Subcutaneous C1 Inhibitor for Long-term Prophylaxis of Hereditary Angioedema: A Real-life Experience

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Hereditary angioedema (HAE) is a rare disabling and potentially fatal genetic disorder caused by C1-esterase inhibitor (C1-INH) deficiency (HAE type 1) or quantitative normal but nonfunctional C1-INH (HAE type 2), although other forms of HAE with normal levels and function of C1-INH have been described (HAE-nC1-INH) [1,2]. Patients with HAE experience recurrent attacks of swelling due to inadequate control of the contact system and accumulation of bradykinin [1].

Long-term prophylaxis (LTP) can reduce the burden of HAE by preventing or attenuating attacks and should be considered in symptomatic patients, depending on disease activity, the frequency of attacks, quality of life (QOL), and the lack of control with on-demand therapy [3].

Intravenous (IV) C1-INH replacement effectively reduces both the frequency and the severity of HAE attacks [4]. The subcutaneous (SC) formulation was developed and approved for LTP in order to facilitate technical concerns with IV C1-INH and has also proven to be effective [5].

We report on 22 patients with C1-INH HAE who started SC C1-INH replacement treatment as LTP during the COVID-19 pandemic. Laboratory tests and clinical data were prospectively collected at 1 or more visits before initiation of LTP with SC C1-INH, and at a follow-up visit, at least 8 weeks after switching to it. Patients reported QOL using a visual analog scale (VAS) before and after the switch and using the Angioedema Quality of Life Questionnaire after the switch. All patients and the parents of pediatric patients gave their written informed consent for publication of this report.

Age, sex, HAE type, weight, body mass index, comorbid conditions, and HAE treatment during the previous year are presented in Supplementary material 1. Previous C1-INH antigen levels and C1-INH activity are presented in Supplementary material 1 as a single number or, when values from different visits were available, as a range. Before LTP with SC C1-INH, 13 patients experienced 1 or more attacks per week and 7 patients fewer than 1 attack per week but more than 1 per month. Twenty patients had mainly severe attacks, 1 patient had moderate but frequent attacks, and 1 pediatric patient had mild but frequent attacks.

Doses, frequency of administration of SC C1-INH, and follow-up periods are presented in Supplementary material 2. The C1-INH activity of the 22 patients after receiving prophylaxis with SC C1-INH ranged from 2% to 81%. In patient 10, who had the lowest value, disease course was severe but improved clearly in terms of the number and severity of the attacks. Overall, the frequency of attacks was reduced (none or fewer attacks than before per month) after the follow-up period (Table).

Eight patients remained asymptomatic, and 12 patients presented fewer than 1 mild attack per month. Patient 2 experienced an isolated severe attack, and patients 9, 13, and 18 experienced an isolated mild attack, some in the context of a skipped dose or trauma as a trigger.

The median (IQR) self-reported QOL score was 5 (2-5) before the switch and 9 (9-10) after the follow-up period (Supplementary material 3). Improvements were perceived in all patients, except for 1 patient, who could not respond owing to cognitive impairment, and another, who reported no changes.

We found SC C1-INH to be effective as prophylaxis in a series of patients with HAE, most of whom were treated with doses below 40 IU/kg. Patients were evaluated individually and selected for LTP with SC C1-INH owing to the severity of the attacks and the lack of control with previous treatment. An improvement was observed in terms of frequency and severity of attacks. Similar findings were reported in a pivotal study, where administration of SC C1-INH twice weekly reduced the rate of attacks and the need for rescue medication [5]. Moreover, a post hoc exploratory analysis revealed a preventive effect of SC C1-INH in all patients, independently of the location of the attacks [6].

Most of the patients studied had been previously treated with IV C1-INH, which is an effective and safe option for preventing HAE attacks [4]. However, IV administration has drawbacks, such as the loss of venous access [2], which generally leads patients to prefer SC administration [7]. This may impact adherence to treatment and patient QOL. It has also been suggested that the switch from IV to SC C1-INH LTP can result in a clinically significant benefit in terms of reduced frequency of attacks [8].

The efficacy and safety of a fixed dose of SC C1-INH compared with placebo has been demonstrated [9]. In our series, most patients (n=18) were treated with a fixed dose of 2000 IU twice weekly, and the doses administered ranged from 14 to 38 IU/kg per dose. Pediatric patient 21 was treated with 61 IU/kg twice weekly, and patients 10, 11, and 14, whose weight was >100 kg after a period of twice weekly 2000 U of SC C1 INH, switched to SC C1-INH 2000U 3 times weekly. Thus, we hypothesize that the effect of prophylaxis with SC C1-INH might have been even more pronounced if doses from 40 IU/kg to 60 IU/kg had been administered to all patients. We also observed that prolonged stability is achievable and maintainable with lower doses, with the precaution of ensuring that IV C1-INH is available in case of an unexpected attack.

Table. Follow-up Data After Switch to Long-term Prophylaxis With SC C1-INH.

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
	Months of treatment[a]																					
	16	10	13	16	12	15	13	15	14	7/6	5/4	13	16	10/6	12	12	11	53.5	3	15	18	4
	C1-INH dose, IU/k[a]																					
	25	24	29	31	38	31	38	24	33	18	15	25	31	20	33	22	31	37	24	31	61	32
C1 (21-39 mg/dL)	7.7 8.4	9.1	14.3	10.9 - 12.9	5.3 - 7.7	4.4 - 11.4	10.8 - 13.6	7.2 - 7.4	9.6 - 12.4	6.3 - 8.4	8.0 - 9.1	26.6 - 27.6	6.3	4.8 - 7.8	10.5	5.8	5.2	12.3	8.2	10.7 - 12.8	23.8	9.1
C1 activity (70%-130%)	7-18	30-35	26	16-68	49	35	51	36	10	2	12-27	29	36	21-32	81	32	Missing	Missing	33	41-44	66	21-57
	Attacks during follow-up/mo																					
	-	-	-	-	0	0	-	-	-	-	0	+	-	0	-	-	+	-	0	0	0	0

Abbreviation: C1-INH, C1-esterase inhibitor.
[a]In the case of 2 values the first refers to a dose administered twice weekly and the second refers to a dose administered 3 times weekly.
[b]Dose adjusted for weight >100 kg to 2000 U every 48 h.

All adult patients and the parents of the pediatric patients were trained in self-administration in the abdominal area. The 2 pregnant patients (17 and 22) were also recommended to use the quadriceps area in the second and third trimesters.

In addition to the clinical improvement, self-administered SC C1-INH has a positive impact on QOL and on the degree of satisfaction with treatment compared with on-demand treatment [10]. In the current series, an improvement in the patient's QOL was also observed (Supplementary material 3). The use of SC C1-INH reduced the economic costs and disease burden by reducing the number and severity of attacks, the use of rescue medication and health care resources, and the complications associated with IV administration.

SC C1-INH proved to be an effective prophylactic treatment in a series of patients with HAE treated at doses <40 IU/kg. Although our series is small, our data are relevant in a rare disease such as HAE and confirm previous clinical data during the follow-up period.

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Conflicts of Interest

Dr Krasimira Baynova and Dr Stefan Cimbollek have received speaker's fees from Takeda, CSL Behring, and Novartis. The remaining authors declare that they have no conflicts of interest.

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