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GUEST EDITORIAL

Migraine treatment and COVID-19 vaccines: No cause for concern

The advent and availability of coronavirus disease 2019 (COVID-19) vaccines has led patients to pose a number of questions to their headache healthcare providers. In retrospect, it is perhaps surprising that these questions did not come earlier, for example, around annual influenza vaccination campaigns. However, COVID-19 has brought into focus questions about whether vaccines have an impact on the management of migraine and other headache disorders. Currently, only messenger ribonucleic acid (mRNA), adenovirus-vectored, and purified protein COVID-19 vaccines to soon be available. In each of these vaccine platforms, the only severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virally derived immunologic target present is the SARS-CoV-2 full-length S (spike) protein encoded in mRNA (Pfizer and Moderna vaccines), DNA (adenovirus-vectored vaccines; AstraZeneca or Johnson & Johnson), or the purified S protein with a proprietary adjuvant (Novavax). Thus, vaccine-induced protective immune responses are confined to the S protein and its epitopes, and phase III clinical trials across a wide diversity of age, race, sex, and multiple comorbidities have demonstrated excellent efficacy. Notably, while many patients with migraine and other headache disorders likely entered the COVID-19 vaccine clinical trials, specific data on any association between vaccine immunogenicity, safety, or efficacy and migraine treatments have not been reported, and such analyses likely not performed.

The clinical questions fall into two broad categories: (1) Does migraine treatment impair the efficacy, or impact the safety, of the COVID-19 vaccine and (2) Does the COVID-19 vaccine adversely impact the efficacy of migraine treatments? These questions seem to have focused most on onabotulinumtoxinA and the calcitonin gene-related peptide (CGRP) pathway monoclonal antibodies (mAbs), perhaps because they are delivered by injection. In addition, as non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for the acute treatment of migraine, there is also the question of whether their use should be curtailed for a period of time following vaccine administration in order to avoid inhibiting the body's immune response. Below we comment on the common questions that arise in regard to these treatments and COVID-19 vaccine immune response in adults. As there are no published data on these topics, these comments are based on expert opinion.

Abbreviations: CDC, Centers for Disease Control and Prevention; CGRP, calcitonin gene-related peptide; COVID-19, coronavirus disease 2019; mAb, monoclonal antibody; mRNA, messenger ribonucleic acid; NSAID, non-steroidal anti-inflammatory drug.

OnabotulinumtoxinA injections

Some patients may wonder whether onabotulinumtoxinA is considered a "dermal filler," as the Food and Drug Administration has reported that two participants in the Moderna COVID-19 vaccine trial who had dermal fillers experienced facial swelling in those areas after receiving the Moderna mRNA vaccine.[1] Facial fillers are substances injected to provide volume or fullness, and are unrelated to onabotulinumtoxinA. Therefore, this observation is not pertinent to patients receiving onabotulinumtoxinA injections for treatment of chronic migraine. Moreover, to the best of our knowledge, there is no reason to think that onabotulinumtoxinA impairs the immune response to any COVID-19 vaccine, thus being treated with it—and the timing of that treatment relative to when the vaccine doses are given—should not be clinically relevant.

CGRP pathway mAbs

With regard to the four mAbs to CGRP or its receptor, there is no immunological or clinical reason to think that these would impair the body's immunologic response to any COVID-19 vaccine. While there are CGRP receptors on lymphocytes, macrophages, and mast cells, and CGRP may have a role in pro- and anti-inflammatory actions,[2] clinical trial evidence with these mAbs has not suggested that they are immunosuppressive or myelosuppressive—nor would they be expected to be given the molecular engineering they have undergone.[3] While upper respiratory tract infection-like symptomatology and urinary tract infections were reported as adverse events in the adult CGRP clinical trials, rates of these were not higher than what occurred in the placebo groups.[4,5] Moreover, the nature of mAbs is that they have very narrow specificity limited to their defined target, and not broad specificity that might allow non-specific binding to other proteins. A frequent question that arises is whether to defer monthly or quarterly CGRP pathway mAb treatment by 2 weeks from the vaccine. At this point, there are no data to suggest that such treatments would in any way interfere with COVID-19 vaccine immunogenicity, safety, or efficacy.

The three CGRP pathway mAbs that are given by subcutaneous injection can cause local injection site reactions—typically redness or soreness at the site. This could be confused with a local vaccine reaction if the patient administered their CRGP pathway mAb in the same arm in which they recently received a COVID vaccine.

However, many patients administer their injections to the abdomen or thigh, and those who do use the arm could simply be advised to inject in the opposite arm to the one in which the vaccine was given.

NSAIDs and acetaminophen

In some studies, antipyretic use has been associated with decreased laboratory measured antibody response to vaccination in infants.[6] However, the clinical significance of this is unclear, and the effect was seen with primary vaccination and not with boosters.[6] No specific studies of the use of acetaminophen and/or NSAIDs have been done to examine any impact on COVID-19 vaccine immunogenicity in adults. While the Centers for Disease Control and Prevention (CDC) does not recommend routine prophylactic use of NSAIDs or acetaminophen before a vaccine, they do recommend that these medications be taken for treatment of post-vaccination local or systemic symptoms if needed. The CDC's current guidance is that "…routine prophylactic administration of these medications for the purpose of preventing post-vaccination symptoms is not currently recommended, as information on the impact of such use on mRNA COVID-19 vaccine-induced antibody responses is not available at this time."[7]

In addition, in the AstraZeneca clinical trials of the adenovirus-vectored vaccine, several sites utilized pre-injection prophylactic paracetamol to reduce vaccine reactogenicity with no apparent detrimental effect on subsequent antibody response. Furthermore, the mRNA and adenovirus-vectored COVID-19 vaccines appear to induce very high levels of protective antibody levels—higher than what many believe may be needed for protective efficacy. Only one small mouse study has been published demonstrating a small negative effect on humoral immunity after NSAID administration in association with SARS-CoV-2 infection.[8] Whether these results suggest a similar effect on vaccine immunogenicity has not been tested. Nonetheless, at this point in time, given the high level of antibody response and extraordinary efficacy of the mRNA vaccines, and the need for readily available over-the-counter treatment of migraine and other headache disorders, our opinion would be to use either medication as needed for treatment.

Migraine preventive efficacy

On the question of whether antibody production in response to the COVID-19 vaccine would make these migraine preventive treatments less effective, there is no reason to think that antibodies to the spike protein of the SARS-CoV-2 virus would neutralize onabotulinumtoxinA, or antibodies to CGRP or its receptor, given that COVID-19 vaccines induce antibody only to the spike protein of SARS-CoV-2. While it is remotely possible that the body could produce an antibody that would neutralize these treatments, there is no more reason to think that the COVID-19 vaccine would lead to production of such an antibody than any other vaccine, or any other infection. Therefore, there is no apparent rationale to retime these treatments out of concern for impairing their efficacy.

Conclusions

As always, individual patients should make treatment decisions in concert with their treating healthcare professionals, taking into account their individual circumstances. We are aware of no evidence that preventive treatment with CGRP pathway mAbs or onabotulinumtoxinA injections needs to be delayed or retimed with regard to timing of administration of a COVID-19 vaccine. Similarly, no evidence exists that the timing of COVID-19 vaccine administration should impact concurrent treatment with these migraine preventives. The established risks of COVID-19 infection, and the proven efficacy of migraine preventive therapies, further underscore the importance of not delaying either of these interventions. Those patients who administer CGRP pathway mAbs in the upper arm may wish to administer in the opposite arm to the one in which they received the COVID vaccine to avoid confusion as to cause if a local injection site reaction develops. While routine use of NSAIDs or acetaminophen before a vaccine is not recommended, if symptoms develop after the vaccine (e.g., fever or headache), the use of these treatments is not contraindicated and would be considered first-line treatment.

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KEYWORDS

coronavirus disease 2019, migraine, vaccine

CONFLICT OF INTEREST

AAG: In the last 12 months, Dr. Gelfand has received honoraria from UpToDate (for authorship) and *JAMA Neurology*. She receives payment from the American Headache Society for her role as Editor of *Headache*. She receives grant support from Amgen and the Duke Clinical Research Institute. Her spouse reports research support (to UCSF) from Genentech for a clinical trial, honoraria for editorial work from Dynamed Plus, and personal compensation for medical-legal consulting. GP: Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on vaccine development to Merck & Co., Medicago, GlaxoSmithKline, Sanofi Pasteur, Emergent Biosolutions, Dynavax, Genentech, Eli Lilly and Company, Janssen Global Services LLC, Kentucky Bioprocessing, AstraZeneca, and Genevant Sciences, Inc. Dr. Poland holds patents related to vaccinia and measles peptide vaccines. Dr. Poland has received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

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