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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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...
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 (Cimryze) has recently been launched and both products, along with Cetor [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, Rucnest; 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-

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Country</th>
<th>Date</th>
<th>Indicated for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berinert</td>
<td>23 EU countries</td>
<td>2011</td>
<td>Self-administration for acute attacks</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>2012</td>
<td>Self-administration for acute attacks</td>
</tr>
<tr>
<td></td>
<td>23 EU countries</td>
<td>2013</td>
<td>Short-term prophylaxis, including self-administration</td>
</tr>
<tr>
<td>Cinryze</td>
<td>USA</td>
<td>2009</td>
<td>Self-administration for prophylaxis</td>
</tr>
<tr>
<td></td>
<td>EU</td>
<td>2011</td>
<td>Acute attacks, routine prevention and short-term prophylaxis, including self-administration</td>
</tr>
<tr>
<td>Icatibant</td>
<td>EU</td>
<td>2011</td>
<td>Self-administration for acute attacks</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>2011</td>
<td>Self-administration for acute attacks</td>
</tr>
</tbody>
</table>

* Approvals in countries that participated in the survey. 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...
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.

### 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...
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 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.

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

<table>
<thead>
<tr>
<th>Concerns regarding patient ability to receive self-administration therapy</th>
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</thead>
<tbody>
<tr>
<td>Mental ability</td>
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<tr>
<td>Inadequate education</td>
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<tr>
<td>Difficulty with administration</td>
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<tr>
<td>Age</td>
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<tr>
<td>Severe psychiatric disorders</td>
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<tr>
<td>Fear of self-injection</td>
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<tr>
<td>Distance to the hospital</td>
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<tr>
<td>Infrequent acute attacks</td>
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<tr>
<td>Willingness</td>
</tr>
<tr>
<td>Competency</td>
</tr>
<tr>
<td>No home care partner</td>
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</tbody>
</table>

**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.
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 selection 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.

Disclosure Statement

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

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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.


