DOI: 10.4274/jmsr.galenos.2024.2024-4-2

Journal of Multiple Sclerosis Research 2024;4(2):47-51

RESEARCH ARTICLE

Natalizumab in Multiple Sclerosis: A Single Centre Real-World Study

Ayşen Onder, Sedat Sen, Murat Terzi

Ondokuz Mayis University Faculty of Medicine, Department of Neurology, Samsun, Turkey

Abstract

Objective: Natalizumab (NTZ) is an effective immunomodulator therapy (IMT) employed for multiple sclerosis (MS) therapy. This study aimed to investigate the efficacy and safety of NTZ treatment in MS patients.

Materials and Methods: Patients with clinically definite MS who received NTZ treatment were included in the study, and their data were derived from the iMed database. Patient demographics such as age, sex, and disease duration were assessed. The results pertaining to the annual number of attacks, expanded disability status scale (EDSS) results, magnetic resonance data, and no evidence of disease activity-3 (NEDA-3) were obtained.

Results: This study included 153 patients (108 female and 43 male). The patients' ages ranged from 21.63 to 67.60 years, with a mean age of 44.50 years. Prior to undergoing NTZ treatment, 54.3% of the patients had received at least two other IMTs. The mean annual number of assaults was 1.19, and the number of attacks in the year prior to treatment ranged from 0 to 6. The mean number of attacks in the first year following treatment was 0.07, 0.13 in the second year, and 0.09 in the third year. The baseline EDSS values of the patients varied between 0 and 5.5, and the mean baseline EDSS value was 3.08. During the initial year of treatment, the patient's mean EDSS value was 2.58, the second year was 2.32, and the third year was 2.34. Recurrence with increased severity of disease activity or rebound development was observed in 14.6% of the patients whose NTZ treatment was terminated for any reason. The NEDA-3 value decreased from 82.8% (n=145) in the first year to 77.3% (n=132) in the second year and 79.0% (n=81) in the third year.

Conclusion: Patients received NTZ for three years on average. 14.6% of the patients exhibit a recurrence or rebound of disease activity. Anti-John Cunningham virus antibody was detected in 5% of patients during the course of treatment. Approximately 80% of patient achieved NEDA-3 while receiving NTZ over the three-year period.

Keywords: Multiple sclerosis, immunomodulatory therapy, natalizumab, real-world data

Introduction

Natalizumab (NTZ) is a highly efficacious treatment alternative for multiple sclerosis (MS). A 68% decrease in the annualized number of attacks (ARR) is observed with NTZ treatment compared to the placebo (1). NTZ is a high-efficiency immunomodulatory therapy (IMT). It may be a viable option, particularly for patients whose disease activity cannot be managed with first-line therapies. In recent years, NTZ has been characterized by its safety during pregnancy, in addition to its high efficacy. However, despite its effectiveness, NTZ cannot be administered for extended periods due to the risk of developing progressive multifocal leukoencephalopathy (PML), which is caused by the John Cunningham virus (JCV) (2,3). Efficacy and safety data for IMTs utilized in MS patients are first acquired from clinical trials. The outcomes of extended data from clinical trials and real-world results are also present. Furthermore, clinicians may be drawn to real-world data. Real-world data is of the utmost importance to clinicians. Real-world studies may be more intriguing than clinical trials, which are conducted with a limited number of patients. Clinicians may observe implementations that are similar or different from their own. In this respect, experiences spanning many years may be even more significant. The use of NTZ for an extended period may be impeded by the use of immunosuppression prior to IMT, the presence of anti-JCV antibodies, and prolonged use of IMTs (3,4). NTZ may have fewer real-world data than other MS IMTs, and patient data may be scarce for long-term drug use.

Address for Correspondence: Sedat Sen, Ondokuz Mayis University Faculty of Medicine, Department of Neurology, Samsun, Turkey
E-mail: sedatsen83@hotmail.com **ORCID-ID:** orcid.org/0000-0001-8048-6845
Received: 12.07.2024 **Accepted:** 13.09.2024

This study aimed to present the efficacy and safety data of NTZ treatment for MS patients at a single center.

Materials and Methods

Patients who were diagnosed with clinically definite MS based on the McDonald 2017 criteria and were administered NTZ for at least six months were included in the study. The study included patients who were currently under treatment, as well as those who had previously received NTZ and had their treatment terminated for any reason. The study excluded patients with incomplete clinical and demographic data, those with insufficient follow-up periods, and those with comorbidities other than MS that would alter clinical findings. The patient data were accessed from the iMed database. The entries to the iMed database were made in real time for patients who were receiving NTZ treatment. Retrospective data entry could not be made in the database. We included results of radiological evaluations that were conducted by MS specialists with extensive experience in the field, in addition to demographic data pertaining to age, sex, disease duration, and the number of attacks. Expanded disability status scale (EDSS) scoring was performed by neurostatus certified specialists. Magnetic resonance imaging (MRI) findings, EDSS values, and the ARR were used to evaluate the no evidence of disease activity-3 (NEDA-3) results.

Statistical Analysis

Demographic data, including age, sex, and disease duration, are presented as the minimum, maximum, and mean ± standard deviation. The annual number of attacks, MRI findings, and EDSS values are expressed as percentages (%).

Results

This study included 151 patients (108 females and 43 males). The female/male value was 2.51. The patients' ages ranged from 21.63 to 67.60 years, with a mean age of 44.50±10.01. A family history of MS was present in 17 patients (11.3%), with the prevalent family history being the occurrence of MS in a sibling. Although all patients were experiencing relapsing remitting MS when NTZ treatment was initiated, 14 patients transitioned to the secondary progressive form of MS at the end of the study. NTZ treatment was discontinued in all these patients. During NTZ treatment, disease progression occurred only in six patients, while the remaining patients underwent this transformation in the post-NTZ period. Demographic data are illustrated in Table 1. Four patients (2.6%) received NTZ as their initial treatment, while all other patients received NTZ after at least one IMT. In terms of previous treatments, interferon use was the most common. Sixty-five patients (43%) received NTZ as the second line IMT, while 54.3% were administered at least two IMTs before NTZ treatment. Although the disease duration ranged between 2.73 and 30.66 years, the mean disease duration was 16.08±6.59 years. Disease duration at the time of initiation of NTZ treatment ranged between 0.27 and 26.68 years, with a mean of 9.93±6.26 years. The most common reasons for transitioning to NTZ treatment were frequent attacks and EDSS progression (30-42%). The number of attacks in the last year before treatment varied between 0 and 6; however, the mean annual number of attacks was 1.19. In the first year following treatment, the mean number of attacks was 0.07, followed by 0.13 in the second year and 0.09 in the third year. The baseline EDSS values of the patients ranged between 0 and 5.5, and the mean baseline EDSS value was 3.08±1.79. The mean EDSS value during the first year of treatment was 2.58, followed by 2.32 in the second year and 2.34 in the third year (Figure 1).

NTZ treatment is still being administered to 53 study patients. Among patients who discontinued NTZ treatment, the average duration of drug use was 2.71 years (2.34) years, with a range of 0.5 to 11.2 years. The duration of drug use in patients who were still on treatment ranged from 0.5 to 10.99 years, with a mean of 3.53±2.45 years. The duration of drug use for all patients was 0.5-11.2 years with a mean of 3.11±2.42 years. The most prevalent reason for NTZ termination was an increase in EDSS (30.7%). The other reasons included planned discontinuation (expiry of drug use), JCV positivity, pregnancy planning, side effects, and

Table 1. Demographic data

	Minimum	Maximum	Mean ± SD
Age	21.63	67.60	44.50±10.01
Disease duration (year)	0.27	26.68	9.93±6.26
Duration of use of natalizumab (year)	0.50	11.20	3.11±2.42
Annual number of attacks before treatment	0.00	6.00	1.19±2.12
Basal EDSS	0.00	5.50	3.08±1.79

SD: Standard deviation, EDSS: Expanded disability status scale

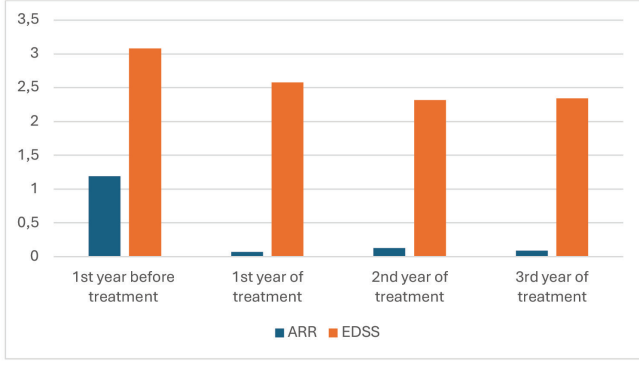

Figure 1. Impact data

ARR: Annual number of attacks, EDSS: Expanded disability status scale

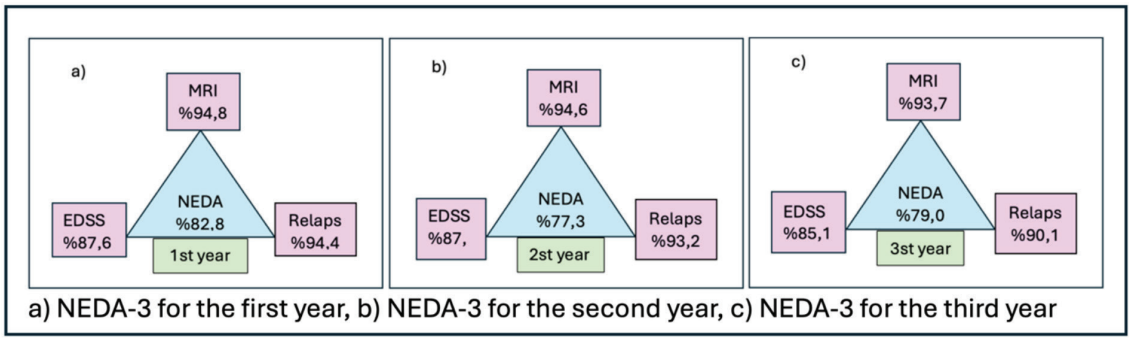

Figure 2. NEDA Outcomes

NEDA: No evidence of disease activity, EDSS: Expanded disability status scale, MRI: Magnetic resonance imaging

patient preference to discontinue NTZ. Frequent flare-ups and increased MRI activity led to the discontinuation of treatment in 8% of patients. Return of high disease activity or rebound activity was observed in 14.6% of patients whose treatment was terminated for any reason. Only three patients experienced severe adverse effects in the form of infusion reactions. These side effects occurred in doses 1, 3, and 7. In 5% of the patients with negative JCV values at the time of NTZ initiation, a return to positive serology was observed during the follow-up period. The NEDA-3 data evaluating ARR status, MRI activity, and EDSS progression were calculated for each year in the three-year period. The NEDA-3 value was 82.8% (n=145) in the first year, 77.3% (n=132) in the second year, and 79.0% (n=81) in the third year (Figure 2).

Discussion

In recent years, the utilization of highly effective IMTs has become increasingly prevalent in the clinical setting of MS. For nearly two decades, NTZ has been utilized in MS treatment and remains one of the most effective treatment options. The prominence of highly effective treatment options in MS practice has been further bolstered by the increase in their availability and prevalence over the past decade. Horizontal transitions between platform treatments in stepwise treatment applications have decreased recently. When disease activity cannot be controlled, switching to the next step in the treatment has become more rapid (6). Although it is possible to use highly effective treatments at the outset, this approach is prohibited by the health authorities in several countries. Therefore, NTZ could be employed as first-line treatment for a very limited number of patients in our study. Our data reveal that NTZ was typically used as a second and mostly as a third choice. Another reason for this situation is that our study included data from approximately 15 years prior. This is also the reason why the average duration of the disease during the NTZ initiation period was nearly ten years.

The mean ARR of the patients during the period when NTZ was initiated was as high as 1.19 in our study. The fact that this number decreased to 0.1s within a three-year period may suggest highly effective disease activity control. This effect on ARR is higher than the clinical study data for NTZ and more consistent with real-world data (1,2,4,7,8). It is observed that the mean EDSS value, which was 3.08 at the commencement of treatment, decreased to 2.5 or even lower over the course of the three-year treatment period.

The most frequent reason for the restricting the use of NTZ is JCV serological positivity. Compared to the periods when the treatment was first employed, JCV-related treatment management is more readily understood today. The risk of PML can be determined based on anti-JCV positivity, past immunosuppressive use and duration of drug use (9,10). In our study, seroconversion developed and positive anti-JCV test occurred in 5% of patients during the course of drug use (mean 3.11 years). Treatment planning for these patients was appropriately modified to include an alternative treatment mode. The annual conversion for seronegative patients has not been determined in any study published in the literature. It is not possible to access this information due to regional differences. This study has revealed that JCV seroconversion occurs at an annual rate of less than 2%, even if the number of patients is limited.

Return of high disease activity or rebound may be observed in patients receiving NTZs when treatment is discontinued for any reason. These two conditions may be confused with each other. In our series, return of elevated disease activity or rebound was observed in 14.6% of patients. Although the literature contains wide ranges for this percentage in the literature (11-16), the sum of incidence of both the conditions in our series was lower than the general data in the literature. The primary reason for this may be that we established appropriate plans for the implementation of an effective alternative treatment following NTZ.

In recent years, the most frequently employed definition for the efficacy data of IMTs used in MS treatment is NEDA. As the number of parameters evaluated increases, the NEDA score also increases. NEDA-3 is the most commonly used endpoint for evaluating efficacy of MS treatment in clinical practice. Patients with no relapse, no increase in EDSS score, and no new-active-growing lesion on MRI are patients who meet the NEDA-3 criteria. (17,18). We obtained the NEDA-3 value, in which relapse, EDSS, and MRI findings were evaluated together at rates up to 80% over a three-year period. This rate is higher than that mentioned in clinical studies published in literature. It is either high or comparable to real-world studies (19-22).

Study Limitations

Our study presents data from a single center. Therefore, it may not adequately reflect heterogeneous and universal information. Furthermore, our study, which was designed as a retrospective data screening, is less comprehensive than prospectively conducted studies. A significant limitation of this study was that cognitive functions were not assessed.

Conclusion

NTZ therapy has been used to treat MS patients because of its efficacy and safety. Patients received NTZ treatment for three years on average. In 14.6% of patients, return of disease activity or rebound was noted after the treatment was discontinued. Anti-JCV antibody was detected in 5% of patients during the course of the treatment. Approximately 80% of patients fulfilled NEDA-3 criteria during NTZ treatment over a three-year period. It is imperative to conduct comprehensive and multicenter studies that analyze real-world data from patients who are receiving natalizumab treatment. Future prospective studies are required to obtain more detailed results regarding the safety of treatment.

Ethics

Ethics Committee Approval: Ethics Committee approval is not required.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.Ö., S.Ş., M.T., Concept: A.Ö., S.Ş., Design: S.Ş., Data Collection or Processing: A.Ö., S.Ş., M.T., Analysis or Interpretation: S.Ş., Literature Search: A.Ö., S.Ş., Writing: A.Ö., S.Ş., M.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Wajgt A, Toal M, Lynn F, Panzara MA, Sandrock AW; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354:899-910.
2. Havrdova E, Galetta S, Hutchinson M, Stefoski D, Bates D, Polman CH, O'Connor PW, Giovannoni G, Phillips JT, Lublin FD, Pace A, Kim R, Hyde R. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. Lancet Neurol. 2009;8:254-260.
3. Butzkueven H, Kappos L, Pellegrini F, Trojano M, Wiendl H, Patel RN, Zhang A, Hotermans C, Belachew S; TYSABRI Observational Program (TOP) Investigators. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results. J Neurol Neurosurg Psychiatry. 2014;85:1190-1197.
4. Butzkueven H, Kappos L, Wiendl H, Trojano M, Spelman T, Chang I, Kasliwal R, Jaitly S, Campbell N, Ho PR, Licata S; Tysabri Observational Program (TOP) Investigators. 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. 2020;91:660-668.
5. Yamout B, Al-Jumah M, Sahraian MA, Almalik Y, Khaburi JA, Shalaby N, Aljarallah S, Bohlega S, Dahdaleh M, Almahdawi A, Khoury SJ, Koussa S, Slassi E, Daoudi S, Aref H, Mrabet S, Zeineddine M, Zakaria M, Inshasi J, Gouider R, Alroughani R. Consensus recommendations for diagnosis and treatment of Multiple Sclerosis: 2023 revision of the MENACTRIMS guidelines. Mult Scler Relat Disord. 2024;83:105435.
6. Clerico M, Artusi CA, Liberto AD, Rolla S, Bardina V, Barbero P, Mercanti SF, Durelli L. Natalizumab in Multiple Sclerosis: Long-Term Management. Int J Mol Sci. 2017;18:940.
7. Guger M, Enzinger C, Leutmezer F, Di Pauli F, Kraus J, Kalcher S, Kvas E, Berger T; Austrian MS Treatment Registry (AMSTR). 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. 2021;268:4303-4310.
8. Pucci E, Giuliani G, Solari A, Simi S, Minozzi S, Di Pietrantonj C, Galea I. Natalizumab for relapsing remitting multiple sclerosis. Cochrane Database Syst Rev. 2011:CD007621.
9. Plavina T, Subramanyam M, Bloomgren G, Richman S, Pace A, Lee S, Schlain B, Campagnolo D, Belachew S, Ticho B. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol. 2014;76:802-812.
10. Lanza Cariccio V, Bramanti P, Mazzon E. Biomarkers identification for PML monitoring, during Natalizumab (Tysabri®) treatment in Relapsing-Remitting Multiple Sclerosis. Mult Scler Relat Disord. 2018;20:93-99.
11. Prosperini L, Kinkel RP, Miravalle AA, Iaffaldano P, Fantaccini S. Post-natalizumab disease reactivation in multiple sclerosis: systematic review and meta-analysis. Ther Adv Neurol Disord. 2019;12:175628641983780.
12. Iaffaldano P, Lucisano G, Pozzilli C, Brescia Morra V, Ghezzi A, Millefiorini E, Patti F, Lugaresi A, Zimatore GB, Marrosu MG, Amato MP, Bertolotto A, Bergamaschi R, Granella F, Coniglio G, Tedeschi G, Sola P, Lus G, Ferrò MT, Iuliano G, Corea F, Protti A, Cavalla P, Guareschi A, Rodegher M, Paolicelli D, Tortorella C, Lepore V, Prosperini L, Saccà F, Baroncini D, Comi G, Trojano M; Italian iMed-Web database. Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis. Brain. 2015;138:3275-3586.
13. Prosperini L, Annovazzi P, Capobianco M, Capra R, Buttari F, Gasperini C, Galgani S, Solaro C, Centonze D, Bertolotto A, Pozzilli C, Ghezzi A.

Natalizumab discontinuation in patients with multiple sclerosis: Profiling risk and benefits at therapeutic crossroads. Mult Scler. 2015;21:1713-1722.

14. Clerico M, Schiavetti I, De Mercanti SF, Piazza F, Gned D, Brescia Morra V, Lanzillo R, Ghezzi A, Bianchi A, Salemi G, Realmuto S, Sola P, Vitetta F, Cavalla P, Paolicelli D, Trojano M, Sormani MP, Durelli L. Treatment of relapsing-remitting multiple sclerosis after 24 doses of natalizumab: evidence from an Italian spontaneous, prospective, and observational study (the TY-STOP Study). JAMA Neurol. 2014;71:954-960.
15. Sorensen PS, Koch-Henriksen N, Petersen T, Ravnborg M, Oturai A, Sellebjerg F. Recurrence or rebound of clinical relapses after discontinuation of natalizumab therapy in highly active MS patients. J Neurol. 2014;261:1170-1177.
16. Vellinga MM, Castelijns JA, Barkhof F, Uitdehaag BM, Polman CH. Postwithdrawal rebound increase in T2 lesional activity in natalizumab-treated MS patients. Neurology. 2008;70:1150-1151.
17. Giovannoni G, Turner B, Gnanapavan S, Offiah C, Schmierer K, Marta M. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? Mult Scler Relat Disord. 2015;4:329-333
18. Banwell B, Giovannoni G, Hawkes C, Lublin F. Editors' welcome and a working definition for a multiple sclerosis cure. Mult Scler Relat Disord. 2013;2:65-67.
19. Perumal J, Balabanov R, Su R, Chang R, Balcer L, Galetta S, Campagnolo DI, Avila R, Lee L, Rutledge D, Fox RJ. Natalizumab in Early Relapsing-Remitting Multiple Sclerosis: A 4-Year, Open-Label Study. Adv Ther. 2021;38:3724-3742.
20. Diem L, Nedeltchev K, Kahles T, Achtnichts L, Findling O. Long-term evaluation of NEDA-3 status in relapsing-remitting multiple sclerosis patients after switching from natalizumab to fingolimod. Ther Adv Neurol Disord. 2018;11:1756286418791103.
21. Kalincik T, Sharmin S, Roos I, Freedman MS, Atkins H, Burman J, Massey J, Sutton I, Withers B, Macdonell R, Grigg A, Torkildsen Ø, Bo L, Lehmann AK, Havrdova EK, Krasulova E, Trnený M, Kozak T, van der Walt A, Butzkueven H, McCombe P, Skibina O, Lechner-Scott J, Willekens B, Cartechini E, Ozakbas S, Alroughani R, Kuhle J, Patti F, Duquette P, Lugaresi A, Khoury SJ, Slee M, Turkoglu R, Hodgkinson S, John N, Maimone D, Sa MJ, van Pesch V, Gerlach O, Laureys G, Van Hijfte L, Karabudak R, Spitaleri D, Csepany T, Gouider R, Castillo-Triviño T, Taylor B, Sharrack B, Snowden JA; MSBase Study Group Collaborators; MSBase Study Group Authors; Mrabet S, Garber J, Sanchez-Menoyo JL, Aguera-Morales E, Blanco Y, Al-Asmi A, Weinstock-Guttman B, Fragoso Y, de Gans K, Kermode A; MSBase Study Group. Comparative Effectiveness of Autologous Hematopoietic Stem Cell Transplant vs Fingolimod, Natalizumab, and Ocrelizumab in Highly Active Relapsing-Remitting Multiple Sclerosis. JAMA Neurol. 2023;80:702-713.
22. Prosperini L, Fanelli F, Pozzilli C. Long-term assessment of No Evidence of Disease Activity with natalizumab in relapsing multiple sclerosis. J Neurol Sci. 2016;364:145-147.