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

Mehran Alizadeh Aghdam[1], Zonne Hofman[1], Michelle Meertens[1], Ans Lebens[1], Erik Hack[1], André Knulst[1], Coen Maas[1], and Heike Rockmann[1]

[1]Universitair Medisch Centrum Utrecht

April 16, 2024

Abstract

Background Idiopathic non-histaminergic acquired angioedema (InH-AAE) does not respond to anti-histamines and is possibly mediated by bradykinin. **Objective** To investigate the efficacy and safety of recombinant human C1-esterase inhibitor (rhC1-INH), for prophylaxis of InH-AAE, and to evaluate contact system parameters as biomarkers for attacks. **Methods** A prospective, open-label study of patients with InH-AAE with > 2 AE attacks/month. rhC1-INH (50 IU/kg was administered intravenously; maximum 4200 IU) twice weekly for 2 months, preceded and followed by a one-month period of observation. The primary endpoint was a >50% reduction in attack frequency. C1INH-function and plasma levels of high molecular weight kininogen, factor XII, plasma prekallikrein, C4, cleaved kininogen, d-dimer were evaluated as potential biomarkers. Post-trial follow-up was evaluated in all patients. **Results** Six patients (mean age 41 years; four female) were enrolled. One patient showed a reduction in attack frequency of 84% (3 versus 19) during rhC1-INH treatment, and showed clinical response to plasma-derived C1-INH but not to omalizumab post-trial. Restarting rhC1-INH treatment resulted in a similarly rapid response. The other 5 patients showed no improvement. No major adverse events were reported. None of the measured biomarkers were related to treatment response. Post-trial, omalizumab was administered to four patients, of which two reported response. **Conclusion** rhC1-INH treatment was effective in 1 of 6 InH-AAE patients, suggesting a bradykinin-dependent mechanism of attacks in this patient. Response to omalizumab or tranexamic acid during follow-up in a number of the patients points to a heterogeneous pathogenesis of InH-AAE disease requiring a personalised treatment approach.

Introduction

Angioedema (AE) is characterized by episodes of acute submucosal or subcutaneous swellings,[1] and strongly influences quality of life.[2] The pathophysiological mechanisms of AE are not yet fully understood. Generally, two vasoactive peptides are thought to mediate acute AE swellings; namely, histamine and bradykinin. Histamine is released from activated mast cells and basophils, possibly through activation of the FcεRI, and is associated with allergic AE and AE in patients with chronic spontaneous urticaria. [2, 3] Bradykinin is generated upon activation of the plasma contact system, which comprises of factor XII (FXII), plasma prekallikrein (PK) and high molecular weight kininogen (HK). Active FXII (FXIIa) activates PK into plasma kallikrein (PKal) that cleaves bradykinin from HK.[4] By binding to mainly the Bradykinin receptor 2 (B2), bradykinin increases vascular permeability and mediates AE.[5] The bradykinin pathway is claimed to mediate hereditary AE (HAE) and angiotensin converting enzyme (ACE) induced AE.[5]

The pathomechanisms of attacks in idiopathic AE are less clear. 64-84% of patients with idiopathic AE respond to antihistamine treatment suggesting histaminergic AE in most of these patients.[6-8] Patients that do not respond to antihistamine therapy are diagnosed as idiopathic non-histaminergic AE (InH-AAE).[9] Elevated bradykinin levels were found in four patients with idiopathic non-histaminergic AE (InH-AAE) during acute attacks compared to normal levels during remission and in healthy controls.[10] Measurements of bradykinin as biomarker are challenging due to its short half-life and high sensitivity to pre-analytical

procedures. Therefore several other contact system parameters have been proposed as biomarkers, including complexes between C1-INH and contact system proteases (FXIIa, PKal), HK antigen levels, and cleaved HK (cHK).[11] The fibrin breakdown product D-dimer is also elevated in HAE[12] and CSU[13] and appears to reflect a condition with increased vascular permeability.

In HAE, C1-INH is supplemented in order to inhibit coagulation factor XIIa and PKal, preventing excess generation of bradykinin.[14] Restoring functional C1-INH levels above the 40% threshold has been reported to protect against AE attacks.[15] Effectiveness of C1-INH therapy has also been reported in patients with hereditary angioedema with normal C1 inhibitor (HAE-nC1-INH). Three case-studies reported a complete (n=2) or partial (n=1) effect of prophylactic plasma-derived C1 esterase inhibitor (pdC1-INH). Icatibant showed effect within two hours in three of these described patients.[16-18]

Recombinant human C1 esterase inhibitor ((rhC1-INH), Conestat alfa/Ruconest®), is an effective and safe treatment for acute attacks and prophylaxis of AE in HAE type 1 and 2.{Riedl, 2017 #424} Given the unresponsiveness to antihistamine treatment in patients with Inh-AAE, indicating possible involvement of the bradykinin route, the objective of our study was to investigate the effectiveness and safety of rhC1-INH prophylaxis in InH-AAE in a prospective clinical trial. Furthermore, we evaluated if plasma levels of C1-INH, C1-INH function, C4, FXII, PK, HK, and cHK, markers of the bradykinin pathway can be used to predict a therapeutic response to rhC1-INH in InH-AAE.

Methods

Study participants

This phase 2 prospective, single-center, open-label study was performed from March 2018 to February 2021 at the dermatology and allergology department of the University Medical Center, Utrecht in the Netherlands.

Patients aged 18 years and older suffering from AE attacks with at least two attacks per month during the last six months despite treatment with four times the standard daily dose of antihistamines, and no known cause for AE were eligible for inclusion. Patients were excluded in cases of accompanying wheals; pregnancy or breastfeeding; a history of rabbit allergy; ACE-inhibitor use in the past six months; recent or current use of methotrexate, azathioprine, mycophenolic acid, omalizumab or cyclosporine. Patients with clinically relevant conditions that had the potential to compromise the safety of the patient such as renal or hepatic insufficiency or malignancies or when another diagnosis was deemed more likely (e.g. allergic AE, drug-hypersensitivity, mastocytosis or HAE) were also excluded. Patients were allowed to use rescue medication during acute AE attacks including antihistamines, oral steroids and intramuscular adrenaline.

All patients provided written informed consent, and the study was approved by the local ethics committee (protocol number 17-139).

Study design

All enrolled patients completed a four-week observation period, followed by an eight-week treatment period with rhC1-INH (Recombinant human C1 esterase inhibitor (rhC1-INH), Conestat alfa/Ruconest®; Pharming Technologies; Leiden , The Netherlands), followed by another four-week observation period (Supplemental figure 1). Throughout the entire trial, patients continued using 4dd antihistamines. The total dose of rhC1-INH was calculated based on body weight (50 IU/kg; max 4200 IU) and was twice-weekly administered intravenously over a time course of five minutes.

A detailed medical history and physical examination were recorded at first visit and adverse events and concomitant drug use were registered at each following visit.

The attack frequency and severity were recorded in the AE activity score (AAS) form.[19] Weekly AAS results (AAS7) were combined into AAS scores per four weeks (AAS28). An attack was separated from a subsequent attack when there had been an AE free period between reported swellings on subsequent days as scored on the AAS form. The AE Quality of Life score (AE-QoL) was used to assess the effect of AE on quality of life,[20] with 0 to 23 indicating "no effect", 24 to 38 indicating a "small effect" and [?] 39 indicating a "moderate

to large effect".[21] The primary endpoint of the study was a reduction in attack frequency of 50% in the treatment period compared to the cumulative observation period. Secondary outcomes were AAS over 28 days (AAS28) and AE-QoL scores during the treatment period compared to observation period. Outcomes were assessed per case. Follow-up data was collected by analysing patient records.

Collection of blood samples and laboratory assessments

Blood was obtained at visit 2,4 and 17 (prior to C1-INH dose administration) and at 18 (follow-up visit). C1-INH function was measured with a chromogenic assay (Sanquin, the Netherlands). C4 levels and total IgE were determined at visit 1. In women <50 years of age, pregnancy was excluded via a urine dipstick βHCG test. CRP, d-dimer and leukocyte count were determined with routine assays. C1-INH, FXII, PK and HK levels were analysed using immunoblot. For this, EDTA plasma was diluted 40 times in four times reducing sample buffer (15.5% glycerol, 96.8 mM Tris-HCL, 3.1% SDS, and 0.003% bromophenol blue, 25 mM DTT), boiled for 10 minutes, and 5 µL per sample was loaded and ran on a 4-12% Bis-Tris gel at 165V for 60 minutes and transferred onto Immobilon-FL membranes at 125V for 55 minutes. For detection, polyclonal goat anti human IgG antibodies (anti-human FXII Cl20055AP, anti-human PK Cl20090A, anti-human HK Cl20027AP, anti-human C1-INH CL200323AP, Cedarlane, Burlington, Canada) and Alexa Fluor 680 donkey anti-sheep IgG (lot#1878516, Dako, Glostrup, Denmark) were used.

Levels of cHK in EDTA plasma, an indirect marker for bradykinin release, were determined with ELISA as described above.[22] The upper normal limit was assessed using values of ˜50 healthy individuals for cHK and ˜20 healthy controls for C1-INH complexes.

Data analysis

Due to the small sample size, data was analysed using descriptive statistics.

Statistics and graphical demonstration of clinical data and laboratory outcomes were performed with GraphPad Prism 8.3.0 software.

Role of the funding source

The study was designed and performed by the study team of the UMC Utrecht at the Dermatology and Allergology clinic, and partly financed by Pharming Technologies, which was informed about the study protocol and was notified regarding inclusion of patients and progress in order to organize drug delivery. The company also donated rhC1-INH for patient 1 for six months treatment after the last study visit.

RESULTS

Clinical response to rhC1-INH in one out of six patients

Six patients were included in the study, four females and two males. C1-INH function and C4 levels were normal in all patients. At the start of the study, the mean age was 41 years and the median disease duration was 8 years. Frequency of AE attacks varied from 2.6 attacks to 15.8 attacks per month in the six months prior to the study. Other baseline characteristics are presented in table 1. None of the patients had been treated with long term immunosuppressive treatment (methotrexate, azathioprine, mycophenolic acid, cyclosporine), Icatibant or omalizumab before the study.

In patient 1, the attack frequency was reduced by 84% (6.3-fold) during the treatment period compared to that during the observation period (3 versus 19 attacks, respectively; Figure 1). One of the three attacks in this patient during the second treatment month occurred 7 days after the last rhC1-INH administration when the patient had missed a treatment visit. The AAS28 scores of this patient decreased 8-fold during treatment months compared to the observation period with an accumulated AAS score of 29 in the two treatment months versus 233 in the two observational months (table 2). AE related quality of life (AE-QoL) scores improved, from 26 (small effect on AE-QoL) during the observation period to 12,5 (no effect on AE-QoL) during treatment.

None of the other patients (patients 2 to 6) showed a clinical response to rhC1-INH either measured as attack frequency or accumulated AAS28 scores. No improvement of AE-QoL during treatment was observed (Supplementary table 2). Patient 3 showed a trend of a higher AAS score during the treatment period. Patients 4, 5 and 6 had lower AAS scores in the second treatment and observation periods compared to those during the first treatment and observation period.

No major adverse events and minimal use of escape medication during treatment were reported

Administration of rhC1-INH in patients with normal C1-INH levels did not lead to any severe adverse events, including thrombotic events. Three patients reported episodes of headache during the treatment. One patient reported an uncomplicated herpes labialis flare-up in treatment week 7. Escape medication used by patient 1 in the first observation period was one dose of 50mg prednisolone and one-time use of the adrenaline auto-injector (0.3mg). No escape medication was used during the treatment period. In the second observation period (after 8 weeks of treatment) seven doses of prednisolone were used ranging from 20 to 60 mg and four adrenaline auto-injector over two episodes were used by patient 1. Patient 3 used one dose of 20mg prednisolone during the treatment period and one during the second observation period. Patient 4 used one dose of 60mg prednisolone during the first observation period. The other patients did not use escape medication during the study period.

Lack of biomarkers predicting treatment response

Levels of C1-INH, HK, PK and FXII during treatment did not differ from those during the observation periods (Figure 2). These levels were all normal except for PK levels in patient 3, which were decreased but did not change during rhC1-INH treatment.

All measured % cHK levels were within the normal range with little variation throughout the study in all patients (upper normal limit cHK <20%; mean levels in patient 1 15± 4 (SD)%; patient 2 3± 2%; patient 3 2± 1%; patient 4 15± 4%; patient 5 7± 1%; patient 6 4± 3%) (Supplemental Figure 2A).

Mean D-dimer levels were slightly elevated compared to the reference range (<0.50 mg/L) in patient 1 (0.54 ± 0.06 mg/L), patient 3 (1.42 ± 0.15) and patient 4 (1.62 ± 0.94,), whereas they were normal in patients 2, 5 and 6. None of the patients had an attack when blood samples were collected (Supplemental Figure 2B).

CRP and leukocyte counts in patients were within, or slightly above the normal range (Supplemental figure 2C&2D).

Post-trial follow-up reveals a heterogeneous treatment response *Patient 1* restarted rhC1-INH treatment after the second observation period initially with a standard treatment interval of 3-4 days achieving again rapid and complete remission (table 3). This was maintained when extending the treatment interval to 5 days. After seven months, due to health insurance limitations, treatment was switched to omalizumab 300mg/4wks and tranexamic acid 1000mg twice daily for three months, resulting in frequent and severe AE with 15 (AAS28:87) and 11 (AAS28: 101) attacks in the first two months and also in month 3, of which detailed data are missing. In this period, admission to emergency room or intensive care was required seven times. Treatment of attacks with 1000 IU pdC1INH was effective. Subsequently, health insurance approval was granted and prophylactic treatment with 1000 IU pdC1-INH every 3-4 days was initiated, which again led to immediate symptom control. After one year, treatment was switched to 4200IE rhC1-INH since herewith, remission could be achieved with longer intervals of 5-6 days. After one year, treatment was switched to 4200 IU rhC1-INH every 5-6 days, which successfully prevented the development of attacks. Additional genetic analysis supported the InH-AAE diagnosis (see supplemental table 1).

Patient 2 initiated omalizumab after the study and reported partial response after six months of treatment. Consequently, the treatment dose was increased incrementally to 600mg/3wks, which resulted in a good treatment response after 28 doses.

Patient 3 wished for no further treatment additional to antihistamines and accepted symptoms with no further follow-up.

Patient 4 started post-trial tranexamic acid three times daily 500mg alongside desloratadin 5 mg four times daily, resulting in a decrease in frequency and severity.

Patient 5 started icatibant as attack medication during a two-month period. Due to ineffectiveness, icatibant was ceased and the patient recently started omalizumab treatment. The first three doses did not yet result in improvement.

Patient 6 showed an immediate near complete response after the first dose of omalizumab with an AAS28 score of 5 after the first omalizumab dose compared to a mean AAS28 score of 32 in the six weeks before omalizumab treatment.

DISCUSSION

This is the first prospective trial describing the successful use of rhC1-INH as prophylactic treatment in one out of six patients with InH-AAE (patient 1). Restart resulted in an equally fast and beneficial response. pdC1-INH also appeared to be effective. We hypothesize that the bradykinin route is pathomechanistically involved although we found no formal proof after biomarker investigations. Post-trial, patients 1, 2, 5 and 6 received omalizumab treatment. Patients 2 and 6 experienced a good, and a near complete response respectively. Patients 1 and 5 reported no clinical effect of omalizumab.

We observed an almost complete and fast improvement of AE activity in patient 1, with only 3 mild attacks in the treatment period versus 19 attacks in the observation period. Equal effectiveness was found during post-trial follow-up upon restart of rhC1-INH treatment on two different treatment periods with a similarly fast and near complete response. This was unlikely a placebo effect, since post-trial follow-up data showed a similar response to pdC1-INH, whereas treatment with omalizumab had no effect and resulted in an increased attack rate. The effect of rhC1-INH was in line with that in HAE, in which a sustained effect of 72 hours or longer was observed in 93% of HAE patients despite the short half-life of approximately 3 hours.[23] Clinical response to recombinant (r)hC1-INH in patients with InH-AAE was not published before. Three previous case reports describe successful use of plasma derived (p)dC1-INH prophylaxis in four patients with InH-AAE.[16-18] However, from these reports, it is not clear to what extent the observed responses were due to a placebo effect, and what proportion of patients may respond to such therapy. Our data show that only a proportion of the patients with InH-AAE may respond to C1-INH treatment. Failure of efficacy of rhC1-INH in the other 5 InH-AAE patients may suggest that bradykinin is not involved in generating attacks in these patients. However, we favour another explanation. A dose of 50 IU rhC1-INH per kg increases circulating C1-INH levels by approximately 2-fold. This increase may have been too low, especially since factor XIIa bound to an activator is less well inhibited by C1-INH.[24]

None of the biomarkers of the bradykinin route (C1-INH, FXII, PK, HK) differentiated the responding patient from the others. Moreover, none of these biomarkers pointed to an increased activation of the contact system. One may argue that levels of bradykinin could provide a better biomarker for such activation. This is supported by the finding of elevated bradykinin levels in InH-AAE patients at the time of AE attacks.[10] Considering the technical issues, such as processing of plasma samples, we did not assess bradykinin levels in the patients described here.

After the study period, treatment of patient 1 with both rhC1-INH and pdC1-INH resulted in an immediate effect, though the effective treatment interval appeared to be 3-4 days for pdC1-INH versus 5-6 days for rhC1-INH. Previous studies show that there is no fundamental difference in efficacy between pdC1-INH and rhC1-INH in patients with HAE, when similar doses, expressed as IU, are given.[34] However, doses given to patient 1, who had a body weight of 100 kg, were different, 4200 IU of rhC1-INH versus 1000 IU of pdC1-INH per administration. Thus, the increase of C1-INH activity, which was approximately 1 U per ml in case of rhC1-was considerably lower, about 0.25 IU, when pdC1-INH was administered. Therefore, C1-INH levels may have decreased below a critical level more rapidly in cases of pdC1-INH administration, in spite of its longer half-life.

The restart of C1-INH treatment in patient 1 resulted in an immediate effect with a clear difference of the

effective treatment interval of 3-4 days for pdC1-INH versus 5-6 days for rhC1-INH. Previous studies show that there is no fundamental difference in efficacy between pdC1-INH and rhC1-INH in patients with HAE.[25] The observed difference in treatment interval is therefore most likely explained by dosage inequivalence since rhC1-INH is dosed at 50IU/kg with a maximum of 4200IU and pdC1-INH at a fixed dose of 1000IU.[26, 27] In our patient with body weight 100kg, 1000IU pdC1-INH might have been relatively under dosed compared to 4200IU rhC1-INH resulting in lower effectivity and the need for shorter treatment intervals.[28]

C1-INH treatment is generally well tolerated, though recent studies suggest a small risk of trombotic events upon treatment with rhC1-INH and pdC1-INH in HAE patients.[29, 30] We did not observe thrombotic or any other adverse events in the patients studied, even though we supplemented C1-INH in patients with normal levels.

A review of omalizumab for InH-AAE in six small case series, reports a complete response in all 20 patients, with time to response ranging from one day to 16 weeks.[31] Four patients with InH-AAE who did not respond to rhC1-INH treatment, were subsequently treated with omalizumab. Two patients responded to this therapy. Patient 1 and 5 did not show any benefit from three months omalizumab treatment, although the possibility that the treatment period with omalizumab was too short cannot be excluded.[32] Prospective evaluation in an unselected population is needed to gain insight about the real percentage of responders. Response to omalizumab may be interpreted as evidence for histamine as the main mediator of AE in these patients.[32] One should be careful about making this conclusion, as marked activation of FXII, PK, and kininogen has previously been found during anaphylaxis, indicating bradykinin cannot be ruled out as the main mediator of AE even in conditions commonly associated with mast cell activation.[33]

In conclusion, rhC1-INH treatment was effective in 1 of 6 InH-AAE patients. Response to omalizumab and tranexamic acid during follow-up in some of the other patients points to a heterogeneous pathogenesis of this disease and, as a consequence, the need for a personalised treatment approach.

References

1. Schulkes KJG, Van den Elzen MT, Hack EC, Otten HG, Bruijnzeel-Koomen C, Knulst AC. Clinical similarities among bradykinin-mediated and mast cell-mediated subtypes of non-hereditary angioedema: a retrospective study. Clin Transl Allergy. 2015;5(1):5.

2. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The International EAACI/GA(2)LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. Allergy. 2021.

3. Alizadeh Aghdam M, Knol EF, van den Elzen M, den Hartog Jager C, van Os-Medendorp H, Knulst AC, et al. Response of FcepsilonRI-bearing leucocytes to omalizumab in chronic spontaneous urticaria. Clin Exp Allergy. 2020.

4. Busse PJ, Christiansen SC. Hereditary Angioedema. N Engl J Med. 2020;382(12):1136-48.

5. Cicardi M, Zuraw BL. Angioedema Due to Bradykinin Dysregulation. J Allergy Clin Immunol Pract. 2018;6(4):1132-41.

6. Zingale LC, Beltrami L, Zanichelli A, Maggioni L, Pappalardo E, Cicardi B, et al. Angioedema without urticaria: a large clinical survey. CMAJ. 2006;175(9):1065-70.

7. Mansi M, Zanichelli A, Coerezza A, Suffritti C, Wu MA, Vacchini R, et al. Presentation, diagnosis and treatment of angioedema without wheals: a retrospective analysis of a cohort of 1058 patients. J Intern Med. 2015;277(5):585-93.

8. Hofman ZLM, van West N, Hack CE, Knulst AC, Maas C, Rockmann H. High occurrence of antihistamine resistance in patients with recurrent idiopathic angioedema. Clin Transl Allergy. 2019;9:35.

9. Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International

Working Group. Allergy. 2014;69(5):602-16.

10. Cugno M, Tedeschi A, Nussberger J. Bradykinin in idiopathic non-histaminergic angioedema. Clin Exp Allergy. 2017;47(1):139-40.

11. Porebski G, Kwitniewski M, Reshef A. Biomarkers in Hereditary Angioedema. Clin Rev Allergy Immunol. 2021;60(3):404-15.

12. Reshef A, Zanichelli A, Longhurst H, Relan A, Hack CE. Elevated D-dimers in attacks of hereditary angioedema are not associated with increased thrombotic risk. Allergy. 2015;70(5):506-13.

13. Asero R. D-dimer: a biomarker for antihistamine-resistant chronic urticaria. J Allergy Clin Immunol. 2013;132(4):983-6.

14. Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med. 2008;359(10):1027-36.

15. Zuraw BL, Cicardi M, Longhurst HJ, Bernstein JA, Li HH, Magerl M, et al. Phase II study results of a replacement therapy for hereditary angioedema with subcutaneous C1-inhibitor concentrate. Allergy. 2015;70(10):1319-28.

16. Gravante C, Carucci L, Bova M, Petraroli A, Genovese A, Marone G. Prophylactic treatment with plasma-derived C1 inhibitor in idiopathic non-histaminergic angioedema. Pediatr Allergy Immunol. 2016;27(6):658-9.

17. Shroba J, Hanson J, Portnoy J. Current treatment options for idiopathic angioedema. Ann Allergy Asthma Immunol. 2015;115(5):429-33.

18. Stahl MC, Harris CK, Matto S, Bernstein JA. Idiopathic nonhistaminergic angioedema successfully treated with ecallantide, icatibant, and C1 esterase inhibitor replacement. J Allergy Clin Immunol Pract. 2014;2(6):818-9.

19. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development, validation, and initial results of the Angioedema Activity Score. Allergy. 2013;68(9):1185-92.

20. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and construct validation of the angioedema quality of life questionnaire. Allergy. 2012;67(10):1289-98.

21. Kulthanan K, Chularojanamontri L, Rujitharanawong C, Weerasubpong P, Maurer M, Weller K. Angioedema quality of life questionnaire (AE-QoL) - interpretability and sensitivity to change. Health Qual Life Outcomes. 2019;17(1):160.

22. Hofman ZLM, de Maat S, Suffritti C, Zanichelli A, van Doorn C, Sebastian SAE, et al. Cleaved kininogen as a biomarker for bradykinin release in hereditary angioedema. J Allergy Clin Immunol. 2017;140(6):1700-3 e8.

23. Bernstein JA, Relan A, Harper JR, Riedl M. Sustained response of recombinant human C1 esterase inhibitor for acute treatment of hereditary angioedema attacks. Ann Allergy Asthma Immunol. 2017;118(4):452-5.

24. Schousboe I. Binding of activated Factor XII to endothelial cells affects its inactivation by the C1-esterase inhibitor. Eur J Biochem. 2003;270(1):111-8.

25. Hack CE, Relan A, van Amersfoort ES, Cicardi M. Target levels of functional C1-inhibitor in hereditary angioedema. Allergy. 2012;67(1):123-30.

26. Farrell C, Hayes S, Relan A, van Amersfoort ES, Pijpstra R, Hack CE. Population pharmacokinetics of recombinant human C1 inhibitor in patients with hereditary angioedema. Br J Clin Pharmacol. 2013;76(6):897-907.

27. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010;363(6):513-22.

28. Pawaskar D, Tortorici MA, Zuraw B, Craig T, Cicardi M, Longhurst H, et al. Population pharmacokinetics of subcutaneous C1-inhibitor for prevention of attacks in patients with hereditary angioedema. Clin Exp Allergy. 2018;48(10):1325-32.

29. Longhurst H, Farkas H. Biological therapy in hereditary angioedema: transformation of a rare disease. Expert Opin Biol Ther. 2020;20(5):493-501.

30. Valerieva A, Staevska MT, Grivcheva-Panovska V, Jesenak M, Kohalmi KV, Hrubiskova K, et al. Recombinant human C1 esterase inhibitor for hereditary angioedema attacks: A European registry. World Allergy Organ J. 2021;14(4):100535.

31. Bucher MC, Petkovic T, Helbling A, Steiner UC. Idiopathic non-histaminergic acquired angioedema: a case series and discussion of published clinical trials. Clin Transl Allergy. 2017;7:27.

32. Belbezier A, Bocquet A, Bouillet L. Idiopathic Angioedema: Current Challenges. J Asthma Allergy. 2020;13:137-44.

33. Sala-Cunill A, Bjorkqvist J, Senter R, Guilarte M, Cardona V, Labrador M, et al. Plasma contact system activation drives anaphylaxis in severe mast cell-mediated allergic reactions. J Allergy Clin Immunol. 2015;135(4):1031-43 e6.

Hosted file

`Figures Alizadeh Aghdam et al 2021.docx` available at https://authorea.com/users/739562/articles/713075-recombinant-human-c1-esterase-inhibitor-can-be-effective-as-prophylactic-treatment-in-idiopathic-non-histaminergic-angioedema

Hosted file

`Tables Alizadeh Aghdam et al 2021.docx` available at https://authorea.com/users/739562/articles/713075-recombinant-human-c1-esterase-inhibitor-can-be-effective-as-prophylactic-treatment-in-idiopathic-non-histaminergic-angioedema