

ORIGINAL RESEARCH ARTICLE

The first study of real-world efficacy and safety of Natalizumab (Tysabri®) in Iran

Mohammad Amin Shahrba^{1,2}, Monireh Samimi^{1,2}, Shahedeh Karimi^{1,2}, Mehri Salari³, Mehran Ghaffari⁴, Sepideh Yazdanbakhsh², Abbas Najafian², Massoud Vosough^{1,2}, Seyed Massood Nabavi^{1,2,*}

¹ Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, Tehran 16635-148, Iran

² Arya Group for Treatment and Research in Multiple Sclerosis, Tehran 16635-148, Iran

³ Neuro Functional Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran 19839-63113, Iran

⁴ Neurology Department, Shahid Beheshti University of Medical Sciences, Tehran 19839-63113, Iran

* Corresponding author: Seyed Massood Nabavi, seyedmassoodnabavi@gmail.com

ABSTRACT

Objectives: Natalizumab is an injectable DMT (disease-modifying therapy) which used for RRMS (relapsing-remitting multiple sclerosis) since 2006. The drug has been available in Iran since 2014. **Introduction:** This study was aimed to evaluate the real-world effectiveness of Natalizumab in a referral center in Tehran, Iran. This study is the first real world analysis of efficacy and safety of Natalizumab in our country. **Methods:** In this retrospective study, patients with RRMS were investigated in a high-volume center in Tehran from 2019 to 2021. MS (Multiple Sclerosis) patients under treatment with Natalizumab who have received at least 3 infusions of the drug and had completed follow-up data, have been evaluated for safety and efficacy of Natalizumab. **Results:** 100 patients were included in the final analysis. The mean follow-up time was 20 months (6–33 months). The median EDSS (Expanded Disability Status Scale) score of patients reached to 2 from 2.5 after the treatment course ($P < 0.0001$). The annualized relapse rate (ARR) decreased from 0.81 (95% CI: 0.73–0.87) to 0.023 (95% CI 0.009–0.061). The median JCV (John Cunningham virus) index remained unchanged before treatment 0.85 (IQR: 0.21–2.41) compare to after the treatment 0.85 (IQR: 0.21–2.31). The number of patients with active brain and cervical MRI (Magnetic Resonance Imaging) lesions decreased significantly ($P = 0.001$). NEDA-3 (No evidence of disease activity) was improved from 9% to 87% after the treatment with Natalizumab. No serious adverse events except than one progressive multifocal encephalopathy (PML) case have been found. The main reasons of switching from Natalizumab to the other DMDs (Disease Modifying Drugs) were positive JC index, starting phase, noncompliance, pregnancy, MRI activity and seroconversion after starting the drug. **Conclusion:** Natalizumab is a safe and effective choice in RRMS patients for reducing relapse rate, disability score, active MRI lesion, and improving the NEDA (No evidence of disease activity).

Keywords: multiple sclerosis; disease modifying therapy; Natalizumab

ARTICLE INFO

Received: 30 December 2023

Accepted: 16 January 2024

Available online: 12 March 2024

COPYRIGHT

Copyright © 2024 by author(s).

Trends in Immunotherapy is published by EnPress Publisher, LLC. This work is licensed under the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

<https://creativecommons.org/licenses/by-nc/4.0/>

1. Introduction

Multiple sclerosis (MS) is a chronic neuroinflammatory, neurodegenerative disease which is seen in almost 36 per 100,000 population worldwide^[1]. MS is characterized by a progressive disability in affected individuals related to high relapse rate, and impressing the general health related quality of life^[2]. MS can be classified as two major forms: Relapsing-remitting MS (RRMS) which is the most frequent form and primary progressive MS (PPMS), which is characterized by more stable nature and steady progression^[3].

Treatment of RRMS is an important issue. By the approval of disease-modifying therapies (DMTs) since 1993 a revolution has been founded in alleviating the relapse rate and disability in MS patients^[4]. Now, more than twenty DMTs have been approved for treatment of MS^[5].

Natalizumab (Tysabri®, Biogen) is a monoclonal antibody against α4 integrin that was approved in 2004 and usually used for patients with relapsing remitting MS (RRMS) who failed to response to the first-line DMTs or for naïve patients with highly active RRMS^[6]. Because of high efficacy and favorable tolerability profile of Tysabri®, it has been used broadly by MS physicians, as both first-and second-line treatments^[7]. To date, several countries expressed the real-world effectiveness of Natalizumab but the data for Natalizumab is scarce in Asia and Iran. In Iran, because of limitation of MS centers and hesitancy in reimbursement of some DMTs, we could only prescribe Natalizumab in the recent years. In the current study, we aimed to assess the real-world effectiveness of Natalizumab in a referral center in Tehran, Iran.

2. Materials and methods

2.1. Study design

This retrospective study was conducted in a high-volume MS center in Iran to assess the real-world effectiveness of Natalizumab in patients with relapsing remitting multiple sclerosis (RRMS). We have reviewed all medical records from 2019 to 2021 related to patients who treated with Natalizumab for at least three to six months and more than three infusions. All of the patients had complete clinical, brain and spinal MRI and laboratory records including JCV index and COVID-19 data.

2.2. Data collection

We have collected data, including demographics, baseline clinical background of MS such as history of DMT consumption, causes of starting Natalizumab, numbers of Natalizumab infusion, and follow-ups after starting Natalizumab. In addition, clinical information such as EDSS score, relapse rate, JCV index, and brain and cervical MRI activity at the baseline (last one before starting Natalizumab) and after treatment (at the last follow-up) were also recorded. Considering pandemic issue related to corona virus disease 2019 (COVID-19), we also recorded the COVID-19 history in our patients. Furthermore, we have assessed no evidence of disease activity (NEDA-3: no relapse, no EDSS progression and no MRI activity) in our patients in order to find out the final outcome of Natalizumab treatment.

2.3. Statistical analysis

The statistical analysis in this study was conducted by Statistical Package for Social Science (IBM® SPSS® software) version 24. The Kolmogorov-Smirnov test was used to evaluate the normality distribution of data. Continuous data were reported as mean and standard deviation or medica and interquartile range (IQR) based on the normal distribution or non-normal distribution. The categorical variables reported as numerical and percentage data. The Chi-Square test was also used for categorical variables. In addition, in order to determine the annualized relapse rate, Poisson model was used. *P*-value less than 0.05 considered as significant.

2.4. Ethical consideration

According to the enactment of our national ethics committee (<https://ethics.research.ac.ir/>) this kind of studies do not need any ethical approval. Informed consent was filled by all patients before including the study. In addition, all authors assured that the patients' information will remain safe and protected. Furthermore, we used specific code instead of patients name for the statistical analysis. No further intervention was performed for the patients and only follow-ups of patients after the treatment were used for this study. Moreover, patients were not deprived of receiving routine treatment.

3. Results

3.1. Demographics and general information

We evaluated 100 cases (78% were females) treated with Natalizumab. The median follow-up of patients was 20 (6–33) months. The general baseline characteristics of the patients is presented in **Table 1**. The mean age was 36.54 ± 9.19 (range: 19–60) years old and the median duration of the disease was 84 months (range: 4–360, IQR: 60–136.5). Twenty-seven patients (27%) were naïve DMTs and in the others, Interferon-β1a was the commonly used drug before switching to Natalizumab which was followed by Glatiramer acetate, Fingolimod, and Interferon-beta-1b respectively.

Table 1. General characteristics of the patients* ($n = 100$).

Variable	Value
Age (year)	36.54 ± 9.19
Female (%)	78 (78)
Duration of MS (months)	84 (60–136.5)
Disease modifying drug (DMD) history (%)	
Naïve patients	27 (27)
Interferon beta-1a	23 (23)
Glatiramer acetate	16 (16)
Fingolimod	14 (14)
Interferon beta-1a	11 (11)
Teriflunomide	4 (4)
Dimethyl fumarate	4 (4)
Azathioprine	1 (1)
Causes of starting Natalizumab (%)	
Highly active MS (Naïve patients)	27 (27)
MS breakthrough	53 (53)
Side effect of previous drug	14 (14)
Noncompliance of DMD	6 (6)
Median number of Natalizumab infusion	14.5 (6, 24)
Extended infusion therapy	73 (73)
Median follow-up duration (months)	20 (6, 33)

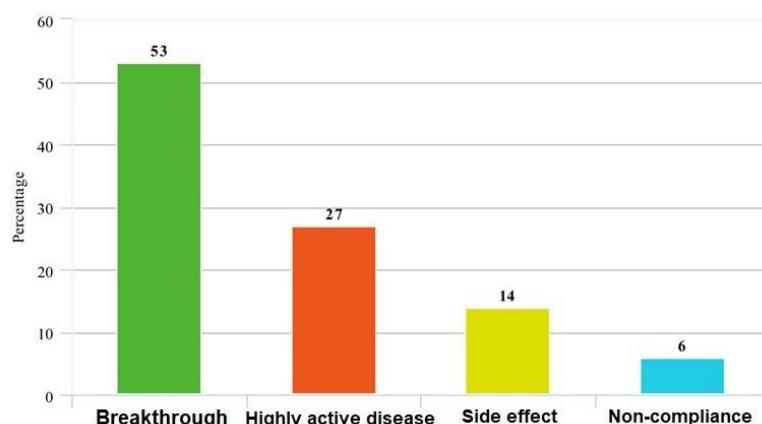


Figure 1. Causes for starting Natalizumab.

The causes for starting Natalizumab was highly active MS in 27 patients (27%), followed by MS breakthrough in 53 patients (53%), and side effects DMTs in 14 patients (14%) and finally, 6% noncompliance of previous DMTs. The causes for starting Natalizumab is presented in **Figure 1**. The median number of

Natalizumab infusion was 14.5 (IQR: 6, 24) with a range of 3–47 months. Furthermore, from all cases, 73 cases (73%) had extended interval infusion therapy. The median time for follow-up was 20 months (IQR: 6–33, range: 2–60 months).

3.2. Clinical information

3.2.1. EDSS score

The clinical characteristic of the patients is presented in **Table 2**. The median EDSS score of the patients at the baseline was 2.5 (range: 0–6, IQR: 2–3) which reached to 2 (range: 0–6.5, IQR: 1–3) after treating with Natalizumab ($P < 0.0001$). As shown in **Figure 2**, fifty-seven patients (57%) had EDSS < 3 and 43 patients (43%) had EDSS ≥ 3 at the baseline, while 69 patients (69%) had EDSS < 3 and 31 patients (31%) had EDSS ≥ 3 after the treatment with Natalizumab ($P = 0.04$). Based on EDSS, 14 patients deteriorated, 36 did not change and 50 cases improved (**Figure 3**).

Table 2. Clinical characteristics of patients ($n = 100$).

Variable	Baseline	After follow-up	P-value
EDSS score	2.5 (2, 3)	2 (1, 3)	< 0.0001 ^a
EDSS ≥ 3 (%)	43 (43)	31 (31)	0.04 ^b
Relapse rate	1 (1, 1)	0 (0, 0)	< 0.0001 ^a
Positive JC index (%)	36 (36)	39 (39)	0.84 ^b
JC index	0.85 (0.21–2.41)	0.85 (0.21–2.31)	0.51 ^a
Active MRI (%)	66 (66)	4 (4)	0.001 ^b
Having GAD lesion (%)	61 (61)	4 (4)	0.001 ^b
Having CUA lesion (%)	4 (4)	0 (0)	0.001 ^b
Median number of GAD lesion	3 (2–5)	2 (1–2)	< 0.0001 ^a
NEDA (%)	9 (9)	87 (87)	0.001 ^b

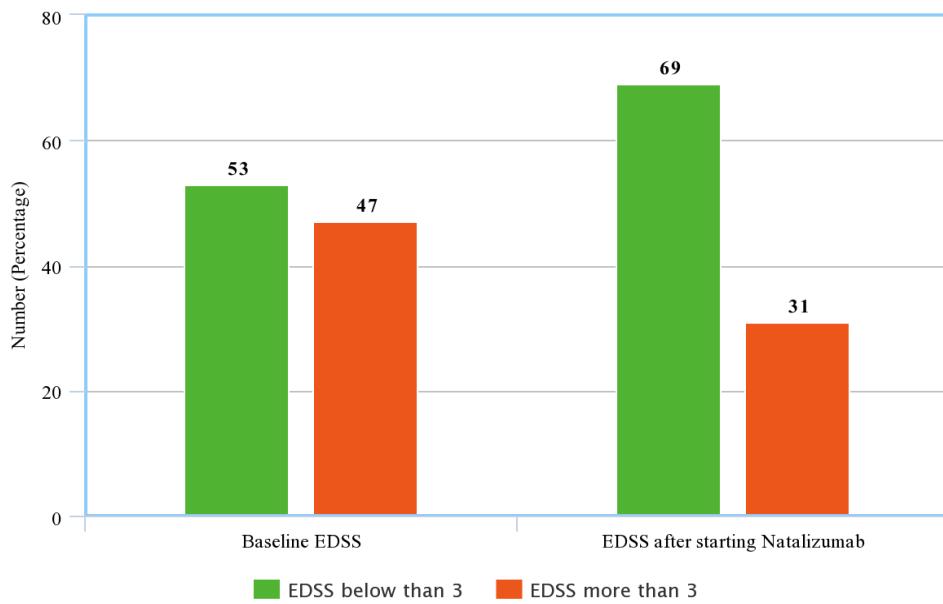


Figure 2. The prevalence of EDSS ≥ 3 and EDSS < 3 before and after Natalizumab therapy.

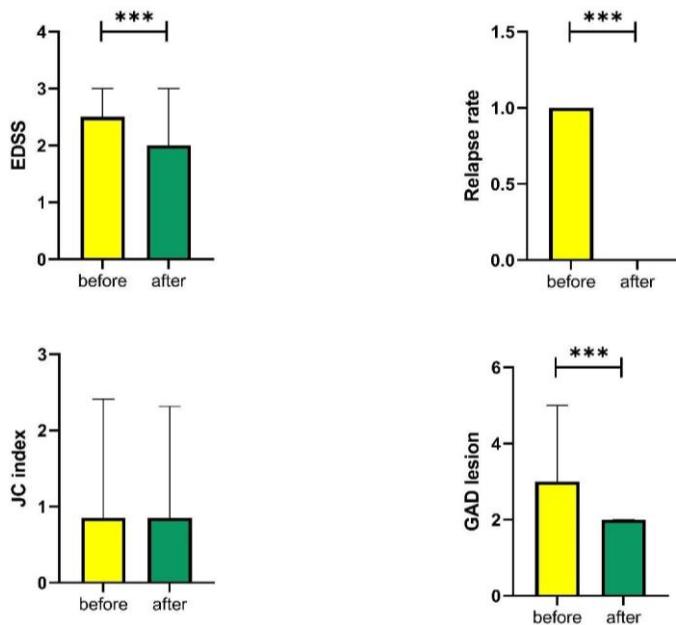


Figure 3. Clinical, MRI activity and JC index changes in patients after Natalizumab therapy.

3.2.2. Relapse rate

In the assessment of relapse rate before and after treating with Natalizumab, the median of annual relapse number before starting the treatment with Natalizumab was 1 (IQR: 1–1, range: 0–2) which decreased to 0 (IQR: 0–0, range: 0–1). The median number of relapses after treating with Natalizumab (0) was significantly lower than the baseline (1) ($P < 0.0001$) (Table 2). During the follow-up period, four relapses observed in 4 patients. All relapses happened between months 18 to 36 of follow-up period. Treatment was switched in 3 of these cases, but the fourth case continued the treatment. The proportion of patients free from relapse increased significantly from 22.5% (95% CI: 15.7%–32.3%) to 96% (95% CI, 92.4%–99.9%) after treating with Natalizumab (P value: 0.0001). In addition, the mean baseline annualized relapse ratio was 0.81 (95% CI: 0.73–0.87) which reached to 0.023 (95% CI 0.009–0.061) after the treatment with Natalizumab (Figure 3).

3.2.3. JCV index

The median of human polyomavirus JCV virus index was 0.85 (IQR: 0.21–2.41; range: 0.01–4.3) before starting the treatment with Natalizumab, and 36 patients (36%) were seropositive with high JCV index (> 1.5). After the treatment with Natalizumab, the median JCV index was 0.85 (IQR: 0.21–2.31; range: 0.01–4.3). There were not significant differences between the JCV index before and after the treatment with Natalizumab ($P = 0.51$); although, two seroconversions were occurred in patients (JCV index seropositive after treatment: 38) (Figure 3).

3.2.4. MRI activity

At the baseline, 66 patients (66%) had active brain MRI (GAD enhancing lesions) which reached to four patients (4%) after starting the Natalizumab ($P = 0.001$). the median number of these lesions was 3 (IQR: 2–5) which reached to 2 (IQR: 1–2) in the follow-up period ($P < 0.0001$). Also, four patients had combined unique active (CUA) lesion in the baseline brain MRI which reached to zero, after starting the Natalizumab ($P = 0.001$). No patients had new spinal cord MRI lesion after the treatment (Figure 3).

3.2.5. COVID-19 history

Ten patients (10%) had positive history of COVID-19 infection, which nine cases experienced mild COVID-19 infection (only mild symptoms without hospitalization) and one case had moderate infection with hospitalization. There were no cases of severe infection which need ICU admission or respiratory support. The likelihood of COVID-19 infection was not associated with baseline JCV index (OR: 0.932, 95% CI: 0.2–4.15,

P value: 0.92) > 15 infusion (OR: 0.3, 95% CI: 0.05–1.6, *P* value: 0.15), or extended interval therapy (OR: 0.000; *P* value: 0.998).

3.3. Final outcome

Overall, 86 patients (86%) had no increase in EDSS and 96 patients (96%) had no relapses. New brain or cervical MRI T2 lesions did not observe in patients and the rate of no evidence of disease activity for three years (NEDA-3) was improved from 9 (9%) to 87 (87%). Overall, 33 patients discontinued Natalizumab or switched from it. The reasons of switching Natalizumab to the other DMTs are shown in **Figures 4** and **5**.

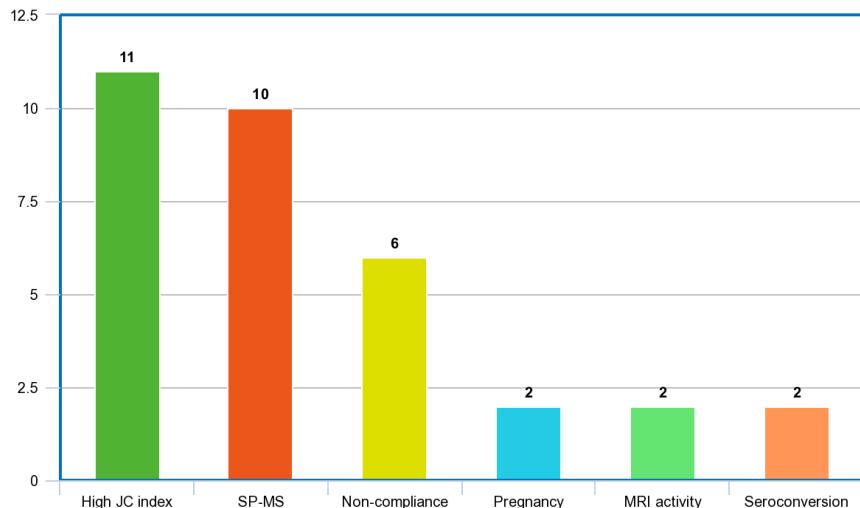


Figure 4. Cause of switch from Natalizumab.

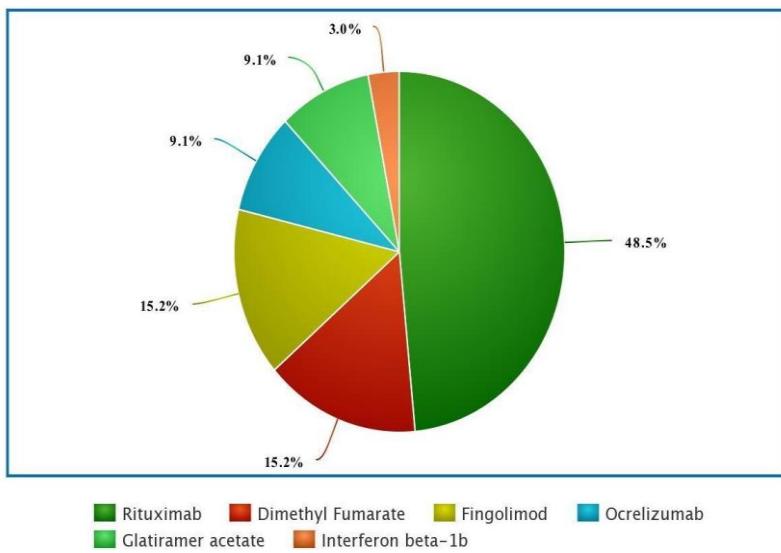


Figure 5. The prevalence of drug after switch from Natalizumab.

3.4. Adverse events

Only three patients had mild and moderate infusion reaction which resolved after one to two hours of infusion (**Table 3**). One patient had scattered urticaria in her extremities which resolved after three to four days. These adverse events revealed after the first infusion and did not repeat. One patient with JCV index: 1.85, after 12 infusions had aggravated limb and axial ataxia. Brain MRI showed bilateral brainstem and cerebellar hemispheres T2 signals associated with low diffusion in DWI (Diffusion Weighted Imaging). Localized posterior fossa PML (Progressive Multifocal Leukoencephalopathy) was highly suspected CSF (Cerebrospinal Fluid) examination confirmed JCV PCR (Polymerase Chain Reaction). Unfortunately, the patient has been missed to follow up. Also another patient with JCV index: 1.25, revealed new headache and

unilateral visual field defect, suspected to be PML. Fortunately, JCV PCR of CSF was negative and the MRI lesion in parietal occipital lobe decreased in size with corticosteroid pulse therapy and the patient has been switched to Rituximab due to diagnosis of tumefactive lesion and the patient is doing in a good condition at the time of this report.

Table 3. Adverse events after Natalizumab therapy.

Adverse Events	Number of patients
Mild to moderate injection reactions	N = 3
Severe injection reaction	N = 0
Any infection (UTI, ...)	N = 3
Liver enzyme abnormalities (nonsignificant AST & ALT \leq 3)	N = 2
Hematological abnormalities	N = 0
PML	N = 1 (confirmed) N = 1 (suspected, no confirmed)
Tumefactive lesion	N = 1
Relapse	N = 4
EDSS progression	N = 14
Wearing off symptom	N = 3
Death	N = 0

3.5. Extended interval

Overall, 73 patients had been infused as extended interval dosing. The median infusion number before starting EID (Extended Interval Dosing) was 8. We started EID slightly earlier than usual infusion numbers because of COVID-19 pandemic. Of 73 patients, 60 had 6 weeks EID and 13 patients had 8 weeks EID.

4. Discussion

In this study, we have assessed the real-world effectiveness of Natalizumab in RRMS patients. We observed that Natalizumab is effective in reducing EDSS, relapse rate, MRI activity, and NEDA, with good tolerance. In both naïve DMTs patients and patients with highly active MS, Natalizumab can be an effective choice for subsiding symptoms in patients. To the best of our knowledge, this is the first study in the Iranian population which assessed the effectiveness of Natalizumab in a real-world setting.

We observed a significant reduction in disability score and relapse rate after starting treatment with Natalizumab during a 20 months follow-up. Ninety-six (96%) patients experienced no relapse in their treatment course with Natalizumab. In fact, treating with Natalizumab significantly reduced the annualized relapse rate (ARR) in patients. Also, the disability score decreased significantly after treating with Natalizumab. In the study of Krysko et al. on 146 RRMS and active SPMS (Secondary Progressive Multiple Sclerosis) treated with Natalizumab in Canada, the ARR (Annualized Relapse Rate) decreased significantly in both SPMS and RRMS patients. Also, in RRMS patients, the median of EDSS decreased significantly after the treatment but there were no significant decreases in disability score in SPMS patients^[8]. In another study by Auer et al. in Austria on 235 patients treated with Natalizumab, the EDSS remained stable or decreased^[9]. In a real word study in India on 116 patients, the EDSS and relapse rate decreased significantly during a nine-year follow-up^[10]. In the study of Saida et al. in Japan on 106 patients with a two-year follow-up, the ARR significantly decrease by 72.9% in patients^[11]. In the study of Lublin et al., it was observed that Natalizumab not only effective in reducing relapse rate, but also can improve relapse recovery in MS patients^[12]. The results of mentioned studies are associated with the current study. These results make us possible to choose Natalizumab as an effective substitute in patients with highly active MS resistant to their previous treatment. Also, we started MS treatment

in 27% of patients with Natalizumab (naïve patients). Thus, Natalizumab can be used as a suitable choice for reducing disability and relapse rate not only for highly active patients, but also for naïve MS patients.

In this study, the MRI of treated patients significantly improved after treating with Natalizumab. The number of patients with active T2 MRI (Magnetic Resonance Imaging) lesion, GAD (Gadolinium) lesions, and overall CUA lesions reduced significantly in treated patients. In MS patients, MRI can be used for exploring disease activity, prognosis, and reflects the therapeutic response^[13]. Therefore, decrease in MRI active lesions may reflect the successes of treatment. In the study of Horakova et al. on 193 patients with RRMS treated with Natalizumab, almost 80% of patients after one year and almost 98% of patients after 2–5 years had no disease activity in their MRI^[14]. In the study of Boziki et al. on 138 patients whom 84 of them were under treatment with Natalizumab, the MRI activity was lower than patients who were under treatment with Fingolimod^[15]. Also, it was observed that discontinuing or switching Natalizumab may increase the risk of MRI lesions^[16]. Our results which are in line with previous results suggest the effectiveness of Natalizumab in revealing MRI activity in MS patients. Also we have no obvious MRI activity or rebound activity after switching of Natalizumab to the other DMTs during the follow up time.

Assessing the seropositivity of JCV index was another goal of this study. We observed no significant changes in JCV index before and after the treatment with Natalizumab; however, seroconversion was observed in two patients. Assessing the anti JCV index, indicative for risk stratification of Progressive multifocal leukoencephalopathy (PML), can help us to make decision about starting, continuing, or stopping treatment in MS patients^[17,18]. Natalizumab treatment is a known risk factor for JCV seropositive especially related to Natalizumab exposure to duration and time of administration^[19]. Therefore, high JCV index is an indication for Natalizumab cessation^[20]. In the context of JCV index, the results of this study were in association with previous studies. In a study in 2017, on 150 patients treated with Natalizumab and 145 controls, seroconversion was significantly higher in Natalizumab group and patients on natalizumab had a larger increase in JCV index during the treatment^[21]. In another multicentric study by Schwab et al. in Germany and French, 43 out of 339 German patients (12.7%) and 41 out of 243 French patients (16.9%) experienced the seroconversion^[22]. In other studies, by Plavina et al.^[23] and Warnke et al.^[24] seroconversion observed in 13% and 10.3% of Natalizumab treated patients. This issue can justify by peripheral accumulation of leucocytes, resulting in increased peripheral immune activity and decrease of gastrointestinal (GI) tract lymphocyte content, resulting in less GI immunity and predispose patient to higher risk of infection^[21].

Considering the pandemic situation due to COVID-19, we also evaluate the occurrence of COVID-19 in the studied patients. It was known that Natalizumab can inhibit the central nervous system (CNS) viral immunosurveillance and can cause PML^[25]. This risk can be decreased by extended infusion therapy, instead of single infusion therapy^[26]. In a study by Borriello et al. in 2020, a case of COVID-19 was observed in a patient under treating with Natalizumab^[27]; however, there was no serious complications for the patient. In the current study, prevalence of COVID-19 was 10% among the patients, which was similar to overall prevalence of COVID-19 in Iran^[28]. In addition, the likelihood of COVID-19 was not associated with JCV index, number of infusion and extended interval therapy. Moreover, just as the study of Borriello et al., the disease was mild in majority of cases without any serious complication^[27]. It seems that Natalizumab treatment in the COVID-19 era is safe, without serious concerns.

In the assessment of final outcome, we did not observe any complication related to Natalizumab safety except than one confirmed PML (0.01). Recent update in 2022 also confirm this issue^[29]. The prevalence of NEDA-3 was significantly improved in patients after starting the treatment with Natalizumab. Similar studies in different parts of the world are also addressed this issue. In a study by Jaklin et al. in 2021 in Norway on 66 patients, more than 50% of MS patients reached to NEDA-3 after starting the treatment with Natalizumab^[30]. In another study by Horakova et al. on 193 patients in Czech Republic During more than 50% of patients reached to NEDA-3 after one year treatment with Natalizumab and the prevalence of NEDA-3 increased to

almost 70%, during a 2-5 year period^[14]. In another multicenter study in Italy, Natalizumab had better effectiveness for reaching NEDA-3, in comparison to Fingolimod^[31]. In the study of Perumal et al. on 222 patients under treating with Natalizumab in USA, almost half of RRMS patients achieved NEDA during a two-year follow-up^[32]. Furthermore, in 33 patients of this study, we have switched the Natalizumab treatment to other DMTs. The major cause for switch from Natalizumab was attributable to high JCV index, associated with the risk of PML^[33]. In the context on switching from Natalizumab, Ocrelizumab^[34], Rituximab and Fingolimod^[35] can be administered. Thus, we have to consider these drugs for switching from Natalizumab, especially in patients with high risk of PML.

This study was the first real-world study for assessing the effectiveness of Natalizumab in the Iranian population, which was in association with Tysabri observational program (TOP)^[36]. We faced with some limitations for this study, first, this study was a single centric study, which conducted in a major referral center in the Capital of Iran. Although, we have considered the majority of patients, but selection bias can be possible. Also we did not have any power calculation for estimating the sample size. The second limitation was lack of a control population, which failed us to compare Natalizumab efficacy with other DMTs. It would be better for future studies to address these limitations, in order to have higher levels of evidence in regards to the Natalizumab treatment.

5. Conclusion

Natalizumab had significant effect on relapse rate, MRI activity and disability in our both highly active and breakthrough RRMS patients. In our study, administration of Natalizumab was associated with a significant achievement of NEDA-3 (87% in 20 months) with no major safety concerns. Developing PML which is the main cause for hesitation of using Natalizumab, can be addressed by selection of the proper cases and considering positive and high JCV index in patients.

Author contributions

Data extraction and drafting the manuscript, MAS and MS (Monireh Samimi); revising the manuscript, SK, MS (Mehri Salari), MG, SY and AN; final revision, MV and SMN. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Since our manuscript is a retrospective one, the patients just signed a comprehensive consent in which we promised not to disclose their personal data anywhere.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Conflict of interest

The authors declare no conflict of interest.

References

1. Ezabadi SG, Sahraian MA, Maroufi H, et al. Global assessment of characteristics of multiple sclerosis registries; A systematic review. *Multiple Sclerosis and Related Disorders*. 2022; 63: 103928. doi: 10.1016/j.msard.2022.103928
2. Killestein J, Wattjes MP. Low JC virus antibody index during natalizumab treatment less safe than assumed? *Multiple Sclerosis Journal*. 2015; 21(14): 1753-1754. doi: 10.1177/1352458515611499

3. Kheradmand M, Afshari M, Nasehi MM, et al. Prevalence of subtypes of multiple sclerosis and the most common clinical symptoms in Iranian patients: A meta-analysis. *Clinical and Experimental Neuroimmunology*. 2018; 10(1): 33-40. doi: 10.1111/cen.12489
4. Cohan SL, Hedin BA, Reder AT, et al. Interferons and Multiple Sclerosis: Lessons from 25 Years of Clinical and Real-World Experience with Intramuscular Interferon Beta-1a (Avonex). *CNS Drugs*. 2021; 35(7): 743-767. doi: 10.1007/s40263-021-00822-z
5. Tsivgoulis G, Katsanos AH, Grigoriadis N, et al. The Effect of Disease Modifying Therapies on Disease Progression in Patients with Relapsing-Remitting Multiple Sclerosis: A Systematic Review and Meta-Analysis. Linker RA, ed. *PLOS ONE*. 2015; 10(12): e0144538. doi: 10.1371/journal.pone.0144538
6. Ysraelit MC, Caride A, Sinay V, et al. Real-world effectiveness of natalizumab treatment in patients with relapsing multiple sclerosis in Argentina and Chile. *Arquivos de Neuro-Psiquiatria*. 2021; 79(5): 407-414. doi: 10.1590/0004-282x-amp-2020-0303
7. Brandstädter R, Katz Sand I. The use of natalizumab for multiple sclerosis. *Neuropsychiatric Disease and Treatment*. 2017; Volume 13: 1691-1702. doi: 10.2147/ndt.s114636
8. Krysko KM, O'Connor PW. The Toronto Observational Study of Natalizumab in Multiple Sclerosis. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*. 2011; 38(3): 422-428. doi: 10.1017/s0317167100011811
9. Auer M, Zinganell A, Hegen H, et al. Experiences in treatment of multiple sclerosis with natalizumab from a real-life cohort over 15 years. *Scientific Reports*. 2021; 11(1). doi: 10.1038/s41598-021-02665-6
10. Mathew T, Kamath V, John SK, et al. A real world multi center study on efficacy and safety of natalizumab in Indian patients with multiple sclerosis. *Multiple Sclerosis and Related Disorders*. 2022; 66: 104059. doi: 10.1016/j.msard.2022.104059
11. Saida T, Yokoyama K, Sato R, et al. Safety and Effectiveness of Natalizumab: First Report of Interim Results of Post-Marketing Surveillance in Japan. *Neurology and Therapy*. 2017; 6(2): 197-211. doi: 10.1007/s40120-017-0084-6
12. Lublin FD, Cutter G, Giovannoni G, et al. Natalizumab reduces relapse clinical severity and improves relapse recovery in MS. *Multiple Sclerosis and Related Disorders*. 2014; 3(6): 705-711. doi: 10.1016/j.msard.2014.08.005
13. Cohan S, Chen C, Baraban E, et al. MRI utility in the detection of disease activity in clinically stable patients with multiple sclerosis: a retrospective analysis of a community based cohort. *BMC Neurology*. 2016; 16(1). doi: 10.1186/s12883-016-0699-8
14. Horakova D, Uher T, Krasensky J, et al. Long-term effectiveness of natalizumab on MRI outcomes and no evidence of disease activity in relapsing-remitting multiple sclerosis patients treated in a Czech Republic real-world setting: A longitudinal, retrospective study. *Multiple Sclerosis and Related Disorders*. 2020; 46: 102543. doi: 10.1016/j.msard.2020.102543
15. Boziki M, Bakirtzis C, Giantzi V, et al. Long-Term Efficacy Outcomes of Natalizumab vs. Fingolimod in Patients With Highly Active Relapsing-Remitting Multiple Sclerosis: Real-World Data From a Multiple Sclerosis Reference Center. *Frontiers in Neurology*. 2021; 12. doi: 10.3389/fneur.2021.699844
16. Hersh CM, Harris H, Conway D, et al. Effect of switching from natalizumab to moderate- vs high-efficacy DMT in clinical practice. *Neurology Clinical Practice*. 2020; 10(6). doi: 10.1212/cpj.0000000000000809
17. Sá MJ, Nunes CC, da Silva AM, et al. JC virus antibodies in Portuguese multiple sclerosis patients: JUSTIFY study results. *Journal of the Neurological Sciences*. 2019; 406: 116426. doi: 10.1016/j.jns.2019.116426
18. Bozic C, Subramanyam M, Richman S, et al. Anti-JC virus (JCV) antibody prevalence in the JCV Epidemiology in MS (JEMS) trial. *European Journal of Neurology*. 2013; 21(2): 299-304. doi: 10.1111/ene.12304
19. Clerico M, Artusi C, Liberto A, et al. Natalizumab in Multiple Sclerosis: Long-Term Management. *International Journal of Molecular Sciences*. 2017; 18(5): 940. doi: 10.3390/ijms18050940
20. McGuigan C, Craner M, Guadagno J, et al. Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. *Journal of Neurology, Neurosurgery and Psychiatry*. 2016; 87(2): 117-125.
21. Peters J, Williamson E. Natalizumab therapy is associated with changes in serum JC virus antibody indices over time. *Journal of Neurology*. 2017; 264(12): 2409-2412. doi: 10.1007/s00415-017-8643-4
22. Schwab N, Schneider-Hohendorf T, Pignolet B, et al. Therapy with natalizumab is associated with high JCV seroconversion and rising JCV index values. *Neurology Neuroimmunology & Neuroinflammation*. 2016; 3(1). doi: 10.1212/nxi.0000000000000195
23. Plavina T, Subramanyam M, Bloomgren G, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. *Annals of Neurology*. 2014; 76(6): 802-812. doi: 10.1002/ana.24286
24. Warnke C, Ramanujam R, Plavina T, et al. Changes to anti-JCV antibody levels in a Swedish national MS cohort. *Journal of Neurology, Neurosurgery & Psychiatry*. 2013; 84(11): 1199-1205. doi: 10.1136/jnnp-2012-304332
25. Chalkley JJ, Berger JR. Progressive Multifocal Leukoencephalopathy in Multiple Sclerosis. *Current Neurology and Neuroscience Reports*. 2013; 13(12). doi: 10.1007/s11910-013-0408-6
26. Ryerson LZ, Foley J, Chang I, et al. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. *Neurology*. 2019; 93(15). doi: 10.1212/wnl.0000000000008243

27. Borriello G, Ianniello A. COVID-19 occurring during Natalizumab treatment: a case report in a patient with extended interval dosing approach. *Multiple Sclerosis and Related Disorders*. 2020; 41: 102165. doi: 10.1016/j.msard.2020.102165
28. Khalagi K, Gharibzadeh S, Khalili D, et al. Prevalence of COVID-19 in Iran: results of the first survey of the Iranian COVID-19 Serological Surveillance programme. *Clinical Microbiology and Infection*. 2021; 27(11): 1666-1671. doi: 10.1016/j.cmi.2021.06.002
29. Morrow SA, Clift F, Devonshire V, et al. Use of natalizumab in persons with multiple sclerosis: 2022 update. *Multiple Sclerosis and Related Disorders*. 2022; 65: 103995. doi: 10.1016/j.msard.2022.103995
30. Jaklin AK, Benjaminsen E, Alstadhaug KB. Effectiveness of Natalizumab in Achieving No Evidence of Disease Activity (NEDA-3)—Data From a Local Norwegian Cohort. *Frontiers in Neurology*. 2021; 12. doi: 10.3389/fneur.2021.765837
31. Prosperini L, Saccà F, Cordioli C, et al. Real-world effectiveness of natalizumab and fingolimod compared with self-injectable drugs in non-responders and in treatment-naïve patients with multiple sclerosis. *Journal of Neurology*. 2016; 264(2): 284-294. doi: 10.1007/s00415-016-8343-5
32. Perumal J, Fox RJ, Balabanov R, et al. Outcomes of natalizumab treatment within 3 years of relapsing-remitting multiple sclerosis diagnosis: a prespecified 2-year interim analysis of STRIVE. *BMC Neurology*. 2019; 19(1). doi: 10.1186/s12883-019-1337-z
33. Hartung HP, Mares J, Meuth SG, et al. Multiple Sclerosis: Switching from Natalizumab to Other High-Efficacy Treatments to Mitigate Progressive Multifocal Leukoencephalopathy Risk. *Neurotherapeutics*. 2021; 18(3): 1654-1656. doi: 10.1007/s13311-021-01102-w
34. van Lierop Z, Toorop A, Coerver E, et al. Ocrelizumab after natalizumab in JC-virus positive relapsing remitting multiple sclerosis patients. *Multiple Sclerosis Journal - Experimental, Translational and Clinical*. 2021; 7(2): 205521732110138. doi: 10.1177/20552173211013831
35. Alping P, Frisell T, Novakova L, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. *Annals of Neurology*. 2016; 79(6): 950-958. doi: 10.1002/ana.24651
36. Butzkueven H, Kappos L, Wiendl H, et al. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). *Journal of Neurology, Neurosurgery & Psychiatry*. 2020; 91(6): 660-668. doi: 10.1136/jnnp-2019-322326