: 743-747.

25. Millán-Pascual J, Turpín-Fenoll L, Del Saz-Saucedo P, Rueda-Medina I, Navarro-Muñoz S. Author information Psoriasis during natalizumab treatment for multiple sclerosis. J Neurol. 2012; 259: 2758-2760.

Cite this article

Clark SJ, Wang Q, Mao-Draayer Y (2016) Switching from Natalizumab to Fingolimod: Case Report and Review of Literature. J Immunol Clin Res 3(1): 1030.