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

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Clinical implications box: Adult patients with HAE due to C1-inhibitor deficiency can be safely vaccinated against COVID-19 without prior administration of short-term prophylaxis, provided that effective on demand treatment is available in the event of an angioedema attack.

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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 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 four COVID-19 vaccines directed against the SARS-CoV-2 spike glycoprotein: two 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, since 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 HAE patients.

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 prior to 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 3-7 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 AECT; a disease specific patient-reported outcome measure. A score of ten or more points is considered well-controlled HAE and a score of less than ten points is considered poorly-controlled disease.(9)

A total of 93 out of 96 eligible patients consented to participate (response rate 97%). The three patients who did not agree to participate refrained from vaccination. Table 1 summarizes characteristics of 63 HAE patients who received at least one dose of COVID-19 vaccine between 6 January 2021 and 17 August 2021, the remaining 30 patients had not yet received a vaccination. A total of 48 patients received a mRNA vaccine (38 received the BNT162b2, Pfizer-BioNTech vaccine, and ten patients received the mRNA-1273, Moderna vaccine) and 15 patients received a vector vaccine (nine patients received the ChAdOx1 nCov-19, AstraZeneca vaccine, and six patients received the Ad26.COV2-S, Janssen vaccine). 11 angioedema attacks were reported following the administration of 111 COVID-19 vaccines (Table 2). 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, two of whom developed an angioedema attack. Of the total of 11 attacks, six arose more than 48 hours after vaccination. Of 63 vaccinated patients, four had used short-term prophylaxis, and three 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 2).

After a total of 111 COVID-19 vaccine doses administered, 90% of our HAE population did not experience an attack, even though the majority 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,

75 which they both successfully treated with C1-INH concentrate before further symptoms emerged.

76 These prodromes were excluded from the analyses, in addition to two angioedema attacks that were
77 reported to have commenced prior to vaccination.

78 An important strength of this study is our prospective recruitment among the entire adult HAE
79 population in our reference center with a response rate as high as 97%. We recognize that the
80 generalizability of this study may be affected by the availability of the various vaccines and
81 prophylactic therapies. Indeed, some of the reported HAE therapeutics (including danazol and
82 tranexamic acid), are no longer recommended as first-line treatment options.⁽³⁾ However, the
83 decision to use these treatments was based on patients' preference, earlier experiences, and the lack
84 of non-intravenously administered prophylactics in the Netherlands. It is notable that the attack rate
85 post vaccination was also low in patients without any prophylaxis. Furthermore, the non-randomized
86 design of our study and the small sample sizes of some vaccine groups do neither allow reliable
87 subgroup analyses on patient characteristics nor on vaccine types. Therefore, the signal that attacks
88 only occurred after mRNA vaccination requires confirmation from larger cohorts.

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

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121

122 **Tables**

123 Table 1: characteristics of COVID-19 vaccinated patients with hereditary angioedema

	Total	mRNA vaccines	Vector vaccines
Number of patients	63	48	15
Number of administered vaccines	111	87	24
Age, mean (SD)	48 (15)	49 (16)	46 (14)
Sex - female, no. (%)	42 (67)	31 (65)	11 (73)
Long-term prophylaxis, no. (%)	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, no. (%)	4 (6)	4 (8)	0 (0)
Well-controlled disease (AECT $\geq$ 10), no. (%)	42 (67)	31 (65)	11 (73)
Previous COVID-19, no. (%)	16 (25)	12 (25)	1 (27)
Confirmed diagnosis	11 (18)	11 (23)	0 (0)
Suspected diagnosis*	5 (8)	1 (2)	4 (27)
HAE attack, no. (% of sum of administered vaccines)	11 (10)	10 (11)	1 (4)

124 * Patients with typical COVID-19 symptoms for whom SARS-CoV-2 detection by real-time PCR on
 125 naso-pharyngeal swabs was not available were classified as suspected COVID-19.

126 AECT = angioedema control test; COVID-19 = coronavirus disease 2019; C1-INH = C1-inhibitor
 127 concentrate; IV = intravenous; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute
 128 respiratory syndrome coronavirus-2; SD = standard deviation

129 Table 2: characteristics of patients with a breakthrough HAE attack following COVID-19 vaccination

Patient	Age (years)	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	N.A.	No	Pfizer/BioNtech	Abdominal and facial	Mild	C1-INH IV	24-48 hours	Yes	No	Cystitis
2	52	Female	Poor: 9	Tranexamic acid	N.A.	No	Moderna	Abdominal	Mild	Tranexamic acid	<24 hours	Yes	No	N.A.
3	50	Male	Poor: 6	Danazol	Danazol	No	Pfizer/BioNtech	Abdominal and peripheral	Mild	Danazol	>48 hours	Yes	No	N.A.
4	47	Female	Well: 15	Experimental	N.A.	Yes	Pfizer/BioNtech	Peripheral	Mild	C1-INH IV	<24 hours	Yes	No	N.A.
5	38	Female	Poor: 3	C1-INH IV and danazol	N.A.	Yes	Pfizer/BioNtech	Peripheral	1st Moderate 2nd Mild	C1-INH IV	1st >48 hours 2nd <24 hours	Yes	Yes	N.A.
6	48	Female	Poor: 3	N.A.	N.A.	No	Pfizer/BioNtech	Peripheral	Moderate	C1-INH IV	>48 hours	Yes	No	N.A.
7	43	Female	Well: 11	Experimental	N.A.	No	Pfizer/BioNtech	Facial	Mild	C1-INH IV	<24 hours	Yes	No	N.A.
8	54	Female	Well: 16	N.A.	N.A.	Suspected*	Janssen	Facial	Moderate	N.A.	>48 hours	Yes	N.A.	N.A.
9	35	Female	Poor: 7	C1-INH IV	N.A.	Yes	Pfizer/BioNtech	Abdominal	Mild	C1-INH IV	>48 hours	Yes	N.A.	N.A.
10	49	Male	Well: 11	N.A.	N.A.	No	Moderna	Peripheral and genital	Moderate	C1-INH IV	>48 hours	No	Yes	N.A.

130 *Patients with typical COVID-19 symptoms for whom SARS-CoV-2 detection by real-time PCR on naso-pharyngeal swabs was not available were classified as
 131 suspected COVID-19.

132 AECT = angioedema control test; COVID-19 = coronavirus disease 2019; C1-INH = C1-inhibitor concentrate; IV = intravenous; N.A. = not applicable