Multiple sclerosis and COVID-19

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This paper reviews currently available data on the novel coronavirus and clinical features of COVID-19, followed by a detailed section on possible modifications of immunomodulatory therapy in multiple sclerosis patients with COVID-19, based on what we know so far. There are discussed: (i) *The COVID-19 disease* (Epidemiological background SARS-CoV-1 coronavirus; Autoimmune response to COVID-19; Asymptomatic course; SARS-CoV-2 test; COVID-19 symptoms), (ii) *Treatment of COVID-19* (Experimental plasma treatment; Antiviral therapy; Antimalarial treatment scheme; Biological treatment; Corticosteroid treatment; Symptomatic treatment; Vaccine preparation) and (iii) *Multiple sclerosis and SARS-CoV-2 infection* (Epidemiological recommendation).

Key words: coronavirus, COVID-19, multiple sclerosis, immunomodulatory therapy

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INTRODUCTION

In December 2019, an infectious disease caused by the newly discovered form of coronavirus known as SARS-CoV-2 (originally referred to as 2019-nCoV) began to spread worldwide from the Chinese city of Wuhan. The World Health Organization (WHO) named the disease caused by the new virus in humans "COVID-19" (from the English "coronavirus disease").

COVID-19 gradually spread to all inhabited continents around the beginning of 2020 and on 11 March 2020, the WHO confirmed this as a global pandemic. The disease has so far appeared in 188 countries around the world, including Europe. According to the WHO, 3,175,207 cases were confirmed as of 1 May 2020 worldwide, including 224,172 deaths[1].

In the following chapters, we describe the etiology and symptoms of the disease and analyze in more detail the therapeutic approaches in patients with multiple sclerosis during the COVID-19 pandemic.

THE COVID-19 DISEASE

COVID-19 is a disease caused by an RNA virus. The disease is highly contagious; according to the WHO, its infectivity index (R0) ranges between 1.4–2.5 (this value is similar to SARS, another disease caused by a similar form of coronavirus) and, based on available information, human-to-human transmission routes include respiratory droplets produced by sneezing, coughing, close body contact, and contact transfer through various types of surfaces. Based on currently available data, the WHO believes that the incubation period is between 1–14 days[1], typically 3–10 days.

Etiological agent: SARS-CoV-1 coronavirus

The newly discovered SARS-CoV-1 virus is a form of the RNA coronavirus that is able to penetrate the human body. An article with the complete RNA sequence of the novel coronavirus was published in the journal Nature on 3 February 2020 (ref.[2]). Sequence analysis showed that it belongs to the same species as SARS-CoV coronavirus, i.e. the virus causing SARS disease[3]. The novel virus differs from SARS-CoV in a sequence of certain viral proteins which suppress antiviral immunity and activate inflammasomes[4]. The novel coronavirus is 96% identical to the sample collected by scientists from bats in southwest China[5]. According to Sherren et al.[6] SARS-CoV-2 is 80% identical to human coronavirus (similar to CoV SAR). The structural proteins are encoded by four genes. According to the phylogenetic tree, SARS-CoV-2 is closest to the group of SARS-coronaviruses. However, some studies have shown significant variations between SARS-CoV and SARS-CoV-2, such as the absence of 8a protein and fluctuations in the number of amino acids in 8b and 3c protein in SARS-CoV-2 (ref.[7]). The following Fig. 1 shows a detailed comparison:

Based on the currently available data and according to some authors, SARS-CoV-2 is of natural origin[8]; it does not show whole genome affinity for other SARS coronavirus strains, which would be typical for a virus which would be created in a laboratory, but it carries changes in the genes coding the receptor which binds the domain responsible for attaching the virus to the target cell's receptor and for the cleavage site, which must be recognized and cleaved by host enzymes, thereby activating the viral protein to enter the cells.

Genetic analysis shows that there are dozens of mutations of the novel coronavirus currently circulating in the population[9]. From December 2019 to April 2020, a total

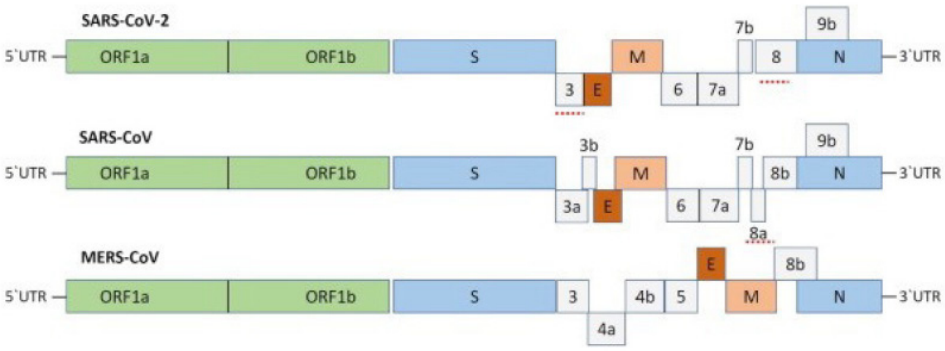

Fig. 1. SARS-CoV2 virus genome chart compared to SARS and MERS coronaviruses[6]

of 4,590 SARS-CoV-2 genomes from different regions of the world were sequenced, and some European types have 11–14 mutations[10]. The high frequency of mutations is caused by their single-stranded RNA nucleic acid as well as viral RNA polymerase, which also introduces frequent errors in replication.

Epidemiological background

It is believed that the COVID-19 outbreak originated in the Chinese city of Wuhan. One of the possible reasons could be transmission at the local wet market, where animals and seafood are traded, and raw meat came into contact with live animals. Bats or pangolins are considered to be one of the possible intermediate hosts[11]. Vendors and traders in the local market were among the first patients. Some researchers had previously warned that markets selling animals captured in the wild, namely bats, could become a potential source of infection for humans[12].

Some authors also point out a possible connection with the Wuhan Institute of Virology in the city of Wuhan[13]. This research institute, established by the Chinese Academy of Sciences as early as 1956, expanded its scope of activities by opening a highest-security biosafety laboratory (BSL-4) in 2015 in cooperation with French engineers from Lyon and the Galveston National Laboratory at the University of Texas; the laboratory performs tests on primates which are banned in Western countries. In 2005, a group of scientists including researchers from Wuhan Institute of Virology, published the results of research on the origin of the SARS-CoV coronavirus conducted on more than 300 bat coronavirus sequences[14].

In 2015, the journal Nature Medicine published conclusions of a team of American scientists and two Chinese scientists from the Wuhan Institute which confirmed the possibility of transferring SHC014-CoV coronavirus from infected bats to human tumor cells grown in the laboratory setting for research purposes (HeLa cell line). The research team developed a hybrid virus combining bat coronavirus with SARS-CoV virus, which was able to infect and proliferate in human cells[15].

According to some authors, another potential site of infection may also have been the Wuhan Center for Disease Prevention, which operates at a lower safety level (BSL-2) and is situated just several hundred metres from the market[16].

The fact that the coronavirus could have escaped from a laboratory despite all the security measures was admitted by Shi Cheng-li, the virologist who herself described dozens SARS-like viruses and coronaviruses studied in bats at the Wuhan Institute for the last fifteen years[17].

In 2014, the United States halted funding for gain-of-function research which could potentially transform viruses and make them more dangerous to humans. Nevertheless, a team from the University of North Carolina at Chapel Hill completed a test in 2015 where they created a chimera of a bat coronavirus (SHC014) with a SARS virus that was able to infect human lung cells in vitro[15].

Autoimmune response to COVID-19

T-lymphocytes play an important part in the antiviral immune response. In a study of typical markers indicating T-lymphocyte depletion (PD-1 and TIM-3), it was found that most elderly patients and ICU patients with COVID-19 had dramatically reduced T-CD4+ and T-CD8+ titers as well as total T-lymphocytes (300/μL, 400/μL, 800/μL), exhibiting a negative correlation with their survival. A decreased T-lymphocyte count also corresponded with increased serum concentrations of some cytokines, especially TNF-a, IL-6 and IL-10 (ref.[18]). Elevated interleukin IL-6 levels were observed in patients with COVID-19 who developed respiratory failure and required pulmonary ventilation[19].

SARS-CoV can be classified as a neurotropic virus that can cause serious CNS disease, especially in children and the elderly. The virus enters the brain by direct penetration from blood vessels, through CSF or by axonal transport from peripheral nerves[20]: for example, through the transmission of infection from the eyes or nose. Suppression of brainstem reflexes induced by hypoxia is manifested by the fact that patients with COVID-19 who have demonstrably low blood oxygen levels do not show a compensatory increased respiratory rate[21]. Some patients present with other neurological symptoms, such as confusion, headache, or anosmia and ageusia. Since more than a third of infected individuals present with signs of central or peripheral nervous system or muscle involvement, early differential diagnosis of neurological disease may help identify potential SARS-CoV-2 carriers[22].

Asymptomatic course

Data gradually collected around the world show that especially in pediatric patients, COVID-19 infection is generally mild or asymptomatic, and children may become carriers of the disease in families. A one example, a study of 565 Japanese citizens who were evacuated from Wuhan and undertook PCR testing for the presence of SARS-CoV-2 revealed 30% of asymptomatic individuals in the group, even after thirty days of quarantine[23]. Some reports from the Chinese National Health Commission indicate that up to four-fifths of the confirmed cases are asymptomatic[24]. Thus, testing is the only way to confirm the disease with certainty.

There have also been reports of a possible latent course of the disease, which is rather typical of retroviruses or some DNA viruses. According to a report from South Korea, virus reactivation was proven in 111 recovered patients. However, it is not yet possible to prove whether this represents a reinfection of SARS-CoV-2 or viral latency. At the same time, patients did not develop a relapse of COVID-19 (ref.[25]).

SARS-CoV-2 test

Considering that the course of the disease may run similar to a severe case of influenza or occur without any symptoms, especially in younger individuals, it is difficult to diagnose the disease or to distinguish it from other types of viral infections. Therefore, PCR diagnostics remains the only reliable method of confirming the infection, where RNA identical to the RNA of SARS-CoV-2 coronavirus is detected in nasopharyngeal and oropharyngeal specimen.

Serological testing may assist in screening if PCR results return negative and there is a strong epidemiological link to COVID-19 infection[26]. Blood samples can be tested for elevated IgM and IgG antibodies titers, as well as possibly IgA. This does not provide direct evidence of the presence of the virus and this test has only a supporting role because the antibody response comes several days after the onset of symptoms[27].

Paired sera (in the acute and convalescent phases) can also confirm the diagnosis. However, new and more effective testing methods are still being developed.

COVID-19 SYMPTOMS

In terms of the clinical course, COVID-19 is much more severe than influenza; its R0 infectivity rate is around 2.5 (compared to 1.5 for influenza). Hospitalization rate is usually 1% for seasonal flu and 5–20% for COVID-19. Case fatality rate is about 0.1 percent for influenza, and can be up to ten times greater (about 1%) in COVID-19 (ref.[28]).

The body of research published so far indicates that the disease is mild in 81% of cases and does not require hospitalization but 14% of patients may develop pneumonia and 5% of those infected have a critical course with organ failure[29]. Patients with a mild course of COVID-19 may be completely asymptomatic; this course has been described especially in younger individuals. A more severe course of the disease occurs in the elderly or in patients suffering from cardiovascular diseases, diabetes, cancer, and other serious conditions.

Milder symptoms most often include cough, shortness of breath, fatigue and fever. More severe cases can lead to pneumonia, acute myocarditis, renal failure, and subsequent death[30]. Other less common symptoms recorded so far included muscle and joint pain and anosmia or ageusia[31].

Diffuse intravascular coagulation, observed in up to 30% of cases, is a serious complication in patients with pneumonia regardless of prophylactic thrombolytic treatment[29]. This leads to acute pulmonary embolism, thrombosis in the lower limbs, or strokes and heart attacks.

In addition to the above, a rash has been described recently, appearing especially in young children or adolescents as the first symptom of the disease. Another sign may be 'covid fingers,' presenting in the form of red bumps on the toes, painful to the touch and sometimes itchy; these may be the only symptom of COVID-19 (ref.[32]).

TREATMENT OF COVID-19

No specific treatment or vaccine for COVID-19 exists as of the time of writing. Research is underway into drugs used to treat malaria and autoimmune diseases or antiviral treatment for other viruses or antibodies from people who have recovered from COVID-19. Through global clinical trials—SOLIDARITY, DISCOVERY, and RECOVERY—the WHO is currently supporting experimental treatment with remdesivir, combinations lopinavir/ritonavir (in combination with beta interferon), chloroquine, hydroxychloroquine and an anti-interleukin-6 monoclonal antibody known as Actemra. In all cases, it is only experimental treatment, as no substance has of yet been officially registered for the treatment of COVID-19. At present, according to the Czech State Institute for Drug Control (SÚKL), over 540 clinical studies with various drugs are in progress[33].

Extensive virtual scanning for potential drugs with known biological effects (ZINC drug database, containing 2,924 drugs and 1,066 herbal drugs) is also underway, and their chemical structure is compared with the structure of potential target proteins involved in virus replication through computer simulation[34].

Experimental plasma treatment

One possibility is the administration of convalescent plasma; convalescent plasma is plasma of recovered patients which has been used for more than 100 years to treat various diseases from measles to polio to SARS (ref.[35]). Donor antibodies help patients fight disease or reduce its severity. For COVID-19, plasma therapy has been approved since March, although it is still considered experimental because no randomized, controlled studies have been performed, and physicians also do not know when it is the best time to administer plasma in the course

of disease progression. Convalescent plasma was administered to 245 patients with COVID-19 in China and the condition of ninety-one of them improved[33].

There are plans to use convalescent plasma to make drugs from hyperimmune immunoglobulins isolated from plasma, and a drug based on hyperimmune immunoglobulin is currently being developed[36]. Leading global pharmaceutical and technology companies involved in plasma processing have joined an alliance that coordinates cooperation in the global fight against COVID-19.

Antiviral therapy

Targeted antiviral therapy for COVID-19 does not exist yet. However, drugs developed to treat other viral diseases are being tested. Much attention is now being paid to remdesivir[37], an anti-viral drug which was originally developed to treat serious viral diseases such as Ebola, mainly because it had successfully targeted the coronaviruses causing SARS and MERS. Its mechanism of action is based on inhibiting the coronavirus's ability to replicate. Two large randomized clinical trials involving 700 patients are currently underway in China, and they are likely to provide the answer as to whether remdesivir is definitely effective for COVID-19 in May[38]. SÚKL emphasizes that, at the time writing, the efficacy of remdesivir in the treatment of COVID-19 cannot be considered as proven, as its efficacy has not been confirmed in a clinical study and the clinical studies are still in progress[33].

Antiviral drugs effective in the treatment of influenza or HIV are also being tested experimentally for the treatment of COVID-19. Favipiravir (Avigan) was approved for experimental treatment in China; favipiravir is a drug registered in Japan for the treatment of influenza; lopinavir (an HIV protease inhibitor) in combination with ritonavir, umifenovir (used for prophylaxis of influenza in Russia and China) and oseltamivir (a neuraminidase inhibitor) are also being tested in experimental studies. In the United States, baloxavir, which is registered as an antiviral drug for influenza treatment, is currently being evaluated clinically in combination with favipiravir and lopinavir/ritonavir.

Some of the registered antiviral drugs tested in the EU are: atazanavir, indicated for the treatment of HIV; darunavir, another anti-HIV drug combined with antiretroviral medicines; or cobicistat, which is also indicated for HIV treatment in combination with antiretroviral medicines. The efficacy of ribavirin, a drug which is used to treat chronic hepatitis C and administered in the Czech Republic in combination with, for example, interferon or in combination with lopinavir/ritonavir, is being investigated as well.

Antimalarial treatment scheme

Reports from China and France suggested that patients with severe COVID-19 symptoms improved more rapidly when they received chloroquine or hydroxychloroquine. Some physicians used a combination of hydroxychloroquine and azithromycin with some positive effects[35]. Hydroxychloroquine and chloroquine are primarily used to treat malaria and several inflammatory diseases, including lupus and rheumatoid arthritis. Azithromycin is a commonly prescribed antibiotic for the treatment of, for example, bacterial pneumonia.

Hydroxychloroquine and chloroquine have been shown to destroy the COVID-19 virus in the laboratory setting. It seems that these substances work through two mechanisms. First, they make it difficult for the virus to attach to the cell, preventing the virus from entering and multiplying, or they kill the virus before it begins to multiply in the cell. The first results from China demonstrated the ability of chloroquine to reduce the severity of pneumonia and shorten the duration of the symptoms of the disease. However, chloroquine has a worse safety profile than hydroxychloroquine and its use is associated with more adverse side effects.

Azithromycin is never used for viral infections. However, this antibiotic has an anti-inflammatory effect. It has been suggested that azithromycin may help suppress the hyperactive immune response to a COVID-19 infection.

However, recent studies have linked the use of hydroxychloroquine and azithromycin to the risk of developing malignant cardiac arrhythmias because these drugs are especially dangerous when used in a combination.

Based on these reports, the FDA now formally cautions against the use of chloroquine or hydroxychloroquine for COVID-19 outside of the hospital setting or a clinical trial.

Biological treatment

Experimental treatment with tocilizumab, a drug used in rheumatoid arthritis treatment, has been described to show an improvement in clinical symptoms without eliciting side effects[39]. Sarilumab (Kevzara), a monoclonal antibody, which is also used as an interleukin-6 inhibitor in patients with rheumatoid arthritis, could have similar effects. Another monoclonal antibody is bevacizumab, currently registered in the EU for the treatment of various types of cancer; its use should lead to a reduction in lung edema and mitigating acute lung damage induced by COVID-19 (ref.[33]). Situximab is a chimeric monoclonal antibody that binds to interleukin IL-6 and neutralizes its biological activity. It is registered in the EU for lymph node diseases, and its safety and efficacy in patients with acute respiratory failure and systemic cytokine release syndrome are being investigated in a clinical study[44]. The use of eculizumab, a humanized monoclonal antibody which binds to the human complement protein C5 and inhibits terminal complement activation, is being investigated in France[40]. It is approved in the EU for the treatment of autoimmune diseases, such as neuromyelitis optica. In Sweden, a study used emapalumab, a monoclonal antibody[41] which binds gamma interferon (INF-γ) and thus reduces its biological activity. It is approved in the USA for the treatment of hemophagocytic lymphohistiocytosis. An experimental monoclonal antibody known as IFX-1, which aims to inhibit complement activation, is being tested in patients with severe pneumonia in the Netherlands[42]. Leronlimab is another experimental monoclonal antibody which specifically binds to the C-C chemokine receptor

type 5 (CCR5) on the surface of leukocytes. According to the results of clinical evaluation so far, it has significantly reduced the activity of proinflammatory cytokines (IL-6 and TNF-alpha) in patients and the treatment helped to reduce the cytokine storm[43].

Other candidates include sargramostim, an immunomodulatory substance that stimulates leukocyte growth and is registered in the USA. Angiotensin-converting enzyme 2 (ACE2) is capable of binding to coronavirus, which is supposed to reduce the virus's binding to ACE2 receptors on the surface of a cell and slow down or stop the spread of the virus in the body. An international clinical trial has also been launched to study anakinra, a human interleukin-1 receptor antagonist and a major proinflammatory cytokine whose levels are elevated during cytokine release syndrome[44].

Corticosteroid treatment

The WHO does not currently recommend the routine use of corticosteroids in patients infected with SARS-CoV-2. The WHO does not currently recommend corticosteroids for other viral diseases either, such as dengue fever, as they may cause lymphocytopenia or promote an enhanced pro-inflammatory response which eventually exacerbates the pathogen[45]. The use of corticosteroids is currently being monitored in clinical trials. Four clinical trials are currently underway with dexamethasone, and hydrocortisone is being studied in one clinical trial[46].

Symptomatic treatment

Standard drugs, such as medicines used to treat influenza or reduce the manifestations of an infection in general, are also used to suppress the symptoms of COVID-19. The WHO initially recommended the use of acetaminophen to reduce fever and pain, and later added ibuprofen, although in some countries (e.g. France) it was not recommended because its use was associated with a more severe course of the disease, including pneumonia[35].

A synthetic peptide known as solnatide is used for reducing lung edema or in patients with the acute respiratory distress syndrome[47].

Anticoagulants, such as fondaparinux[48] are used to prevent the risk of venous thromboembolism in hospitalized patients with severe COVID-19.

The use of high doses of intravenous vitamin C, which could be beneficial in the treatment of COVID-19, is widely discussed; however, the results of studies currently underway in Canada, Italy and China are not yet available.

The FDA has also confirmed that SARS-CoV-2 is effectively blocked by an antiparasitic ivermectin, whose antiviral effects have been demonstrated previously[49]. An in vitro culture of infected Vero/hSLAM cells to which ivermectin was added showed that the virus titer in the supernatant decreased by up to 99.98% within 48 h.

Vaccine preparation

No vaccine against coronavirus SARS-CoV-2 is available yet. In addition, data published so far by Chinese researchers show that almost a third of recovered patients who had milder symptoms developed almost no antibodies[50]. Following the onset of the disease, antibodies are likely to remain in the body for two to three years, which is a value similar to that of SARS, however, in some individuals, the antibodies may not survive that long. The presence of antibodies also does not completely guarantee that recovered patients cannot be reinfected. This is partly because the virus mutates rapidly and individuals can become infected with a different strain of the virus than the one they have developed antibodies against. SARS-CoV-2 reinfections have been documented in China, South Korea, Japan, and Thailand[51]. This complicates the preparation of a vaccine and at the same time complicates the possibility of acquiring herd immunity by gradually exposing the population to the viral infection.

At least a dozen vaccines are currently going through clinical trials, and over eighty are in preclinical testing. The EU first vaccine is the BNT162 clinical trial of BioNTech in Germany[52]. Saiba reported that it has developed a vaccine based on an artificially created viral part in collaboration with the University of Bern in Switzerland.

In addition to attenuated or inactivated virus, SARS-CoV-2 recombinant spike protein or viral vectors carrying this protein also appear to be a suitable target for antibody development[53].

MULTIPLE SCLEROSIS AND SARS-COV-2 CORONAVIRUS INFECTION

Based on what we know so far, individuals with autoimmune diseases do not pose a higher risk of getting the SARS-CoV-2 infection. Intensive data collection is currently underway for patients with multiple sclerosis (MS) who have been diagnosed with COVID-19, but these samples are not statistically significant yet. Thus, we can only build on our experience with smaller groups of patients and mechanisms of action of individual immunomodulatory therapies (DMD).

Most people develop COVID-19 with only mild symptoms. The goal of therapy is to alleviate the symptoms letting the body fight the infection.

Unlike the general population, the course of COVID-19 in MS patients is modified by a number of factors; the chronic disease is often associated with a number of other health complications and the chronic immunomodulatory treatment associated with immunosuppressive effects at various levels of the immune system and the cytokine network. In milder COVID-19 cases, the exacerbation of MS may be only temporary but the risk of relapse or progression of the disease is not negligible. The long-term and systematic modification of the immune response by DMD drugs, immunosuppressants, or corticosteroids is another significant factor. The result can be completely different, and often complicated courses of the COVID-19 infection.

This is the reason why many developed countries include MS patients in the risk groups and emphasize the need to pay increased attention to hygiene and social distancing, including necessary modifications of work activities, such as teleworking, etc.

Epidemiological recommendations

In April 2020, the Neuroimmunology Section of the Czech Neurological Society issued Recommendations for Patients with Multiple Sclerosis During the COVID-19 Epidemic[54]. The recommendations were formulated on the basis of currently available knowledge and awareness of the disease, and have been continuously updated over time.

Modification of the regime of regular visits in MS clinics:

- The procedure is always individual, but in general, the following recommendations apply:
- Wherever possible, replace the planned visits of stable patients with a telephone visit and ask for a healthy individual chosen by the patient to pick up the medication (biological therapy). Other common drugs can be supplied in the form of an electronic prescription. The staff of the clinics are prepared for such telephone and e-mail communication.
- In the case of a risky work environment or the need to travel by public transport, we recommend that especially patients treated with drugs with a greater suppression of immune reactions take sick leave.

These recommendations can be complemented by the statement of the MS Society[55] which issued a set recommendations for patients with MS on 6 March 2020, in which it also recommends social distancing of at least 1 m. MS Ireland also published detailed recommendations for MS patients[56]. In case of COVID-19 symptoms (especially cough, high fever, shortness of breath, or difficulty breathing), it is necessary to contact the hospital and consult the MS team. Patients taking immunosuppressants should avoid unnecessary travel, crowded places, and if possible work from home, and maintain adequate hygiene, especially washing their hands frequently and thoroughly.

In terms of surface decay, the virus has a different half-life for different materials, but different sources report durations in the order of hours up to days. According to recent studies, ozone destroys SARS-CoV-2 more effectively than chlorine and should be used for disinfecting contaminated areas[57]. Other authors report that the half-life of the virus is significantly shorter when it is exposed to sunlight[58].

Recommendations for treatment of multiple sclerosis

The discontinuation of immunomodulatory therapy is generally not recommended, although caution should be exercised with some drugs, and consultation with the attending neurologist is always required. The MS Society[55] recommends not to stop DMD due to the threat of COVID-19 infection. Symptoms will vary from patient to patient depending on a number of factors, including the clinical symptoms of MS and the individuals overall status.

The Neuroimmunological Section of the Czech Neurological Society issued the following recommendations for the treatment of MS of patients who contracted COVID-19 (ref.[54]):

- Most drugs that modify the course of the disease (biological treatment) work on the principle of suppressing or modulating the immune system. Therefore, some MS drugs may increase the probability of complications from COVID-19. Discontinuation/termination/non-initiation of this treatment must always be considered on an individual basis with regard to the mechanism of action of the particular drug vs. risk of MS activity. Other important factors are the patient's age and comorbidities.

In line with currently available information regarding the risk of ongoing viral infection, we recommend:

- Patients should not discontinue treatment themselves to avoid the 'rebound phenomenon,' i.e. the return of original/higher MS activity.
- The following medications usually do not lead to significant suppression of immune responses and can be prescribed according to the usual protocols:
  - Glatiramer acetate (Copaxone)
  - Beta interferons (Avonex, Avopen, Betaferon, Extavia, Plegridy, Rebif 22 and Rebif 44)
  - Teriflunomide (Aubagio)
  - Dimethyl fumarate (Tecfidera)
  - Treatment of an attack with a round of Solumedrol
- The drugs listed below may be associated with a mildly elevated risk. If the patient is already receiving therapy, we believe that its abrupt discontinuation may bring a greater risk of harm to the patient due to the possibility of return of MS activity, and we therefore recommend not to discontinue the treatment. All epidemiological measures must be implemented meticulously; the patient can travel to get the infusion by car and always consult their current status with their MS clinic.
  - Fingolimod (Gilenya)
  - Natalizumab (Tysabri)
  - Ocrelizumab (Ocrevus)
  - Rituximab (Mabthera, Truxima)
- In case of the following drugs, their regular application/initiation of treatment should be subject to careful consideration. Individual circumstances must always be consulted with the attending physician. With high MS activity, it is necessary to take into account the risk of disease activity and the possibility of irreversible damage to the patient due to MS.
  - Cladribin (Mavenclad)
  - Alemtuzumab (Lemtrada)

In terms of global recommendations, according to the Multiple Sclerosis Society of Ireland[56], most therapies used to treat MS are based on the principle of suppressing the immune system. This may make these patients more vulnerable to COVID-19. Because it is a new type of virus, no statistically significant data is available in MS patients with COVID-19. Nevertheless, it is recommended not to stop the treatment of MS, as this may result in relapses in the coming weeks or months, which can be a serious complication not only of MS, but also

of COVID-19. Therefore, individual treatment decisions must be discussed with the attending neurologist.

For Copaxone, Betaferon, Rebif, Avonex, Plegridy, Tecfidera, and Aubagio, MS Ireland recommends continuing MS treatment as usual. It is presumed that these drugs do not have a great effect on how the immune system reacts when it is attacked by the novel coronavirus. Presumably, this is also the case for Tysabri, and MS Ireland recommends maintaining the treatment regimen for this medicine. In the case of Gilenya, the mechanism of action of this medicine and the progression of COVID-19 are discussed but no detailed or statistically significant information is currently available. Therefore, it is possible to continue the therapy, unless the physician decides to discontinue the therapy.

According to the Multiple Sclerosis Trust (MS Society) (ref.[55]), Copaxone, Aubagio, Tecfidera, beta interferons and Tysabri are probably safer than other DMDs because they are not considered immunosuppressive drugs. In MS patients receiving natalizumab, the recommendation is to continue therapy under careful supervision. For Lemtrada, Mavenclad and Ocrevus, physicians should consider delaying therapy as this treatment may affect the patient's immune response. Gilenya may be associated with an increased risk of a more severe course of viral or other infection, including COVID-19. At the same time, however, there is a risk of relapse of MS if treatment is stopped, which may outweigh the risks of COVID-19 in more severe cases.

According to the current view of leading experts on DMD in the treatment of multiple sclerosis it is safe to initiate or continue with beta-1a interferon, beta-1b interferon, glatiramer acetate, teriflunomide, and dimethyl fumarate therapies. It is probable that all of these drugs increase the risk of viral infections, but the risk is usually much smaller than the return of disease activity. While some argue that the risk of viral infections can be predicted by total lymphocyte counts, the literature does not provide a clear answer, and so we do not recommend any change to current guidelines for monitoring these drugs.

With Lemtrada, Mavenclad, Mabthera/Truxima, and Ocrevus, continued treatment may make the patient more vulnerable to COVID-19. Thus, a physician may recommend postponing treatment; however, neurologists will base this decision on individual parameters on a case-by-case basis. These drugs often have a prolonged therapeutic effect, so delaying planned infusions or initiating therapy with of these drugs is not a major problem. On the positive side, Mavenclad does not require premedication with corticosteroids (it does not cause cell lysis with the risk of a cytokine storm), has minimal effect on innate and antiviral immunity, and is not associated with a risk of developing hypogammaglobulinaemia.

The risk of viral infections is significantly higher at three to six months after alemtuzumab and cladribine[59]. It has been recommended that these drugs are not initiated during the coronavirus epidemic; natalizumab and ocrelizumab are safer options for active disease. For those who had already begun the treatment, it has been recommended to delay the next round of both treatments until the risk of coronavirus infection disappears. It is safe to increase the interval between the first and second alemtuzumab treatment to eighteen months without the risk of a return of MS activity. The data are less conclusive for cladribine. If a third or fourth round of alemtuzumab or cladribine treatment is being considered for new disease activity, it is recommended to use another DMD or to delay the beginning of the treatment until the epidemic is over. At the same time, cladribine-induced reconstitution of the immune system allows for future vaccination.

The risk of coronavirus infection with fingolimod is likely to be mildly increased. For patients who are already on the drug, the risk of rebound is likely to outweigh the risk of infection.

Natalizumab does not reduce serum lymphocytes and it prevents lymphocytes from binding to VCAM-1 on the vascular endothelium, their crossing the blood-brain barrier, and settling in the CNS; by blocking molecular interactions, it reduces the inflammatory activity present in the brain and inhibits further migration of immune cells into inflamed tissue[60]. The risk management plan for the systematic monitoring of the risk of progressive multifocal leukoencephalopathy (PML) follows the same algorithms as outside the COVID-19 pandemic; the option of an extended interval dosage of Tysabri to increase treatment safety needs to be considered on an individual basis.

In patients already receiving ocrelizumab, a delay of further infusions is recommended for the duration of the risk of coronavirus infection[59]. From the Swedish experience with rituximab, it is clear that the infusion of ocrelizumab will control MS effectively for more than six months.

Autologous hematopoietic stem cell transplantation (HSCT) is usually a borderline treatment for multiple sclerosis and has the highest risk, as it disrupts the patient's immune system significantly for a period of time. It is recommended that HSCT treatment be postponed or replaced by a safer treatment.

Corticosteroids are generally not recommended (from the immunological point of view) because they suppress the immune system and reduce the ability to resist infection. In case of an increased risk of COVID-19, the administration of methylprednisolone is always subject to individual consideration, including alternative approaches to the treatment of an attack, such as intravenous immunoglobulins (IVIG) or exchange plasmapheresis (VPF).

CONCLUSION

We are currently in a phase where the first global wave of the COVID-19 pandemic is receding. Many of the facts that doctors are now working with have not been sufficiently verified and proven over time, or substantiated in a sufficiently statistically significant number of patients. Until we get sufficiently robust data collected from a sample of patients with autoimmune diseases, we cannot make clear conclusions, and we should follow the recommendations of professional organizations while being aware that such recommendations may change over time

depending on the further development of the COVID-19 pandemic, the virus mutations and their changes, and monitor the longer-term effects of immunomodulatory treatment in MS patients with COVID-19.

Therefore, for the time being, prevention in particular is recommended, such as hygiene and social distancing wherever possible, for example, by maintaining the recommended distance between individuals in common areas and public transport, etc. Prevention of COVID-19 as long as targeted therapy or vaccination is not available is the most sensible approach for individuals with autoimmune diseases. However, if an infection occurs it is necessary to choose an approach that minimizes interference with the ongoing autoimmune disease therapy with the assistance of a neurologist, and individually assesses the risk of relapse or progression on the one side and the risk of severe COVID-19 on the other. At the same time, however, it cannot be ruled out that some type of DMD may reduce the immune response to this coronavirus in some individuals with a certain type of immune response, thereby preventing to the patient's advantage a massive cytokine storm, thus contributing to a less severe progression of COVID-19.

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