Incidence of COVID-19 Hospitalization in Patients with Immune-Mediated Inflammatory Disorders Taking Rituximab

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Disclosures

- Nicole Mastacouris & Andrew Strunk have no relationships to disclose.
- Dr. Garg has received personal fees from AbbVie, Aclaris Therapeutics, Anaptys Bio, Aristea Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Incyte, InflaRx, Insmed, Janssen, Novartis, Pfizer, Sonoma Biotherapeutics, UCB, Union Therapeutics, and Viela Biosciences, and receives honoraria. Dr Garg receives research grants from AbbVie, UCB, National Psoriasis Foundation, and CHORD COUSIN Collaboration (C3). Dr Garg is co-copyright holder of HiSQOL and HS-IGA instruments
- Funding Source: None

Background & Rationale

- Rituximab (RTX) is an anti-CD20 monoclonal antibody that is widely used in the treatment of immune-mediated inflammatory disorders (IMIDs)
- Data on risk of severe COVID-19 hospitalization for IMID patients prescribed RTX is limited
- Previous studies assessing COVID-19 hospitalization in IMID patients taking RTX relative to other therapies are limited by:
  - Lack of adjustment for comorbidities/medications that may influence the outcome[1,2]
  - Selection bias due to method of recruitment/enrollment [3,4]
  - Single-center analysis, limiting generalizability [2,5]

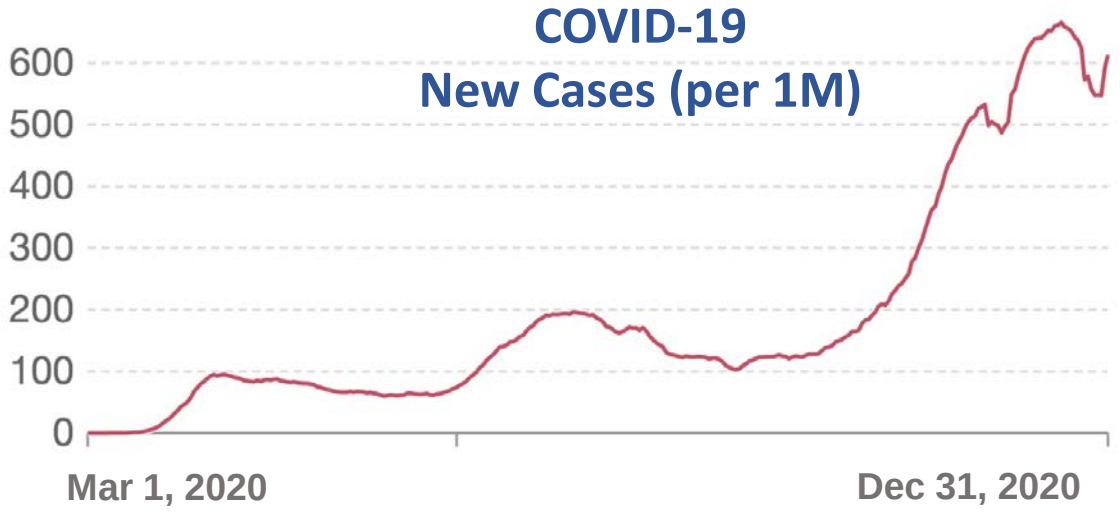
1. Cordtz et al. COVID-19 infection and hospitalization risk according to vaccination status and DMARD treatment in patients with rheumatoid arthritis. Rheumatology (Oxford). 2022;62(1):77-88.
2. Bachiller-Corral et al. Risk of Severe COVID-19 Infection in Patients With Inflammatory Rheumatic Diseases. J Rheumatol. 2021;48(7):1098-1102.
3. Sparks et al. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 Global Rheumatology Alliance physician registry. Annals of the Rheumatic Diseases 2021;80:1137-1146.
4. Avouac et al. COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. Lancet Rheumatol. 2021;3(6):e419-e426.
5. Smith et al. Risk of COVID-19 infection and severe disease in MS patients on different disease-modifying therapies. Mult Scler Relat Disord. 2022;60:103735.

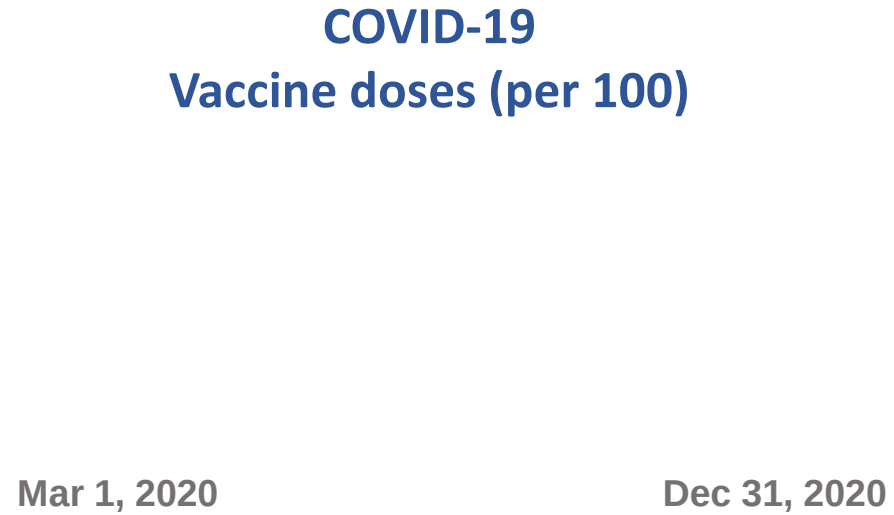
Study Objective

- **Primary Objective:** To compare risk of COVID-19-related hospitalization in adults with IMIDs prescribed RTX and those prescribed conventional immunosuppressants (CI) (cyclosporine, mycophenolate, or azathioprine)
- **Selected IMIDs:**
  - Rheumatoid arthritis (RA)
  - Pemphigus vulgaris (PV)
  - Granulomatosis with polyangiitis (GPA)
  - Microscopic polyangiitis (MPA)
  - Bullous pemphigoid (BP)
  - Dermatomyositis (DM) or polymyositis (PM)
  - Ankylosing spondylitis (AS)
  - Systemic lupus erythematosus (SLE)
  - Multiple sclerosis (MS)
  - Neuromyelitis Optica (NMO)

Methods

- **Study Design:** Retrospective cohort study of IBM Explorys® database from March 1st, 2020, to December 31st, 2020.

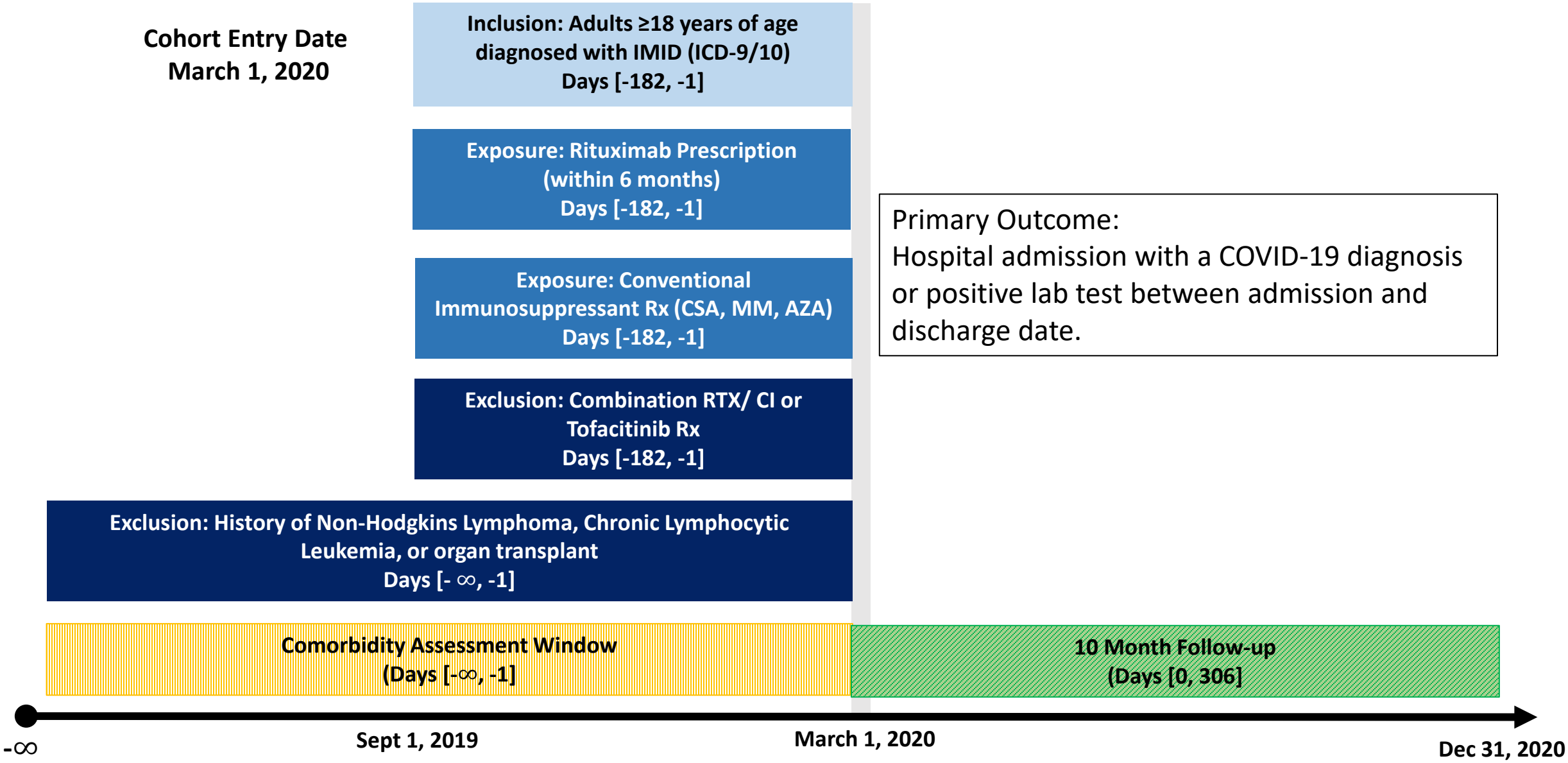




Official data collated by Our World in Data, Johns Hopkins University CSSE COVID-19 Data

**Limited testing and challenges in the attribution of cause of death means the case counts may not be accurate*

Methods



Primary Outcome:
Hospital admission with a COVID-19 diagnosis or positive lab test between admission and discharge date.

Methods

➢Statistical Analysis

- Propensity score weighting was used to account for potential differences in severe COVID-19 risk factors between RTX and CI groups:
  - Demographic data, comorbidities, prednisone and methotrexate exposure prior to index date

➢Sensitivity Analysis

- Repeat of primary analysis, expanding RTX exposure period to ***12 months*** before index

Results- Demographics

Characteristic	RTX Cohort (n=1090)	Conv. Immunosup. Cohort (n=1945)
Age, Mean (SD)	58 (15)	54 (16)
Females (%)	809 (74%)	1583 (81%)
Race/ethnicity		
White	751 (73%)	1077 (58%)
Black	210 (20%)	601 (33%)
Asian	11 (1.1%)	31 (1.7%)
Hispanic/Latino	7 (0.68%)	29 (1.6%)
Other/Multiracial	54 (5.2%)	104 (5.6%)
Medicaid Insurance	95 (12%)	225 (17%)

Results – Distribution of IMIDs

Immune-mediated Inflammatory Disorder (IMID)	RTX Cohort (n=1090)	Conv. Immunosup. (n=1945)
Rheumatoid Arthritis	**614 (58%)**	457 (23%)
Systemic Lupus Erythematosus	102 (9.4%)	1059 (54%)
Dermato/polymyositis	39 (3.6%)	287 (15%)
Granulomatosis with Polyangiitis	**150 (14%)**	88 (4.5%)
Multiple Sclerosis	**139 (13%)**	56 (2.9%)
Neuromyelitis Optica	**117 (11%)**	37 (1.9%)
Microscopic Polyangiitis	**35 (3.2%)**	9 (0.46%)
Bullous Pemphigoid	4 (0.37)	57 (2.9%)
Pemphigus Vulgaris	16 (1.5%)	27 (1.4%)
Ankylosing Spondylitis	3 (0.28%)	22 (1.1%)

Results – Comorbidities

Characteristic	RTX Cohort (n=1090)	Conv. Immunosup. (n=1945)
BMI, Mean (SD)	30 (7.5)	30 (8.2)
Hypertension	564 (52%)	1147 (59%)
COPD	258 (24%)	491 (25%)
Type II DM	214 (20%)	391 (20%)
Asthma	183 (17%)	386 (20%)
Heart Failure	105 (9.6%)	279 (14%)
CKD	270 (25%)	722 (37%)
Stroke	73 (6.7%)	195 (10%)
Cancer (non-hematologic)	180 (17%)	239 (12%)

Results – COVID-19 Related Hospitalizations

6-month medication exposure period

Outcome	Rituximab (n=1,090)	Conv.Immunosup (n=1,945)
# of COVID-19-related hospitalizations	13	18
Cumulative incidence of hospitalization	1.19% (0.70 - 2.03)	0.93% (0.59 -1.46)
Unadjusted HR (95% CI)	1.29 (0.63-2.63)	Reference
Adjusted[a] HR (95% CI)	1.76 (0.60-5.12)	Reference
Adjusted Risk Difference[b] per 1,000 patients	5.12 (-3.88, 14.11)	Reference
P-value (Adjusted HR)	0.30	-

a – Adjusted hazard ratio was calculated based on a propensity score-weighted Cox proportional hazards regression model, with weights trimmed at the 95th percentile.
b – Adjusted risk difference was calculated based on a propensity score-weighted log-binomial regression model with identity link function, with weights trimmed at the 95th percentile.

Statistical Considerations

Outcome	Rituximab (n=1,090)	Conv. Immunosup (n=1,945)
Adjusted HR (95% CI)	1.76 (0.60-5.12)	Reference
P-value (Adjusted HR)	0.30	-

- Absence of a *statistically significant* difference is not the same as affirmative evidence of *no difference.*
- The confidence interval indicates that our data is compatible with a wide range of treatment effects when generalizing outside of the current sample.

Results – COVID-19 Related Hospitalizations

Comparison of Primary and Sensitivity Analysis

	Sensitivity Analysis 12 Month RTX Exposure Period			Primary Analysis 6 Month RTX Exposure Period	
Outcome	Rituximab (n=1,518)	CI (n=1,897)		Rituximab (n=1,090)	CI (n=1,945)
# of COVID-19-related hospitalizations	18	18		13	18
Cumulative incidence of hospitalization	1.19% (0.75-1.87)	Reference		1.19% (0.70 - 2.03)	0.93% (0.59 - 1.46)
Unadjusted HR (95% CI)	1.25 (0.65-2.40)	Reference		1.29 (0.63-2.63)	Reference
Adjusted HR (95% CI)	**1.53 (0.59-3.93)**	Reference		1.76 (0.60-5.12)	Reference
Adjusted Risk Difference per 1000	4.07 (-4.35, 12.5)	Reference		5.12 (-3.88, 14.11)	Reference
P-value (Adjusted HR)	0.38	-		0.30	-

Discussion

Comparison of 12 Mo Analysis and Study by MacKenna et al[6]

	12 Month RTX Exposure Period (Sensitivity Analysis)			MacKenna et al[6] (12 mo RTX exposure period)	
Outcome	Rituximab (n=1,518)	Conv. Immunosup (n=1,897)		Rituximab (n=1,998)	Standard Therapy (n=181,694)
# of COVID-19-related hospitalizations	18	18		40	1787
Unadjusted HR (95% CI)	1.25 (0.65-2.40)	Reference		2.04 (1.49-2.79)	Reference
Adjusted HR (95% CI)	1.53 (0.59-3.93)	Reference		1.51 (1.10-2.06)	Reference
P-value (Adjusted HR)	0.38	-		0.01	-

6. MacKenna et al. Risk of severe COVID-19 outcomes associated with immune-mediated inflammatory diseases and immune-modifying therapies: a nationwide cohort study in the OpenSAFELY platform. *Lancet Rheumatol*. 2022;4(7):e490-e506.

Discussion

Comparison of Sensitivity Analysis & MacKenna Study Methods

Variable	Our Analysis	MacKenna et al[6]
Exposure to *both* RTX + Conventional Immunosuppressant therapy	Excluded	Included in RTX cohort
History of Hematologic Cancer	Excluded	Included
History of Organ Transplant	Excluded	Included

6. MacKenna et al. Risk of severe COVID-19 outcomes associated with immune-mediated inflammatory diseases and immune-modifying therapies: a nationwide cohort study in the OpenSAFELY platform. *Lancet Rheumatol*. 2022;4(7):e490-e506.

Discussion

Literature Review – Risk of COVID-19 hospitalization w/ RTX exposure

Range of effect estimates = 1.51 – 4.71

Study	Population (IMID)	Comparator Group (Treatment)
MacKenna 2022, UK	RA, PsA, AS, IBD, Pso, HS	Leflunomide, MTX, MM, CSA, SSZ, 6-MP, Thioguanine, AZA
Cortdtz 2022, Denmark	RA	cs-DMARDs (MTX, SSZ, AZA, Hydroxychloroquine, and "other")
Raiker 2021, USA	RA	TNF-inhibitor
Sparks 2021, Global Registry	RA	TNF-inhibitor
Avouac 2021 French Registry	RA, ANCA, SS, SLE, DM/PM	CS, MTX, Leflunomide, SSZ, MM, AZA, TNFi, Anti IL6/17A/1, JAKi
Singh 2023, USA	RA	csDMARDs (MTX, Hydroxychloroquine, SSZ, Leflunomide)
Longetti 2022, Sweden	MS	[1] Fingolimod [2] Natalizumab

- ***Other studies suggest increased risk with RTX exposure, despite differences in comparator groups***
- ***Our analysis found similar results while addressing limitations of several previous analyses (ie, selection bias and minimal adjustment for confounders)***

Conclusions

- Among participants in our sample, risk of COVID-19 related hospitalization was higher in patients with IMIDs exposed to RTX compared to those exposed to conventional immunosuppressants
- Results were imprecise, but direction and magnitude of effect was consistent with previous analyses

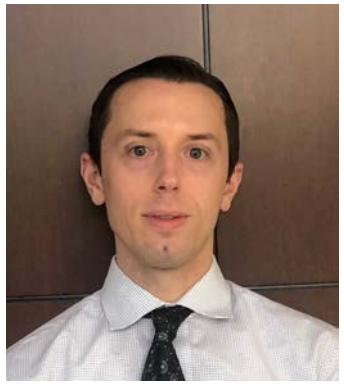
Conclusions

USA CDC Vaccination Data, March 2023

Percent of People Receiving COVID-19 Vaccine by Age and Date Administered, USA December 14, 2020 – March 08, 2023				
Age	18-24	25-49	50-64	65+
Completed Primary Series	**66.6%**	**72.1%**	**83.7%**	94.3%
Updated (Bivalent) Booster Dose	**6.9%**	**11.5%**	**20.9%**	**41.6%**

- Based on our analysis, the available data, and modest vaccination/booster penetration in the US, physicians may emphasize risk mitigation strategies for Rituximab exposure

Acknowledgments



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Questions

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