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Facilitating self-infused intravenous therapy among hereditary angioedema patients in Romania

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Abstract

Background. Hereditary angioedema (HAE) is a rare, potentially life-threatening disease characterized by unpredictable swelling attacks. Early administration of acute treatment is essential, with self-administration playing a key role. This study evaluated the acceptance of intravenous self-administration and the effectiveness of a structured training program among patients with HAE in Romania.

Methods. Two face-to-face training sessions were organized for adults and adolescents with HAE from Romania, as well as for parents of adolescent patients registered in the national HAE Registry. Each session included a theoretical component followed by hands-on training using an artificial arm. Participants completed pre- and post-training questionnaires developed by HAE experts to assess knowledge, experience, skills, and confidence related to the intravenous self-administration.

Results. Of the 93 patients informed about the training, 38 (41%) expressed interest in the first session and 13 (14%) in the second. A total of 24 individuals ultimately participated, with a mean age of 40.8 years. The majority were adults (23, 95.8%), female (18, 75%), and diagnosed with HAE type 1 (23, 95.8%).
Twenty participants (83.3%) rated the training as extremely useful. The practice resulted in significant improvements in self-reported knowledge, experience, and confidence regarding intravenous self-administration, with large effect sizes across all domains. Sixteen patients (66.7%) reported willingness to try this type of self-administration, whereas two (8.3%) indicated they would not prefer this route, and five (20.8%) stated they would not choose it even if administered by a healthcare professional. Notably, during the second session, none of the participants was willing to attempt the practical component.

Conclusions. These findings suggest that while patients generally perceive home treatment as beneficial, the intravenous route remains a significant barrier and may be a suitable option only for selected HAE patients. While structured training improves cognitive and affective domains, continued practical reinforcement is required to ensure consistent technical proficiency.

Keywords: hereditary angioedema, intravenous treatment, self-administration

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Introduction

Hereditary angioedema (HAE) is an autosomal inherited rare disease characterized by recurrent, painful, and debilitating angioedema attacks which affect mainly the skin, gastrointestinal tract and the upper airways [1,2]. Attacks are unpredictable, may occur without warning, and vary in severity. Without treatment they may last for 2-7 days and, in the case of laryngeal involvement, can lead to death by asphyxiation [3].

Therapeutic modalities for HAE include acute (emergency, on-demand) treatment of swelling episodes and prophylactic treatment, comprising short-

term prophylaxis and long-term prophylaxis (LTP), aimed at preventing attacks [4].

While on-demand treatment must be constantly available for each HAE patient, prophylaxis is recommended on an individual basis, established through a shared decision-making process [5]. For this purpose, plasma-derived C1-inhibitor (pdC1INH) replacement therapy (administered intravenously or subcutaneously) or novel kallikrein inhibitors (administered subcutaneously or orally) should be used. When these specific drugs are unavailable, attenuated androgens may be recommended [6].

Emergency treatment includes intravenously administered C1- inhibitor (C1INH) concentrate (plasma-derived or human recombinant form) or the subcutaneously used bradykinin receptor antagonist, icatibant. The kallikrein inhibitor ecallantide is licensed only in the United States and a several Latin American countries and is administered subcutaneously [7].

In case of the inaccessibility of these on-demand therapies, fresh frozen plasma can be administered.

According to the International WAO/EAACI HAE treatment guideline [6], for all patients prescribed on-demand treatment licensed for self-administration, this route should be recommended, including pediatric patients.

A review of six studies on C1INH home therapy found several benefits, including faster resolution of acute attacks, fewer hospital admissions, reduced time away from work or school, and overall improvements in quality of life [8,9].

The self-administration procedure involves a training course and should ideally include a home therapy partner, such as a family member or friend, who can provide support, guidance, and administer therapy when the patient is compromised, unable, or uncomfortable with self-treatment [10].

Since 2015, Romanian HAE patients had access to specific treatments. If until 2018 these were only available through administration at the emergency department, since then, both the subcutaneously administered (since 2018), and the intravenously administered drugs (since 2021) have also been approved for home-based self-administration therapy.

The approval of intravenous treatments took place during the pandemic, when face-to-face training was not possible. In this period, an online meeting was organized, followed by two face-to-face trainings in the post-pandemic period.

This study aimed to evaluate the degree of acceptance of self-administered intravenous drug administration and to assess the impact of training on participants' knowledge, experience, skills, and confidence regarding this type of self-administration.

Methods

The study was a non-interventional (observational) investigation conducted at the Romanian Angioedema Excellence and Reference Center (ACARE), encompassing two face-to-face training sessions organized for HAE patients in November 2022 and February 2023.

In both cases all eligible adult and adolescent patients (12 years of age or older) as well as parents of the adolescent patients enrolled in the Romanian HAE Registry were invited to participate in the program. Invitations were sent by email or phone one month before the event. Reminders were sent two weeks and again one week prior to the event. Patients were eligible if the following criteria were met: aged 12 years or above, confirmed diagnosis of HAE due to C1INH deficiency (HAE-C1INH) type 1 or 2, and providing informed consent. For adolescent patients, parents were also invited.

The face-to-face training sessions included the following steps:

1. A brief presentation of treatment options for HAE, including both on-demand and prophylactic therapies, was delivered by an HAE expert physician. The presentation addressed global and national (Romanian) treatment approaches and emphasized the importance of self-administration, including intravenous therapies too.
2. Signing the informed consent.
3. Completion of the first questionnaire.
4. Viewing the video-material regarding the drug preparation and the intravenous technique.
5. Drug preparation and administration demonstrated by a nurse using an artificial arm.
6. Patients and/or parents practiced drug preparation and intravenous administration using the artificial arm.
7. Completing the post-training questionnaire.

The two questionnaires were specifically developed for this study by experts from the Romanian ACARE Center.

The first questionnaire included 21 items focusing on the currently used on-demand medication, including its route of administration, whether it was self-administered, perceived effectiveness, patient satisfaction, the patient's opinion regarding the difficulty and usefulness of home-based therapy, and the level of knowledge regarding the intravenous self-administration procedure.

The second questionnaire included five questions regarding the usefulness of the training and the patient's opinion on whether they would prefer to self-administer the intravenous on-demand treatment or have it administered by a healthcare professional.

Both questionnaires used predefined response options based on a five-point Likert scale. The questionnaires are available upon request.

Informed consent was obtained from all participants after they were informed about their right to participate, refuse, or withdraw at any time. Full confidentiality of participants' data was ensured throughout the study. Participation in the study did not alter the patient's treatment plan.

The socio-demographic data, disease and personal characteristics were collected from the Romanian HAE Registry.

The study was approved by the Ethics Committee of the George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures (Decision no. UMFST- nr 1914/02.11.2022, REG-74-F03-Ed.02).

Statistical analysis

Descriptive statistics were calculated to summarize patient demographics and the therapeutic management of HAE.

Questionnaire responses were evaluated using the following grading: "Extremely" = 5 points; "Quite a lot" = 4 points; "Moderately" = 3 points; "A little" = 2 points; "Not at all" = 1 point.

The normality of numerical variables was assessed using the Kolmogorov–Smirnov test.

Self-reported knowledge, experience, skills, and confidence in intravenous self-administration were compared between baseline (T0) and post-training (T1) using the Wilcoxon signed-rank test for paired ordinal data. Effect sizes were calculated using the formula $r = Z/\sqrt{N}$, where Z represents the standardized Wilcoxon test statistic and N the number of non-zero paired differences included in the analysis. This measure provides a standardized estimate of the magnitude of change independent of sample size. Effect sizes were interpreted according to Cohen's conventions, whereby r values of approximately 0.10, 0.30, and 0.50 indicate small, medium, and large effects, respectively. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM Corp., Armonk, NY, USA).

Results

At the time of the study, 123 patients aged 12 years or older were registered at our Center, and 93 of them (75.6%) were informed about the training sessions. In 30 cases (24.4%), the provided email or phone number was invalid.

Of these, 38 individuals (response rate: 41%) responded positively to the first invitation expressing their intention to participate. Finally, 19 patients (18 adults and one adolescent) and one parent participated in the November training.

For the second training, 13 patients (response rate: 14%) responded positively. Five adult patients and one parent attended the February session.

One patient and the parent of a non-participating adolescent attended both sessions; however, they were included in the statistical analysis only in the first group.

The study flow chart is presented in figure 1.

The patient-related data (socio-demographic and disease-related) were collected from the Romanian HAE Registry and are presented in table I.

Pre-training questionnaire (T0)

At the time of the study, all 24 patients had access to on-demand home treatment with the subcutaneous bradykinin B2 receptor antagonist icatibant through the National HAE Treatment Program. In addition, seven patients (29%) had access to the intravenous form of pdC1-INH.

Among those using the subcutaneous treatment, 19 patients (79%) self-administered the medication, while the remaining five (21%) relied on a caregiver for administration. Regarding intravenous treatment, all doses were administered by healthcare professionals, except for two patients who self-injected a single dose of pdC1INH.

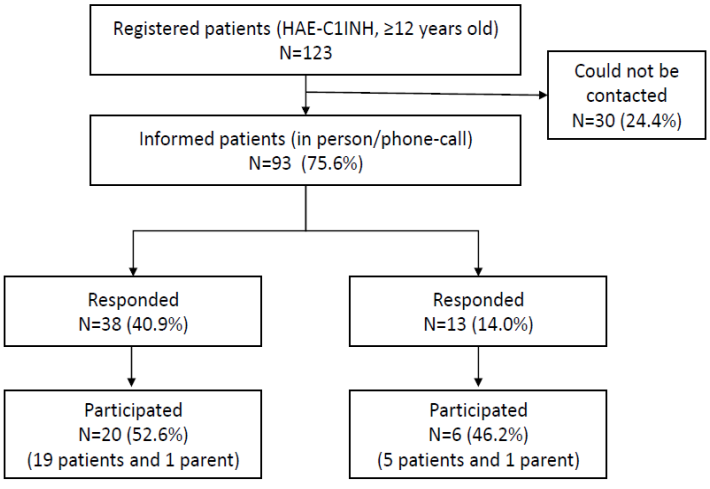

Figure 1. Study flow chart.

Table I. Socio-demographic and disease-related characteristics of the participants.

Variable	Numerical values	Percentual values
Age, years: mean (SD)	40.8	
12-17	1	4.2%
≥ 18	23	95.8%
Gender: n (%)		
Female	18	75%
Male	6	25%
HAE type: n (%)		
HAE type I	23	95.8%
HAE type II	1	4.2%
Residence		
Urban	18	75%
Rural	6	25%
Availability/use of internet		
Availability	24	100%
e-mail	15	62.5%
Social media	19	79.2%
Participation at the previous online training		
Yes	13	54.2%
No	11	45.8%

Table II. Pre-training (T0) responses regarding the currently used on-demand treatment.

Question	High (Extremely + Quite a lot) n (%)	Moderate n (%)	Low (A little + Not at all) n (%)	Did not respond n (%)
Satisfaction with efficacy	17 (70.8)	6 (25.0)	0 (0.0)	1 (4.2)
Satisfaction with route	16 (66.7)	7 (29.2)	1 (4.2)	0 (0)
Satisfaction with accessibility	21 (87.5)	2 (8.3)	0 (0.0)	1 (4.2)
The side effects (pain, redness, swelling) are tolerable?	19 (79.2)	4 (16.7)	0 (0.0)	1 (4.2)
Level of anxiety when self-injecting	7 (29.2)	9 (37.5)	7 (29.2)	1 (4.2)
Confidence in the current treatment method	19 (79.2)	3 (12.5)	1 (4.2)	1 (4.2)
Difficulty of self-administering emergency medication	6 (25)	4 (16.7)	14 (58.3)	0 (0.0)
Comfort level with current treatment	18 (75)	4 (16.7)	1 (4.2)	1 (4.2)
Importance of the route of medication administration	20 (83.3)	3 (12.5)	1 (4.2)	0 (0.0)
Perceived benefit of self-administration/home treatment	22 (91.7)	2 (8.3)	0 (0.0)	0 (0.0)

Participants responses regarding their currently used emergency medication - specifically its efficacy, route of administration, accessibility, tolerability of side effects, perceived security, difficulty of the self-administration technique, comfort level, anxiety level, and the importance of the administration route - are presented in table II.

Twenty-one patients (87.5%) reported that the possibility to self-administer the on-demand treatment had a significant positive impact on both their own and their family's quality of life, while in three cases (12.5%) the impact was described as moderate.

Nineteen patients (79.17%) made the decision to begin self-administration independently.

Twelve respondents (50%) reported participating in the previous online training, and all of them found it very useful in their decision to attempt practical self-administration. Factors that would encourage intravenous self-administration included: ineffectiveness of subcutaneous medication (4 participants), severe adverse effects of current medication (2 participants), unavailability of subcutaneous medication (5 respondents), and a faster onset of effect with emergency medication (2 respondents).

Finally, when asked how they believed family and friends would react to this treatment method, 21 patients felt they would agree with it, one believed they would somewhat agree, and one thought they would disagree.

Table III. Wilcoxon signed-rank analysis for pre- and post-training self-assessment scores.

Outcome	N pairs	Pre-training Median (IQR)	Post-training Median (IQR)	Z	p-value	r
Knowledge	17	4 (2)	5 (2)	−2.593	0.01	0.63*
Experience	14	3 (2)	4 (2)	−2.071	0.038	0.55*
Skills	13	3 (2)	4 (2)	−1.461	0.144	0.41**
Confidence	14	4.5 (3)	5 (1)	−2.058	0.04	0.55*

Note. Z values are from Wilcoxon signed-rank tests. Effect sizes are reported as r = Z / √N, where N represents the number of non-zero paired differences (ties excluded). * Large effect; ** Moderate effect.

The pre- and post-training comparisons of self-reported knowledge, experience, skills, and confidence related to intravenous self-administration, analyzed using Wilcoxon signed-rank tests for paired ordinal data, are presented in table III.

Sixteen patients reported willingness to try this form of self-administration, whereas two indicated that they would prefer not to, and five stated they would not choose it even if administered by a healthcare professional.

Discussion

This observational study evaluated the level of acceptance of intravenous self-administration among patients with HAE in Romania, as well as the effectiveness of the associated training program.

In line with the international HAE treatment guidelines, home therapy and self-administration should be considered for all HAE patients. Furthermore, reference centers should offer self-administration as a best practice for this potentially life-threatening rare disease [11, 12, 13].

This approach has also been successfully applied to other chronic conditions, such as hemophilia or immunodeficiencies. In HAE patients, previous studies have shown that self-administration is safe and allows for early attack treatment, leading to better outcomes [11], as faster relief of symptoms, reduced severity of attacks and decreased hospital admissions [8].

With the availability of specific medications in Romania, offering this treatment option has become increasingly important.

As the subcutaneous home-based treatment was already used by the majority of the Romanian HAE patients (since 2018), our present study focused on the intravenous self-administration procedure.

The participants were predominantly adults (95.8%), females (75%), and with HAE type 1 (95.8%). Most of them live in urban area (75%) and all had access to a form of internet. Half of respondents reported that they had participated in the previous online training and all of them considered it useful and helpful in their decision to learn and attempt the intravenous administration technique.

Although the face-to-face training sessions were open to all patients aged 12 years or older, as well as parents of adolescents, only a small number of patients and parents participated.

This can most likely be explained, on the one hand, by the fact that all of our HAE patients currently have access to and have been using subcutaneous medication on-demand as home treatment for several years, mostly through self-administration. On the other hand, the majority of participants (66.7%) reported satisfaction with the current method of administration, and most respondents indicated that they were satisfied and comfortable with both the efficacy (70.8%) and the administration procedure itself (75%). Only two attendees rated the subcutaneous technique as moderately difficult. Given all these data, we can conclude that intravenous administration is not an attractive or more advantageous alternative for these patients. This could also be the reason for the low number of participants: the vast majority of those present at the online event, where the procedure itself was presented, did not participate in the training. In addition, when intravenous pdC1INH (twice weekly) became available for LTP, only ten patients agreed to use it [14] and all switched to the subcutaneous form of LTP lanadelumab [15] when it became available.

This interpretation is further supported by the study findings: during the second training session, none of the participants expressed willingness to attempt the intravenous technique in practice, despite the fact that 50% reported high (33%) or moderate (17%) levels of self-perceived knowledge, experience, and skills, and 67% reported confidence in this method of administration.

Analysis of self-reported outcomes before and after training showed statistically significant improvements in knowledge, experience, and confidence in intravenous self-administration, with large effect sizes across domains. In particular, knowledge showed a significant increase ($r = 0.73$), indicating a better understanding of the procedure itself, while experience ($r = 0.62$) and confidence ($r = 0.78$) also improved significantly after the intervention. In contrast, although self-reported skills improved numerically, this change did not reach statistical significance and was associated with a moderate effect size ($r = 0.41$), suggesting that procedural competence may require repeated practice or supervised real-world application beyond a single

training session. The high proportion of ties observed for confidence underscores the heterogeneity of baseline readiness among participants and suggests that while training may reinforce confidence in some patients, others may require additional individualized support.

Overall, these results indicate that structured exercise effectively improves cognitive and affective domains related to intravenous self-administration, while emphasizing the need for continued practical reinforcement to translate perceived preparation into stable technical skills.

These data are consistent with the results of the SABHA study published by Zanichelli et al. on the safety and efficacy of self-administered intravenous treatment, in which enrolled patients participated in several courses of administration, in small groups of patients and caregivers (maximum 10 people), with the possibility of taking a second course and also performing the first self-infusion under the supervision of healthcare professionals [11]. The results of this study (including 15 patients), together with the data published by Levi et al. (34 patients) [16], showed that home intravenous infusion is not only safe and effective, but also a viable therapeutic option that benefits not only patients but also their families, caregivers and healthcare professionals involved in their care.

Based on our results, we can conclude that the training program was useful and can be continued in small groups and among selected patients. In these cases, home intravenous treatment may be a good option for these patients.

On the other hand, our results show that although home treatment is considered beneficial by all, the method of administration remains a critical factor. In this context, simpler alternatives, such as subcutaneous or oral therapies, may be a more favorable option. However, further research is needed to confirm these suggestions. Further studies would also be needed to determine how many patients participating in the training will choose intravenous self-administration.

Limitations

This study has several limitations. First, the time allocated to the practical component of the training was limited. Second, the study population was relatively small, comprising only 24 participants and representing a modest proportion of eligible patients. Third, because participation was voluntary, selection bias cannot be excluded, as individuals who were already motivated to learn self-administration may have been more likely to participate in the training sessions.

Additional limitations include the use of non-validated questionnaires, the absence of pilot testing, and the reliance on self-reported outcomes, which may have affected the accuracy and reliability of the findings. Furthermore, no long-term follow-up was conducted to evaluate the implementation and sustainability of intravenous self-administration practices following the training.

In **conclusion**, although all patients perceived home treatment as beneficial, the intravenous route remains a significant barrier and may be suitable only for selected patients with HAE.

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Authors' contributions

NAB: Investigation, Conceptualization, Project administration, Data curation, Writing – original draft

VN: Writing –review & editing, Visualization, Methodology, Formal analysis, Software, Data curation.

DD: Validation, Supervision, Writing – review & editing.

All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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