Vaccination in neuromyelitis optica spectrum disorders: Friend or enemy?

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**ABSTRACT**

Neuromyelitis optica spectrum disorders (NMOSDs) are uncommon antibody-mediated autoimmune diseases of the central nervous system (CNS), mainly occurring in optic nerves and spinal cord, which can cause visual impairment, paralysis, and occasionally bulbar dysfunction. Such neurological deficits can adversely affect pulmonary functions and increase complicated infection risk. Besides, most NMOSD patients undergo immunosuppressive therapy. All these factors make NMOSD patients the potential high-risk group under the current pandemic of coronavirus disease 2019 (COVID-19). Meanwhile, COVID-19 infection has already been demonstrated as a risk factor for NMOSD relapses. This review discusses the basic immunology of vaccination and common problems, including immunogenicity, safety, and efficacy of vaccination on NMOSD patients. Additionally, we offered vaccination recommendations, health care and treatment advice for NMOSD patients under the background of COVID-19.

### 1. Introduction

Currently, the pandemic of COVID-19 has impacted our lives in every aspect. Meanwhile, with preventive medicine development, vaccine hesitancy has gradually increased and become an emerging clinical problem (MacDonald and Hesitancy, 2015). Although healthy individuals can be infected, certain groups are at a higher risk of developing complications from severe infections, particularly those with impaired coughing or pulmonary function caused by chronic disabling neurological conditions and those receiving immunosuppressive therapy (Abboud et al., 2020).

NMOSDs are uncommon antibody-mediated autoimmune diseases of CNS, mainly occurring in optic nerves and spinal cord (Lucchetti et al., 2014). NMOSD frequency is generally similar worldwide, and its reported prevalence ranges broadly across different researches between 0.5 and 10 per 100,000 (Asgari et al., 2011) (Flanagan et al., 2016) (Mealy et al., 2012) (Cabrera-Gómez et al., 2009). There is an apparent female predilection like other autoimmune disorders. In the most recurrent forms of disease (80%–90%), the overall ratio of female patients is 5 to 10:1 (Sellner et al., 2010). The core symptoms of NMOSD are usually recurrent optic neuritis and longitudinally extensive transverse myelitis. NMOSD is distinguished from demyelinating CNS diseases by the existence of aquaporin 4-immunoglobulin G (AQP4-IgG), a serologic antibody against AQP4 (Patterson and Goglin, 2017). According to previous statistics, approximately 20% of NMOSD patients are serologically negative for AQP4-IgG and have antibodies against myelin oligodendrocyte glycoprotein (MOG) or no recognizable antibodies (Jiao et al., 2013) (Uzawa et al., 2014). A cohort study demonstrates a slightly elevated proportion of patients with AQP4-IgG among Asians with idiopathic demyelinating CNS disorders than whites (Uzawa et al., 2014). Since NMOSD usually tends to first attack optic nerves, spinal cord, and brainstem, it can directly cause visual impairment, paralysis, and even bulbar dysfunction (Wingerchuk et al., 2015). Such neurological deficits lead to limited mobility and impaired coughing, adversely affecting pulmonary functions and increasing complicated infection risk (Lee et al., 2019). Besides, most NMOSD patients require immunosuppression, predisposing them to complicated COVID-19 infection.

Also, a growing body of literature has suggested that virus infection may trigger or exacerbate the development of NMOSD in genetically susceptible patients (Zhong et al., 2018) (Sellner et al., 2010). The possible mechanism is bystander activation, in which infectious agents attack AQP4-rich tissue activating AQP4-specific T- and B-cells against the CNS or molecular mimicry, causing B-cells produces antibodies that recognize both microbial epitopes and self-epitopes (Turco et al., 2020) (Koga et al., 2011). So far, researches have shown an association between COVID-19 infection and different types of CNS demyelination. Although causality cannot be absolutely determined, para-infectious or post-infectious immune-mediated etiology might be implicated in patients with COVID-19 (Apostolos-Pereira et al., 2021).

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With the introduction of COVID-19 vaccinations and their injection into millions of bodies, it is vital to consider vaccination immunogenicity, safety, and efficacy in NMOSD patients, especially those undergoing immunotherapy. Moreover, basic immunology of vaccination and health care advice for NMOSD patients under COVID-19 pandemic are provided.

2. Immunological principles of vaccination

Vaccine-induced immunoprotection is a highly complicated process involving a series of mediators and mechanisms. After injection into muscles, the vaccine can cause attraction, activation, uptake, and processing in antigen-presenting cells (APCs), which then migrate to lymphatic tissue (Zrzavy et al., 2019). Subsequently, activation of APC-stimulated lymphocytes leads to T-cell immune response and B-cell activation. These activated APCs from innate immune system are so-called ‘immunogenic potential’, which subsequently present epitopes to T-cells (Coffman et al., 2010). As B-cells recognize the antigen, they become activated and migrate toward T-B cell border in the lymph node, where they are further stimulated by CD40 interaction and secretion of cytokines by activated T-helper-cells, ultimately transforming B-cells into plasma cells that primarily secrete antibodies (MacLennan et al., 2003). This primary immune response is associated with the early appearance of low-affinity antibodies and is usually transient. These produced low-affinity antibodies can later be replaced by high-affinity antibodies activated by germinal center responses (Zrzavy et al., 2019). Dendritic cells also play an indispensable role because of their enhanced capability of stimulating naïve T-cells (Jenkins et al., 2001). They cause migration towards draining lymph nodes by providing costimulatory signals like CD40 to differentiate naïve T-cells into immunologic effector cells by increasing MHC molecules expression and chemokine receptors following immune cascade activation, causing survival and further proliferation of B-cells with the highest affinity to antigens (Goodnow et al., 2010; Zrzavy et al., 2019). Eventually, vaccination-induced protection contains an integrated combination of T-cells, antibodies, and cytokines.

In a nutshell, vaccination-induced immune responses vary depending on vaccine administration, vaccine type, and adjuvant choice (Zrzavy et al., 2019). In the whole process of vaccination-induced immune protection, antibodies directly prevent and reduce infections by binding to antigens and neutralizing pathogens, while CD4+ and CD8+ T-cells eventually control and clear pathogens by secreting cytokines, perforins, and granzymes (Zrzavy et al., 2019). According to previous studies, some vaccines may adversely impact self-autoimmune system, primarily when adjuvant exists. Therefore, analyzing and monitoring vaccination adverse effects related to autoimmunity is quite indispensable.

3. Will vaccination trigger NMOSD or cause relapse?

Vaccines are designed as effective preventive treatment options by evoking host’s protective immune response to infection for over 200 years. The immunity system can distinguish itself from non-self (i.e., immune tolerance), which is essential for self-immunoprotection against autoimmune destruction. The self-tolerance breakdown to highly conserved auto-antigens is closely correlated with the exposure to environmental stimuli such as infectious antigens (Shoenfeld et al., 2008). The host’s response to a vaccine is initially to generate protective immunity, a process analogous to infectious invasion. As infectious agents can cause autoimmune, recombinant or live attenuated antigens are expected to be employed for vaccination (Tishler and Shoefield, 2004). Vaccines, commonly containing both attenuated infectious agents or their main antigenic proteins and chemical adjuvants, are among the most controversial and characteristic examples of “environmentally”-induced autoimmunity (Karussis and Petrov, 2014). When combined with antigens, adjuvants enhance immunological response, enabling faster and more effective recognition of “non-self”. Previous findings suggest that vaccine adjuvants may trigger autoimmunity, of which aluminum compounds have been the most studied and widely used (Radenska-Lopovok and Volkova, 2018) (Agmon-Levin et al., 2009).

The potential impact between vaccination and autoimmunity is usually bidirectional. Vaccines can protect against infectious and some autoimmune diseases induced by infections, while vaccines could originally trigger autoimmune diseases (Vadala et al., 2017). A nested case-control study reveals that younger patients are at higher risk of developing their first symptoms of an acquired CNS demyelinating syndrome within 30 days of any vaccination (Langer-Gould et al., 2014). However, there seems no long-term correlation between vaccination and acquired CNS demyelinating syndrome. This research indicates that vaccine is critical in accelerating pre-existing autoimmunity (Langer-Gould et al., 2014). Adverse events about vaccination-induced NMOSD have recently been constantly reported. Many studies describe trigger or relapses of NMOSD after vaccination (Table 1) (Mealy et al., 2018) (Emmanouliotou et al., 2020) (Menge et al., 2012) (Furukawa et al., 2011) (Kitazawa et al., 2012) (Cho et al., 2013) (Schoberl et al., 2017) (Chang et al., 2016) (Kline et al., 1982). Among reported cases, HPV was one of the most common NMOSD-related vaccines, and four cases were reported after receiving Gardasil, a quadrivalent recombinant vaccine, containing the main capsid (L1) protein of human papillomavirus (HPV) types 6, 11, 16, and 18 in highly-purified virus-like particles (Menge et al., 2012). The average time between vaccination and onset of symptoms is three days to four months (Menge et al., 2012). In another study, three patients had an optic neuritis history before NMOSD-related vaccines, suggesting that vaccination may induce onset and relapse of NMOSD (Cho et al., 2019). In a multicenter study of 50 patients, two cases of NMOSD relapses were temporally associated with preceding vaccination (Jarius et al., 2016). Some findings have revealed that vaccination may put untreated NMOSD patients at risk of recurrence, but it may benefit NMOSD patients who regularly receive preventive immunotherapy. In a retrospective study, nine NMOSD patients with relapses after influenza vaccination are all without preventive immunotherapy, and the annual recurrence rate of patients receiving routine immunotherapy is lower than that of non-vaccinated patients (Mealy et al., 2018). An anonymous survey about COVID-19 vaccines was distributed to patients with rare neuroimmunological diseases recruited via social media. A total of 73 participants (16.7%) reported new or worsening neurological symptoms following vaccination, and most symptoms occurred within the first week after vaccination and resolved within three days (Lotan et al., 2021). Therefore, vaccination may trigger NMOSD or cause relapse, especially in those who have not been vaccinated for a long time.

Table 1. Clinical characteristics of NMOSD associated with vaccinations.

<table>
<thead>
<tr>
<th>Type of vaccine</th>
<th>Number of reported cases</th>
<th>Average vaccine-to-event days</th>
<th>Background immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap</td>
<td>2</td>
<td>18.0</td>
<td>MMF (1);None(1)</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>1</td>
<td>13.0</td>
<td>None(1)</td>
</tr>
<tr>
<td>Influenza</td>
<td>11</td>
<td>36.8</td>
<td>AZA(1);None(10)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>2</td>
<td>27.5</td>
<td>GA(1);None(1)</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>2</td>
<td>Not available</td>
<td>Methylprednisolone (1);None(1)</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>2</td>
<td>19.0</td>
<td>None(2)</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>5</td>
<td>112.6</td>
<td>None(5)</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>1</td>
<td>21.0</td>
<td>None(1)</td>
</tr>
<tr>
<td>Rubella</td>
<td>1</td>
<td>11.0</td>
<td>None(1)</td>
</tr>
<tr>
<td>Diphtheria, tetanus, pertussis, polio</td>
<td>1</td>
<td>14.0</td>
<td>None(1)</td>
</tr>
</tbody>
</table>
4. Will vaccination be safe for NMOSD patients on immunotherapy?

Vaccines can be divided into several types according to their distinct platforms. Classical vaccine platforms include a whole-inactivated virus, live-attenuated virus, protein subunit, and virus-like particle, while next-generation platforms contain viral vector, DNA, RNA, and antigen-presenting cells (Fig. 1) (van Riel and de Wit, 2020). Some of these vaccines can induce cellular and humoral immune responses, while some of them primarily elicit humoral immune responses.

The vaccine-induced disease is extremely rare among most immunocompetent patients. However, immunocompromised patients are particularly vulnerable to bacteria and viruses existing in live-attenuated vaccines. Therefore, live-attenuated vaccines are usually contraindicated in patients taking immunosuppressive agents or some immunomodulating agents (Goyal et al., 2015). The safety of virus-vector vaccines in immunocompromised patients remains unclear so far. However, at least, all inactivated vaccines can be safely used in patients with altered immunity, whether vaccine is an inactivated whole organism or a recombinant, subunit, split virus, toxoid, polysaccharide, or polyglycoprotein conjugate vaccine (ACIP, 2021). While it is generally safe to receive inactivated or viral protein vaccines for patients taking immunosuppressive agents, the immune response of these patients may still be diminished (Abboud et al., 2020). Regarding mRNA vaccination, while recent years have witnessed a rapid pace of innovation in mRNA manufacturing, in vivo delivery, and immunogenicity, much remains to be improved and investigated (Pardi et al., 2020). Therefore, the safety of NMOSD patients receiving mRNA vaccines remains uncertain. The situation of DNA vaccines is similar to mRNA vaccines. Due to good biocompatibility, low production cost, and long shelf life of plasmid DNA, DNA vaccine-based immunotherapeutic strategies have been researched and developed to treat tumors, infections, allergies, and autoimmune diseases (Hobernik and Bros, 2018). Using DNA vaccines caused a series of safety concerns. The main reason is that transfected DNA has the risk of stably integrating into somatic cell genome or even germ cells, resulting in gene expression disorders and mutations (Hobernik and Bros, 2018). So far, there is no officially approved DNA vaccine for human use, implying that their exact safety is completely clarified. (Thanh Le et al., 2020). Candidate COVID-19 vaccines include viral protein and nucleic acid vaccines, artificial antigen-presenting cell vaccines, surrogate viral vector vaccines, and live-attenuated vaccines (Prompatchara et al., 2020; Thanh Le et al., 2020; Wang et al., 2020). We can assume that it is safe to administer viral or immunotherapy-inactivated protein vaccines to NMOSD patients, whereas we advise those who receive immunomodulators to avoid all types of live vaccines (Goyal et al., 2015). The safety of NMOSD patients using viral vector vaccines, RNA vaccines, and DNA vaccines has not yet been confirmed.

5. Will vaccination be effective for patients on immunotherapy?

Currently, common immunomodulators to treat NMOSD patients include corticosteroid, azathioprine, mycophenolate mofetil (MMF), rituximab, eculizumab, satralizumab, and so on (Bichuetti et al., 2019; Damato et al., 2016; Torres et al., 2015) (Huang et al., 2018). One of the maintenance treatments of NMOSD is chronic corticosteroids (Romeo and Segal, 2019), and the current standard of acute relapses for NMOSD patients is high-dose corticosteroids usually combined with plasma exchange (Abboud et al., 2016) (Kleiter et al., 2016). Corticosteroids inhibit the function of T cells (Davis et al., 2013) and can interfere with early immune reaction to infection and are therefore not used in patients with co-infection because they may affect virus clearance and are prone to induce secondary bacterial infections. So far, no consensus has been reached on the effect of glucocorticoids on humoral immunity, but using glucocorticoids generally decreases the concentration of immunoglobulins. Only a few reports revealed that long-term glucocorticoid therapy has little impact on antibody titers produced by vaccination (Cain and Cidlowski, 2017).

Most physicians believe that prednisone doses of over 20 mg/day and continuously used for over 14 days are commonly referred to as high doses. Long-term use of such high doses of corticosteroids may also reduce the body’s immune response to vaccines. On the one hand, vaccination providers should postpone vaccination for at least one month after discontinuing high-dose systemically absorbed corticosteroid therapy administered for more than 14 days. On the other hand, the vaccination should not end immunosuppressive therapy, but there is currently no specific recommendation on when to restart immunosuppressive agents following vaccination. Some clinical practice guidelines suggest that providers should start immunosuppressive therapy two

Fig. 1. An overview of the different vaccine platforms.
purines, while MMF inhibits de novo purine synthesis by inhibiting the fact that rituximab can cause long-term immunosuppression and newly-diagnosed NMOSD patients, the benefits of rituximab treatment revealed that rituximab during COVID-19 pandemic may be associated with vaccination (Abbond et al., 2020). A study for MS patients to the vaccine. A live-attenuated vaccine is usually avoided during rituximab treatment should receive inactivated vaccines at least six months after vaccination to confirm the effective immune response (McLeod et al., 2020). In the past few years, the number of patients treated with azathioprine and mycophenolate mofetil in NMOSD continues to decline because of their inferior efficacy compared with rituximab, as demonstrated in several retrospective studies (Kimbrough et al., 2012) (Hollroyd et al., 2020) (Etemadifar et al., 2017). The efficacy of rituximab has been proved by several previous studies (Damato et al., 2016) (Colongues and de Seze, 2016) (Tahara et al., 2020) (Nikoo et al., 2017) (Kaegi et al., 2019) (Torgashina and Vasilyev, 2018). Rituximab is an anti-CD20 monoclonal antibody depleting B cells; its exact mode of action in NMOSD is uncertain. However, it is hypothesized that rituximab prevents NMOSD relapse by reducing the production of pathogenic antibodies, reducing B-cell-dependent antigen presentation T-cells, and inhibiting proinflammatory cytokines (Abbond et al., 2020) (Bennett et al., 2015). Within two weeks after rituximab infusion, CD20-positive B-cells may be selectively depleted for a longer time, usually for an average time of six months after dosing, but this effect may persist in some patients up to three years (Cohen et al., 2006) (Rituximab prescribing information 2020). Rituximab reduces humoral response to the viral protein or inactivated vaccine that appears time-dependent relative to rituximab infusion (van Assen et al., 2010). A weaker humoral response occurs during maximum B-cell depletion when vaccination is performed immediately after infusion (Friedman and Winthrop, 2017; van Assen et al., 2010). In a recent cohort study about COVID-19 vaccine, even if IgG index is very heterogeneous in the general population, it is worth noting that none of the 5 MS/NMOSD patients on anti-CD20 was serologically positive (Maillard et al., 2020). Therefore, vaccination during rituximab treatment should be avoided if possible because the immune response of antibodies could temporarily be suboptimal, while vaccines that trigger immune responses mainly relying on T-cells (such as tetanus toxoid) are less affected by rituximab. Patients who have been vaccinated within 14 days before or during immunosuppressive therapy should be considered unimmunized. If immunity has recovered, they should be re-vaccinated at least 3–6 months after stopping therapy. So patients receiving anti-B-cell antibody (such as rituximab) chemotherapy should receive inactivated vaccines at least six months after treatment. For those patients, serological examination should be recommended after vaccination to confirm the effective immune response to the vaccine. A live-attenuated vaccine is usually avoided during rituximab treatment (Abbond et al., 2020). A study for MS patients revealed that rituximab during COVID-19 pandemic may be associated with a low risk of relapse or MRI activity (Maorouf et al., 2020). For newly-diagnosed NMOSD patients, the benefits of rituximab treatment should be weighed against the possibility of infection and reduced effectiveness of vaccination. Careful consideration should be provided to the fact that rituximab can cause long-term immunosuppression and irreversible infection (Abbond et al., 2020).

In a randomized and double-blind clinical trial, eculizumab has fully demonstrated its strong efficacy as add-on or monotherapy for AQP4 antibody-positive NMOSD (Abbond et al., 2020) (Pittock et al., 2019). Eculizumab is a monoclonal antibody of terminal complement inhibitor against C5 protein. It can effectively prevent membrane attack complex formation, which mainly contributes to inflammation and destruction of astrocytes in NMOSD (Abbond et al., 2020) (Pittock et al., 2019, 2013). Because it acts locally on the complement system, eculizumab theoretically has little effect on immunity. Leukopenia and lymphopenia both rarely appear when using eculizumab, and complement inhibitors are usually not associated with hypogammaglobulinemia (Alashkar et al., 2020). However, using eculizumab can increase bacterial pneumonia risk (Eculizumab prescribing information 2020), which is the most common serious adverse event in the eculizumab group during NMOSD clinical trial (Pittock et al., 2019). Regarding vaccination influence, eculizumab does not affect any vaccination type because it does not affect the effective immune response to the vaccine. Besides, there is no such vaccination restriction for patients receiving eculizumab (ACIP, 2021). Therefore, eculizumab is preferred over B-cell therapies (e.g., rituximab and inebilizumab) from a vaccination standpoint. It is also probably safe to use live-attenuated or viral vector vaccines for patients with eculizumab (ACIP, 2021).

As a monotherapy for NMOSD patients with or without AQP4 antibody, inebilizumab’s efficacy was confirmed in a randomized double-blind, placebo-controlled clinical trial (Cree et al., 2019). Inebilizumab is a monoclonal antibody against CD19-positive B-cells, and it reduces the pathogenic antibody production and dampsens B-cell-dependent T-cell activation and inflammatory cytokines production by selectively causing depletion of CD19-positive B-cells (Chen et al., 2016). Although inebilizumab in NMOSD clinical trial did not affect the immune response to tetanus toxoid, it remains unclear whether it affects humoral response to other inactivated or viral protein vaccines (Abbond et al., 2020). According to previous rituximab studies, inebilizumab may influence the efficacy of viral protein vaccines, and live-attenuated vaccines may also be prohibited from being used simultaneously with inebilizumab.

As add-on therapy to current immunosuppressants, satralizumab’s efficacy has been later proven in a randomized double-blind, placebo-controlled clinical trial and can be used to treat NMOSD patients with or without AQP4-IgG (Yamamura et al., 2019). Satralizumab is a monoclonal antibody against IL-6 receptor and can stop IL-6 proinflammatory signaling pathway, promoting T-cells activation and B-cells maturation into antibody-producing plasmablasts and plasma cells (Traboulsee et al., 2020). The specific impact of satralizumab on inactivated or viral protein vaccines is unclear, while live-attenuated vaccines should generally be contra-indicated in patients receiving IL-6 inhibitors (Abbond et al., 2020).

6. NMOSD patients under COVID-19 pandemic

The pandemic of severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) has brought the world to a standstill. The typical clinical symptoms of disease include fever, dry cough, fatigue, muscle pain, and dyspnea, which is highly contagious (Lai C et al., 2020). The studies have confirmed that SARS-CoV-2 enters the human body through angiotensin-converting enzyme-2 (ACE-2) receptors on the cell surface (Wan et al., 2020). These ACE-2 receptors on the surface of type II alveolar epithelial cells in human lungs are similarly expressed by other cell types, including glial cells and neurons (Reyfman et al., 2019). SARS-CoV-2 infects CNS by attacking both endothelial and epithelial cells of blood-brain barrier or by retrograde axonal pathway (through Cranial Nerves III, V, IX, and X of peripheral nerves) (Batum et al., 2020). Then, the virus causes elevated levels of inflammatory cytokines and chemokines, such as interleukin (IL)-1 beta (IL-1β), IL-2, IL-6, IL-7, IL-10, tumor necrosis factor-α (TNF-α), granulocyte colony-stimulating factor (GM-CSF), and monococyte chemotactic protein-1 (MCP-1),...
while the level of complement 3 and 4 has been decreased (Huang et al., 2020). In addition to the hyperactivation of proinflammatory T cells, significant lymphocytopenia and a decrease in regulatory T cells can also result in impaired immune responses (Qin et al., 2020). The cases have revealed that SARS-CoV-2 causes adverse conditions by attacking both central and peripheral nervous systems, such as hemorrhagic and ischemic stroke, acute hemorrhagic necrotizing encephalopathy, transverse myelitis, Gullian-Barré syndrome, and Miller Fisher Syndrome (Moriguchi et al., 2020) (Virani et al., 2020) (Munz et al., 2020) (Gutiérrez-Ortiz et al., 2020). Several cases of SARS-CoV-2 induced neuromyelitis optica and six cases of NMOSD patients with secondary SARS-CoV-2 infection have also been reported (Satam et al., 2020) (de Ruijter et al., 2020) (Mirmosayyeb et al., 2020). One case study even proposes that COVID-19 may provoke a postinfectious autoimmune response, particularly targeting AQP4 (Correa et al., 2020). Among recent reported NMOSD patients in North America, a high mortality rate was observed, and the presence of comorbid conditions was associated with worse COVID-19 outcomes. These results suggest that it is extremely important for NMOSD people to be especially vigilant and avoid exposure and adopt measures to minimize the risk of COVID-19 infection (Newsome et al., 2021). Researches have previously indicated that anxiety and stressful life events can also change autoimmune conditions and trigger relapses. A pilot study containing nine NMOSD patients demonstrated that two of them had worsened neurological symptoms, suggesting a relapse corresponding to a previous stress perception increase. It is hypothesized that uncertainty and pressure triggered by this COVID-19 pandemic may have also played particular role in affecting neurological conditions (Tomczak and Han, 2020). However, whether NMOSD patients are exactly at higher risk of COVID-19, or more susceptible to severe and complicated infection, remains uncertain temporarily (Fan et al., 2020).

A randomized poll of 186 NMOSD patients in a closed group was conducted through social media about their most concerns during COVID-19 pandemic (Salama et al., 2020). It suggested that the top concern of 80.6% of NMOSD patients was acquiring infection. When asked about their intention to change medications, 85% of patients had never intended to discontinue medical treatment (Salama et al., 2020). This poll reveals that most NMOSD patients may do not require changing or stopping their medications despite the possibility of acquiring COVID-19. When asked about vaccination attitudes, a study containing 262 NMOSD patients in China reveals that vaccine hesitancy is not believed to exist (Xu et al., 2021).

Another study of 600 cases from Global Rheumatology Alliance registry, about 46% of which were hospitalized due to COVID-19, found no elevated level of hospitalization risk related to immunosuppressive treatments (Gianfrancesco et al., 2020). Since every relapse for NMOSD patients can be fatal, patients should be encouraged to keep receiving medications for recurrence prevention, including corticosteroids, azathioprine, mycophenolate mofetil, rituximab, ecuclizumab, inebilizumab, and satralizumab (Loupre et al., 2020). If it becomes necessary to discontinue or postpone treatments in NMOSD patients for clinical reasons, moderate dose corticosteroids (e.g., prednisolone 20 mg) can be considered an effective short- to medium-term way to prevent recurrences (Brownlee et al., 2020). Notably, severe COVID-19 infections are more frequent in elder patients (>60 years) with a higher case-fatality rate (CCDC, 2021). Considering the increased risk of death associated with other underlying diseases (cardiopulmonary disease and diabetes mellitus) and the modest benefit of disease-modifying treatment for elderly NMOSD patients, treatment decisions for this group should be individualized (Hamdy et al., 2020) (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020).

### 7. Conclusion

Although vaccination-induced NMOSD cases or relapses have been reported, and these studies demonstrate that vaccination can accelerate the transition to overt disease in patients with subclinical autoimmune disease, it is still difficult to determine whether the interaction between vaccination and autoimmune disease is causal or coincidental. However, there is convincing evidence that infection can induce relapses in NMOSD, and SARS-CoV2 infection has already been demonstrated as a risk factor for NMOSD relapses (Apostolos-Pereira et al., 2021), which is why NMOSD patients are recommended to reduce their risk of infections by receiving COVID-19 vaccines. For vaccination safety, it is safe to provide NMOSD patients receiving immunotherapy inactivated or viral protein vaccines, while all live vaccines are prohibited in patients receiving immunomodulatory agents. The safety of NMOSD patients using a viral vector, RNA, and DNA vaccines still requires confirmation. The impact of immunomodulators on efficacy of vaccines has also been illustrated (Table 2). However, these concerns of immunotherapy (especially some biological agents on vaccines’ effectiveness are generally theoretical, based on their possible mechanisms of action so far. Besides, immunization and immunosuppressive therapy must be well-timed to ensure the best possible vaccine success. As a result, further studies and continuous surveillance of vaccination-related NMOSD are essential (Cho et al., 2019).

Although both symptoms of NMOSD patients and the need for immunotherapy make them theoretically more susceptible to COVID-19 infection. So far, there is no conclusive evidence suggesting that having NMOSD increases the risk of COVID-19 or develops into severe COVID-19. A study of New England COVID-19 registry of patients with CNS demyelinating disease indicated that using disease-modifying therapy did not increase hospitalization risk but was associated with an increased need for respiratory support, and hospitalization was associated with increased disability, age, and comorbidities but not disease-modifying therapy use (Money et al., 2021). More evidences are required to formulate specific recommendations about COVID-19 for NMOSD patients receiving immunomodulatory therapy. As some immunomodulators may increase the risk of more serious infections, individualized risk assessment is necessary for each patient, including immunosuppressive impact of different treatments and other factors of patients (such as age, comorbidities, exposure risk, and healthcare). Besides, strengthening patient education of self-protection during the pandemic is equally essential. More researches and evidences are needed.

### Table 2.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Possible impact on the efficacy of vaccines</th>
<th>Other advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>1.Suppression of T-cells</td>
<td>1.Little impact caused by standard dose</td>
<td>Vaccination should be at least 6 month after stopping high dose Corticosteroids.</td>
</tr>
<tr>
<td>2.Interference with early immune response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine and MMF</td>
<td>Non-selective lymphopenia</td>
<td>Decreased humoral response</td>
<td>Live-attenuated vaccines are contraindicated.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Selective CD-20 positive B-cell depletion</td>
<td>Decreased humoral response</td>
<td>1.Live-attenuated vaccines are contraindicated.</td>
</tr>
<tr>
<td>2.Vaccination should be at least 3–6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eculizumab</td>
<td>CS complement inhibitor</td>
<td>None</td>
<td>Increasing the risk of bacterial pneumonia</td>
</tr>
<tr>
<td>Inebilizumab</td>
<td>Selective CD-19 positive B-cell depletion</td>
<td>Positively decreased humoral response</td>
<td>Live-attenuated vaccines are contraindicated.</td>
</tr>
<tr>
<td>Satralizumab</td>
<td>IL-6 inhibitor</td>
<td>Unknown but likely no or limited impact</td>
<td>Live-attenuated vaccines are not recommended.</td>
</tr>
</tbody>
</table>

*MMF: mycophenolate mofetil, CD: cluster of differentiation, IL-6: interleukin 6.*
required for the interaction between NMOSSD patients and COVID-19 vaccines in the future.

8. Author contributions

HY and QZ were responsible for providing academic resources. HC performed summary and interpretation. RZ and FJ helped with data collection. All authors contributed to manuscript writing and approved the submitted version.

Declaration of Competing Interest

The authors do not have any possible conflicts of interest.

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Eculizumab prescribing information 2020.
Rituximab prescribing information 2020.
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