

Original article

A real world multi center study on efficacy and safety of natalizumab in Indian patients with multiple sclerosis

Thomas Mathew^{a,*}, Vikram Kamath^b, Saji K John^a, M Netravathi^c, Rajesh B Iyer^d, S Raghavendra^d, Suresh Kumar^e, M.L. Neeharika^f, Salil Gupta^g, Uday Murgod^h, R. Shivakumarⁱ, Ravi K Annadure^j, Nasli Ichaporia^k, Anshu Rohatgi^l, Sruthi S Nair^m, Sireesha Yareeda^f, Bawani Anand^{h,i}, Prabhjeet Singhⁿ, Umashankar Renukaradhya^o, V. Arulselvan^p, Y Muralidhar Reddy^q, Nirmal Surya^r, G.R.K. Sarma^a, Raghunandan Nadig^a, Saikanth Deepalam^a, G.G. Sharath Kumar^a, P. Satishchandra^s, Bhim Sen Singhal^r, Gareth Parry^a

^a Department of Neurology, St. John's Medical College Hospital, Sarjapura Road, Bengaluru, Karnataka 560034, India

^b Department of Neurology, Trustwell Hospitals, Chandrika tower 5 JC Road Sudama Nagar, Bengaluru, Karnataka 560002, India

^c Department of Neurology, NIMHANS, Hosur Road, Near Bangalore Milk Dairy, Hombegowda Nagar, Bengaluru 560029, India

^d Department of Neurology, Manipal Hospital, Millers Road 71/1 Millers Road Opp to St Annes College, Vasant Nagar, Bengaluru 560052

^e Department of Neurology, Renai Medicity Multi Super Speciality Hospital, Palarivattom Edapally, Road Near Palarivattom Metro Station Palarivattom, Kochi, Kerala 682025, India

^f Department of Neurology, Nizam's Institute of Medical Sciences, Punjagutta rd, Punjagutta market, Hyderabad, Telangana 500082

^g Department of Neurology, Command Hospital Air force, Agram post, Bengaluru 560007, India

^h Department of Neurology, Manipal Hospital, HAL Airport Road, Bangalore 560017, India

ⁱ Department of Neurology, Sakra World Hospital, Devarabeesanahalli Varthur Hobli Opp intel, Outer Ring Road, Marathahalli, Bengaluru 560103, India

^j Department of Neurology, AFC Delhi, Defence Office Complex, Central Vista, KG Marg, New Delhi 110011

^k Department of Neurology, Sahyadri Super Speciality Hospital Nagar Raod Shastrinagar, Yerawada, Pune, Maharashtra 411006, India

^l Department of Neurology, Sir Ganga Ram Hospital, Rajinder Nagar New Delhi 110060, India

^m Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, GWCG, Jai nagar w Rd chalakkuzhi, Thiruvananthapuram, Kerala 695011, India

ⁿ Department of Neurology, Dr Prabhjeets Neuro Centre, F-1/338, Kashmir Avenue, Amritsar 143001, India

^o Department of Neurology, Bengaluru Neuro Centre, 10th Cross Margosa road, Malleshwaram, Bangalore 560003, India

^p Department of Neurology, Royal Care Super Speciality Hospital, NO 1/520, L&T Road Neelambur, Coimbatore 641062, India

^q Department of Neurology, Care Hospital, Rd Number 1 Prem Nagar, Banjara Hills, Hyderabad, Telangana 500034, India

^r Department of Neurology, Bombay Hospital and Medical Research Centre, 12 Vitthaladas, Thackersey Marg, Near Liberty Cinema, New Marine Lines Mumbai 400020, India

^s Department of Neurology, Apollo Speciality Hospital, 14 th Cross 3rd Block Near Madhavan Park, Jaynagar, Bengaluru 560011, India

ARTICLE INFO

Keywords:

Multiple sclerosis

Natalizumab

Relapse rate

EDSS score

Progressive multifocal leukoencephalopathy

JC virus

ABSTRACT

Background: Natalizumab (NTZ) is increasingly being used in Indian multiple sclerosis (MS) patients. There are no reports on its safety and efficacy, especially with respect to the occurrence of progressive multifocal leukoencephalopathy (PML).

Objectives: To describe the patient characteristics, treatment outcomes, and adverse events, especially the occurrence of PML in NTZ-treated patients.

Methods: A multicentre ambispective study was conducted across 18 centres, from Jan 2012 to Dec 2021. Patients at and above the age of 18 years treated with NTZ were included. Descriptive and comparative statistics were applied to analyze data.

Results: During the study period of 9 years, 116 patients were treated with NTZ. Mean age of the cohort was 35.6 ± 9.7 years; 83/116 (71.6%) were females. Relapse rate for the entire cohort in the year before NTZ was 3.1 ± 1.51 while one year after was 0.20±0.57 ($p = 0.001$; CI 2.45 -3.35). EDSS of the entire cohort in the year before

* Corresponding author.

E-mail address: chakkuthom@hotmail.com (T. Mathew).

<https://doi.org/10.1016/j.msard.2022.104059>

Received 18 June 2022; Received in revised form 9 July 2022; Accepted 15 July 2022

Available online 25 July 2022

2211-0348/© 2022 Elsevier B.V. All rights reserved.

NTZ was 4.5 ± 1.94 and one year after was 3.8 ± 2.7 ($p = 0.013$; CI 0.16–1.36). At last follow up (38.3 ± 22.78 months) there were no cases of PML identified.

Conclusions: Natalizumab is highly effective and safe in Indian MS patients, with no cases of PML identified at last follow up.

1. Introduction

Natalizumab (NTZ, Tysabri) is a humanized IgG4 antibody that blocks the $\alpha 4$ subunit of $\alpha 4\beta 1$ integrin expressed on the surface of leukocytes. The glycoprotein $\alpha 4\beta 1$ integrin is an important mediator of cell adhesion and trans-endothelial migration and a regulator of immune-cell activation within inflamed tissue (Miller et al., 2003). Blocking of the $\alpha 4\beta 1$ by NTZ prevents the transmigration of lymphocytes, both T and B, through the blood-brain barrier. NTZ may also modulate ongoing inflammatory reactions by inhibiting the binding of $\alpha 4$ -positive leukocytes with fibronectin and osteopontin (Polman et al., 2006). Data from clinical trials and real world studies have shown that NTZ to be a highly efficacious drug for the treatment of relapsing-remitting multiple sclerosis (RRMS) (Polman et al., 2006; Butzkueven et al., 2020), but the Achilles's heel for NTZ is the occurrence of progressive multifocal leukoencephalopathy (PML) especially with prolonged treatment. Since becoming available in India in 2012, NTZ is increasingly being used in Indian multiple sclerosis (MS) patients, especially for those with aggressive disease. There are no reports on efficacy and safety of NTZ in Indian patients, especially with respect to the occurrence of PML. Here we report the Indian experience with NTZ from 18 MS centers over a period of 9 years.

2. Methods

This was a multi-center ambispective study from 18 participating MS clinics in India, involving MS patients, at and above the age of 18 years who were treated with NTZ. The study period was from Jan 2012 to Dec 2021. Diagnosis of MS was made in all patients by McDonald 2010 criteria. Patients with NMO and MOG spectrum disorders were excluded from the study based on radiological features and standard cell-based assays. NTZ 300 mg was administered intravenously every 4 weeks as an infusion over 1 h as per standard protocols. JC virus antibody serology and titers were measured at baseline and every 6 months while on treatment. All JC virus-positive patients underwent MRI of the brain every 6 months while JC virus negative patients were evaluated with yearly MRI to detect any PML lesions.

The demographic and clinical data were taken from the case records with respect to type of MS, duration of MS, duration of NTZ treatment, relapse rate and EDSS score at base line and follow up, adverse effects especially occurrence of PML, and treatment administered before and after NTZ. Neurological examinations including the expanded disability status scale (EDSS) was done at baseline and every six months. A clinical

relapse was defined as new or recurrent neurological symptoms not associated with fever, lasting for ≥ 24 h and followed by 30 days of stability or improvement. Confirmed disability worsening was defined as an increase in EDSS, confirmed 24 weeks later, of 1.0 point for patients with baseline EDSS ≤ 5.5 and of 0.5 point for baseline EDSS > 5.5 . Confirmed disability improvement was defined as a decrease of ≥ 1.0 point from baseline score, confirmed 24 weeks later, among patients with baseline EDSS scores ≥ 2.0 . Reactivation was defined as disease activity following NTZ discontinuation in the form of relapses and/or MRI activity, while rebound was defined as recurrence of disease activity with at least two of the following features: (i) an annualized relapse rate increase in comparison with pre-NTZ disease course; (ii) one or more severe relapses with sustained disability progression (one-step EDSS increase); (iii) three or more new large T2 lesions and/or Gd+ lesions on MRI; and (iv) one or more new tumor-like demyelinating lesions on MRI (Lo Re et al., 2015). Descriptive statistics were used to summarize the data; results were reported as medians and ranges or means and standard deviations, as appropriate. Categorical variables were summarized as counts and percentages. Comparisons between pre- and post-treatment relapse rates were performed using the paired 't' test. A p -value less than 0.05 was considered statistically significant. Study was approved by the institutional review board of the main center and the coordinating centers. All participants provided written informed consent.

3. Results

During the study period of nine years, 116 MS patients, 92 (79.3%) RRMS and 24 (20.7%) SPMS received NTZ. Mean age of the cohort was 35.6 ± 9.7 years. 83/116 (71.6%) were female. 91% of patients had previously received at least one first line disease modifying drugs (DMDs) while 8.6% (10/116) was given NTZ as initial treatment. Treatments given prior to NTZ included dimethyl fumarate (20%), interferon $\beta 1a$ IM (13.3%), glatiramer acetate (11.1%), pegylated interferon $\beta 1a$ (4.5%), interferon $\beta 1a$ sc (2.2%), interferon $\beta 1b$ sc (2.2%), teriflunomide (2.2%), oral steroids (13.3%), pulsed methyl prednisolone (8.8%) and multiple DMDs sequentially in 13.3%. JCV Status at baseline was available for 60 patients (51.7%) of which 31 (51.6%) had positive anti-JCV virus antibody (Table 1). Antibody titre at baseline was 0.81 ± 1.13 (Range 0.11 to 3.59). Relapse rate for the entire cohort in the year before NTZ was 3.1 ± 1.51 while one year after NTZ, it was 0.20 ± 0.57 ($p = 0.001$; CI 2.45 – 3.35) (Fig. 1a). 92.2% (107/116) had more than two relapses in the year before NTZ, while after one year of NTZ only 5.2% (6/116) had more than two relapses, 11.2% (13/116) patients had one relapse, while 83.6% (97/116) were relapse free. EDSS of the entire cohort before NTZ was 4.5 ± 1.94 , while a year after NTZ it was 3.8 ± 2.7 ($p = 0.013$; CI 0.16–1.36) (Fig. 1b). In patients with RRMS the relapse rate in the year before NTZ was 2.76 ± 1.20 while after NTZ it was 0.15 ± 0.56 ($p = 0.001$; CI 2.15 – 3.08) (Fig. 2a). EDSS before NTZ was 3.99 ± 1.84 and after NTZ it was 2.63 ± 2.26 ($p = 0.001$; CI 0.65–2.05) (Fig. 2b). In the SPMS group the relapse rate in the year before NTZ was 3.76 ± 1.85 while after NTZ it was 0.29 ± 0.58 ($p = 0.001$; CI 2.49–4.45) (Fig. 3a) while EDSS before NTZ was 5.58 ± 1.73 and after NTZ it was 6.0 ± 2.05 ($p = 0.38$; CI –1.3 – 0.57) (Fig. 3b).

Allergic reaction in the form of pruritus, rash and lip edema was seen in two patients (2/116; 1.7%). Both reactions occurred during the second infusion. They were treated with antihistamines and hydrocortisone and the reactions subsided completely. In both these patients NTZ was continued subsequently after premedication with antihistamine and

Table 1
Patient Distribution and Demography.

Patient Demographics (N = 116)	RRMS (n = 92)	SPMS (n = 24)
Age		
≤ 30 years	31 (34%)	4 (16.6%)
31 - 40 years	38 (41%)	7 (29.2%)
> 40 years	23 (25%)	13 (54.1%)
Gender		
Females	66 (71.7%)	17 (70.8%)
Males	26 (28.23%)	7 (29.2%)
Previous Rx-wise Distribution		
Treatment Naïve	10 (11%)	0 (0%)
Previous Treatment	82 (89%)	24 (100%)
Baseline JCV Distribution	Out of Total Cases (N = 60)*	
JCV Positive Patients	31 (52%)	

* Baseline JCV data was available for only 60 patients at the time of analysis.

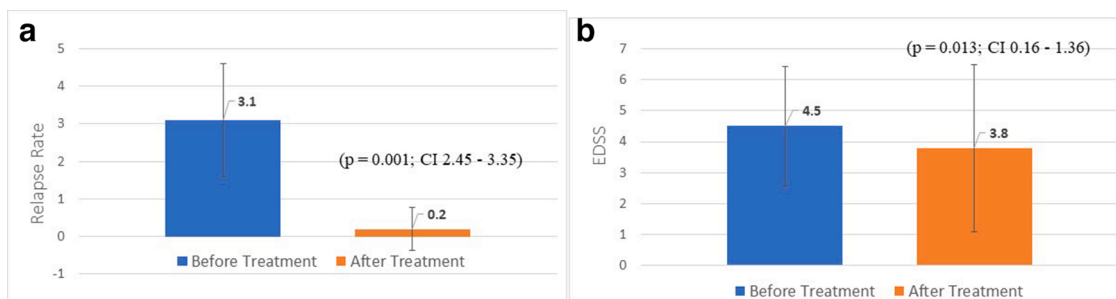


Fig. 1. Overall Efficacy Results: (a): Relapse Rate Reduction ($N = 116$), A year Before and After Treatment, (b): EDSS ($N = 116$), A year Before and After Treatment.

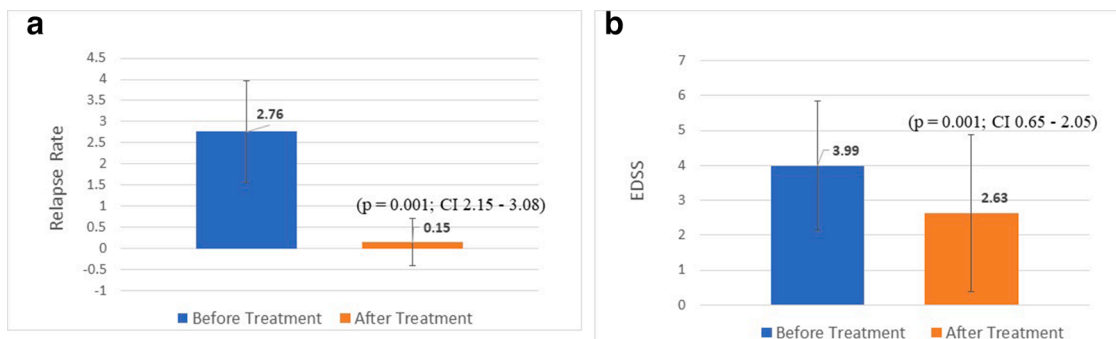


Fig. 2. RRMS Sub-group Efficacy Results: (a): Relapse Rate Reduction ($N = 92$), A year Before and After Treatment, (b): EDSS ($N = 92$), A year Before and After Treatment.

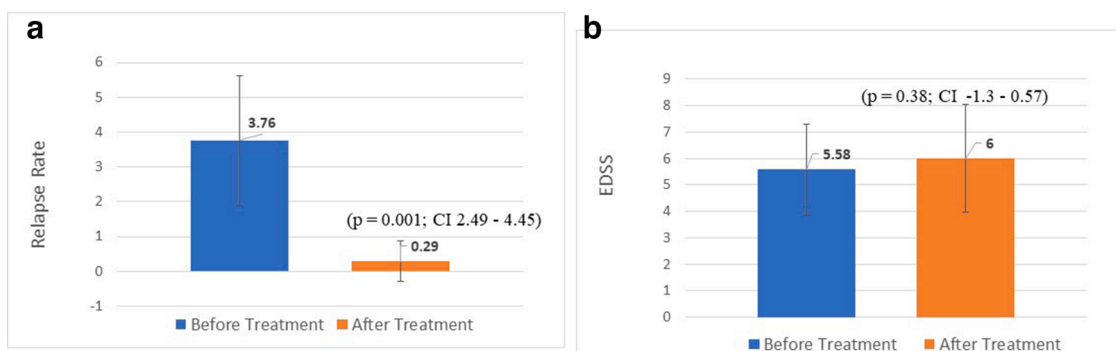


Fig. 3. SPMS Sub-group Efficacy Results: (a): Relapse Rate Reduction ($N = 24$), A year Before and After Treatment, (b): EDSS ($N = 24$), A year Before and After Treatment.

hydrocortisone and at a slower infusion rate over 2 h.

Total duration of NTZ treatment was 22 ± 19.3 months (range 6–108 months). The proportion of patients who received treatment for more than 2 years was only 24.1% (28/116). The main reasons for stopping NTZ was fear of PML (104/116; 89.6%) and lack of efficacy and disease progression in SPMS patients (12/116; 10.3%). Post NTZ, 65.5% (76/116) were treated with rituximab, 6% with interferon β 1a IM, and 6% with dimethyl fumarate. 3.4% underwent autologous bone marrow transplantation and 4.4% were on Ayurvedic medications. 14.7% patients of SPMS were not on any treatment. Rituximab was started after NTZ, following a washout period of 4 to 10 weeks. There were no cases of reactivation or rebound observed in the current cohort. During the last follow up (38.3 ± 22.78 months; range 6–108 months) there were no cases of PML identified.

4. Discussion

Natalizumab (NTZ) is a highly effective treatment strategy for

patients with RRMS, especially for those with highly active disease (Polman et al., 2006). Here we describe the Indian experience of NTZ over a period of 9 years, from 18 centres, involving 116 MS patients. In the present study, NTZ was shown to be highly effective, and reduced relapse rate from 3.1 per year to 0.2 per year, a reduction of 93.5%. These findings are in alignment with that of Tysabri Observational Program (TOP) where a 92.5% reduction in annualized relapse rate was observed with NTZ (Butzkueven et al., 2020). Both relapse rate and disability status improved in the RRMS cohort, while in the SPMS cohort only relapse rate improved, with no effect on disability progression. These observations highlight the importance of starting a highly effective treatment like NTZ early in the disease course when inflammation is active, as it may help in preventing disability and disease progression. In a real-world study reported by Foley et al., lower baseline disease activity and earlier treatment were related to better outcomes, the latter highlighting the importance of starting NTZ early in the disease course (Foley et al., 2017). In a recent retrospective international observational study, based on data from the MSBase registry and the Swedish MS

registry, it was found that high-efficacy therapy commenced within 2 years of disease onset was associated with less disability after 6–10 years than when commenced later in the disease course (He et al., 2020). In another cohort study where prospective data was collected from 68 neurology centers, in 21 countries, involving patients with RRMS, initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a lower risk of conversion to secondary progressive MS compared to initial treatment with glatiramer acetate or interferon beta (Brown et al., 2019).

The greatest disadvantage of NTZ is the risk of PML, which increases especially beyond 24 infusions (Clifford et al., 2010). In a 10 year old real-world observational study, it was found that the median time to the onset for various types opportunistic infections was 14 months from NTZ initiation and 67.9% of PML cases occurred in those receiving NTZ for more than three years (Clifford et al., 2010; Sangalli et al., 2014). Risk of PML increases with increasing duration of treatment, previous exposure to immunosuppressive medications like mitoxantrone, azathioprine, methotrexate, cyclophosphamide, and/or mycophenolate mofetil, presence of JC virus serology and a JC virus antibody titre of more than 0.9 (Ho et al., 2017). However, in present study, there were no cases of PML detected, despite a baseline JC virus positivity status of 51% and a duration of treatment of 22±19.3 months (range 6 months to 9 years). Though the sample size is too small to make firm conclusions, the most likely reasons for the absence of PML, was the short duration of NTZ treatment, lack of prior exposure to immunosuppressants and optimum use of JCV antibody assay stratification. Data from the TOUCH (TYSABRI Outreach: Unified Commitment to Health) Prescribing Program, involving 206,439 patients treated with NTZ worldwide, representing 793,008 patient-years of NTZ exposure, showed the global overall cumulative incidence of NTZ associated PML to be 4.02 per 1000 patients (95% confidence interval, 3.75 to 4.30 per 1000). The overall cumulative incidence of NTZ associated PML climbed from 2009 to 2016; however, from 2016 to the 2019, it has been stable with a downward trend. The reason for this downward trend was thought to be the increase in vigilance for PML associated with NTZ with the help of JCV stratification (GiovannoniG and Berger, 2020).

Another disadvantage of NTZ is the risk for reactivation and rebound after the cessation of treatment. Relapses after stopping NTZ ranges from 9 to 80% and usually start at 3 months, peaks at 4–7 months, and returns to the pre-NTZ level at approximately 12 months (Lo Re et al., 2015). Rebound, which is an increase in activity beyond the pre-NTZ level, is reported to occur in 8% to 22% after cessation of NTZ treatment (Prosperini et al., 2019). In the current study, there were no cases with reactivation or rebound after NTZ cessation. This probably was due to early initiation of disease modifying treatment within 4–10 weeks of NTZ stoppage. Rituximab was the commonest disease modifying therapy used after NTZ and is a very effective and affordable treatment strategy in resource-limited settings (Mathew et al., 2020; Piehl and Mathew, 2022). A recent retrospective cohort study of 256 patients discontinuing NTZ because of anti-JCV antibody positivity showed that rituximab was superior to fingolimod in prolonging the beneficial effect of NTZ after its discontinuation (Alping et al., 2016).

The present study is one of the largest from a developing country like India. The limitations of the study are small sample size, ambispective nature and unavailability of JC virus serology in a significant number of patients. However, the study has shown NTZ to be highly effective in Indian MS patients particularly those with RRMS, with no major safety concerns. The findings of this study are in concordance with the findings of randomized controlled trials and other real world observational studies.

NTZ is an immune-blocker/immune-modulator and not an immune-depletor and does not cause any long-term immunological changes (Sangalli et al., 2014). NTZ prevents the entry of both B and T cells into the brain and has relatively rapid onset of action (Polman et al., 2006; Derfuss et al., 2017). The treatment effect with NTZ can be seen as early as three months after therapy initiation (Foley et al., 2017). This makes

NTZ an ideal treatment in the early phases of MS when inflammation is active. The strategy of giving NTZ early may give a “head start” for MS treatment and keeping the therapy for less than 24 months will lower the risk of PML. Following this with an effective B cell depleting agent like rituximab within in 4–10 weeks will optimize the likelihood of long term disease remission without risk of reactivation or rebound. This appears to be a very effective sequencing strategy with a favourable benefit risk ratio and economic benefits in resource-limited settings.

5. Conclusions

Natalizumab is a highly effective treatment strategy in Indian patients with MS. The risk benefit ratio appears highly favorable with no reports of PML as of now. A short course of natalizumab and lack of prior exposure to immunosuppressant therapy may be the reason for the lack of PML in the present study. Patients with RRMS and SPMS benefit with respect to relapse rate while EDSS improvement was observed only in the RRMS cohort. Initiating natalizumab early in the disease course, before other immunosuppressive medications and keeping the duration of treatment shorter is important for optimum safety and efficacy.

Financial disclosure

No funding was received for this project.

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

Acknowledgments

The authors of this paper would like to thank Mr. Maria Anandan, and Sister Annie George for the secretarial assistance.

References

- Alping, P., Frisell, T., Novakova, L., 2016. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. *Ann. Neurol.* 79, 950–958.
- Brown, J.W.L., Coles, A., Horakova, D., Havrdova, E., Izquierdo, G., Prat, A., Girard, M., Duquette, P., Trojano, M., Lugaes, A., Bergamaschi, R., Grammond, P., Alroughani, R., Hupperts, R., McCombe, P., Van Pesch, V., Sola, P., Ferraro, D., Grand' Maison, F., Terzi, M., Lechner-Scott, J., Flechter, S., Slee, M., Shaygannejad, V., Pucci, E., Granella, F., Jokubaitis, V., Willis, M., Rice, C., Scolding, N., Wilkins, A., Pearson, O.R., Ziemssen, T., Hutchinson, M., Harding, K., Jones, J., McGuigan, C., Butzkueven, H., Kalinick, T., Robertson, N., MSBase Study Group, 2019. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA* 321 (2), 175–187. <https://doi.org/10.1001/jama.2018.20588>. Erratum in: *JAMA*. 2020 Apr 7;323(13):1318. PMID: 30644981; PMCID: PMC6439772.
- Butzkueven, H., Kappos, L., Wiendl, H., Trojano, M., Spelman, T., Chang, I., Kasliwal, R., Jaitly, S., Campbell, N., Ho, P.R., Licata, S., 2020. 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* 91 (6), 660–668.
- Clifford, D.B., De Luca, A., Simpson, D.M., Arendt, G., Giovannoni, G., Nath, A., 2010. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol.* 9 (4), 438–446. [https://doi.org/10.1016/S1474-4422\(10\)70028-4](https://doi.org/10.1016/S1474-4422(10)70028-4).
- Derfuss, T., Kovarik, J.M., Kappos, L., Savelieva, M., Chhabra, R., Thakur, A., Zhang, Y., Wiendl, H., Tomic, D., 2017. α 4-integrin receptor desaturation and disease activity return after natalizumab cessation. *Neurol. Neuroimmunol. Neuroinflamm.* 4 (5), e388. <https://doi.org/10.1212/NXI.0000000000000388>. PMID: 28856176; PMCID: PMC5572051.
- Foley, J.F., Nair, K.V., Vollmer, T., Stephenson, J.J., Niecko, T., Agarwal, S.S., Watson, C., 2017a. Long-term natalizumab treatment is associated with sustained improvements in quality of life in patients with multiple sclerosis. *Patient Prefer. Adherence* 11, 1035–1048. <https://doi.org/10.2147/PPA.S134865>. PMID: 28670113; PMCID: PMC5481282.
- Foley, J.F., Nair, K.V., Vollmer, T., Stephenson, J.J., Niecko, T., Agarwal, S.S., Watson, C., 2017b. Long-term natalizumab treatment is associated with sustained improvements in quality of life in patients with multiple sclerosis. *Patient Prefer. Adherence* 11, 1035–1048. <https://doi.org/10.2147/PPA.S134865>. PMID: 28670113; PMCID: PMC5481282.
- GiovannoniG, Kappos L, Berger, J., 2020. Updated Incidence of Natalizumab Associated Progressive Multifocal Leukoencephalopathy (PML) and its relationship with

- natalizumab exposure overTime. In: Presented at: 2020 American Academy of Neurology (AAN) Annual Meeting. Toronto, Canada. April 25th May 1st.
- He, A., Merkel, B., Brown, J.W.L., Zhovits Ryerson, L., Kister, I., Malpas, C.B., Sharmin, S., Horakova, D., Kubala Havrdova, E., Spelman, T., Izquierdo, G., Eichau, S., Trojano, M., Lugaesi, A., Hupperts, R., Sola, P., Ferraro, D., Lycke, J., Grand'Maison, F., Prat, A., Girard, M., Duquette, P., Larochelle, C., Svenningsson, A., Petersen, T., Grammond, P., Granella, F., Van Pesch, V., Bergamaschi, R., McGuigan, C., Coles, A., Hillert, J., Piehl, F., Butzkueven, H., Kalincik, T., 2020. MSBase study group. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol.* 19 (4), 307–316.
- 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](https://doi.org/10.1016/S1474-4422(17)30282-X).
- Lo Re, M., Capobianco, M., Ragonese, P., 2015. Natalizumab discontinuation and treatment strategies in patients with multiple sclerosis (MS): a retrospective study from two Italian MS centers. *Neurol. Ther.* 4, 147–157.
- Mathew, T., John, S.K., Kamath, V., Murgod, U., Thomas, K., Baptist, A.A., Therambil, M., Shaji, A., Nadig, R., Badachi, S., Souza, D.D., Shivde, S., Avati, A., Sarma, G.R.K., Sharath Kumar, G.G., Deepalam, S., Parry, G.J., 2020. Efficacy and safety of rituximab in multiple sclerosis: experience from a developing country. *Mult. Scler. Relat. Disord.* 43, 102210 <https://doi.org/10.1016/j.msard.2020.102210>. Epub 2020 May 24. PMID: 32485634.
- Miller, D.H., Khan, O.A., Sheremata, W.A., et al., 2003. A controlled trial of natalizumab for relapsing multiple sclerosis. *N. Engl. J. Med.* 348, 15–23.
- Piehl, F., Mathew, T., 2022. Low-dose rituximab should be used for treating MS in resource-limited settings: yes. *Mult. Scler.*, 13524585221089890 <https://doi.org/10.1177/13524585221089890>. Epub ahead of print. PMID: 35437089.
- Polman, C.H., O'Connor, P.W., Havrdova, E., Hutchinson, M., Kappos, L., Miller, D.H., Phillips, J.T., Lublin, F.D., Giovannoni, G., Wajgt, A., Toal, M., Lynn, F., Panzara, M. A., Sandrock, A.W., 2006. AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N. Engl. J. Med.* 354, 899–910.
- Prosperini, L., Kinkel, R.P., Miravalle, A.A., Iaffaldano, Pietro, Fantaccini, S., 2019. Post-natalizumab disease reactivation in multiple sclerosis: systematic review and meta-analysis. *Ther. Adv. Neurol. Dis.* 12, 1756286419837809 <https://doi.org/10.1177/1756286419837809>.
- DeLuca, Andrea [corrected to De Luca, Andrea]. PMID: 20298967. Sangalli, F., Moiola, L., Ferrè, L., Radaelli, M., Barcella, V., Rodegher, M., Colombo, B., Martinelli Boneschi, F., Martinelli, V., Comi, G., 2014a. Long-term management of natalizumab discontinuation in a large monocentric cohort of multiple sclerosis patients *Mult. Scler. Relat. Disord.* 3 (4), 520–526. <https://doi.org/10.1016/j.msard.2014.04.003>. Epub 2014 Apr 13. PMID: 25877065).
- Sangalli, F., Moiola, L., Ferrè, L., Radaelli, M., Barcella, V., Rodegher, M., Colombo, B., Martinelli Boneschi, F., Martinelli, V., Comi, G., 2014b. Long-term management of natalizumab discontinuation in a large monocentric cohort of multiple sclerosis patients. *Mult. Scler. Relat. Disord.* 3 (4), 520–526. <https://doi.org/10.1016/j.msard.2014.04.003>. Epub 2014 Apr 13. PMID: 25877065.