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Original article

COVID-19 outcomes in persons with multiple sclerosis treated with rituximab

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ABSTRACT

Background: Outcomes of COVID-19 in PwMS (persons with Multiple Sclerosis) on immunosuppressive therapies, particularly B-cell depletors, can be unpredictable. There has been a concern for postponing or avoiding use of Rituximab (RTX) during the COVID-19 pandemic. We report the course and outcomes of COVID-19 in PwMS receiving RTX.

Methods: PwMS receiving RTX who contracted COVID-19 were closely monitored by tele-consultation and/or evaluated during hospital visits. Those requiring hospitalization for oxygen therapy or admission to ICU or expiring due to COVID-19 were considered to have severe disease. Those without desaturation and manageable at home were considered to have mild disease. Disease course and outcomes were noted.

Results: Twelve out of 62 (19.4%) PwMS on RTX therapy developed COVID-19. Four (age 35–49 years; mean 43.5) had severe COVID; three of whom had Secondary Progressive MS (SPMS). One PwMS expired. Two had prolonged fever lasting >1 month. One demonstrated features of SARS-CoV-2 reactivation. Interval from last RTX infusion (average dose 750 mg) to COVID-19 onset ranged 1–4 (mean 3.7) months. Eight PwMS had mild COVID-19 (age 26–54 years; mean 37.7); six had RRMS and two SPMS. RTX dose was lower (average dose 625 mg) and infusion to COVID-19 onset duration was longer, ranging 4–20 (mean 9.5) months. Four patients, two each from mild and severe COVID-19 groups had neurological deterioration, but none had true relapses.

Conclusion: RTX treated PwMS may have unpredictable disease outcomes if they contract COVID-19, but may be at risk of severe disease and persistent infection. In our series higher age, SPMS, shorter interval from RTX infusion to COVID-19 onset and higher dose of RTX were noted amongst those developing severe disease. RTX should be use cautiously during the COVID-19 pandemic and if unavoidable, less frequent and lower doses should be considered. Patients receiving RTX must be counselled to follow strict COVID-19 preventive measures.

1. Introduction

Rituximab (RTX), an anti-CD20 B-cell monoclonal antibody, is commonly used in neuro-immunological disorders. RTX acts by depleting the B-cells and suppresses the humoral immune response. It is a relatively inexpensive disease modifying therapy (DMT) for persons with multiple sclerosis (PwMS) and has been found effective in Remitting Relapsing MS (RRMS) and useful in Progressive MS (Chisari et al., 2021). RTX has however been associated with an increased risk of infections (Luna et al., 2020).

The natural course and outcomes of SARS-CoV-2 infection ranges from asymptomatic infection to severe disease, leading to death. PwMS on RTX therapy may be expected to have increased risk of severe COVID-19 disease, should they get infected by the SARS CoV-2 virus. However, COVID-19 outcomes in subjects receiving B-cell therapies have been non-uniform, ranging from mild course to severe disease and death (Esmaeili et al., 2021; Langer-Gould et al., 2021;Möhn et al., 2020; Montero-Escribano et al., 2020). We observed a high incidence of severe COVID-19 disease in our PwMS on RTX when compared to the general prevalence of severe disease. We analysed the course and outcomes of COVID-19 in our PwMS receiving RTX and discuss the safety aspects of its use during the pandemic.

2. Methods

2.1. Data collection

Data was prospectively collected from August 2020 to July 2021.

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PwMS treated at our institute who reported getting COVID-19 infection were included for this study. Diagnosis of COVID-19 was based on a positive SARS-CoV-2 RT-PCR report. Patients were closely monitored by tele-consultation and/or evaluated during hospital admission or subsequent hospital visits. Patients developing increase in disability (SPMS) or new deficits (RRMS) after clinical examination were considered to have worsening of MS. MRI scans were generally avoided and were done only if an acute relapse was suspected.

2.2. Disease severity characterization

Those developing oxygen desaturation on pulse-oximetry and requiring hospitalization for either oxygen therapy or admission to ICU or those who expired due to COVID-19 were considered to have severe disease. Those who did not develop oxygen desaturation or breathlessness and were manageable at home were considered to have a mild disease. Disease course and outcomes were noted.

2.3. Protocols for RTX treatment

RTX had been prescribed in patients with SPMS, those transiting from RRMS to SPMS and some RRMS patients. RTX was typically initiated after baseline investigations for complete blood counts, CD19 and CD20 cell counts, Liver function tests, Kidney functions tests and exclusion of HIV, HCV and HBV viral infections. Subsequent RTX doses were guided by re-population of CD19/20 cells. Tests were repeated after six to eight months. In patients with CD 19/20 counts $< 1\%$, RTX was deferred for 2-3 months and the tests repeated. RTX was infused once repopulation was $>1\%$. In patients receiving RTX for $>$ two years, S. Immunoglobulin-G level was additionally done to decide the dose. After an initial dose of 1000–2000 mg, subsequent doses were usually 500–1000 mg.

3. Results

Sixty-two PwMS were on RTX infusions at our institute. Twelve PwMS (19.4%), five males and seven females reported having contracted COVID-19. Their demographic and clinical characteristics are given in Table 1.

3.1. Severe COVID-19

Four PwMS, two males and two females, developed severe COVID-19 (mean age 43.5 years). Interval from last dose of RTX to COVID-19 onset was 1–4 months (mean 3.7 months). The dose of RTX ranged from 500 to 1000 mg (mean 750 mg). One had remitting RRMS with no disability (Expanded Disability Status Score [EDSS] -0), while the other three had secondary progressive MS (SPMS). One of these three patients was bed bound (EDSS-9) and had developed bed sores during hospitalization for COVID-19. He expired three days after discharge from hospital. The exact cause of death was not clear but was likely a complication of COVID-19 pneumonia. The other two had mild walking disability with EDSS 2.5 and 3, one of whose deficits worsened. These two PwMS also had persistent fever for more than four weeks. Both had undetectable CD19/CD20 cells done about six-eight weeks after COVID-19 diagnosis. One of these subjects, a 49-year-old male (Table 1, patient no.1) contracted COVID-19 two months after RTX infusion. He showed progressive COVID-19 lung changes in CT scans done at three weeks, five weeks and ten weeks from symptom onset, characterized by development of new viral pneumonitic lesions. RT-PCR repeated by nasopharyngeal swab was positive at five weeks. He also had low immunoglobulin-G levels. Anti SARS-CoV-2 antibodies were not detectable at five weeks after initial COVID diagnosis and after 10 weeks, were found in very low titres (0.03 U/ml). His fever and cough persisted despite symptomatic treatment and abated after re-treating with Favipiravir.

3.2. Mild COVID-19

Among eight PwMS with mild COVID-19 (age 26–54yrs; mean 38.8yrs), five had RRMS and two SPMS (Table-1). Interval from last dose of RTX to COVID onset was 4–20 months with a mean of 9.5 months. Subjects who had mild COVID-19 had received a lower dose of RTX (average 625 mg) when compared to those with severe COVID-19 (mean 750mg). One patient was pregnant and had asymptomatic infection detected during routine testing prior to hospital admission for confinement.

3.3. Effect of COVID-19 on MS course

Four PwMS had neurological deterioration after COVID-19 onset. But none had true relapses. One patient with RRMS (Table 1, patient no.10) developed paraparesis following two days of fever. MRI brain and spinal cord did not show any new or gadolinium enhancing lesions or increase in T2 lesion size. She improved rapidly after intravenous steroids. Three SPMS patients (Table 1, patient no.1, 4 and 6) had worsening of existing disabilities after onset of COVID-19 symptoms. This was attributed to fever and not considered as relapses. One of these patients expired while the other two recovered and attained their

Table 1
Summary of reported cases of reversible hemichorea due to carotid stenosis and treatment outcomes.

No.	Sex/Age	Type of MS	RTX to COVID Interval (month)	Last dose of RTX (mg)	COVID-19 Course	EDSS	MS Course
1	M/49	SPMS	2	500	Severe[a]	3→6	Worsened[b]
2	F/45	SPMS	4	1000	Severe[a]	2.5	No change
3	F/35	RRMS	1	1000	Severe	0	No change
4	M/45	SPMS	4	500	Severe	9→10	Expired
5	M/26	RRMS	1	500	Mild	0	No change
6	M/43	SPMS	15	500	Mild	6→7	Worsened[b]
7	F/43	RRMS	4	1000	Mild	2.5	No change
8	M/32	RRMS	8	500	Mild	0	No change
9	F/54	SPMS	20	500	Mild	6.5	No change[c]
10	F/35	RRMS	13	500	Mild	2.5→8	Worsened[d]
11	F/26	RRMS	11	1000	Asymptomatic	0	No change[e]
12	F/43	RRMS	4	500	Mild	0	No change

[a] These two PwMS had an initial mild disease which worsened after two weeks, needing hospitalization and subsequently had fever lasting >1month. They had 'zero' CD19 and CD20 cells post COVID suggesting persistent B-cell depletion.
[b] Both these patients developed worsening of gait and increase in EDSS after COVID-19 onset, which persisted even after 1 month.
[c] This PwMS had diabetes mellitus as comorbidity. None of the others had any comorbidities.
[d] This PwMS presented with fever and acute paraparesis, with grade -2 lower limb power, that rapidly improved to baseline status with steroids.
[e] This patient was pregnant and was detected to be SARS-CoV-2 RT-PCR +ve on routine testing prior to admission for confinement, as per hospital norms. She remained asymptomatic.

baseline EDSS scores after fully recovering from COVID-19.

The characteristics of PwMS developing mild and severe COVID-19 are summarized in Table 2.

4. Discussion

Studies of large MS data bases prior to the CoVID-19 pandemic have shown increased risk of infection in PwMS when compared with non-MS population (Luna G et al., 2020). However, the incidence of SARS-CoV-2 infections in PwMS was found to be comparable to the general population. In a study of 4647 PwMS, COVID-19 infection rate of 1.46% was observed (Langer-Gould et al., 2021; Sahraian et al., 2020). More recent studies involving larger numbers of PwMS have reported occurrence of COVID-19 infections in 0.5% to 4% (Moghadasi et al., 2021; Reder et al., 2021). The risk of developing COVID-19 was significantly higher in anti-CD20 (Ocrelizumab or RTX) treated patients. 123 (3.4%) out of 3568 PwMS on anti-CD20 therapy developed COVID-19 compared to 221 out of 26,910 ($p< 0.0001$) PwMS on other DMTs (Reder et al., 2021).The incidence of COVID-19 amongst our 62 PwMS on RTX was 19.4%. We focused only on those PwMS receiving RTX rather than other DMTs because of its significant immunosuppressive implications in relation to COVID-19.

RTX is a widely used DMT in PwMS. It is cost effective and has a high efficacy with a reasonable safety profile (Chisari et al., 2021). But amongst DMTs, RTX was associated with the highest rate of serious infections (Luna et al., 2020). RTX can induce replication of hepatitis viruses and has been associated with cytomegalo virus, herpes simplex virus, varicella zoster virus and West Nile virus infections (Chisari et al., 2021; Gea-Banacloche, 2010).

COVID-19 outcomes in PwMS receiving RTX have been variable and conflicting, ranging from very mild disease to severe disease and death. The severity of COVID-19 can be simplistically measured based on the necessity for hospitalization, ventilator requirement or death. We considered oxygen desaturation with hospitalization for oxygen therapy or ICU care/ventilator requirement or death as severe disease.

Initial reports on COVID-19 in PwMS receiving RTX did not indicate severe disease or unfavorable outcomes (Devogelaere et al., 2020; Fallet et al., 2020). In smaller case series, a lower incidence of severe COVID-19 and need for hospitalization were reported (Montero-Escribano et al., 2020; Sahraian et al., 2020). Patients treated with anti-CD20 agents were found to have adequate resolution of COVID-19 despite undetectable antibodies against SARS-CoV-2, suggesting limited role of humoral immunity in determining outcomes (Meca-Lallana et al., 2020). There have even been arguments for a beneficial and protective effect of immunosuppressive and anti-CD20 therapies in COVID-19. Mortality due to COVID-19 in PwMS has been attributed to various comorbidities rather than DMTs (Mehta et al., 2020; Möhn et al., 2020).

Several other reports have implicated association of RTX with severe COVID-19. Esmaeili et al. reported severe COVID-19 in five out of nine infected PwMS receiving RTX, with two mortalities (Esmaeili et al., 2021). In another pooled analysis of 2493 subjects with demyelinating disorders who contracted COVID-19, the overall mortality was 1.8%. But there was a mortality of 4% amongst 113 subjects receiving RTX, which was the highest among all the DMTs (Sharifian-Dorche., 2021). Langer-Gould et al. reported increased risk for hospitalization with RTX, suggesting more severe disease. Amongst 1895 PwMS receiving RTX, 24 contracted COVID-19, eight (33%) of whom developed severe disease (Langer-Gould et al., 2021). Amongst 12 of our PwMS who developed COVID-19, four had severe COVID-19 with one succumbing to death due to COVID-19 related complications. The incidence of severe COVID-19 in PwMS on RTX seems higher than the general population. In the general population, amongst 44,415 subjects who contracted COVID-19, it was observed that 81% had mild disease, 14% had severe disease, and 5% became critically ill (Wu and McGoogan, 2020).

Knowing the risk factors for RTX associated severe COVID-19 may critically help treatment decisions. RTX doses of 1000mg and shorter infusion to infection interval (mean 2.5 months) were associated with severe disease (Langer-Gould et al., 2021). Older age, presence of cardiovascular comorbidities, obesity, progressive disease, higher EDSS scores and non-ambulatory status were also associated with severe disease and death (Möhn et al., 2020; Sharifian-Dorche et al., 2021; Louapre et al., 2020). However, Sormani et al. observed that anti-CD20 therapy (Ocrelizumab or RTX) was significantly associated with an increased risk of severe COVID-19, after adjusting for other variables like region, age, sex, progressive MS course, Expanded Disability Status Scale, disease duration, body mass index and comorbidities (Sormani et al. 2021). Use of methylprednisolone in the month preceding COVID-19 infection was also associated with a worse outcome (Sormani et al., 2021). One of our PwMS had diabetes mellitus as a comorbidity but had a mild COVID-19 course. None of the other subjects including those with severe COVID-19 were obese or had any other comorbid illnesses. These observations implicate an independent association of RTX with severe COVID-19.

RTX has been reported to be associated with prolonged COVID-19 course, with fever lasting for more than a month and delayed worsening after an initial recovery (Leipe et al., 2020). Bose and Galetta reported a case of RTX associated reactivation of COVID-19 after three weeks and one of our cases confirms this potential risk (Bose and Galetta., 2021). Two of our subjects had prolonged COVID-19 course with fever lasting more than one month after initial recovery from mild COVID-19, requiring subsequent hospitalization due to worsening of symptoms and oxygen desaturation. Ten weeks after disease onset, one of these subjects had new COVID-19 patches in lungs suggesting viral reactivation. He had undetectable CD 19+ B cells, reduced immunoglobulin-G levels and very low SARS-CoV-2 antibody titres. The other subject also had undetectable CD+19 cells.

Our sample size was small to run statistical tests. Nevertheless, we noted shorter infusion to infection interval (mean 3.7 months), higher dosages (mean 750 mg), higher age (mean 43 years), and SPMS with severe COVID-19. Rituximab causes sustained B-cell depletion. Although the half-life of rituximab is about one-week, active levels persist in the blood for about 3 months (Ghielmini., 2005). In another study, median serum levels of RTX were found to be 20.3 μg/ml after three months of infusion which declined to 1.3 μg/ml after six months (Berinsten et al., 1998). The time taken for B cell reconstitution is dependent on the dose of RTX as well. Hogan et al., observed B cell reconstitution to occur after 2.5 months with RTX doses of 100 mg/m^2, five months with 375 mg/m^2 and after 6.6 months with 750 mg/m^2 (Hogan et al., 2019). Although we could not test CD+19 in all subjects, in two of the patients with severe disease there was non-repopulation of B cells. Thus, higher doses of RTX and shorter infusion to infection time resulting in an effective B-cell depleted state at the time of infection could result in severe COVID-19 infections.

SPMS is associated with increasing age, duration of MS and worsening disability (Fambiatos et al 2020). Advancing age is also a risk

Table 2
Characteristics of PwMS developing mild *vs.* severe COVID-19.

	Mild COVID-19	Severe Covid-19
Number of patients	8	4
Age in years	26–54 (mean 37.7)	35–49 (mean 43.5)
Sex	Male- 3, Female-5	Male -2, Female-2
Type of MS	RRMS-6 SPMS-2	RRMS-1 SPMS-3
Interval from last dose of RTX	4–20 months (mean 9.5 months)	1–4 months (mean 3.7 months)
Average last dose [a]	625 mg	750 mg
Neurological deterioration	2	2
Mortality[b]	0	1

[a] Dosages were either 500 or 1000mg

[b] This patient was discharged after 11 days of hospitalization and expired at home likely due to COVID-19 complications

factor for severe COVID infections and fatality. Several reasons have been hypothesised for this including "immunosenescence"- the aging of the immune system and "inflammaging"- the increased systemic inflammation due to an overactive, but ineffective immune system (Mueller et al., 2020). These dynamics may be responsible for our observation of higher age and SPMS with severe COVID-19.

It will be of interest to know the outcomes of COVID-19 in patients on other immunosuppressive medications. The incidence of developing COVID-19 was similar in PwMS and patients with Systemic lupus erythematosus (SLE). In analysis of large data bases, 761 amongst 30,478 (1.13%) PwMS contracted COVID-19 while 693 amongst 58,466 (1.19%) patients with SLE contracted COVID-19 (Reder et al., 2021). The COVID-19 Global Rheumatology Alliance (GRA) physician-reported registry observed that exposure to DMARDs and NSAIDs were not associated with hospitalisation risks in patients with rheumatic disease (Gianfrancesco et al., 2020). But in a follow-up study, the GRA raised concerns regarding higher risk of poor outcomes with rituximab, sulfasalazine, and certain immunosuppressants and expressed caution in their use (Strangfeld et al., 2021). Avouac et al. compared the outcomes of COVID-19 in patients with inflammatory rheumatic and musculoskeletal diseases receiving RTX (n=63) and those not on RTX (n=1027) and observed that RTX was associated with more severe COVID-19 (Avouac et al., 2021).

In our series, the COVID-19 course ranged from asymptomatic disease to death. The majority of available literature and our study do suggest a risk for severe COVID-19 course in subjects on RTX. Therefore, it may be desirable to explore alternate DMTs in PwMS otherwise deemed suitable for initiating on RTX.

RTX induced depletion of B-cells may be responsible for prolonged and severe disease course and indicates the importance of humoral immunity in COVID-19 recovery. Since the initial antiviral response is primarily T-cell mediated, subjects on RTX with intact T-cells can be expected to have an initial mild disease like most general population. This might be misleading as there could be subsequent worsening and progression of disease.

The performance of the COVID-19 vaccines in B-cell depleted patients will be known in near future. In a study on five subjects on RTX who were vaccinated with BNT162b2 (Pfizer/BioNTech) vaccine, antibodies against SARS-CoV-2 were detected only in patients (n=2) who had measurable CD19+ B cells at the time of vaccination, suggesting the development of a humoral immune response only after the peripheral B cells are repopulated (Bonelli et al., 2021). The timing of vaccination in relation to RTX administration is critical in the immune response. Patients can be vaccinated about four-six weeks before administering RTX or after five to six months of RTX infusion after confirming the commencement of repopulation of CD19/20 cells.

5. Conclusion

The outcomes of COVID-19 infections in PwMS on RTX can range from asymptomatic disease to death, but RTX does carry an increased risk for severe disease and persistent infection. A thorough risk-benefit consideration must be carried out before prescribing RTX during the present pandemic scenario. We recommend caution in prescribing RTX during the present pandemic. If there are no other suitable treatment options available, then choosing the lowest possible RTX dose, younger patients with lesser disability and those without other systemic comorbidities could be potential considerations. Patients receiving RTX must be counselled to strictly adhere to all protective measures to prevent COVID-19 infection.

Credit author statement

Rajesh B Iyer: Conceptualization, Data curation, Investigations, Methodology, Formal analysis, Validation, Writing original draft, Writing review and editing.

Raghavendra S: Conceptualization, Data curation, Methodology, Supervision, Writing review and editing.

Javeria Nooraine M: Data curation, Methodology, Formal analysis, Validation Writing original draft.

Jaychandran R: **:** Data curation, Investigation, Formal analysis, Validation, Supervision, Writing: review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Disclosures

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