Journal of Microbiology, Immunology and Infection 58 (2025) 272–275

Contents lists available at ScienceDirect

Journal of Microbiology, Immunology and Infection

journal homepage: www.e-jmii.com

Increased SARS-CoV-2-related hospitalization and mortality in rheumatoid arthritis patients receiving rituximab therapy-a monocentric retrospective study

Chrong-Reen Wang [a,*], Chih-Hui Hsu [b], Wei-Chieh Lin [c]

[a] Division of Rheumatology and Immunology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan
[b] Biostatistics Consulting Center, Clinical Medicine Research Center, National Cheng Kung University Hospital, Tainan, Taiwan
[c] Division of Critical Care Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan

ARTICLE INFO

Keywords:
SARS-CoV-2
Rheumatoid arthritis
Rituximab
Hospitalization
COVID19 pneumonia
Mortality

ABSTRACT

From 2022 April to 2024 August, retrospective analyses by multivariable logistic regression were conducted in 341 rheumatoid arthritis patients receiving rituximab (RTX), tofacitinib (TOF) or disease-modifying-anti-rheumatic drug (DMARD) alone therapy. Compared to DMARD alone or TOF treatment, RTX therapy had increased adjusted odds ratios of SARS-CoV-2-related hospitalization, pneumonia and mortality.

1. Introduction

In the era of coronavirus disease 2019 (COVID-19), there are higher infection risk and poorer disease outcome in systemic rheumatic diseases like rheumatoid arthritis (RA).[1] Besides compromised immune system due to disease itself, corticosteroids (CS) or immunosuppressants (IS) therapy makes such patients susceptible to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection with more serious illness.[2] Accumulated evidence has shown that administration of rituximab (RTX), a B-cell depleting monoclonal antibody, increases the severity in SARS-CoV-2 infection.[2,3] Persistent depletion of B lymphocytes harms the immune responses with insufficient production of antiviral antibodies, leading to protracted course and fatal outcome due to the difficulty in clearing viral invasion.

The severity of SARS-CoV-2 has declined throughout the inception of COVID-19 pandemic with different waves of variants. The omicron variant has dominated with increased viral transmissibility since December 2021. RA had increased COVID-19 illness during the initial pandemic wave, while such patients remain at risk in the omicron variant prevailing period, requiring vaccination and anti-viral medication.[4] In Taiwan, owing to the modification of COVID-19-zero to -coexisting policy, a domestic epidemic of omicron variant has initiated since April 2022. Furthermore, omicron lineages have higher transmissibility with rapidly increasing occurrences of KP.2, KP.3 and LB.1 variants in domestic specimens since June 2024. Till now, there are more than ten million infected citizens with an over 44 % infection rate.

Since this domestic omicron outbreak, despite the reported RA case with fatal COVID-19 pneumonia under RTX treatment,[5] larger-scale monocentric studies for the impact of such therapy on SARS-CoV-2 infection consequences are unavailable. A retrospective investigation was conducted in RA patients for COVID-19 disease severity under RTX therapy at the National Cheng Kung University Hospital (NCKUH).

2. Methods

2.1. Patients enrollment

A retrospective review of medical records was performed in patients who met the 2010 RA classification criteria and received regular follow-up at the outpatient clinics from April 1, 2022 to August 31, 2024. This study was approved by the NCKUH Institutional Review Board.

3. Data collection

28-joint Disease Activity Score (DAS28) was obtained for evaluating articular activity. Laboratory parameters comprised anti-citrullinated

* Corresponding author.
E-mail address: wangcr@mail.ncku.edu.tw (C.-R. Wang).

https://doi.org/10.1016/j.jmii.2025.01.004
Received 3 September 2024; Received in revised form 20 November 2024; Accepted 19 January 2025
Available online 28 January 2025

Table 1
Baseline data of 341 RA patients under RTX, TOF or DMARD alone therapy and their SARS-CoV-2 infection consequences.

Group (no.)	RTX (n = 99)	TOF (n = 118)	DMARD alone (n = 124)	RvT/ RvD/TvD *p* value
Total patient-years of follow-up	195.4	236.6	255.0	
Female no. (%)	80 (80.8)	97 (82.2)	100 (80.6)	NS/NS/ NS
Age (years)	63.5 ± 14.0 (24~89)	62.2 ± 13.0 (26~88)	61.5 ± 11.9 (25~85)	NS/NS/ NS
Seropositivity no. (%)	90 (90.9)	101 (86.4)	106 (85.5)	NS/NS/ NS
Presence of comorbidity[a] no. (%)	56 (56.6)	59 (50.0)	63 (50.8)	NS/NS/ NS
DAS28 score	2.94 ± 0.67 (1.6~5.0)	2.82 ± 0.65 (1.5~4.7)	2.87 ± 0.71 (1.7~4.9)	NS/NS/ NS
Remission or low activity (%)	70.7	79.7	75.8	NS/NS/ NS
Prednisolone no. (%)	42 (42.4)	45(38.1)	52 (41.9)	NS/NS/ NS
Dosage (mg/day)	5.9 ± 2.5 (2.5~10)	5.0 ± 2.1 (2.5~10)	5.1 ± 2.2 (2.5~10)	NS/NS/ NS
Methotrexate no. (%)	46 (46.5)	47 (39.8)	58 (46.8)	NS/NS/ NS
Dosage (mg/week)	10.4 ± 3.2 (7.5~15)	9.8 ± 2.6 (7.5~15)	9.7 ± 2.6 (7.5~15)	NS/NS/ NS
Leflunomide no. (%)	4 (4.0)	4 (3.4)	5 (4.0)	NS/NS/ NS
Dosage (mg/day)	17.5 ± 5.0 (10 or 20)	12.5 ± 5.7 (10 or 20)	16.0 ± 5.5 (10 or 20)	NS/NS/ NS
Hydroxychloroquine no. (%)	22 (22.2)	21 (17.8)	34 (27.4)	NS/NS/ NS
Dosage (mg/day)	304.3 ± 102.2 (200 or 400)	324.0 ± 99.5 (200 or 400)	311.8 ± 100.8 (200 or 400)	NS/NS/ NS
Sulfasalazine no. (%)	18 (18.2)	15 (12.7)	27 (21.8)	NS/NS/ NS
Dosage (gram/day)	1.7 ± 0.5 (1 or 2)	1.9 ± 0.4 (1 or 2)	1.8 ± 0.4 (1 or 2)	NS/NS/ NS
Infected no. after therapy (%)	57 (57.6)	58 (49.1)	61 (49.2)	NS/NS/ NS
Hospitalization[b] no. (% infected)	12 (21.1)	3 (5.2)	3 (4.9)	0.013/ 0.012/NS
Pneumonia[c] no. (% infected)	7 (12.3)	0 (0)	0 (0)	0.006/ 0.005/NS
Death[d] no. (% infected)	6 (10.5)	0 (0)	0 (0)	0.013/ 0.011/NS
Maximum score at each admission	7.1 ± 2.5 (4~10)	4.3 ± 0.6 (4 or 5)	4.0 ± 0.0 (4)	0.048/ 0.005/NS

CPS: clinical progression scale, DAS28: 28-joint Disease Activity Score, DMARD: disease-modifying anti-rheumatic drugs, no.: number, NS: not significant, RTX: rituximab, RvD: RTX versus DMARD alone, RvT: RTX versus TOF, TvD: TOF versus DMARD alone, TOF: tofacitinib.

[a] Comorbidity including obesity, pregnancy, smoking, cancer, diabetes, cardiovascular, cerebrovascular, mental, neurodegenerative, chronic infection, kidney, lung and liver disease.

[b] Hospitalization with a ≥4 score by WHO CPS.

[c] Chest image with ground-glass opacity requiring hospitalization and oxygen support with a ≥6 score.

[d] Death due to SARS-CoV-2 infection with a 10 score.

peptide antibody (ACPA), rheumatoid factor (RF), B-cell counts and serum IgG levels. Seropositivity was the presence of ACPA or RF. Medication profiles included CS, disease-modifying anti-rheumatic drugs (DMARD) with hydroxychloroquine (HCQ), leflunomide (LEF), methotrexate (MTX) and sulfasalazine (SAZ) as well as biologics and Janus kinase inhibitors (JAKi) like RTX and tofacitinib (TOF), respectively. Data were the information at initial enrollment of patients into this study.

SARS-CoV-2-associated data comprised infection-related history, viral confirmation tests, the presence co-morbidity (obesity, pregnancy, smoking, cancer, diabetes, cardiovascular, cerebrovascular, mental, neurodegenerative, chronic infection, kidney, lung, liver disease),[6] anti-viral/immunomodurating agents, chest images and WHO clinical progression scale (CPS).[7]

3.1. Statistical analyses

Data were expressed as the mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Numerical data between two groups were compared by Mann-Whitney test. Categorical data between two groups were analyzed by chi-square/ Fisher's exact test.

In RA patients, CS use can enhance the COVID-19-related death, while the presence of co-morbidity is associated with increased SARS-CoV-2-associated mortality.[2,8] Multivariable logistic regression with Firth's penalized likelihood was performed, and adjusted for demographic age/sex, CS use and the presence of co-morbidity to evaluate the association between RTX treatment and SARS-CoV-2 infection consequences including infection, hospitalization, COVID-19 pneumonia and COVID-19-related death, with DMARD alone or TOF therapy as referent category. Crude odds ratios and adjusted odds ratios (AOR) with 95 % confidence intervals were shown.

All analyses were conducted by using SAS software 9.4 version (SAS Institute Inc, Cary, NC, USA). A p value less than 0.05 was considered significant.

4. Results

In Table 1, 99 patients, 80 females aged 28–89 years (63.5 ± 14.0), received RTX therapy, with 1 g × two fortnightly every 6 months regimen and 1 to 50 (17.8 ±

11.7) infusion. DAS28 was 2.94 ± 0.67, 70.7 % of patients in remission or low activity (DAS28 < 3.2). 57.6 % of patients had SARS-CoV-2 infection after therapy. There were 12 hospitalized patients and 15 admissions with 8–42 preceding RTX infusion (23.5 ± 11.3). In Supplemental Table 1, COVID-19 pneumonia was identified in 7 cases, 3 females aged 51–80 years (68.3 ± 10.4), receiving 8 to 38 (20.3 ± 11.2) infusion with the zero B-cell count. Initial chest images showed ground-glass opacity, all requiring oxygen support (Supplemental Figs. 1A and 1D). Except case no. 1 with resolved pneumonia (Supplemental Fig. 1F), other 6 patients expired. There was 10.5 % mortality in SARS-CoV-2-infected RA patients under RTX therapy.

We further evaluated the impact of TOF therapy. In Table 1, 118 patients, 97 females aged 26–88 years (62.2 ± 13.0), received TOF therapy with 5 mg twice-daily or 11 mg once-daily regimen. No differences were found in age/sex, seropositivity, DAS28, co-morbidity occurrences, and administration frequencies/dosages of prednisolone or DMARD between RTX and TOF groups. There were comparable therapeutic periods (RTX 54.1 ± 35.0 versus TOF 52.4 ± 29.1 months) and similar SARS-CoV-2 infection frequencies between two groups, TOF-treated patients had lower occurrences of hospitalization, pneumonia and death and maximum hospitalized CPS scores than those of RTX group (hospitalization, $p = 0.013$, pneumonia, $p = 0.006$, death, $p = 0.013$, CPS, $p = 0.048$).

Furthermore, 124 RA patients under DMARD alone without biologics and JAKi therapy, were enrolled for comparing the influence of RTX or

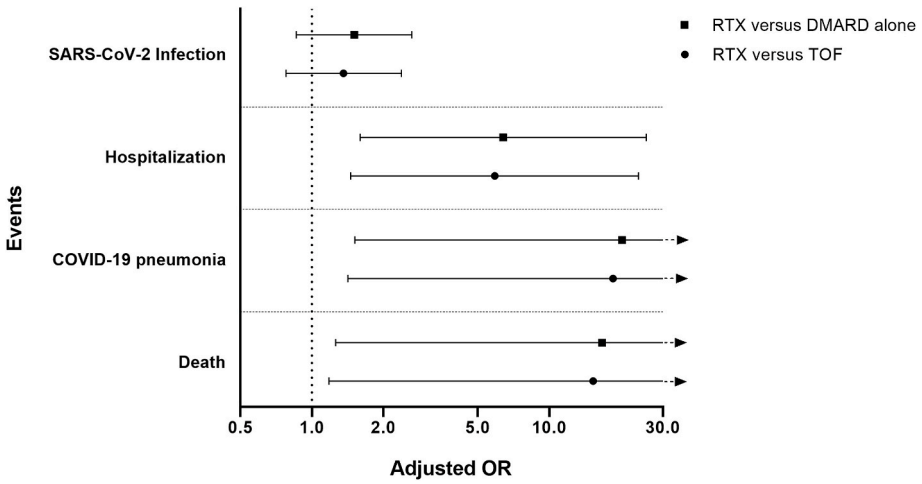


Fig. 1. The forest plot summarized the AOR, adjusted for age/sex, CS use and the presence of co-morbidity, to assess the association between RTX treatment and SARS-CoV-2 consequences in comparison with DMARD alone or TOF therapy.

TOF therapy on COVID-19 disease severity (Table 1). There were no differences in age/sex, seropositivity, co-morbidity occurrences and administration frequencies/dosages of prednisolone and DMARD between DMARD alone and RTX or TOF groups. DMARD alone group had similar SARS-CoV-2 infection frequencies, but lower occurrences of hospitalization, pneumonia and death and maximum hospitalized CPS scores than those of RTX group (hospitalization, $p = 0.012$, pneumonia, $p = 0.005$, death, $p = 0.011$, CPS, $p = 0.005$). No differences were found between DMARD and TOF groups in SARS-CoV-2 infection consequences.

In Supplemental Table 2, multivariable logistic regression adjusted for age/sex, plus CS use or plus CS use/the presence of co-morbidity, was performed to assess the association between RTX treatment and SARS-CoV-2 infection consequences. In comparison with DMARD alone group, RTX-treated patients had increased AOR of COVID-19-related hospitalization, pneumonia and death (hospitalization, AOR 7.15, $p = 0.009$; pneumonia, AOR 22.1, $p = 0.023$; death, AOR 18.2, $p = 0.033$). As compared with TOF-treated patients, RTX group had increased AOR of COVID-19-related hospitalization, pneumonia and death (hospitalization, AOR 6.39, $p = 0.013$; pneumonia, AOR 19.5, $p = 0.026$; death, AOR 16.0, $p = 0.037$). In Supplemental Table 3, compared to those of DMARD alone group, TOF-treated patients were not associated with SARS-CoV-2 infection consequences. Fig. 1 is the forest plot summarized the AOR to assess the association between RTX treatment and SARS-CoV-2 consequences in comparison with DMARD alone or TOF therapy.

5. Discussion

For DMARD prescribed in RA patients, although LEF and MTX are classified as IS, there was no increased mortality in SARS-CoV-2-infected RA patients receiving either therapy.[2] Large-scale studies enrolling RA patients from Europe and US have shown higher COVID-19-related hospitalization and mortality in those under RTX therapy.[2,8] From the information of US National COVID-19 Cohort Collaborative, compared to DMARD alone treatment, RTX therapy was associated with increased COVID-19-related hospitalization.[3] No association with COVID-19-associated hospitalization or mortality was identified in RA patients receiving JAKi treatment.[2,8] Similar to the aforementioned findings, in the present investigation, increased SARS-CoV-2-related hospitalization and mortality were found in domestic RTX-treated RA patients, whereas TOF therapy was not associated with consequence of SARS-CoV-2 infection.

RTX use in RA patients can cause poor vaccination efficacy with reduced antibody levels and seroconversion rates, leading to increased breakthrough of SARS-Cov-2 infection.[2,5] Interestingly, RA patients under the treatment of RTX, but not other biologics like etanercept, could generate antibodies with lower neutralizing activities against wild-type, omicron or other variants after SARS-CoV-2 vaccination.[9] In this series, non-reactive anti-S protein levels were found in four examined cases with COVID-19 pneumonia in spite of their multiple-dose vaccination history during the RTX therapeutic period.

Notably, CS use and existent co-morbidity were in association with increased SARS-CoV-2-associated mortality in RA patients.[2,8] In our study, there were no differences in the prescribed frequencies/dosages of prednisolone and occurrences of co-existing diseases among RA patients receiving RTX, TOF and DMARD alone treatment. By applying multivariable logistic regression adjusted for age/sex, CS use and existent co-morbidity, an association was identified between RTX therapy and SARS-CoV-2-related death.

Severe SARS-CoV-2 infection has made physicians and patients avoid to receive RTX infusion despite its well-recognized efficacy in RA as shown in RTX-treated patients from our series.[5,10] Although WHO has ended the public health emergency of international concern for the COVID-19 outbreak in May 2023, SARS-CoV-2 infection continues to circulate with emerging JN.l, KP.2, KP.3 and LB.1 variants of high transmissibility. Indeed, to decrease the impact of RTX use on COVID-19 severity, further investigations might evaluate the potential of reduced doses and adjusted schedules for treating RA patients.

In conclusion, for this monocentric retrospective study with 341 domestic RA patients, compared to DMARD alone or TOF therapy, RTX treatment had increased adjusted odds ratios of SARS-CoV-2-related hospitalization, pneumonia and mortality.

CRediT authorship contribution statement

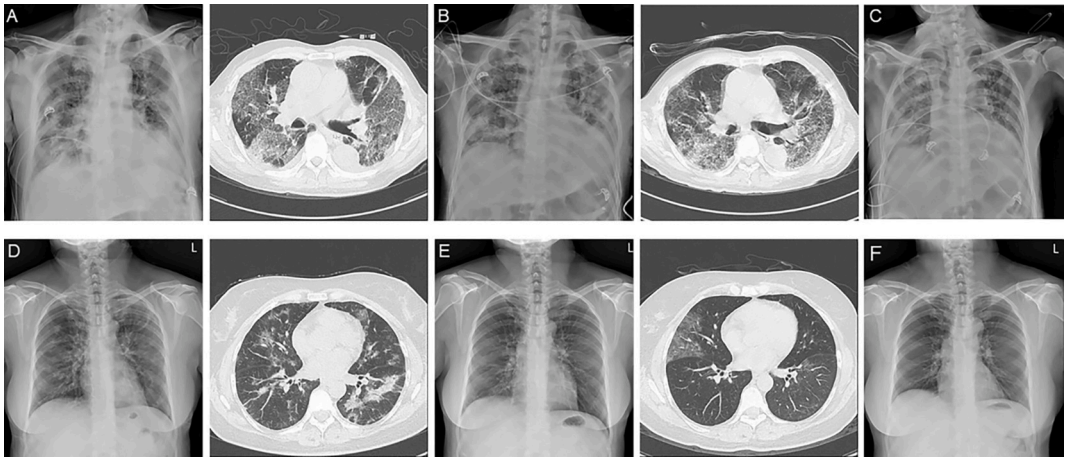
Chrong-Reen Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Chih-Hui Hsu:** Software, Investigation, Formal analysis, Data curation, Conceptualization. **Wei-Chieh Lin:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Acknowledgments

The NCKUH Institutional Review Board approved this study (B-ER-105-108). The authors are indebted to Prof. Sheng-Hsiang Lin for providing the statistical consulting services (Biostatistics Consulting Center, Clinical Medicine Research Center, NCKUH), and physicians and nurses involved in managing these reported RA patients. This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors have no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2025.01.004.



Supplemental Fig. 1. Chest images with bilateral diffuse ground-glass opacity (GGO) in computed tomography and x-ray of COVID-19 pneumonia in two RA patient under long-term RTX therapy. A initial bilateral GGO in case no. 4 after SARS-CoV-2 infection. B refractory to anti-viral/immunomodulating therapy, and C progression into mortality. D initial bilateral GGO in case no. 1 after SARS-CoV-2 infection. E response to anti-viral/immunomodulating therapy with resolution, and F normalized image with survival.

References

1. England BR, Roul P, Yang Y, et al. Risk of COVID-19 in rheumatoid arthritis: a national veterans affairs matched cohort study in at-risk individuals. *Arthritis Rheumatol*. 2021;73(12):2179–2188.
2. Strangfeld A, Schäfer M, Gianfrancesco MA, et al. COVID-19 Global Rheumatology Alliance. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis*. 2021;80(7):930–942.
3. Singh N, Madhira V, Hu C, et al. Rituximab is associated with worse COVID-19 outcomes in patients with rheumatoid arthritis: a retrospective, nationally sampled cohort study from the U.S. National COVID Cohort Collaborative (N3C). *Semin Arthritis Rheum*. 2023;58, 152149.
4. Bournia VK, Fragoulis GE, Mitrou P, et al. Outcomes of COVID-19 Omicron variant in patients with rheumatoid arthritis: a nationwide Greek cohort study. *Rheumatology*. 2024;63(4):1130–1138.
5. Wang CR, Lin WC. Fatal COVID-19 pneumonia in a rheumatoid arthritis patient receiving long-term rituximab therapy. *Ann Pharmacother*. 2023;57(5):617–619.
6. *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [Internet]*. Bethesda (MD): National Institutes of Health (US); 2021 Apr 21- 2024 Feb 29.
7. WHO Working Group on the Clinical Characterization and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192–e197.
8. Ye Y, Yue X, Krueger WS, et al. Factors associated with severe COVID-19 among patients with rheumatoid arthritis: a large, nationwide electronic health record cohort study in the United States. *Adv Ther*. 2023;40(9):3723–3738.
9. Lin WH, Du PX, Tsai PS, et al. Rituximab, but not other biologics, impairs humoral immunity in patients with rheumatoid arthritis-a study using CoVariant protein arrays. *Rheumatol Adv Pract*. 2023;7(3), rkad085.
10. Elahee M, Sattui SE. Navigating use of rituximab during the COVID-19 pandemic. *Lancet Rheumatol*. 2023;5(2):e63–e64.