# Clinical Communications

## Recombinant human C1 esterase inhibitor as short-term prophylaxis in patients with hereditary angioedema

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***Clinical Implications***

- Limited data are available on recombinant human C1 esterase inhibitor as short-term prophylaxis. A case series of 51 patients (70 procedures) indicated that recombinant human C1 esterase inhibitor short-term prophylaxis administered within several hours before a medical/dental procedure was efficacious and well tolerated.

*TO THE EDITOR:*

Hereditary angioedema (HAE), an inherited deficiency of functional C1 esterase inhibitor (C1-INH), is characterized by recurrent episodes of disabling and often painful swelling in subcutaneous and/or submucosal tissues.[1] HAE attacks are generally unpredictable, but triggers for an attack can include having a dental or medical procedure (eg, surgery), other trauma, or stress.[1,2] A preemptive management plan for patients undergoing these types of situations may reduce the risk of HAE attacks.[2] Recommendations include administration of short-term prophylaxis in patients with HAE before invasive medical procedures, especially those involving the upper airways or digestive tract, with C1-INH concentrate typically the medication of choice.[2]

Recombinant human C1-INH (rhC1-INH) is a C1-INH concentrate indicated in the United States and the European Union for the treatment of acute attacks in adults and adolescents with HAE, and several studies have demonstrated that rhC1-INH is efficacious and well tolerated.[3-7] Weight-based dosing is recommended for rhC1-INH (<84 kg, 50 IU/kg; ≥84 kg, 4200 IU). rhC1-INH has also been shown to be efficacious and well tolerated as long-term prophylaxis in patients with frequent attacks of HAE.[8] However, data are needed on the efficacy and safety of rhC1-INH as short-term prophylaxis. The objective of the present study was to assess rhC1-INH as short-term prophylaxis in patients with HAE/angioedema due to C1 inhibitor deficiency.

In this retrospective study, patients diagnosed with C1 inhibitor deficiency from the United States and Europe were treated with rhC1-INH before medical procedures or stressful life events. Patients from this study population who were not receiving long-term prophylaxis and underwent medical procedures or stressful life events without short-term prophylaxis were included as part of a self-control group, and these procedures were included in the control analyses. HAE attacks were recorded through 7 days postprocedure/event.

Fifty-one patients from 7 countries (Bulgaria [n = 11], Czech Republic [n = 7], Croatia [n = 2], North Macedonia [n = 10], Serbia [n = 3], Slovakia [n = 11], and the United States [n = 7]) were included in this study. Most of the study population was female (n = 32; 62.7%), with a median age and weight of 44 years (range, 17-73 years) and 74.0 kg, respectively. Most patients had type I HAE (n = 47; 92.2%). Overall, the patients in this case series had a median of 14 attacks annually. Twelve (23.5%) of the 51 patients were receiving long-term prophylaxis and received either danazol (n = 10; dose range, 100-300 mg of varying frequency [eg, daily, every other day, 6 times per week]) or tranexamic acid (n = 2; dose range, 1000-2000 mg/d). For 1 of these 12 patients, the prophylactic dose was increased from danazol 200 mg/d to 600 mg/d for 1 day before and 2 days after surgery.

A total of 70 procedures were recorded for the 51 patients, for which the median rhC1-INH dose given was 3075 IU (range, 2100-4200 IU). More than half the administrations of rhC1-INH were in conjunction with dental procedures (52.9%); there was 1 case of a stressful life event (Table I). Most (97.3%) dental procedures in patients administered rhC1-INH were characterized as high risk, and included tooth extraction, oral surgery, and cutting of soft tissues. Nineteen (27.1%) of the 70 procedures were from 12 patients receiving long-term prophylaxis. The rhC1-INH prophylaxis was administered a median of 60 minutes before the procedures; in most cases (n = 48; 68.6%), the rhC1-INH was administered 10 to 65 minutes before the procedure. Of these 48 procedures in which rhC1-INH was administered within 10 to 65 minutes preprocedure, 25 were dental (52.1%), 16 were surgical (33.3%), and 7 were endoscopy (14.6%). A subset of patients served as a self-control set of procedures and included 16 patients who had undergone 26 procedures with no long- or short-term prophylaxis preprocedure. Most of these 26 control procedures were dental (n = 17; 65.4%) or surgical (n = 6; 23.1%; Table I).

Overall, 97.1% of the 70 procedures with rhC1-INH short-term prophylaxis administration were attack-free during the 2 days after the procedure, compared with 23.1% of the 26 procedures in the self-control group (Figure 1). For the 2 HAE attacks (peripheral [hand, knee]) that occurred within 2 days postprocedure in the rhC1-INH group, rhC1-INH was administered 230 minutes and 24 hours or more preprocedure, respectively. Within 7 days postprocedure, 88.6% of the 70 cases with rhC1-INH short-term prophylaxis administration were attack-free, compared with 19.2% of the 26 control cases (Figure 1). For the 6 rhC1-INH cases in which an attack occurred between 2 and 7 days postprocedure, the timing of rhC1-INH administration preprocedure was 60 minutes or less (n = 3), 120 minutes (n = 1), 280 minutes (n = 1), or not reported (n = 1). When the 19 procedures for the patients on

**TABLE I.** Types of procedures

| Category | Cases, n (%) | |
|---|---|---|
| | rhC1-INH prophylaxis (n = 70) | Self-control group* (n = 26) |
| Dental procedure† | 37 (52.9) | 17 (65.4) |
| High risk | 36 (97.3) | 16 (94.1) |
| Low risk | 1 (2.7) | 1 (5.9) |
| Surgical procedure | 21 (30.0) | 6 (23.1) |
| Endoscopy procedure | 11 (15.7) | 2 (7.7) |
| Stressful life event‡ | 1 (1.4)§ | 1 (3.8)§ |

*NOS*, Not otherwise specified.

*Cases in self-control group in which patients did not receive long- or short-term prophylaxis.

†Dental procedures characterized as high risk for the rhC1-INH group: tooth extraction(s) (n = 24), dental procedure NOS (n = 6), root canal (n = 3), cavity/filling under local anesthesia (n = 1), dental veneer (n = 1), and dental abrasion (n = 1); for the self-control group: tooth extraction(s) (n = 14), cavity obturation (n = 1), and root canal (n = 1). For both groups, teeth cleaning was classified as low risk (1 in each group).

‡Classified as a "procedure" for ease of presentation. Stressful life event was identified as an adventure holiday in the mountains.

§The same patient went on 2 adventure holidays in the mountains, 1 y apart. During the first stressful life event, the patient did not receive short-term prophylaxis (self-control group); for the second event, the patient received rhC1-INH as short-term prophylaxis (rhC1-INH prophylaxis group).

long-term prophylaxis were excluded from the analysis, 96.1% and 88.2% of the 51 procedures with rhC1-INH short-term prophylaxis administration were attack-free during the first 2 and 7 days postprocedure, respectively (Figure 1). These data are consistent with those observed for the overall data set of 70 procedures, supporting a high rate of success with rhC1-INH as prophylaxis, irrespective of concomitant long-term prophylaxis use. For the 70 procedures, short-term prophylaxis with rhC1-INH was safe and well tolerated, with no adverse events reported.

As noted earlier, guidelines for the management of HAE recommend preprocedural prophylaxis with a C1-INH concentrate before procedures that can induce an HAE attack (eg, medical and dental procedures), but data are limited.[2] There have been several reports of plasma-derived C1-INH (pdC1-INH) administered as preprocedure short-term prophylaxis in patients with HAE.[9-12] Analysis of data from a patient registry showed a cumulative HAE attack rate of 0.04 (95% CI, 0.015-0.088) and 0.06 (95% CI, 0.028-0.115) per infusion at 1 and 2 days postprocedure, respectively, after the administration of pdC1-INH preprocedure.[9] A retrospective analysis of 705 dental procedures observed that 78.5% of 577 procedures were attack-free with no prophylaxis and 92.4% of 53 procedures were attack-free after the administration of pdC1-INH 1000 IU preprocedure.[10] A second retrospective analysis reported that 97.8% of 91 procedures were attack-free after short-term prophylaxis with pdC1-INH.[11] Finally, 100% of 24 surgical procedures were attack-free after pdC1-INH administration preprocedure.[12] As suggested by an international guideline, C1-INH concentrate should be administered as close as possible to the time of procedure initiation.[2] On-demand treatment should also be available to manage breakthrough HAE attacks that may occur despite preprocedural prophylaxis.[2]

Although the HAE attack rate in the self-control group was high (76.9% of procedures within 2 days postprocedure) in the present study, other published control data have also reported high rates of HAE attacks. In a retrospective study of 202 procedures, 139 (68.8%; 100 dental procedures and 39 diagnostic surgical procedures) had a postprocedural HAE attack

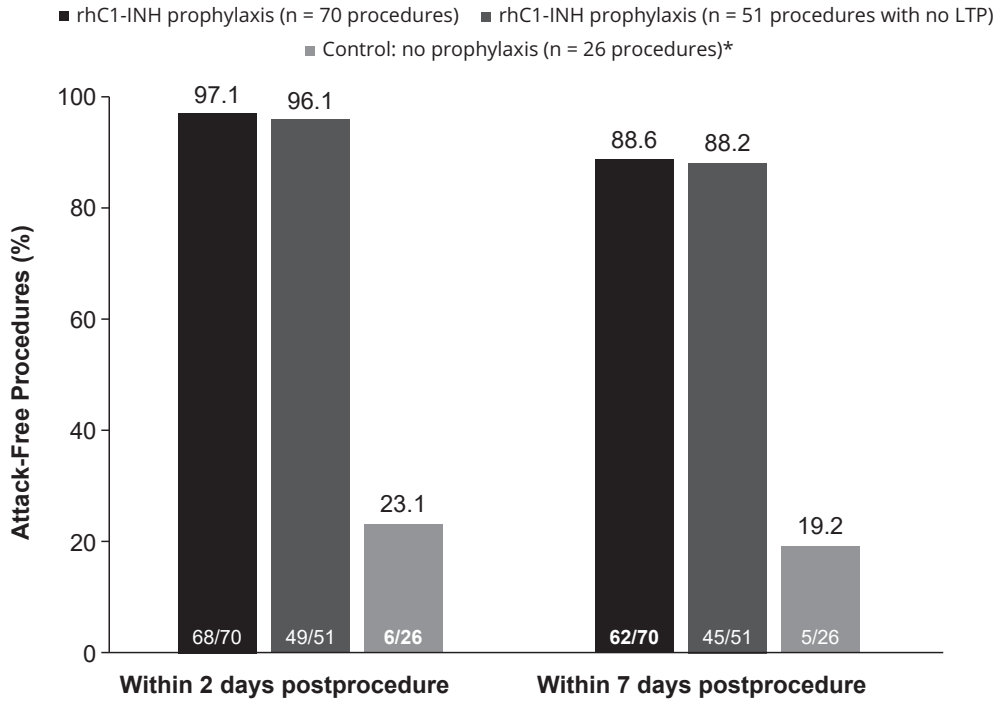


**FIGURE 1.** Percentage of procedures that were HAE attack-free at 2 and 7 days postprocedure. *LTP*, Long-term prophylaxis. *Self-control group that did not receive long- or short-term prophylaxis preprocedure.

within 2 days postprocedure.[13] In another retrospective study, 12 (100%) patients had a history of HAE attacks, predominantly in the orofacial-pharyngeal-laryngeal area, after invasive dental procedures with no short-term prophylaxis. Subsequent administration of short-term prophylaxis allowed subsequent dental/maxillofacial procedures to be conducted without attacks.[14]

Although children and adolescents younger than 17 years with HAE were not included in the current case series, short-term prophylaxis is also recommended for medical and dental procedures in all children and adolescents with HAE.[15] In the present study, we report that rhC1-INH short-term prophylaxis reduced the rate of postprocedure HAE attacks compared with control procedures that had no prophylaxis. Furthermore, these results were comparable with results of published reports of short-term prophylaxis with pdC1-INH.[9-12] In conclusion, short-term prophylaxis with rhC1-INH administered as close as possible to the start of a medical or dental procedure was efficacious and safe in patients with HAE.

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## REFERENCES

1. Zuraw BL, Bernstein JA, Lang DM, Craig T, Dreyfus D, Hsieh F, et al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor–associated angioedema. J Allergy Clin Immunol 2013;131:1491-3.
2. Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2017 revision and update. Allergy 2018;73:1575-96.
3. Riedl MA, Bernstein JA, Li H, Reshef A, Lumry W, Moldovan D, et al. Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. Ann Allergy Asthma Immunol 2014;112:163-9.
4. Zuraw B, Cicardi M, Levy RJ, Nuijens JH, Relan A, Visscher S, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. J Allergy Clin Immunol 2010;126:821-7.
5. Li HH, Moldovan D, Bernstein JA, Reshef A, Porebski G, Stobiecki M, et al. Recombinant human-C1 inhibitor is effective and safe for repeat hereditary angioedema attacks. J Allergy Clin Immunol Pract 2015;3:417-23.
6. Riedl MA, Levy RJ, Suez D, Lockey RF, Baker JW, Relan A, et al. Efficacy and safety of recombinant C1 inhibitor for the treatment of hereditary angioedema attacks: a North American open-label study. Ann Allergy Asthma Immunol 2013;110:295-9.
7. Moldovan D, Reshef A, Fabiani J, Kivity S, Toubi E, Shlesinger M, et al. Efficacy and safety of recombinant human C1-inhibitor for the treatment of attacks of hereditary angioedema: European open-label extension study. Clin Exp Allergy 2012;42:929-35.
8. Riedl MA, Grivcheva-Panovska V, Moldovan D, Baker J, Yang WH, Giannetti BM, et al. Recombinant human C1 esterase inhibitor for prophylaxis of hereditary angio-oedema: a phase 2, multicentre, randomised, double-blind, placebo-controlled crossover trial. Lancet 2017;390:1595-602.
9. Magerl M, Frank M, Lumry W, Bernstein J, Busse P, Craig T, et al. Short-term prophylactic use of C1-inhibitor concentrate in hereditary angioedema: findings from an international patient registry. Ann Allergy Asthma Immunol 2017;118:110-2.
10. Bork K, Hardt J, Staubach-Renz P, Witzke G. Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema

with and without prophylaxis with C1 inhibitor concentrate: a retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:58-64.

11. Grant JA, White MV, Li HH, Fitts D, Kalfus IN, Uknis ME, et al. Preprocedural administration of nanofiltered C1 esterase inhibitor to prevent hereditary angioedema attacks. Allergy Asthma Proc 2012;33:348-53.
12. Gavigan G, Yang WH, Santucci S, Harrison R, Karsh J. The prophylactic use of C1 inhibitor in hereditary angioedema patients undergoing invasive surgical procedures: a retrospective study. Allergy Asthma Clin Immunol 2014; 10:17.
13. Farkas H, Zotter Z, Csuka D, Szabó E, Nébenführer Z, Temesszentandrási G, et al. Short-term prophylaxis in hereditary angioedema due to deficiency of the C1-inhibitor—a long-term survey. Allergy 2012;67:1586-93.
14. Farkas H, Gyeney L, Gidofalvy E, Fust G, Varga L. The efficacy of short-term danazol prophylaxis in hereditary angioedema patients undergoing maxillofacial and dental procedures. J Oral Maxillofac Surg 1999;57:404-8.
15. Farkas H, Martinez-Saguer I, Bork K, Bowen T, Craig T, Frank M, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Allergy 2017;72:300-13.