



Original article

Evaluating the perspective of patients with MS and related conditions on their DMT in relation to the COVID-19 pandemic in one MS centre in Australia

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ABSTRACT

Objective: Patients with Multiple Sclerosis (MS) and on disease modifying therapies (DMTs) that can be immunosuppressive or immunomodulatory form a special group where risk of continuation of DMT needs to be taken into account with risk of contracting Covid-19. This concept can pose a degree of anxiety for patients as well as neurologists. We aimed to evaluate patient perspectives regarding the use of Natalizumab and anti-CD20 therapies (Rituximab and Ocrelizumab) in the context of the COVID-19 pandemic.

Methods: cross-sectional study conducted via voluntary survey filled in by patients with MS and related disorders receiving their infusional treatment in one MS centre in Australia, exploring their concerns regarding their therapy, their therapy and COVID-19, precautions undertaken in response to the pandemic, and factors impacting their decision-making.

Results: 170 patients completed the survey. Of patients on Natalizumab, the majority had either no or mild concern regarding their DMT and COVID-19, and of patients on B-cell depleting therapies, again, the majority had no or mild concern, though a slightly higher proportion had a moderate level of concern. Asked to delineate their concerns, an increased risk of contracting COVID-19 was more commonly conveyed than MS-specific factors or poor outcomes pertaining to COVID-19 if contracted, by patients in both groups. Conversely, being invited to specifically consider the possibility of contracting COVID-19 or experience a relapse of MS, almost half of the cohort rated both of equal of concern. More than half of the cohort were self-isolating more stringently than general government advice and government-related resources followed by information provided by patient's neurologist where the commonest means of information to guide decision making.

Conclusions: Whilst a large proportion of patients had some concern regarding the impact of their DMT on COVID-19, whether on their risk of contracting COVID-19 or a theoretical risk for more severe disease, the overall level of concern in most cases was at most mild. Patients on B-cell depleting therapies were more inclined to express a higher level of concern. A similar concern was ascribed to a risk of a relapse or worsening MS symptoms compared to the risk of contracting COVID-19. Such attitudes may underscore a willingness of patients to continue their DMT where benefits outweigh risks during future phases of the COVID-19 pandemic.

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Table 1
Baseline demographic data.

	Natalizumab	OCR, RTX	Total
Number that undertook survey	100	70 (OCR 68, RTX 2)	170
Female, %	81 (81%)	50 (71%)	131 (77%)
Age, mean (yrs, range)	39.1 (17.7-64.5)	42.7 (24.7-63.2)	40.6 (17.7-64.5)
Disease phenotype	100 RRMS (100%)	63 RRMS (90%) 3 SPMS (4%) 2 MOGAD (3%) 1 PPMS (1%) 1 NMOSD (1%)	163 RRMS (96%) 3 SPMS (2%) 2 MOGAD (1%) 1 PPMS (0.6%) 1 NMOSD (0.6%)
Disease duration, mean (yrs; range)	8.7 (0.4-32.5)	8.3 (0.61-30.5)	8.5 (0.4-32.5)
Latest EDSS (mean, median, range)	Mean: 1.7; Median: 1.5; Range: 0-4.5	Mean: 2.5; Median: 2; Range: 0-6.5	Mean: 2.1; Median: 2; Range: 0-6.5
Treatment duration, mean (months, range)	44.2 (0-150.4)	19.0 (0-69.8)	33.0 (0-150.4)

OCR: ocrelizumab; RTX: rituximab.

RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; MOGAD: myelin-oligodendrocyte glycoprotein antibody disease; NMOSD: neuromyelitis optica spectrum disorder; EDSS: expanded disability status scale.

1. Introduction

Since its identification in Wuhan in December 2019 (Zhu et al., 2020), the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected 11,874,226 people globally, causing 545,481 deaths, as of July 9; (<https://www.who.int>). In Australia, there have been over 7,491 cases with 102 deaths reported (Team, 2020). More severe disease and mortality are associated with older age, medical comorbidities, such as hypertension, diabetes, cardiovascular and respiratory disease (Wu and McGoogan, 2020; Yang et al., 2020; Docherty et al., 2020). Though patients with multiple sclerosis (MS) have a higher rate of infection, and hospitalisation due to infection compared to the general population (Montgomery et al., 2013; Persson et al., 2020; Wijnands et al., 2017) and disease modifying therapies (DMT's) are associated with a variably increased infection risk [Luna et al., 2019], the risk of infection, morbidity and mortality with COVID-19 in patients with multiple sclerosis on DMT's remains unknown.

Decision making in relation to commencing, continuing or altering a patient's DMT, beyond theoretical considerations of risk, may be impacted by real-world outcomes of patients with multiple sclerosis contracting COVID-19, and the state of the pandemic at a more local level; patient factors, such as age, disability and comorbidities; disease factors, such as recent clinical and radiologic activity, and DMT-related factors, such as the risk of rebound activity in the context of stopping Natalizumab or S1P modulators (Brownlee et al., 2020).

Central to any decision, is a patient's acceptance and willingness to undertake treatment with a given DMT, factoring in the aforementioned considerations. In order to further characterise the latter, we conducted a survey to evaluate patient's perspectives on the COVID-19 pandemic in relation to their DMT in one MS centre in Australia, to assist clinicians in better managing patient expectations during the COVID-19 pandemic.

2. Methods

From 24th April until June 1st 2020, all patients with multiple sclerosis and related disorders attending the Royal Melbourne Hospital infusion centre, either for Natalizumab, Ocrelizumab or Rituximab infusions, were invited to complete a voluntary survey (please see Appendix 1), evaluating their perspectives in relation to COVID-19, their disease and DMT. Patients receiving intravenous immunoglobulin or other infusional or oral MS therapies were excluded.

Patients were asked to evaluate five questions (see appendix1), namely, (i) what their level of concern was regarding their DMT and the COVID-19 pandemic; (ii) to detail their two greatest concerns regarding

their disease and the pandemic; (iii) to identify if potentially contracting COVID-19, or sustaining a relapse or worsening MS symptoms, was more concerning, or equally concerning; (iv) what precautions they had undertaken in response to the pandemic, and (v) what resources they had used to guide their decisions.

Information regarding patient's disease phenotype, disease duration, therapy duration and latest EDSS (Expanded Disability Status Scale) score was extracted from the iMed patient record system (local MS database).

The study protocol and survey was reviewed and approved by the Melbourne Health Human Research Ethics committee.

3. Results

A total of 170 out of 178 (95%) patients completed the survey; 70 on Ocrelizumab or Rituximab and 100 on Natalizumab. No patients in our cohort contracted COVID-19 during the study period. Variability in the proportion of patients responding to a given question accounted for the different total figures represented for the respective questions, with a proportionately lower total for question (v) due to this question being added later in the study. The baseline demographics are detailed in Table 1. The mean age in our cohort was 40.6 years, and 77% of patients were female. The majority of patients had relapsing remitting multiple sclerosis (96%). The mean disease duration was 8.5 years, and the mean and median EDSS scores for the cohort were 2.1 and 2 respectively. The mean treatment duration was 33 months.

In relation to question (i), patient's level of concern regarding their DMT in relation to the pandemic is detailed in Table 2.

Being asked of their two greatest concerns regarding COVID-19 and their MS (Table 3), 26% (31 of 117 patients who responded) expressed MS-related concerns, such as not having access to their DMT due to COVID-19 or sustaining a relapse either because of missed treatment or contracting COVID-19, whilst 87% (102 of 117) expressed COVID-19 related concerns, with 57% (67 of 117) expressing concern regarding an increased risk of contracting COVID-19 and 30% (35 of 117) expressing concern over a risk of poorer outcomes if they contracted the virus, with

Table 2
Patient's level of concern regarding their DMT in relation to COVID-19.

	NTZ = 99	OCR = 54, RTX = 2	Total = 155
Not at all	50 (50%)	21 (38%)	71 (45%)
Mildly	37 (37%)	26 (46%)	63 (41%)
Moderately	8 (8%)	9 (16%)	17 (11%)
Highly	4 (4%)	0 (0.0%)	4 (3%)

NTZ = Natalizumab; OCR = Ocrelizumab; RTX = Rituximab.

Table 3
Patient's two greatest concerns regarding COVID-19 and their MS.

Nature of concern	NTZ (N = 74)	OCR (N = 43)	Total (N = 117)
MS-specific	23 (31%)	8 (19%)	31 (26%)
Increased risk contracting COVID-19	40 (54%)	27 (63%)	67 (57%)
Increased risk poor outcomes from COVID-19	21 (28%)	14 (33%)	35 (30%)
Lifestyle factors	3 (4%)	4 (9%)	7 (6%)
No concerns	9 (12%)	6 (14%)	15 (13%)
Miscellaneous	4 (5%)	0 (0%)	4 (3%)

NTZ = Natalizumab; OCR = Ocrelizumab; RTX = Rituximab.

examples including “reduced ability to fight virus”, “symptoms of COVID being more severe” and “not recovering if contract COVID-19”. 13% (15 of 117) reported having no particular concerns. A slightly higher proportion of patients receiving Ocrelizumab (63%) expressed concern over their risk of contracting COVID-19 compared to patients receiving Natalizumab (54%), though responses were otherwise fairly similar. Few patients reported concern over life-style factors (with examples given including an inability to leave the house, not being able to find employment). Additional concerns (miscellaneous) included concern over comorbid heart and lung disease and keeping one's family safe.

Risk of an MS relapse or worsening MS symptoms (Table 4) was of greater concern than the prospect of contracting COVID-19 in 38% (30 of 78), whilst the converse was reported in 14% (11 of 78), with a further 45% (35 of 78) deeming both scenarios of equal concern.

Regarding precautions undertaken by patients during the pandemic (Table 5), 97% of patients (152 of 156) had either been following government advice in relation to social distancing and hand hygiene or isolating with greater stringency than general recommendations. 37% of patients (57 of 156) were working from home because of their disease or their therapy, though it should be noted that in Victoria Australia, the population was advised to work from home for the early months of the pandemic where possible. A low proportion of patients (12%) wore masks or gloves in public, but this again may be reflective of public-health advice given to the Australian community (health.gov.au) for the majority of the study period, discouraging use of masks for people not suspected of being infected with COVID-19.

Finally, though only answered by 85 patients, the most common source of guidance (Table 6) for patients was government-based resources (61%), followed by consultation with their neurologist (35%) and consultation with their GP (26%).

4. Discussion

From the outset of the pandemic, and as it has evolved at varying paces in different parts of the world, it is understandable that throughout, a significant component of the care of patients with MS and related disorders has been a discussion of the impact conferred by their DMT on their risk of contracting COVID-19, potentially experiencing a more severe course of the disease, and attempting to address patient's concerns regarding these issues. With real-world data still in nascent stages, such discussions have been limited by continued uncertainty in

Table 4
Comparison of COVID-19 and MS-related concerns.

	NTZ N = 49	OCR = 29	Total = 78
Possibility of contracting COVID-19	8 (16%)	5 (17%)	11 (14%)
MS relapse or worsening symptoms	19 (39%)	11 (38%)	30 (38%)
Both	22 (45%)	13 (45%)	35 (45%)

NTZ = Natalizumab; OCR = Ocrelizumab; RTX = Rituximab.

Table 5
Precautions undertaken during pandemic.

	NTZ (N = 100)	OCR/RTX (N = 56)	Total (N = 156)
Following government advice	40 (40%)	23 (41%)	63 (40%)
Self-isolating more than government advice	60 (60%)	29 (52%)	89 (57%)
Working from home because of MS or therapy	43 (43%)	14 (25%)	57 (37%)
Wearing masks/gloves in public	8 (8%)	10 (18%)	18 (12%)
Self-altering MS therapy to reduce medications on board	7 (7%)	0 (0%)	7 (4%)
Reduced compliance with appointments to avoid COVID-19 exposure	9 (9%)	9 (16%)	18 (12%)

NTZ = Natalizumab; OCR = Ocrelizumab; RTX = Rituximab.

Table 6
Information used to guide decision making.

	NTZ = 52	OCR = 28	Total = 85
No specific guidance	13 (25%)	3 (11%)	16 (19%)
health.gov.au OR government advice via other platforms	32 (62%)	20 (71%)	52 (61%)
GP consultation	14 (27%)	8 (29%)	22 (26%)
Neurologist routine consultation	15 (29%)	15 (54%)	30 (35%)
Neurologist/MS unit contacted	6 (12%)	6 (21%)	12 (14%)
ANZAN COVID-19 consensus position letter (Broadley et al., 2020)	0 (0%)	2 (7%)	2 (2%)
Msaustralia.org.au	12 (23%)	6 (21%)	18 (21%)
Other MS websites	3 (6%)	1 (4%)	4 (5%)
Other	0 (0%)	2 (7%)	2 (2%)

NTZ = Natalizumab; OCR = Ocrelizumab; RTX = Rituximab.

ANZAN: Australian and New Zealand Association of Neurologists.

defining the true risk of various DMT's and COVID-19 related outcomes (Brownlee et al., 2020; Giovannoni et al., 2020).

Preliminary data from case-series of COVID-19 infections in patients on anti-CD20 therapy and Natalizumab has been reassuring, and largely commensurate with data from the general population. The majority of 232 patients with MS with confirmed or suspected COVID-19 in an Italian cohort experienced a mild course, with 25, 26 and 2 patients on Natalizumab, Ocrelizumab and Rituximab respectively (Sormani, 2020). In a series 60 patients on anti-CD20 therapy from Spain, COVID-19 infection was reported in 9 patients with no patients showing serious complications (Montero-Escribano et al., 2020). A series of 543 patients with multiple sclerosis in Iran, of which 42 and 12 were on Rituximab and Natalizumab respectively, revealed 66 suspected cases, with 9 patients diagnosed with COVID-19 (of which 2 were RT-PCR confirmed); one patient with an EDSS of 6.5 on Rituximab died (Barzegar et al., 2020).

In our cohort, 63% and 33% of patients on Ocrelizumab or Rituximab had concerns over an increased risk of contracting COVID-19, and worse outcomes if contracted, respectively. A cross-sectional survey of 712 patients with MS, with 34 suspected COVID-19 in Iran revealed only two patients required hospitalisation, both of whom were on Rituximab, which was represented relatively higher (61.8% cf. 40.0%) among suspected COVID-19 patients compared to the cohort at large, though both recovered (Safavi et al., 2020). A pharmacovigilance case-series reported 100 patients with multiple sclerosis treated with Ocrelizumab with either confirmed (n=74) or suspected (n=26) COVID-19 infection in whom 26 were hospitalised, 5 developed critical illness, but no patients died (Hughes et al., 2020). In an observational study evaluating outcomes of 76 actively treated patients with multiple sclerosis with confirmed (n=37) or suspected (n=39) COVID-19, a slightly higher rate (34 of 65 patients who were on DMT's) of patients were receiving anti-CD20 therapy compared to the centre's overall

proportion of patients on such therapy, though the significance of this finding was uncertain, and overall hospitalisation (24%) and mortality rates (7%) were comparable to the general population (Parrotta et al., 2020).

That none of our patients had contracted COVID-19 may have reflected the overall low incidence in Melbourne and Victoria Australia during the study period, though notwithstanding this, was in keeping with the results of a study of 1,836 patients with MS and 3,128 patients with NMOSD from 10 centres across China, where no increased risk COVID-19 could be detected despite 61.9% of patients being on DMT's, including 108 patients on Rituximab, with only 2 confirmed cases (Fan et al., 2020). The authors noted the effect of preventive protocols instituted across the country offsetting the number of cases could not be excluded, and of relevance to our cohort, none of these patients received Ocrelizumab or Natalizumab. Similarly, in a cohort of 52 patients on DMT's in Chile, no COVID-19 cases were reported (Guevara et al., 2020).

Overall, almost a third of our cohort were concerned with worsened COVID-19 outcomes as a result of their DMT. Factors associated with COVID-19 severity in patient with MS included age, progressive disease course and a higher degree of disability in a series of 40 PCR-confirmed cases, but not DMT use (Chaudry et al., 2020), whilst older age, non-ambulatory status, progressive disease and medical comorbidities in a series of 76 confirmed or suspected cases were risk factors for hospitalisation (Parrotta et al., 2020). Similarly, increasing age, male sex, EDSS score, a progressive disease course, medical comorbidities and obesity, but not DMT exposure, were found to be associated with an increased risk of severe COVID-19 in a multi-centre observational cohort study from France (Louapre et al., 2020).

A potential cause for concerns in patients receiving anti-CD20 therapy is the impact on antibody responses to SARS-CoV-2, either post-infection, or possibly more pertinent to our cohort, post-vaccination. Such a concern, however, was not expressed by any of the patients in our cohort. Results of patients with suspected and PCR-confirmed COVID-19 receiving Ocrelizumab, without subsequent detectable SARS-CoV-2 serologic responses but with nonetheless favourable outcomes (Meca-Lallana et al., 2020; Thornton and Harel, 2020) may underscore the uncertainty around the significance of a potentially blunted humoral memory response.

The hypothesis that certain DMT's may protect against severe complications of COVID-19, accounting for some of the favourable outcomes in reported cases, including anti-CD20 therapy (Ghajarzadeh et al., 2020; Giovannoni, 2020; Novi et al., 2020), Natalizumab (Aguirre et al., 2020) and interferon therapy (Gemcioglu et al., 2020) may require consideration in decision-making regarding DMT's as further real-world data emerges, but, based on the resources used for patient decision-making, is unlikely to have been pertinent to the relatively high proportion of patients who voiced a 'low' level of concern relating to their DMT use during the pandemic as low.

Patient perspectives regarding their DMT have been previously reported in the context of COVID-19 pandemic. In a poll recently conducted, though COVID-19 represented the most frequent concern among patients with multiple sclerosis and NMOSD, a similar proportion of patients also had not considered the prospect of treatment cessation (Salama et al., 2020). Though patients undertaking our survey had implicitly demonstrated a willingness to continue their DMT, 45% (35 of 78) of patients shared similar concern regarding the risks of COVID-19 and a relapse of MS and 38% were more concerned with the latter, with only 14% more concerned with the risk of contracting COVID-19, underscoring a willingness of patients to continue their DMT despite their concerns, and indicating an underlying level of education as to the importance of DMT's in relation to reducing clinical and radiological disease activity.

In our cohort, 86% of patients were either not concerned or only mildly concerned regarding their therapy, though patients on B-cell

therapy were more likely to express a mild or moderate level of concern. The majority of patients were either following government advice or self-isolating more stringently, and 37% of patients were working from home because of their MS or DMT, noting that in Victoria, recommendations to work from home if able were made to the general public by the government, for much of the study period.

Though data was available only from a subset of patients regarding resources used for overall decision making, reassuringly, a significant proportion of patients were apprised of general public health advice. Information from patient's GP's (26%), neurologist (35%) and ad-hoc contact with MS-unit (14%) served relatively lower amounts of patients, which in part may have been due to a patient's last consultation being prior to the pandemic, but may reflect also the relatively low level of concern among patients in this cohort. Consequently, a more refined exploration of the relationship between patient education and counselling and COVID-19 concerns could not be meaningfully assessed.

Early in the course of the pandemic, the Italian Society of Neurology and Association of British Neurologists, have issued guidelines regarding DMT use, included delaying temporarily re-dosing of lympho-depleting therapies (such as Ocrelizumab) (Giovannoni et al., 2020), whilst a statement from the ANZAN MS neurology group (Broadley et al., 2020) encouraged a discussion with a patient's neurologist regarding delaying such therapies. More recently, national guidelines have issued warning about a potential increased risk of severe COVID-19 in patients on anti-CD20 therapy (<https://www.msif.org/news/2020/02/10/the-coronavirus-and-ms-what-you-need-to-know/>.) The impact of such guidance on patient attitudes also was beyond evaluation given the relatively low proportion of patients utilising such resources.

Limitations of our study include a lack of information regarding patient's understanding of the risk-benefit profile of their therapy, including infection risk. Further, there was an inability to correlate patient concerns with the evolving nature of the pandemic. It should be noted that the overall burden and rate of COVID-19 infections in Australia has been significantly lower than Europe, North and South America and parts of Asia, and indeed, despite concerns of a second wave, a significant proportion of the study-period spanned over a time when the rate of new infections had been significantly reduced by public-health measures. Clearly, patient perspectives will vary according to the incidence of COVID-19 in a given geographic area. Further, the number of patients were relatively limited, and generalisability is limited, given our cohort represented a single public hospital in Australia. Further, we did not have data on COVID-19-motivated treatment decisions (such as delayed infusions) and disease outcomes.

Our study highlights that at this stage in the pandemic, patients with MS and related disorders on higher-efficacy therapies such as Natalizumab and Ocrelizumab, though mostly conscious of theoretical risks carried by their DMT in relation to COVID-19, remain, for the most part, open to continuing their therapy without significant apprehension, with the majority expressing at most a mild level of concern regarding their therapy and COVID-19. Patients receiving B-cell therapies were more inclined to express a higher-level of concern, however.

As reported outcomes become increasingly available as the pandemic evolves, clinicians may better be able to address patient concerns regarding their DMT safety in relation to COVID-19, drawing on real-world data, and where appropriate, counsel patients to continue their DMT's, where the benefit of continuing is thought to outweigh the risks pertaining to COVID-19.

Credit author statement

NS assisted with ethics submission, collected the data, and participated in day to day acquisition of the information, analysed the data and wrote the first draft of the paper. VL, AN, IR, KB, RA, CD, MM, TK

assisted with intellectual content with initial design of the study and subsequent input for revision of the paper. NT, KT, JC, HF, LT, JB assisted with data collection from individual patients who participated in the study. TK provided intellectual input in original design of the study, assisted with data analysis and interpretation and provided editorial and statistical input in the drafts of the manuscript. MM conceptualised the study and formulated the ethics submission. She assisted with data analysis and interpretation and provided intellectual and editorial input in various manuscript preparation and revision.

Declaration of Competing Interest

None of the authors have any conflict of interests to declare. None of the authors have received any funding of relevance to this study.

Appendix 1. survey questions.

1. How concerned are you about **your therapy** in relation to the COVID-19 pandemic:

- Not concerned at all
- Mildly concerned
- Moderately concerned
- Highly concerned

2. What are your **2 biggest concerns** about the COVID-19 pandemic and your MS

1. _____
2. _____

3. Which concerns you more:

- Possibility of contracting COVID-19
- Possibility of having relapse of MS or worsening MS symptoms
- Both similarly concerning

4. What precautions have you taken in response to the coronavirus pandemic? (Mark one or more):

- following government advice regarding social distancing and good hygiene
- self-isolation more than current government recommendation
- working from home because of having MS / being on therapy
- wearing masks/gloves in public
- self-altering your MS therapy to decrease amount of medication on board
- reduced compliance with appointments to avoid potential exposure to COVID-19
- other _____

5. Which of the following resources have you used to guide decisions in relation to self-isolation and/or your MS therapy during the pandemic? (Mark one or more)

- no specific guidance
- health.gov.au OR government recommendations on social media,

TV, other platforms

- general practitioner (GP) consultation (including over the phone)
- routine consultation with neurologist
- contacted neurologist or MS unit for advice
- ANZAN COVID19 letter
- msaustralia.org.au
- msif.org OR mssociety.org.uk OR mstrust.org.uk OR multiplesclerosisnewstoday.com
- other: _____

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