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Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic raised concerns among neurologists treating people with multiple sclerosis (MS) about the potential impact of COVID-19 on patients, particularly on those receiving disease modifying therapies (DMTs).

Initially, it was suggested to discontinue or postpone some immunosuppressive DMTs. Publications soon emerged, bringing about better understanding of the risks and benefits of DMTs use during the pandemic. However, the impact of the therapy on predisposition to more severe forms of COVID-19 is not clear enough yet. Therefore, it is important to generate evidence through case studies to inform clinical practice.

Most of the literature available to date has focused on second-generation therapies (as their immunosuppressive mechanism of action raised the greatest concerns) or consists of reviews with overall data analysis (Rostami Mansoor and Ghasemi-Kasman, 2021; Sormani et al., 2021; Sharifi-an-Dorche, 2021).

Detailed publications on clinical presentation and outcomes of COVID-19 in MS patients treated with first-line therapies are scarce. A few case reports of SARS-CoV-2 infection in patients receiving teriflunomide describe a self-limiting and mild course of the disease (Bollo et al., 2020; Capone et al., 2021; Ciardi et al., 2020; Maghzi et al., 2020; Mantero et al., 2020; Mohn et al., 2020; Verkin et al., 2021).

To our knowledge, there are no publications assessing COVID-19 in Latin American MS patients under teriflunomide treatment. We report COVID-19 presentation, course and outcomes in the sub-group of teriflunomide-treated MS patients in Argentina.

Study methodology

This was a descriptive observational, retrospective, multicentre, open-label study.

We included all MS patients receiving teriflunomide (14 mg PO daily) with clinical follow-up at reference MS centres in Argentina, who were also included in a nationwide registry and developed COVID-19 from June 1st 2020 to January 31st 2021. (Alonso R et al., 2021)

Data were retrospectively obtained from medical records. Each treating neurologist completed a comprehensive form developed for the purposes of this study. The following variables were collected: gender; age; MS phenotype, years from MS diagnosis, Expanded Disability Status Scale (EDSS) score, years on teriflunomide treatment; comorbidities; COVID-19 symptoms, date of initiation and duration, diagnostic method, treatment, and hospitalization need; teriflunomide discontinuation during infection; oxygen requirement; outcomes; MS relapse during or after COVID-19; white blood cell count (WBC), absolute lymphocyte count (ALC); MRI scan during or after infection; post-COVID symptoms; anti-SARS-CoV-2 antibodies titre, and vaccination against COVID-19.

All patients signed a written informed consent. This study was based on anonymized and de-identified data. Researchers ensured data confidentiality and all personal information was protected according to the Personal Data Protection Act of Argentina (Act 25,326 and regulations in force).

Case series

Eighteen MS patients under teriflunomide treatment from eight MS centres developed COVID-19 and were included in this case series (Table 1).

Patient’s mean age was 41.2 ±12.6 years and 72% of them were female; 94% (n=17) had diagnosis of relapsing-remitting MS and 6% (n=1) presented a radiologically isolated syndrome. The mean time since MS diagnosis was 6.17 ±5.6 years and mean time on teriflunomide therapy was 3 ±1.5 years. Patient’s median EDSS score was
Table 1
Demographic and clinical characteristics of teriflunomide-treated Argentine MS patients with COVID-19.

| Patient # | Gender | Age (years) | MS type | Year from MS diagnosis | EDSS (ongoing) | Comorbidities | Teriflunomide therapy | COVID-19 symptoms | COVID-19 diagnosis | COVID-19-related complications | COVID-19 severity | Recovery | Post-COVID-19 symptoms | WBC and ALC | MS response (during COVID-19) | MRI (during or after COVID-19) | MRI (lesion load/ gadolinium enhancement) | anti-SARS-CoV-2 antibodies |
|-----------|--------|-------------|---------|------------------------|---------------|--------------|-------------------|---------------------|-------------------|------------------------|----------------|----------|------------------------|------------|--------------------------|------------------------|--------------------------------|------------------------|
| 1         | F      | 45          | RR      | 3                      | No            | 3            | 12/12/2020       | Fever, dry cough, sore throat | Nasal swab           | No                | 4-7                    | Mild           | Full     | No                     | Normal    | No                       | No                      | No                              | No                     |
| 2         | M      | 37          | RR      | 5                      | No            | 2            | 10/10/2020       | Fever, fatigue             | Nasal swab           | No                | 1-3                    | Mild           | Full     | No                     | Normal    | No                       | No                      | No                              | No                     |
| 3         | F      | 53          | RR      | 9                      | No            | 5            | 16/11/2020       | Fever, fatigue, smell/taste loss | Nasal swab           | No                | 1-3                    | Mild           | Full     | No                     | Normal    | No                       | No                      | No                              | No                     |
| 4         | F      | 50          | RR      | 4                      | Diabetes      | 1,5         | 06/09/2020       | Dry cough, nasal congestion, smell/taste loss, fatigue | Clinical criteria  | No                | 4-7                    | Mild           | Full     | No                     | Normal    | Yes (1/2/2020)            | No                      | No                              | No                     |
| 5         | F      | 31          | RR      | 1                      | Hypertension   | 1.5         | 07/09/2020       | Nasal congestion, smell/taste loss, myalgia | Nasal swab           | No                | 4-7                    | Mild           | Full     | Headaches and fatigue | Normal    | Yes (12/12/2020)          | No                      | No                              | No                     |
| 6         | M      | 52          | RR      | 20                     | Diabetes      | 1.0         | 30/11/2020       | Fever, dry cough, myalgia, fatigue | Nasal swab (PCR-Quick test) | No                | 4-7                    | Mild           | Full     | NA                     | No         | No                       | No                      | No                              | No                     |
| 7         | F      | 29          | RR      | 5                      | Diabetes      | 2.0         | 09/01/2021       | Fatigue, dry cough, smell/taste loss | Nasal swab           | No                | 1-3                    | Mild           | Full     | No                     | Normal    | No                       | No                      | No                              | No                     |
| 8         | F      | 54          | RR      | 3                      | Diabetes      | 2.0         | 21/10/2020       | Diarrhea, nausea/vomiting, headache, fatigue, pruritus, sore throat | Clinical criteria  | No                | 4-7                    | Mild           | Full     | No                     | Normal    | Yes (19/12/2020)          | No                      | Yes Positive                    | No                     |
| 9         | F      | 28          | RR      | 3                      | Diabetes      | 1.0         | 06/01/2021       | Nasal congestion, smell/taste loss, fatigue | Nasal swab           | No                | 1-3                    | Mild           | Full     | No                     | Normal    | No                       | Yes (04/02/2021)          | No                              | No                     |
| 10        | F      | 25          | RR      | 1                      | Diabetes      | 1.0         | 18/12/2020       | Fever, myalgia, pruritus, sore throat | Clinical criteria  | No                | 4-7                    | Mild           | Full     | No                     | Normal    | No                       | No                      | No                              | No                     |
| 11        | F      | 27          | RR      | 5                      | Diabetes      | 0.0         | 31/08/2020       | Dry cough, nasal congestion, myalgia, headache, fatigue | Clinical criteria  | No                | 4-7                    | Mild           | Full     | Headaches and fatigue | Normal    | Yes (10/12/2020)          | No                      | No                              | No                     |
| 12        | M      | 32          | RR      | 3                      | Diabetes      | 1.0         | 15/09/2020       | Fever, headache, fatigue | Nasal swab (PCR-Quick test) | No                | 4-7                    | Mild           | Full     | No                     | NA         | No                       | Yes (18/01/2021)           | New lesions No Gd+        | Yes Negative                       |
| 13        | F      | 49          | RR      | 3                      | Diabetes      | 1.0         | 12/08/2020       | Fever, dry cough, nasal congestion, smell/taste loss, myalgia | Clinical criteria  | No                | 4-7                    | Mild           | Full     | No                     | Normal    | No                       | No                      | No                              | No                     |
| 14        | F      | 69          | RR      | 20                     | Diabetes      | 5.5         | 03/06/2020       | Fever, smell/taste loss             | Clinical criteria  | No                | 1-3                    | Mild           | Full     | No                     | Normal    | No                       | No                      | No                              | No                     |
| 15        | F      | 38          | RR      | 7                      | Diabetes      | 3           | 10/11/2020       | Fever, smell/taste loss | Nasal swab           | No                | 1-3                    | Mild           | Full     | No                     | Normal    | No                       | No                      | No                              | No                     |
| 16        | M      | 29          | RR      | 13                     | Diabetes      | 3           | 09/09/2020       | Fever, dry cough, nasal congestion | Nasal swab           | No                | 1-3                    | Mild           | Full     | No                     | Normal    | No                       | No                      | No                              | No                     |
| 17        | M      | 52          | RR      | 4                      | Diabetes      | 3           | 10/02/2021       | Fever, dry cough, smell/taste loss, myalgia, headache, fatigue | Nasal swab           | No                | 14                    | Mild           | Full     | NA                     | No         | No                       | No                      | No                              | No                     |
| 18        | F      | 55          | RR      | 2                      | Diabetes      | 3           | 29/08/2020       | Fever, fatigue, smell/taste loss             | Clinical criteria  | No                | 14                    | Mild           | Full     | No                     | NA         | No                       | No                      | No                              | No                     |

ALC: absolute lymphocyte count; EDSS: Expanded Disability Status Scale; Gd: gadolinium; Gd+: gadolinium-enhancing lesions; MS: multiple sclerosis; NA: not available; ND: not determined; RIS: radiologically isolated syndrome; RR: relapsing-remitting; WBC: white blood cell count. Table format based on Capone et al., 2021, Mantero et al., 2020 and Maghzi et al., 2020.

ALC: absolute lymphocyte count; EDSS: Expanded Disability Status Scale; Gd: gadolinium; Gd+: gadolinium-enhancing lesions; MS: multiple sclerosis; NA: not available; ND: not determined; RIS: radiologically isolated syndrome; RR: relapsing-remitting; WBC: white blood cell count. Table format based on Capone et al., 2021, Mantero et al., 2020 and Maghzi et al., 2020.
2 (range 0-5.5). Four patients (22%) had comorbidities, which were well-controlled.

Regarding COVID-19, diagnosis was made with nasal swab in 11 patients (61%) and was based on clinical criteria in 7 patients (39%). The most frequent symptoms were: fever 67% (n=12) and fatigue 61% (n=11), followed by loss of smell/taste in 56% of the patients (n=10).

Upper airways symptoms like dry cough and nasal congestion were present in 44% and 33% of patients respectively; myalgia was reported by 33% and headache by 28% of the cases. Gastrointestinal symptoms (diarrhoea, nausea/vomiting) and sore throat were less frequent (17% and 11%, respectively). Only one patient reported pruritus (6%) (Fig. 1).

All patients were managed in the outpatient setting. Only symptomatic treatment with ibuprofen or acetaminophen was used and none of the patients required anti SARS-CoV-2-specific drugs. The clinical course was mild in all the patients, who fully recovered from the acute-phase with symptom resolution within 7-14 days. Furthermore, 39% of the patients showed a very mild infection course and recovered within 1-3 days. Data on WBC and ALC were available for 15/18 patients and were within normal limits.

None of the patients discontinued their teriflunomide scheduled therapy during COVID-19 course. No MS relapses occurred during or after COVID-19 course.

Only two patients developed prolonged fatigue after acute infection, both of whom recovered within 3 months.

MRI was performed in 6 patients between 1 and 6 months after COVID-19. None of them showed contrast-enhancing lesions. Only one patient (#12) showed non-enhancing new lesions (it was not possible to determine if these new lesions were related to SARS-CoV-2 infection or were pre-existing because the previous MRI that was used for comparison had been performed one year before).

Antibodies against SARS-CoV-2 were only determined in 2 patients more than a month post-infection; titres were positive in one of them. None of the patients in this series has been immunized until this manuscript submission date.

Final comments

A number of reviews (Rostami Mansoor et al., 2021; Sormani et al., 2021; Sharifian-Dorche et al., 2021) and seven original reports (Bollo et al., 2020; Ciardi et al., 2020; Maghzi et al., 2020; Mantero et al., 2020; Mohn et al., 2020, Capone et al., 2021; Yetkin et al, 2021) describing in detail 16 MS patients who developed Sars-Cov-2 infection while on teriflunomide therapy, have been published since the pandemic began. Most of these publications were from Europe, where COVID-19 peak preceded in months the Latin American dissemination.

Our patients were younger compared to other case series (41.2 years vs. 50.5 years), but had similar median EDSS scores (2 vs. 2.25) and average time on teriflunomide treatment (3 vs. 3.7 years) (Capone et al., 2021). Symptom resolution took less time (within 7 days) for most patients in our series than in other reports (Bollo et al., 2020; Ciardi et al., 2020; Maghzi et al., 2020; Mantero et al., 2020; Mohn et al., 2020, Capone et al., 2021). In our series, the most frequent symptoms were fever and fatigue, while loss of smell/taste occupied the third place; as previously described, this last symptom was associated with mild-course COVID-19 (Lechien et al., 2021). None of the patients in our series required anti SARS-CoV-2-specific drugs, hospitalization nor oxygen therapy. The outcomes were favourable for 100% of our patients, only two of whom developed mild post-COVID symptoms that resolved within 3 months.

Louapre et al. (2020) have pointed out that older age, cardiovascular disease, obesity and neurological disability are the main risk factors for severe COVID-19 in MS patients, irrespective of the DMT administered. Sormani et al. (2021) found no association between DMT therapy and COVID-19 severity, except for B-cell depletors and methylprednisolone pulse within the previous month of severe infection. In a recent review on DMTs used during pandemic, first line drugs like glatiramer acetate, teriflunomide and dimethyl fumarate may be considered safe and β-interferons could be protective in early stages of the Covid-19 disease but may become detrimental in the hyper inflammation stage (Alborghetti et al., 2021).

The data published so far, either as detailed case reports or reviews, support the continuity of teriflunomide therapy, which has shown to be safe during COVID-19 course.

To our knowledge, this is the first Argentine and Latin American case series about COVID-19 in teriflunomide-treated MS patients.

In conclusion our observations suggest that teriflunomide therapy in MS patients might be safe during the course of Covid-19 and should not be discontinued during the infection. Our report also adds to the

![Symptoms of Covid-19 in MS patients treated with Teriflunomide](https://example.com/symptoms.png)

Fig. 1. Symptoms of COVID-19 in Argentine MS patients compared to other case series in the literature.
evidence that COVID-19 is mild in patients receiving teriflunomide therapy.

Declaration of Competing Interest

GL has received honoraria for advisory boards from Merck Serono Argentina and Schering Bayer Argentina; Travel grants for meetings and Congresses from Tuteur, Synthon Bagó, Merck Argentina; clinical trials from Novartis, Biogen, Genzyme and Merck Serono.

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 and Novartis Argentina

RA has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Biogen, Merck Serono, Novartis, Sanofi -Genzyme and Roche.

ECC has received reimbursement for developing educational presentations, educational and research grants, consultation fees, and/or travel stipends from Biogen Argentina, Merck Argentina, Merck and LATAM, Roche Argentina and LATAM, Raffo, and Novartis Argentina.

ND has received honoraria for advisory boards from: Bayer Argentina, Latin-america and Global; Merck Serono Argentina and Global; Genzyme Argentina; Latin-america and Global and Sanofi Global; travel grants for congresses from: Schering; Bayer; Merck Serono; Biogen Idec Argentina; Genzyme Argentina; Latin-america and Global and Sanofi Argentina, Latin-america and Global; Merck Serono Argentina and Novartis Argentina.

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