Brief report

Infection risk of rituximab monotherapy versus combination therapy with rituximab and mycophenolic acid in systemic sclerosis: A retrospective cohort study

To the Editor: Systemic sclerosis (SSc) is a clinically heterogeneous fibrosing disease driven by immune dysregulation.[1] The B-cell-depleting monoclonal antibody rituximab (RTX) is an important treatment but carries increased infection risk.[2] Often SSc patients are treated with dual immunomodulation by combining RTX with agents like mycophenolic acid (MPA), an inhibitor of lymphocyte proliferation.[3] However, it is unclear if adding MPA increases infection risk relative to RTX alone.[4] In this retrospective cohort study, we studied infection risk in SSc patients treated with RTX monotherapy versus RTX with MPA.

We reviewed the charts of patients with SSc treated with RTX at 2 large academic medical centers, Brigham and Women's and Massachusetts General Hospitals, from 2004 to 2024. Patients were included if their diagnosis was confirmed by a dermatologist and/or rheumatologist and were excluded if they had undergone lung transplantation, received RTX for malignancy, received methotrexate concurrently, or had incomplete records. We defined the RTX active treatment window as the 6-month period following infusion; if patients received multiple infusions, we combined the time periods following each infusion together.[5] We defined each patient's follow-up period as the overlap between the RTX treatment window and any concurrent use of MPA (either as mycophenolic sodium or its prodrug mycophenolate mofetil). Infection risk was measured by the number of antimicrobial prescriptions during the follow-up period, controlling for sex, systemic steroid use (average monthly prednisone-equivalent dose), and

Table I. Cohort characteristics

	RTX	RTX with MPA	Overall	*P* value
Number of patients	51	43	94	
Age at first RTX dose (y)				
Mean (SD)	53 (14)	52 (14)	52 (14)	.99
Median [min, max]	52 [24, 83]	57 [23, 73]	55 [23, 83]	
Sex				
F	44 (86.3%)	27 (62.8%)	71 (75.5%)	.017
M	7 (13.7%)	16 (37.2%)	23 (24.5%)	
Follow-up duration (mo)				
Mean (SD)	32 (28)	14 (11)	24 (23)	.00053
Median [min, max]	20 [1.9, 115]	12 [0.90, 51]	15 [0.90, 115]	
Average prednisone-equivalent monthly steroid use (mg)				
Mean (SD)	160 (270)	120 (190)	140 (240)	.56
Median [min, max]	48 [0, 1500]	42 [0, 960]	48 [0, 1500]	
Number of antimicrobials				
Mean, absolute (SD)	3.1 (3.8)	2.3 (4.5)	2.8 (4.1)	.45
Median, absolute [min, max]	2 [0, 17]	1 [0, 22]	1 [0, 22]	
Mean, per mo (SD)	0.16 (0.29)	0.19 (0.34)	0.18 (0.31)	
Median, per mo [min, max]	0.065 [0, 1.7]	0.034 [0, 1.3]	0.050 [0, 1.7]	

Patient demographics (age, sex), duration of follow-up, and number of antimicrobial prescriptions. Both the absolute number of prescriptions and number normalized by treatment duration (per month) are shown. For continuous demographic variables (eg age, follow-up duration), *P* values are derived from a Wilcoxon rank sum test. For categorical variables (eg sex), *P* values are derived from a Chi-squared test. For antimicrobial prescriptions, we show the Wald *P* values from negative binomial regression, testing the association between absolute number of prescriptions and treatment group, controlling for sex, steroid dosage, and follow-up duration.
MPA, Mycophenolic acid (as mycophenolate mofetil or mycophenolate sodium); *RTX*, rituximab; *SD*, standard deviation.

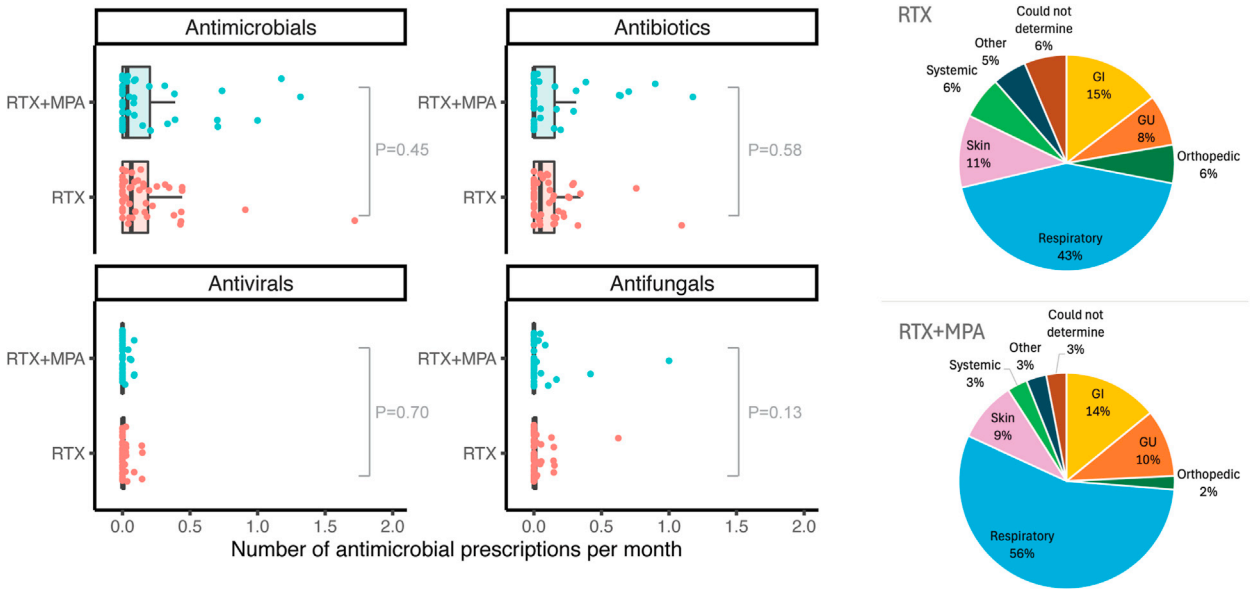

Fig 1. Antimicrobial prescriptions by infection type and affected organ system in systemic sclerosis. Patients received either rituximab monotherapy (RTX, *blue*) or RTX with mycophenolic acid (RTX + MPA, *red*). On the left, boxplots show the number of total antimicrobial prescriptions, then separated by antibiotic, antiviral, and antifungal. Because the number of RTX cycles differed across patients (6-month follow-up period per cycle), the x-axis is normalized by total follow-up duration. Boxplot *center line* represents the median; lower and upper box limits represent the 25% and 75% quantiles, respectively; whiskers extend to box limit ±1.5 × IQR; all individual points are overlaid. *P* values represent Wald *P* values derived from negative binomial regression. On the right, pie charts show breakdown of infection type for each treatment group. *GI*, Gastrointestinal; *GU*, genitourinary.

follow-up duration using negative binomial regression. Antimicrobials prescribed for prophylaxis (eg trimethoprim-sulfamethoxazole, valacyclovir), non infectious indications (eg doxycycline for rosacea), and duplicate therapies (eg outpatient prescription carried over from inpatient) were excluded.

Three hundred twenty patient records were reviewed, and 94 patients (23 males, 71 females) were retained after applying the inclusion and exclusion criteria. These patients were divided into 2 groups (Table I): RTX monotherapy ($n = 51$) and RTX with MPA ($n = 43$). The average follow-up period was 24 months (range 0.9-115). Two hundred sixty antimicrobial prescriptions were recorded (194 bacterial, 26 viral, and 40 fungal).

We found no significant difference in infection risk between RTX monotherapy and RTX with MPA (Fig 1, Table I). Patients receiving RTX monotherapy had an average of 0.16 antimicrobial prescriptions per month, compared to 0.19 for RTX with MPA ($P = .45$). Similarly, no significant differences were observed when analyzing bacterial ($P = .58$), viral ($P = .70$), or fungal ($P = .13$) infections individually (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/5tj8phdkj8/1), or when considering only antimicrobials prescribed while inpatient ($P = .75$). When restricting the analysis to patients prescribed at least one antimicrobial, there was no significant difference in number of subsequent prescriptions between the groups ($P = .09$). In both groups, the most common infection types were respiratory and gastrointestinal (Fig 1).

This study informs patients and physicians considering combining RTX with MPA in SSc. Our findings suggest that adding MPA to RTX therapy does not result in a statistically significant increase in infection risk. The use of antimicrobial prescriptions as a surrogate for infection risk is both objective and quantifiable; however, it may not capture all infections, especially those not requiring treatment. Further studies with larger patient populations are needed to fully characterize infection risks of dual immunomodulation in SSc.

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Conflicts of interest

Dr S. Smith is a consultant and/or investigator for Biogen. Drs Kang, Nabel Smith, Silverman, LaChance, and Authors Meara and Cho have no conflicts of interest to declare.

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