REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 357–368
DOI: 10.5603/PJNNS.a2021.0051

ISSN: 0028-3843, e-ISSN: 1897-4260

# Multiple sclerosis immunomodulatory therapies tested for effectiveness in COVID-19

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## ABSTRACT

**Introduction.** The global pandemic of COVID-19 began in Wuhan, China in December 2019. Research into effective therapies has been conducted worldwide. Currently, there is no antiviral treatment and many patients develop a severe course of the disease, including severe respiratory failure. Due to similar pathomechanisms of inflammation in multiple sclerosis (MS) and COVID-19, immunomodulatory drugs that are registered for the treatment of MS are under study in the SARS-CoV-2 infection in clinical trials.

**Materials and methods.** Using clinicaltrials.gov, we found information related to ongoing clinical studies on potential drugs for COVID-19 which are also used in MS therapy. The outcomes of several trials were published on pubmed.ncbi.nlm.nih.gov.

**Results.** There were 18 clinical trials evaluating the effectiveness and safety of interferon-β, fingolimod, or leflunomide in COVID-19. Some trial outcomes available at pubmed.ncbi.nlm.nih.gov suggested an association of these drug treatments with improvements in signs and symptoms, and the disease course.

**Conclusion.** The administration of immunomodulatory drugs in COVID-19 may result in potential beneficial effects probably associated with their anti-inflammatory and antiviral properties. Further research is warranted to confirm the long-term effects of immunomodulatory therapies in patients with COVID-19.

**Key words:** multiple sclerosis, COVID-19, SARS-CoV-2, immunomodulatory therapies

(*Neurol Neurochir Pol 2021; 55 (4): 357–368*)

## Introduction

Previously, two epidemics were caused by coronaviruses: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [1]. Coronaviruses (CoVs) are responsible for many diseases in humans and animals. The resulting infections may affect respiratory, enteric, hepatic, and neurological systems with varying severity [2]. The current COVID-19 is caused by an RNA virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The outbreak of COVID-19 was first reported in Wuhan, China in December 2019. The global pandemic was declared in March, 2020 [3]. According to data from the World Health Organisation, 66,243,918 laboratory-confirmed cases, including 1,528,984 deaths, had been reported by 7 December, 2020 [4]. Respiratory droplets and contact transmission are the major routes of SARS-CoV-2 infection [5]. There are different courses of the disease, i.e. asymptomatic infections or mild cases (80–90%), severe cases with dyspnoea and hypoxemia (10%), critical cases with respiratory failure, shock and multiorgan failure (5%), and, in the most serious cases, death associated with progression to acute respiratory distress syndrome (ARDS) and multiorgan failure [6]. The most common symptoms of infection include fever (98%), cough (76%), myalgia or fatigue (44%) [1]. Of note, the severity, course, and rapid progression to ARDS are related to comorbidities and older age of patients. In-hospital mortality is approximately

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Received: 20.01.2021 Accepted: 30.03.2021 Early publication date: 3.08.2021

60% for patients aged > 80 years and about 5% in patients under the age of 40 [7].

Many clinical studies on COVID-19 are underway worldwide. However, currently there has been no effective therapy available. Trials of experimental agents for treatment and chemoprophylaxis are under way. Most patients are monitored and given symptomatic supportive treatment such as oxygen and antipyretics. Umbilical cord blood and convalescent plasma are also used. Research studies have tested antiviral drugs and other molecules [8–10].

Multiple sclerosis (MS) is a chronic immune-mediated central nervous system (CNS) disorder. Immune response plays a key role in the pathogenesis, course, and progression of the disease. Immunomodulatory drugs used in the treatment of MS target the peripheral immune system. These treatments have side effects, but are also specific and selective for molecules of the immune system [11]. Some of these medications are currently under study for their efficacy in COVID-19.

Disorders in the cytokine system have been reported in the course of MS and immunomodulatory therapy is believed to silence the immune system and halt disease progression. Interestingly, the significant role of cytokine dysregulation and immune response in the pathogenesis of COVID-19 has led to a hypothesis about the potential effectiveness of immunomodulatory drugs in the treatment of the disease. This is important in patients with MS infected with SARS-CoV-2. In the future, appropriate modification of the immunomodulatory treatment during infection may result in a milder course of both diseases and a shorter hospital stay. These drugs can be effective in both diseases by regulating the immune response, reducing the activity of cytokines and proinflammatory factors.

The present paper reviews immunomodulatory drugs used in the treatment of MS which are currently under study for COVID-19.

## Materials and methods

We searched clinicaltrials.gov and found 18 ongoing clinical studies on potential drugs for COVID-19 which are currently used in MS therapy (Tab. 1). Through the pubmed.ncbi.nlm.nih.gov database, we found several trial outcomes. Three immunomodulatory drugs registered for MS treatment are under study in COVID-19. These are interferon (IFN)-β, fingolimod, and leflunomide (with teriflunomide as its active metabolite). Vidofludimus calcium (IMU-838), an inhibitor of dihydroorotate dehydrogenase, is in Phase II clinical trials for effectiveness in relapsing-remitting MS [12]. This drug is also under study for the treatment of COVID-19. There are four ongoing trials investigating IMU-838 in the SARS-CoV-2 infection but, currently, it is not officially registered as a treatment for MS. Therefore, we did not include it in our research.

## Results and discussion

### Pathophysiology of multiple sclerosis *vs.* pathophysiology of COVID-19

The precise aetiology of MS is still unclear. Many factors have an impact on the development of MS, including environmental and genetic factors such as vitamin D deficiency, Epstein–Barr Virus (EBV) and smoking. All of these agents initiate immune-mediated mechanisms that contribute to demyelination and neurodegeneration [13]. The disease process starts when autoreactive T-lymphocytes with a pro-inflammatory activity cross the blood-brain barrier.

In turn, the immune response to the SARS-CoV-2 infection consists of two phases, i.e. the immune phase and tissue damage [14]. The virus has an affinity for angiotensin-converting enzyme 2 (ACE2) receptors, which are located on epithelial cells in the apical parts of the lungs. Other organs expressing ACE2 include the oral and nasal mucosa, nasopharynx, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney and brain, which may also be affected by SARS-CoV-2 [15].

The virus consists of four proteins which are important in the immune response. The spike protein (S) binds to ACE2 receptors. Neutralising antibodies and T-cell receptors recognise it during the immune response. Nucleocapsid proteins (N) in complex with viral RNA are the target for antibodies. The matrix protein (M) forms epitopes of T-cell receptors and interacts with the envelope protein (E). The S protein may as well bind to CD26 or CD147 and may enable SARS-CoV-2 to enter cells which do not express ACE2 [16]. The antiviral response is mainly mediated by CD4+ and CD8+.

During the development of MS, primary activation of T-cells occurs in the blood. There are different hypotheses related to this phenomenon. It may occur as a result of infection with EBV [17] or contact with myelin antigens in the lymph nodes [18]. Activated T-lymphocytes show increased adhesion molecule activity, facilitating their interaction with endothelial cells. It appears that the presentation of viral antigens may play a role in the development of MS and the excessive inflammatory response in COVID-19 (Fig. 2).

In MS, dendritic cells, microglia, and B-lymphocytes are the main antigen-presenting cells (APCs). Adhesive molecules, matrix metalloproteinases and chemokines play an important role in cell migration to the CNS [19]. In the CNS, another activation of CD4+ lymphocytes occurs.

In COVID-19, pattern recognition receptors (PRRs), such as toll-like receptors (TLR-7, TLR-8), NOD-like receptors (NRL) and RIG-I-like receptors (RLR), recognise viral antigens, which results in production of IFN I, III and several chemokines by infected cells [20]. Dendritic cells and macrophages are APCs. The virus binds to dendritic cells via the specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) and DC-SIGN-related protein. DC-SIGN is highly expressed

**Table 1.** Ongoing trials on potential COVID-19 therapies used in MS treatment based on clinicaltrials.gov and studies with published outcomes according to pubmed.ncbi.nlm.nih.gov/

| Drug | Mechanism of action | Ongoing trial | Phase of study | Details of study | Area and country |
|---|---|---|---|---|---|
| Interferons | — antiviral properties<br>— increase in expression of anti-inflammatory agents<br>— reduction in expression of pro-inflammatory cytokines | Efficacy and safety evaluation of therapeutic regimen of lopinavir/ritonavir and interferon-β-1b (IFNβ-1b) in patients with COVID-19 | Phase II-III | N: 70<br>Age: 18+<br>Gender: both<br>Date of registration: April 2020<br>Estimated study completion date: no information | Sari, Iran |
| | | Effect of interferon-β 1 (zifron) on clinical improvement and prognosis of COVID-19 | Phase II | N: 60<br>Age: no age limit<br>Gender: both<br>Date of registration: May 2020<br>Estimated study completion date: no information | Tabriz, Iran |
| | | Clinical study for treatment with interferon-β-1a (IFNβ-1a) of COVID-19 patients: randomised, controlled, open label | Phase II | N: 126<br>Age: 18+<br>Gender: both<br>Date of registration: June 2020<br>Estimated study completion date: April, 2021 | Milan, Italy |
| | | Comparative study of effects of tocilizumab, interferon-gamma and vitamin C on recovery of critically ill COVID-19 patients and cytokine storm | Phase II | N: 60<br>Age: 18–65<br>Gender: both<br>Date of registration: July 2020<br>Estimated study completion date: no information | Tabriz, Iran |
| | | Evaluation of effect of raltegravir and raltegravir/interferon-β combination on COVID-19 patients | Phase III | N: 60<br>Age: 18+<br>Gender: both<br>Date of registration: June 2020<br>Estimated study completion date: no information | Jahrom, Iran |
| | | Using interferon to treat COVID-19 | Phase II/III | N: 76<br>Age: 18+<br>Gender: both<br>Date of registration: June 2020<br>Estimated study completion date: no information | Mashhad, Iran |
| | | Effect of interferon on treatment of COVID-19 patients | Phase III | N: 60<br>Age: 18–70<br>Gender: both<br>Date of registration: May 2020<br>Estimated study completion date: no information | Qom, Iran |
| | | Efficacy evaluation of inhalation therapy (nasal spray) of interferon-β-1a in hospitalised COVID-19 patients | Phase III | N: 50<br>Age: 20–65<br>Gender: both<br>Date of registration: May 2020<br>Estimated study completion date: no information | Tehran, Iran |
| | | Evaluation of interferon treatment in high-risk COVID-19 patients | Phase III | N: 60<br>Age: 18–70<br>Gender: both<br>Date of registration: May 2020<br>Estimated study completion date: no information | Qom, Iran |

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**Table 1 cont.** Ongoing trials on potential COVID-19 therapies used in MS treatment based on clinicaltrials.gov and studies with published outcomes according to pubmed.ncbi.nlm.nih.gov/

| Drug | Mechanism of action | Ongoing trial | Phase of study | Details of study | Area and country |
|---|---|---|---|---|---|
| Interferons | | Heberon Alfa R in COVID-19 | Phase IV | N: no information<br>Age: no age limit<br>Gender: both<br>Date of registration: May 2020<br>Estimated study completion date: no information | Havana, Cuba |
| | | Phase II, randomised, controlled, open-label study to evaluate efficacy and safety of pegylated-IFN alpha-2b in treatment of adult patients diagnosed with SARS-CoV-2 (COVID-19) | Phase II | N: 40<br>Age: 18–85<br>Gender: both<br>Date of registration: June 2020<br>Estimated study completion date: no information | Gujarat, India |
| | | Determination and comparison of effect of two antiviral drugs (interferon-β-1a and interferon alpha-2A) on prognosis of patients with COVID-19 | Phase II/III | N: 76<br>Age: 18+<br>Gender: both<br>Date of registration: June 2020<br>Estimated study completion date: no information | Mashhad, Iran |
| | | Interferon-β-1b in COVID-19 | Phase II/III | N: 70<br>Age: 18+<br>Gender: both<br>Date of registration: April 2020<br>Estimated study completion date: no information | Sari, Iran |
| | | Investigating efficacy and safety of interferon-β-1a nasal spray in controlling symptoms of patients with COVID-19 | Phase III | N: 100<br>Age: 18+<br>Gender: both<br>Date of registration: May 2020<br>Estimated study completion date: no information | Tehran, Iran |
| | | Safety and efficacy of inhaled nebulised interferon-β-1a (SNG001) for treatment of SARS-CoV-2 infection: randomised, double-blind, placebo-controlled, phase II trial (Monk et al., 2020)double-blind, placebo-controlled, phase 2 pilot trial at nine UK sites. Adults aged 18 years or older and admitted to hospital with COVID-19 symptoms, with a positive RT-PCR or point-of-care test, or both, were randomly assigned (1:1) | Phase II Published outcomes | N: 100<br>Age: 18+<br>Gender: both<br>Date of registration: May 2020<br>Estimated study completion date: May, 2021 | United Kingdom |
| | | Evaluating efficacy and safety of interferon β-1b (IFN β-1b) in treatment of COVID-19 (Rahmani et al., 2020) | Phase II/III Published outcomes | N: 33<br>Age: 18–75<br>Gender: both<br>Date of registration: March 2020<br>Estimated study completion date: no information | Tehran, Iran |
| | | Evaluating therapeutic and adverse effects of interferon-β-1a subcutaneous administration in patients with novel Coronavirus (COVID-19) (Dastan et al., 2020) | Phase III Published outcomes | N: 20<br>Age: 18+<br>Gender: both<br>Date of registration: March 2020<br>Estimated study completion date: no information | Tehran, Iran |

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**Table 1 cont.** Ongoing trials on potential COVID-19 therapies used in MS treatment based on clinicaltrials.gov and studies with published outcomes according to pubmed.ncbi.nlm.nih.gov/

| Drug | Mechanism of action | Ongoing trial | Phase of study | Details of study | Area and country |
|---|---|---|---|---|---|
| | | Repurposed Antiviral Drugs for COVID-19 - Interim WHO Solidarity Trial Results (Pan et al., 2021)hydroxychloroquine, lopinavir, and interferon beta-1a - in patients hospitalized with coronavirus disease 2019 (COVID-19) | Phase III Published outcomes | N: 11,330<br>Age: 18+<br>Gender: both<br>Date of registration: March 2020<br>Estimated study completion date: March 2023 | Multi-country study (30 countries) |
| Fingolimod | — angiogenic factor<br>— preventing lymphocyte T and B egress from lymphoid tissues<br>— reduction in IL-17, IL-10, IL-12 levels<br>-reduction in levels of CD4+ and CD8+ | Effect of fingolimod for treatment of COVID-19-induced cytokine storm | Phase III | N: 40<br>Age: 18–80<br>Gender: both<br>Date of registration: April 2020<br>Estimated study completion date: no information | Tabriz, Iran |
| Leflunomide | — antiviral properties<br>— reduction in expression of pro-inflammatory cytokines<br>— killing activated T- and B-lymphocytes | Multicentre, randomised, double-blind, controlled clinical trial for leflunomide in treatment of novel coronavirus pneumonia (COVID-19) | Phase III | N: 100<br>Age: 18–70<br>Gender: both<br>Date of registration: February 2020<br>Estimated study completion date: no information | Wuhan, China |
| | | Efficacy and safety of leflunomide for refractory novel coronavirus pneumonia (COVID-19): non-randomised controlled study | Phase 0 | N: 30<br>Age: 43–70<br>Gender: both<br>Date of registration: May 2020<br>Estimated study completion date: no information | Shandong, China |
| | | DEFEAT-COVID Study | Phase III | N: 178<br>Age: 18+<br>Gender: both<br>Date of registration: July 2020<br>Estimated study completion date: no information | Chertsey, Surrey, United Kingdom |
| | | Treatment of Coronavirus Disease 2019 Patients With Prolonged Postsymptomatic Viral Shedding With Leflunomide: A Single-Centre Randomised Controlled Clinical Trial (Wang et al., 2020) | Published outcomes | N: 50<br>Age: 18–70<br>Gender: both<br>Date of registration: May 2020<br>Published: September, 2020 | Wuhan, China |
| | | A Small-Scale Medication of Leflunomide as a Treatment of COVID-19 in an Open--Label Blank-Controlled Clinical Trial (Hu et al., 2020) | Published outcomes | N: 10<br>Age: 18–70<br>Gender: both<br>Date of registration: February 2020<br>Published: July, 2020 | Wuhan, China |

on dendritic cells and macrophages. Then APCs phagocytose cells infected with the virus migrate to the lymph nodes to present the antigen to T-lymphocytes [21]. In the development of COVID-19 and MS, the presentation of antigen in lymph nodes by dendritic cells may play a significant role (Fig. 2).

In MS, CD4+ lymphocytes have the ability to differentiate into Th1, Th2 and Th17 cells [22]. Th1 lymphocytes are involved in inflammatory processes related to the activity of macrophages and the production of pro-inflammatory cytokines such as IFN-γ, tumour necrosis factor-α (TNF-α), interleukin (IL)-2, IL-12, and IL-15. Th2 lymphocytes have an anti-inflammatory activity and produce anti-inflammatory cytokines such as IL-4, IL-5 and IL-13 [23, 24]. They can also stimulate an autoreactive B-cell response. Th17 lymphocytes secrete IL-17 and other pro-inflammatory cytokines (IL-21, IL--22) [24]. An increase in IL-17 expression in the cerebrospinal

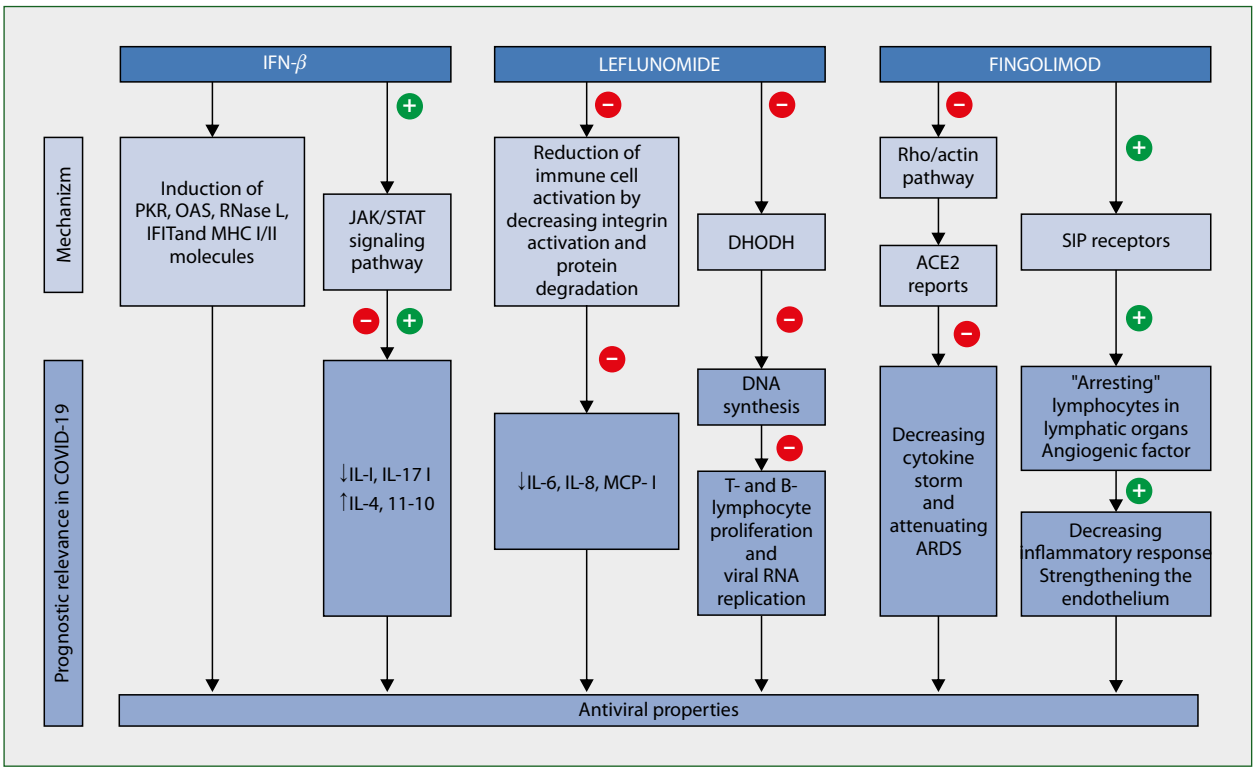


**Figure 1.** Prognostic relevance of IFN-β, leflunomide and fingolimod in COVID-19 according to their mechanisms. IFN-β induces proteins important in antiviral action (PKR, OAS, RNase, IFIT, MHC I/II molecules). This results in inhibition of viral entry, transcription, replication, translation, assembly, or egress. IFN-β increases expression of anti-inflammatory factors (IL-10, IL-4), whereas it reduces expression of pro-inflammatory cytokines (IL-1, IL-17 and osteopontin) via JAK/STAT pathway. Leflunomide suppresses DHODH, which results in inhibition of *de novo* pyrimidine synthesis and reduction in lymphocyte proliferation (diminishing release of proinflammatory cytokines IL-6, IL-8 and MCP-1). Leflunomide impairs viral RNA replication. Fingolimod decreases inflammation by binding to S1P receptors (S1P1, S1P3, S1P4 and S1P5), arresting lymphocytes in lymphoid organs and reducing macrophage movement via RhoA/actin pathway. Fingolimod acts as angiogenic factor; it enhances lung endothelial cell integrity and possibly reduces cytokine storm and ARDS by inhibiting ACE2 receptor expression and recruiting macrophages to lungs.
ACE2 — angiotensin-converting enzyme 2; ARDS — acute respiratory distress syndrome; DHODH — dihydroorotate dehydrogenase; IFIT — IFN-induced protein with tetratricopeptide repeats; JAK/STAT — Janus kinase-signal transducer and activator of transcription; OAS — 2'-5'-oligoadenylate synthetase; PKR — protein kinase R; S1P — sphingosine-1-phosphate

fluid (CSF) and blood is characteristic of patients with MS, especially during a relapse [25].

In COVID-19, CD8+ lymphocytes kill infected cells [21]. Immune dysregulation leads to cytokine storm and tissue damage. The concentration of pro-inflammatory cytokines correlates with the severity of the disease. In COVID-19 patients, higher levels of the following have been found: IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-17, macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-induced protein-10 (IP-10), monocyte chemotactic protein-1 (MCP-1), TNF-α, IFN-γ and vascular endothelial growth factor (VEGF) [26]. IL-6 level is particularly related to the severity of the disease [27, 28].

In the development of MS, T-regulatory (Treg) lymphocytes have a weakened ability to control immune reactions, which also leads to demyelination and neurodegeneration [29]. CD8+ cells are the main components of demyelinating plaques. They can recognise brain antigens and destroy oligodendrocytes and neurons [30]. B-lymphocytes are responsible for the humoral response. They produce antibodies, specifically recognise the antigen, present the antigen, produce cytokines, and regulate the differentiation and function of dendritic cells and T-lymphocytes.

During COVID-19, many patients develop lymphopenia. A decrease in the levels of CD4+, CD8+, B-lymphocytes and natural killer (NK) cells is also reported [31]. T-cell levels correlate negatively with IL-6, IL-10 and TNF-α concentrations [32]. There is also an increase in the release of IFNs, mainly IFN I and III. Their function is to limit the spread of the virus. However, SARS-CoV-2 inhibits IFN release [42]. In terms of the humoral response, CD4+ cells activate B-lymphocytes to generate natural IgM and IgG antibodies against the virus.

According to the described data, overexpression of both interleukins and chemokines may be characteristic of MS and

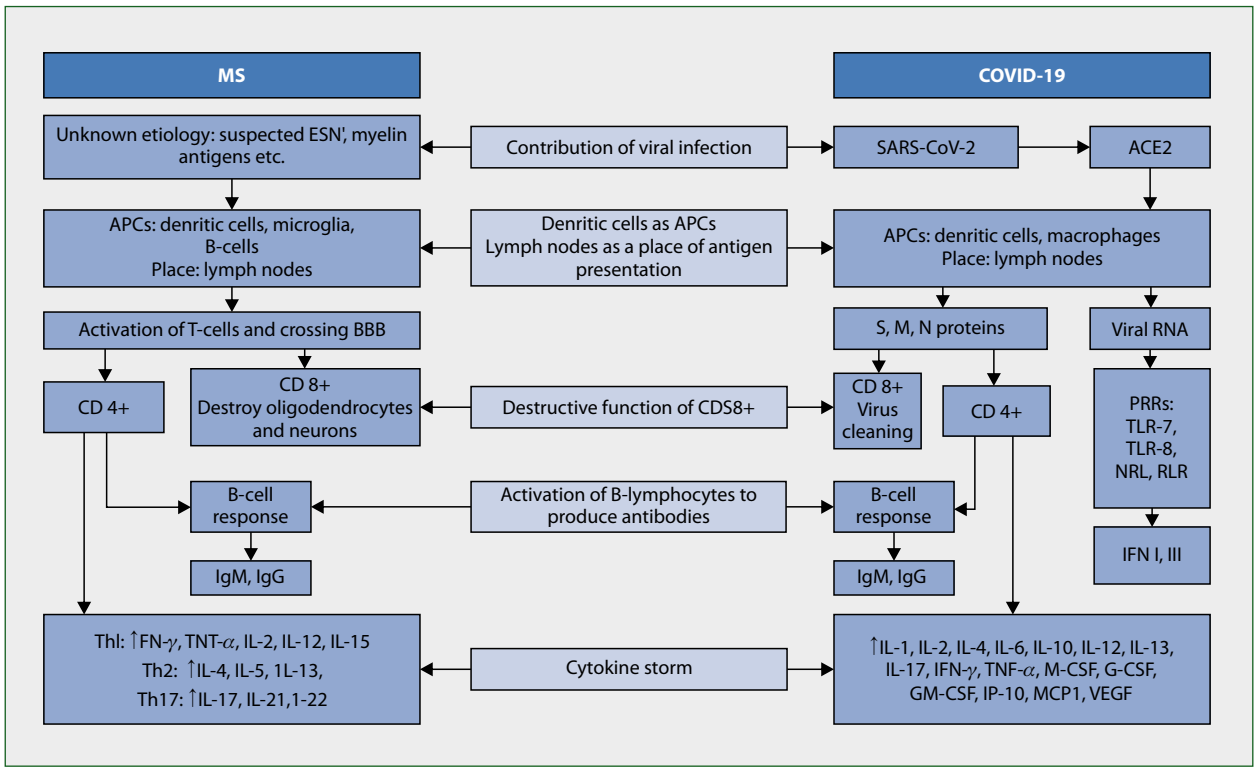


**Figure 2.** Comparison of pathophysiology of MS and COVID-19 and their common mechanisms. Aetiology of MS is unknown. However, important role of EBV, myelin antigens and other factors is suspected. In COVID-19, SARS-CoV-2 is causative pathogen. In both cases, viral infection may contribute to disease development. In MS and COVID-19, dendritic cells are main APCs, whereas antigen presentation occurs in lymph nodes. CD4+ and CD8+ play an important role in immune response in both diseases. CD 4+ activation leads to B-cell response and cytokine overproduction. Cytokine storm is present in MS or COVID-19. Probable common elements of pathomechanisms shown in bold. APCs — Antigen-Presenting Cells; BBB — Blood-Brain Barrier; EBV — Epstein-Barr Virus; G-CSF — Granulocyte Colony-Stimulating Factor; GM-CSF — Granulocyte-Macrophage Colony-Stimulating Factor; IFN-γ — Interferon Gamma; IgG — immunoglobulin G; IgM — immunoglobulin M; IL — interleukin; IP10 — Interferon-induced protein-10; MCP-1 — Monocyte Chemotactic Protein-1; M-CSF — Macrophage Colony-Stimulating Factor; NRL — NOD-like receptors; PRRs — Pattern Recognition Receptors; RLR — RIG-I-like receptors; IFN I, III — Interferon I, III; TLR — Tolllike receptors; TNF-α — Tumour Necrosis Factor Alpha; VEGF — Vascular Endothelial Growth Factor

COVID-19. In MS, the loss of immune system control due to the impaired function of regulatory T-lymphocytes has been reported (Fig. 2). SARS-CoV-2 may also cause impairment of the immune system. The development of both diseases is closely related to the dysfunction of CD4+ and CD8+ lymphocytes, as well as B-lymphocytes (Fig. 2). As discussed above, certain elements of the pathomechanisms are common to COVID-19 and MS. Therefore, immunomodulatory drugs may be highly effective in disease-modifying treatment.

## MS immunomodulatory drugs tested for COVID-19

### Interferon-β

#### *Mechanism of action*

IFN-β is an immunomodulatory agent. It increases the expression and concentration of some anti-inflammatory factors such as IL-10, II-4, whereas it reduces the expression of pro-inflammatory cytokines such as IL-1, IL-17 and osteopontin. Pro-inflammatory cytokines induce the activation and proliferation of additional T-cells, B-cells and macrophages, stimulate major histocompatibility complex (MHC) class II expression on APCs, decrease the level of anti-inflammatory cytokines, and intensify the cytolytic activity of CD8+ cells, macrophages and certain NK cells [33]. IFN-β leads to a reduction in the number of inflammatory cells which cross the blood-brain barrier, and increased production of nerve growth factor. These cells are important in the production of anti-inflammatory mediators, and have the potential to reduce neuronal inflammation [33, 34].

#### *Prognostic relevance in COVID-19*

The IFN response is the first line of defence against viruses. Diagnosis of viral infections is possible due to innate immune vigilance activating, in particular, IFN I and III responses. Type I IFN (IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω) binds to the common type I IFN receptor (IFNAR) on the cell surface. IFN induced by virus-infected cells acts in autocrine and paracrine

ways, binding to cell surface receptors, and leads to the expression of antiviral IFN-stimulated genes (ISGs), 2'-5'-oligoadenylate synthetase (OAS), RNase L, dsRNA-dependent protein kinase R (PKR) and IFN-induced protein with tetratricopeptide repeats (IFIT) to perpetuate antiviral signalling [35]. This activates the antiviral defence mechanism made up of hundreds of ISGs, thereby interfering with every step of the virus replication (Fig. 1) [36, 34]. IFN-mediated signalling and transcriptional activation of cellular gene expression are best understood in the context of the JAK-STAT pathway protein. The signal transducer and activator of transcription (STAT) family of proteins are latent cytoplasmic transcription factors that become tyrosine phosphorylated by the Janus family of tyrosine kinase (JAK) enzymes in response to cytokine stimulation. Different members of the JAK and STAT families have distinct functions in cytokine signalling. Receptor-associated JAKs are activated following the binding of IFNs to their cognate multi-subunit transmembrane receptor. This plays central roles in mediating IFN-dependent biological responses and could shift the pathogenic Th1/Th17 responses to Th2/Treg responses, which results in increased production of anti-inflammatory cytokines such as IL-2, IL-4, IL-5 and IL-10 (Fig. 1) [37, 38]. An insufficient IFN response promotes uncontrolled viral replication, increases viral load, and leads to poor outcomes in SARS-CoV infection. A strong IFN response has been observed following SARS-CoV-2 infection. ISG expression was significantly increased in COVID-19 patients [39]. Blanco-Melo et al. showed a similar relationship after analysis of serum from COVID-19 patients [40]. Pro-inflammatory cytokines and chemokines were significantly elevated with no detectable levels of IFN I and III. Moreover, IFN-β may show beneficial antiviral activity against SARS-CoV-2 in combination with conventional antiviral drugs as shown in a recent open-label Phase II clinical trial. This study showed that the triple action of injectable IFN (IFN-β 1b), an oral protease inhibitor (lopinavir-ritonavir) and an oral nucleoside analogue (ribavirin) administered for seven days from the day of symptom onset completely inhibited the excretion of SARS-CoV-2, not only in nasopharyngeal swabs, but in all clinical specimens compared to lopinavir and ritonavir alone. Additionally, the duration of a positive RT-PCR reaction and the duration of viremia were shorter. It was associated with clinical improvement and shortening of hospital stay [41]. Initiating IFN-β treatment in patients with newly diagnosed MS appears safe. The action of IFN-β rarely lowers lymphocyte levels. The associated lymphopenia is mild. Therefore, it is unlikely that it will affect the early or delayed immune response to SARS-CoV-2 or will significantly increase the susceptibility to infections. Despite the optimal safety of IFN-β compared to other drugs, and the fact that it is an appropriate treatment option for patients with mild MS, its potency is low and it may not be suitable for patients with highly active MS during the pandemic [42].

On clinicaltrials.gov, we found 16 ongoing trials on IFNs for COVID-19, 11 of which are focused on IFN-β. Most of them are in Phases II or III (Tab. 1). We found some outcomes evaluating the effectiveness of IFN-β among patients with COVID-19. The efficacy and safety of inhaled nebulised IFN-β-1a were assessed among hospitalised patients with COVID-19 in the UK. This was a randomised, double-blind, placebo-controlled, Phase II pilot trial including 101 patients. The symptoms of infection improved more rapidly in patients who received IFN-β compared to those who received a placebo. Moreover, there were three deaths in the placebo group and none in the active treatment group [43]. Another clinical trial was conducted in Imam Khomeini Hospital Centre in Iran from 20 April to 20 May, 2020 and included 66 patients. IFN-β was administered subcutaneously every other day for two weeks. The control group received lopinavir/ritonavir or atazanavir/ritonavir plus hydroxychloroquine. Rahmani et al. showed a shorter time to clinical improvement and discharge and lower mortality in patients with IFN therapy compared to the control group [39]. IFN-β is often combined with other drugs. Hong et al. described five severe COVID-19 pneumonia patients who recovered 7–15 days after treatment with lopinavir/ritonavir, hydroxychloroquine and IFN-β-1b [44]. On 2 December, 2020, the New England Journal of Medicine published interim WHO SOLIDARITY trial results of four antiviral drugs, i.e. remdesivir, hydroxychloroquine, lopinavir, and IFN-β-1a in patients hospitalised with COVID-19. None of the above drugs had a significant effect on the disease course as indicated by overall mortality, initiation of ventilation, or duration of hospital stay. Only remdesivir slightly reduced time to recovery. Given the size of the trial, these findings seem reliable [45]. Dastan et al. conducted a prospective non-controlled trial [46]. They also used IFN-β-1a in combination with hydroxychloroquine and lopinavir/ritonavir. Their study revealed a reduction of disease symptoms, which were supported by lung CT and chest X-ray images. Davoudi-Monfared et al. carried out a very similar study with IFN-β-1a added to hydroxychloroquine plus lopinavir-ritonavir or atazanavir-ritonavir [47]. They showed that only early IFN-β-1a administration was related to a significant reduction in mortality. Their study did not reveal an influence of IFN on shortening hospital stay or the duration of mechanical ventilation. Many randomised clinical trials aimed at evaluating the efficacy and safety of IFN-β in COVID-19 treatment have shown that treatment with IFN-β could lead to faster recovery from infection. The trials are still underway and their aim is to confirm the benefits of this form of therapy.

## Fingolimod

### *Mechanism of action*

Fingolimod, sphingosine-1-phosphate (S1P) analogue, is the first oral disease-modifying drug for relapsing-remitting MS. Fingolimod binds to four of the five known S1P receptors

(S1P1, S1P3, S1P4 and S1P5) on lymphocytes, leading to receptor internalisation and lymphocyte 'arrest' in lymphatic organs (Fig. 1). As a result, the damaging infiltration into the CNS is reduced [48, 49]. It also inhibits the expression of RhoA and RhoA/actin-dependent macrophage receptors (Fig. 1) [50].

### *Prognostic relevance of fingolimod in COVID-19*

The action of fingolimod in COVID-19 is complex. Acting as an immunomodulatory drug, it inhibits naive T-cells and memory T-cells in the lymph nodes, thus preventing autoimmune reactions. However, memory effector T-cells, which are less affected by fingolimod treatment, are of crucial importance in defending against infectious disease antigens [51]. The pathological process of infection in COVID-19 includes pulmonary oedema and diffuse alveolar injury with cellular fibromyxoid exudates [52]. Fingolimod is a potent angiogenic factor and its action enhances the integrity of lung endothelial cells. S1P enhances vascular permeability and alveolar hemorrhage in preclinical animal models of acute lung injury. Moreover, in the case of a cytokine storm, immunomodulation may be beneficial in reducing mortality [53]. Fingolimod inhibits macrophage movement and expression of macrophage receptors via the RhoA/actin pathway. It may also inhibit the expression of ACE2 receptors and macrophage recruitment to the lung tissue, which is the main cause of ARDS (Fig. 1) [50].

We found one ongoing trial on fingolimod in COVID-19, which was conducted at the Tabriz University of Medical Sciences in Iran (Phase III study involving 40 patients) (Tab. 1). Unfortunately, no outcomes of COVID-19 treatment with fingolimod have been published yet. Therefore, further research is warranted.

## Leflunomide

### *Mechanism of action*

Leflunomide acts by suppressing dihydroorotate dehydrogenase (DHODH), which results in the inhibition of *de novo* pyrimidine synthesis and reduction in B- and T-lymphocyte proliferation. The effect of leflunomide is related to a decrease in the release of pro-inflammatory cytokines such as IL-6, IL-8 and MCP-1 (Fig. 1) [54, 55]. The inflammatory imbalance seems to be crucial in the onset and propagation of MS [56]. Leflunomide has already been clinically used in autoimmune diseases to inhibit pathogenic cytokines and chemokines [57]. Teriflunomide is the main active metabolite of leflunomide. The effectiveness of therapy with leflunomide is possible, but this drug has not been registered for the treatment of MS yet, as opposed to teriflunomide, which is a licenced drug in MS. However, its efficacy in COVID-19 has not been confirmed [58].

### *Prognostic relevance in COVID-19*

Leflunomide reduces the level of immune activation without cell apoptosis. It kills only rapidly proliferating lymphocytes. On the other hand, it can use the salvage pathway to proliferate and self-renew [59]. Thus, an adequate defence against the virus may be provided, while decreasing host immune response [54]. That mechanism could prevent the cytokine storm that occurs in severe acute infections, including influenza and COVID-19 [57].

Three clinical trials are currently underway to investigate the efficacy of leflunomide in COVID-19 (Tab. 1). We also found two completed randomised controlled clinical trials. The former was performed by scientists from RenMin Hospital of Wuhan University, China. This trial assessed the effects of treatment with leflunomide and IFN-α-2a compared to IFN-α-2a alone. The study group consisted of 50 patients. No differences were found in duration of hospital stay or viral shedding. Two patients in the leflunomide group were unable to complete therapy due to adverse effects [60]. The latter study was performed on a small group of 10 patients. This small-scale investigation is a part of the Open-Label Blank-Controlled Clinical Trial which is currently in Phase III as reported by clinicaltrials.gov. The study revealed a decrease in C-reactive protein levels in the leflunomide treatment group. In this group, a shorter duration of viral shedding was also found. The chest CT imaging from one representative patient showed much smaller areas of ground-glass opacity and obvious absorption of lesions in the bilateral lung after seven days of treatment with leflunomide [61]. Despite the small size of the group, the outcomes from the above investigation may be crucial, although the findings require further analysis.

### *Drugs in NMOSD tested for COVID-19*

Neuromyelitis optica spectrum disorder (NMOSD) is another neurological disease with an important role in the inflammatory process. NMOSD is an autoimmune disorder characterised by inflammatory and demyelinating lesions in the optic nerve, spinal cord brainstem, and cerebrum, which can lead to a decrease or loss of vision and disability [62]. NMOSD is often misdiagnosed as MS. Therefore, it seems necessary to mention the drugs which are tested in COVID-19 and used in the treatment of neuromyelitis optica (NMO) and which are registered and used in clinical trials.

There are studies on the effectiveness of anti-IL-6 receptor monoclonal antibodies (sarilumab, tocilizumab, satralizumab), anti-IL-6 monoclonal antibody (siltuximab) and inhibition of the C5 protein of the complement system (eculizumab) [63,64,65].

Inhibition of IL-6 may attenuate the early immune response against the virus by T-cell suppression. It could also increase the risk of secondary bacterial infection in COVID-19 patients. On the other hand, inhibition of the IL-6 signalling pathway could result in a decrease in the cytokine storm [62]. Suppression of the inflammatory process would certainly be very beneficial for patients with severe COVID-19 pneumonia. There are also studies on a potential benefit of complement inhibition in the SARS-CoV-2 infection. A clinical trial of

eculizumab in COVID-19 patients is underway (clinicaltrials.gov, NCT04288713).

Currently, the guidelines by the National Institutes of Health (NIH) suggest against the routine use of anti-IL-6 receptor monoclonal antibodies (tocilizumab and sarilumab) or anti-IL-6 monoclonal antibody (siltuximab) for hospitalised patients with COVID-19 outside clinical trials [64].

## Conclusion

Many drugs are under study for their effectiveness in the treatment of COVID-19. According to most scientists, the pandemic will last for months or even years. Due to the presented pathophysiology of COVID-19 and the crucial role of the immune response, the above immunomodulatory drugs may be effective in some cases of the SARS--CoV-2 infection.

IFN-β largely counteracts the pathogenic processes by increasing the production of anti-inflammatory factors, while inhibiting the pro-inflammatory cytokines. It has been shown to have antiviral activity and inhibit the SARS-CoV-2 replication. Some of the cited clinical studies revealed that administration of IFN-β with other antiviral drugs resulted in a reduction of symptoms as evidenced by chest CT scans and X-rays. It may also contribute to a shorter time to clinical improvement.

Fingolimod acts as an angiogenic factor. It may inhibit ACE2 receptors. As an immunomodulatory drug, fingolimod inhibits lymphocytes in lymphatic nodes, thus reducing the inflammatory response. There are no published outcomes about its efficacy in COVID-19. However, some studies suggest that it may prevent the development of ARDS.

Leflunomide, an inhibitor of DHODH, leads to a reduced proliferation of both T- and B-lymphocytes. Moreover, it lowers pro-inflammatory cytokine levels, thus reducing inflammation. Studies show that it could contribute to a shorter duration of viral shedding and a reduction in disease symptoms.

The findings that we have presented suggest that immunomodulatory drugs may be effective in some cases of COVID-19. Due to the similar pathophysiology of COVID-19 and MS, IFN- β, leflunomide and fingolimod may be equally effective in both conditions due to their antiviral activity and the influence on the immune response.

Of note, many drugs used or tested in MS have also been included in COVID-19 clinical trials, which may suggest that these drugs have a common mechanism of action in both diseases. Currently, data on their potential effects is limited. Most studies have not been completed yet and there have been no published outcomes. Until solid outcomes from patient samples are published, drawing conclusions about drug effectiveness is impossible. The recommendations of professional organisations should be followed. However, they will change over time depending on the further development of the COVID-19 pandemic or viral mutations and changes. The long-term effects of MS immunomodulatory treatment in patients with COVID-19 should be monitored.

**Conflict of interest** *The authors declare no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.*

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