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Research Article

# Coronavirus and Multiple Sclerosis, Autopsy and Biopsy and Choice of Therapy

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## Abstract

**Background:** Coronavirus in trigeminal nerve (TGN) has for decades been studied as a candidate neurotropic virus associated with multiple sclerosis (MS). The novel coronavirus 2019 (COVID-19) outbreak in infected cases is challenging the whole immune system. The lesson from MS treatment and a new era of COVID-19 therapies are of value to review.

**Method:** Searched databases to identify the strongest evidence of biopsy, autopsy, and cerebrospinal fluid (CSF), when using keywords MS and coronavirus, from January 1940 to April 2020. The result presents a solid knowledge of biopsy and autopsy for the association of COVID-19 and MS, then COVID-19 single and combination therapies being evaluated as presented in clinical use or clinical trials and compare common sites with MS.

**Results:** All therapies with proven clinical efficacy against COVID-19 and its current deployment in COVID-19 and their common aspect with MS therapies (MSTR) and immunology are screened. Some MSTR despite some different side-effect e.g. risk for infection or cardiac arrest are candidates of being used as COVID-19 life-saving therapy.

**Conclusion:** This global health disaster caused by airborne virus COVID-19, has created a new break to learn more about MS etiology and this airborne agent and future drug choices when reviewing the five months COVID-19 data through significant medical reports on World Wide Web.

**Keywords:** Multiple Sclerosis; Coronavirus; Trigeminal Nerve; Biopsy; Autopsy; Immunology

## Abbreviations

BBB: Blood Brain Barrier; BCB: Blood Cerebrospinal Fluid Barrier; CNS: Central Nervous System; EAE: Experimental Autoimmune Encephalomyelitis; IL: Interleukin; IFN-: Interferon-; MS: Multiple Sclerosis; MP: Methylprednisolone; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematosus; TNF: Tumor Necrosis Factor; TGN: Tgrigeminal Nerve; CSF: Crebrospinal Fluid; MSTR: MS Therapies; ARDS: Acute Respiratory Distress Syndrome; CSF: Cerebrospinal Fluid

## Introduction

The patient with Multiple Sclerosis (MS) receives disease-modifying therapies (DMTs) that act on the immune system, they may

face an increased risk of being infected with the coronavirus and developing more severe symptoms. Coronavirus as other neurotrophic viruses has been studied in association with MS [1], nevertheless lacking the latest update on COVID-19. The current issue needs briefing the previous data and brings together a list of therapeutic options that are of value in both MS and COVID-19 when historical evidence is discussed.

Previous experiments describe that the nasal cavity is the route of entry of mice hepatitis virus strain JHM (MHV-JHM) into the CNS. During the early stage of the mice infected intranasally, viral RNA could be detected only in the trigeminal and olfactory nerves. A few days later, MHV-JHM RNA was found throughout the brain in mice dying of acute encephalomyelitis but remained confined to the entry sites in mice that did not develop acute disease [2]. The same could be reproduced in a rat study and 30% of animals develop subacute encephalitis with fresh microscopic demyelinating lesions located in bilateral spinal tracts of TGN [3]. The analysis of white matter plaque and nonplaque regions by in situ hybridization using randomly primed "S- labeled complement DNA (cDNA) probes derived from genomic coronavirus RNA. Total genomic cDNA probes increase the likelihood of detection of closely related coronaviruses, which is consistent with detection of viruses in CNS tissue of MS. MS and control brain with probed cDNA specific for human, murine, porcine, and bovine coronaviruses were also studied. The in-situ hybridization of coronavirus RNA in 12 of 22 MS brain samples displayed cDNA probes of coronavirus [4]. Furthermore, tissue was screened for coronavirus antigen by immunohistochemical methods; antigen was detected in two patients with rapidly progressive MS. Significant amounts of coronavirus antigen and RNA were observed in active demyelinating plaques from these two patients [4] and even some adding studies with larger sample had confirmed the same when analyzing brain biopsies [1] and tested RNA sequences, which confirmed a neurotropic and neuroinvasive potential of coronavirus in MS [5]. These findings show that coronaviruses can have potential neurotropism and neuroinvasive character to contribute as a candidate pathogen in MS in the human model [4] however, in a more recent, the results were not reproducible and there was no difference in the proportion of positive signals from the MS patients compared to controls when a Danish study applied PCR assays of human coronavirus strain 229E and strain OC43 [6]. Following that, in the latest presentation, airborne pathogens as coronavirus [7] are still an unsolved association with MS [6,8]. Despite the multiple pandemic disasters of coronavirus in last decades and current international COVID-19 health crises [9] in accompanying previous animal model and trigeminal mediated airborne CNS spreading of coronavirus, no following study has yet been done from MS perspectives and using its therapies in COVID-19. Furthermore, it is known that patients with coronavirus (PwC) found with a cytokine storm, manifesting elevated serum levels of Interleukin (IL), IL-1b, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, and G-CSF, GM-CSF, IFNg, TNFa, IP10, MCP1, MIP1A and MIP1B [10] and following attacks with encephalitis or other neurological manifestation [11], whatever, some of these cytokines and a encephalitis-like picture are also related as a risk to chronical MS-relapses [12] or MSTR side effect.

The treatment of COVID-19 [13] has challenged the entire medical world and especially as the MS diagnosis and MSTR are getting more advance and probably make the immune system in patients with MS (PwMS) more untrained and result in one or more immune failures, which in such a global crisis like COVID-19 demanding for MS centers to take action worldwide. Herein, we search the World Wide Web entirely to see the latest update for MS in association with COVID-19. Here novel approaches to capture the therapeutic properties of COVID-19 are of interest for MS.

## Materials and Methods

An interdisciplinary search following international medical guidelines for reviews was conducted (PRISMA Flow Diagram). This article sets out to review and incorporate the most up-to-date evidence for COVID-19 in association with MS following the announcement of a pandemic outbreak. The data was drawn in figure.

### Data sources

Subsequently, we searched databases to identify single and combination therapies being evaluated in clinical use or clinical trials. The literature was reviewed using MEDLINE, Google Scholar, Google search engine and any other online scientific library. The search strings: coronavirus in combination with, multiple sclerosis (MS), trigeminal nerve (TGN), biopsy, autopsy, immunology, MS therapy, autoimmune, respiratory disorders, SARS-CoV-2, and COVID-19. The search was not restricted and all type articles (accepted or preprint) from January 1940 to April 2020 were included. Although older references were cross-referenced if mentioned in recent publications. The homepages for MS center's, MS clinics and universities were reviewed.

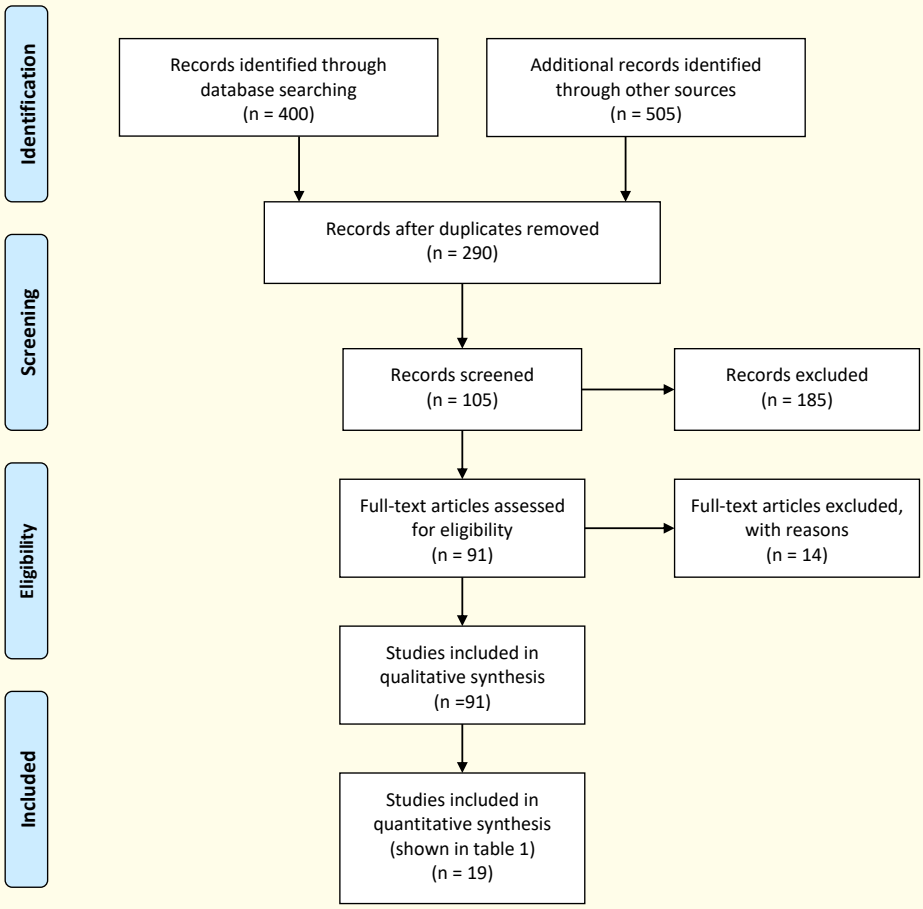


**Figure :** PRISMA Flow Diagram of MS and COVID-19 hits

## Results

The result is displayed in the accordance to following description. The coronavirus in association with MS according to the above description was searched. The same procedures for each section were performed and included in the search method and generated 905 hits. The English hits with a tumor, bleeding, trauma or publication without abstract were excluded. The animal model was reviewed and if relevant, the information was used to support the findings in humans.

Those drugs, which have been approved for MS or have some impact on MS have been included also some for completion.

### Monoclonal antibodies (MAB)

The use of humanized and chimeric MAB has greatly been expanded under the COVID-19 outbreak. Those MAB which is related to MS [14] are displayed in table 1. There is not enough information about which MAB included in the following trials in table 1 are affecting coronaviruses four structural proteins, including E, M, N, and S protein, however major impact comes through humanized immunomodulatory effect using IgG1 or IgG4 (Table 1).

| | Framework | Pathway to determine action | | | | | Evidence |
|---|---|---|---|---|---|---|---|
| MABs | IgG | Leukocyte migration | cytolytic | cytokines | Chemokine** | complement | Approved in MS |
| Natalizumab[1] | IgG4 | + | | | | | + |
| Rituximab[1] | IgG1 | | + | | | | (+) |
| Ocrelizumab[1] | IgG1 | | + | | | | + |
| Ofatumumab[1] | IgG1 | | + | | | | + |
| Alemtuzuma[1] | IgG1 | | + | | | | + |
| Daclizumab[1] | IgG1 | | | + | | | +* |
| Ustekinumab[1] | IgG1 | | | + | | | N.I |
| Tabalumab[1] | IgG4 | | | + | | | T.S |
| Eculizumab[1] | IgG2/4 | | | | | + | N.A |
| Secukinumab[1] | IgG1 | | | + | | | P.C.R |
| Ixekizumab[1] | IgG4 | | | + | | | N.A |

**Table 1:** The overview of those monoclonal antibodies (MAB) which have been related to MS.

Humanized chimeric, *Withdrawn because of side-effect, T.S: Trial stopped because of lacking efficacy, N.I: Not indicated as the drug rasing risk of developing MS, N.A: Not Applied, P.C.R: Positive beneficial case report, +: related, (+): with some local restriction to sue. **At present of time no MAB is tested on MS, however MP and first line therapies are major impactor of chemokines (Cortese, Lucchetti., *et al*. 2019). [1]Immunomodulators uses primarily in RRMS.

## Approved MAB for MS

- **Natalizumab (Tysabri):** The S protein of SARS-CoV-2 produced an evolutionary mutation of K403R and forming an adjacent RGD motif at the interaction surface. The RGD motif, integrin-binding domain, is suggested to bind the S protein of SARS-CoV-2 and it may facilitate the infection process of the virus. Agents that block integrin binding may provide a promising path of research [15]. Known blockers of integrin-binding include the antibody natalizumab (an α4β1/β7 integrin antagonist, IgG4, very late antigen 4 (VLA-4)) for the treatment of MS or Crohn's disease [16]. This is a very important break-through as natalizumab is also under focus for causing progressive multifocal leukoencephalopathy (PML) in PwMS, which is caused by JC-virus [17].
- **Ocrelizumab (Ocrevus):** An Italian research group published the first case of COVID-19 positive in MS patients with ongoing ocrelizumab treatment. This patient develops fever and cough, he was admitted to our hospital in Genova, however after reviewing discharge from hospital. The immune system with depleted B cells that developed COVID-19 antibody is associated with a moderately reduced immune response against COVID-19, due to lack of peripheral B cell response, however, a favorable role in this patient, as persistence of B cells within secondary lymphoid organs are suggested still functioning adequately. However, not yet any trial against COVID-19 is yet been applied to investigate the safety and efficacy of Ocrelizumab [18].

## Not approved for MS

- **Fedratinib (Inrebic):** Several cytokines are involved in TH17 type responses. IL-1β and TNFa express by TH17 and TH1 cells, and both promote TH17 responses and vascular permeability and leakage. TH17 cells themselves produce IL-17 under the stimulation of another IL. IL-22 produced by innate lymphoid cells and CD4+ T cells plays an important role for IL-17 secretion and mucosal homeostasis. IL-17 has broad pro-inflammatory effects on the induction of cytokines G-CSF associated with Janus Associated Kinase 2 (JAK2). The same mechanism in COVID-19 was the background to use Fedratinib [19] to inhibit the JAK2 on IL-17. In approved form it is an oral kinase inhibitor with activity against wild type and mutational activated IL. This inhibitor is used against myeloproliferative neoplasms and turn-down the cytokine production of TH17 [20]. Fedratinib treatment decreased the expression of IL-17 by murine TH17 cells [19]. In MS studies IL-23R positive and negative Th17 cells survive and produce IL-17 equally well, but only IL-23R-positive Th17 cells migrate to the site of inflammation in a mouse model of MS. In a murine model of MS with autoimmune brain lesion, driven by TH17 and TH1, JAK2 inhibitor tyrphostin B42, subcutaneously administrated, could greatly decrease the disease severity [21].

- **Tocilizumab (Roactemra):** The *coronaviridae*, such as SARS-CoV and MERS-CoV cascade cytokine and chemokine production is known as a "cytokine storm", and the same mechanism is displaying for COVID-19. The process cascades the over-activation of effector T cells and the bulk production of pro-inflammatory cytokines, which in turn lead to plasma leakage, vascular permeability, and disseminated intravascular coagulation. PwC treated with the anti-interleukin-6 (IL-6) receptor antibody, Tocilizumab (Actemra or Roactemra), previously approved for rheumatoid arthritis (AR), showed evidence of efficacy stop the symptom progression in PwC [22]. The trial, COVACTA, will clarify the efficacy of COVID-19. In a case report, the RA patient with ongoing Tocilizumab develops MS diagnosis. This negative association, MS and tocilizumab, may also have an important impact on patients suffering from other CNS disorders, including patients with neuromyelitis optica spectrum disorder (NMOSD) in whom the efficacy of tocilizumab is currently being evaluated in clinical trials [23]. Trigeminal engaged side-effect has also been reported [24]. Tocilizumab and rituximab, using real-world data, have comparable effectiveness in RA [25], however, rituximab is not mentioned in the latest COVID-19 trials.

- **Adalimumab (HUMIRA):** The therapeutic role of adalimumab, anti-Tumor Necrosis Factor-α antibody (anti-TNF-α), used for the treatment of inflammatory RA and inflammatory bowel diseases. The potential role of anti- TNFα antibodies in treating COVID-19 patients has strictly linked SARS-CoV-2 functional receptor, angiotensin-converting enzyme 2 (ACE2) and causes enhanced TNFα-production and TNFα-converting enzyme (TACE)-dependent detaching of the ectodomain of ACE2, that facilitates viral entry [26]. The adalimumab anti-COVID-19 effect has permitted scientists in the US to express the recommendation that patients on treatment with anti-TNF-α infliximab or adalimumab should continue with their therapy. However, the side-effect for HUMIRA is an increased risk of developing serious infections. A previous study from Sweden shown that adalimumab is concerned with raising the risk of MS [27] and TGN palsy [28].

- **Eculizumab (Soliris):** Eculizumab a humanized monoclonal antibody against terminal complement C5 that inhibits terminal complement activation [29]. It is believed that there is a preclinical scientific rationale for stopping symptom progression in PwC with severe pneumonia or acute respiratory distress syndrome (ARDS) when administering Eculizumab [30]. The trial SOLID-C19, Soliris will be used to investigate the safety and efficacy to halt the mortality. The use of Eculizumab is well established in NMOSD [31] and confined with some bacterial infection risk [32], and under COVID-9 outbreak patients with NMOSD are encouraged to continue this treatment [30]. This drug is implicated in ceasing the pathophysiology of several ocular surface diseases with TGN involvement [33], however insufficient evidence in MS or optic neuritis.

- **Ixekizumab (Taltz):** Ixekizumab is a MAB against interleukin-17A mostly used for dermatological disorders, e.g. psoriatic arthritis. A trial has been carried out using this medicine to reduce or halt the COVID 19 symptom progression. However, the expert announces that because of symptom deterioration in infected patients it may force the proinflammatory process. The Ixekizumab also is known with risks of viral influenza and the respiratory tract infection. These side-effects, however, be temporarily ignored and even recommended not discontinued. The skin manifestation of COVID-19 can present with a rash and be mistaken for Dengue [34], this could give some dermatological common side to use Ixekizumab in COVID-19. Despite this drug's significant effect in psoriasis [35], and the significant increase of IL-17A during RRMS attack [36], however, the experience of using Ixekizumab in MS is lacking.

- **Meplazumab:** It has been proved that the host-cell-expressed CD147-spike. Antibody against CD147 could suggest blocking the SARS-CoV-2 virus. An open-label study aiming to measure efficacy and safety of Meplazumab, a humanized anti-CD147 antibody, as add-on therapy in patients with COVID-19 pneumonia [37]. In MS microRNA profiles from active and inactive MS lesions showed a wide range of microRNA including microRNA-155. This microRNA modulates immune responses in different ways but so far had not been assigned to CNS resident cells. This microRNA-155 is associated with CD47, which functions as a 'don't eat me' signal inhibiting macrophage activity and modulated the CD147. The microRNA-155 is a promotor of the progression of neuropathic pain in TGN [38] and decreased mitochondrial DNA. It may suggest that microRNA dysregulated in lesions of PwMS reduce CD47 in brain host cells, [39], however, no trial yet applied for test the of Meplazumab regulation of macrophage activation in MS.

- **Sarilumab (Kevzara):** The Sarilumab is a human IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6Rs. The Kevzara may mitigate the effects of cytokines released in response to the COVID-19 and limit lung damage in patients with severe disease; as designed in a clinical trial. Sarilumab has a long history in RA, and it is on the trial for NMO [40], however, lacking experience in MS.

## None-MABs

There is a board-spectrum of small and medium-size molecule therapies that are taken into trials to investigate their safety and efficacy in COVID-19, however, some are approved as MS conventional therapies and may deserve some attention.

- **Fingolimod (Gilenya):** Although immune-inflammatory treatment is not routinely recommended to be used for SARS-CoV-2 pneumonia, according to the pathological findings of pulmonary edema and hyaline membrane formation, timely and appropriate use of immune modulator together with ventilator support should be considered for the severe patients to prevent ARDS development. The sphingosine-1-phosphate (S1P1) receptor regulators, fingolimod, is an effective immune modulator that has been widely used in MS. Now included in the trial to assess reducing the mortality rate caused by COVID-19 [41]. This is another encouraging challenge as fingolimod is also reported with PML cases [42]. In COVID-19 new beneficial cardiovascular effect [43] which can convert cardio-coagulopathy devastation is suggested [44]. The fingolimod has been approved as second-line therapy in MS, however with a case-report of TGN viral infection [45].
- **Ozanimod (Zeposia):** The oral Ozanimod sphingosine-1-phosphate (S1P) receptor modulator approved as an effective treatment of clinically isolated syndrome (CIS), relapsing-remitting disease (RRMS), and active secondary progressive multiple sclerosis (SPMS) [46]. This therapy now has to delay commercialization due to the COVID-19 pandemic. It is not yet known when it will be made available, as the producer will not have a new unknown side-effect when MS starts this treatment under the affection of coronavirus.
- **Methylprednisolone:** The use of corticosteroids in the different formulas has been reported under the coronavirus pandemic. The case-reports commonly equivocally recommend the use of methylprednisolone (MP), as an add-on to the other therapy in the late phase of pneumonia or treatment of severe ARDS [47], as a negative impact raised when MP was started in the early infection phase, this could be confined with its chemokine depended on effect. The long term experience in the use of MP in PwMS is very wide not limited to orally, subcutaneously, intravenously or intrathecally [43] and the early use concerning attack is probably more often in summer times whereas the current COVID-19 is dominating as well. The MS center advises that because of the very real risk of relapse on discontinuing advanced therapies the corticosteroid should be continued as pulse therapy [48].
- **Interferon-alpha-2b (IFNα-2b):** The interferon alfa-2b is manufactured by recombinant DNA technology. This protein made and released by host cells in response to several viruses and used in Dengue fever in the 1980s and later found success in using it to combat HIV, human papillomavirus, Hepatitis B, Hepatitis C, and other diseases. The infected cells in SARS-CoV-2 may make the body generate interferon-alpha and interferon-beta, mobilizing the human immune system to act. The most rigorous information came from Chinese physicians who used the Cubans IFN-α-2b with great success in saving a life when accompanied or used in combination with antiviral therapies. The coming trials will clarify the efficacy and its antiviral significance. Nonetheless, numerous case-reports and case-series describe new inflammatory disorders, inclusive of MS, during interferon therapy [49].
- **Stem cells therapy:** Both mesenchymal stem cells (MSCs) [50] and synthetic stem transplantation have been shown to possess a comprehensive powerful immunomodulatory function in PwC. The nanotechnology synthetic stem cells are available as "LIF-Nano" with a 1000 times increase in potency [51]. In a preclinical model of MS, the timelines of reversal of paralysis (4 days) are in accord with those reported for COVID-19 pneumonia when using MSC therapy [52]. The biodegradable nanoparticles through LIF-Nano provide therapeutic synergy for suppression of autoimmune attack, repair of myelin within damaged CNS tissue, and creation of surrogate micro-stromal niche [53]. Despite this finding the MS expert has classified HSCT as a high risk for coronavirus.
- **Intravenous immune globulin ("IvIg"):** IvIg has been used to treat patients with autoimmune and chronic systemic and CNS or PNS inflammatory diseases, such as systemic lupus erythematosus (SLE) and MS [14]. Furthermore, IvIg has also been used as an anti-infectious agent against viruses, bacteria, and fungi [54]. Derived immune IgG obtained from survived PwC infection and from the same city to increase the chance of neutralizing the virus, treatment was used on other new PwC [55]. Overall, immunotherapy IvIg combined with antiviral drugs could provide alternative treatment against COVID-19 [55]. IvIg has been studied and suggested as a valuable alternative for the treatment of relapsing-remitting MS (RRMS) however no beneficial effect in secondary progressive or primary progressive MS. It is not fully clear in which optimizing dosage or interval the IvIg is indicated in MS, furthermore, there is no data if the IvIg regained from RRMS recovered from an attack will have any similar effect as experienced in COVID-19.
- **Bacillus Calmette-Guérin (BCG):** The BCG vaccine was suggested for COVID-19 as BCG accelerates the "resetting" of the immune system [3] or "turn on" immunity mechanism that

agrees with its pleiotropic repurposing for many diseases. Multiple-dose BCG vaccine was used for reversing type-1 diabetes (T1D) [56] and for treating bladder cancer and MS [57]. The BCG in MS animal model has confirmed the redirected trafficking of activated CNS antigen-specific CD4+ T cells to local inflammatory sites induced by BCG infection modulates the initiation and progression of a Th1-mediated CNS autoimmune disease [58]. BCG is in treatment topic for COVID-19 and should be considered as a concern for MS when vaccination is on pipeline.

- **Chloroquine:** The exception is 4-aminoquinoline, (hydroxyl) chloroquine, an immunomodulatory drug with known antiviral activity but that has been used primarily for over 60 years to treat malaria and, more recently, autoimmune diseases [59]. The non-FDA approved or repositioned use of chloroquine (CQ) includes the potential treatment of a wide spectrum of diseases, both non-infectious and infectious such as a range of cancers [60], RA, SLE, systemic sclerosis, and MS. The CQ was urgently repositioned as an ideal antiviral prophylactic and recovery against PwC [61].
- **Melatonin:** The possible beneficial effects of melatonin as adjuvant use in COVID-19 in anti-inflammation, anti-oxidation, immune response regulation has been repeatedly demonstrated. Previously 8-week oral intake of 6 mg/d melatonin caused a significant decrease in serum levels of IL-6, TNF-α, and high-sensitivity C-reactive protein (hs-CRP) in patients with diabetes mellitus and periodontitis [56]. In another trial of PwMS, orally 25 mg/d of melatonin for 6 months also promoted a significant reduction in serum concentrations of TNF-α, IL-6, IL-1β and, lipoperoxides [57]. In an MS study, PRIMS, show the same significant increased level of the hs-CRP during MS attack [62], however, it is not mentioned if this level decreased, when PwMS were treated with melatonin.
- **Vitamin D:** Vitamin D is known to improve the immune system, and vitamin D deficiency increases vulnerability to viral infections [63]. Especially during the winter months, unless supplements are taken, serum 25(OH)D concentrations are low in most people. Levels begin to rise only at the beginning of the summer. Considering its many biological and physiological aspects, the immunoregulatory and stimulation effects of vitamin D occur via several mechanisms. It is suggested that vitamin D adequacy would help control and reduce the risks of current COVID-19 infection. It is advisable to maintain serum 25(OH)D concentrations above 30 ng/mL (75 nmol/L), preferably at a level greater than 40 ng/L (100 nmol/L), together with a sufficiency of other micronutrients, such as zinc, selenium, and antioxidants. The use of vitamin D is for decades a hot discussion for MS as an interplay between susceptibility genes and environmental factors are suspected. High-dose vitamin D supplements appear to aggravate inflammation and myelin loss in the CNS, and reduce worsen the Expanded Disability Status Scale associated (EDSS), however "no evidence of disease activity", has not formally reached [64]. As a study in a mouse model of EAE [65] reported that the overtake of vitamin D can act pro-inflammatory. The excessive use of vitamin D causes calcium levels to spike, which directly increases the proinflammatory mechanism and their capacity to infiltrate the CNS [66], this contravention may need be clarified through the coming trial.
- **ACE2:** The SARS-CoV-2 adjacent glycoprotein RGD on spike protein (S protein) lies in the receptor-binding domain at the border of the subdomain that is specifically involved in the binding to human ACE2 (angiotensin-converting enzyme inhibitors-II) [67]. ACEI and AT1R (angiotensin II type-I receptor) inhibitors have been suggested to modify individual susceptibility to COVID19 by influencing SARSCov-2 virulence. However, for patients with severe lung affection or at risk of acute lung injury, a higher level of ACE2 expression may prevent the risk of acute lung failure. Therefore, it may be clinically relevant to identify both types of drugs, i.e. those leading to elevated ACE2 expression as well as those leading to reduced expression. The possible inhibition is suggested by human recombinant soluble angiotensin-converting enzyme 2 (hrsACE2) [68], when a Swedish based study is going to phase III trials. In CNS disease, the previous data have shown that Quantitative RT-PCR analyses showed an up-regulation of renin, ACE, as well as AT1R in the inflamed spinal cord and the immune system, including antigen-presenting cells (APC). Treatment with the renin inhibitor aliskiren, the ACE2 inhibitor enalapril, as well as preventive or therapeutic application of the AT1R antagonist losartan, resulted in a significantly ameliorated course of MOG-EAE [69]. Furthermore, clinical studies are warranted to clarify the role of ACE2 and whether drugs targeting ACE2 may be therapeutically useful in COVID-19 and MS.

## The trials of antiviral therapies and MS

There is some previous data of using antiviral therapy against herpesvirus [70], however not yet a significant disease-modifying

effect published. Some newer antiviral drugs are mentioned to be of choice against COVID-19, Lopinavir plus ritonavir (Kaletra), combination therapy with previous experiences on HIV patients. Another drug, Umifenovir tested on the influenza virus which also as Oseltamivir (Tamiflu) been prescribed without confirming evidence on COVID-19. Other antiviral therapies like Remdesivir (anti- Ebola) are on the investigational pathway in European countries. Favipiravir (Avigan) has in 340 Chinees patients shown improved abnormalities on CT-chest. An even more unknown pediatrics drug Baloxavir, another anti-influenza inhibitor set to begin clinical trials on COVID-19. In MS using Combivir (zidovudine/lamivudine) which inhibit Epstein-Barr virus (EBV) has been effective [71]. An MS dedicated MAB and in nature build up as antiviral therapy, Temelimab (GNbAC1), is a candidate for COVID-19 therapy. This drug targets a human endogenous retrovirus, which is suggested to be associated with MS. This treatment is on one-year trial intends to build on the results of two previous studies of RRMS and extend to treat the progressive form of MS [72], however despite the potential antiviral effect this drug is not listed in trials for COVID-19 yet.

## Discussion

Some murine coronaviruses are spreading along with TGN and are neurotropic, neuroinvasive, and are capable of MS-like demyelinating disease [2], some discrepancies may challenge these two conditions therapeutic options. Herein, it has provided an in-depth rapid review of previous knowledge, and the preclinical and clinical treatment options for COVID-19 to better understand the immunological impact on MS. Some therapies characterized by lymphocytopenia in most patients, thus combination with immunomodulatory drugs in PwMS may be highly problematic at least in early pneumonia [6].

The COVID-19 in majority attaches to proximal and nasal respiratory airway [7] and it should come to the MS focus with results from that study which discussed the association with TGN biopsy and coronavirus. T cell clones from patients with MS have been shown to react with both HCoV229E antigens and myelin basic protein, suggesting molecular mimicry as a basis of pathogenesis [73]. All data of MS cases and brain magnetic resonance imaging (MRI), conducted during COVID-19 MAB treatment, are of major interest. This will help to clarify if new cytological, cytokine or chemokine alteration has any impact on disease's natural duration.

This review could also be helpful to learn of the US, UK and Italian recommendations during the COVID-19 pandemic [74]. If we trust that SARS-CoV-2, the cause of COVID-19, is a new human pathogen that is likely to have recently crossed species, we need to renew our basic and advance understanding of COVID-19 in MS. When we visit different MS authorities, centers and clinics located all over the world we find some paradoxes between recommendations and what those 22 trials are applying to be tested on PwC. F. ins they recommended an intermediated risk for PwMS when treated with S1P1 modulators (Fingolimod (Gilenya), Siponimod (Mazent), Ozanimod, Ponesimod)), however, some of these drugs are on trial to halt mortality in PwC. Collecting data on the impact of COVID-19 on PwMS and related functional scales, and particularly the risks of a novel pathogen in patients on immunosuppressive treatments is a priority for national and international MS registries. The level of EDSS and frequency of COVID-19 morbidity and mortality can in any MS register be linked and generate valuable information as we assumed that ambulation impacts on respiratory function and more COVID-19 associated underlying respiratory illnesses. Furthermore, some MS therapies may have been protective, could these MS registers confirm a lower frequency of COVID-19 in MS pool?

The symptoms in PwC describes with common presentations of sneezing, fever, fatigue, dry cough, upper airway congestion, sputum production, shortness of breath, myalgia/arthralgia. Some proportion of COVID-19 patients develop ARDS, which leads to pulmonary edema and lung failure, and have liver, heart, and renal failure [44]. These symptoms might be differently registered in PwMS or the older 'S-type' which is less infectious, than the 'L-type' of COVID-19, which emerged later, spreads quickly, and is currently more aggressive than the S-type. The PwMS should be screened in available CSF to learn of those cytokine and chemokine, which we reviewed here as cytokine storming. There might be some indication we should advise IvIg for MS when the COVID-19 is nearly proceeding toward ARDS. An IvIg additional studies are needed to establish the role of IvIg in the management of MS with COVID-19.

The therapies mentioned in this review can help us to differentiate the trained contra untrained immune system in MS, and then learn about the cytological, cytokines, and chemokines in the pro-inflammatory process in association with CNS.

Those many publications which were reviewed for the current MS-related review at the time of editing the draft were the citable or approved information.

Future possibilities, an increasing number of potential therapies are currently undergoing clinical evaluation during the COVID-19 outbreak. These include MABs, T-cell vaccination, IvIg, vitamin D, and some other drugs, which can be of interest for MS. We need to collect information about neurological manifestations of COVID-19 disease and compare it with MS symptoms.

The impact of the coronavirus outbreak on regulatory activities and MS expert centers create a new task and they should with solid pathophysiological evidence take a promising decision in the current and coming alteration of MS immune system caused by COVID-19. COVID-19 can give us the chance to revise the RNA strains of coronaviruses, which we have missed in association with MS and need to go in previous autopsies and biopsies to find the missing puzzle.

## Limitations

There is a risk of confounding factors especially in those cases which the drugs only used a few times and without controls. This would result in selection bias since a protective effect of the aimed treatment against developing progressive pneumonia might exist. In addition, the mentioned study (with only 5 months duration and few cases) lacks statistical power to ascertain any statistically significant association. While the results from this study are encouraging, the current study was influenced by non-randomized, open-label, and on a small number of patients, all from the same short period.

## Conclusion

Therapies used during COVID-19 virus infection has caused growing concern in the neurology community. The airborne mechanism of the virus spreading to the upper respiratory tract makes a unique task that trigeminal nerve gets direct attachment with the coronavirus and engage the CNSs immunity against this virus. Therefore, the immunological reaction should be evaluated early in association with MS investigation. The wide spectrum of registered trials to test the safety and efficacy against COVID-19 should bring a chance to learn more about MS therapies, which are recommended against COVID-19.

## Competing Interest

The authors have declared no competing interest.

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## Author Declarations

All relevant ethical guidelines have been followed.

## Authors Contribution

The author contributes equally to this work.

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