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Role of Natalizumab in Relapsing-Remitting Multiple Sclerosis: A review.

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ABSTRACT:
Introduction: Multiple sclerosis is a non-traumatic neurological disease caused by an immune-mediated reaction leading to a chronic inflammatory demyelinating disorder of the central nervous system. The treatments for multiple sclerosis are mainly divided into three categories: treatment of exacerbation, slowing disease progression with disease-modifying therapies, and symptomatic therapies. Natalizumab is a monoclonal antibody that works by preventing the adhesion of lymphocytes into the endothelium of the blood-brain barrier, reducing lymphocyte infiltration into the central nervous system. This review aims to study the efficacy and safety of natalizumab in relapsing-remitting multiple sclerosis. **Methods:** The review was performed using databases like PubMed, Cochrane library, Google scholar from which 48 relevant articles were selected based on the various inclusion criteria. The following keywords were used: "Natalizumab", "Multiple sclerosis", "side effects", "Relapsing-remitting multiple sclerosis", "progressive multifocal leukoencephalopathy" in different combinations. **Results:** The literature review suggests that natalizumab reduces the rate of sustained progression of the disease and disability, and was associated with a lower relapse rate in patients with relapsing-remitting multiple sclerosis. However, Progressive multifocal leukoencephalopathy is one of the serious side effects of natalizumab. **Conclusion:** The literature review suggests that Natalizumab has favorable outcomes in patients with relapsing-remitting multiple sclerosis. Since progressive multifocal leukoencephalopathy is one of the serious side effects of natalizumab, risk stratification should be done.
Keywords: Relapsing-Remitting Multiple Sclerosis, Progressive multifocal leukoencephalopathy, Natalizumab.

Introduction:

Multiple sclerosis (MS) is an immune mediated chronic inflammatory demyelinating disorder of the central nervous system leading to damage of the axons and progressive neurodegeneration from the early stages. As of late, its incidence has been increasing worldwide. Looking at the United States Center for Disease Control and Prevention data, the prevalence of MS varies from 58 to 95 per 100,000 populations in the United States.[1] The cause of MS is not known, but it has been determined that genetic and environmental factors play a role in increasing an individual's risk. Although the symptoms vary in each individual, some of the common presenting symptoms are mononuclear painful loss of vision, hemiparesis, paresthesia, urinary incontinence, vertigo, ataxia, tremors, etc. MS has been divided into four different categories as per its presentation pattern which are Relapsing remitting Multiple Sclerosis (RRMS), Secondary progressive Multiple Sclerosis (SPMS), Primary progressive Multiple Sclerosis (PPMS), Progressive relapsing Multiple Sclerosis

(PRMS). RRMS is defined as an episode where there is worsening of the neurological function with total or partial recovery and no apparent progression of the disease.

The treatments for MS are mainly divided into three categories: treatment of exacerbation, slowing disease progression with disease-modifying therapies, and symptomatic therapies. Currently, more than a dozen disease-modifying therapies have been approved for the treatment of MS mostly for RRMS. Natalizumab (NTZ) is a monoclonal antibody that belongs to disease-modifying therapy and works by preventing the adhesion of lymphocytes into the endothelium of the blood-brain barrier, reducing lymphocyte infiltration into the central nervous system.[2]

Since the approval of NTZ by the FDA in 2004, it has shown to be effective in the treatment of MS but with the increased risk for progressive multifocal leukoencephalopathy (PML). After three incidences of PML, NTZ was temporarily withdrawn from the market. However, due to its efficacy, NTZ was again reinstated in 2006 for the treatment of MS.[3] Presently, the global incidence for PML in NTZ-treated patients is 4.08 per 1000.[4]

The main objectives of this review article are to elucidate the effectiveness of NTZ in the treatment of RRMS, to review the association between MS and PML, and to determine the immunological and hematological changes after treatment with NTZ in patients with MS.

Methods:

Electronic source and search:

An electronic search of literature published in English was carried out using PubMed, Cochrane Library, and Google Scholar. The search was done using the keywords like "Natalizumab", "Multiple sclerosis", "side effects", "relapsing-remitting multiple sclerosis", "progressive multifocal leukoencephalopathy" in different combinations. The inclusion criteria for the articles in this review were articles based on human studies, ease of accessibility of the article, published in English literature within the year 2005-2020, and adults of age more than 18 having MS.

Results:

Initially, 65 original articles were selected from the search based on the inclusion criteria out of which five articles were duplicates. After removing the duplicates, 60 articles were assessed by full-text review out of which 48 articles were found relevant and those 48 articles were used for research.

Discussion:

Role of Natalizumab in Relapsing-Remitting Multiple Sclerosis

NTZ consists of neutralizing humanized monoclonal antibodies against leukocyte integrin which suppresses the entry of leukocytes in the central nervous system by blocking leukocyte integrin. For those patients who have RRMS, there are several treatment options including corticosteroids, immunosuppressive therapies, and NTZ.

Nine hundred and forty-two patients in a two-year phase three clinical trial evaluating the efficacy and safety of NTZ in RRMS (AFFIRM) were randomly assigned out of which 627 received NTZ and 315 patients received placebo every four weeks for two years. Natalizumab reduced sustained progression of disability by 42% over the two years ($p < 0.001$). The cumulative probability of progression was 17% in the NTZ group compared to 29% in the placebo group. Furthermore, NTZ reduced the rate of relapse by 68% in the first year and led to an 83% reduction in the accumulation of new or enlarging hyperintense lesions in T2 MRI over two years. There

were 92% fewer lesions in the NTZ treated patients as compared to patients receiving placebo.[5]

In the SENTINEL trial (The Safety and Efficacy of NTZ in Combination with Interferon Beta-1a in Patients with RRMS), 1171 patients with RRMS having relapses of the disease in the past year were randomly allocated into two groups. Patients either received treatment with interferon-beta and NTZ or with interferon beta and placebo. Sustained disease progression was present in 29% of the patients in the placebo group as compared to 23% of patients in the combination group (24% relative risk reduction, p=0.002).[6]

Buetzkueven et al. evaluated the long-term efficacy and safety of NTZ in 4821 patients with RRMS. The mean annualized relapse rate decreased from 1.99 in the 12 months prior to the baseline to 0.31 after NTZ therapy ($p<0.0001$) remaining low even after five years. A lower annualized relapse rate was observed in patients who used NTZ as a first therapy for MS.[7]

In a systematic review and meta-analysis by Prosperini et al, post-NTZ disease reactivation in RRMS was studied. 35 articles were included in the study. Clinical relapses were seen in 9-80% of the patients and 7-87% of patients revealed the radiological evidence of disease activity starting after six weeks of discontinuation of NTZ. The meta-analysis of six articles including 1183 patients showed younger age at the onset of disease, presence of disease activity in MRI before the start of treatment, and fewer NTZ infusions were associated with an increased risk of post-NTZ disease reactivation ($p<0.05$).[8]

A systematic review by Pucci et al. studied the efficacy, safety, and tolerability of NTZ in RRMS. The study showed statistically significant evidence in the favour of NTZ for both the primary and secondary outcomes. A 40% reduction in the risk of experiencing at least one exacerbation at two years and a 25% reduction in experiencing progression as compared to the control group was found. In addition, MRI parameters showed favorable outcomes for NTZ.[9]

In a systematic review and meta-analysis by Tsivgoulis et al, the efficacy of NTZ was compared to fingolimod (FGD) in patients with RRMS. NTZ was associated with a greater reduction in a two-year annualized relapse rate as compared to FGD. When comparing the proportions of the patients who remained relapse-free and those with disability progression at two years, no significant differences were found between both therapies.[10]

A study by Havla et al. recurrence of disease activity after the discontinuation of NTZ was studied in 13 patients who either did not receive disease-modifying therapy or received treatment with glatiramer acetate. It was observed that recurrence of the disease activity was found in both groups after NTZ cessation. One of the patients who had glatiramer and three patients who did not receive disease-modifying therapy had a relapse of disease. Patients with relapse had higher disease activity before the initiation of NTZ as compared to patients who did not have relapse of disease.[11]

In a retrospective observational study of 146 patients by Krysko et al. 72% of the patients had RRMS and the remaining 28% had SPMS. Comparison of annualized relapse rate (ARR) and expanded disability status scale were done (EDSS) between RRMS and secondary progressive MS (SPMS). There was a 76% reduction in ARR in RRMS patients as compared to a 68% reduction in SPMS patients. Although there was an 11% reduction in EDSS in RRMS patients, there were no significant changes in EDSS in SPMS patients.[12]

In a study by Sargento-Freitas et al. 48 patients with MS who were treated with NTZ for at least 12 months were included. The variables with optimal response were an

age of 37.5 years or less at the first administration of NTZ, a baseline EDSS score of 4.5 or less, disease duration of 9.5 years or less, progressive-phase duration of 9.5 years or less in patients with SPMS and ARR in the previous year of at least two. Responsiveness to treatment with NTZ was not associated with characteristics of the disease at the onset indicating that patients with highly active disease and low disability were ideal candidates for NTZ treatment.[13]

Results of the various studies showed NTZ to be effective for RRMS by reducing the rate of sustained progression of the disease and the rate of clinical relapse.[7,9] The effect of NTZ on reducing the ARR and EDSS progression was further highlighted by the study done by Butzkueven where treatment with NTZ was associated with a lower relapse rate and it helped to stabilize disability levels in patients with RRM.[7] Some patients experience disease reactivation post-NTZ treatment. A study done by Prosperini et al. showed younger age at the onset of disease and the presence of disease activity in MRI before the treatment with NTZ was associated with disease reactivation.[8] However, the lower age of the onset of disease, and limited disability were considered to be favorable outcomes by Sargento-Freitas et al.[13] FDA has approved various drugs for the treatment of RRMS.[14] Interferon and Glatiramer Acetate are present in the injectable forms and Fingolimod are therapeutic options available in oral form. In addition, various immunotherapies such as Alemtuzumab and Rituximab are available in the infusion forms. Tsivgoulis et al showed that in terms of indirect analysis of RCT data, NTZ might be more effective than oral Fingolimod in reducing disease activity in patients with RRMS.[10] Discontinuation of NTZ might be associated with disease reactivation which was further highlighted by Havla et al and thus patients require treatment with other available options after discontinuation of NTZ.[11] Diseases like MS can affect the quality of life, however, studies by Krysko et al showed NTZ can have beneficial outcomes to improve quality of life in patients with MS in addition to the reduction of relapse rate and stabilization of EDDS.[12] Table number one (1) shows various studies that revealed an association between NTZ and RRMS.

Safety of Natalizumab in Multiple sclerosis:

1. Progressive Multifocal Leukoencephalopathy (PML)

The major concern about the use of NTZ is PML. It is a rare but severe opportunistic brain infection of the brain caused by the reactivation of a polyomavirus, the John Cunningham (JC) virus. The virus is present latent in about 50-70% of the population, mostly in the kidneys. The major risk factors for PML on NTZ therapy are anti-JCV positive status, prior immunosuppressant use, and duration of NTZ therapy.[15] The clinical features of a classic PML include altered mental status, motor deficits (hemiparesis or monoparesis), limb ataxia, gait ataxia, and visual symptoms such as hemianopia and diplopia. It may be asymptomatic in an earlier stage and symptoms may vary from patient to patient depending upon the location of the lesion in the brain; it typically spares the optic nerve and the spinal cord. The MRI classically shows hyper-intense lesions in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images with hypointensity seen on T1-weighted images. Although contrast enhancement has been reported in about 40% of cases of NTZ-associated PML, the PML lesions typically do not show contrast enhancement.[16,17] Lesions are often multifocal and are present in frontal and parieto-occipital regions of the brain, but solitary lesions can be found anywhere in the brain. The diagnosis of PML is made based on history, imaging, and polymerase chain reaction (PCR) testing of cerebrospinal fluid (CSF). PML has a very bad prognosis with a high fatality

rate. The factors associated with improved survival are younger age, lower viral load, and more localized brain involvement, while old age and higher viral load are associated with poor survival.[2] Early detections of PML with MRI monitoring prior to the onset of symptoms have been associated with good prognosis and outcome compared with PML diagnosed after symptom onset.[18]

The SENTINEL study was halted one month early on February 28, 2005, due to reports of PML in NTZ-treated patients. One of these patients was enrolled in SENTINEL and another was participating in an open-label safety study of NTZ and IFN beta-1a after completing SENTINEL. A third PML patient was discovered after postmortem analysis of a NTZ-treated patient with Crohn's disease who had mistakenly received a diagnosis of astrocytoma. SENTINEL study was suspended and the drug was also temporarily removed from the market. A global risk-management program was then created to develop a risk stratification paradigm for PML.[6]

The Tysabri Global Observational Program in Safety (TYGRIS) study is a large post-marketing observational study.[19] The study prospectively followed 4938 patients with MS to determine the rate of serious adverse events. In the study, PML was seen in three out of 2207 US patients and 41 out of 4227 European/Canadian patients. In 23 out of total PML cases, anti-JCV antibody status was positive for six or more months prior to PML diagnosis.[20,21] The antibody status in the other 21 cases was unknown or not reported. Serious opportunistic infections such as tuberculosis, candida pneumonia, aspergillosis, atypical mycobacterial infection, cryptococcal infection, and herpetic meningoencephalitis were seen in 11/6434 patients. There were 77 deaths reported, 94.8% of deaths were considered not related or unlikely to be due to NTZ.[20]

The Tysabri Observational Programme (TOP), is a 10 year (2007-2017) long open-label multinational prospective observational study evaluating the long-term safety and effectiveness of Natalizumab in RRMS. The study included 6148 patients, out of which 829 patients (13.5%) experienced one or more serious events, with infection being the most common (4.1%). In the entire cohort, 53 patients (0.9%) had confirmed PML. PML patients received a median of 42 doses or months of exposure (range 11–124); 36 of 53 PML cases (67.9%) occurred in patients receiving NTZ for more than three years. The overall PML incidence rate per 1000 patient-years was 2.034 (95% CI 1.554 to 2.662). Prior immunosuppressant use was reported by 14 PML patients (26.4%). Of the 36 PML cases with reported anti-JCV antibody serostatus available six months prior to PML development, 35 (97.2%) were confirmed positive.[22]

A review study was carried out in 2012 to study the relationship between NTZ and PML according to the anti-JC virus positivity status, prior use of immunosuppressants, and the duration of the NTZ therapy. In the study, 99,571 patients were treated with NTZ out of which there were 212 confirmed cases of PML (2.1/1000 patients). In 54 patients with PML for whom samples were available before the diagnosis were positive for anti–JC virus antibodies. The risk of PML was stratified according to three risk factors; the risk of PML was lowest among the patients who were negative for anti–JC virus antibodies, with the incidence estimated to be ≤0.09/1000 patients (95% CI, 0-0.48). Patients who were positive for anti–JC virus antibodies, had taken immunosuppressant's before the initiation of NTZ therapy, and had received 25 to 48 months of NTZ treatment had the highest estimated risk (incidence, 11.1 cases/1000 patients ,95% CI, 8.3 to 14.5).[23]

Table 1: Overview of studies showing results of various studies that demonstrate better clinical outcomes in patients with RRMS after treatment with NTZ.

Reference	Study Design	Aim of the study	Sample size	Results
Butzkueven et al. 2013	Open-label, multinational, 10-year prospective study	To evaluate the long-term safety of NTZ and its impact on annualized relapse rate and Expanded Disability Status Scale progression in RRMS	4821 patients were enrolled	NTZ is associated with lower rate of relapse and stabilized disability levels in patient with RRMS
Prosperini et al. 2019	Systematic review and meta-analysis	To identify which patients will experience post-NTZ disease reactivation	35 articles were included in the systematic review and six articles were used in the meta-analysis.	Younger age of the onset, presence of disease activity in MRI before the start of treatment, and fewer NTZ infusions were associated with an increased risk of post-NTZ disease reactivation
Pucci et al., 2011	Systematic review	To study the efficacy, safety, and tolerability of NTZ in RRMS.	One placebo-controlled trial and two add-on placebo-controlled trial	A reduction in relapses and disability at Two years in RRMS patients treated with NTZ
Tsivgoulis et al., 2016	Systematic review and meta-analysis	To compare the efficacy of NTZ with fingolimod in patients with RRMS.	Three Randomized Controlled trials (2498 patients) and five observational studies (2576 patients).	Indirect analyses of RCT data and head-to-head comparisons of observational findings indicate that NTZ may be more effective than FGD in terms of disease activity reduction in patients with RRMS.
Havla et al.	Prospective study	To study the recurrence of disease activity after the discontinuation of NTZ.	Thirteen patients who stopped NZ and either did not receive any disease-modifying therapy (Six patients) or received glatiramer (Seven patients)	Discontinuation of NTZ was associated with the reappearance of disease activity and thus necessitating further treatment.
Krysko et al.	Retrospective observational study	To study the efficacy and safety of NTZ	146 patients out of which 72% had RRMS and 28% had SPMS	Reduction in relapse rate, stabilization in EDSS and improvement in quality of life with NTZ.
Sargento-Freitas et al.	Retrospective study	To identify and quantify clinical predictors of an optimal response to NTZ.	48 patients with MS	Lower age of the onset of disease and limited disability were associated with favorable outcomes.

Incidence of PML stratified according to the risk factors. Estimates of the incidence of PML are shown, stratified according to prior or no prior use of immunosuppressant's and duration of NTZ treatment (Figure 1) and according to positive or negative status for anti–JC virus antibodies, prior or no prior use of immunosuppressant's, and duration of NTZ treatment (Figure 2).

If the patient on NTZ becomes anti- JCV positive or has a rising antibody index, then both the clinician and the patient must jointly discuss the risk versus benefit of continuing NTZ therapy. Switching to alternate disease-modifying therapy carries the risk of worsening of symptoms and disability progression. The patient must understand the full consequences of the risk of PML, including the death versus the risk of worsening, and progression of disability.[24]

An observational cohort study carried out by Foley et al studied the pharmacokinetic and pharmacodynamics parameters of standard interval dosing (SID) and extended interval dosing (EID) of NTZ. Results showed lower serum concentration for EID as compared to SID (18.2 versus 35.7 μg/ml, respectively; $p < 0.001$). The occupancy of α4-integrin receptor sites was more with SID than EID. Furthermore, the α4-integrin cell surface expression was higher for EID than SID.[25] In a retrospective cohort study by Ryerson et al, included anti-JC virus antibody-positive patients (n = 35,521). The risk of PML with NTZ in patients with MS was compared between EID and SID. Relative risk reductions were 94% and 88% in favor of EID for the primary and secondary analyses, respectively. The tertiary analysis showed no cases of PML.[26] In another retrospective study by Ryerson et al the clinical effectiveness was similar in EID and SID group but four patients in the SID cohort reported having PML as compared to none in the EID group.[27]

Results from the study of Foley et al showed that EID of NTZ reduces the serum drug levels, the occupancy of α4-integrin receptor sites but increases the α4-integrin cell surface expression. The increase in the number of open α4-integrin might enhance immune surveillance and prevention of PML. Association between the clinical and statistical reduction in the risk of PML with EID of NTZ was shown by the study done by Ryerson et al. In addition, another retrospective study of Ryerson et al demonstrated that EID reduced the risk of PML without diminishing the clinical efficacy of NTZ in patients with MS.

2. Other side-effects:

The most frequent side effects reported in NTZ-treated MS patients include headache, urinary tract infection(UTI), lung infection, myalgia, vaginitis, abdominal pain, arthralgia, depression, diarrhea, rash, and nausea, though all these symptoms also occurred at a similar rate in placebo-treated patients. Fatigue and allergic reaction were seen more frequently in NTZ-treated patients compared to placebo. Hepatotoxicity with occasional hepatic failure has also been reported with NTZ.[2]

Immunological and hematological changes after treatment with Natalizumab in patients with multiple sclerosis:

NTZ treatment in MS can bring certain immunological changes, can also bring variation in serum and CSF cytokines level, and may affect activation of the T-cell. Villar et al studied the cell subsets and molecules that changed in patients in MS with an optimal response to treatment. Study of intrathecal immunoglobulin synthesis and cerebrospinal fluid lymphocyte subsets in patients with MS before and one year after treatment with NTZ was done. All patients showed a decrease in cerebrospinal fluid CD4+ cells after NTZ treatment

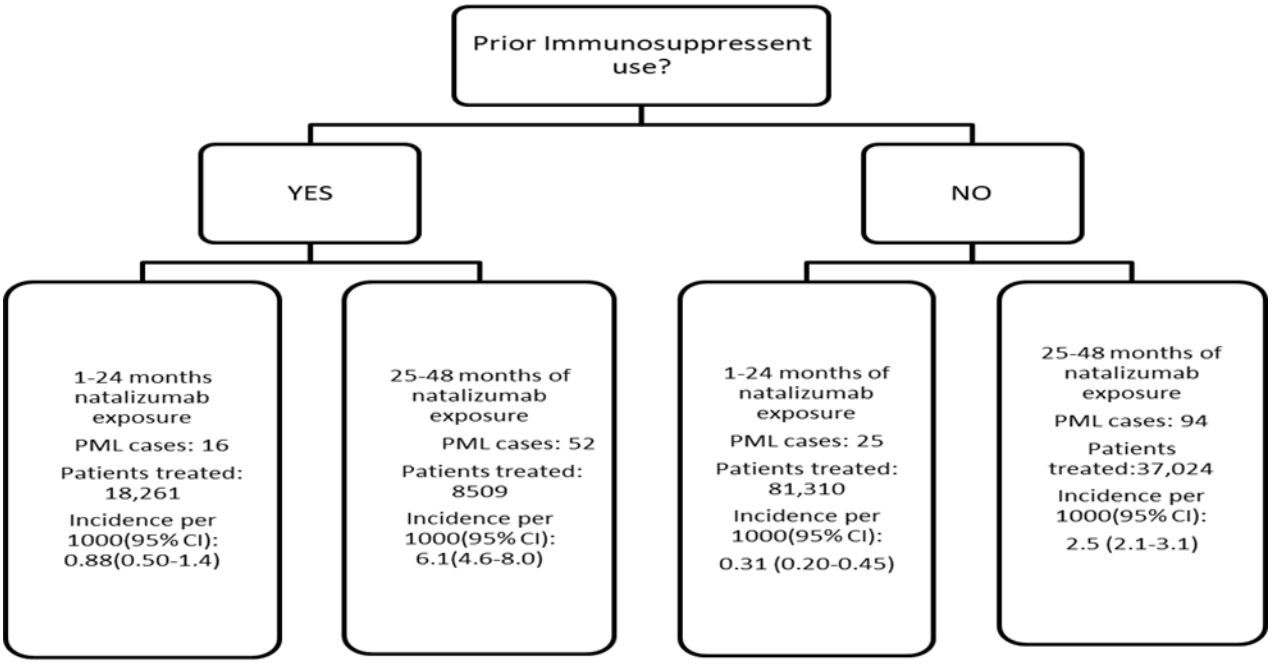

Figure 1: Estimates of the incidence of PML are shown, stratified according to prior or no prior use of immunosuppressant and duration of NTZ treatment

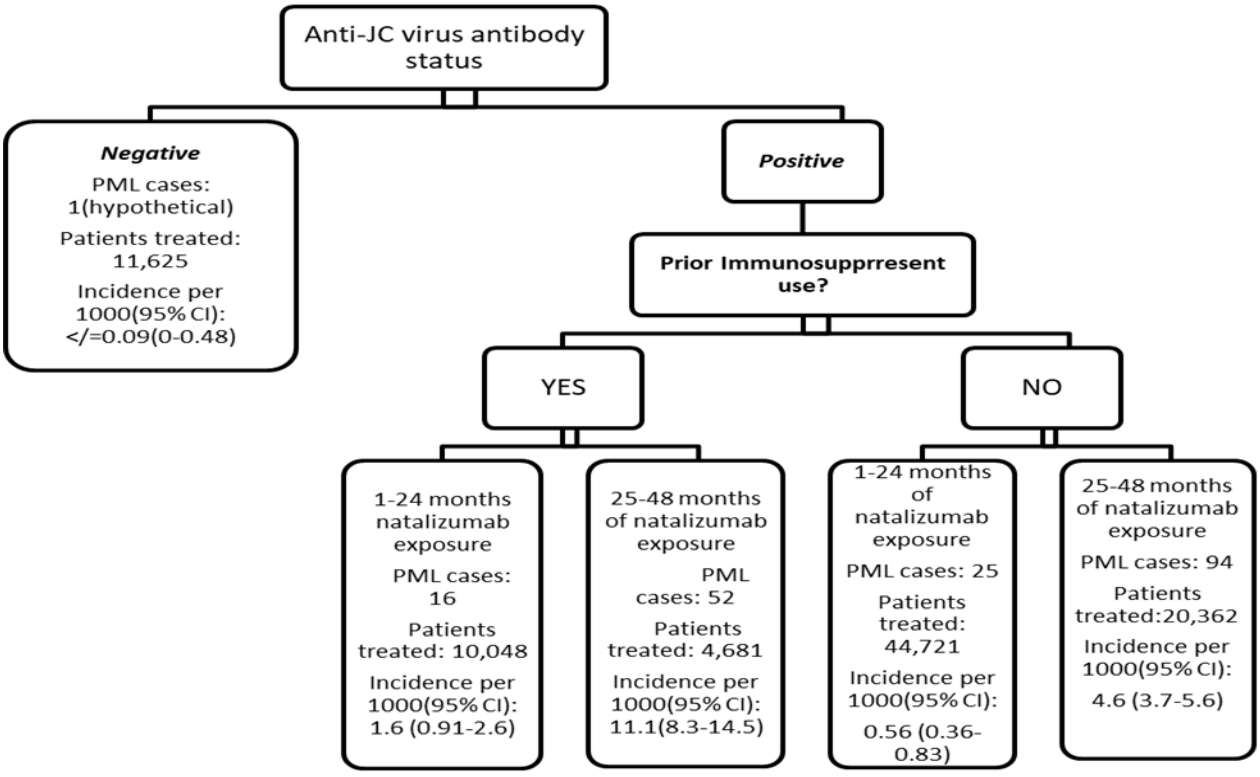

Figure 2:: Estimates of the incidence of PML are shown, stratified according to positive or negative status with respect to anti–JC virus antibodies, prior or no prior use of immunosuppressant, and duration of NTZ treatment

regardless of treatment response. However, only patients who were free of disease showed a decrease in local IgM and IgG synthesis. Lower percentages of B cells, particularly of CD5+ were noted in those patients.[28] Hematopoietic mobilizations after treatment with NTZ were studied by Mattoscio et al. in a prospective study where an increased number of circulating hematopoietic stem and progenitor cells was induced by NTZ. NTZ-induced hematopoietic cells were quiescent suggesting recent migration from the bone marrow. However, in patients where there was no significant mobilization of hematopoietic stem and progenitor cells, there was the persistence of disease activity and thus adding immunological and clinical relevance of mobilization.[29] In a study by Skarica et al. hematological and immunological changes in 26 RRMS patients with MS were studied over 12 months. The proportions of NK cells and hematopoietic stem cells increased after NTZ treatment. Although the numbers of CD20+ B cells were increased, the proportion of CD20+ cells expressing high levels of α4β1 integrin was decreased.[30]

A study by Mattoscio et al showed that hematopoietic stem and progenitor cell mobilization is associated with remission of the disease and early hematopoietic stem and progenitor cell counts could be a biomarker predicting the responsiveness to NTZ.[29] Studies suggested that NTZ decreases the number of lymphocytes in the CSF further emphasizing the concept that NTZ works by blocking the entry of lymphocytes into the central nervous system. Furthermore, inhibition of intrathecal synthesis of antibodies was associated with favorable clinical outcomes after treatment with NTZ as per the study done by Villar et al.[28]

Conclusions: The literature review suggested that NTZ has favorable outcomes in patients with MS. NTZ reduced the rate of sustained progression of the disease and disability, and was associated with a lower relapse rate in patients with relapsing-remitting multiple sclerosis. NTZ reduced the CSF lymphocytes count suggesting that it works by blocking the entry of lymphocytes into the central nervous system. The risk associated with NTZ therapy has also been identified, PML is the most important side effect; the risk stratification of PML with anti-JCV antibody status with index testing is a key component to guide the health care provider. Although studies suggested that NTZ was associated with better clinical outcomes in patients with MS, further studies are required to compare the long-term efficacy and safety of NTZ with newer immunomodulatory drugs.

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