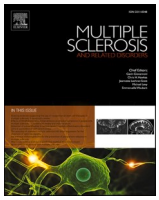
Multiple Sclerosis and Related Disorders 92 (2024) 105921

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



# Inflammatory vaginitis in women with multiple sclerosis: a retrospective analysis of B-cell depleting therapy compared to other disease modifying therapies

SHORT SUMMARY

This study investigates the occurrence of inflammatory vaginitis in women with Multiple Sclerosis (wwMS) undergoing B-cell depleting therapy versus other disease-modifying therapies (DMTs). Retrospective analysis of medical records from Stanford University between 2015–2023 shows similar rates of vaginitis in both groups, suggesting no significant association with B-cell therapy. Despite this, inflammatory vaginitis remains prevalent in both treatment groups, warranting further investigation into its mechanisms and management.

## Introduction

B-cell depleting therapy is an effective treatment for preventing relapses and stabilizing disease in multiple sclerosis (MS). (Shirani et al., 2024) There are multiple B-cell depleting therapies currently in use for the treatment of MS. Initial clinical trials demonstrated their safety and tolerability profiles. However, increased rates of complications have been noted with long term use of B-cell depleting therapies, including hypogammaglobulinemia, infections, and colitis. (Margoni et al., 2022, Quesada-Simó et al., 2023)

Vaginal mucosal inflammatory disorders have also been described in case reports of women with MS (wwMS) and rheumatologic disorders who are treated with B-cell depleting therapies. (Parrotta et al., 2023, Viera-Baptista, 2023, Sobel and Shukla, Yockey et al., 2021, Levine et al., 2024) Pyoderma gangrenosum is the best-known entity, in which patients present with painful perineal ulcerations and discharge, and biopsies show neutrophilic dermatoses. (Parrotta et al., 2023) Recently a new entity, inflammatory vaginitis, has been described in patients with vaginal discomfort, dyspareunia, and discharge with elevated white blood cell count. (Yockey et al., 2021, Levine et al., 2024) The underlying pathophysiology for inflammatory vaginitis without infection in wwMS is poorly understood. B-cells play an important role in urogenital mucosa secretory immunoglobulin (Ig) A and IgG production. (Anjuère et al., 2012) It has been hypothesized that B-cell depleting therapies may cause vaginal dysbiosis and disrupt humoral immunity at the vaginal mucosa as is seen in colitis. (Yockey et al., 2021)

There is currently no published data on risk factors or outcomes for inflammatory vaginitis in wwMS who received B-cell depleting therapy or other disease modifying therapies (DMTs). While in clinical practice we have seen cases of inflammatory vaginitis that are temporally associated with B-cell depleting therapy, it is unclear if they are associated with B-cell depleting therapy specifically or use of DMTs in general.

## Objectives

To characterize rates of inflammatory vaginitis in wwMS treated with B-cell therapy compared to those on other DMTs over a minimum of two years.

## Methods

Institutional review board approval was obtained from Stanford University. This was a retrospective review of de-identified electronic medical record data of adult female patients evaluated in the Stanford Research Repository database between 2015–2023 diagnosed with MS. Patients included in the study had initiation of DMT and a minimum of 2 years of subsequent follow up data. Demographic data was collected. ICD10 codes for MS and inflammatory vaginitis (G35; N76 and N77.1, respectively) and RxNorm and ATC Codes for B-cell therapy and DMT were used (Appendix1). Charlson comorbidity scores were generated.

The rate of vaginitis diagnosis was compared using Fischer's exact test, with a two-sided p-value less than 0.05 considered significant. To control for confounders, the arms were matched with inverse probability of treatment weighting (IPTW) based on a high dimensionality propensity score (hdPS). Stabilized weights were used to convert propensity scores into analytic weights (Appendix 2). A PS model of the hdPS covariates was fitted using a logistic regression with LASSO. Logistic regression was used for all outcome models. Analyses were performed using R version 4.2 on the Atropos Health platform.

## Results

There were 168 wwMS treated with ocrelizumab, rituximab, or ofatumumab and 714 wwMS treated with other DMT (S1P inhibitors, fumarates, interferons, natalizumab, cladribine and glatiramer acetate) for at least two years. Baseline characteristics were similar between the groups in terms of age, racial distribution, and other medical comorbidity (Table 1). Amongst patients treated with B-cell therapy there were 5 cases of inflammatory vaginitis (2.98%) compared with 17 cases (2.38%) among those treated with other DMT. The odds ratio for non-infectious vaginitis was 1.07 (95% CI 0.33–3.49, p=0.92) suggesting no significant association.

https://doi.org/10.1016/j.msard.2024.105921
Received 20 May 2024; Received in revised form 19 September 2024; Accepted 5 October 2024
Available online 17 October 2024

**Table 1**
. Baseline characteristics of patients on B-cell therapy and other disease modifying therapy.

| | Other DMT | B-cell therapy | P-value |
|---|---|---|---|
| N | 714 | 168 | |
| Female (%) | 714 (100%) | 168 (100%) | |
| Mean age years (SD) | 47.6 (13.1) | 46.7 (13.8) | 0.745 |
| Race | | | 0.182 |
| White | 497 (69.6%) | 105 (62.5%) | |
| Other | 126 (17.6%) | 33 (19.6%) | |
| Black | 51 (7.1%) | 14 (8.3%) | |
| Asian | 40 (5.6%) | 28 (9.5%) | |
| Hispanic | 72 (10%) | 28 (16%) | 0.015 |
| Charlson Comorbidity Index | 1.2 (1.6) | 1.2 (1.8) | 0.919 |
| Mean follow up time, years (SD) | 5.85 (2.36) | 4.64 (2.2) | |
| Vaginitis | 17 (2.38%) | 5 (2.98%) | 0.920 |

## Conclusion

In this retrospective case-controlled study, we sought to assess the relation between B-cell depleting therapy and inflammatory vaginitis in wwMS. This study did not find an association between inflammatory vaginitis and treatment with B-cell depleting therapy after controlling for multiple covariates. Despite the absence of difference between treatment groups, 2.98% of wwMS on B-cell depleting therapy and 2.38% of patients receiving other DMTs developed inflammatory vaginitis. The prevalence, mechanism, and treatment for inflammatory vaginitis in the general population and in wwMS are poorly understood, and this investigation contributes new data about the prevalence of this disorder.

Recent studies have explored the effects of B-cell depleting therapy on other mucosal inflammatory disorders in patients with MS and rheumatologic disease, namely inflammatory colitis. (Quesada-Simó et al., 2023) B-cell suppression leads to a reduction in gastrointestinal mucosal IgA and IL-10 and has been associated with severe colitis in patients with inflammatory bowel disease on rituximab. (Goetz et al., 2007, Suzuki et al., 2003) There are numerous hypotheses for how B-cells may influence the development of mucosal inflammatory disorders. B-cells provide local immunity to gastrointestinal mucosa by producing secretory IgA and IgM. Secretory immunoglobulins defend against colonization of microbes, aid in microbial clearance, and suppress the recruitment of other immune cells and their secretion of inflammatory cytokines. (Brandtzaeg et al.) In addition, B-cells secrete IL-10, an anti-inflammatory cytokine that inhibits antigen presentation and antigen-specific proliferation of T-cells. (Goetz et al., 2007)

B-cells also maintain the vaginal mucosa via secretory Ig production, and it has been hypothesized that B-cell depleting therapies may disrupt vaginal humoral immunity in a similar manner as has been shown in colitis. (Yockey et al., 2021, Anjuère et al., 2012) While this study did not show a difference in the rate of inflammatory vaginitis among patients receiving B-cell depleting therapy compared to those on other DMTs, this entity was prevalent in both treatment groups. It is possible vaginitis may be due to an autoinflammatory process for which wwMS are at higher risk than patients without a propensity for autoimmunity. Inflammatory vaginitis is increasingly observed in clinical neuroimmunology practice and further studies are needed to better understand the mechanism, provoking factors, and optimal treatment for this condition.

Desquamative inflammatory vaginitis has been described in patients with vaginal inflammation found to have colonization of facultative aerobic bacteria causing purulent discharge. While desquamative inflammatory vaginitis has a prevalence of 2–25% worldwide, it has been observed specifically in patients with autoimmune disorders and in those who received B-cell depleting therapy. (Viera-Baptista, 2023, Sobel and Shukla) In our review of inflammatory vaginal mucosal disorders described in the literature, we note that there may be overlap between inflammatory vaginitis and desquamative inflammatory vaginitis. Both disorders present with non-infectious vaginal irritation and have findings of purulent discharge and abnormal vaginal flora in desquamative inflammatory vaginitis, and discharge with elevated white blood cell count in inflammatory vaginitis. (Viera-Baptista, 2023, Yockey et al., 2021) Clinical criteria for diagnosing these disorders are ill-defined, and further research is needed to delineate these entities better.

This is the first published study to assess rates of inflammatory vaginitis in a larger population of wwMS, however, there are a few limitations to recognize. First, this was a retrospective case-controlled study in which we used ICD codes to identify patients with inflammatory vaginitis, which may not have fully captured the population of wwMS with vulvovaginal symptoms. Due to inherent imprecision in the chosen ICD10 codes, it is plausible that some of the patients with the outcome of interest were more accurately attributed to infectious vaginitis, rather than non-infectious. Of note, there is variability in the time to onset of inflammatory vaginitis and amongst patients taking DMT and there was a difference in length of follow-up between our two groups. In addition, this study did not explore differences among MS subtype, level of disability, relevant labs such as CD19 and CD20 counts, serum Ig levels, treatments or outcomes. These factors present future areas for exploration to better predict which wwMS are at risk for developing inflammatory vaginitis. This study also did not include data about length of time on DMT. This is another important factor that should be looked at in future studies.

## CRediT authorship contribution statement

**Sarah Conway:** Writing – original draft, Conceptualization. **Cory Dodson:** Writing – review & editing, Writing – original draft. **Gavin Hui:** Writing – review & editing, Formal analysis, Data curation. **C. William Pike:** Writing – review & editing, Formal analysis. **Kristin Galetta:** Writing – original draft, Validation, Investigation, Conceptualization.

## Declaration of competing interest

Kristin Galetta has no disclosures, Sarah Conway has served on advisory boards for Bristol-Myers Squibb, EMD Serono, Horizon Therapeutics and Genentech, Cory Dodson has no disclosures, C. William Pike has no disclosures, Gavin Hui has no disclosures

## Role of funding

There was no funding for this project.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.105921.

## References

Anjuère, F, Bekri, S, Bihl, F, et al., 2012. B cell and T cell immunity in the female genital tract: Potential of distinct mucosal routes of vaccination and role of tissue-associated dendritic cells and natural killer cells. Clin. Microbiol. Infection 18, 117–122.
Brandtzaeg P, Carlsen HS, Halstensen TS. *The B-Cell System in Inflammatory Bowel Disease*.
Goetz, M, Atreya, R, Ghalibafian, M, et al., 2007. Exacerbation of ulcerative colitis after rituximab salvage therapy. Inflamm. Bowel. Dis. 13, 1365–1368.
Levine, L, Son, J, Yu, A, et al., 2024. Inflammatory vaginitis in four B-cell suppressed women with Multiple Sclerosis. Mult. Scler. Relat. Disord. 82. https://doi.org/10.1016/j.msard.2023.105387. Epub ahead of print 1 February.
Margoni, M, Preziosa, P, Filippi, M, et al., 2022. Anti-CD20 therapies for multiple sclerosis: current status and future perspectives. J. Neurol. 269, 1316–1334.
Parrotta, E, Kopinsky, H, Abate, J, et al., 2023. It's not always an infection: Pyoderma gangrenosum of the urogenital tract in two patients with multiple sclerosis treated with rituximab. Mult. Scler. Relat. Disord. 70. https://doi.org/10.1016/j.msard.2022.104483. Epub ahead of print 1 February.
Quesada-Simó, A, Garrido-Marín, A, Nos, P, et al., 2023. Impact of Anti-CD20 therapies on the immune homeostasis of gastrointestinal mucosa and their relationship with de

novo intestinal bowel disease in multiple sclerosis: a review. Front. Pharmacol. 14. https://doi.org/10.3389/fphar.2023.1186016. Epub ahead of print.
Shirani, A, Stuve, O, Cross, AH., 2024. Role of B Cells in Relapsing-Remitting and Progressive Multiple Sclerosis and Long-Term Effects of B Cell Depletion. Neurol. Clin. 42, 137–153.
Sobel JD, Shukla A. Clinical Research in Infectious Diseases Desquamative Inflammatory Vaginitis as an extra-articular Manifestation of Rheumatoid Arthritis?
Suzuki K, Meek B, Doi Y, et al. *Aberrant expansion of segmented filamentous bacteria in IgA-deficient gut*, www.pnas.orgcgidoi10.1073pnas.0307317101 (2003).
Viera-Baptista, PSCK, 2023. SJ. *International Society for the Study of Vulvovaginal Disease Recommendations for the Diagnosis and Treatment of Vaginitis*. Ad Médic, Lda. https://doi.org/10.59153/adm.rdtv.001. Epub ahead of print 2023.
Yockey, L, Dowst, S, Zonozi, R, et al., 2021. Inflammatory vaginitis in women on long-term rituximab treatment for autoimmune disorders. BMC. Womens Health 21. https://doi.org/10.1186/s12905-021-01423-0. Epub ahead of print 1 December.

Sarah Conway[a], Cory Dodson[b], Gavin Hui[c], C. William Pike[c], Kristin Galetta[b,*]

[a] *Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA*

[b] *Department of Neurology, Stanford University, Palo Alto, CA, USA*

[c] *Atropos Health, New York, NY, USA*

[*] Corresponding author at: 203 Quarry Rd, Department of Neurology, Stanford University, Palo Alto, CA, USA.
*E-mail address:* kgaletta@stanford.edu (K. Galetta).