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Original article

Decision-making on management of ms and nmosd patients during the COVID-19 pandemic: A latin american survey



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ABSTRACT

Background: The emergence of COVID-19 and its vertiginous spreading speed represents a unique challenge to neurologists managing multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD). The need for data on the impact of the virus on these patients grows rapidly. There is an urgent necessity of sharing information to enable evidence-based decision making on the clinical management. There are no data on what physicians are doing on clinical practice in Latin American countries.

Aim: to investigate current management opinion of Latin American MS and/or NMOSD expert neurologists based on their experience and recommendations.

Methods: we developed a voluntary web-based survey based on hypothetical situations that these patients may encounter, while taking into account the potential risk of developing severe COVID-19 infection.

Results: 60% of the experts had the possibility of monitoring their patients by telemedicine. Most neurologists postpone magnetic resonance. Laboratory blood tests delay is associated with the type of treatment. Platform therapies, dimethyl-fumarate and natalizumab are considered safe options to initiate in naive patients.

Conclusion: decision-making about MS and NMOSD patients has become even more complex in order to adapt to the COVID-19 pandemic. Risks and benefits should be taken into consideration throughout the patient follow-up.

1. Introduction

The first case of coronavirus disease-2019 (COVID-19) was reported in China (Wuhan) in December 2019 as an unexplained pneumonia. In a few days, the new coronavirus would rapidly spread from person to person. On March 11th, the World Health Organization (WHO) declared COVID-19 as a pandemic (Cucinotta and Vanelli, 2020). On February 25th 2020, Brazil was the first country in Latin America to report a case of COVID-19. Currently, a continuous increase of mild, severe and fatal COVID-19 number of cases has been reported in most Latin American countries and on April 14th, our region registered more than 65 000 cases (Rodríguez-Morales et al., 2020).

The typical COVID-19 symptoms can range from mild to severe respiratory illness. Cold- or flu-like symptoms usually appear after a

coronavirus infection and are typically mild. However, symptoms vary from person to person, and risk factors for fatal disease have been identified and documented (Huang et al., 2020). Patients with underlying lung and heart illness and those aged over 60 years are more likely to experience complications (Yang et al., 2020). In addition to this group, multiple sclerosis (MS) and neuromyelitis optic spectrum disorders (NMOSD) patients seem to have a higher risk of developing a severe disease than the general population, especially those with additional comorbidities, mobility issues and those receiving immunosuppressive therapy (Giovannoni et al., 2020; Brownlee et al., 2020).

Considering the recent discovery of this new infection and the vertiginous speed of its spread, this situation represents a unique challenge to neurologists managing MS and NMOSD (Carnero Contentti

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and Correa, 2020). The need for data on the impact of the virus on these patients grows rapidly. There is an urgent necessity to share information to enable evidence-based decision making on the clinical management of MS and NMOSD patients during the COVID-19 pandemic.

Different scientific societies from Latin America have responded quickly by issuing recommendations based on expert opinions for the management of patients during the COVID-19 pandemic. Despite this, there are no data on what physicians are doing on clinical practice in the region. Given that the management of MS and NMOSD patients is a challenge during the COVID-19 pandemic, reports of survey results based on MS and/or NMOSD experts' opinion might give neurologists some guidance in order to optimize clinical and therapeutic decision-making for patients.

For this reason, the aim of this study is to investigate current management opinion of Latin American MS and/or NMOSD expert neurologists based on their experience and recommendations.

2. Methods

A cross-sectional study was performed. An anonymous, voluntary web-based survey, was designed in order to investigate clinical and therapeutic decision-making during the COVID-19 pandemic era by Latin American MS and NMOSD experts. This survey was based on clinical situations that MS and NMOSD patients may encounter, while taking into account the potential risk of developing severe COVID-19 infection (Fig. 1). These scenarios included initiation and monitoring of disease-modifying drugs (DMDs), DMDs treatment failure and relapse management.

The questions included:

- Patients follow-up: blood test, magnetic resonance imaging (MRI) and telemedicine.
- Which DMD would they choose in case of patients who must initiate DMD therapy,
- DMD monitoring, in addition to decision-making in DMD treatment if a patient has COVID-19 under DMD therapy
- Choice of DMD therapy in a treatment failure scenario
- Treatment selection in patients with relapse activity

The survey was sent via email (7 April 2020) to potential respondents and was available online for only one week to avoid bias regarding epidemic change in our region. Respondents were identified from the Demyelinating Disease Working Group of the Argentinean Neurological Society and LACTRIMS members. This survey was developed by RA and subsequently revisited, corrected a modified by JIR, ECC, BS and PAL. Neurologists were asked to indicate whether they identified themselves as experts in MS, NMOSD, or both. Seventy-one experts in MS were identified; 61 of them were also experts in NMOSD. We only considered MS responses to MS experts and we did the same

Table 1
General characteristics of the survey responses.

General characteristics	Responses
Size sample	71
Gender (%)	
Female	38 (53.5)
Male	33 (46.5)
Mean age years, (SD)	48.1 (11.7)
Work at (%)	
Public Hospital	31 (43.7)
Private Hospital	40 (56.3)
Self-reported specialty (%)	
Only MS patients	10 (14.1)
Only NMOSD patients	0
Both	61 (85.9)
Country with mandatory quarantine (%)	
Yes	66 (92.9)
No	5 (7.1)
Attending at the hospital (%)	
Regular follow-up (monitoring)	4 (5.7)
Postponed visit	67 (94.3)
Possibility of telemedicine (%)	
Yes	48 (67.6)
No	23 (42.4)
Countries	
Mexico and Caribbean*	6 (8.5)
South American**	65 (91.5)

* Mexico (n = 2), Nicaragua (n = 1), Honduras (n = 1), Cuba (n = 1) and Costa Rica (n = 1).

**South America: Argentina (n = 47), Bolivia (n = 2), Brazil (n = 3), Chile (n = 3), Colombia (n = 6), Ecuador (n = 1), Paraguay (n = 2) and Venezuela (n = 1).

with NMOSD.

2.1. Statistical analysis

No individual responses were known by the authors and survey results were analyzed using excel software. Descriptive statistics (proportions and percentages) were reported based on the survey results. The data were also analyzed through the GraphPad Prism software, version 6.00 for Windows (GraphPad Software, San Diego, CA, USA).

3. Results

A total of 93 Latin American MS and/or NMOSD experts were invited to participate and 71 (76%) of them completed the survey. Almost 57% of the neurologists develops their activity at private hospitals, while 44% works at public institutions. In 93% of the respondents, the quarantine was mandatory in their countries and 67% had the possibility to use telemedicine. The rest of baseline description of the group of respondents as well as country distribution are summarized in

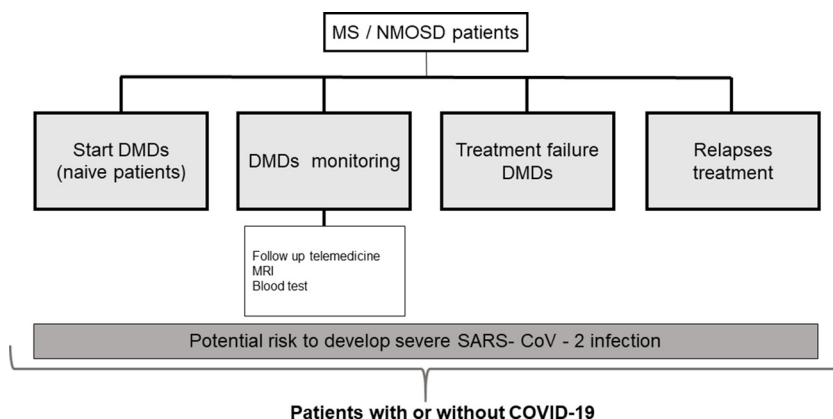


Fig. 1. Schematic presentation of the structure of the survey carried out on neurologists. The survey was based on hypothetical situations about MS and NMOSD patients' management situations, including start and monitoring disease-modifying drugs (DMDs), DMD treatment failure, relapses management in COVID-19 and non-COVID-19 patients, in terms of potential risk of developing severe COVID-19 course.

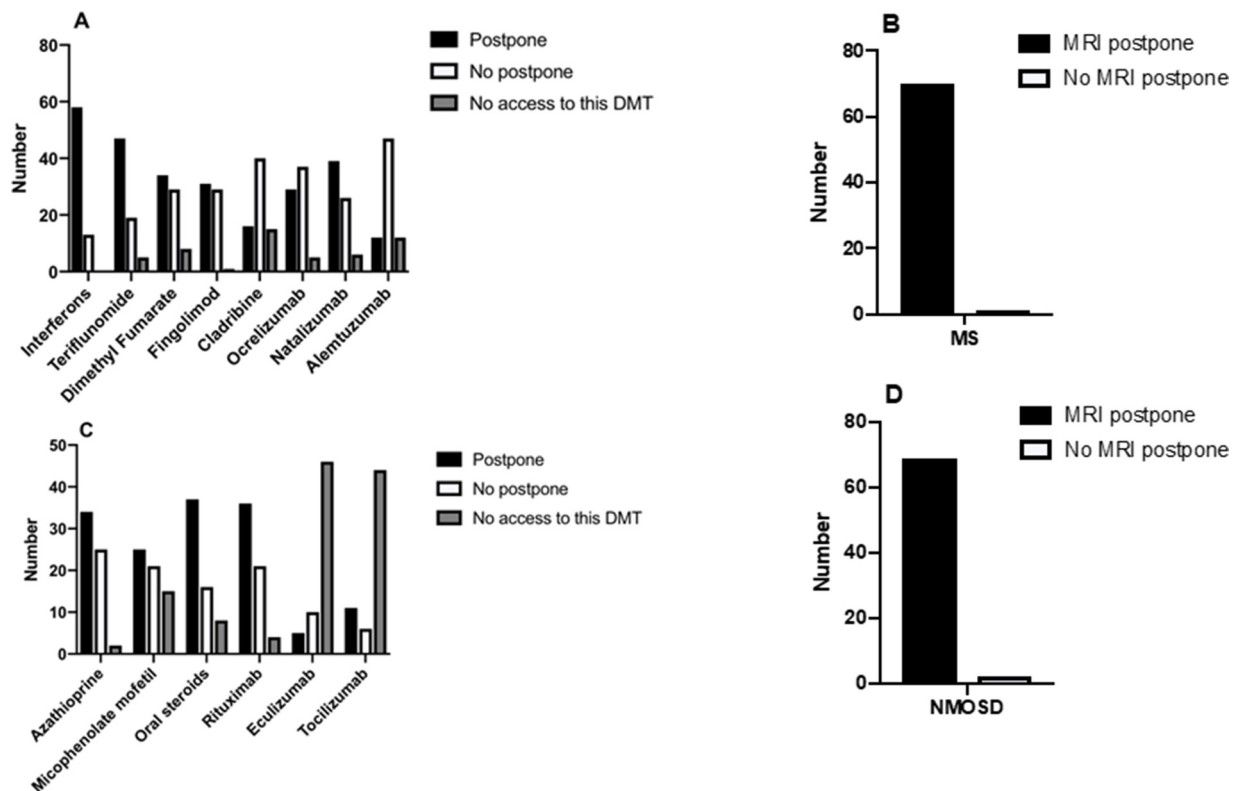


Fig. 2. Laboratory test and MRI control in MS and NMO/SD patients. (A) postponing laboratory tests in MS patients. (B) postponing MRI tests in MS patients. (C) postponing laboratory tests in NMO/SD patients. (D) postponing MRI tests in NMO/SD patients.

Table 1.

3.1. Clinical and therapeutic decisions in MS patients

3.1.1. MRI and laboratory tests

Neurologists were asked about their current practice in MS patients with regard to MRI and laboratory test. For the analysis of laboratory test to determine blood count as well as liver function, responses were stratified based on current treatment in use for MS. In patients receiving beta interferons, teriflunomide, glatiramer acetate or natalizumab, most respondents postpone the test or monitoring. In the case of MS patients receiving cladribine, ocrelizumab or especially alemtuzumab most respondents do not postpone the test, while in MS patients under treatment with fingolimod or dimethyl fumarate half of respondents postpone the test (Fig. 2A). Regarding MRI scans, most of neurologists postpone the test in MS patients (Fig. 2B).

3.2. Treatment initiation in MS patients

Most respondents consider that glatiramer acetate, interferons, teriflunomide, dimethyl fumarate and natalizumab were safe treatment options to initiate in MS patients during the COVID-19 pandemic. Regarding fingolimod, cladribine, ocrelizumab (in RRMS and PPMS) and alemtuzumab, most respondents consider that these were not safe strategies to start with and other options should be considered (Fig. 3A).

3.3. Treatment continuation in MS patients without COVID-19

For the analysis of decision-making in treatment continuation in MS patients without COVID-19, responses were stratified taking into account the potential risk of severe COVID-19 infection associated with DMDs. As shown in supplementary figure 1A, most respondents will continue treatments with interferons (73.2%), glatiramer acetate

(71.8%) or teriflunomide (50.7%), regardless the grade of lymphopenia of MS patients. Additionally, the most frequent cause of suspension of treatment was grade 3 lymphopenia for these three DMDs. In the case of dimethyl fumarate and fingolimod treatments, about one-third of respondents will suspend the DMD with grade 3 lymphopenia and it was the most frequent answer for this group of drugs. In addition, with regard to fingolimod treatment, 24.5% of respondents will suspend the DMD with grade 4 lymphopenia. Between 18.3% – 22.5% of respondents will continue with fingolimod and dimethyl fumarate, regardless the grade of lymphopenia. Almost half of respondents (46.5%) will postpone the ocrelizumab infusion in PPMS patients regardless of the CD19/CD20 count. On the other hand, more than one-third of respondents (38%) will continue with regular ocrelizumab infusions in highly activity RRMS patients regardless of the CD19/CD20 count. Additionally, 19.7% will suspend it and 19.7% will only continue depending on CD19/CD20 count (Supplementary Figure 1B). In the case of cladribine treatment, many respondents (40.8%) will postpone the next cycle independently of the disease activity and CD4/CD8 count, followed by 18.3% of respondents, who will only continue with cladribine treatment in highly active MS patients. Regarding alemtuzumab, most respondents (62%) will suspend it regardless the disease activity or CD4/CD8 count (Supplementary Figure 1C). Lastly, about one-third of respondents will continue with extended interval dosing of natalizumab regardless the disease activity. The next option in order of frequency was continuation with the normal schedule during the first year of treatment and extended interval dose in patients with more than twelve months of treatment (29.6%) (Supplementary Figure 1C). General characteristics on survey responses for this topic are summarized in supplementary figure 1.

3.4. Treatment continuation in MS patients with mild COVID-19 infection

For the analysis of decision-making in treatment continuation of MS patients with mild COVID-19 infection, responses were stratified in

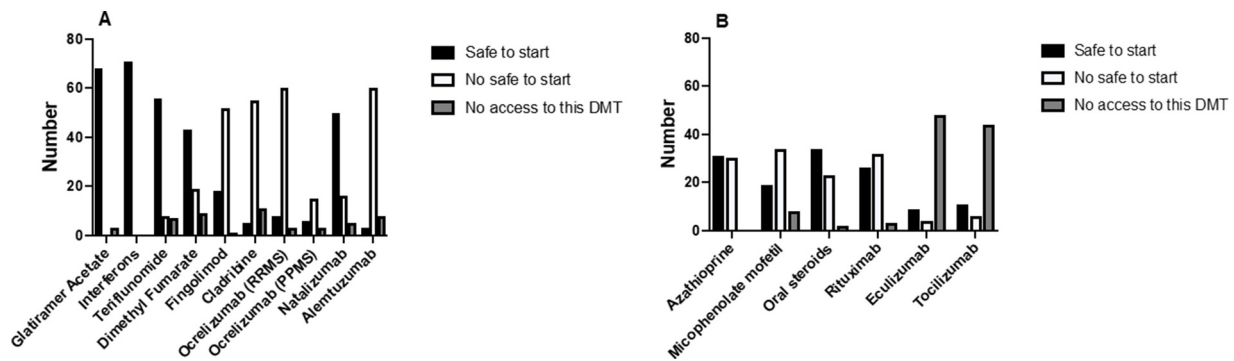


Fig. 3. Treatment initiation in MS and NMOSD patients. Analysis of decision-making in treatment continuation in MS (A) and NMOSD (B) patients without COVID-19.

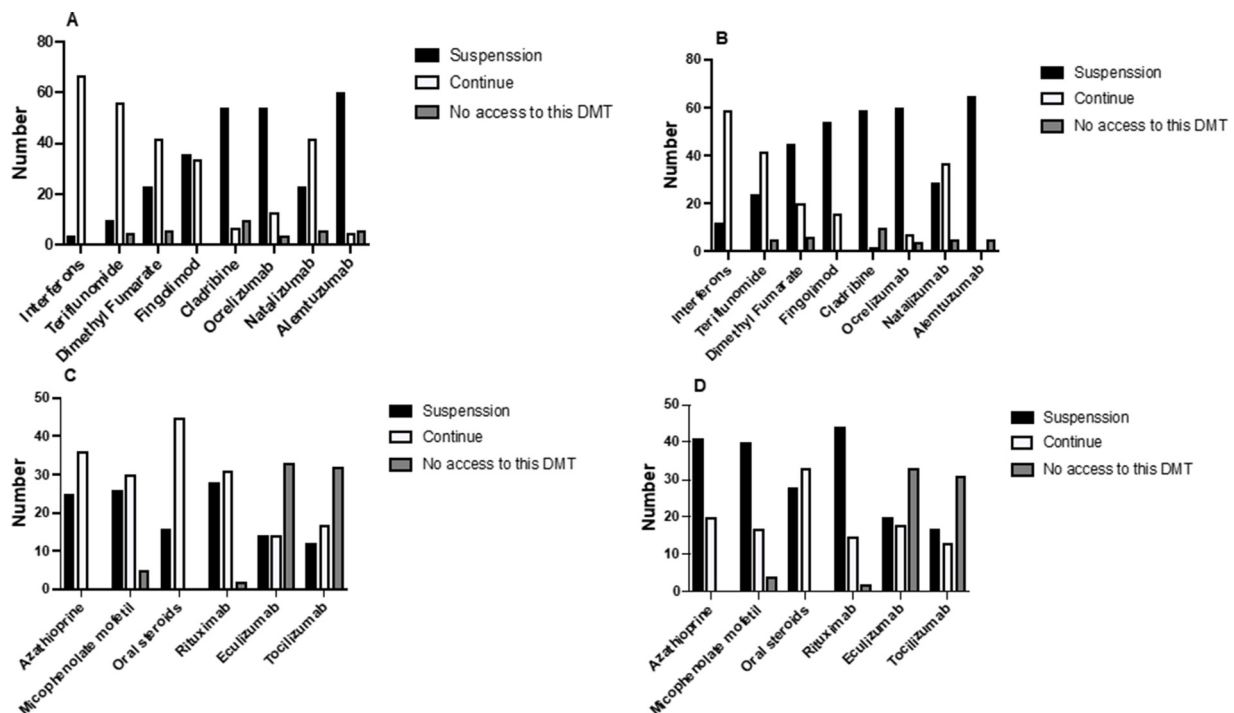


Fig. 4. Treatment continuation in MS or NMOSD patients with mild COVID-19 infection (with and without lymphopenia). Analysis of decision-making in treatment continuation of MS and/or NMOSD patients with mild COVID-19 infection. (A) MS patients without lymphopenia. (B) MS patients with lymphopenia. (C) NMOSD patients without lymphopenia. (D) NMOSD patients with lymphopenia.

patients with and without lymphopenia (less than 500 lymphocytes count). In MS patients without lymphopenia, respondents consider that patients treated with interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate or natalizumab should continue their treatment, while MS patients under treatment with cladribine, ocrelizumab or alemtuzumab should suspend or postpone it. For patients receiving fingolimod and without lymphopenia, half of respondents consider that the treatment should continue (Fig. 4A). In MS patients with lymphopenia, respondents consider that patients receiving glatiramer acetate, interferon beta or teriflunomide might continue their treatment, while MS patients under treatment with dimethyl fumarate, fingolimod, cladribine, ocrelizumab or alemtuzumab should stop or postpone their treatment. With regard to MS patients under natalizumab, almost half of respondents consider that patients with lymphopenia might continue (Fig. 4B).

3.5. Treatment failure in MS patients

Clinical scenarios of treatment failure were presented to respondents. In MS patients under interferons, glatiramer acetate or

teriflunomide and treatment failure, most respondents consider that the switch options during the COVID-19 pandemic are dimethyl fumarate and natalizumab. In MS patients under dimethyl fumarate, fingolimod, ocrelizumab and treatment failure, most respondents consider that the most appropriate option is natalizumab, while in patients under natalizumab and treatment failure, most respondents consider that ocrelizumab is the most appropriate option (Fig. 5)

3.6. Treatment of MS relapses

Most respondents agree that the use of intravenous (IV) steroids should be considered for MS patients suffering from a severe relapse and orals steroids could be an option to IV steroids in order to avoid hospitalization (Fig. 6A).

3.7. Clinical and therapeutic decisions in NMOSD patients

3.7.1. MRI and laboratory tests

In NMOSD patients, most respondents agree to postpone laboratory tests in patients under azathioprine, mycophenolate mofetil (MMF) and

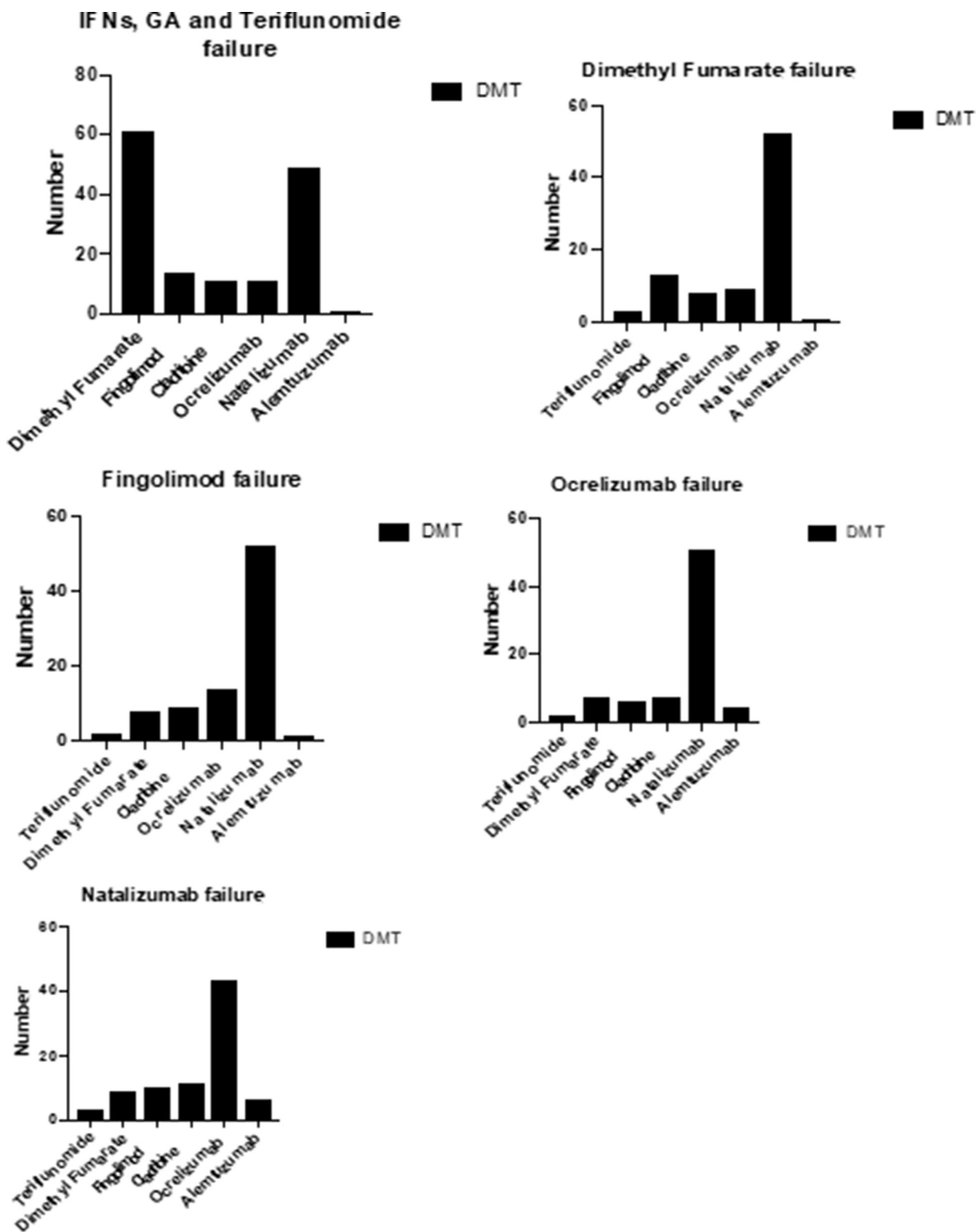


Fig. 5. Treatment failure in MS patients. Analysis of decision-making regarding treatment failure in MS patients.

rituximab as well as to postpone MRI tests during the COVID-19 pandemic (Fig. 2C and 2D).

3.7.2. Treatment initiation in NMOSD patients

Half of respondents consider that azathioprine is a safe option to start with during COVID-19 pandemic. Regarding MMF and rituximab, neurologists consider that these were not safe options to start with during this period (Fig. 3B).

Treatment continuation in NMOSD patients without COVID-19 thinking about thinking about/in order to prevention of complications.

As mentioned for MS patients, responses were stratified taking into account the potential risk of severe COVID-19 infection associated with DMDs. As shown in **supplementary figure 2**, most respondents will suspend oral steroids (32.4%), azathioprine (26.8%) and MMF (where available; 18.3%) with grade 3 lymphopenia. The next option in order of frequency is to continue with oral steroids (26.8%), azathioprine

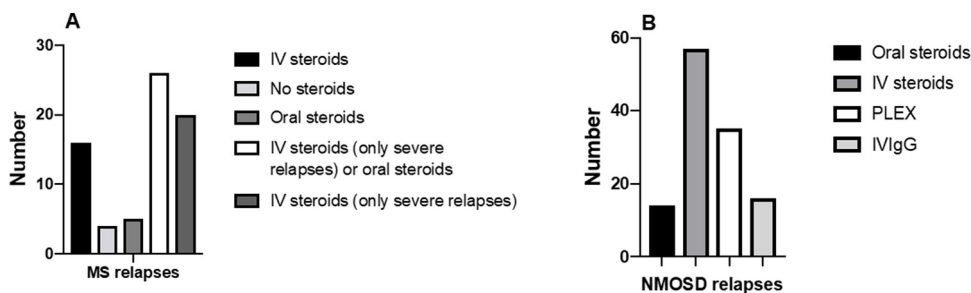


Fig. 6. Treatment of relapses in MS and NMOSD patients. Management of relapses in MS (A) and NMOSD (B) patients.

(19.7%) and MMF (where available; 15.5%). For rituximab, about one-third of respondents (32.4%) will continue with regular infusions in highly active NMOSD patients depending on the CD19/CD20 count, followed by about one fourth of them (23.9%), who will continue with regular infusions regardless the CD19/CD20. For eculizumab and tocilizumab, no access to these options was the most frequent response (76.1% and 73.2%, respectively). For both treatments, a few respondents (14,1% for both drugs) will continue with regular infusions (where available). General characteristics on survey responses for this topic are summarized in **supplementary figure 2**.

3.8. Treatment continuation in NMOSD patients with mild COVID-19 infection

For the analysis of decision-making in treatment continuation of NMOSD patients during the COVID-19 pandemic, responses were stratified in NMOSD patients with and without lymphopenia (less than 500 lymphocytes count). In patients without lymphopenia, respondents consider that NMOSD patients under azathioprine and oral steroids should continue their treatment. In the case of patients receiving MMF, rituximab, eculizumab and tocilizumab (where available), half of respondents consider that the treatment should be stopped (Fig. 4C). In NMOSD patients with lymphopenia, respondents consider that patients under azathioprine, MMF, oral steroids and rituximab should discontinue the treatment, whereas for patients under eculizumab and tocilizumab (where available), almost half of respondents consider that patients with lymphopenia might continue and the other half of them think that patients should suspend the treatment (Fig. 4D).

3.8.1. Treatment failure in NMOSD patients

Clinical scenarios of treatment failure were presented for respondents. In patients under azathioprine or MMF and treatment failure, most respondents consider that the switch options during the COVID-19 pandemic are rituximab in the first place, followed by eculizumab. In patients under rituximab and treatment failure, most respondents consider that the most appropriate options are tocilizumab in the first place or continuation with rituximab during the COVID-19

pandemic (Fig. 7).

3.8.2. Treatment of NMOSD relapses

Most respondents agreed that the use of IV steroids should be consider for patients under a relapse and plasma exchange (PLEX) as a treatment option to IV steroids in NMOSD patients with a relapse (Fig. 6B).

4. Discussion

MS and NMOSD experts are frequently confronted with uncertainties concerning the diagnosis, prognosis, clinical course of these diseases on one hand, and DMDs efficacy and their safety on the other (Bermel et al., 2013). Appropriate disease management involves complex medical decisions, as it requires consideration of multiple short and long-term factors. Therefore, the risks and benefits should be taken into consideration throughout the patient follow-up.

Over the past few weeks, decision-making about MS and NMOSD patients has become even more complex in clinical practice in order to adapt to the COVID-19 pandemic. Hence, different scientific associations have elaborated recommendations about MS patients care and management. MS International Federation (MSIF) guidelines recommend that MS patients should take extra care to minimize their exposure to the virus and use alternatives to face-to-face medical appointments (Multiple Sclerosis International Federation 2020). In our survey we identified that only 60% of the experts had the possibility of monitoring their patients by telemedicine. The decision to postpone laboratory blood tests was associated with the type of treatment. In MS patients receiving cladribine, ocrelizumab and particularly alemtuzumab most respondents did not postpone the test. This attitude is probably related to the mechanism of action of these drugs and their safety profile over time (Chisari et al., 2019). In NMOSD patients, most respondents agreed to postpone laboratory test even in those under treatment with rituximab. Recently, there has been an increasing awareness of the relevance of hypogammaglobulinemia and its risk of serious infections. In fact, hypogammaglobulinemia is present as a complication in over half of the patients treated with mid- to long-term

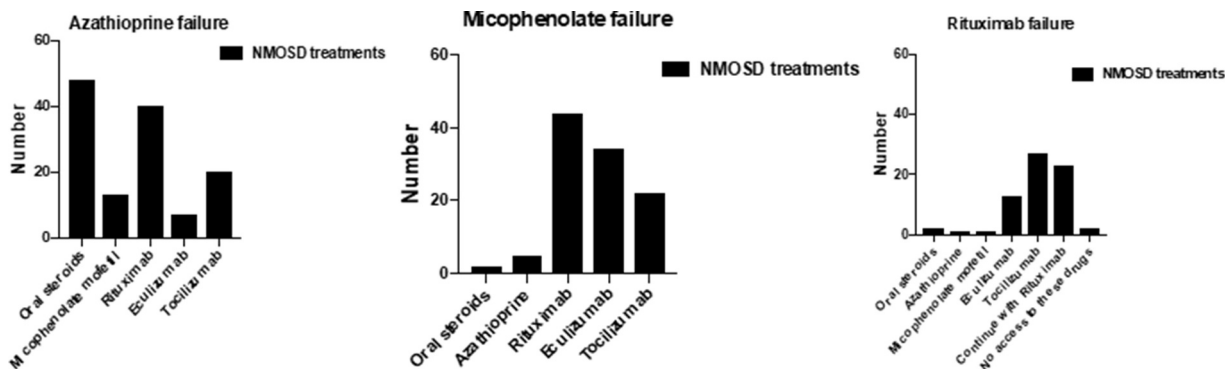


Fig. 7. Treatment failure in NMOSD patients. Analysis of decision-making regarding treatment failure in NMOSD patients.

B cell depleting therapy in the British cohort and Italian cohort of patients treated for NMO or NMOSD (Tallantyre et al., 2018; Radaelli et al., 2016).

Regarding MRI test, most of neurologists postpone the test in MS and NMOSD patients. Studies on MS disease activity, such as clinical drug trials, indicate that the appearance of new MRI lesions is approximately 4–12 times more frequent than the occurrence of new clinical relapses during the same time frame (Vagberg et al., 2017). For this reason, routine brain MRI follow-up of MS patients after treatment initiation is recommended to identify ongoing inflammatory disease activity (Cristiano et al., 2018). Unlike MS, there are currently no recommendations and/or consensus regarding MRI follow-up in NMOSD patients. Despite previously published recommendations, during the COVID 19 era, MRI frequency and timing should be adapted to the clinical situation, as well as the risk of exposure to the virus.

Recommendations have recently been published regarding MS treatments and the potential risk of a serious complication due to COVID 19 (Giovannoni et al., 2020; Brownlee et al., 2020; Willis and Robertson, 2020). (Giovannoni et al., 2020) affirm that: glatiramer acetate, interferon beta, teriflunomide, dimethyl-fumarate and natalizumab are considered low-risk therapies. In our study, most respondents also considered these MS therapies as safe treatment options to initiate during the COVID-19 pandemic in naive patients.

In order to prevent severe COVID-19 infections, respondents consider that patients under fingolimod treatment should stop the medication if they present grade 3 lymphopenia (less than 500 lymphocytes count). Patients treated with fingolimod may develop prolonged lymphopenia. According to the manufacturer, discontinuation of therapy with fingolimod should be considered in patients with persistent lymphocyte counts <200 (European Medicine Agency. Gilenya, INN Fingolimod 2020). Two studies in patients with systemic autoimmune diseases, found that lymphopenia was associated with an about 5-fold increased risk of infection (Merayo-Chalico et al., 2013; Ng et al., 2006). Respondents considered that only highly active MS patients should continue with ocrelizumab infusions (Diaz et al., 2019). Based on potential similar memory B cell depletion mechanisms as cladribine and alemtuzumab, CD20-depletion of B cells by ocrelizumab may exhibit a duration of response exceeding the current licensed treatment interval. Therefore, ocrelizumab appears to induce durable relapsing disease inhibition, within 3 treatment cycles (Baker et al., 2020). Respondents consider that patients under alemtuzumab or cladribine treatment should stop it in all cases. The highest risk in the immune reconstitution therapies is during the depletion phase of the treatment. Even though both therapies produce sustained depletion of T and B cells, cladribine differs from alemtuzumab in the fact that it induces a modest depletion in T and NK cells (Baker et al., 2017). Regarding patients under natalizumab treatment, respondents consider that the extended interval dosing (EID) could be used. Recent publications in context of COVID-19 pandemic, also emphasize that EID could be a therapeutic strategy (Ryerson et al., 2019). While EID is associated with statistically significantly lower progressive multifocal leukoencephalopathy (PML) risk than standard interval doses (SID), the benefit-risk profile of EID compared with SID was not assessed (Ryerson et al., 2019).

Concerning MS patients with mild COVID 19 infection under treatment, respondents consider that patients receiving cladribine, ocrelizumab and alemtuzumab should stop or postpone the treatment. In patients with lymphopenia, respondents consider that MS patients receiving dimethyl fumarate or fingolimod should stop their treatment. In a large study of 98,344 individuals from the general population, it was found that lymphopenia was associated with increased risk of hospitalization due to any infection. In addition, it was associated with a 1.7-fold increased risk of infection-related death (Warny et al., 2018). This risk seems to increase progressively the lower the absolute lymphocyte counts gets, particularly when the lymphocyte count drops below 800/mm (WHO grade 2) (Warny et al., 2018).

The increase in available DMDs has led to greater emphasis on treatment sequencing paradigms and the need for a strategic approach to the treatment switch (Rotstein and Montalban, 2019; Alonso et al., 2018). Previous studies have shown that patients switching horizontally in terms of efficacy (for example interferon beta to glatiramer acetate or vice-versa), did not do as well as patients switching vertically to high efficacy DMDs (Coyle, 2013; He et al., 2015). Clinical scenarios of treatment failure were presented to respondents. Most of them consider natalizumab an appealing option when COVID-19 pandemic issues are a factor, in addition to breakthrough activity; the risk of systemic immunosuppression is low and prolonged lymphocyte depletion does not occur with natalizumab. Koudriavtseva et al. informed that natalizumab was associated with stable increase of peripheral lymphocytes, mainly B cells, and an unchanged proportion of T cell subsets in long-term follow-up (for at least 24–48 months) (Koudriavtseva et al., 2014). Although the incidence of natalizumab-associated PML in Latin America is unknown, appears to be higher in Europe than in North America. On the other hand, the risk of PML increases with increasing duration of treatment, with the greatest increase in risk occurring after 2 years of therapy (Bloomgren et al., 2012).

In regard with NMOSD patients, different clinical scenarios were presented, and respondents consider that azathioprine is the best treatment options to start with during the COVID-19 pandemic. In NMOSD patients under treatment, most respondents consider that oral steroids, azathioprine followed by mycophenolate are the safest therapies (even in some cases of patients with a mild COVID-19 infection). Previous studies have shown that both MMF and azathioprine were effective in patients with NMOSD and the probability of maintaining a relapse-free state was not significantly different between MMF and azathioprine. In addition, fewer and milder adverse events were attributed to MMF than to azathioprine (Chen et al., 2017; Yang et al., 2018). In patients treated with rituximab, most respondents suggest continuing treatment, although most of them recommend it only in patients with high disease activity. In patients receiving azathioprine or MMF and treatment failure, most respondents considers that the switch option during the COVID-19 pandemic is rituximab. A systematic review and network meta-analysis have shown that rituximab was hierarchically superior than azathioprine with significant standardized mean difference; MMF was ranked the most tolerable therapy (Huang et al., 2019). Recently, randomized controlled trials on NMOSD treatment with eculizumab, satralizumab, inebilizumab or tocilizumab have shown to reduce the risk of new relapses compared with placebo or azathioprine (Zhang et al., 2020; Pittock et al., 2019; Cree et al., 2019; Yamamura et al., 2019; Tahara et al., 2020). Unfortunately, most respondents do not have access to this kind of treatment, results related to these therapies cannot be evaluated in the context of our region.

5. Conclusion

As the COVID-19 pandemic increases exponentially worldwide, the demand for data on the impact of the virus on MS and NMOSD patients is rapidly growing. There is an urgent need to gather and share information to enable evidence-based decision making on the clinical management of MS and NMOSD during the COVID-19 pandemic. Therefore, to understand how Latin America experts are managing and treating both MS and NMOSD patients during the COVID-19 pandemic is crucial in order to optimize the care of affected patients in the region.

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CREDIT author STATEMENT

RA and JR conceived and planned the survey and manuscript. BAS and ECC performed statistic analysis and materials and methods. PL,

OG, FH, FG and VR provided critical feedback and helped shape the manuscript.

Declaration of Competing Interest

RA has received personal compensation for consulting, serving on a scientific advisory board, lecturing as well as professional travel/accommodation stipends among other activities from Biogen Idec, Genzyme, Merck-Serono, Raffo, Novartis, Teva, Roche. E.C.C. has received personal compensation for consulting, serving on a scientific advisory board, lecturing as well as professional travel/accommodation stipends among other activities from Biogen Idec, Genzyme, Merck-Serono, Raffo, Novartis, Teva, Roche. BAS has received financial compensation for the development of educational, scientific activities and travels to conferences from Biogen, Novartis, Merck, Genzyme, TEVA, Bayer, Tuteur and Roche. PL has received personal compensation for consulting, serving on a scientific advisory board, lecturing as well as professional travel/accommodation stipends among other activities from Biogen Idec, Genzyme, Merck-Serono, Raffo, Novartis, Teva, Roche. JIR has received honoraria from Novartis as a scientific advisor. He has received travel grants and attended courses and conferences on behalf of Merck-Serono Argentina, Novartis Argentina. OG, FH, VR, FG have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.msard.2020.102310](https://doi.org/10.1016/j.msard.2020.102310).

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