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Recombinant human C1 esterase inhibitor as prophylactic treatment in idiopathic non-histaminergic angioedema

To the Editor,

Idiopathic angioedema is characterized by cutaneous and mucosal swellings in the absence of diagnostic laboratory parameters and family anamnesis.[1] Patients who do not respond to prophylactic antihistamine therapy are diagnosed as idiopathic non-histaminergic AE (InH-AAE) according to the definition of the Hereditary Angioedema International Working Group.[2] Recombinant human C1 esterase inhibitor ([rhC1-INH], Conestat alfa/Ruconest®) is an effective and safe treatment for acute attacks and prophylaxis of angioedema (AE) in hereditary angioedema (HAE) type 1 and 2.[3] Given the unresponsiveness to antihistamines in part of Inh-AAE patients, indicating possible involvement of the bradykinin route, we investigated the effectiveness and safety of rhC1-INH prophylaxis in InH-AAE.

In this phase 2, explorative, prospective, single-centre, open-label study, six patients with InH-AAE were enrolled (Table 1)(ethics approval number 17–139). A four-week observation period was followed by an eight-week treatment period with rhC1-INH (twice weekly 50 IU/kg; max 4200 IU), and another four-week observation period (Figure 1; see also supplemental for detailed information about inclusion criteria, study design and funding source). In patient 1, attack frequency was reduced by 85% (6.7-fold) (3 versus 20 attacks, respectively; Figure 1). Angioedema activity scores over 28 days[4] (AAS28) decreased 8-fold with an accumulated AAS score of 29 in the two treatment months versus 233 in the two observational months. Of patients 2 to 6, none showed a clinical response to rhC1-INH. rhC1-INH treatment did not lead to adverse events, or thrombotic events. The percentage of cleaved high molecular weight kininogen (%cHK), C1-esterase inhibitor (C1-INH), high molecular weight kininogen (HK), plasma kallikrein (PK) and factor XII (FXII) (see Figures S1, S2 and supplemental for method) did not differ between treatment and observation period and were not indicative of treatment response. Mean D-dimer, C-reactive protein (CRP) and leukocyte counts in patients were within, or slightly above normal. None of the patients had an AE attack during blood sampling. Genetic analysis in patient 1 supported the diagnosis InH-AAE, since no known gene mutations associated with HAE were identified (Table S1).

Post-trial, patient 1 restarted rhC1-INH treatment achieving again rapid and complete remission for 6 months, even being able to extend the treatment interval to 5 days. Due to health insurance limitations, treatment was switched to omalizumab 300 mg/4 weeks and tranexamic acid 1000 mg twice daily for 3 months, resulting in recurrence of frequent and severe attacks. Restarting treatment with 1000 IU plasma derived C1-INH (pdC1-INH) every 3–4 days for 1 year led to immediate and complete symptom control. After 1 year, treatment was switched to 4200 IE rhC1-INH since herewith, remission could be achieved with longer intervals of 5–6 days. Similar response to pdC1-INH and rhC1-INH, but not to omalizumab, made a placebo response unlikely. Patients 2, 5 and 6 (rhC1-INH non-responders) also initiated omalizumab treatment, with good/near complete response in patients 2 and 6, respectively, and no effect in patient 5 (Table 1). Patient 5 also showed no response to icatibant attack treatment. This first prospective trial showed successful rhC1-INH treatment in one out of six patients with InH-AAE. Three previous case reports described effectiveness of plasma derived (p)dC1-INH prophylaxis in four patients with InH-AAE.[5–7] Our data show that only a proportion of patients may respond to C1-INH treatment. Failure of rhC1-INH in the other 5 InH-AAE patients may suggest that bradykinin is not involved or a dose of 50 IU rhC1-INH per kg was too low. None of the measured biomarkers of the bradykinin route was indicative for the observed effect in the responding patient. However, recent studies showed that in InH-AAE the clinical picture might be caused by different and in part unknown genetic defects, leading to impairment of different factors of the contact system and resulting in a reduced control of the kallikrein system and alteration of bradykinin as main mediator.[8,9] Levels of bradykinin might provide a better biomarker for such activation, however, obtaining reliable samples during an attack is complex. According to the current guidelines, omalizumab is the first choice of treatment for patients with idiopathic angioedema not responding to high dose antihistamins.[10] Response to omalizumab may support mast cell driven disease mechanisms in patients 2 and 6. However, bradykinin cannot completely be ruled out as the main mediator of AE even in conditions commonly associated with mast cell activation, for example in anaphylaxis.[11] This study was limited by its monocentric design and the small sample size. In conclusion, rhC1-INH treatment was effective in 1 of the 6 InH-AAE patients, and omalizumab in 2 out of 4 suggesting a heterogeneous pathogenesis of AE and, consequently, the need for personalized treatment.

TABLE 1 Demographic and clinical characteristics of included patients

	Weight (kg)	Disease duration (months)[a]	Attack intervention[a]	Attack frequency/ month[a]	Baseline C1-INH function	Baseline C4 level	Baseline total IgE	Dose of rhC1INH	Post-trial prophylactic treatment during follow-up	
									Effective	Ineffective
Patient 1 31 y/oFemale	100	47	ER visit 1× Adrenalin i.m. 0.3 mg 4× [b]Prednisone 0.5 mg/kg 3× AH 1dd 1-2×	2.8	1.25	0.30	275	4200 U	rhC1-INH (1000 IE 2/w) pdC1-INH (4200 IE 2/w)	Prednisolone Omalizumab (300 mg/4 w) TA (1000 mg 3 d)
Patient 2 37 y/o Female	72	6	ER visit 1× Adrenalin 1× [b]Prednisone 0.5 mg/kg 6× AH 1-2dd 8×	3.7	0.95	0.15	163	3615 U	Omalizumab (600 mg/3 w)	
Patient 3 56 y/o Male	85	103	Prednisone 60 mg 1×	2.6	1.19	0.27	254	4200 U		
Patient 4 33 y/o Male	74	8	Prednisone 30 mg 8×	15.8	1.54	0.52	98	3715 U	TA (500 mg 3 d) AH (5 mg 1 d)	
Patient 5 25 y/o Female	85	84	–	2.8	1.70	0.34	87	4200 U		Omalizumab (300 mg/4 w) Icatibant (attack treatment)
Patient 6 60 y/o Female	116	21	AH 1dd 2×	4.2	1.21	0.23	95	4200 U	Omalizumab (300 mg/4 w)	

Note: Reference values for C1-INH function: 0.63–1.82 U/mL. C4 level: 0.1–0.47 g/L. IgE level: 0–100 kU/L. All patients used four times the standard daily dose antihistamines during follow-up.

Abbreviations: TA, tranexamic acid; AH, antihistamine; ER, emergency room; w, weekly; d, daily; i.m., intramusculair; i.v., intravenous; p.o., Per os (orally).

[a]Number of attack interventions during 6 months before study.

[b]Equivalent dose of other glucocorticosteroid.

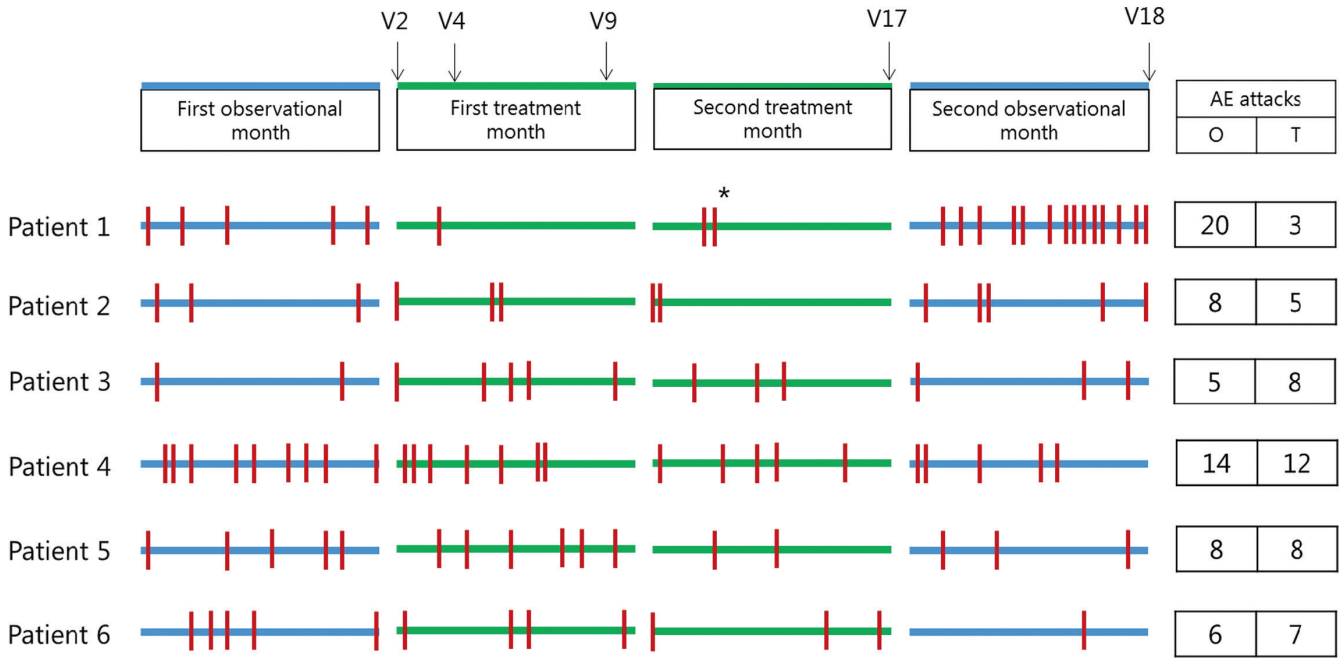

FIGURE 1 Four-month study sequence and attack episodes per month. Trial visits at which blood is drawn (V2, V4, V9, V17, V18) are indicated with an arrow. Treatment visits occur twice a week during the treatment months in which rhC1-INH is administered. Visit 18 marks the end of the trial, no pdC1-INH was administered during this visit. One attack episode is indicated with a vertical line and could last for multiple days. Cumulative angioedema (AE) attacks in the observation months (O) versus the treatment months (T) is presented. *AE attack occurred 7 days after last rhC1-INH administration due to a missed treatment visit

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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The nasopharyngeal and salivary microbiomes in COVID-19 patients with and without asthma

To the Editor,

So far, our understanding of the associations between respiratory infections and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the context of asthma is limited. Although our previous study and others did not find a correlation between preexisting asthma and increased risks of severe coronavirus disease 2019 (COVID-19) outcomes,[1–3] people with asthma usually have an increased vulnerability to conventional respiratory viral infections. Thus, continuous investigation on SARS-CoV-2 infection in people with asthma is important.

People with asthma harbor altered airway microbiota, which has been suggested to mediate an increased susceptibility to severe illnesses upon viral respiratory infections.[4] However, the microbiomes of patients with asthma during SARS-CoV-2 infection have not yet been characterized. To this end, we performed a microbiome study using nasopharyngeal samples and saliva samples from COVID-19 patients with and without preexisting asthma.

This study was approved by the Institutional Review Board of Washington University in St. Louis (IRB number 202003085), and all patients who were enrolled in the study provided informed consent. A total of 105 samples were collected from patients with COVID-19 within 14 days from the onset of any relevant symptoms between March and September of 2020. For the nasopharyngeal samples, seven were from patients with asthma and 41 were from patients with no asthma diagnosis. For the salivary samples, 16 were from patients with asthma and 41 were from patients with no asthma diagnosis. Demographics and clinical characteristics of the COVID-19 patients are shown in Table S1. Study participants were enrolled in both outpatient and inpatient settings. Nine patients ($n = 3$ asthma, and $n = 6$ non-asthma) provided both saliva and nasopharyngeal samples. The detailed methods and sequencing analysis procedures are presented in the Appendix S1. The read number of each sample and rarefaction curves are plotted in Figure S1A, B. The microbial communities of the nasopharyngeal and saliva samples were significantly different in alpha diversity represented by the Shannon Index (p-value <0.001, Figure 1A) and beta diversity based on weighted UniFrac distances (p-value = 0.001, Figure 1B). For the 48 nasopharyngeal samples, seven were from COVID-19 patients with asthma and 41 were from those who did not have an asthma diagnosis. There were no marked differences in relative abundance for any of the top five abundant phyla in nasopharyngeal samples between the asthma and non-asthma groups (Figure 1C). For the 57 saliva samples, the relative abundance of phylum Actinobacteria was significantly decreased in COVID-19 patients with asthma compared with those without preexisting asthma (adjusted p-value = 0.02, Figure 1D). The top ten abundant genera in the nasopharyngeal samples and saliva samples are displayed in Figure 1E, F, respectively.

Differences at the genus-level, but not at the community level (Figure S2), were observed in the nasopharyngeal and salivary microbiomes between patients with and without preexisting asthma. In differential abundance tests using DESeq2 for nasal samples, seven genera were significantly different between the two groups, with all being less abundant (including *Porphyromonas*, *Haemophilus*,