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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 (C1-INH) 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.¹ Disruption of the vascular endothelium has been recognized as a crucial factor in angioedema formation,² and triggers for these attacks include febrile illness, medical procedures, pain, fatigue, psychological stress, and physical trauma.³ Short-term prophylaxis with C1-INH concentrate has been shown to effectively prevent HAE attacks following invasive medical procedures,⁴ but current guidelines do not particularly mention prophylaxis before intramuscular injections.³ 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 spike glycoprotein: 2 nucleoside-modified RNA vaccines (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.⁵⁻⁷ Furthermore, the new mRNA vaccines may additionally increase the risk of angioedema attacks, because RNA is a potent activator of the contact system.⁸ We performed a prospective cohort study to assess the angioedema attack rate following COVID-19 vaccination in patients with HAE.

The Medical Research Ethics Committee of the Amsterdam University Medical Centers granted dispensation regarding the Medical Research Involving Human Subjects Act. The study was conducted in the national reference center for HAE in the Netherlands. All adult patients with an established diagnosis of HAE 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

TABLE I. Characteristics of COVID-19–vaccinated patients with HAE

Characteristic	Total	mRNA vaccines	Vector vaccines
No. of patients	63	48	15
No. of administered vaccines	111	87	24
Age (y), mean ± SD	48 ± 15	49 ± 16	46 ± 14
Sex: female, n (%)	42 (67)	31 (65)	11 (73)
Long-term prophylaxis, n (%)	45 (71)	39 (81)	6 (40)
C1-INH IV	12 (19)	11 (23)	1 (7)
Danazol	22 (35)	16 (33)	6 (40)
Lanadelumab	1 (2)	1 (2)	0 (0)
Tranexamic acid	3 (5)	3 (6)	0 (0)
Experimental	8 (13)	8 (17)	0 (0)
Short-term prophylaxis, n (%)	4 (6)	4 (8)	0 (0)
Well-controlled disease (AECT score ≥ 10), n (%)	42 (67)	31 (65)	11 (73)
Previous COVID-19, n (%)	16 (25)	12 (25)	1 (7)
Confirmed diagnosis	11 (18)	11 (23)	0 (0)
Suspected diagnosis*	5 (8)	1 (2)	4 (27)
HAE attack, n (% of sum of administered vaccines)	11 (10)	10 (11)	1 (4)

AECT, Angioedema Control Test; IV, intravenous; 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.

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.⁹

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 I 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 II). Nine 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

TABLE II. Characteristics of patients with a breakthrough HAE attack following COVID-19 vaccination

Patient	Age (y)	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	Mild	Tranexamic acid	<24 h	Yes	No	NA
3	50	Male	Poor: 6	Danazol	Danazol	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 Second Mild	C1-INH IV	First >48 h Second <24 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 before vaccination.

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.³ However, the decision to use these treatments was based on patients' preference, earlier experiences, and the lack of nonintravenously 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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