Current Status of Implementation of Self-Administration Training in Various Regions of Europe, Canada and the USA in the Management of Hereditary Angioedema

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Key Words

Hereditary angioedema · Self-administration · Current status · Benefits · Quality of life

Abstract

Results from a 16-question survey about self-administration of hereditary angioedema (HAE) therapy, administered in Europe, Canada and the USA, were used to guide discussion at an international HAE expert meeting. The aim was to capture information about current practice in self-administered HAE therapy in these countries, including self-administration training, the key benefits of switching to self-administration, the barriers to self-administration and trends in self-administration. Overall, switching to self-administration therapy is looked upon favourably from both patient and clinician perspectives by virtue of the potential improvement in quality of life arising from optimisation of therapy and early intervention. The recent changes to product licences allowing self-administration provide additional options for the management of HAE.

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Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disorder with an estimated prevalence between 1:10,000 and 1:50,000 [1]. The rarity of the disease means there are often delays in the diagnosis and treatment of HAE [2, 3], an example is a recent Danish survey which found that the mean diagnostic delay was 16 years [4]. In addition, even with a family history of HAE, family screening is not always undertaken which may further delay diagnosis [5].

HAE types I and II, the two most common forms, involve the deficiency or decrease in function of C1 esterase inhibitor (C1-INH), leading to spontaneous attacks of angioedema at various body sites, including the skin and abdomen, resulting in a significant negative impact on health-related quality of life [6]. Laryngeal attacks are less common but can prove to be the most dangerous and even fatal because of the risk of asphyxiation. Normally, HAE symptoms increase over 24 h and then subside over 24–72 h [6]. Patients may experience prodromal symptoms such as unusual fatigue, a rash on the arms and legs

Table 1. Summary of approved HAE treatments for self-administration^a [11–13, 15, 22–25]

Drug	Country	Date	Indicated for
Berinert	23 EU countries	2011	Self-administration for acute attacks
	USA	2012	Self-administration for acute attacks
	23 EU countries	2013	Short-term prophylaxis, including self-administration
Cinryze	USA	2009	Self-administration for prophylaxis
	EU	2011	Acute attacks, routine prevention and short-term prophylaxis, including self-administration
Icatibant	EU	2011	Self-administration for acute attacks
	USA	2011	Self-administration for acute attacks

^a Approvals in countries that participated in the survey. HAE = Hereditary angioedema.

and muscle aches. In a US survey developed by staff and patients at Penn State University, Hershey Medical Center, and sent to 158 HAE patients (46 returned completed surveys), a majority (87%) of HAE patients reported having a prodromal symptom prior to an attack [7]. The recognition of prodromal symptoms could provide an opportunity for early treatment and faster resolution of attack episodes [8].

Plasma-derived C1-INH (Berinert) has been the first-line therapy for HAE for several decades in Europe [9]. Another plasma-derived C1-INH (Cinryze) has recently been launched and both products, along with Ceter [10], are now nanofiltered C1-INH concentrates licensed for self-administration [10–13]. Currently, there are other therapies available for HAE attacks: a subcutaneous bradykinin receptor blocker [icatibant (Firazyr)] indicated for self-administration [14, 15], a subcutaneous kallikrein inhibitor [ecallantide (Kalbitor); not approved in Europe and not indicated for self-administration] [16, 17], and recombinant C1-INH (rC1-INH; Rhucin, Ruconest; not indicated for self-administration) [18]. Two of these products, rC1-INH and ecallantide, carry an anaphylactic risk, which limits their use for self-administration [17, 19]. Treatment regimens may involve short- or long-term prophylaxis as well as on-demand treatment for acute HAE attacks. The options for HAE management and available therapies have been reviewed recently [19]. Treatment of attacks has conventionally been administered in hospital or by healthcare providers; however, recent guidelines advise that all HAE patients

should be considered for self-administration therapy [20, 21].

Recent licence changes to some HAE therapies have provided excellent opportunities for more patients to switch to self-administered therapy (table 1) [11–13, 15, 22–25]. Home-based self-administration of HAE therapy permits rapid treatment in the early stages of an HAE attack and has been shown to reduce the duration of such attacks [26]. Early administration of Berinert and Firazyr has been shown to reduce the duration of an acute attack [27, 28]. Short-term prophylaxis used prior to a procedure or an important event and long-term prophylaxis are both amenable to self-administration and have been reviewed recently [6, 29].

The purpose of this study was to report the results of a survey and follow-up on feedback from an international HAE expert meeting into current self-administration practices in Europe, Canada and the USA.

Methods

An online survey was prepared to collate current experience and trends in the uptake and training of C1-INH self-administration. The survey consisted of 16 questions examining: current practices in self-administration training and HAE therapy, benefits/concerns relating to self-administration and current trends in self-administration use. The questions were assessed by a mixture of multiple choices and written (free text) answers (table 2). The survey was sent to 21 HAE centres across Europe, Canada and the USA, to include those experts and centres invited to participate in the international HAE expert meeting.

For further details of current guidelines, practicalities of administration and perceived challenges please refer to the articles within this supplement by Cicardi et al. [30], Symons et al. [31] and Boysen et al. [32], respectively.

Results and Discussion

Ten centres across Europe (n = 8), Canada (n = 1) and the USA (n = 1) responded to the survey and were represented at the international HAE expert meeting.

Current Practices in Self-Administration Training and HAE Therapy (P1–P6)

All the centres who responded to the survey (n = 10) offered self-administration as a therapy option to their patients. The experience in offering self-administration training varied within and between countries, with Germany having a much longer experience than, for example, Italy, where this approach is still in the early stages of development. The majority of centres (n = 9) provid-

Table 2. Questions and assessments employed in the questionnaire 'HAE Self-Administration Survey'

No.	Question	Assessed by	Answer range
<i>Current practices in self-administration training and HAE therapy (P)</i>			
P1	Do you currently offer your HAE patients the option of self-administration (or administration by other non-healthcare professionals, e.g. a family member outside of the physician office/hospital)?	Multiple choice	Yes/no
P2	Who trains your patients for self-administration?	Multiple choice	You/your staff/home nursing agency
P3	If you offer self-administered therapy to your patients is it with:	Multiple choice	Firazyr/Berinert/Cinryze
P4	Did the recent licence change for Berinert to include self-administration change your practice behaviour?	Multiple choice	Yes/no/unaware of licence change
P5	Did the recent licence change for Firazyr to include self-administration change your practice behaviour?	Multiple choice	Yes/no/unaware of licence change
P6	In your opinion what are the main (top 3) requirements for a patient to qualify for self-administration?	Written answer	
<i>Benefits/concerns relating to self-administration (B)</i>			
B1	What are the key benefits of switching from assisted infusion of Berinert to self-administered therapy from your perspective and from a patient perspective?	Written answer	
B2	Does your patient's quality of life improve with self-administration?	Multiple choice	Yes/no
B3	Do you think cost reduction occurs with self-administration?	Multiple choice	Yes/no
B4	What features of self-administered Berinert therapy may make a patient less likely to switch and, in your opinion, how could these clinical/psychosocial barriers be addressed?	Written answer	
B5	What are your concerns regarding self-administration?	Multiple choice	Infection/contamination/air emboli/other drugs/monitoring/poor venous access/no strong concerns
B6	What are the main (top 3) hurdles to enable/train patients to self-administer Berinert?	Written answer	
B7	What activities/resources would be most valuable to improve patient uptake of self-administered Berinert?	Written answer	
<i>Trends in self-administration use (T)</i>			
T1	Is the share of patients learning/practising self-administration...	Multiple choice	Increasing/decreasing/not changing
T2	What percentage of your patients self-administers their treatment?	Multiple choice	0/10/25/50/75/90/100
T3	Please provide a rough estimate of the percentage of your patients who self-administer using Firazyr, Berinert or Cinryze (% of total number of patients on respective therapy).	Written answer	

HAE = Hereditary angioedema.

ed training to patients by centre staff (either physicians or nurses) whilst the US centre utilised home care agencies.

There are a wide variety of experiences in the development and implementation of training programmes and these are summarised in table 3.

Of the three therapies indicated for self-administration, Firazyr, Berinert and Cinryze, the survey indicated that Firazyr or Berinert were the most popular therapies offered for self-administration (fig. 1). At the time of the survey, Cinryze was not available in some of the countries

that took part in the survey. At some centres (n = 7) patients were only offered Firazyr or Berinert, while at another centre patients were able to choose between Firazyr, Berinert or Cinryze. At the remaining two centres choice was limited to either Firazyr only or Berinert only.

Survey respondents were divided equally as to whether the recent licence changes to Firazyr and Berinert regarding possibility for self-administration had influenced practice behaviour: yes (n = 5) and no (n = 5). Three of the responders who answered 'yes' commented that these changes had made it easier to offer self-administration to

Table 3. Status of self-administration training programmes

Country	Development and practice of self-administration training programmes
Canada	<ul style="list-style-type: none"> – Patients are taking 2–3 h to train. – Shortage of nurses to perform the training.
France	<ul style="list-style-type: none"> – Angioedema reference centre nurses ran training programme: 95% of patients already trained for self-administering Firazyr subcutaneously for on-demand treatment of acute attacks. – Started intravenous home therapy training with a few patients: angioedema nurses will improve their skills with the help of a German team to be able to train patients for intravenous self-administration.
Germany	<ul style="list-style-type: none"> – Post-training checks. – Training should include discussions of side effects and actions.
Italy	<ul style="list-style-type: none"> – Relatively new to home therapy training. Eleven patients have been successfully trained in Sicily with help from haemophilia staff. – Yet to determine strategy for refresher training.
Spain	<ul style="list-style-type: none"> – Nurse-led training programmes, supervised by physicians with some patients trained with help from haemophilia staff. Includes several sessions, post-training checks or refresher sessions. – The majority of patients are self-administering Firazyr for on-demand treatment of acute HAE attacks and a minority are administering Berinert, some of which are using off-label for long-term treatment.
UK	<ul style="list-style-type: none"> – Training supervised by immunology specialist nurses; variable number of training sessions depending on route of administration (often a single session for subcutaneous, more for intravenous) and patient competency and confidence. Refresher course at clinic review.
USA	<ul style="list-style-type: none"> – Home therapy companies/agencies provide training.

HAE = Hereditary angioedema.

their HAE patients and would lead to an increase in the number of self-administering patients.

Since the licence changes, it was commented that more patients have been trained to self-administer 'Firazyr for acute attacks as the subcutaneous technique is easy for the patient'. It was also suggested that the licence changes for Berinert would make it easier to offer self-administration for an intravenous drug and that it would increase the number of patients that are offered Berinert during acute attacks and for long-term prophylaxis.

Fig. 1. Self-administration treatments offered by HAE clinical centres. At the time of the survey, Cinryze was not available in some of the countries surveyed.

The survey recorded 15 separate answers from respondents when asked what the three main requirements were for a patient to qualify for self-administration (fig. 2). The most popular answers were patient motivation, patient mental ability and clinical need. Notably, most of the requirements mentioned were patient related (60%) compared to clinical requirements (40%).

Key Benefits of Switching to Self-Administration (B1–B3)

The survey respondents agreed that self-administration improved patients' quality of life and outlined the key benefits as time saved, independence and convenience. From the clinicians' perspective the key benefits included early treatment, optimised therapy, lower dose and fewer visits to the emergency department. The benefits from the patients' perspective, as identified by the clinicians, included independence, convenience and more free time.

Cost savings were identified as a key benefit by all of the respondents, with savings in areas such as dose reduction due to early treatment, use of fewer resources at the physician's office and fewer visits to hospital emergency departments.

Barriers to Self-Administration (B4–B7)

Several barriers and concerns were perceived in relation to the introduction of self-administered HAE therapy, including funding and resource issues, legal/regulatory requirements and patient characteristics and functionality.

Legal and regulatory issues varied between countries and healthcare providers. For example, in Germany the

Fig. 2. Requirements for a patient to qualify for self-administration.

Table 4. Concerns regarding patient readiness to receive/switch to self-administration therapy

Concerns regarding patient ability to receive self-administration therapy

Mental ability
Inadequate education
Difficulty with administration
Age
Severe psychiatric disorders
Fear of self-injection
Distance to the hospital
Infrequent acute attacks
Willingness
Competency
No home care partner

variations, keeping blood banks stocked with pasteurised-nanofiltered HAE products, the threat of increased infections and lack of therapy monitoring. Concerns were also raised about patients' readiness to switch to self-administration and the distance from home to their clinic (table 4). Patients who live close to the clinic would not see distance to the hospital as being a disadvantage; however, the benefits of self-administration in such situations would include a greater freedom to travel.

The physicians in the international HAE expert meeting commented that some of these issues can be addressed by providing sufficient training and support for self-administration, e.g. fears of intravenous or subcutaneous administration, difficulty in obtaining venous access and fear of self-injection.

Trends in Self-Administration (T1–T3)

All the centres reported that the number of patients learning/practising self-administration was increasing. No data were collected in relation to patients who, having tried self-administration, had reverted to hospital-based treatment or switched between different routes of administration i.e. intravenous or subcutaneous.

prescribing physician remains legally responsible even though the treatment is being administered at home, either on-demand by the patient themselves or by a trained caregiver; this deters some physicians from prescribing self-administration therapy.

From the healthcare providers' perspective, barriers included: providing sufficient nurse resources, funding

Fig. 3. Percentage of patients who are self-administering their treatment (across all centres).

The majority of centres ($n = 7$) reported that more than half (50–89%) of their patients were receiving self-administration therapy (fig. 3). As previously mentioned, most patients are offered a choice between Firazyr and Berinert, and these two products accounted for 96% of the HAE products used in self-administration (49% and 47%, respectively). Cinryze was reported to be used by a minority of patients (4%); however, at that time, Cinryze was not available in some of the countries that participated in the survey.

Conclusions

As the awareness of self-administration grows, an increasing number of patients are being offered and are using self-administration HAE therapy. Switching to self-administration therapy is looked upon favourably from both the patient [33] and clinician perspectives by virtue of the potential improvement in quality of life arising from optimisation of therapy and early intervention, with the total length of an attack being decreased with early intervention. However, future efforts should focus on encouraging more patients to take up self-administration and the key to this appears to be training in the skills needed, together with the availability of nurse/physician backup support, if required. Although some reference centres have initiated their own training programmes for patient self-administration, support should be provided, especially to centres dealing with small patient numbers.

A limitation of the survey was that it was restricted to those experts and centres invited to participate in the international HAE expert meeting, which could entail a se-

lection bias. It should be noted that this survey largely reflects the current status of self-administration across Europe as 80% of the responding centres were European. Some centres also offered self-administration as an option to patients before it was licensed. Overall, in the majority of European countries, Berinert and Firazyr are equally used by patients opting for self-administration. However, national preferences may become apparent, for example in France where both Berinert and Firazyr are offered to patients, but most patients choose Firazyr for self-administration. The recent changes to product licences, which allow their use for self-administration, provide additional options for the management of HAE.

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Dr. Sala-Cunill speaks for Shire, consults for CSL Behring and Shire and does research for Shire, Pharming and ViroPharma.

Professor Cancian is a consultant for ViroPharma, Sobi, CSL Behring and Shire.

Dr. Craig speaks for CSL Behring, ViroPharma, Shire and Dyax. He does research for Pharming, CSL Behring, ViroPharma, Shire and Dyax. He is a consultant for CSL Behring and Dyax and has received educational grants from Dyax, ViroPharma and CSL Behring.

Prof. Neri has participated in advisory boards and symposia and has received educational grants from Shire, CSL Behring, ViroPharma and Pharming.

Dr. Keith has served on advisory boards for CSL Behring, Shire and ViroPharma. He has received research funding from Shire.

Dr. Boccon-Gibod has received consultancy fees from CSL Behring and Shire HGT Inc.

Dr. Bethune has been involved in advisory boards for Shire, ViroPharma and Swedish Orphan Biovitrum. She has received support to attend meetings from Shire, ViroPharma and CSL Behring. Her department has received support from Shire and CSL Behring.

Dr. Bork is a consultant for CSL Behring, Shire and ViroPharma.

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