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Intravenous Self-Administration of C1-INH Concentrate for Hereditary Angioedema: A Retrospective Report of Real-World Experience in 13 Patients

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ABSTRACT

Background: The concept of home-based management of hereditary angioedema (HAE) has been gaining favor in recent years and is recommended in recent major HAE consensus guidelines. These data were collected to provide a retrospective view of treatment patterns, safety, and feasibility of C1 esterase inhibitor (C1-INH) self-administered at home under real-world conditions.

Methods: This retrospective, case-cohort analysis examined longitudinal data from 13 patients with type I or type II HAE who were trained to self-administer C1-INH concentrate (Berinert®/CSL Behring or Cinryze®/ViroPharma Inc). Seven patients were trained in on-demand use of C1-INH and 6 were trained in prophylactic use.

Results: Four patients trained in on-demand use elected to continue and were followed for a mean of 13.6 months (range, 4.5–18.6 months). Three of these patients self-administered C1-INH rarely and 1 self-administered ~350 vials over 29 months. The 6 patients trained in prophylactic use self-administered ~945 doses of C1-INH over a mean follow-up of 18.1 months (range, 7.7–27.5 months), including the treatment of 37 acute breakthrough attacks. In both groups, almost all acute attacks of HAE were successfully managed with self-administered C1-INH. Two patients reported mild adverse effects; no serious adverse effects related to C1-INH or the intravenous procedure occurred.

Conclusions: Self-administration of C1-INH as on-demand therapy or prophylaxis is a feasible strategy that can be used successfully to manage HAE. These data highlight the wide variability evident in HAE disease characteristics and treatment patterns.

BACKGROUND

Hereditary angioedema (HAE) is a rare autosomal dominant disorder affecting ~ 1/50,000 persons.[1] It causes frequent attacks of nonpitting, nonpruritic edema without urticaria, usually of the skin of the extremities or gastrointestinal tract.[2] Gastrointestinal attacks may cause severe pain, while attacks in the oropharyngeal region may lead to asphyxiation and death.[3] HAE usually manifests in childhood or adolescence and persists throughout life.[4] It is caused by mutations that result in low levels of functional C1 esterase inhibitor (C1-INH), a serine protease inhibitor that has regulatory roles in the contact, complement, and fibrinolytic systems.[5] Low C1-INH function results in overproduction of bradykinin, the primary cause of HAE symptoms.[5]

Treatment of HAE may include both on-demand treatment to arrest acute attacks and regular, scheduled administration to prevent attacks.[6] Given the unpredictable course of the disease and its potential to cause serious consequences, recent consensus guidelines agree that treatment of HAE should be individualized to the patient's needs, with the goals of providing optimal care and restoring normal quality of life (QoL).[6-8] The most current consensus guidelines[6,7] include the following key recommendations:

1. Any angioedema attack in a patient with HAE can become disabling and/or life threatening: therefore, all patients with HAE caused by C1-INH deficiency, even if still asymptomatic, should have access to therapy.

2. Whenever possible, patients should have on-demand medication to treat up to 2 acute attacks at home and should be trained to self-administer it.

3. All attacks, irrespective of location, are eligible for treatment as soon as they are clearly recognized by the patient.

4. On-demand treatment for acute attacks should be the initial goal for all patients, because it may prevent mortality and reduce morbidity.

5. Long-term prophylactic treatment is appropriate for patients in whom on-demand acute therapy is inadequate to minimize the suffering related to HAE.

Home-based, self-managed treatment has been used successfully for many years for the treatment of such chronic diseases as hemophilia, immunodeficiencies, and cystic fibrosis, and has the potential to significantly improve the management of HAE. In patients with HAE, home-based self-administration of C1-INH as on-demand therapy for acute attacks has been shown to contribute to improved QoL,[9] reduce the time from onset of symptoms to initiation of therapy and the time to symptom

improvement in both children and adults,[10,11] and reduce the time to complete resolution of an attack.[11] It has also been demonstrated to reduce the severity and duration of acute attacks and the amount of prescription pain medication used.[12] Prophylactic administration of C1-INH has been shown to reduce the frequency, severity, and duration of HAE attacks.[11,13]

Several studies describing home-based self-administration of C1-INH have been conducted in Europe,[9-11,14,15] but thus far only one such study has been reported in the United States.[12] The present report was designed to retrospectively evaluate treatment patterns, safety, and feasibility of self-administered C1-INH in patients with varying disease severity and treatment needs. While not enough data were available at the time of writing to perform a robust analysis, our clinic's experience with training patients to self-administer C1-INH over the past several years provides a useful insight into real-world scenarios in HAE management.

METHODS

This was a retrospective, case-cohort review of longitudinal data gathered in the routine follow-up of 13 patients with HAE who were trained to self-administer IV C1-INH concentrate (Berinert®/CSL Behring or Cinryze®/ViroPharma Inc). In our clinic, patients with HAE are offered the option of learning to self-administer intravenous (IV) C1-INH concentrate at home, either as on-demand treatment for acute attacks or as ongoing prophylaxis. Training in the self-administration of C1-INH concentrate is provided by clinic staff to the patient and/or a parent, spouse, or caregiver.

Patients were eligible for inclusion in this review if they had received a diagnosis of type I or type II HAE; had been appropriately trained in IV self-administration of C1-INH for either prophylaxis or on-demand therapy; and had at least 3 months of chart data available for review following training. Data were collected using case report forms and were analyzed descriptively. Institutional review board approval was sought (Chesapeake Research Review, Inc), but ruled unnecessary. Patient identities were kept strictly confidential.

RESULTS

Data on 13 patients were reviewed. Twelve patients had type I HAE and 1 patient had type II HAE. Their mean age was 40.3 years (range, 17–73 years) and 8 (62%) patients were female.

Patients Trained for On-Demand Therapy

Seven patients were trained to administer IV C1-INH as on-demand therapy for acute attacks of HAE (**Table 1; Figure 1).** Their mean age was 42.1 years (range, 17–73 years) and 2 were female. Three of the 7 patients completed the self-infusion training but eventually decided not to self-administer IV C1-INH because of the associated expense, lack of insurance coverage, or as a matter of preference.

Four patients proceeded with self-administration of IV C1-INH as their primary on-demand treatment method. All attacks that these patients treated with self-administered C1-INH resolved successfully. Two patients relied on danazol to treat milder HAE attacks and used C1-INH only for attacks that did not respond to danazol treatment. Patient B had mild disease and eventually chose to use icatibant for on-demand therapy. Patient C self-treated 4 HAE attacks with C1-INH over a 4.5-month period, but subsequently moved out of the area and was lost to follow-up. Patient F had frequent attacks. Her pattern of administration ranged over time from frequent on-demand treatments to a more regular prophylactic regimen, which she would adjust according to her comfort level. Patient F is estimated to have self-administered ~350 vials of C1-INH over a period of 29 months.

Patients Trained for Prophylactic Therapy

Six patients were trained to administer IV C1-INH prophylactically **(Table 2; Figure 2).** Their mean age was 38.2 years (range, 20–56 years) and all were female. Five had type I HAE and 1 had type II HAE. In addition to their prophylactic regimen, all were instructed to use IV C1-INH for the acute treatment of breakthrough attacks.

Based on the prescribed dosing regimens, these patients administered a combined total of ~945 doses of prophylactic IV C1-INH over a mean follow-up of 18.1 months. There were no instances in which prophylactic IV C1-INH could not be self-administered or was associated with complications.

A total of 37 breakthrough HAE attacks were reported in this cohort, all but 1 of which were managed with self-administered IV C1-INH and required no other medical intervention. One attack was treated with fresh frozen plasma because the patient (H) was on vacation and did not bring a supply of C1-INH concentrate. One attack could not be self-treated because the patient's arms and hands were affected; this attack was treated with C1-INH concentrate in the clinic. Three attacks required a repeat dose of C1-INH.

Four laryngeal attacks were reported, all in patient K. In 2 of these attacks, diphenhydramine, steroids, and epinephrine were also administered, and 1 attack was followed by a 24-hour hospital stay for observation.

Safety

These data reflect a large sample of IV self-administrations of C1-INH. The 6 patients in the prophylactic cohort performed between 900 and 1000 self-administrations and 1 patient trained for on-demand

therapy used ~350 vials of C1-INH. Adverse events were rarely reported. One patient reported 1 event of mild headache and a brief change in peripheral vision, and 1 patient reported occasional nausea and headache. Some patients switched from one C1-INH product to another, but no patient discontinued C1-INH because of adverse events. There were no reported adverse events associated with the IV self-administration procedure.

Table 1. Patients Trained for On-Demand IV C1-INH

Patient	Age/Sex; HAE Type	Data Collection Period for C1-INH Self-Administration	Treated Attacks; C1-INH Dose	Adverse Events/ Administration Difficulties	Comments
A	54/M Type I	Patient never active with home administration	NA	NA	• Patient trained; first attack treated in the clinic under supervision • Patient never followed through with home-based treatment • Lost insurance coverage, had very bad attacks, was not reliable
B	45/F Type I	5/12/10 through 11/30/11	13 attacks; 1000–1500 U, with or without 100–200 mg danazol	1 episode of mild headache/brief peripheral vision changes	• Patient would first try danazol for milder attacks, adding C1-INH if necessary • Switched C1-INH brands occasionally • Switched to icatibant 11/30/11; mild disease, not that many attacks
C	33/M Type I	12/1/10 through 4/16/11	4 attacks; 1500 U	None reported	• Patient moved 4/11 with no further follow-up available
D	17/M Type I	Patient never active with home administration	NA	NA	• Patient and mother trained, initially interested in learning home administration • On initial 2 attacks after training, patient and mother came into clinic to be dosed • Ultimately decided against the idea of self-administration
E	37/M Type I	Patient never active with home administration	NA	NA	• Patient received training, but opted to continue on androgen prophylaxis because of cost issues
F	36/F Type I	5/1/09 through 1/11/11 *(ongoing)*[a]	Numerous	None reported	• Occasional switches between C1-INH products for cost or perceived efficacy reasons • In 5/10, patient converted to more of a regular, prophylaxis regimen because of attack frequency (1000 U Q3–5d) • Would self-adjust prophylactic dosing frequency, extending interval to 4 or 5 days if no attack within that time • Drug supply records indicate that patient self-administered close to 350 vials of C1-INH over a 29-month period
G	73/M Type I	7/7/10 through 11/1/11 *(ongoing)*[a]	0 attacks requiring C1-INH		• Patient trained and willing to use C1-INH; uses danazol as prophylaxis and prefers to use danazol PRN for attacks if possible

C1-INH, C1 esterase inhibitor; F, female; IV, intravenous; M, male; PRN, as needed; Q3–5d, every 3 to 5 days.
[a] At the time chart review ended.

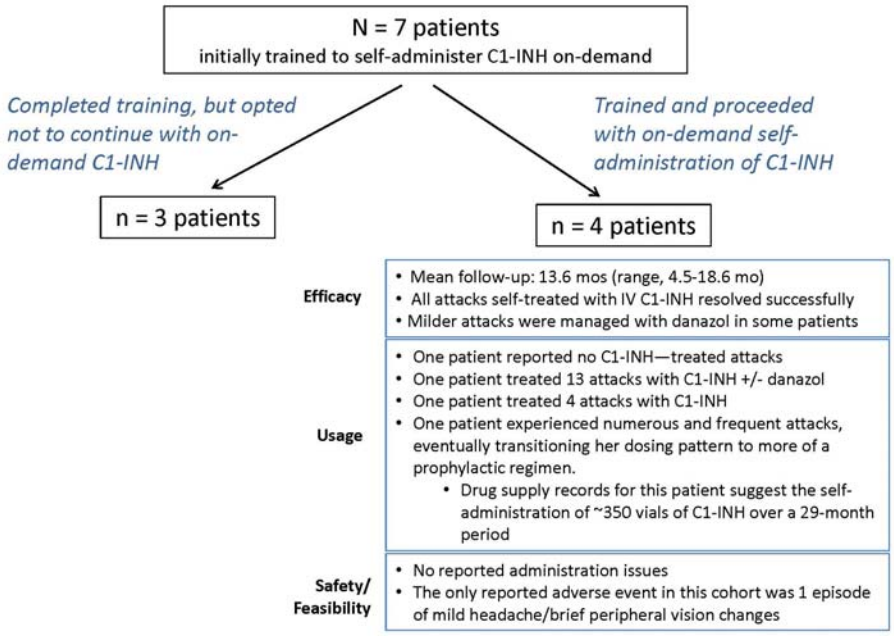

Figure 1. Summary of intravenous (IV) C1 esterase inhibitor (C1-INH) self-administered on-demand experience in 7 patients .

DISCUSSION

In this study we report findings that provide a glimpse into the real-world experience of patients with HAE who were trained to manage their disease through self-administered IV infusions of C1-INH. These data reflect a large number of self-administered doses of IV C1-INH, during which no apparent complications occurred, and with only one occasion in which the location of swelling interfered with the ability to self-administer an IV injection. Although these data are retrospective and were not collected during a rigorous clinical trial, they reflect patients' actual experience with self-administration of IV C1-INH over periods of months to years.

Among the patients in our study who chose to use on-demand C1-INH at home, all acute attacks were successfully managed with self-treatment. Similarly, all breakthrough attacks in patients who were using prophylactic therapy were successfully treated with C1-INH (adjunctive medications given in 2 laryngeal attacks). The only attack that was not managed with C1-INH occurred in a patient who was on vacation and did not bring her self-administration supplies. One patient underwent 24-hour hospital observation following self-treatment of a laryngeal event.

Other studies of self-management of HAE with C1-INH have reported successful implementation and good clinical outcomes with this strategy.[9-12,14,15] Investigators at the HAE Center at Frankfurt University, where patients have been trained in self-administration of C1-INH for 3 decades, have reported their experience with 450 adult and 107 pediatric patients. At the time of manuscript development, 55% of their adult patients and 24% of their pediatric patients were self-administering C1-INH at home. The investigators reported a rapid response to treatment with no treatment-related adverse events.[15]

Among the most important benefits of C1-INH self-administration for patients with HAE is the reduction in time to treatment that can be achieved. An observational study of 20 pediatric patients with HAE found that the median time from symptom onset to initiation of treatment was 15 minutes during home therapy and 67 minutes when the same patients were receiving physician-administered therapy.[10] A growing body of evidence suggests that more rapid initiation of HAE therapy is associated with more rapid symptom relief. For example, in a study of 43 patients with HAE trained to self-administer C1-INH, time to treatment was reduced by 2 hours when home care replaced clinic care (1.4 ± 1.0 hours vs 3.4 ± 2.1 hours), but time to complete resolution of symptoms was reduced by almost 8 hours (5.9 ± 2.2 hours vs 13.8 ± 2.9 hours).[11]

Patients using on-demand C1-INH at home have been shown to have significant decreases in attack duration and severity and use of pain medication compared with their experience when treated in a clinic.[12] Moreover, use of prophylactic C1-INH at home has been shown to reduce the frequency of HAE attacks, including laryngeal

attacks.[14] A small study of pediatric patients with HAE who were either intolerant of or unsuccessfully controlled by danazol therapy noted a reduction in the number of days spent in a hospital and in the number of patients reporting missing days from school after initiating either on-demand or prophylactic C1-INH administration.[10]

Table 2. Patients Trained for IV C1-INH Prophylaxis

Patient	Age/ Sex; HAE Type	Data Collection Period for C1-INH Self-Administration	Prophylactic C1-INH Dose	Breakthrough Attacks/ Treatment	AEs/ Administration Difficulties	Comments
H	41/F Type I	7/19/09 through 11/1/11 *(ongoing)*[a]	1000 U Q3d	1 attack; FFP	Occasional nausea, headache	• Only 1 breakthrough attack during C1-INH prophylaxis; treated with FFP because patient was on vacation and forgot to bring C1-INH • Throughout pregnancy (delivery 9/11) patient stopped using C1-INH, except for 2 doses • Patient switched C1-INH products on 2 occasions
I	49/F Type I	4/9/10 through 11/1/11 (therapy ongoing)*	1000 U Q3–5d	2 attacks; C1-INH 1000 U	None noted	
J	22/F Type I	5/12/10 through 11/1/11 *(ongoing)*[a]	1000 U QW (more frequent if symptoms are mild)	8 attacks; C1-INH 1000 U	No AEs; swelling interfered with IV on 1 occasion	• Breakthrough attacks treated at school, except for 1 treated at the clinic/hospital (site of swelling interfered with IV placement)
K	20/F Type I	4/2/10 through 11/1/11 *(ongoing)*[a]	1000 U BIW	11 attacks (4 laryngeal); C1-INH 1000–1500 U ± diphenhydramine, steroids, and epinephrine	None reported	• All breakthrough attacks self-treated at school or camp • Additional dose of C1-INH administered in 3 attacks (2 laryngeal, 1 peripheral) • In 2 laryngeal attacks, diphenhydramine, steroids, and epinephrine were also administered • 1 laryngeal attack (self-treated) was followed by 24-hour hospital observation
L	41/F Type I	3/11/11 through 11/1/11 *(ongoing)*[a]	1000 U Q3d	6 attacks; C1-INH 1000 U	None reported	• For first month after training, patient administered C1-INH in the clinic under supervision of a nurse; 6 attacks since then were treated at home
M	56/F Type II	11/8/09 through 11/1/11 *(ongoing)*[a]	1000 U BIW	9 attacks; C1-INH 1000 U (1 required 1500 U)	None reported	

AEs, adverse events; BIW, twice weekly; C1-INH, C1 esterase inhibitor; F, female; FFP, fresh frozen plasma; IV, intravenous; M, male; Q3d, every 3 days; Q3–5d, every 3 to 5 days; QW, weekly.

[a] At the time chart review ended

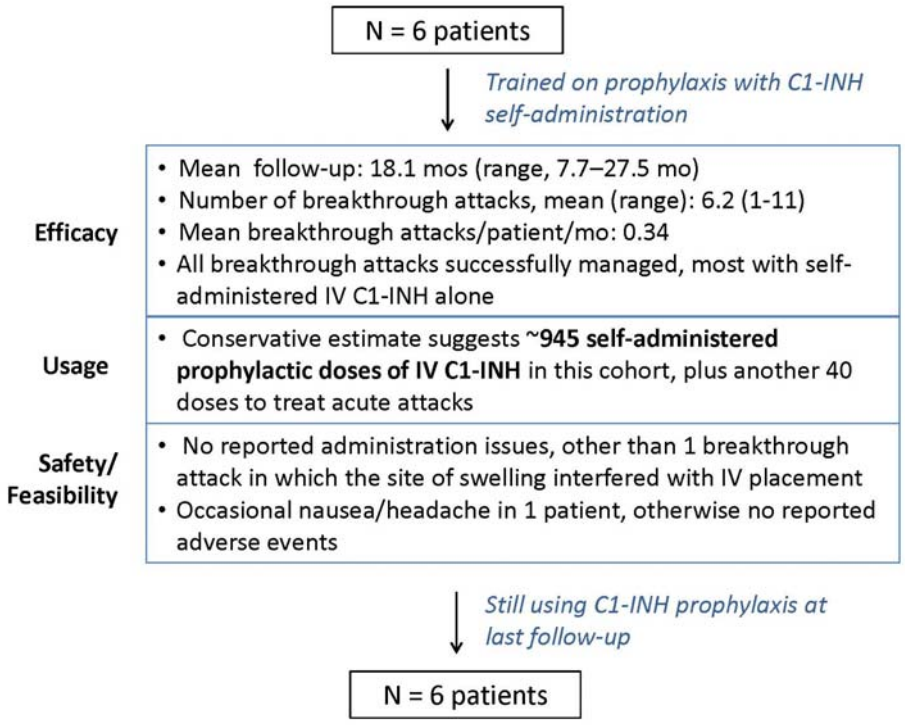

Figure 2. Summary of intravenous (IV) C1 esterase inhibitor (C1-INH) self-administered prophylaxis experience in 6 patients.

Despite the clinical benefits of C1-INH self-administration, patients may decide for various reasons that this strategy is not suitable for them. Some of our patients with milder disease chose to continue danazol as prophylactic therapy while keeping C1-INH available for treatment of breakthrough attacks. One teenage patient and her mother, despite expressing an interest in learning self-administration and completing the training, chose not to continue with the regimen. Physicians and nurses who treat patients with HAE play an important role in identifying good candidates for training in IV self-administration. Their familiarity with the patients and clinical judgment help them select individuals who are motivated, reliable, and capable of learning self-administration, which will likely increase the chances of success for a self-administration program.

The patients who were trained to use C1-INH as on-demand treatment exhibited tremendous variability in their needs and usage. One patient with fairly severe disease was able to adjust the frequency of C1-INH administration based on her comfort level and attack frequency. Initially trained to self-administer C1-INH as on-demand therapy for frequent acute attacks, she found that her attack frequency was so high that she was administering on-demand therapy 1 or 2 times per week. At one point, she modified her dosing schedule into a regular regimen that was more frequent than her usual attack pattern in order to prevent acute attacks; she went on to experiment with extending the interval between infusions as far as she could while still minimizing breakthrough attacks. One young adult who had frequent laryngeal attacks of HAE was able to successfully manage her disease in school and camp settings. Some of the patients with mild disease who continued on prophylactic danazol treatment rarely or never needed to use C1-INH during the chart review period.

Throughout the 900 to 1000 self-administrations of C1-INH that took place during the study period, including 1 patient who was estimated to have self-administered almost 350 vials of C1-INH over a 29-month period, patients encountered no technical difficulties or safety issues, except for one case in which swelling of the hands and arms prevented the patient from self-administering the IV injection.

HAE is a chronic, lifelong disease with significant morbidity and possibly life-threatening consequences. Therefore, an important goal of any treatment strategy is to enable patients to maintain some degree of normalcy and enjoy the greatest possible QoL. Patients who are trained in self-treatment become more active partners in their disease management and gain a greater sense of empowerment, control, and independence.[13] The retrospective design of our chart review did not allow us to

measure the effects of self-administration of C1-INH on QoL, but studies that have evaluated this aspect of home treatment have consistently demonstrated QoL improvements in patients who initiate home therapy.[9,14] In a study of patients who switched from prophylactic danazol therapy to self-administered prophylactic C1-INH therapy, improvements were seen in various QoL domains including social activities, occupation, life support activity, general condition, and condition during attacks.[14] Prophylactic C1-INH therapy was also associated with significantly fewer missed days of work or school compared with prophylactic danazol therapy (median values, 0 days vs 24 days/year).[14] In another study, self-administration of C1-INH was associated with significant improvements in the Dermatology Life Quality Index measured between 3 and 48 months after the start of home treatment.[9]

CONCLUSIONS

This analysis of real-world experience with self-administration of IV C1-INH by patients with HAE contributes to the growing body of experience demonstrating the success and feasibility of this strategy. Expert guidelines consistently advocate home-based treatment, and real-world experience supports this recommendation. This report of real-world treatment scenarios confirms the wide range of variability in HAE disease characteristics and individual patient treatment needs and attitudes. In many situations, self-administration of IV C1-INH is a viable management strategy that can help improve clinical outcomes, independence, and self-management of the disease, which may lead to improved QoL.

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REFERENCES

1. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol*. 2005;139:379-394.

2. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(suppl 3):S51-S131.

3. Frank MM. Hereditary angioedema. *J Allergy Clin Immunol*. 2008;121(2 suppl):S398-S401.

4. Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036.

5. Zuraw BL, Christiansen SC. Pathogenesis and laboratory diagnosis of hereditary angioedema. *Allergy Asthma Proc.* 2009;30:487-492.

6. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy.* 2011;67:147-157.

7. Craig T, Aygoren-Pursun E, Bork K, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J*. 2012;5:182-199.

8. Bowen T, Cicardi M, Farkas H, et al. 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin.* 2010;6:24.

9. Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. *Eur J Dermatol*. 2009;19:147-151.

10. Kreuz W, Rusicke E, Martinez-Saguer I, et al. Home therapy with intravenous human C1-inhibitor in children and adolescents with hereditary angioedema. *Transfusion*. 2012;52:100-107.

11. Levi M, Choi G, Picavet C, Hack CE. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. *J Allergy Clin Immunol*. 2006;117:904-908.

12. Tourangeau LM, Castaldo AJ, Davis DK, et al. Safety and efficacy of physician-supervised self-managed C1 inhibitor replacement therapy. *Int Arch Allergy Immunol*. 2012;157:417-424.

13 Longhurst HJ, Carr S, Khair K. C1-inhibitor concentrate home therapy for hereditary angioedema: a viable, effective treatment option. *Clin Exp Immunol*. 2006;147:11-17.

14. Kreuz W, Martinez-Saguer I, Aygoren-Pursun E, et al. C1-Inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. *Transfusion*. 2009;49:1987-1995.

15. Aygoren-Pursun E, Martinez-Saguer I, Rusicke E, et al. On demand treatment and home therapy of hereditary angioedema in Germany—the Frankfurt experience. *Allergy Asthma Immunol.* 2010;6:21.

DISCLOSURE

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