

Systematic Review and Meta-Analysis Comparing the Safety of Natalizumab, Ocrelizumab, and Alemtuzumab in Treating Relapsing–Remitting, Primary Progressive, and Secondary Progressive Multiple Sclerosis

Journal of Pharmacology and
Pharmacotherapeutics
13(1) 14–23, 2022
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DOI: 10.1177/0976500X221080225
journals.sagepub.com/home/pha

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Abstract

Three monoclonal antibodies—natalizumab (NTZ), ocrelizumab (OCR), and alemtuzumab (ALM)—are the mainstays for the treatment of both relapsing and progressive forms of multiple sclerosis (MS). Here, their safety in patients with MS is analyzed and compared for rational use, especially during the COVID-19 pandemic. All clinical studies published between 2016 and 2020 with the primary outcome of the occurrence of adverse events (AEs) with the use of NTZ, OCR, and ALM in the treatment of MS were systematically searched in the PubMed database. In this review, the percentage of patients reporting AEs was calculated and compared. The most common AEs associated with the use of NTZ, OCR, and ALM were infection and infestation. The percentage of patients reporting urinary tract infection, upper respiratory tract infection, and herpes was 16% using natalizumab, 7% using natalizumab and ocrelizumab, and 2% with ocrelizumab, respectively. The most common AEs, such as rashes, pyrexia, and influenza, were reported with ocrelizumab and alemtuzumab. Additionally, alemtuzumab was associated with immune thrombocytopenia (2%), respiratory infections (7%), and thyroid dysfunction (43%). All these data outcomes show that of the three monoclonal antibodies, natalizumab and ocrelizumab were associated with a reduced incidence of adverse events, making them a safer choice for MS.

Keywords

Adverse event, Multiple sclerosis, Monoclonal antibody, Safety

Received 29 September 2021; accepted 13 December 2021

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease affecting both brain and spinal cord. It is mainly an inflammatory autoimmune disorder mediated by stimulation and activation of circulating T-cell lymphocytes in the peripheral blood.¹ It affects more than 2.5 million people worldwide.² In India, its approximate rate of prevalence stands at 0.17 to 1.33 per 100,000 population.^{3,4} Based on evidence-based treatment algorithms and the management guidelines from American Academy of Neurology (AAN) and The European Committee for Treatment and Research in Multiple Sclerosis/ European Academy of Neurology (ECTRIMS/ EAN), the pharmacotherapy of MS includes corticosteroids (methylprednisolone) and other disease-modifying treatments, such as interferons, glatiramer acetate, fingolimod,

teriflunomide, dimethyl fumarate, and mitoxantrone.⁵ However, these treatment selections have limited efficacy against relapsing remitting multiple sclerosis (RRMS) or primary progressive multiple sclerosis (PPMS) and lack target

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specificity. Their safety profile has severe shortcomings as they can induce the formation of neutralizing antibodies, neuroinflammation, myelotoxicity, gastrointestinal AE, and even sustained lymphopenia.⁶ In recent developments, monoclonal antibodies, such as natalizumab (NTZ, 2004), alemtuzumab (ALM, 2014), ocrelizumab (OCR, 2017), have been approved by the US-FDA for RRMS and PPMS as they are highly specific and reduce the chances of drug interactions.⁷

Natalizumab, approved for RRMS, is a fully humanized IgG1 that inhibits the transport of lymphocytes across the blood–brain barrier. The recommended dose is 300 mg, iv, every four weeks. Alemtuzumab, another humanized IgG, provokes cell-mediated lysis and rapid depletion of cluster of differentiation 4 (CD4), cluster of differentiation 8 (CD8) B, and natural killer (NK) cells. It is indicated for the treatment of RRMS and PPMS. The treatment is initiated with 12 mg/day $\times$ 5 days, followed by 12 mg/day $\times$ 3 days, after an interval of 12 months, and finally, 12 mg/day $\times$ 3 days. Ocrelizumab is a CD20-directed cytolytic antibody, which causes immunosuppression. It is approved for RRMS and PPMS. The treatment includes 300 mg, iv, followed by 300 mg, iv, after two weeks, and single dose of 600 mg, iv, every six months, thereafter.

The present pandemic due to the SARS-CoV-2 virus has globally caused an additional challenge in the management of autoimmune diseases including MS. These patients are prone to changes in the immune system, which may make them more vulnerable to viral infections and need to be closely monitored for treatment outcomes and safety.⁸

TNF- α , interleukin (IL)-2R, and IL-6 are all elevated in COVID-19 patients, but lymphocyte subsets, including B cells, T cells, and natural killer cells, are low. The severity of the disease is worsened by an increase in inflammatory cytokines and a reduction in cell numbers. As a result, it is critical to examine the risk-to-benefit ratio of the monoclonal antibodies in order to rationally design a therapeutic regimen in the light of COVID-19.

Against this backdrop, the use of monoclonal antibodies has emerged as a novel strategy in the management of MS.

However, they can be judiciously employed as an evidence-based clinical choice in light of the accurate assessment of their safety, tolerability, and efficacy. In the present study, the available data have been systematically reviewed and analyzed to assess their safety in the treatment of MS.

Methodology

Literature Search

A systematic study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. The PubMed database was searched on January 29, 2021, with limits applied for Title/Abstract fields and period (2016–2020). The search terms included “Pharmacovigilance” OR “safety” AND “multiple sclerosis” AND “Natalizumab” OR “Ocrelizumab” OR “Alemtuzumab.”

Inclusion Criteria: (a) All papers including accepted manuscripts relevant to clinical studies, clinical trials, and observational studies on the use of NTZ, OCR, and ALM in the treatment of multiple sclerosis. (b) All types and subtypes of MS were selected. (c) Search options were kept limited only through “PubMed” database. (d) The period selected for the collection of published reports was from January 1, 2016, to December 31, 2020.

Exclusion Criteria: (a) Published reports of clinical trials on other monoclonal antibodies for the treatment of multiple sclerosis. (b) Published trial reports on multiple sclerosis with any other small-molecule drugs. (c) Clinical studies with NTZ, OCR, and ALM in treatment of MS, which were published either before January 1, 2016, or after December 31, 2020.

Data Extraction

The selected published clinical trial reports as per the defined inclusion–exclusion criteria were screened, and data were extracted in an excel sheet under the following fields: author name, year of publication, study design, sample size,

Table 1. Demography of Clinical Studies Belonging to Natalizumab, Ocrelizumab, and Alemtuzumab

Monoclonal Antibody	Medication Prior to MAb	(N)*	Average Duration of MS (years)	Subject Mean Age (years)	Treatment Duration	References
Natalizumab (300 mg, iv)	AZA, FNG	59	9.6 $\pm$ 6.2	41.6	24 weeks	9
	NR	439	PPMS-16.8 SPMS-4.7	47.3	96 weeks	10
	NR	69	NR	29.1	12 months	11
	GA, IFN- β	88	11.9 $\pm$ 7.3	38.4	36 months	12

(Table 1 continued)

(Table 1 continued)

Monoclonal Antibody	Medication Prior to MAb	(N)*	Average Duration of MS (years)	Subject Mean Age (years)	Treatment Duration	References
Ocrelizumab (600 mg, iv)	NR	486	2.9 ± 3.2	44.7	120 weeks	13
	GA, IFN-β, DMF	825	3.82 ± 4.95	37.2	96 weeks	14
	IFN-β	1311	NR	NR	120 weeks	15
	NR	644	NR	44.7	24 weeks	16
	NR	68	NR	39.7	24 weeks	17
Alemtuzumab (12–24 mg, iv)	NR	1485	NR	NR	48 months	18
	NTZ, FNG	50	12.9	35.7	64 weeks	19
	Teriflunomide, Mitoxantrone, GA, IFN-β, DMF	90	6.9	NR	NR	20
	GA, FNG, DMF	35	16.9 ± 5.8	43	36 months	21
	IFN-β, GA, NTZ	58	NR	36.4	12 months	22
	IFN-β, GA	1314	4.5	34.8	12 months	23
	NTZ, FNG, DMF, Mitoxantrone	40	11.7 ± 5.9	34.1	36 months	24
	IFN-β	918	3.0 ± 1	34.2	72 months	25

Abbreviations: MAb, monoclonal antibody; AZA, azathioprine; FNG, fingolimod; GA, glatiramer acetate; IFN-β, interferon beta; DMF, dimethyl fumarate; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; NR, not reported.

(N)* = Patients randomized in the recommended dose of monoclonal antibodies (MAbs).

approved doses of monoclonal antibodies, mean/average duration of the disease at the time of entry in the trial, subject mean age data, and adverse events (% AEs; Table 1).^{9–25}

Statistical Analysis

The association of reported AEs with the use of monoclonal antibodies was identified in each study and was statistically analyzed using Graph-pad Prism 9 software (Graph-StatsTechnology Ltd., Bangalore, India). The quartile (lower Q1 and upper Q3), median (Q2), and their interquartile range (IQR) were calculated and represented as box and whisker plots.

Results and Discussion

With no filters, the electronic search of the PubMed database identified 38 records, of which 21 were manually excluded based on the mentioned inclusion and exclusion criteria. The remaining 17 studies were included in this meta-analysis (Figure 1), which comprises data from a total of 7979 patients with MS. The total number of patients using NTZ, OCR, and ALM was 655, 3334, and 3990, respectively (Table 2). In this

review analysis, 13 studies belonged to the patients with RRMS, followed by PPMS and secondary progressive multiple sclerosis. The patients were of either gender. The mean age ranged between 30 and 47 years, whereas the mean range of duration of MS was 2.9 to 16.9 years. Prior to starting the monoclonal antibody treatment, the previous treatment was ceased.

The reported AEs from each of the unique studies were categorized according to System Organ Class and were grouped by etiology (e.g., infections and infestations), manifestation site (e.g., gastrointestinal disorders), or purpose (e.g., surgical and medical procedures). These reported AEs were then further subcategorized according to the preferred term (Table 2). Miscellaneous AEs reported in two or less than two studies are tabulated (Table 3).

The AEs related to infection and infestations were reported in 94% of studies. These AEs were mostly reported with NTZ and OCR; however, their severity was not as high. Urinary tract infection was reported in 16.9%, 9.7%, and 0.1% of patients using NTZ, OCR, and ALM, respectively (Table 2). Herpes infection was reported in 0.7%, 2.2%, and 0.2% of patients using NTZ, OCR, and ALM, respectively (Table 2). Upper respiratory tract infection was reported in 7.3%, 7.4%, and 0.1% of patients using NTZ, OCR, and ALM, respectively

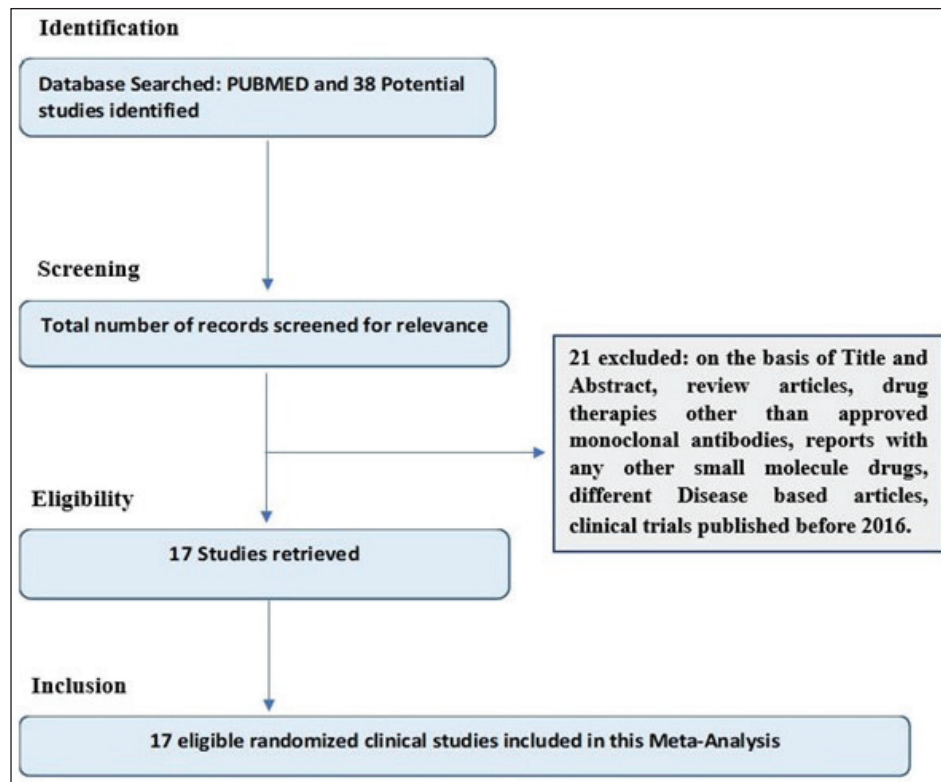


Figure 1. PRISMA Flowchart.

Table 2. Comparison of Reported AEs Among Natalizumab, Ocrelizumab, Alemtuzumab

Reported AEs (Preferred Term)	Mean % of patients reporting specific AEs		
	Natalizumab (S = 4) N = 655 AE = 9/16* T = 69.3%	Ocrelizumab (S = 5) N = 3334 AE = 13/16* T = 54.4%	Alemtuzumab (S = 8) N = 3990 AE = 15/16* T = 53.6%
UTI	16.9	9.7	0.1
Herpes infection	0.7	2.2	0.2
URTI	7.3	7.4	0.1
Nasopharyngitis	17.0	11.4	0
Pyrexia	0	1.1	0.4
Fatigue	9.0	0.9	0.1
Rashes	0	3.7	0.8
Flushing	0	2.7	0.1
Nausea	0.3	0.2	0.2
Headache	10.9	5.2	0.8
ITP	0	0	2.0
Thyroid dysfunction	0	0	43.5
Back pain	7.1	4.1	0.02
Influenza	0	5.0	4.3
Pneumonitis	0.4	0	0.5
Myalgia	0	0.2	0.07
References	9–12	13–17	18–25

Abbreviations: S, no. of studies; N, total patients; T, total % of patients reporting adverse events; AEs, adverse events; UTI, urinary tract infection; URTI, upper respiratory tract infection; ITP, immune thrombocytopenia.

*Number of reported adverse events with specific MAb from the total frequent AEs mentioned in the table.

Table 3. Mean (%) of Patients Reporting Specific AEs in ≤ 2 Studies.

AEs Class	(Mean % of Patients Reporting Specific AEs)		
	Natalizumab	Ocrelizumab	Alemtuzumab
Infection and Infestation	Progressive multifocal leukoencephalopathy (46); Urosepsis (0.2)	Bronchitis (2)	Bordetella pertussis infection (2); Listeria (0.1); Tuberculosis (0.1); Mumps (3); Meningoencephalomyelitis (3); Viral hepatitis (5); Vulvovaginal candidiasis (2.1); Urosepsis (0.1)
GIT disorder	Diarrhea (2)	NA	Constipation (5); Upper abdominal pain (17); Diarrhea (7)
Musculoskeletal disorder	Muscle/joint pain (6) Arthralgia (10)	Arthralgia (11)	Muscle stiffness (5)
General disorder	Fever (1)	Asthenia (0.3)	Chest discomfort (7); Fever (1); Asthenia (3)
Skin-related disorder	Eczema (5); Dermatitis (5)	Pruritus (11); Erythema (1); Urticaria (3)	Pruritus (14); Erythema (14); Dermatitis (3); Urticaria (10)
Neoplasm	NA	Basal cell carcinoma (0.6)	Carcinoma of salivary gland (2); Breast cancer (1.2); Cervical intraepithelial neoplasia (3)
Blood and lymphatic disorders	NA	NA	Albuminuria (3); Pancytopenia (3); Hemolytic anemia (8)
Psychiatric disorders	Insomnia (7)	Depression (1)	Insomnia (15)
Vascular disorder	NA	Hypertension (1)	Hemorrhage (3); Hypertension (3);
Respiratory disorders	NA	NA	Dyspnea (7)
Cardiac disorders	Tachycardia (1)	NA	Bradycardia (10); Tachycardia (2)
Autoimmune disorder	Dizziness (1)	Dizziness (1)	Hypersensitivity (2); Acquired hemophilia-A (3)
Endocrine disorders	NA	NA	Hyperthyroidism (3)
Injury/procedural complications	Fall (20)	Injury Poisoning (18)	NA
Hepatobiliary disease	NA	NA	Hepatocellular injury (2)

Note: NA, not available.

(Table 2). Nasopharyngitis was reported in 17%, 11.4%, and 0% of patients using NTZ, OCR, and ALM, respectively. The IQR of urinary tract infection, herpes infection, upper respiratory tract infection, and nasopharyngitis was calculated as 9.5, 3, 9.5, and 17.5%, respectively (Figure 2a–d).

In the general disorders, fatigue was reported in 9.0%, 0.9%, and 0.1% of patients using NTZ, OCR, and ALM, respectively (Table 2). The AE of rashes was reported in 0%, 3.7%, and 0.8% patients using NTZ, OCR, and ALM, respectively. Similarly, flushing was reported by 0%, 2.7%,

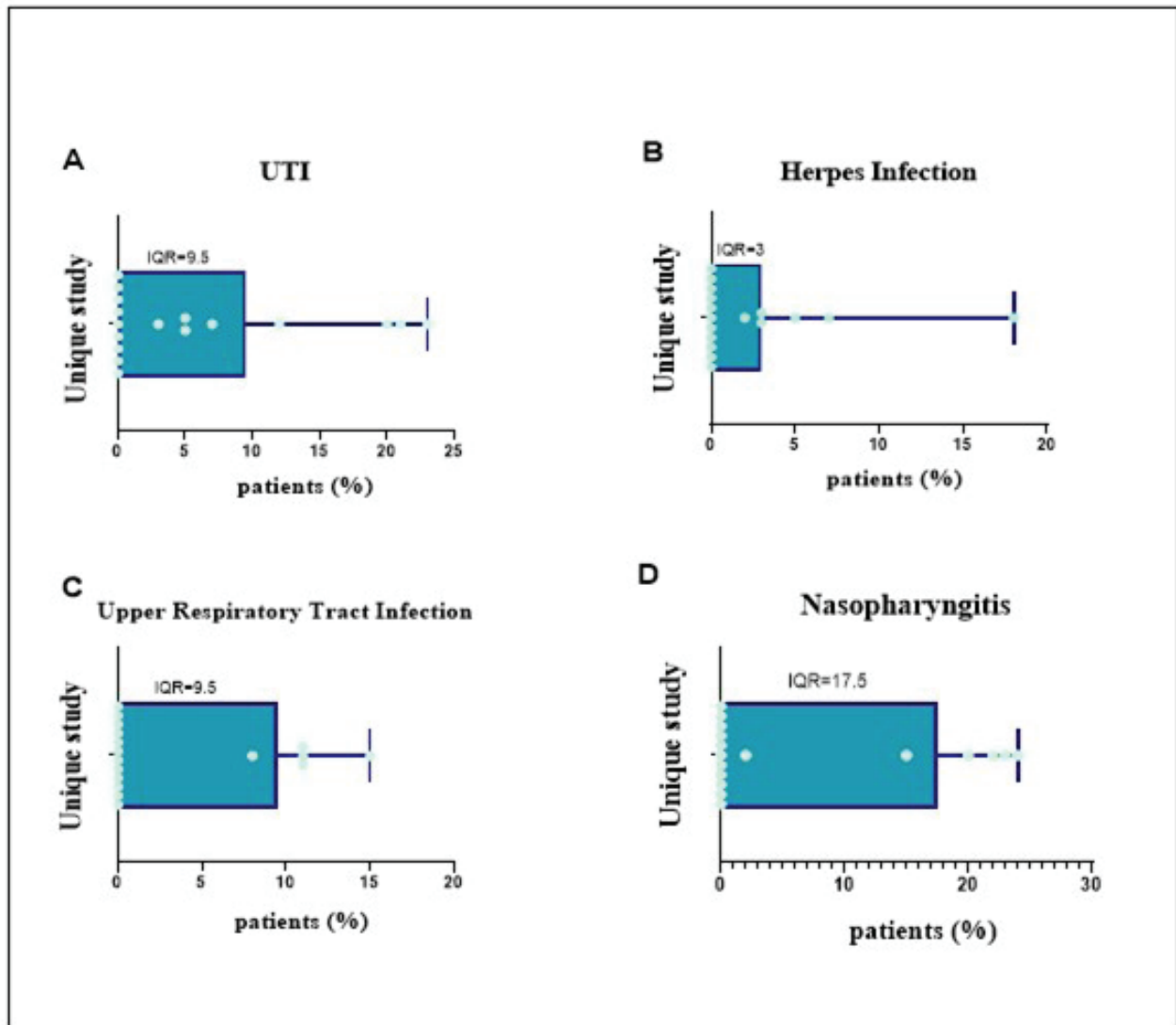


Figure 2. Box and Whisker Representation of the Percentage of Patients in Each of the 17-Studies vs Reported Particular AEs According to SOC. (a) UTI. (b) Herpes Infection. (c) Upper Respiratory Tract Infection. (d) Nasopharyngitis. UTI and Upper Respiratory Tract Infection Were Reported With an IQR of 9.5, Whereas Herpes Infection and Nasopharyngitis Were Reported With an IQR of 3.0 and 17.5, respectively.

Abbreviation: IQR, interquartile range.

and 0.1% of patients using NTZ, OCR, and ALM, respectively (Table 2). Pyrexia was reported in 23% of studies, with an IQR of 1.5% (Figure 3a). The IQR of fatigue, rashes, and flushing was 1.0%, 3%, and 0%, respectively (Figure 3b–d).

Nausea was the prominent GIT disorder reported in 0.3%, 0.2%, and 0.2% of patients using NTZ, OCR, and ALM, respectively, with an overall IQR of 2% (Table 2, Figure 4a). Headache was reported in 10.9%, 5.2%, and 0.8% of patients using NTZ, OCR, and ALM, respectively (Table 2). Of the three monoclonal antibodies, ALM was majorly associated with severe AEs, such as immune thrombocytopenia (ITP 2%) and thyroid dysfunction (43%).

On the other hand, OCR and NTZ, unlike ALM, had no severe adverse events recorded (Table 2). The IQR for headache, ITP, and thyroid dysfunction was calculated as 9.0%, 2%, and 15.5% (Figure 4b–d).

Other adverse events, such as back pain, were reported by 7.1%, 4.1%, and 0.02% of patients using NTZ, OCR, and ALM, respectively (Table 2). Influenza was reported by 0%, 5%, and 4.3% of patients using NTZ, OCR, and ALM, respectively (Table 2). Pneumonitis was reported in 0.4%, 0%, and 0.5% of patients using NTZ, OCR, and ALM, respectively (Table 2). Myalgia was reported in 0%, 0.2%, and 0.07% of patients using NTZ, OCR, and ALM,

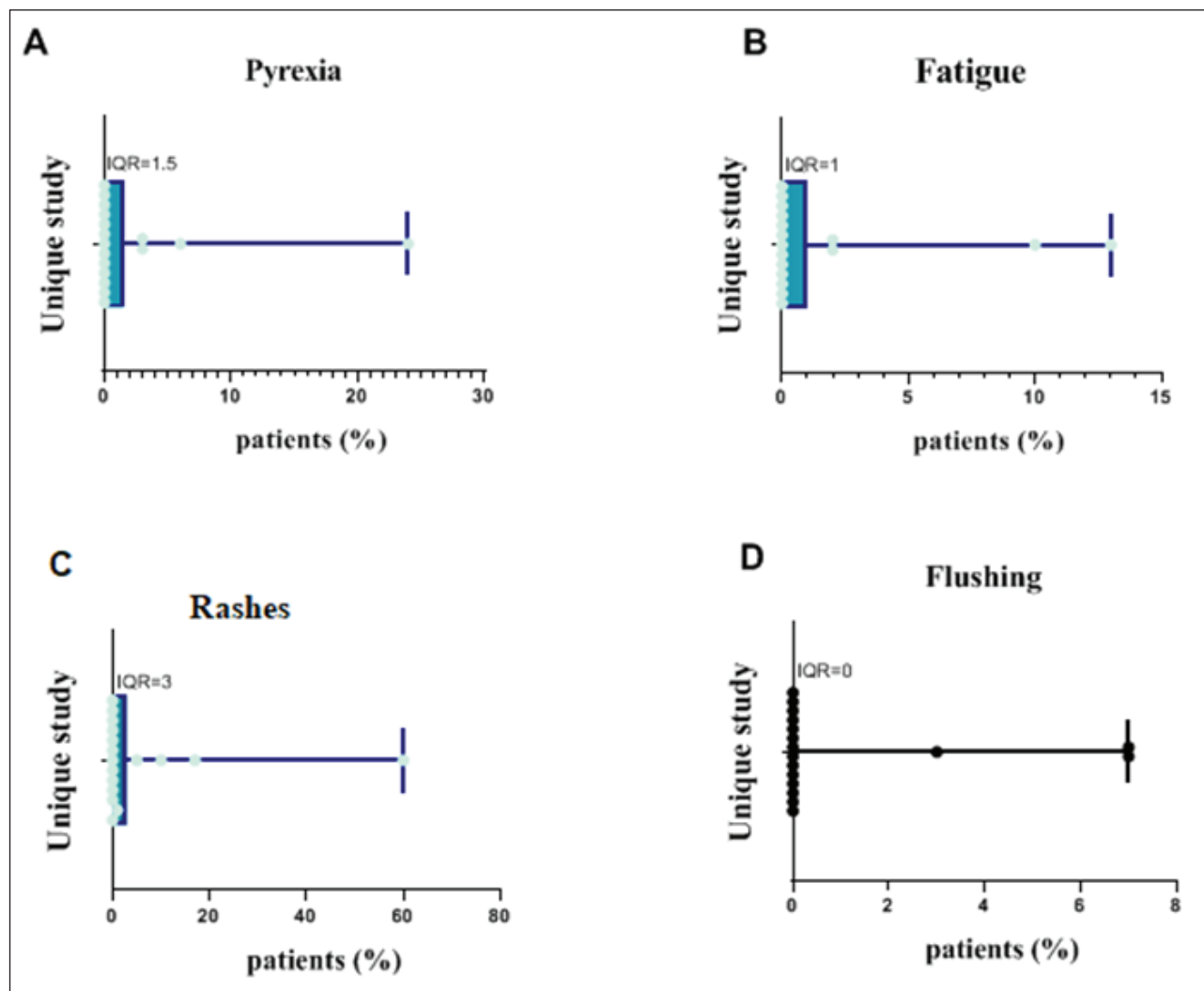


Figure 3. Box and Whisker Representation of the Percentage of Patients in Each of the 17-Studies vs Reported Particular AEs According to SOC. (a) Pyrexia. (b) Fatigue. (c) Rashes. (d) Flushing. Pyrexia and Fatigue Were Reported With an IQR of 1.5 and 1.0, respectively, Whereas Rashes and Flushing Were Reported With an IQR of 3.0 and 0, respectively.

Abbreviation: IQR, interquartile range.

respectively (Table 2). The calculated IQR for back pain, influenza, pneumonitis, and myalgia was 1.0%, 6.0%, 0%, and 0%, respectively (Figure 5a–d).

The AEs related to cardiac, hepatobiliary, psychiatric, and respiratory disorders were the least common. Of the three monoclonal antibodies, ALM was also frequently associated with the less common AEs that were related to infections and neoplasms, such as carcinoma of the salivary gland (2%) and breast cancer (1.2%), whereas NTZ and OCR appear to be safe.

The incidence of AEs related to NTZ may be because of the production of antibodies against NTZ, which in turn suppresses the immunity.²⁶ The OCR is a CD20 antibody that may cause reductions of immunoglobulins, primarily IgG, and cause antibody-dependent cell-mediated cytotoxic effects,

which may contribute to the risk of infections.²⁷ The ALM is associated with an increased risk of ITP and thyroid dysfunction because of immediate cytokines release syndrome following intravenous administration, which causes significant elevation of IL-6, TNF- α , and interferon-gamma (IFN- γ) that forms a cytokine storm and potentially increases the risk of these side effects.²⁸

Previously, meta-analysis has been conducted to determine the safety of various monoclonal antibodies for MS. In contrast to our study, Xu et al.²⁹ compared monoclonal antibodies with placebo in RRMS and found that they had less significant AEs. In a similar study, McCool et al.³⁰ investigated OCR and found that it had a better or equivalent safety profile when compared with

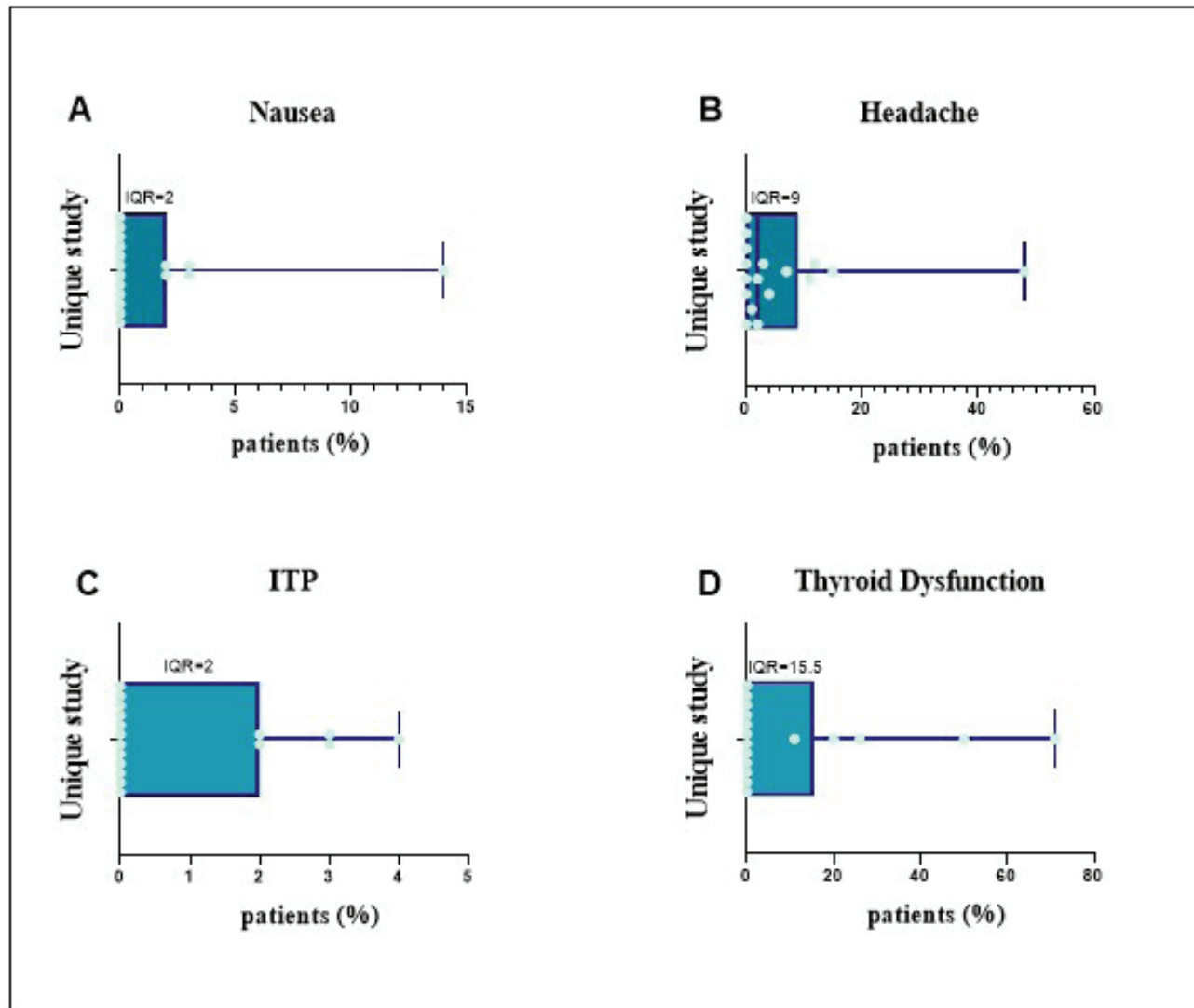


Figure 4. Box and Whisker Representation of the Percentage of Patients in Each of the 17-Studies vs Reported Particular AEs According to SOC. (a) Nausea. (b) Headache. (c) ITP. (d) Thyroid Dysfunction. Nausea and Headache Were Reported With an IQR of 2.0 and 9.0, respectively, Whereas Immune Thrombocytopenia (ITP) and Thyroid Dysfunction Were Reported With an IQR of 2.0 and 15.5, respectively.

Abbreviation: IQR, interquartile range.

other disease-modifying medicines for RRMS across all endpoints. In a similar study, Lucchetta et al.³¹ found that NTZ, OCR, and ALM showed higher efficacy than other disease-modifying medicines, but more meta-analysis is needed to understand the prevalence of AEs in order to assess their safety profile.

Rapidly increasing cases of MS worldwide has created an ongoing research interest for developing new therapies for MS. Different biological treatments have been studied and tested, and among them, monoclonal antibodies are working as a pillar for MS treatment. Moreover, new advancements in the production of monoclonal antibodies are being

incorporated to optimize their safety and tolerability profiles, which is a promising factor.

This review provides a comprehensive overview of the safety profile of approved monoclonal antibodies for MS. This information can potentially assist the clinicians in the selection of the most appropriate therapeutic intervention considering the COVID-19 pandemic. Natalizumab and ocrelizumab, according to our analysis, are the preferable therapeutic options than other licensed monoclonal antibodies for MS treatment, especially during COVID-19, because they were found to be associated with a lower incidence of infections, particularly respiratory infections.

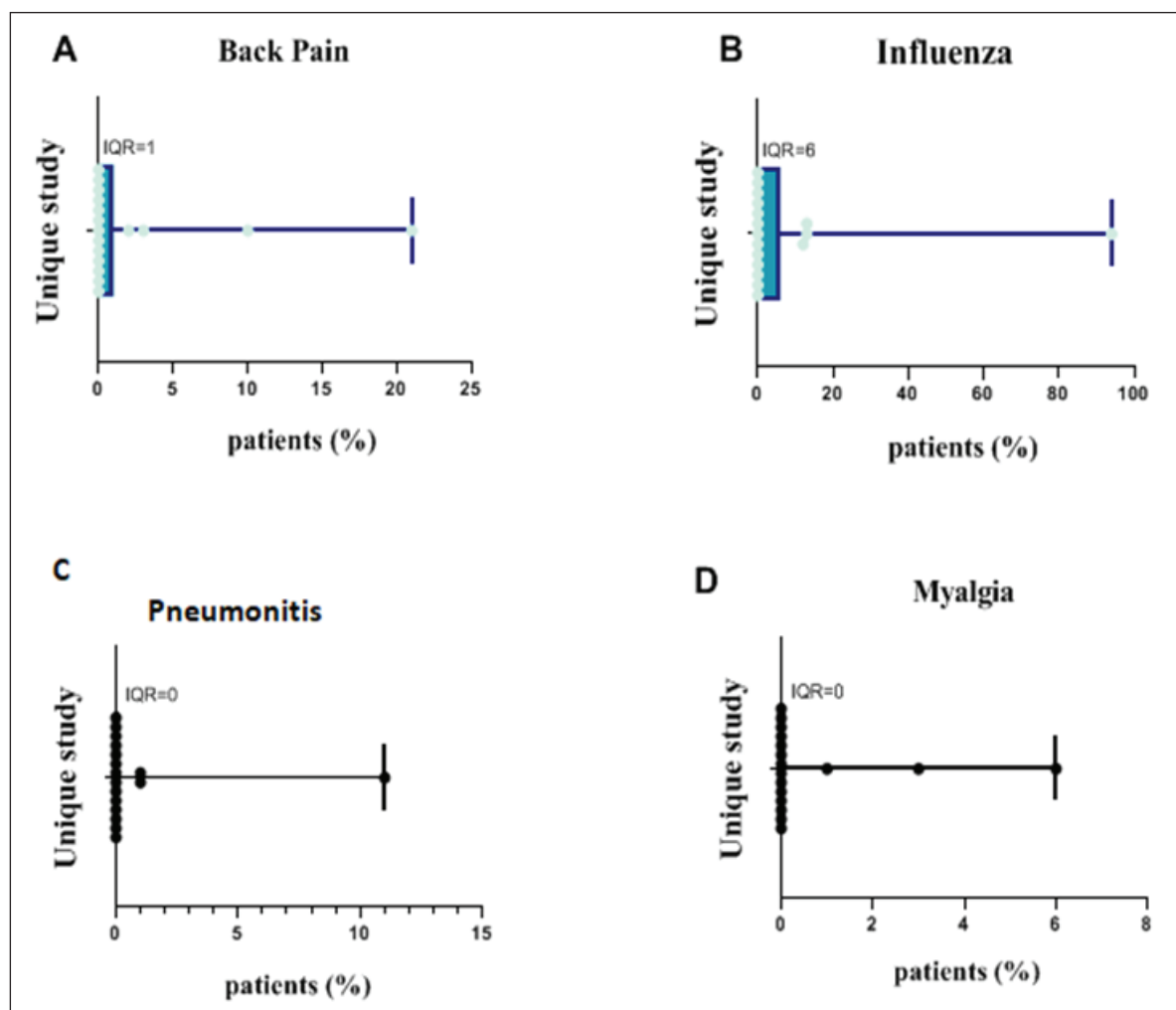


Figure 5. Box and Whisker Representation of the Percentage of Patients in Each of the 17-Studies vs Reported Particular AEs According to SOC. (a) Back Pain. (b) Influenza. (c) Pneumonitis. (d) Myalgia. Back Pain and Influenza Were Reported With an IQR of 1.0 and 6.0, respectively, Whereas Pneumonitis and Myalgia Were Reported With an IQR of 0.

Abbreviation: IQR, interquartile range.

Acknowledgment

The authors thank Arshvir Kaur, Department of Pharmacology, DIPSAR, DPSRU for helping in manuscript formatting and proofreading.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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