Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Review article

Current and emerging therapeutics for neuromyelitis optica spectrum disorder: Relevance to the COVID-19 pandemic

Hesham Abboud, Crystal Zheng, Indrani Kar, Claire Kaori Chen, Crystal Sau, Alessandro Serra

Multiple Sclerosis and Neuroimmunology Program, University Hospitals of Cleveland, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Ohio Northern University School of Pharmacy, Ada, OH, USA

System Pharmacy Services, University Hospitals of Cleveland, Cleveland, OH, USA

VA Multiple Sclerosis Center of Excellence, Cleveland VA Medical Center, Cleveland, OH, USA

ARTICLE INFO

Keywords:
Neuromyelitis optica spectrum disorder
NMOSD
COVID-19
SARS-CoV-2
Immunotherapy

ABSTRACT

Neuromyelitis optica spectrum disorder (NMOSD) can lead to immobility and bulbar weakness. This, in addition to the older age of onset and the higher rate of hospitalization compared to multiple sclerosis, makes this patient group a potential target for complicated COVID-19 infection. Moreover, many of the commonly used preventive therapies for NMOSD are cell-depleting immunosuppressants with increased risk of viral and bacterial infections. The emergence of several new NMOSD therapeutics, including immune-modulating agents, concurrently with the worldwide spread of the COVID-19 global pandemic call for careful therapeutic planning and add to the complexity of NMOSD management. Altering the common therapeutic approach to NMOSD during the pandemic may be necessary to balance both efficacy and safety of treatment. Selection of preventive therapy should take in consideration the viral exposure risk related to the route and frequency of administration and, most importantly, the immunological properties of each therapeutic agent and its potential impact on the risk of SARS-CoV-2 susceptibility and severity of infection. The impact of the therapeutic agent on the immune response against the future SARS-CoV-2 vaccine should also be considered in the clinical decision-making. In this review, we will discuss the immune response against SARS-CoV-2 and evaluate the potential impact of the current and emerging NMOSD therapeutics on infection risk, infection severity, and future SARS-CoV-2 vaccination. We propose a therapeutic approach to NMOSD during the COVID-19 pandemic based on analysis of the mechanism of action, route of administration, and side effect profile of each therapeutic agent.

1. Introduction

The pandemic of the severe acute respiratory syndrome corona virus type-2 (SARS-CoV-2), commonly referred to as COVID-19, has influenced every aspect of modern life. Although the virus can infect healthy individuals, several high-risk groups are more vulnerable to complications secondary to a more severe infection course. In addition to elderly patients with cardiopulmonary comorbidities and/or diabetes, patients with chronic disabling neurological conditions that impair coughing or limit pulmonary function, and those on immunosuppressive therapy are also considered high risk. Neuromyelitis optica spectrum disorder (NMOSD) is a chronic relapsing autoimmune disorder of the central nervous system caused by pathogenic antibodies against the aquaporin-4 (AQP4) water channels on the surface of astrocytes. About 20% of NMOSD patients do not have AQP4-IgG and either have an antibody against myelin oligodendrocyte glycoprotein (MOG) or no recognizable antibodies (double seronegative). NMOSD preferentially attacks the optic nerves, spinal cord, and brainstem commonly resulting in visual impairment, paralysis, and occasionally bulbar dysfunction. Such neurological deficits that limit mobility and impair coughing can have deleterious effects on pulmonary functions and risk of pneumonia. This, in addition to the need for immunosuppression in most NMOSD patients, make them a potential target for complicated COVID-19 infection. Many of the existing effective preventive therapies in NMOSD are delivered intravenously increasing the risk of infection through contact at infusion centers or with home infusion personnel. Moreover, acute NMOSD relapses are often more severe than MS and usually require...
treatment with high dose corticosteroids and plasma exchange (PLEX) in a hospital setting further increasing the potential risk of SARS-CoV-2 exposure (Wingerchuk et al. 1999; Abboud et al., 2016; Kleiter et al., 2016). NMOSD also affects older adults more than MS. Some NMOSD therapeutics may have implications on the future vaccination against SARS-CoV-2 (van Assen et al., 2010). This important new variable should be taken into consideration when starting a newly-diagnosed NMOSD patient on preventive therapy or when deciding on re-dosing current treatment. Interestingly, an exaggerated immune response against the virus is thought to contribute to lung injury and morbidity from the SARS-CoV-2 infection (Huang et al., 2020; Mehta et al., 2020). This has created a scientific interest in the utility of certain immunotherapies in COVID-19 treatment (Chinese Clinical Trial Registry, 2020; Eculizumab 2014). Some of the agents of interest are therapies that are used for NMOSD or have shown efficacy in recent NMOSD clinical trials (Pittock et al., 2019; Araki et al., 2014; Yamamura et al., 2019). In this review, we will discuss the immune response against SARS-CoV-2 and evaluate the potential impact of NMOSD therapeutics on infection risk, infection severity, and future SARS-CoV-2 vaccination. We propose a therapeutic approach to NMOSD during the COVID-19 pandemic based on analysis of the mechanism of action (MOA), route of administration, and side effect profile of each therapeutic agent. The majority of the therapeutics discussed in this review have shown efficacy in NMOSD with AQ4P4-IgG; therefore, the review will focus mainly on this disease subtype. MOG-IgG related and double seronegative NMOSD subtypes have distinct clinical features and lack sufficient evidence for definitive therapies.

1.1. The SARS-CoV-2 immune response

Insights regarding the immune response against SARS-CoV-2 are partially based on studies from other corona viruses such as SARS-CoV-1 and the Middle East Respiratory Syndrome-related Corona Virus (MERS-CoV) (Promptcheara et al., 2020). The initial response relies mainly on the innate immune system mediated by macrophages, natural killer cells, cytokines, and type-1 interferons. The early adaptive immune response relies mainly on T-cells. T-helper cells induce macrophage-mediated phagocytosis of the virus while cytotoxic T-cells attack virally-infected cells. The B-cell based humoral response is mainly implicated in the long-term immunity against the virus and reduction of reinfection risk (Promptcheara et al., 2020; Zhao et al., 2019). 

1.2. Immune dysregulation and cytokine storm in SARS-CoV-2 infection

In some SARS-CoV-2-infected patients, a delayed hyperimmune response takes place leading to severe lung injury due to excessive inflammatory infiltrates (Promptcheara et al., 2020; Cao, 2020). This hyperimmune response is characterized by elevated levels of pro-inflammatory cytokines including interleukin-6 (IL-6) constituting a cytokine storm (Mehta et al., 2020; Promptcheara et al., 2020; Cao, 2020). In addition to lung injury, the cytokine storm leads to secondary haemophagocytic lymphohistiocytosis (HLH)-like reaction and multi-organ failure. The immune dysregulation in COVID-19 infection is also characterized by lymphopenia (Cao, 2020). Based on animal models of the SARS-CoV-1, complement activation is thought to be involved in severe corona virus-related respiratory complications (Gralinski et al., 2018).

1.3. Future vaccines against SARS-CoV-2 infection

It is currently unknown if humoral immunity against SARS-CoV-2 is protective although recent studies have identified neutralizing antibodies with potential therapeutic and prophylactic effects (Cao, 2020; Cao et al., 2020). Several vaccines are currently being developed but the effectiveness and safety of these vaccines are yet to be elucidated (Thanh Le et al., 2020). Candidate vaccines include viral protein and nucleic acid vaccines, artificial antigen-presenting cell vaccines, surrogate viral vector vaccines, and live-attenuated vaccines (Promptcheara et al., 2020; Thanh Le et al., 2020; Yu et al., 2020; Wang et al., 2020). Some of these vaccines can elicit both cellular and humoral immune response and some mainly elicit a humoral response. Live-attenuated vaccines are contraindicated in patients on immunosuppressive agents and may be contraindicated with some immunomodulating agents as well. The safety of viral vector vaccines (target viral protein delivered via another less virulent surrogate virus) in immunocompromised patients is unknown. Although it is usually safe to give inactivated or viral protein vaccines to patients on immunosuppressants, the immune response against these vaccines may be dampened in those patients.

1.4. Current and emerging preventive therapies in NMOSD

1.4.1. Azathioprine and mycophenolate mofetil

Azathioprine and mycophenolate mofetil (MMF) have been used off label to prevent NMOSD attacks for decades (Kimbrough et al., 2012). Their efficacy in NMOSD has been demonstrated in several prospective studies and case series (Kimbrough et al., 2012; Costanzi and Matiello, 2011; Jacob and Matiello, 2009). In recent years, their use in NMOSD has declined in favor of rituximab owing to their comparative lower efficacy as demonstrated in multiple retrospective studies (Kimbrough et al., 2012; Mealy et al., 2014). A recent randomized prospective open-label study demonstrated the efficacy of combined azathioprine and prednisone therapy in reducing annualized relapse rate (ARR) in NMOSD patients with and without AQ4P4-IgG compared to pre-treatment rate (Nikoo et al., 2017). However, the same study showed that rituximab was more effective and better tolerated than azathioprine.

Mechanism of action: azathioprine inhibits purine synthesis preferentially reducing the proliferation of T- and B-lymphocytes. MMF inhibits de novo purine synthesis by inhibiting synthesis of guanosine nucleotides producing a more selective anti-proliferative effect on T- and B-lymphocytes (Kimbrough et al., 2012).

Impact on the immune system: both agents produce non-selective lymphopenia leading to broad immunosuppression. Neutropenia, leukopenia, pancytopenia, and severe myelosuppression can all occur. Live-attenuated vaccines are contraindicated during treatment with these agents and the protective immune response against inactivated or viral protein vaccines may be reduced (Mycolphenolate, 2020).

Infectious side effects: because of their broad immunosuppression, patients receiving azathioprine or MMF are at increased risk of common and opportunistic viral, bacterial, and fungal infections (Kimbrough et al., 2012; Costanzi and Matiello, 2011; Jacob and Matiello, 2009; Mealy et al., 2014; Nikoo et al., 2017; Mycolphenolate, 2020). Sepsis and fatal infections can occur in patients with severe myelosuppression (Mycolphenolate, 2020).

Potential relevance to the COVID-19 pandemic: in-vivo studies of MERS-CoV animal models suggest that MMF could be associated with more severe disease (Russell et al., 2020). In humans, there has only been limited and inconclusive experience with the use of MMF in corona virus-infected patients (Russell et al., 2020). NMOSD patients on azathioprine or MMF may have increased susceptibility to SARS-CoV-2 infection and may be at risk for a more severe infection course based on their lymphocyte-depleting properties and observed risk of viral infections with these agents. The risk is likely higher in patients with severe leukopenia. Those patients may also have a reduced protective immune response against the future SARS-CoV-2 viral protein vaccine and would not qualify for the live-attenuated vaccine (Mycolphenolate, 2020). On the other hand, the oral route of administration of these agents is preferable over the intravenous route of other preventive therapies commonly used in NMOSD (e.g. rituximab, eculizumab) because of the decreased risk of exposure/contact at infusion centers or
with home-infusion personnel. Possible risk mitigation strategies: it is probably safe to maintain treatment in NMOSD patients who have been stable on azathioprine or MMF without significant total or selective leukopenia. The risk of relapse and subsequent hospitalization if treatment is interrupted likely outweighs the risk of maintaining immunsuppression during the pandemic. In addition, switching to a more selective immunotherapy like rituximab or eculizumab comes with the increased exposure risk at infusion centers, which is likely unnecessary in patients who have been stable on oral agents. However, patients maintained on azathioprine or MMF should practice strict social-distancing and avoidance measures. Although careful monitoring of the differential white cell count is recommended for those patients, the benefit of monitoring should be weighed against the exposure risk at the laboratory or outpatient office at the time of blood drawing especially in patients who have had stable blood counts for extended time. Since treatment-associated leukopenia is dose-related with both agents, treatment should be interrupted or the dose reduced in patients with severe leukopenia (MycoPhenolate, 2020). When the future SARS-CoV-2 viral protein vaccine becomes available, patients should be aware of the possibility of reduced vaccine efficacy and the probable need for serological confirmation of effective immunity after vaccination. Stopping azathioprine or MMF should be considered in NMOSD patients who develop severe symptomatic COVID-19 infection after consulting with infectious disease specialists. Treatment can be resumed after resolution of respiratory symptoms and clinical recovery. Although there is no real-life evidence that patients on azathioprine or MMF will have a more severe COVID-19 infection, the data from MERS-CoV animal models are concerning and support stopping MMF during the infection. On the other hand, clinicians should also consider the risk of a higher dysregulated immune response against the virus and/or rebound NMOSD activity after stopping immunosuppression. Therefore, consultation with infectious disease specialists and immunologists is advisable in this situation. Careful patient monitoring, perhaps in a hospital setting, may be needed after stopping those agents in COVID-19 patients. It is probably safer to avoid starting newly-diagnosed NMOSD patients on azathioprine or MMF during the pandemic given the availability of more selective immunotherapies with potentially less negative effect on the susceptibility to SARS-CoV-2 and the efficacy of its future vaccine.

1.5. Rituximab

Rituximab is one of the most commonly used off-label preventive therapies in NMOSD. Its efficacy is based on several retrospective and open-label studies (Kimbrough et al., 2012; Mealy et al., 2014). It has also shown superiority to azathioprine in a recent open-label prospective study as mentioned earlier (Nikoo et al., 2017). Mechanism of action: rituximab is a monoclonal antibody (MAB) against CD20-positive B-cells which include pre B-cell, immature B-cell, and memory B-cell lineage but not plasmablasts or plasma cells. Its exact MOA in NMOSD is unknown but is hypothesized to involve reduction of pathogenic antibody production, dampening of pro-inflammatory cytokines, and decreasing B-cell-dependent antigen presentation to T-cells (Bennett et al., 2015).

Impact on the immune system: rituximab causes prolonged selective depletion of CD20-positive B-cells within two weeks of infusion that usually lasts for an average of six months after proper dosing but can linger up to 3 years in some patients (Cohen et al., 2006; Rituximab, 2020). Late onset neutropenia can occasionally occur with rituximab (Tesfa et al., 2011). Hypogammaglobulinemia with low IgG and IgM levels can also occur and can lead to recurrent infections (Barmettler et al., 2018). The frequency of rituximab-associated hypogammaglobulinemia varies across studies with a range of 5%–56% (Cohen et al., 2006; Roberts et al., 2015). Rituximab decreases the humoral response to inactivated and viral protein vaccines and this effect seems to be dependent on the timing in relation to rituximab infusion (van Assen et al., 2010). A weaker humoral response occurs when the vaccine is given soon after the infusion during maximum B-cell depletion (van Assen et al., 2010; Friedman, 2017). Vaccines that trigger a predominantly T-cell dependent immune response (e.g. tetanus toxoid) are less impacted by rituximab. Live-attenuated vaccines are contraindicated during rituximab therapy (Rituximab, 2020).

Infectious side effects: rituximab can cause reactivation of hepatitis-B virus leading to fulminant liver failure. According to the rituximab prescribing information, in placebo-controlled rheumatoid arthritis (RA) studies, the infection rate in patients receiving rituximab was only slightly higher than placebo (39% versus 34%) including serious infections (2% versus 1%). The most common infections seen with rituximab were upper respiratory tract viral infections (URTIs), nasopharyngitis, and bronchitis. The most common serious infections were pneumonia and sepsis including rare fatal cases.

Potential relevance to the COVID-19 pandemic: it is unknown if rituximab increases the susceptibility to SARS-CoV-2 or if it predisposes to a more severe infection. Since the early immune response against the SARS-CoV-2 virus is predominantly T-cell dependent, it is possible that rituximab has little impact on infection susceptibility. However, rituximab affects T-cells indirectly by reducing B-cell dependent antigen presentation, potentially interfering with the early immune response against the virus. The fact that upper and lower respiratory infections are common with rituximab is also concerning. Even more concerning are patients with rituximab-associated hypogammaglobulinemia who are susceptible to severe and recurrent infections (Barmettler et al., 2018; Roberts et al., 2015). Rituximab may potentially decrease the long-term antibody-mediated immunity via its action on B-cells, rendering patients possibly susceptible to repeated SARS-CoV-2 infections after initial recovery. More importantly, rituximab may decrease the efficacy of the future SARS-CoV-2 inactivated or viral protein vaccine especially if the vaccine relies on a predominantly humoral protective response. If a live-attenuated vaccine is developed, it will likely be contraindicated in patients receiving rituximab. The infrequent dosing of rituximab (typically two 1000 mg infusions two weeks apart repeated every six months or when CD19 cells replete) is favorable compared to agents that require more frequent infusions (eculizumab) but it is less suitable for home infusion due to long infusion hours and high rate of infusion reactions. The intravenous route of administration is less preferred than the oral or subcutaneous routes because of the increased exposure risk at infusion centers. Recent published expert opinions suggest that the risk of using anti-CD20 agents during the COVID-19 pandemic is low to moderate (Giovannoni, 2020; Giovannoni et al., 2020). Likewise, recent case series of MS and NMOSD patients treated with anti-CD20 agents (rituximab or eculizumab) also suggest limited risk for severe COVID-19 infection, although critical and fatal cases have happened in a subset of those patients (Hughes et al., 2020; Montero-Escribano et al., 2020). One case series demonstrated increased SARS-CoV-2 susceptibility in MS patients on anti-CD20 agents (Safavi et al., 2020).

Possible risk mitigation strategies: NMOSD patients who are already on rituximab should continue their treatment during the pandemic to avoid disease relapse and hospitalization. However, immunoglobulin levels should be checked and prophylactic replacement therapy with intravenous immunoglobulin (IVig) should be strongly considered if levels are low. Extending the interval between infusions (guided by CD19 counts) may be beneficial to reduce exposure risk at the infusion center but significant B-cell repletion should be avoided to prevent breakthrough disease activity. When the SARS-CoV-2 inactivated or viral protein vaccine becomes available, patients should be vaccinated towards the end of their treatment cycle and at least 4 weeks prior to their subsequent dose to reduce the negative impact on the humoral response to the vaccine. Checking post-vaccination serology to confirm the development of immunity against the vaccine is advisable. Patients on rituximab should practice caution against exposure and implement strict social distancing measures. For newly-diagnosed NMOSD patients, treatment should be interrupted or the dose reduced in patients with severe leukopenia.
patients, the benefits of rituximab therapy should be weighed against the risk of infection and the possibility of decreased future vaccination efficacy. The fact that rituximab causes prolonged immunosuppression that is not readily reversible in case of infection should be thoroughly considered. Non-depleting agents especially those given subcutaneously may be safer options for newly-diagnosed NMOSD patients during the pandemic. As in other severe infections and per the prescribing information (Rituximab, 2020), SARS-CoV-2-infected NMOSD patients should not be re-dosed with rituximab until they recover from COVID-19 although the risks of NMOSD rebound activity and a more severe hyperimmune response remain theoretical concerns with this approach.

1.6. Eculizumab

Eculizumab is the only Food and Drug Administration (FDA)-approved therapy for NMOSD with AQP4-IgG based on a recent randomized, double-blinded, placebo-controlled trial in which it showed robust efficacy as an add-on or monotherapy (Pittock et al., 2019). It significantly prolonged time-to-relapse and reduced ARR compared to placebo. It was not studied in anti-MOG or double-seronegative NMOSD.

Mechanism of action: eculizumab is a humanized MAB against C5 protein of the complement system preventing formation of the membrane attack complex, which is a major contributor to inflammation and astrocyte destruction in NMOSD.

Impact on the immune system: apart from its effect on the complement system, eculizumab has little impact on immunity otherwise. Leukopenia and lymphopenia are extremely rare with eculizumab each encountered in 5% of the patients during the seminal NMOSD clinical trial (Pittock et al., 2019; Eculizumab, 2020). Complement inhibitors have not been associated with hypogammaglobulinemia (Ashkar et al., 2020). Eculizumab does not affect the immune response to vaccines of any kind and patients on eculizumab have no vaccination restrictions (Vaccines, 2019).

Infectious side effects: complement inhibition increases the risk of infection with encapsulated bacteria especially Neisseria meningitides. Therefore, eculizumab has a boxed warning for serious meningococcal infections, and meningococcal vaccination is mandatory before starting treatment (Eculizumab, 2020). Many of the bacteria associated with pneumonia are encapsulated and it is possible that eculizumab increases the risk of bacterial pneumonia, as this was the most common serious adverse event in the eculizumab arm during the NMOSD clinical trial (Pittock et al., 2019). The single death that occurred during the trial was secondary to infectious pleural effusion in a patient with pre-existing lung disease in the active eculizumab arm. In a recent 9-year safety analysis of eculizumab in patients with paroxysmal nocturnal hemoglobinuria, pneumonia was the most common non-meningococcal infection reported in 11.8% of patients (Socié et al., 2019). In addition, common viral infections were seen more frequently in the eculizumab arm compared to the placebo arm in the NMOSD clinical trial including URTI (29%), nasopharyngitis (21%), influenza (11%), pharyngitis (10%), and bronchitis (9%) (Pittock et al., 2019; Eculizumab, 2020).

Potential relevance to the COVID-19 pandemic: it is unknown if eculizumab increases the susceptibility to SARS-CoV-2. The complement system does not seem to play a major role in the defense against the virus; (Prompetchara et al., 2020) however, it might be implicated in the hyperimmune response that contributes to severe lung injury. This concept is based on animal models of the related SARS-CoV-1 virus in which complement-deficient mice fared better than those with intact complement system after induced SARS-CoV-1 infection (Gralinski et al., 2018). This led to a scientific interest in the potential benefit of complement inhibition in SARS-CoV-2 infection. In fact, a clinical trial of eculizumab in COVID-19 patients is currently underway (Clinicaltrials, 2020). One concern is whether eculizumab will increase the risk of secondary bacterial pneumonia that can happen on top of SARS-CoV-2 infection (Li et al., 2020). The route of administration of eculizumab (2-weekly IV infusion) is not ideal during the COVID-19 pandemic due to the increased exposure risk at infusion centers. However, unlike rituximab, eculizumab infusion is usually short and infusion reactions are rare making it more suitable for home infusion. This, however, does not eliminate the risk of exposure related to home infusion personnel. In terms of future SARS-CoV-2 vaccine, eculizumab is not expected to impact the efficacy of the vaccine and is preferred over B-cell therapies (e.g. rituximab and inebilizumab) from the vaccination standpoint (Vaccines, 2019). It is also likely safe to administer live-attenuated or viral vector vaccines in patients receiving eculizumab (Vaccines, 2019). The Advisory Committee on Immunization Practices lists no vaccine contraindications in complement-deficient patients or in those taking eculizumab (Vaccines, 2019).

Possible risk mitigation strategies: NMOSD patients who are already on eculizumab should continue their treatment to avoid disease activation. Patients should receive their infusions at home as much as possible to minimize exposure risk. It is unclear if SARS-CoV-2 infected patients should continue eculizumab but it is likely safe (and possibly beneficial) to continue treatment while carefully watching for evidence of secondary bacterial infection. Prophylactic antibiotics and/or pneumococcal vaccine administration are strategies worth considering in this situation especially in severely ill patients. For newly-diagnosed NMOSD patients during the pandemic, the risk of SARS-CoV-2 exposure secondary to frequent infusions should be weighed against the relative favorable impact of eculizumab on the immune system and future vaccination. A new C5 inhibitor with a longer duration of action (raluzumab) is currently being tested in NMOSD as a monthly infusion (An Efficacy, 2019). A subcutaneous formulation is also being tested.

1.7. Inebilizumab

Inebilizumab has recently shown efficacy in a randomized double-blinded, placebo-controlled clinical trial. The trial tested inebilizumab as a monotherapy in NMOSD patients with or without AQP4-IgG (Cree et al., 2019). It achieved the primary outcome of delaying the onset of first per-protocol relapse compared to placebo. It also achieved the secondary outcome of decreasing disability worsening compared to placebo. Subgroup analysis showed that efficacy was mainly achieved in AQP4-IgG-positive patients. There was not enough data to determine efficacy in patients without AQP4-IgG. FDA-approval is expected in the near future.

Mechanism of action: inebilizumab is a humanized MAB against CD19-positive B-cells which include pre-B cell, immature B-cell, memory B-cell, and plasmablasts. Inebilizumab produces selective depletion of CD19-positive B-cells therefore reducing production of the pathogenic antibody and dampening B-cell-dependent T-cell activation and inflammatory cytokines production.

Impact on the immune system: in addition to selective B-cell lymphopenia, rare cases of neutropenia and leukopenia have been reported in B-cell lymphoma patients treated experimentally with inebilizumab (Ohmachi et al., 2019). A 15% reduction in immunoglobulin levels (all types) was observed in inebilizumab-treated MS patients in a phase-1 clinical trial but the total immunoglobulin level did not fall below the normal range (Agius et al., 2019) No leukopenia, neutropenia, or hypogammaglobulinemia were reported with inebilizumab in the NMOSD clinical trial. There was also no reduction of anti-tetanus toxoid antibody in inebilizumab-treated patients.

Infectious side effects: all respiratory infections in the NMOSD clinical trial were not statistically or numerically higher in the inebilizumab arm compared to the placebo arm except for one case of atypical pneumonia in the inebilizumab arm. No other cases of bacterial pneumonia occurred with inebilizumab. The most frequent respiratory infections in the inebilizumab arm included nasopharyngitis (7%), URTI (3%), influenza (2%), influenza-like illness (1.5%), and bronchitis (1.5%). Similar benign infectious side effect profile was also seen in phase-1 clinical trials of inebilizumab in MS and systemic sclerosis.
However, the overall patient-year experience with inebilizumab across all studies is low and more experience is needed to elucidate its full spectrum of infectious and immunological side effects.

Potential relevance to the COVID-19 pandemic: It is unknown if inebilizumab increases the susceptibility to SARS-CoV-2 or if it predisposes to a more severe infection. The overall benign infectious side effect profile of this agent is encouraging. B-cell lymphopenia may impact T-cell activation which is involved in the early immune response against SARS-CoV-2 but more importantly may influence antibody-mediated long-term immunity against the virus potentially increasing reinfection risk similar to rituximab. Although inebilizumab did not reduce the antibody response to tetanus toxoid in the NMOSD clinical trial, its impact on the humoral response to inactivated or viral protein vaccines is unknown. Based on rituximab studies, it is possible that inebilizumab may impact efficacy of viral protein vaccines including future SARS-CoV-2 vaccine when it becomes available. If a live-attenuated vaccine is developed, it will likely be contraindicated with inebilizumab. The intravenous mode of administration is less favorable than the oral or subcutaneous routes because of the exposure risk at infusion centers. However, the frequency of dosing (second infusion two weeks after the initial dose then 6-monthly infusions afterwards) is favorable compared to eculizumab although home infusion is less feasible with inebilizumab.

Possible risk mitigation strategies: NMOSD patients who are currently receiving inebilizumab in a clinical trial setting should continue treatment to avoid disease relapse and need for hospitalization. Monitoring blood counts and immunoglobulin levels should be considered if not part of the clinical trial protocol. Prophylactic IV Ig replacement therapy may be considered in patients with hypogammaglobulinemia as in rituximab patients. Like any other serious infections, patients who develop severe COVID-19 infection while on inebilizumab should not be redosed with the medication until their infection clears as per the prescribing information of other B-cell therapies. Rituximab, 2020 When the future SARS-CoV-2 vaccine becomes available, vaccination should be spaced out from infusions similar to rituximab, and serological confirmation of vaccine efficacy is advisable post-vaccination. If inebilizumab becomes commercially available during the pandemic, starting newly diagnosed NMOSD patients on this medication should be considered with caution. The use of non-lymphocyte-depleting agents with less immunosuppressive effect and less potential impact on future vaccine efficacy may be a safer option during the pandemic. A subcutaneous formulation of inebilizumab is currently under study and may be a safer option from the exposure risk standpoint.

1.8. Satralizumab

Satralizumab has recently shown efficacy in a randomized double-blind placebo-controlled clinical trial in which it was used as an add-on therapy to existing immunosuppressants in NMOSD patients with or without AQP4-IgG (Yamamura et al., 2019). It achieved the primary outcome of delaying the onset of first per-protocol relapse compared to placebo. Subgroup analysis showed that the efficacy was notable mainly in AQP4-IgG-positive patients. In a separate clinical trial, satralizumab has also shown efficacy as monotherapy in NMOSD and the results have been recently published (Traboulsee et al., 2020). FDA approval is expected in the near future.

Mechanism of action: satralizumab is a humanized MAB against IL-6 receptor preventing IL-6 pro-inflammatory signaling pathway, which promotes T-cell activation and maturation of B-cells into antibody-producing plasmablasts and plasma cells. Satralizumab has a longer duration of action than the prototype IL-6 inhibitor tocilizumab (Yamamura et al., 2019).

Impact on the immune system: leukopenia occurred in 14.6% of patients receiving satralizumab in the NMOSD clinical trial. There was no report of selective lymphopenia or hypogammaglobulinemia. Tocilizumab has been associated with neutropenia in RA trials (Emery et al., 2019). It can also lead to a reduction of memory B-cells and immunoglobulin levels (Roll et al., 2011). Total lymphopenia and pancytopenia have been reported with tocilizumab as well (Le Stradic et al., 2014; Klein et al., 2019). IL-6 inhibition is believed to be a key step in the reduction of cytokine storm and secondary HLH. The exact impact of IL-6 inhibition on the humoral response to inactivated or viral protein vaccines is unknown but in one study, tocilizumab did not impact the response to the influenza vaccine in 111 RA patients (Mori et al., 2012).

Infectious side effects: The overall infection rate in the satralizumab arm in the NMOSD clinical trial was 68% compared to 62% in the placebo arm. Serious infections were reported in 5% of patients in the satralizumab arm compared to 7% in the placebo arm. Nasopharyngitis (24.4%) and URTI (24.4%) were the most common infections in the satralizumab arm occurring more frequently than placebo. Pneumonia rates during the trial were not published but pneumonia was the most common infection in tocilizumab RA trials (Nishimoto et al., 2009). Opportunistic infections especially mycobacterial infections including tuberculosis have been reported with tocilizumab as well (Schif et al., 2011).

Potential relevance to the COVID-19 pandemic: it is unknown if satralizumab increases the susceptibility to SARS-CoV-2. The fact that there was a slight increase in the rates of URTIs in the satralizumab arm compared to placebo suggests increased susceptibility to respiratory viral infections. From the MOA standpoint, IL-6 is involved in the activation of T-cells; therefore, IL-6 inhibition may affect the early immune response against the virus. More importantly, IL-6 inhibitors may increase the risk of secondary bacterial infection in COVID-19 patients based on the rates of bacterial pneumonia in tocilizumab-treated patients. On the other hand, IL-6 inhibition could have a beneficial effect in COVID-19 infection by decreasing cytokine storm and secondary HLH. Several clinical trials are currently testing the utility of tocilizumab in COVID-19 infected patients (Chinese Clinical Trial Registry, 2020). The route of administration of satralizumab (monthly subcutaneous injection) is favorable compared to intravenously-administered agents like rituximab, inebilizumab and eculizumab owing to the reduced exposure risk at infusion centers or home infusion settings. The impact of satralizumab on the future SARS-CoV-2 inactivated or viral protein vaccine is unknown but the data from the tocilizumab influenza vaccine study is encouraging. Live-attenuated vaccines are generally not recommended in patients receiving IL-6 inhibitors (Tanrıöver et al., 2016).

Possible risk mitigation strategies: NMOSD patients who are currently on satralizumab within a clinical trial should continue treatment. It is likely safe (and possibly beneficial) to continue treatment in SARS-CoV-2 infected NMOSD patients based on the potentially beneficial effect of IL-6 inhibition on the associated cytokine storm. Antibacterial prophylaxis against common and opportunistic pathogens may be considered in this setting to reduce the chances of secondary bacterial infection. When satralizumab becomes commercially available in the near future, it could be preferred over B-cell based therapies for newly diagnosed NMOSD patients during the pandemic. This is due to its safe route of administration, limited immunosuppressive effect, potential benefit in infected patients, and the fact that it is less likely to decrease the humoral response to the future SARS-CoV-2 vaccine. Compared to eculizumab, satralizumab has a safer route of administration but eculizumab has a more well-defined safety in terms of its potential impact on the future SARS-CoV-2 vaccine response and compatibility with live-attenuated vaccines.

1.9. Other NMOSD therapeutics

Unlike MS, NMOSD attacks are usually severe and relapse management can change the neurological outcome (Abboud et al., 2016; Kleiter et al., 2016). Therefore, NMOSD patients who experience...
| Agent          | Mechanism of action                      | Other possible impact on the immune system | Route and frequency of maintenance dose | Possible impact on future SARS-CoV-2 vaccine | Possible impact on ongoing treatment during the COVID-19 pandemic | Starting new treatment during the COVID-19 pandemic | Interruption of treatment in COVID-19 infected patients | Other risk mitigation strategies |
|----------------|------------------------------------------|-------------------------------------------|----------------------------------------|----------------------------------------------|---------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|----------------------------------|
| Azathioprine   | Non-selective lymphocyte depletion       | Leukopenia, neutropenia, pancytopenia     | Usually twice daily oral dosing         | Yes, likely increased                        | No, unlikely                                                  | No but consider in patients with severe leukopenia | Not recommended                      | Yes, recommended in symptomatic patients | Dose reduction should be considered in patients with mild to moderate leukopenia |
| MMF           |                                          |                                            |                                        |                                              |                                                               |                                                        |                                                  |                                  |                                  |
| Rituximab     | Selective CD20-positive B-cell depletion | Possible neutropenia, hypogammaglobulinemia | Two intravenous doses two weeks apart repeated every 6 months or upon CD19 cell depletion | Yes, possibly increased                     | No, unlikely                                                  | Yes, decreased humoral response to inactivated vaccine, Live vaccine contraindicated | No                                             | Less preferred than eculizumab and satralizumab | Consider replacement IVIg in patients with hypogammaglobulinemia. Consider spacing out infusions. |
| Eculizumab    | CS complement inhibitor                   | Rare leukopenia and lymphopenia           | Intravenous infusion every two weeks    | No, unlikely to have an impact              | Yes, possible benefit                                         | No                                              | No                                              | Yes                              | Home infusion preferred over infusion centers to decrease exposure risk. Consider antibacterial prophylaxis in COVID-19 infected patients |
| Inebilizumab* | Selective C19-positive B-cell depletion   | Possible neutropenia, hypogammaglobulinemia | One dose of intravenous infusion every 6 months | Yes, possibly increased                     | No, unlikely                                                  | Possible decreased humoral response to inactivated vaccine, Live vaccine contraindicated | No                                             | Less preferred than eculizumab and satralizumab | Consider replacement IVIg in patients with hypogammaglobulinemia. Consider spacing out infusions. |
| Satralizumab** | IL-6 inhibitor                           | Possible rare leukopenia, lymphopenia, neutropenia, and hypogammaglobulinemia | Monthly subcutaneous injection          | Yes, possibly increased                     | Yes, possible benefit                                         | No                                              | No                                              | Yes                              | Consider antibacterial prophylaxis in COVID-19 infected patients |

* Some of the information under inebilizumab are based on data from other B-cell based therapies.

** Some of the information under satralizumab are based on data from other interleukin-6 inhibitors. MMF: mycophenolate mofetil, CD: cluster of differentiation, IVIg: intravenous immunoglobulins, IL-6: interleukin 6.
attacks during the COVID-19 pandemic should receive treatment for their acute relapse. The current standard of care is using high dose corticosteroids often combined with PLEX (Abboud et al., 2016; Kleiter et al., 2016). Corticosteroids suppress T-cells (Davis et al., 2013) and may interfere with the early immune response against SARS-CoV-2. Their use is also not recommended in COVID-19 infected patients as they may delay viral clearance and predispose to secondary bacterial infections (Clinical, 2019). The main value of corticosteroids during the COVID-19 pandemic comes from the feasibility of treating relapses at home with oral prednisone at an equivalent dose to standard in-hospitalization-related exposure risk. However, this is only suitable for mild infections (Clinical, 2019). The main value of corticosteroids during the COVID-19 pandemic comes from the feasibility of treating relapses at home with oral prednisone at an equivalent dose to standard hospitalizations. Although COVID-19 data from MS patients on various immunotherapies are relatively reassuring (Sormani, 2020), altering the common therapeutic approach to NMOSD during the pandemic may be necessary to balance both efficacy and safety of treatment. Although the use of cell-depleting immunosuppressants has been the standard of care for decades, the use of more selective immunomodulating agents during the pandemic may be safer to reduce infection-related risks. Selective depletion of B-cells (rituximab and inebilizumab) may be safer than non-selective immunosuppression (azathioprine and MMF) but may negatively impact the response to the future SARS-CoV-2 infection. IVIg is not routinely used for the acute or long-term management of NMOSD with AQP4-IgG. However, early data suggest that IVIg may have some value as a preventive therapy in patients with anti-MOG disease (Hacohen et al., 2018) and it may be a preferred option for those patients during the COVID-19 pandemic given its anti-viral and immune-boosting properties.

### 2. Discussion and conclusion

The emergence of several new NMOSD therapeutics concurrently with the worldwide spread of the novel COVID-19 global pandemic call for careful therapeutic planning and add to the complexity of NMOSD management. Although COVID-19 data from MS patients on various immunotherapies are relatively reassuring (Sormani, 2020), altering the common therapeutic approach to NMOSD during the pandemic may be necessary to balance both efficacy and safety of treatment. Although the use of cell-depleting immunosuppressants has been the standard of care for decades, the use of more selective immunomodulating agents during the pandemic may be safer to reduce infection-related risks. Selective depletion of B-cells (rituximab and inebilizumab) may be safer than non-selective immunosuppression (azathioprine and MMF) but may negatively impact the response to the future SARS-CoV-2 infection. IVIg is not routinely used for the acute or long-term management of NMOSD with AQP4-IgG. However, early data suggest that IVIg may have some value as a preventive therapy in patients with anti-MOG disease (Hacohen et al., 2018) and it may be a preferred option for those patients during the COVID-19 pandemic given its anti-viral and immune-boosting properties.
on the same treatment but risk mitigation strategies should be considered as appropriate (e.g. dose reduction for iatrogenic leukopenia, IVIg replacement therapy for iatrogenic hypogammaglobulinemia, spacing-out infusions, etc.). Considerations for acute relapse management during the pandemic include oral corticosteroids at home for mild relapses and PLEX monotherapy for severe relapses. Avoiding high dose corticosteroids in the inpatient setting should be considered especially in elderly patients with multiple comorbidities or who have COVID-19 infection. The therapeutic approach to NMOSD during the COVID-19 pandemic should continue to emphasize the importance of initiating preventive therapy in newly diagnosed patients, continuation of ongoing safe therapy, and timely treatment of relapses. Table 1 summarizes the relevant considerations for each NMOSD therapeutic to the COVID-19 pandemic. Table 2 compares the advantages and disadvantages of each therapeutic agent in relation to COVID-19.

Appendix

| Name           | Location                                      | Role                  | Contribution                                                                 |
|----------------|-----------------------------------------------|-----------------------|------------------------------------------------------------------------------|
| Hesham Abboud, MD, PhD | Case Western Reserve University, University Hospitals of Cleveland | First author          | Review concept and design, Literature search, writing the first draft, accepts responsibility and final approval of the manuscript |
| Crystal Zheng   | University Hospitals of Cleveland             | Co-author             | Literature search, review and critique                                       |
| Indrani Kar, PharmD | University Hospitals of Cleveland             | Co-author             | Literature search, review and critique                                       |
| Claire Koert, PharmD | University Hospitals of Cleveland             | Co-author             | Literature search, review and critique                                       |
| Crystal Sau, PharmD | University Hospitals of Cleveland             | Co-author             | Literature search, review and critique                                       |
| Alessandro Serra, MD, PhD | Case Western Reserve University, University Hospitals of Cleveland, and Cleveland VA Hospital | Review concept and design, Literature search, writing the first draft, accepts responsibility and final approval of the manuscript |

Funding
None for this review.

Declaration of Competing Interest
Dr. Abboud is a consultant for Biogen, Genentech, Sanofi-Genzyme, Celgene, Alexion, and Viela Bio. He receives research support from Novartis and Genentech. Dr. Serra is a consultant for Biogen and is supported in part by Career Development Award #K23RX001180 from the U.S. Department of Veterans Affairs, Rehabilitation Research and Development Service.

References

https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html#ref-43 accessed 4/16/2020.
Clinicaltrials.gov. accessed April 16, 2020.
Eculizumab (Soliris) in Covid-19 Infected Patients (SOLID-C19), 2014. Clinicaltrials.gov, accessed April 15, 2020.
Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected2019.
An Efficacy and Safety Study of Ravalizumab in Adult Participants With NMOSD, 2019. Clinicaltrials.gov/ accessed 4/19/2020.
Eculizumab prescribing information 2020.
Rituximab prescribing information2020.
Mycopeponone motifref prescribing information 2020. https://www.cdc.gov/coronavirus/2019-ncov/faq.html. Accessed April 15, 2020.
Abboud, H., Petruk, A., Mealy, M., Sadidharan, S., Siddique, L., Levy, M., 2016. Treatment of acute relapses in neuromyelitis optica: steroids alone versus steroids plus plasma exchange. Mult. Scler. 22 (2), 185–192.
Agius, M.A., Kowolskudua, G., Maciejowski, M., et al., 2019. Safety and tolerability of inebilizumab (MEDI-551), an anti-CD19 monoclonal antibody, in patients with relapsing forms of multiple sclerosis: results from a phase 1 randomised, placebo-controlled, escalating intravenous and subcutaneous dose study. Mult. Scler. 25 (2), 235–245. https://doi.org/10.1177/1352458519764819.
Alashkar, F., Rottinghaus, S., Vance, C., et al., 2020. No evidence for hypogammaglobulinemia in patients with paroxysmal nocturnal hemoglobinuria (PNH) chronically treated with ravalizumab. PloS One 15 (3), e0230869. https://doi.org/10.1371/journal.pone.0230869. Published 2020 Mar 27.
Araki, M., Matsuoka, T., Miyamoto, K., et al., 2014. Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: a pilot study. Neurology 82 (15), 1302–1306. https://doi.org/10.1212/WNL.0000000000000317.
Barnett, S., Ong, M.S., Farmer, J.R., Choi, H., Walter, J., 2018. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. JAMA Neurol. Open 1 (7), e184169. https://doi.org/10.1001/jamaneurol.2018.4169. Published 2018 Nov 2.
Bennett, J.L., O’Connor, K.C., Bar-Or, A., et al., 2015. B lymphocytes in neuromyelitis optica. Neurology 75 (4), 478–487. https://doi.org/10.1212/WNL.0000000000002173.
Brilot, T.J., Jacob, A., Matiello, M., et al., 2009. Treatment of neuromyelitis optica with ocrelizumab - a pharmacovigilance case series [published online ahead of print, 2020 May 18]. Cell. https://doi.org/10.1016/j.cell.2020.05.025.

Chinese Clinical Trial Registry. A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19),Feb 13, 2020. http://www.chictr.org.cn/.
Cohen, S.B., Emery, P., Greenwald, M.W., et al., 2006. for the REFLEX Trial Group. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind,placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 54 (9), 2793–2806.
Costanz, C., Maiolo, M., et al., 2011. Azathioprine: tolerability, efficacy, and predictors of benefit in neuromyelitis optica. Neurology 77 (7), 659–666.
Cree, B.A.C., Bennett, J.L., Kim, H.J., et al., 2019. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet 394 (10206), 1352–1363. https://doi.org/10.1016/S0140-6736(19)31817-3.
Davis, T.E., Kee-Toh, K., Szanto, A., et al., 2013. Glucocorticoids suppress T cell function by upregulating microRNA 98. Arthritis Rheum. 65 (7), 1882–1890.
Emery, P., Rondon, J., Parrino, J., et al., 2019. Safety and tolerability of subcutaneous satirumab and intravenous tocilizumab in patients with rheumatoid arthritis. Rheumatology (Oxford) 58 (5), 849–858. https://doi.org/10.1093/rheumatology/key361.
Friedman, M.A., Winthrop, K.L., 2017. Vaccines and disease-modifying antirheumatic drugs: practical implications for the rheumatologist. Rheum. Dis. Clin. North Am. 43 (1), 1–13. https://doi.org/10.1016/j.rdc.2016.09.003.
Giovannoni, G., 2020. Anti-CD20 immuno suppressive disease-modifying therapies and COVID-19 [published online ahead of print, 2020 Apr 18]. Mult. Scler. Relat. Disord. 41, 102135. https://doi.org/10.1016/j.msard.2020.102135.
Giovannoni, G., Hawkes, C., Leecher-Scott, J., Levy, M., Waubant, E., Gold, J., 2020. The COVID-19 pandemic and the use of MS disease-modifying therapies. Mult. Scler. Relat. Disord. 39, 102073. https://doi.org/10.1016/j.msard.2020.102073.
Gralinski, L.E., Sheahan, T.P., Morrison, T.E., et al., 2018. Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis. mBio 9 (5). https://doi.org/10.1128/mBio.01753-18. e01753-18Published 2018 Oct 9.
Hacohen, Y., Wong, Y.Y., Lechner, C., et al., 2018. Disease course and treatment responses in children with relapsing myelin oligodendrocyte glycoprotein antibody–associated disease. JAMA Neurol. 75 (4), 478–487. https://doi.org/10.1001/jamaneurol.2017.4601.
Huang, C., Wang, Y., Li, X., et al., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China. Lancet 395, 497–506.
Hughes, R., Pedotti, R., Koedgen, H., 2020. COVID-19 in persons with multiple sclerosis treated with ocrelizumab - a pharmacovigilance case series [published online ahead of print, 2020 May 16]. Mult. Scler. Relat. Disord. https://doi.org/10.1016/j.msard.2020.102192. 102192.
Jacob, A., Maiolo, M., et al., 2009. Treatment of neuromyelitis optica with...
mycophenolate mofetil: retrospective analysis of 24 patients. Arch. Neurol. 66 (9), 1128–1133.

Jiao, Y., Fryer, J.P., Lennon, V.A., et al., 2013. Updated estimate of AQP4-IgG seroreactivity and disability outcome in neuromyelitis optica. Neurology 81 (14), 1197–1204. https://doi.org/10.1212/WNL.0b013e31829ac5bc.

Kimbrough, D.J., Fujihara, K., Jacob, A., et al., 2012. Treatment of neuromyelitis optica: review and recommendations. Mult. Scler. Relat. Disord. 1 (4), 180–187. https://doi.org/10.1016/j.msard.2012.06.002.

Klein, A., Klotsche, J., Hügle, B., et al., 2019. Long-term surveillance of biologic therapies in systemic-onset juvenile idiopathic arthritis: data from the German BIKER registry [published online ahead of print, 2019 Dec 17]. Rheumatology (Oxford) kez577. https://doi.org/10.1093/rheumatology/kez577.

Kleiter, I., Gahlen, A., Boeck, N., et al., 2016. Neuromyelitis optica: evaluation of 871 attacks and 1,153 treatment courses. Ann. Neurol. 79 (2), 206–216. https://doi.org/10.1002/ana.24554.

Kumara, B.L., Chhoudary, R., Sharma, C.M., Jain, D., Häremath, A., 2019. Plasma exchange as a first line therapy in acute attacks of neuromyelitis optica spectrum disorders. Ann. Indian Acad. Neurol. 22 (4), 389–394. https://doi.org/10.4103/ain. AIAN.365.19.

Le Stradic, C., Galeotti, C., Koné-Paut, I., 2014. Traitement par tocilizumab : expérience d’un centre de rhumatologie pédiatrique [Tocilizumab experience in a French rheumatological pediatric center]. Arch. Pediatr. 21 (12), 1299–1304. https://doi.org/10.1016/j.arcped.2014.08.018.

Lee, H.S., Moon, J., Shin, H.R., et al., 2019. Pneumonia in hospitalized neurologic patients: trends in pathogen distribution and antibiotic susceptibility. Antimicrob. Resist. Infect Control 8, 25. https://doi.org/10.1186/s13756-019-0475-9. Published 2019 Feb 1.

Lennon, V.A., Wingerchuk, D.M., Kryzer, T.J., et al., 2004. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 364, 2106–2112.

Li, X., Wang, L., Yan, S., et al., 2020. Clinical characteristics of 25 death cases with COVID-19: a retrospective review of medical records in a single medical center, Wuhan, China [published online ahead of print, 2020 Apr 3]. Int. J. Infect. Dis. https://doi.org/10.1016/j.ijid.2020.03.053.

Ma, J., Xia, P., Zhou, Y., et al., 2020. Potential effect of blood purification therapy in reducing cytokine storm as a late complication of critically ill COVID-19 [published online ahead of print, 2020 Apr 30]. Clin. Immunol. 214, 108408. https://doi.org/10.1016/j.clim.2020.108408.

Mealy, M.A., Wingerchuk, D.M., Palace, J., Greenberg, B.M., Levy, M., 2014. Comparison of relapse and treatment failure rates among patients with neuromyelitis optica: multicenter study of treatment efficacy. JAMA Neurol. 71 (3), 324–330. https://doi.org/10.1001/jamaneurol.2013.5699.

Mehta, P., McAuley, D.F., Brown, M., et al., 2020. COVID-19: consider cytokine storm syndromes and immunosuppression [published online ahead of print, 2020 Mar 16]. Lancet 394 (10163), 1033–1042. https://doi.org/10.1016/S0140-6736(20)30628-0.

Montero-Escobar, P., Matias-Guiu, J., Gómez-Iglesias, P., Porta-Buttassam, J., Pytel, V., Matias-Guiu, J.A., 2020. Anti-CID20 and COVID-19 in multiple sclerosis and related disorders: a case series of 60 patients from Madrid, Spain [published online ahead of print, 2020 Mar 30]. Lancet Neurol. https://doi.org/10.1016/S1474-4422(20)30147-2.

Tang, F., Kream, R.M., Stefano, G.B., 2020. An evidence based perspective on mRNA-vaccines and COVID-19. Eur. J. Intern. Med. 78, 102185. https://doi.org/10.1016/j.ejim.2020.102185.

Thanh Le, T., Andreadakis, Z., Kumar, A., et al., 2020. The COVID-19 vaccine development landscape [published online ahead of print, 2020 Apr 9]. Nat. Rev. Drug Discov. https://doi.org/10.1038/s41573-020-00073-5.

Traboulsee, A., Greenberg, B.M., Bennett, J.L., et al., 2020. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. Lancet Neurol. 19 (5), 402–412. https://doi.org/10.1016/S1474-4422(20)30078-8.

Wang, F., Terenghi, G., Bencze, C.A., 2010. et al: Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. Arthritis Rheum. 62, 75–81.

Wang, F., Kream, R.M., Stefano, G.B., 2020. An evidence based perspective on mRNA–SARS-CoV-2 vaccine development. Med. Sci. Monit. 26, e924700. https://doi.org/10.12659/MSM.924700. Published 2020 May 5.

Wingerchuk, D.M., Banwell, B., Bennett, J.L., et al., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85 (2), 177–189. https://doi.org/10.1212/WNL.0000000000001729.

Wingerchuk, D.M., Hogancamp, W.F., O’Brien, P.C., Weinshenker, B.G., 1999. The clinical course of neuromyelitis optica (Devic’s syndrome). Neurology 53 (5), 1107–1114. https://doi.org/10.1212/WNL.53.5.1107.

Yamamura, T., Kleiter, I., Fujihara, K., et al., 2019. Trial of satralizumab in neuromyelitis optica spectrum disorder. N. Engl. J. Med. 381 (22), 2114–2124. https://doi.org/10.1056/NEJMoa1901747.

Yu, J., Tostanoski, L.H., Peter, L., et al., 2020. DNA vaccine protection against SARS-CoV-2 in chimeras [published online ahead of print, 2020 May 20]. Science. ecabe284. https://doi.org/10.1126/science.abc284.

Yucesan, C., Arslan, O., Arat, M., et al., 2007. Therapeutic plasma exchange in the treatment of neuromyelitis optica disorders: review of 50 cases. Transfus. Apher. Sci. 36 (1), 103–107. https://doi.org/10.1016/j.transci.2006.06.008.

Zhao, J., Yuan, Q., Wang, H., Liu, W., Liao, X., Su, Y., Wang, X., Yuan, J., Li, T., Li, J., Qian, S., Hong, C., Wang, F., Liu, Y., Wang, Z., He, Q., Li, Z., He, B., Zhang, T., Fu, Y., Ge, S., Liu, X., Zhang, J., Xia, N., Zhang, Z., 2019. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease. Clin. Infect. Dis. ciaa344. https://doi.org/10.1093/cia/ciaa344.