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COVID-19 vaccination and the risk of swellings in patients with hereditary angioedema

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Clinical Implications

Adult patients with hereditary angioedema due to C1-inhibitor deficiency can be safely vaccinated against coronavirus disease 2019 without prior administration of short-term prophylaxis, provided that effective on-demand treatment is available in the event of an angioedema attack.

Hereditary angioedema (HAE) due to C1-inhibitor deficiency leads to disabling and potentially life-threatening recurring swellings in cutaneous and submucosal tissues. These swellings result from inadequate control of the contact system, causing excessive bradykinin formation with a localized, transient increase in vascular permeability. Disruption of the vascular endothelium has been recognized as a crucial factor in angioedema formation, and triggers for these attacks include febrile illness, medical procedures, pain, fatigue, psychological stress, and physical trauma. Short-term prophylaxis with C1-INH concentrate has been shown to effectively prevent HAE attacks following invasive medical procedures, but current guidelines do not particularly mention prophylaxis before intramuscular injections. Between December 2020 and March 2021, the European Medicines Agency approved 4 coronavirus disease 2019 (COVID-19) vaccines directed against the severe acute respiratory syndrome coronavirus 2: a nucleoside-modified RNA vaccine (BNT162b2; Pfizer-BioNTech and mRNA-1273; Moderna); a recombinant chimpanzee adenoviral vector (ChAdOx1 nCov-19; AstraZeneca); and a recombinant adenovirus type 26 vector (Ad26.COV2.S; Johnson & Johnson/Janssen). To date, it is unknown whether short-term prophylaxis before COVID-19 vaccination should be considered, because these vaccines may cause side effects including fatigue, fever, and pain even more frequently than other vaccines. Furthermore, the new mRNA vaccines may additionally increase the risk of angioedema attacks, because RNA is a potent activator of the contact system. We performed a prospective cohort study to assess the angioedema attack rate following COVID-19 vaccination in patients with HAE.

Our study included all adult patients with an established diagnosis of HAE who were invited to participate. Those who consented received monthly reminders and were instructed to provide their planned vaccination date(s) to the study team. Short-term prophylaxis before vaccination was neither recommended nor discouraged given the lack of evidence regarding the risk of angioedema following COVID-19 vaccination. All patients were in possession of acute treatment and an individualized emergency treatment plan. The study team contacted vaccinated patients to complete a questionnaire by telephone in 3 to 7 days after their vaccination(s) to allow sufficient time for developing an angioedema attack and to reduce the risk of recall bias. Among the variables collected was the Angioedema Control Test score, a disease-specific patient-reported outcome measure. A score of 10 or more points is considered well-controlled HAE, and a score of less than 10 points is considered poorly controlled disease.

A total of 93 of 96 eligible patients consented to participate (response rate 97%). The 3 patients who did not agree to participate refrained from vaccination. Table 1 summarizes characteristics of 63 patients with HAE who received at least 1 dose of COVID-19 vaccine between January 6, 2021, and August 17, 2021; the remaining 30 patients had not yet received a vaccination. A total of 48 patients received an mRNA vaccine (38 received the BNT162b2, Pfizer-BioNTech vaccine, and 10 patients received the mRNA-1273, Moderna vaccine) and 15 patients received a vector vaccine (9 patients received the ChAdOx1 nCov-19, AstraZeneca vaccine, and 6 patients received the Ad26.COV2-S, Janssen vaccine). Eleven angioedema attacks were reported following the administration of 111 COVID-19 vaccines (Table 1). None of these attacks occurred following the first vaccine, all were of mild or moderate severity, and most were treated with on-demand medication. There were no laryngeal attacks or hospital admissions. A total of 48 patients had received a second COVID-19 vaccination, 2 of whom developed an angioedema attack. Of the total of 11 attacks, 6 arose more than 48 hours after vaccination. Of 63 vaccinated patients with an established diagnosis of HAE who were invited to participate, all were of mild or moderate severity, and most were treated with on-demand medication. There were no laryngeal attacks or hospital admissions. A total of 48 patients had received a second COVID-19 vaccination, 2 of whom developed an angioedema attack. Of the total of 11 attacks, 6 arose more than 48 hours after vaccination. Of 63 vaccinated patients with an established diagnosis of HAE who were invited to participate, all were of mild or moderate severity, and most were treated with on-demand medication. There were no laryngeal attacks or hospital admissions. A total of 48 patients had received a second COVID-19 vaccination, 2 of whom developed an angioedema attack. Of the total of 11 attacks, 6 arose more than 48 hours after vaccination. Of 63 vaccinated
TABLE II. Characteristics of patients with a breakthrough HAE attack following COVID-19 vaccination

| Patient | Age | Sex | Disease control (AECT score) | Long-term prophylaxis | Short-term prophylaxis | Previous COVID-19 Vaccine | Location of attack | Maximal attack severity | On-demand treatment used | Interval between vaccination and attack | Attack after first dose | Attack after second dose | Alternative eliciting factor |
|---------|-----|-----|-------------------------------|-----------------------|-----------------------|---------------------------|-------------------------|------------------------|---------------------------|------------------------------------------|------------------------|---------------------------|----------------------------|
| 1       | 89  | Female | Poor: 4 | C1-INH IV and danazol | NA | No | Pfizer/BioNtech | Abdominal and facial | Mild | C1-INH IV | 24-48 h | Yes | No | Cystitis |
| 2       | 52  | Female | Poor: 9 | Tranexamic acid | NA | No | Moderna | Abdominal and facial | Mild | Tranexamic acid | <24 h | Yes | No | NA |
| 3       | 50  | Male | Poor: 6 | Danazol | Na | No | Pfizer/BioNtech | Abdominal and peripheral | Mild | Danazol | >48 h | Yes | No | NA |
| 4       | 47  | Female | Well: 15 | Experimental | NA | Yes | Pfizer/BioNtech | Peripheral | Mild | C1-INH IV | <24 h | Yes | No | NA |
| 5       | 38  | Female | Poor: 3 | C1-INH IV and danazol | NA | Yes | Pfizer/BioNtech | Peripheral | First/Moderate | C1-INH IV | First >48 h | Yes | Yes | NA |
| 6       | 48  | Female | Poor: 3 | NA | NA | No | Pfizer/BioNtech | Peripheral | Moderate | C1-INH IV | >48 h | Yes | No | NA |
| 7       | 43  | Female | Well: 11 | Experimental | NA | No | Pfizer/BioNtech | Facial | Mild | C1-INH IV | <24 h | Yes | No | NA |
| 8       | 54  | Female | Well: 16 | NA | NA | Suspected* | Janssen | Facial | Moderate | NA | >48 h | Yes | NA | NA |
| 9       | 35  | Female | Poor: 7 | C1-INH IV | NA | Yes | Pfizer/BioNtech | Abdominal | Mild | C1-INH IV | >48 h | Yes | NA | NA |
| 10      | 49  | Male | Well: 11 | NA | NA | No | Moderna | Peripheral and genital | Moderate | C1-INH IV | >48 h | No | Yes | NA |

*AECT, Angioedema Control Test; IV, intravenous; NA, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

*Patients with typical COVID-19 symptoms for whom SARS-CoV-2 detection by real-time PCR on nasopharyngeal swabs was not available were classified as suspected COVID-19.
patients, 4 had used short-term prophylaxis, and 3 of these used C1-INH concentrate and were attack-free. The remaining patient had an angioedema attack despite deciding to use danazol for short-term prophylaxis (Table II).

After a total of 111 COVID-19 vaccine doses administered, 90% of our HAE population did not experience an attack, even though most did not use short-term prophylaxis. Almost all attacks occurred following mRNA vaccine administrations, but it is notable that these vaccines accounted for the majority of administered vaccines. Two patients noticed erythema marginatum after vaccination, which they both successfully treated with C1-INH concentrate before further symptoms emerged. These prodromes were excluded from the analyses, in addition to 2 angioedema attacks that were reported to have commenced after vaccination, which they both successfully treated with danazol before further symptoms emerged. These attacks occurred following mRNA vaccine administrations, but it is notable that these vaccines accounted for the majority of administered vaccines. Two patients noticed erythema marginatum after vaccination, which they both successfully treated with C1-INH concentrate before further symptoms emerged.

An important strength of this study is our prospective recruitment among the entire adult HAE population in our reference center with a response rate as high as 97%. We recognize that the generalizability of this study may be affected by the availability of the various vaccines and prophylactic therapies. Indeed, some of the reported HAE therapeutics (including danazol and tranexamic acid) are no longer recommended as first-line treatment options. However, the decision to use these treatments was based on patients’ preference, earlier experiences, and the lack of nonintraocularly administered prophylactics in the Netherlands. It is notable that the attack rate postvaccination was also low in patients without any prophylaxis. Furthermore, the nonrandomized design of our study and the small sample sizes of some vaccine groups do not allow reliable subgroup analyses on patient characteristics or on vaccine types. Therefore, the signal that attacks occurred mostly after mRNA vaccination requires confirmation from larger cohorts.

Currently, the COVID-19 vaccine landscape is rapidly evolving and vaccines with new mechanisms of action have become available to increasing numbers of people globally. Our findings reassure that adult patients with HAE due to C1-INH deficiency can be safely vaccinated against COVID-19 without short-term prophylaxis, provided that effective on-demand treatment is available.

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