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## Review article

# Would it be recommended treating multiple sclerosis relapses with high dose oral instead intravenous steroids during the COVID-19 pandemic? Yes



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## ABSTRACT

The emergence of novel Coronavirus 2019 and the subsequent pandemic are presenting a challenge to neurologists managing patients with multiple sclerosis (MS). The clinical management has dramatically altered and it was necessary to change and/or adapt it to the new situation. Regarding relapses management, the use of intravenous corticosteroids and hospitalization during MS relapses increase the risk of viral exposure. Objective: To review the efficacy and safety of high dose oral corticosteroids in acute relapses treatment compared to intravenous corticosteroids. Methods: Descriptive review of the utility of high dose oral corticosteroids for MS relapses treatment was performed. We searched the literature available on PubMed and Scientific Electronic Library Online (SciELO). We focused on different trials comparing the use of high dose intravenous vs oral corticosteroids. Results: Five studies were selected. One hundred and eighty two patients receiving treatment with high dose oral corticosteroids were included. The most frequent schedule was oral methylprednisolone 1000 mg (over three days). There were no significant differences between both routes of corticosteroids administration. Conclusion: Neurologists should be aware of the current evidence on the similar efficacy of both oral and intravenous corticosteroids for MS relapses. Using oral steroids during the pandemic would be a safe option for patients.

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a novel disease entity caused by SARS-CoV-2 virus that recently spread throughout the world. The disease appears to be mild in the majority of patients, however, about 15% of affected individuals can develop a severe disease with respiratory insufficiency, that may require mechanical ventilation and intensive care (Guan et al., 2020). Whether people with MS are at increased risk of COVID-19 infection, or at higher risk of more severe infection, is unknown (Thakolwiboon et al., 2020; Willis and Robertson, 2020). Although, immunosuppression is thought to increase risk of severe infections compared with the general population. MSIF (Multiple Sclerosis International Federation) 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 (4). Healthcare systems were rapidly having to change and adapt in the face of the pandemic [5]. Patients are seen virtually using telemedicine or phone calls and they were advised to take all preventive measures to reduce COVID-19 transmission (social-distancing, frequent hand-washing, respiratory hygiene) and also were recommended to avoid contact with the hospital and other medical institutions as much as possible (Repovic, 2019). Oral corticosteroids (oCS) may be preferable to intravenous corticosteroids in some patients with MS relapse (Burton et al., 2012). This administration route may relieve pressure on

the hospitals that may be affected due to the pandemic and reduces the risk of COVID-19 transmission in these patients. In Argentina, there are no recommendations regarding relapses treatment during the COVID-19 pandemic. Therefore, patients are still hospitalized and receiving intravenous methylprednisolone (IVMP). The objective of this study is to make a descriptive review of the available literature about the efficacy of high doses oral corticosteroids for MS relapses treatment. In addition, we propose an algorithm of management and treatment during this pandemic context.

## 2. Methods

We searched for the following terms in PubMed and Scientific Electronic Library online (SciELO): “Multiple Sclerosis”, “MS”, “relapse treatment”, “oral corticosteroids”, “high dose oral corticosteroids”, “corticosteroids”, “oral methylprednisolone”, “oral prednisone”, “intravenous corticosteroids”, “IVMP”, “oMP”. Articles published from 1990 to March 2020 were selected. We identified 1021 potential relevant records. Duplicate records, reviews, comments, nonrandomized trials or unrelated to topic were excluded. Studies were selected when they met the following entry criteria: randomized controlled trials, blinded or unblinded, comparing the use of high dose oCS and IVMP for MS relapses treatment. Five articles were selected and following variables were described: number of patients, dose and route

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<https://doi.org/10.1016/j.msard.2020.102449>

Received 4 June 2020; Received in revised form 10 August 2020; Accepted 12 August 2020

Available online 20 August 2020

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**Table 1**  
Characteristics of the trials included in the revision comparing IVMP versus oC in the treatment of acute MS relapses.

Author/Year	Design	Patients and Methods	Outcomes	Safety/Tolerability	Results
<b>SM Alam (7)</b> 1993 United Kingdom	Randomized double-blind placebo-controlled trial	35 patients Severity of relapse: not reported MRI: not evaluated Schedule: - 500 mg IVMP + five placebo tablets for 5 days. - 500 mg oMP + 100 ml of placebo intravenously for 5 days. (15 patients)	- Disability improvement: Mean EDSS at day 5 and 28 - MRI: not evaluated. - Others: not evaluated.	- Major adverse effects: not reported. - Minor adverse effects: headache, indigestion, acne, dizziness, flushed feeling, phlebitis, ankle oedema and mild depression. There were no increase in gastrointestinal symptoms in the group that received methylprednisolone orally.	The EDSS score had improved at day 28 in 16 of the 20 in the intravenous group, mean score of the whole group falling from 4.85 to 3.50, and in 10 of the 15 in the oral group, mean score falling from 4.80 to 3.67. This improvement was statistically significant in both group ( $p < 0.001$ ).
<b>V Martinelli (8)</b> 2009 Italy	Randomized clinical trial.	40 patients Severity of relapse: moderate or severe relapse At least 1 gadolinium (Gd) enhancing lesion Schedule: - 1000 mg oMP for 5 days (20 patients) - 1000 mg IVMP for 5 days (20 patients)	- Disability improvement: mean EDSS at weeks 1 and 4. - MRI: reduction of number of Gd-enhancing lesions after 1 week of treatment. - Others: safety, tolerability.	- Major adverse effects: not reported. - Minor adverse effects: At least 1 adverse event was reported by 26 (65%) patients, 11 receiving IV MP and 15 oMP. The most frequently were gastric pyrosis, anxiety, insomnia and dysgeusia (particularly metallic taste)	The 2 groups showed a reduction of Gd-enhancing lesions over time ( $p = 0.002$ for oMP and $p = 0.001$ for IV MP) with a "non-inferiority effect" between the 2 routes of administration at week 1. Both groups showed an improvement of EDSS over time ( $p < 0.001$ ) without between- group difference at week 4.
<b>Ramo-Tello (9)</b> 2013 Spain	Randomized, double-blind, multicenter clinical trial	49 patients Severity of relapse: moderate or severe relapse MRI baseline: the number of T2 and Gd enhancing lesions were similar in both groups. Schedule: - 1000 mg IVMP plus oral placebo for 3 days. - 1250 mg oMP plus IV placebo for 3 days (25 patients)	- Disability improvement: non-inferiority assessment of the oral MP arm in EDSS improvement at four weeks' post-treatment initiation - MRI: number and volume of T1 Gd-enhancing, and new or enlarged T2 lesions at four weeks' post-treatment. - Others: safety and tolerability	- Major adverse effects: not reported - Minor adverse effects: All except one patient reported adverse effects. The most common were headache, mood disorder and insomnia. Other side effects included a metallic taste in mouth, nausea, stomach pain, diarrhea, rash, edema and palpitations. No statistical differences were found between the groups.	An improvement in the EDSS score was observed in both treatment groups at one and four weeks vs baseline ( $p < 0.001$ for both groups at both time points). No differences were found in the EDSS between groups during the study period. At one week and four weeks' post-treatment initiation, the median change in the volume of Gd+ lesions and median increase in T2 lesions number was 0 in both groups, and the median change in T2 lesion volume was 0 in both groups
<b>Le Page (10)</b> 2013 France	Multicentre, double-blind, randomized, controlled, non-inferiority trial	199 patients Severity of relapse: not reported. MRI: not evaluated Schedule: - 1000 mg IVMP plus oral placebo for 3 days - 1000 mg oMP plus IV placebo for 3 days (100 patients)	- Disability improvement: decrease of at least one point in most affected score on functional system scale (FSS) by day 28 - MRI: not evaluated - Others: safety and tolerability	- Major adverse effects: 12 moderate-to-severe adverse events were reported. 2 in the oral group (one case of nausea and vomiting and one of profound depression) and 10 in the IV group (3 cases of abdominal pain, one of vomiting, 5 of insomnia, and one of profound depression) - Minor adverse effects: the most frequent reported were metallic taste, hot flashes, headache, anxiety and insomnia (this last was more frequently in the oral group).	In the per-protocol population, 66 (81%) of 82 patients in the oral group and 72 (80%) of 90 patients in the intravenous group achieved the primary endpoint (improved by at least one point on the most affected FSS score). The absolute treatment difference was 0.5% (90% CI -0.95 to 1.0-4).
<b>Morrow (11)</b> 2018 Canada	Single-blind randomized clinical trial, not blinded	55 patients Severity of relapse: not reported. Optic neuritis MRI: not evaluated Schedule: - 1000 mg IV MP for 3 days (23 patients) - 1250 mg oral Prednisone for	- Disability improvement: best-corrected visual acuity (BCVA) and scores on low-contrast letters at 1 and 6 months. - MRI: not evaluated. - Others: recovery of the latency of the P100 component of the visual evoked potential at 6 months	- Major adverse effects: not reported. - Minor adverse effects: 25 patients experienced at least 1 adverse effect. The most frequent were: gastrointestinal (5 in the IV group and 8 in the oral group), insomnia (4 in the IV group and 6 in the oral group); and tiredness or fatigue (5 in the IV group and 1 in the oral group).	At 6 months' recovery, P100 latency in both groups have improved, with no significant difference between groups ( $P = .07$ ). For BCVA, recovery between the groups did not reach statistical significance at 1 month or 6 months. In addition, improvements in low-contrast BCVA

(continued on next page)

Table 1 (continued)

Author/Year	Design	Patients and Methods	Outcomes	Safety/Tolerability	Results
		3 days (22 patients)			were not significantly different between treatment groups at 1 or 6 months' recovery.

administration of the treatment, outcomes, comparative efficacy and safety and/or tolerability.

### 3. Result

Table 1 summarizes the most important characteristics of each research. Out of five selected studies, three were double blind and four used high dose oral methylprednisolone (oMP) (Alam et al., 1993, Martinelli et al., 2009, Ramo-Tello et al., 2014, Le Page et al., 2015, Morrow et al., 2018). High dose oral prednisone (oP) as a treatment was applied in one trial. One hundred and eighty two patients receiving treatment with high dose oCS were included (160 oMP and 22 oP). The dose was from 500 mg to 1250 mg (three to five days). The most frequent oMP dose was 1000 mg (over three days). Three clinical trials provided initial evidence that high dose oMP can be administered to similar efficacy than IVMP in reducing EDSS and Gd-enhancing lesions after an MS relapse (Alam et al., 1993, Martinelli et al., 2009, Ramo-Tello et al., 2014). Even though, the main weakness of these studies was the low number of enrolled patients. In 2015, COPOUSEP trial (Oral Versus Intravenous High-dose Methylprednisolone for Treatment of Relapses in Patients With Multiple Sclerosis), was the first multicenter, double-blind, randomised, controlled trial, with a large number of subjects included, being primary strength compared to other studies (Le Page et al., 2015). This study assigned 100 patients to oMP and 99 patients to IVMP (1000 mg daily for 3 days in both regimes). The mean time from relapse onset to treatment was 7 days. The primary aim of this study was to compare the proportion of patients who improved by day 28 without additional corticosteroid treatment. Eighty-one percent of oral and 80% of IV subjects met this end point, offering the strongest evidence of noninferiority between these two routes of steroid administration (absolute treatment difference 0.5%, 90% CI -9.5 to 10.4). In 2018, Morrow et. al. evaluated the recovery of vision following treatment of acute optic neuritis with high dose oP versus IVMP. Participants were randomized 1:1 to the IVMP (1000 mg) or oP (1250 mg) group. Primary outcome was recovery of the latency of the P100 component of the visual evoked potential at 6 months and no significant difference between groups was found (Morrow et al., 2018).

Regarding side effects, there were no major adverse effects reported and no statistical differences were found between the groups, including gastrointestinal disorders. In COPOUSEP trial insomnia was more frequently reported in the oral group (77%) than intravenous group (64%).

### 4. Discussion

Corticosteroids are usually the first choice of treatment for MS relapses (Burton et al., 2012). Several clinical trials and two meta-analysis provide evidence that high dose corticosteroids hasten the neurologic recovery and improved the Expanded Disability Status Scale (EDSS) after MS relapse (Miller et al., 2000, Filippini et al., 2000). To date, considerable variability remains about dosing, type, and duration of corticosteroid regimens used for MS relapses. In intravenous administration, the most used corticosteroids are MP followed by dexamethasone. Due to its long duration of action, intravenously dexamethasone is not recommended for routine use. On one hand, the most used regimen is 1000 mg/daily IVMP for 3 to 5 days, but this usually means hospitalization. On the other hand, considering this pandemic context, 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 (Brownlee and Bourdette, 2020). Bearing this in mind, high dose oCS may be preferable to treat acute relapses, since patients might avoid IVMP infusions at the hospital. Despite that oral dexamethasone use has been described (De Keyser et al., 1999), high-dose of oral methylprednisolone and prednisone were the most oCS reported (De Keyser and Zwanikken, 1997, Burton et al., 2012). In the present review, we could identified five clinical trials that provided

evidence that high dose oMP can be administered to similar efficacy than IVMP in reducing EDSS and Gd-enhancing lesions after an MS relapse. In addition, Morrow et al. (2004) compared the total amount of steroid absorbed after 1250 mg oP versus 1000 mg IVMP in 16 patients with MS relapses. They considered the difference in potency between methylprednisolone and prednisone (5:4) by administering a 25% higher dose of prednisone. At 24 hours, the mean area under the concentration-time curve did not differ between groups (p 0.122). This study suggests that bioavailability does not differ, although peak concentration and time to peak concentration do (Strupp, 2005). Furthermore, all corticosteroids are thought to exert their glucocorticoid effects primarily through the same receptor (the glucocorticoid receptor) (Kalincik, 2015).

Even though oMP is not available in Argentina, like many other countries, high doses of oP (1250 mg/daily) may be useful. With the currently available formulations, this translates into a daily regimen of 25 tablets of 50 mg prednisone which is the equivalent to 40 tablets of dexamethasone 4 mg. In our center, we have experience using oCS, in selected patients, even before COVID-19 pandemic. Based on the reviewed studies (Alam et al., 1993, Martinelli et al., 2009, Ramo-Tello et al., 2014, Le Page et al., 2015, Morrow et al., 2018), we suggest that the use of high dose oCS treatment for MS relapses in this pandemic context should be evaluated (Figure 1). The first step is to rule out that the patient has fever and/ or symptoms consistent with COVID-19. The association of COVID-19 symptoms and increased relapses has not been demonstrated. To date, evidence suggests that systemic infections (viral or bacterial) are associated with increased risk of MS relapses, presumably by eliciting helper T cell type 1 (Th1) immune response and pro-inflammatory cytokines changes (Kalincik, 2015). Therefore, a patient with MS presenting COVID-19 infection could also have a relapse. On the other hand, previous symptoms may be exacerbated by fever (pseudo-relapse) and in the clinical practice context, it is not always easy to distinguish from a relapse (D'Hooghe et al., 2010). In this scenario, the decision of the pharmacological relapse treatment should be discussed in each case with the infectious disease and Neurology

team. If a pseudo-relapse is ruled out, the second step is to evaluate the relapse severity. In general, a relapse that affects a patient's function, regardless of his or her particular symptoms, would be considered severe enough to recommend treatment (Multiple Sclerosis International Federation 2009 Jan). The severity of an MS relapse is one factor to consider when determining an appropriate management strategy. The Canadian Multiple Sclerosis Working Group recommended that severity of the relapses should be taken in considerations. Therefore, the effect of the relapse affecting daily living activities, and the type and number of systems involved (i.e., polysymptomatic relapses or affection on the cerebellar/motor systems) may establish a severe relapse (Freedman et al., 2004). In order to have a close patient monitoring, we suggest hospitalization and IVMP treatment in case of a severe limitation on activities of daily living (i. e. severe motor deficit, disabling cerebellar symptoms). Otherwise, high dose oCS treatment can be started at home and follow up by telemedicine. Telemedicine could be a good monitoring option and a potential solution to minimize the MS patient's exposure to the virus. A recent review involving 28 studies and 3252 participants showed that telemedicine have been demonstrated to be technically feasible (Yeroushalmi et al., 2019). Additionally, the American Academy of Neurology (AAN) has published recommendations for implementing a telemedicine service, suggesting that an adapted neurological examination (ANE) is feasible remotely (American Academy of Neurology 2020). Regarding to MS patients, patient-reported outcome measures (PROMs) would be usefully additional to the ANE. The Patient Determined Disease Steps (PDDS) is strongly correlated to EDSS, mainly to visual, cerebellar, pyramidal, sensory, bowel/bladder, and ambulatory functional systems. Besides, it has been validated in multiple languages, and also as an online tool (Lavorgna et al., 2017). Therefore, PPDS could become a recommended tool to measure the evolution of patients treated with oral corticosteroids (see decision making flowchart for management of acute MS relapses during COVID-19 pandemic)

Finally, since there are asymptomatic people with COVID-19 infection and it is not possible to ensure the absence of infection, we

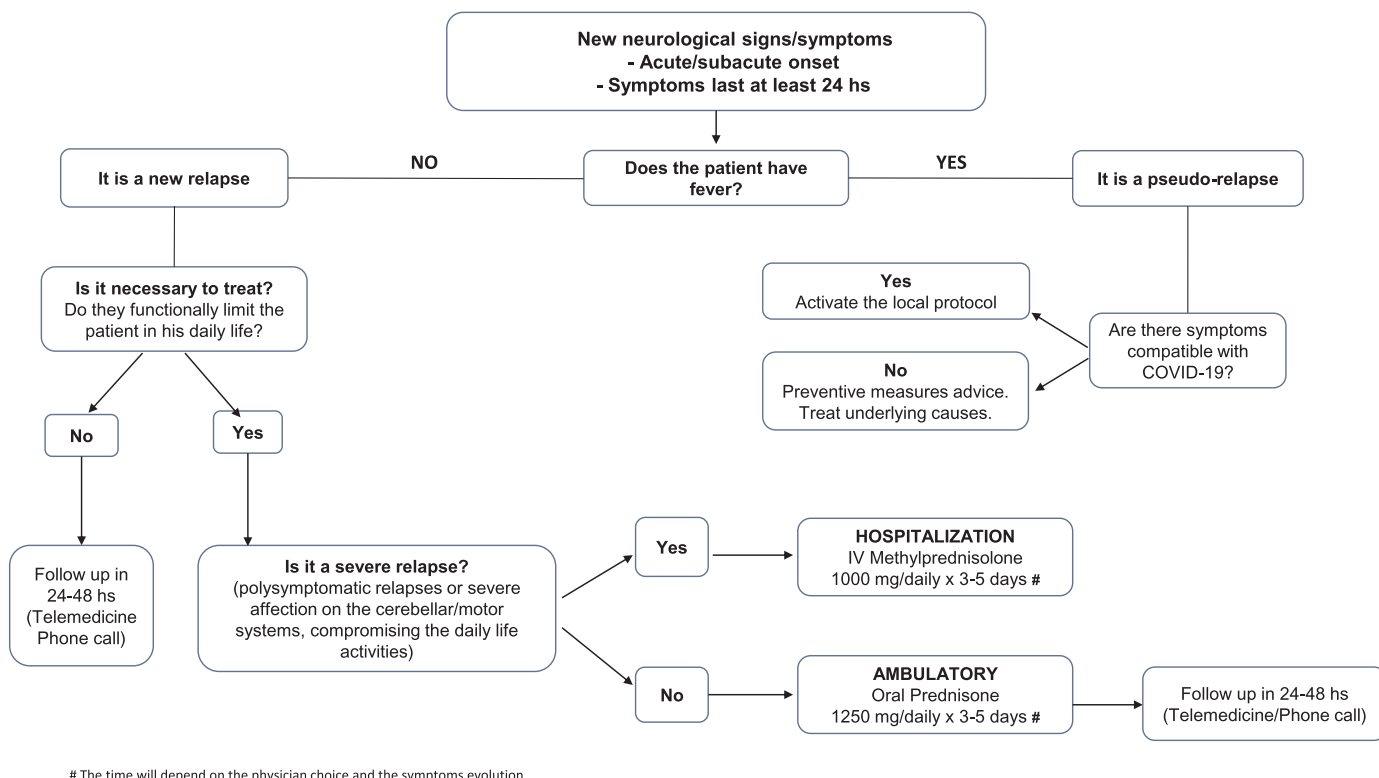


Fig. 1. Decision making flowchart for management of acute MS relapses during COVID-19 pandemic.

suggest carefully evaluation of any COVID-19 symptoms on follow-up and testing if consistent with local recommendations. A recently published systematic review including 542 Chinese patients, analyzed the use of corticosteroids in SARS-CoV2 infected patients. Two studies reported negative findings regarding corticosteroids, one reported no significant association between corticosteroids and clinical outcomes, and one concluded that methylprednisolone was associated with a significant reduction of mortality in patients with COVID-19 pneumonia developing acute respiratory distress syndrome. Although, there is no data about the risk or benefit of corticosteroids treatment in patients with mild COVID-19 symptoms or asymptomatic (Veronese et al., 2020).

## 5. Conclusion

There were no significant differences between both oral and intravenous routes of corticosteroids administration. Neurologists should be aware of the current evidence on the efficacy of high doses oCS for MS relapses in order to apply into clinical practice. The goal in MS relapse treatment is to reduce the impact on patient quality of life. Any decision on relapse treatment during COVID-19 pandemic will need to be taken carefully considering patients' symptoms and ruling out an underlying infection.

## Funding sources

The authors did not require a source of funding for this research.

## Declaration of Conflict of 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.

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.

OG, PS and CS have no conflicts of interest

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