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Infections in patients with multiple sclerosis treated with disease-modifying therapies: A comparative risk assessment cohort study

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Keywords
Multiple Sclerosis; Infections; Interferons; Fingolimod; Rituximab; Azathioprine

Abstract

Background: The major treatment regimens for multiple sclerosis (MS) are disease-modifying therapies (DMTs). Fungal, viral, and bacterial infections are common complications of these drugs. Also, MS itself is an immune-related chronic disease that can compromise their subjects to infections. Therefore, MS can be a risk factor for infectious complications.

Methods: This paper is a retrospective cohort study conducted from February 2020 to January 2022 using prospectively collected data from every patient registered at the Multiple Sclerosis Referral Research Center in Tehran, Iran. We inducted patients with MS who were diagnosed based on McDonald's criteria and exposed to DMTs for at least 6 months prior to this study. Being under 18 years of age, diagnosis change during the study, and mortality were the exclusion criteria of this study.

Results: We inducted a total of 979 patients into this study.

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Finally, data from 798 participants were analyzed. Rituximab and natalizumab were associated with a higher risk of urinary tract infection (UTI) and bacterial vaginitis. Moreover, rituximab, glatiramer acetate, and dimethyl fumarate were associated with HSV-associated ulceration. None of the investigated DMTs were associated with an altered risk of COVID-19.

Conclusion: The use of DMTs can result in an increased risk of infections in patients. The selection of these DMTs should be based on their efficacy and risk of complications. Healthcare providers should familiarize themselves with these complications to select the appropriate DMTs with the highest efficacy.

Introduction

Multiple sclerosis (MS) is an ongoing challenge in the twenty-first century. MS is a chronic neurological autoimmune disease caused by neuron demyelination in the brain, spinal cord, and optic nerve.[1,2] Therefore, MS can cause various neurological defects like paranesthesia, neuropathic pain, tonic muscle spasms, paroxysmal itching, facial myokymia, episodic dysarthria, and visual defects leading to disabilities.[1] These disabilities can be quantifiably described by the Expanded Disability Status Scale (EDSS).[3] Also, MS has different subtypes based on the progression of the disease. They are relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS).[4] In 2018, approximately 810504 patients struggled with MS in the United States, the majority of which are women.[5] Furthermore, the prevalence of MS is around 54.51 in every 100000 in Iran.[6] In conclusion, MS is considered a relatively common chronological disorder that causes severe disabilities if left unchecked. Therefore, disease-modifying treatment of this condition is necessary if the patient's outcome is to be altered.

To change the outcome of patients with MS, Disease-Modifying Therapies (DMTs) were added to the MS treatment regimen.[7] These drugs are categorized into two groups: moderate-efficacy (ME) DMTs (Interferon-beta [IFNβ], Glatiramer Acetate, Dimethyl Fumarate, and Teriflunomide) and high-efficacy (HE) DMTs (Natalizumab, Fingolimod, Rituximab, Ocrelizumab, and Alemtuzumab).[8,9] In addition, azathioprine is used as off label treatment.[10] As a side effect, several infections may occur during these treatments.[11,12] These infections can be caused by viral, bacterial, and fungal agents.[13] Rituximab can cause hepatitis B reactivation, progressive multifocal leukoencephalopathy (PML), dangerous encephalitis caused by the polyomavirus JC, tuberculosis reactivation, and pneumonia.[14,15] Fingolimod and mycophenolate mofetil increase the risk of herpes zoster, leading to disseminated varicella infection.[16] Interferon may increase the risk of viral upper respiratory infections.[17] Cyclophosphamide can increase the risk of opportunistic infections like warts.[18] Azathioprine can increase the risk of infections with Staphylococcus aureus, Nocardia, Escherichia coli, Salmonella, and Legionella pneumophila.[19] Teriflunomide usage is related to an increased risk of urinary tract infections (UTIs).[20] Dimethyl fumarate may increase the risk of pneumonia caused by Legionella pneumophila.[21] The coronavirus disease of 2019 (COVID-19) infection can also be a complication following DMT usage, particularly rituximab.[22] Consequently, the anticipation of these infections can alter the treatment regimen based on what types of infections the patient is susceptible to.

In previous studies, DMTs were examined individually regarding general terms of infection events rather than the exact type of infection and its related DMT exposure. Moreover, these studies did not investigate MS subtypes as risk factors for infection.[11,13] Thus, the present study was conducted to demonstrate the infectious complications that are associated with DMTs used in patients registered at the MS Referral Research Center of Tehran, Iran.

Materials and Methods

This study is reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[23]

Study design and setting: This retrospective cohort study was conducted at the Multiple Sclerosis Referral Research Center, a tertiary center affiliated with Tehran University of Medical Sciences, Tehran, Iran, and a contributor to the national MS registry.[24] All registered patients who met the inclusion criteria from February 2020 to January 2022 were included. Patients received standard care with at least 2 scheduled visits per year and additional visits for complications or treatment changes. At each visit, medical history was updated, physical examination was performed, and patients were assessed for infections, complications, or treatment modifications. Data were entered into a secure electronic registry. Written informed consent was obtained from all participants, and the study was approved by the

Ethics Committee of Sina Hospital.

Participants: This study included adults (≥ 18 years) with a confirmed diagnosis of MS, who had received at least one DMT for a minimum of 6 months and had completed a minimum of 3 clinical visits. Diagnoses were established by board-certified neurologists using the 2017 revised McDonald criteria.[25] Patients were excluded if they were under 18 years of age or had chronic immunological, infectious, or systemic conditions known to independently increase infection risk, including vesicoureteral reflux (VUR), common variable immunodeficiency (CVID), severe combined immunodeficiency (SCID), chronic bronchitis, malignancy, cerebrovascular accident, pregnancy, and chronic infections such as Lyme disease, tuberculosis, syphilis, untreated gonorrhea, viral hepatitis B or C, and HIV.

Variables and data sources: The primary exposure variable was the DMT used by each patient, identified by calculating treatment intervals from medical records and registry data, allowing identification of the specific DMT in use at the time of each infection. DMTs were categorized by efficacy into 3 groups:[26] moderate-efficacy (ME) (interferon beta1-a, interferon beta1-b, dimethyl fumarate, and glatiramer acetate), high-efficacy (natalizumab, fingolimod, rituximab, and ocrelizumab), and off-label (azathioprine).

The primary outcomes were clinically significant infections, for the signs and symptoms of which patients were systematically screened at each visit. Suspected infections were evaluated by board-certified physicians and included only if confirmed through clinical examination or supported by relevant laboratory or paraclinical evidence. Outcomes were treated as binary variables for infections with a single occurrence, and as count variables for recurrent infections.

Covariates and potential confounders included age, sex, MS subtype, Expanded Disability Status Scale (EDSS) score, disease duration, and comorbidities including diabetes mellitus, hypertension, ischemic heart disease, arthritis, autoimmune disorders, and thyroid dysfunction. MS subtype was determined using the 2017 revised McDonald criteria.[25] EDSS scores were assessed in person by trained neurologists using standardized tools.[27] Comorbidities were based on documented diagnoses in the medical record. Self-reported symptoms were considered valid only if confirmed during clinical assessment or supported by additional diagnostic workup.

Bias: Several strategies were implemented to minimize potential sources of bias. Confounding was addressed by adjusting for key variables, including age, sex, MS subtype, EDSS score, disease duration, and relevant comorbidities. To reduce misclassification bias, only infections confirmed by board-certified physicians through clinical evaluation and, when necessary, laboratory or paraclinical testing were included.

Selection bias was limited by including all eligible patients with complete data and a minimum of 3 clinical visits and comparing baseline characteristics between included and excluded patients to confirm no major differences. While recall bias remains a potential concern, particularly for infections not initially reported by patients, it was mitigated by verifying all infections through clinical assessment, with additional diagnostic workup when appropriate.

Nonetheless, residual confounding remains possible due to unmeasured variables that may influence infection risk independently of DMT exposure. These include lifestyle and physiological factors such as frequency of sexual activity, occupational exposure, personal hygiene, smoking status, and bladder dysfunction, including neurogenic bladder and urinary retention.

Study size: As this was a retrospective study based on existing registry data, the study size was determined by data availability. No formal sample size or power calculation was performed prior to analysis. All eligible patients with available data between February 2020 and January 2022 were included to maximize sample size and generalizability, resulting in a final cohort of 798 patients.

Quantitative variables and statistical methods: All analyses were conducted using R version 4.[28] For infection types with at most 1 event per patient, logistic regression was used when event counts were sufficient (fungal infection, COVID-19, and upper respiratory infection), and Firth's penalized logistic regression was applied for rare outcomes (≤ 3%) (Herpes zoster, fungal dermatitis and vaginitis, dental abscess, and appendicitis) to reduce small-sample bias and address data separation. For infections with multiple occurrences [UTI, herpes simplex virus (HSV), and bacterial vaginitis], Poisson regression was used, with patients taking interferon beta-1a as the reference. Overdispersion was assessed using Pearson's chi-square statistics; all dispersion values were below 1.5, supporting the use of

Poisson models. The codes used for our analyses are provided in the supplementary file.

Age, EDSS score, and disease duration were treated as continuous variables. DMT exposure duration was log-transformed to improve model fit. Infection counts were modeled as count outcomes; single-episode infections as binary outcomes. No other transformations or categorizations were applied. Covariates included age, EDSS score, and disease duration (all modeled as continuous variables) as well as sex, MS type, and comorbidities (diabetes, hypertension, ischemic heart disease, arthritis, autoimmune disorders, thyroid dysfunction). Backward elimination was used for treatment-related predictors, while clinically relevant covariates were retained. To compare baseline characteristics between excluded and retained patients, chi-square test, Fisher's exact test, or t-test was used, as appropriate. To assess bias from incomplete follow-up, we applied inverse probability weighting based on a logistic model using baseline variables, and truncation at a weight = 10 was used to ensure stability.

A two-sided P-value < 0.05 was considered significant. β0 (intercept) and β1 (slope) coefficients for each model alongside the P-value for each slope and the Akaike information criterion (AIC) for each model have been reported to enable model comparison.[29]

Results

Participants and descriptive data: The data for a total number of 979 patients with MS were available for this study. Sixty-eight patients were excluded for not meeting the eligibility criteria. An additional 72 patients were lost to follow-up and excluded from the analysis; the reasons included death (n = 6), enrollment in clinical trials (n = 18), poor adherence to scheduled visits (n = 41), and pregnancy (n = 7). Finally, the data from 41 cases were discarded due to missing values for their basic demographic data. Except for a lower EDSS score in the total excluded group compared to the final cohort (3.28 vs. 4.04) and differences in DMT exposure (lack of ocrelizumab and a higher rate of rituximab use among patients lost to follow-up) no other significant differences were observed in baseline characteristics (Supplementary Table S1). Eventually, data from 798 participants were included in this study.

The majority of the participants were women (78.2%). The mean age of the participants was 37.01 ± 9.17 years. Patients with relapsing-remitting MS (RRMS) constituted the majority of the participants (73.9%), followed by secondary progressive MS (SPMS) (20.4%). Patients with primary progressive MS (PPMS) consisted of only 5.6% of the sample size. The mean duration of the disease was 19.51 ± 9.17 months. Finally, the mean EDSS score was 4.04 ± 2.36. DMT prescription for the patients was strictly followed and recorded for this study. Table 1 presents the demographic and medication history of the participants of this study, Interferon beta1-a, a moderate-efficacy DMT, was the most prescribed DMT for the patients with 473 (59.3%) patients taking it. It also had the highest duration of prescription with a mean of 29.02 ± 41.27 months. From the high-efficacy DMT category, rituximab had the highest number and duration of prescriptions with 394 (49.4%) patients taking it for an average of 5.46 ± 7.20 months. Figure 1 depicts the distribution of the duration of DMT prescriptions for the patients.

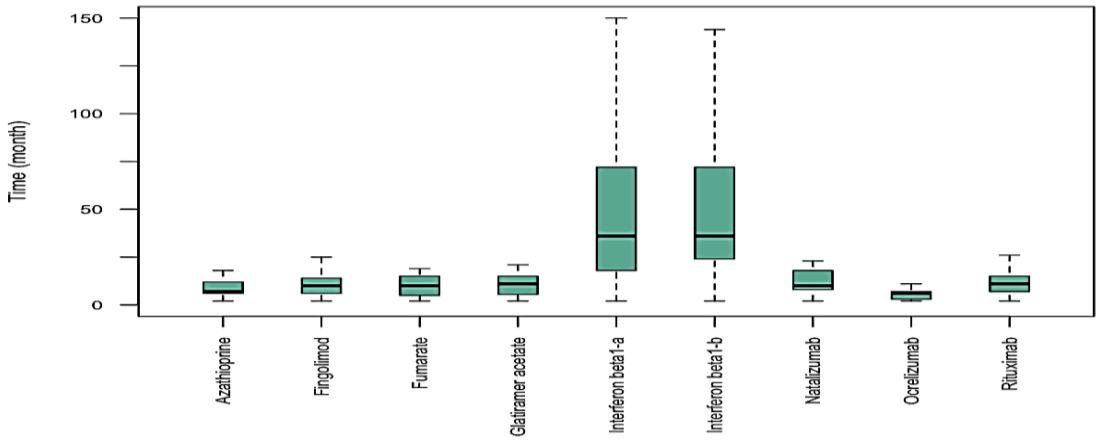

Figure 1. Disease-modifying therapies (DMTs) prescribed and the duration of use (in months) in our samples (Note that the outliers have been removed from the illustration.)

Table 1. Demographic data of patients with multiple sclerosis (MS)

Variable		Results
Female/Male [n (%)]		624 (78.2)/174 (21.8)
Age (mean ± SD)		37.01 ± 9.17
MS subtype [n (%)]	PP	45 (5.6)
	RR	590 (73.9)
	SP	163 (20.4)
Duration of the disease (month) (mean ± SD)		19.51 ± 13.47
EDSS scores (mean ± SD)		4.04 ± 2.36
Underlying disorders [n (%)]	Arthritis	12 (1.5)
	Autoimmune disorders	10 (1.3)
	Diabetes	7 (0.9)
	Hypertension	21 (2.6)
	Hyperthyroidism	12 (1.5)
	Hypothyroidism	63 (7.9)
	Ischemic heart disease	6 (0.8)
Class (mean ± SD)	Medication	Time (month) Mean ± SD
Moderate-efficacy DMTs (mean ± SD)	Dimethyl Fumarate (n = 60)	0.76 ± 3.05
	Glatiramer acetate (n = 179)	2.47 ± 5.37
	Interferon beta1-a (n = 473)	29.02 ± 41.27
	Interferon beta1-b (n = 153)	9.49 ± 26.56
High-efficacy DMTs (mean ± SD)	Fingolimod (n = 189)	2.52 ± 5.54
	Natalizumab (n = 172)	2.69 ± 5.87
	Ocrelizumab (n = 45)	0.33 ± 1.52
	Rituximab (n = 394)	5.46 ± 7.20
Off-label DMTs (mean ± SD)	Azathioprine (n = 41)	0.44 ± 2.12

EDSS: Expanded disability status scale; NA: Not applicable; PP: Primary progressive; RR: Relapsing-remitting; SP: Secondary progressive

It should be noted that for illustration purposes, outlying samples were discarded from the plots.

Outcome data: UTI was the most prevalent infection among the patients with 199 (24.9%) patients experiencing at least 1 episode of UTI. COVID-19 was the second most frequent infection with 118 (14.8%) cases. Finally, bacterial vaginitis and HSV-associated ulceration also had high prevalence among the patients with 108 (13.5%) and 56 (7.0%) cases, respectively. Figure 2 illustrates the frequency of various infections observed in the study cohort, while supplementary table S2 presents the incidence of each infection by DMT exposure.

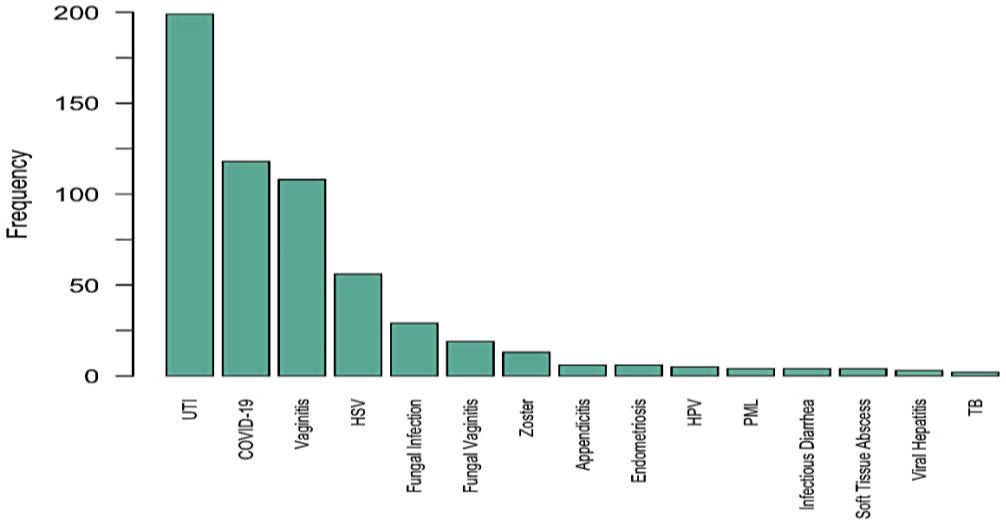

Figure 2. The frequency of infections in our sample
HPV: Human papillomavirus, HSV: Herpes simplex virus, PML: Progressive multifocal leukoencephalopathy, TB: Tuberculosis, UTI: Urinary tract infection

Main results

DMTs and rate of infections: Next, we performed Poisson, logistic, or Firth's penalized logistic regression analyses by taking the rate of each infection as the dependent variable and exposure to each DMT as independent variables to find any association between the use of DMTs and the occurrence of each infection. Table 2 presents the results of these analyses.

After adjusting for demographic variables, EDSS score, and comorbidities, treatment with rituximab and natalizumab was associated with an increased risk of UTI and HSV-associated infections compared to interferon beta-1a. Additionally, bacterial vaginitis was more frequent among patients treated with dimethyl fumarate, glatiramer acetate, and rituximab. None of the investigated DMTs showed a significant association with altered susceptibility to COVID-19. While some DMTs were excluded from the final models due to low infection incidence (< 5 events), initial analyses revealed notable associations. Specifically, ocrelizumab was linked to a decreased rate of UTIs, whereas dimethyl fumarate and azathioprine were associated with an increased risk of HSV-related infections. Inverse probability weighting analysis to account for loss to follow-up yielded comparable results, reinforcing the robustness of these findings (Supplementary Table S3 and Figure S1).

Demographic characteristics and rate of infections: We also checked for any statistical correlation between the baseline characteristics, namely the EDSS score, duration of the disease, and past medical history of the participants with the rates of infections. Table 3 presents the results of these analyses for the top 3 common infections.

There was no significant association between the duration of the disease or EDSS score and the rates of infections after adjusting for DMT exposure. There seems to be a positive correlation between the history of hypothyroidism and the rate of bacterial vaginitis. Similar to DMT exposure, although a history of autoimmune disease and hyperthyroidism was excluded from the final model for bacterial vaginitis due to low infection incidence, initial analyses indicated a notably decreased risk. Additionally, despite being excluded from the final model, a history of diabetes and ischemic heart disease was associated with a reduced risk of HSV-associated ulcerations.

Goodness-of-fit tests: We then performed goodness-of-fit tests on our models to check which models could predict the rate of infections better. First, we compared the models for predicting infection rates based on the use of DMT, demographic characteristics of patients (age, sex, disease duration, and type of MS), EDSS score, or past medical history of the individual. The AICs of the models were extracted and are presented in figure 3.

Table 2. The effect of disease-modifying therapies (DMTs) on infection rate in patients with multiple sclerosis (MS)

DMT Class	Infection		UTI	Bacterial vaginitis	HSV-associated ulceration	COVID-19
Moderate-efficacy DMTs	DMT	β0	-4.925	-6.551	-5.682	-2.946
	Dimethyl fumarate	β1	0.253	1.049	1.725	0.216
		P	0.470	0.010	0.017*	0.115
	Glatiramer acetate	β1	0.156	1.524	1.073	-0.034
		P	0.565	0.000	0.118*	0.687
	Interferon beta1-b	β1	-0.089	0.139	-0.610	0.008
		P	0.742	0.758	0.579*	0.917
	Interferon beta1-a	Reference		Reference	Reference	-0.029
						0.607
High-efficacy DMTs	Fingolimod	β1	0.233	0.751	0.926	-0.008
		P	0.316	0.013	0.175*	0.919
	Natalizumab	β1	0.449	0.492	1.892	-0.057
		P	0.044	0.263	0.005	0.536
	Ocrelizumab	β1	-14.617	-0.617	1.198	-0.097
		P	0.000[a]	0.558[a]	0.179*	0.673
	Rituximab	β1	1.061	1.494	2.075	0.049
		P	0.000	0.000	0.000	0.452
Off-label DMTs	Azathioprine	β1	0.243	0.462	1.587	0.198
		P	0.549	0.487[a]	0.045*	0.194
AIC			1481.17	877.57	357.35	667.25

*Excluded from the final models due to low infection incidence

HSV: Herpes simplex virus; NA: Not applicable; UTI: Urinary tract infection

Table 3. The Effect of demographic characteristics effect on infection rate in patients with multiple sclerosis (MS)

Dependent variable	UTI		Bacterial vaginitis		HSV-associated ulceration	
	β1	P	β1	P	β1	P
EDSS	0.095	0.087	-0.124	0.154	-0.154	0.286
Duration of disease	0.001	0.497	0.002	0.308	-0.001	0.817
History of arthritis	-1.516	0.213	-0.855	0.466	0.670	0.480
History of autoimmune disorders	-0.007	0.993	-15.431	< 0.001*	0.907	0.349
History of diabetes	0.031	0.976	0.150	0.888	-12.726	< 0.001*
History of hypertension	-0.048	0.857	0.121	0.863	-0.026	0.976
History of hyperthyroidism	-1.333	0.153	-15.190	< 0.001*	0.591	0.496
History of hypothyroidism	0.302	0.147	0.874	0.002	0.253	0.628
History of ischemic heart disease	0.591	0.082	1.626	0.078	-13.766	< 0.001*

*Excluded from the final models due to low infection incidence
EDSS: Expanded disability status scale; HSV: Herpes simplex virus; UTI: Urinary tract infection

According to our results, none of the independent variables were substantially superior to the others in the prediction of the infection rates. Next, we evaluated if the addition of any of the baseline characteristics of patients (demographics, EDSS score, or past medical history) to a model with the DMTs as the independent variable and each infection rate as the dependent variable could improve the performance of the model. The results of these analyses are presented in figure 4.

Our results indicated that the addition of the demographic variables, EDSS score, or past medical history to DMTs in a model for predicting any of the infection rates would not improve the model's performance substantially, and, in some cases, it might even decrease the performance of the model.

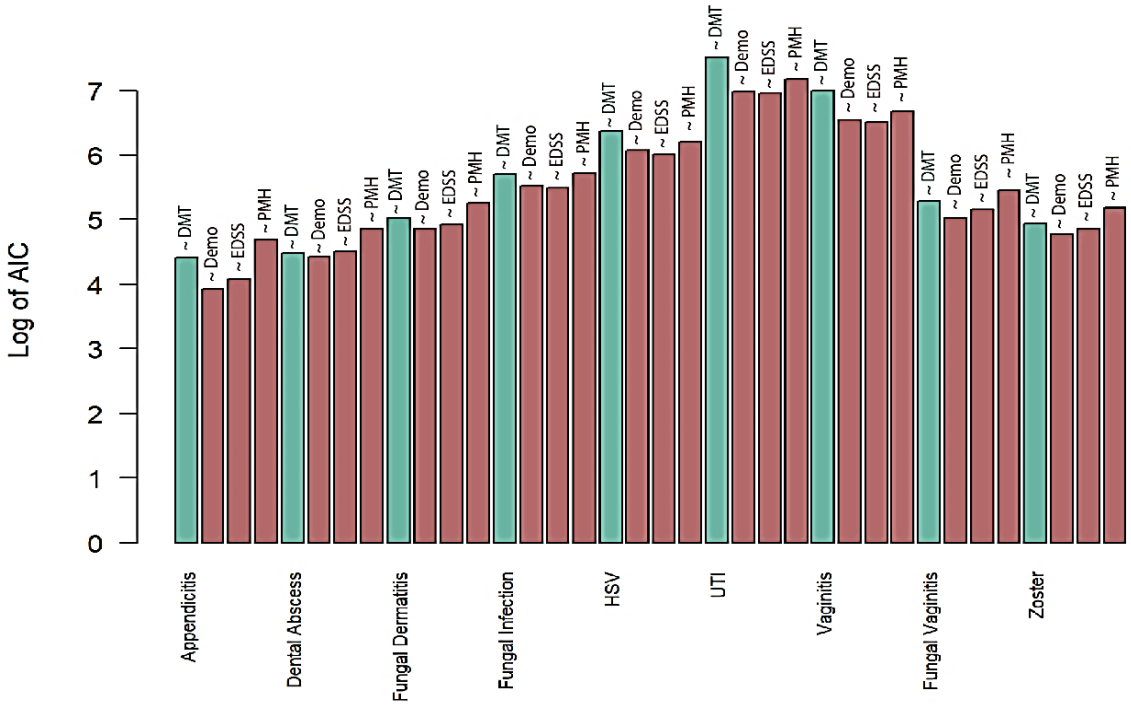

Figure 3. Log of Akaike information criterion (AIC) for different models (Each green bar is a regression model with the infection of interest as the dependent variable and disease-modifying therapies (DMTs) as independent variables. Three red bars follow each green bar: The first one is a regression model for that infection but with demographic characteristics [age, sex, disease duration, and multiple sclerosis (MS) type] as the only independent variables. The second one is a regression model for that infection but with Expanded Disability Status Scale (EDSS) as the sole independent variable. The third one is a regression model for that infection but with the past medical history of the patients solely as independent variables.)

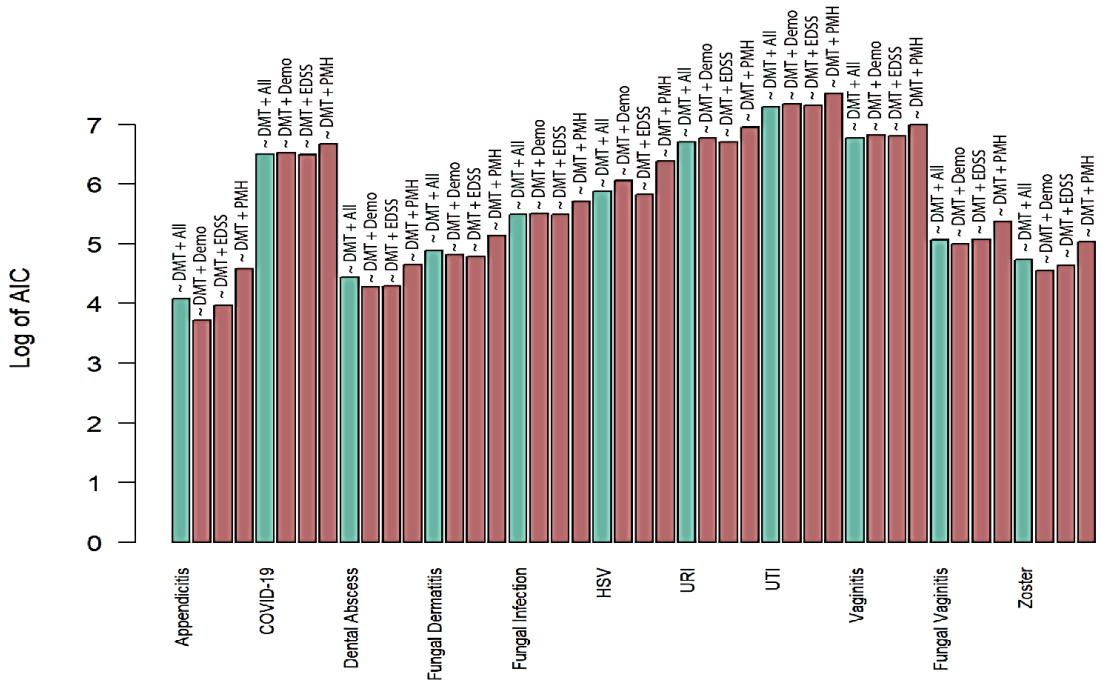

Figure 4. Log of Akaike information criterion (AIC) for different models incorporating possible confounders (Each green bar is a regression model with the infection of interest as the dependent variable and disease-modifying therapies (DMTs), demographic characteristics [age, sex, disease duration, and multiple sclerosis (MS) type], Expanded Disability Status Scale (EDSS), and past medical history as independent variables. Three red bars follow each green bar in which DMTs are independent variables: the first one is a regression model for that infection with the demographic characteristics as an extra independent variable, the second one is a regression model for that infection with EDSS as an extra independent variable, and the third one is a regression model for that infection with the past medical history of the patients as extra independent variables.)

Discussion

Key results: This retrospective cohort study suggests that exposure to certain DMTs may increase the risk of specific infections in patients with MS. Rituximab was associated with a higher incidence of UTI, HSV-associated infections, and bacterial vaginitis compared to the moderate-efficacy interferon beta1-a, which had the lowest infection rates. Natalizumab, another high-efficacy DMT, was also linked to increased rates of UTI and HSV infections. Among moderate-efficacy DMTs, dimethyl fumarate and glatiramer acetate were associated with a higher risk of bacterial vaginitis. In contrast, none of the studied DMTs showed a significantly increased risk of COVID-19 compared to interferon beta1-a. Interestingly, although patient characteristics and comorbidities, particularly EDSS score, initially appeared to influence infection risk, these associations became non-significant after adjusting for DMT exposure. The only exception was hypothyroidism, which remained significantly associated with an increased risk of bacterial vaginitis.

MS itself is associated with a higher incidence of UTIs;[30] therefore, DMTs may play a dual role by either mitigating disease severity or increasing infection risk through their immunosuppressive effects. A recent study indicated that interferon exposure does not increase UTI risk in patients with MS.[31] Although our study lacked non-MS controls or patients with MS not receiving DMTs, our comparison of other DMTs to interferon beta-1a provides valuable insight. Regarding the high-efficacy DMTs, in a recent cohort study, treatment with natalizumab, fingolimod, and rituximab was linked to higher UTI rates, not only compared to healthy individuals and untreated patients with MS, but also to those receiving interferon or glatiramer acetate.[31] However, large randomized trials found similar UTI rates between fingolimod and either interferon beta-1a or glatiramer acetate, with no differences observed compared to placebo.[32-34] Additionally, dimethyl fumarate and glatiramer acetate showed UTI rates comparable to placebo.[35,36] In our cohort, natalizumab and rituximab were the only high-efficacy DMTs

associated with increased UTI risk, with rituximab showing a stronger effect, while no moderate-efficacy DMT showed a higher risk compared to interferon beta-1a. Moreover, EDSS and hypothyroidism were initially linked to higher UTI rates, but these associations became non-significant after adjusting for DMT exposure, indicating confounding.

Findings regarding vaginitis in patients under DMTs are limited; however, a cohort study suggested comparable rates of both bacterial and fungal vaginitis among patients treated with rituximab, natalizumab, fingolimod, and glatiramer acetate to either untreated or interferon-treated patients with MS, except for fingolimod-treated patients who showed a higher rate of fungal vaginitis compared to interferon-treated patients.[31] Additionally, another cohort study suggested that overall vaginitis rates were higher in treatment with glatiramer acetate and fingolimod.[9] Our results show higher rates of bacterial vaginitis during treatment with rituximab, fingolimod, dimethyl fumarate, and glatiramer acetate, when compared to interferon beta-1a, but no difference in the susceptibility to fungal vaginitis across different DMTs. Hypothyroidism was also linked to increased bacterial vaginitis, supported by a 28.6% incidence in patients with hypothyroidism versus 13.5% in the overall study population. However, data correlating vaginitis with hypothyroidism in MS, autoimmune diseases, or the general population remain limited. No other baseline characteristics were associated with either bacterial or fungal vaginitis after adjusting for DMT exposure.

Evidence on the role of DMTs in HSV-related infections is mostly limited to case reports.[37,38] While a cohort study suggested a higher incidence of herpetic infections other than herpes zoster in fingolimod-treated patients compared to untreated and interferon- or glatiramer acetate-treated patients,[31] 2 randomized controlled trials suggest that fingolimod increases susceptibility compared to interferon beta-1a, but not placebo.[32,33] In contrast to previous findings, in our study, patients treated with natalizumab and rituximab had a higher prevalence of HSV-associated infections, along with azathioprine and dimethyl fumarate, though low event counts warrant cautious interpretation of the latter 2 treatments. Additionally, herpes zoster infection rates were higher in patients treated with fingolimod, rituximab, and dimethyl fumarate. This aligns with previous studies reporting increased rates in fingolimod- and rituximab-treated patients compared to untreated individuals, supported by odds ratios of 5.6 and 3.8, respectively, based on reported incidences.[31,39] Several case reports have documented herpes zoster reactivation during dimethyl fumarate treatment, often linked to CD8+ and CD4+ T cell depletion.[40,41]

Regarding COVID-19, MS itself is not considered a risk factor for infection;[42,43] however, sphingosine-1-phosphate receptor modulators (fingolimod) and anti-CD20 therapies (rituximab and ocrelizumab) have been associated with increased incidence, reduced vaccine response, and greater severity of COVID-19.[44,45] Nevertheless, our study showed no differential effects of DMTs on COVID-19 incidence. Findings on URI have also been inconsistent; while a meta-analysis and randomized trial found no difference between DMTs and placebo, a recent cohort study reported higher URI rates, in comparison to untreated patients, in patients treated with rituximab, fingolimod, natalizumab, interferons, and glatiramer acetate. Our results suggest that ocrelizumab may increase URI risk compared to interferon beta-1a.[46]

Regarding dental abscess and fungal dermatitis, our findings showed that fingolimod was associated with an increased rate. Data on DMT-related dental abscess is limited, and a recent cohort study found no differential effect of DMTs on fungal dermatitis compared to untreated patients.[31] Previous findings on incidence or reactivation of rare infections during DMT therapy is limited, and similarly in our study rare complications did not reach a sufficient number of events to perform statistical analyses. PML development has been linked to natalizumab treatment in previous research, which aligns with the results of our study in which 4 out of 5 PML cases occurred in patients with natalizumab exposure, yielding a 2.3% incidence among natalizumab treated versus 0.6% in the overall study population.[47] Tuberculosis developed in 2 patients, both of whom were treated with fingolimod, 1 also received rituximab and interferon beta-1a, and the other had prior natalizumab and glatiramer acetate exposure. Among 5 patients with hepatitis, 3 had rituximab and 4 had interferon beta-1a treatment histories. Both patients with endometriosis had been exposed to rituximab and interferon beta-1a, with additional fingolimod or dimethyl fumarate use.

Among the models assessed for risk of infections, most of the models including EDSS as covariate yielded the lowest AICs, despite not reaching statistical significance in these infections. In contrast, models incorporating DMTs included several statistically significant predictors, yet showed higher AICs. EDSS may reflect a composite of functional impairment, bladder and bowel dysfunction, immobility, and increased device use, all of which contribute to infection susceptibility. Generally, the poorest fits were observed in models incorporating comorbidities, likely reflecting heterogeneous conditions with low prevalence or weaker mechanistic links to infection susceptibility in this population. Overall, these findings emphasize that while DMTs may exert direct immunological effects, EDSS may serve as a broader marker of cumulative clinical vulnerability, making it a useful indicator in infection risk modeling.

Interpretation and generalizability: This study provides real-world insight into infection risk profiles associated with various DMTs in MS. While observational in nature and, therefore, unable to confirm causality, our findings suggest that high-efficacy DMTs, particularly rituximab and natalizumab, are associated with increased risks of UTI and HSV infections, and, in the case of rituximab, bacterial vaginitis. These associations may warrant closer monitoring, especially in patients with higher disability scores or comorbidities. Fingolimod was linked to herpes zoster and, less consistently, UTI, while ocrelizumab was associated with URI. Moderate-efficacy agents such as glatiramer acetate and dimethyl fumarate were associated with increased rates of bacterial vaginitis, highlighting that even less immunosuppressive agents may carry specific risks. Interferon beta-1a, which demonstrated the lowest infection rates and is well established for safety, served as the reference.

Clinicians should consider both efficacy and infection risk when selecting DMTs, especially in vulnerable patients. While our findings support more individualized prescribing and infection surveillance, definitive treatment decisions should consider broader clinical context and be supported by future prospective studies. The study's large sample size, real-world registry data, and broad inclusion criteria enhance the generalizability to routine MS care settings. However, considering the absence of an a priori sample size calculation, given that all eligible patients were included, the results may have limited statistical power for rare outcomes. The single-center design may also reduce external validity, as local clinical practices, diagnostic thresholds, and patient characteristics might not fully reflect those in other geographic or healthcare contexts. Additionally, variation in follow-up duration, the lack of microbiological confirmation, and the non-randomized design necessitate cautious interpretation and highlight the need for confirmatory studies in broader populations.

Limitations: This study has several limitations. As an observational and retrospective cohort, it cannot establish causality, and residual confounding remains a concern despite adjustment for age, sex, EDSS, disease duration, MS subtype, and comorbidities. Several unmeasured behavioral, clinical, and lifestyle factors including smoking, hygiene, sexual activity, and bladder dysfunction were not recorded. The absence of these variables may have influenced the observed associations and limited our ability to fully adjust for confounding. Neurogenic bladder and urinary retention, known contributors to UTI, could not be directly assessed; however, EDSS and disease duration were included as indirect proxies. Additionally, asymptomatic infections and undocumented self-reports were excluded, potentially underestimating true infection rates.

Follow-up duration varied, and the overall 2-year period may have been insufficient to capture long-term or delayed-onset infections from extended DMT exposure. The lack of precise timing precluded time-to-event analysis, so outcomes were modeled using Poisson or logistic regression based on event structure. Microbiological confirmation was not feasible due to resource constraints, limiting pathogen-specific insights. Treatment responses and infection outcomes were not systematically tracked, and some rare infections could not be analyzed due to low event counts. No formal power analysis was conducted beforehand, as all available registry data were used. This may have limited our ability to detect associations for rare infections. Lastly, the single-center setting may reduce generalizability to other populations, particularly in healthcare settings with different infection surveillance protocols or treatment preferences. Future prospective, multicenter studies with predefined power calculations should incorporate these unmeasured confounders, include longer

follow-up, microbiological testing, and detailed infection outcome monitoring to validate and extend these findings.

Conclusion

This retrospective cohort study demonstrates that infection risk varies across DMTs in MS management. Rituximab and natalizumab were associated with higher rates of UTI and HSV–related ulceration, while dimethyl fumarate and glatiramer acetate showed increased bacterial vaginitis. No DMT affected COVID-19 incidence. Given limitations including retrospective design, unmeasured confounders, and low event counts for rare infections, larger prospective studies are needed to confirm these associations and guide safer, individualized DMT selection.

Conflict of Interests

The authors declare no conflict of interest in this study.

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