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Acute and chronic inflammatory neuropathies and COVID-19 vaccines: practical recommendations from the task force of the Italian Peripheral Nervous System Association (ASNP)

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Running title: Inflammatory neuropathies and COVID-19 vaccine

Abstract

Background and Aims: to develop recommendations for vaccination for coronavirus-19 (COVID-19) in patients with inflammatory neuropathies.

Methods: key questions were formulated in order to perform a literature review on the safety and efficacy of vaccines in patients with inflammatory neuropathies. Based on the best evidence and expert opinion, a list of recommendations was formulated to inform decision on vaccination for COVID-19 in patients with inflammatory neuropathies and increase adherence to vaccination programmes.

Results: recommendations addressing safety and efficacy of vaccination in patients with inflammatory neuropathies were formulated. No data are currently available on the safety and efficacy of COVID-19 vaccines in patients with inflammatory neuropathies or other immune-mediated conditions. There is only sparse data on the safety of previous available vaccines in patients with inflammatory neuropathies, but studies on other autoimmune disorders indicate that these are safe and mostly efficacious. Patients with inflammatory neuropathies might be at increase risk for severe illness from COVID-19

Interpretation: patients with inflammatory neuropathies should be encouraged to adhere to the vaccination campaign for COVID-19. These recommendations provide guidance on the management of vaccinations for COVID-19 in patients with inflammatory neuropathies. More research is needed regarding the safety and efficacy of vaccination in patients with inflammatory neuropathies and other immune conditions.

Key words: inflammatory neuropathies, coronavirus disease, COVID-19, vaccination, vaccine

Introduction

The global vaccination campaign in response to the coronavirus-19 (COVID-19) pandemic has started with an unprecedented speed. Considering the severity of the pandemic, a massive effort has been made internationally to shorten the timing of vaccine development and dissemination in order to guarantee adequate protection against the risk of getting COVID-19 disease. Given the high efficacy observed, it was not possible, for ethical reasons, to evaluate the long term efficacy and safety of the vaccines for COVID-19 in comparison to a placebo group.[1] The occasional association of vaccines with the onset of inflammatory neuropathies together with the sparse information on the safety and efficacy of the vaccines for COVID-19 in people with autoimmune diseases raised some concerns about safety in patients with immune-mediated neuropathies. The Italian Association of the Peripheral Nervous System (ASNP) has developed a joint document to provide the neurological community and patients with the best evidence for informing decision on vaccination for COVID-19 in patients with immune-mediated neuropathies and increase adherence to vaccination programmes. The following document should be interpreted as a collection of indications or advice developed by neurologists with expertise in immune-mediated polyneuropathies [i.e. Guillain-Barré syndrome (GBS) and its variants; chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), polyneuropathies associated with monoclonal gammopathy with or without anti-MAG antibodies and vasculitic neuropathies].

Are vaccines a risk factor for the development of inflammatory neuropathies?

The possible association between vaccines and inflammatory neuropathies has been a matter of concern since the year 1976, when a vaccination campaign was interrupted in the

U.S. due to an increased number of GBS cases after receiving the swine influenza vaccine.[2] Since then, a number of studies addressed the possible association of vaccines with GBS.[3-7] These epidemiological studies gave mixed results, with the majority of them failing to show evidence of the association of GBS with vaccines.[8,9] However, these studies were underpowered to detect a small relative risk.[8-10] A few studies on a larger number of patients and meta-analyses reported a small but significant increased risk of GBS after influenza vaccine (1 additional case of GBS per million persons vaccinated).[10-16] In an attempt to determine the presence of any possible confounding factor due to the simultaneous circulation of wild-type influenza virus (a known risk factor of GBS)[17,18] and influenza vaccine, one study evaluated the cumulative risk of GBS in the vaccinated and unvaccinated population.[19] The cumulative risk of GBS was significantly higher among the unvaccinated population than in the vaccinated population.[19] The lesson we can learn from these studies is that an increased risk of GBS has been found to be associated with both influenza infections and some influenza vaccines; however, the slightly risk of GBS following vaccination should be weighed against the potential benefits of vaccination against influenza and against the much higher risk of GBS caused by influenza virus infection.

Apart from GBS, only a few studies have evaluated the association between vaccines and chronic inflammatory neuropathies.[20-22] A proportion of CIDP patients ranging from 1.5% to 11% report a preceding vaccination within 8 weeks from the onset of the first symptoms.[20,22] Limitations of these studies include the retrospective design, the risk of recall bias, and the difficulty of accurately dating the onset of chronic disorders. There are also isolated reports on vasculitic neuropathies following vaccination.[23,24] However, higher quality studies and a systematic review found no causal association between vaccination and subsequent development of vasculitis.[25-27] No studies have investigated vaccination as a risk factor for MMN and anti-MAG antibody neuropathy.

Are vaccines safe and efficacious in people with inflammatory neuropathies?

Another matter of concern is the putative risk of relapse following vaccination in patients with immune-mediated neuropathies. Only two retrospective studies have investigated this issue in GBS and CIDP, while no studies focused on MMN or anti-MAG antibody neuropathy.[20,21] One study found that 11/311 (3.5%) previously diagnosed GBS patients and 5/65 (8%) CIDP patients reported worsening of neurological symptoms after immunisation.[21] Only one of the GBS patients however experienced transient worsening of disability and only one of the CIDP patients required treatment while in all other patients symptoms were self-reported, mild, and resolved spontaneously. In another study, 0/106 GBS patients and 5/24 (21%) CIDP patients reported an increase in symptoms after one or more vaccinations.[20] It is difficult to draw firm conclusions from these studies given their small sample size and the retrospective design. Keeping these limitations in mind, these studies suggest a low risk of worsening of GBS and CIDP after vaccines. Two retrospective studies and two randomized controlled trials confirmed safety of influenza vaccine in anti-neutrophil cytoplasmic antibody associated vasculitis.[28-31] Unfortunately, the proportion of patients with peripheral neuropathy among those included in these studies is not reported. No studies have evaluated the efficacy of vaccination in patients with inflammatory neuropathies.

What is the evidence on the safety and efficacy of vaccination in autoimmune diseases?

High quality studies conducted on patients with different autoimmune disorders, such as vasculitis,[28,29] lupus erythematosus,[32] rheumatoid arthritis,[32-36] multiple sclerosis,[37,38] myasthenia gravis,[39,40] or diabetes mellitus,[41] showed that vaccination is safe and it is not associated with an increased risk of relapse. Most of the studies demonstrated similar rates of immunogenicity among patients with autoimmune disorders and healthy subjects.[28-41] No

data are currently available on the safety and efficacy of COVID-19 vaccines in people with autoimmune diseases.

Is vaccination safe and efficacious for people with inflammatory neuropathy under immune-modulating or immune-suppressive therapy?

Only a minority of patients with CIDP are immunosuppressed. According to the data of the Italian CIDP database, the percentage of patients with CIDP under immunosuppressive treatment, excluding those receiving intravenous immunoglobulin or corticosteroids or plasma exchange (see below) is 16%.[42] This percentage is much lower in patients with MMN, whereas it reaches 86% in patients with anti-MAG antibody neuropathy.[43] There is no data in literature on the safety of vaccination in patients with inflammatory neuropathy under immunosuppressive treatment. There are however several studies that assessed safety and immunogenicity of vaccination in patients with different autoimmune disorders under immunosuppressive treatment. These studies showed that non-live vaccines are safe in the setting of immunosuppression, and that immunosuppressive therapies have a variable impact on the response to immunisation with vaccines, with the majority of patients reaching a satisfactory serological response, although usually reduced compared to immunocompetent people.[44-49] Rituximab profoundly reduces vaccine immunogenicity.[36,50] The evidence coming from these studies suggest that, to ensure the best chance of response, whenever possible immunisation should be administered prior to initiation of immunosuppressive medications.[36,44-50] Live vaccines are contraindicated in immunosuppressed patients.[44-49] None of the approved COVID-19 vaccines however contain any active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.

Is vaccination safe and efficacious in people with inflammatory neuropathy under treatment with intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg)?

Antibodies to COVID-19 may not be found yet in therapeutic IVIg or SCIg, thus patients under treatment with these therapies are not protected against COVID-19. Since there is the potential risk of a reduced effectiveness of the COVID-19 vaccines if IVIg are administered with, or shortly before or after the vaccine, some authors[51] and some national guidelines on immunisation[52-54] recommend vaccination more than two weeks before the cycle of IVIg or at least eight weeks after. This would be quite difficult in patients with chronic immune-mediated neuropathies in whom IVIg need to be periodically administered every 2 to 5 weeks to avoid clinical deterioration. Administration of SCIg can also reduce the efficacy of vaccines for a similar period.[55,56] There are no additional safety concerns if IVIg or SCIg are administered with, or shortly before or after the vaccine. It is however recommendable to prefer another site of injection for COVID-19 vaccine respect to those usually used to administer SCIg.

Is vaccination safe and efficacious in people with inflammatory neuropathy under treatment with corticosteroids?

The amount of systemically absorbed corticosteroids and the duration of administration needed to suppress the immune system of an otherwise immunocompetent person are not well defined. A dose equivalent to either ≥2 mg/kg of body weight or ≥20 mg/day of prednisone or equivalent for people who weigh >10 kg when administered for ≥14 consecutive days is considered as sufficiently immunosuppressive to raise concern about the safety of vaccination with live-virus vaccines.[57] In patients initiating steroid therapy, it is recommended to start treatment at least four weeks after live vaccines and two weeks after inactivated vaccines.[57] In patients under chronic steroid therapy the main risk would be however a reduced efficacy of the vaccines.

Is vaccination safe and efficacious in people with inflammatory neuropathy under treatment with plasma exchange?

Some studies suggest that antibody titers correlated with protection to diphtheria, Epstein-Barr virus, and tetanus remained above thresholds associated with protection for most patients after plasma exchange.[58] Other studies showed that antibodies against pneumococcus, haemophilus polysaccharide, and measles antigens were significantly reduced, in some patients even below the protective threshold values.[59-61] The effect of chronically administered plasma exchange on the levels of protective antibodies is uncertain.[62] The evidence coming from these studies suggest that, to ensure the best chance of response, immunizations should be administered prior to initiation of plasma exchange whenever possible.

COVID-19 vaccines

Since January 2020, 172 and 63 vaccines are in pre-clinical and clinical development, respectively; 21 of them are in experimental stage 3 or late 2/early 3.[63] Virtually all possible kind of vaccines are in the pipeline to prevent COVID-19, from whole virion SARS-CoV-2 vaccines (inactivated and live attenuated) to those based on spike (S) protein (replicating or non-replicating viral vectored vaccine, recombinant protein vaccine, virus like particles vaccine, peptide based vaccine, DNA/RNA vaccine, plant based vaccine).[64] To develop useful vaccines the main target is the S protein, because spike-specific antibodies can interfere with interaction between SARS-CoV-2 virus and human cells, preventing the infection.

Currently the European Medicines Agency (EMA) has granted for European Unit (EU) conditional marketing authorisation for two mRNA vaccines, Pfizer for ages ≥16 yrs, and Moderna for ≥18 yrs while the AstraZeneca vaccine, in which chimpanzee-adenoviral vector contains the SARS-CoV-2 structural surface glycoprotein antigen gene, has been just recently approved for adults ≥18 yrs.[1,65-67]

There are three more vaccines on EMA rolling review (the step before conditional marketing authorisation): Ad26.COV2.S (developer: Janssen-Cilag International N.V.), an adenovirus vectored vaccine; NVX-CoV2373 (by Novavax CZ AS), a full length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M and CVnCoV (by CureVac AG), a mRNA vaccine similar to Pfizer and Moderna vaccines.[68]

All these vaccines are classified as non-replicating vaccines. In mRNA vaccines, the mRNA molecules are included in lipid nano-particles that allow the fusion with cellular membranes of host cells and hence the mRNA is released in the cytoplasm, where it is translated to build the spike protein. The spike protein has two punctiform mutations, to get the best structural conformation for antigenic behaviour, inducing both humoral and cellular immune response against SARS-CoV-2 infection. The mRNA vaccines do not contain the entire viral genetic information, lacking M, N and E proteins and other subgenomic RNAs, so it is impossible any replication or integration in the host DNA.[1,67,68] The Janssen-Cilag and AstraZeneca vaccines are DNA-based COVID-19 vaccines. In AstraZeneca vaccine, the gene for the coronavirus spike protein is added to a modified version of a chimpanzee adenovirus that can enter cells, but it cannot replicate inside them; in the Janssen-Cilag vaccine, the gene for the coronavirus spike protein is added to a replication-incompetent human recombinant adenovirus vector (AD26). Anyway, the gene for the SARS-CoV-2 spike protein can be read by the cell and copied into mRNA and ultimately translated to build spike protein. Protruding spikes or spike fragments are presented on the surface of infected cells and can be recognized by the immune system, developing neutralizing antibodies.[69,70]

NVX-CoV2373 is a nanoparticle-based vaccine, containing viral proteins without the accompanying genetic material. NVX-CoV2373 consists of a recombinant SARS-CoV-2 constructed from the full-length wild-type SARS-CoV-2 spike glycoprotein with resistance

to protease and a M1 saponin-based adjuvant. It has demonstrated high immunogenicity and an acceptable safety.[71]

Among vaccines being administered out of EU and not yet on EMA review we must cite “Sputnik V”, (rAd26-S+rAd5-S – Gamaleya National Research Centre, Russia), the first vaccine to be approved for preventing COVID-19. This vaccine is a non-replicating vaccine consisting on two recombinant components, both based on human adenovirus containing S-protein gene.[72]

Are the vaccines for COVID-19 efficacious and safe in patients with inflammatory neuropathies?

People with an immunocompromised condition or treated with immunosuppressive therapy were excluded from participation in the COVID-19 vaccine trials, and thus there is no information on safety and response after immunisation in these patients.[1,66,73,74] The Center for Disease Control and Prevention (CDC) and, in Italy, the National Federation Drug (Agenzia Italiana del Farmaco - AIFA), have published their recommendations where it is stated that people with autoimmune conditions or under medication with immunosuppressive agents may receive a COVID-19 vaccine although they should be aware of the limited safety data.[75,76] A multicentre Italian prospective study designed to evaluate the risk of relapse after vaccination and the safety of COVID-19 vaccines in patients with chronic inflammatory neuropathies is ongoing.

What are the risks of getting COVID-19?

Estimated worldwide mortality of COVID-19 is about 0.3/1000 persons,[77] but the data of western countries tend to have higher numbers.[78] In Italy mortality of COVID-19 is 1.5/1000, with a case fatality ratio of 3.5% and an average intensive care unit (ICU) admission rate of 21.4%.[78,79] Currently there are limited data and information about the

impact of many underlying medical conditions on the risk for severe illness from COVID-19. Based on what we know at this time, the CDC includes neurologic conditions and an immunocompromised state from the use of corticosteroids or other immune weakening medicines as two independent conditions that might be at increased risk for severe illness from COVID-19.[80]

Recommendations

- The vaccination programme for COVID-19 should be explained to the patients with inflammatory neuropathies providing a basis for shared decision-making. The patients should be informed that no data are currently available on the safety and efficacy of COVID-19 vaccines in people with autoimmune and immune-mediated conditions. However, evidence coming from previous vaccines suggest that patients who had GBS in the past, patients with chronic inflammatory neuropathy and those with an autoimmune disorder do not have an increased risk of relapse following vaccination, thus they should be encouraged to adhere to the vaccination campaign for COVID-19.

- Vaccination for COVID-19 in patients with chronic inflammatory neuropathy should preferably be administered during a remission phase of the disease. The rationale for this recommendation is that most vaccination studies conducted in people with autoimmune disorders included patients with disease in remission. Clinicians should delay vaccination of people with chronic inflammatory neuropathy who are experiencing a relapse until clinical resolution or until the relapse is no longer active

- Until further data comes from vaccine surveillance for COVID-19 under real-life conditions, patients who had GBS in the past or with chronic inflammatory neuropathy who decide to get vaccinated should continue to follow all local current guidance to protect themselves against COVID-19 after they are vaccinated.

- Vaccination for COVID-19 should be administered at least two weeks prior to initiation of steroid therapy whenever possible. In patients with chronic inflammatory neuropathy requiring steroid therapy it is not recommended to delay or interrupt treatment for vaccination. In patients under long-term steroid therapy in immunosuppressive regimen it is recommended to monitor seroconversion with antibody testing two weeks after the second dose of vaccine. Monthly intravenous bolus of methylprednisolone is not considered an immunosuppressive treatment, so vaccines could be administered two weeks after the therapy.

- Vaccination for COVID-19 should be administered at least two weeks prior to initiation of IVIg or SCIg therapy whenever possible. In patients with chronic inflammatory neuropathy requiring IVIg or SCIg therapy it is not recommended to delay or interrupt treatment for vaccination. In patients under IVIg treatment, vaccination should be administered at least two weeks before or eight weeks after the infusion of IVIg whenever possible. If not possible, vaccines should preferably be administered in the middle of two cycles. Monitoring of serologic conversion two weeks after the second dose of vaccine is advisable in patients under IVIg or SCIg treatment. In patients treated with SCIg, it is recommendable to choose a site of injection for COVID-19 vaccine different from that usually used for SCIg.

- Vaccination for COVID-19 should be administered at least two weeks prior to initiation of methotrexate, azathioprine, mycophenolate mofetil or cyclophosphamide therapy whenever possible. In patients with chronic inflammatory neuropathy requiring treatment with the above-mentioned drugs it is not recommended to delay or interrupt treatment for vaccination. In patients under treatment with intravenous cyclophosphamide, the two doses of COVID-19 vaccine should be administered between two infusions. Monitoring of

serologic conversion two weeks after the second dose of vaccine is advisable in these patients.

- A suboptimal efficacy of the vaccine for COVID-19 in patients under treatment with rituximab is possible. In patients with chronic inflammatory neuropathy requiring treatment with rituximab it is not recommended to delay or interrupt treatment for vaccination. Monitoring of serologic conversion two weeks after the second dose of vaccine is advisable in these patients.

- Regarding COVID-19 vaccines administered in two doses, the protective effect of immunization vaccination reaches full efficacy one (1**)** or two (66**)** weeks after the second dose.

- The possibility of a third vaccine booster dose could theoretically be considered in patients under immunosuppressive therapy that do not exhibit serologic conversion, even if this has not been yet considered by regulatory agencies.

In conclusion, evidence from previous vaccines in people with inflammatory neuropathies or autoimmune disorders suggests that vaccination in these groups of patients is safe and effective in most cases. The safety and efficacy of vaccination in patients under treatment with immune-modulating or immune-suppressive therapies need however to be further evaluated. We provide recommendations to guide physicians in the use of vaccination for COVID-19 and encourage our patients to join vaccination programmes.

Authors contributions

Pietro E. Doneddu and Emanuela Spina, screened the articles, assessed quality, extracted data, analysed the data, and wrote the first draft of the manuscript. Fiore Manganelli and Eduardo Nobile-Orazio, conceptualized the manuscript, reviewed and revised the

manuscript for intellectual content. Chiara Briani and Gian Maria Fabrizi, reviewed and revised the manuscript for intellectual content. All authors read and approved the final version of the manuscript.

Data availability

Data are available on request from the corresponding author

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