Subcutaneous C1 inhibitor for the long-term prophylaxis of hereditary angioedema -a real life experience

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Hereditary angioedema (HAE) is a disabling, potentially fatal, rare genetic disorder caused by C1-esterase inhibitor (C1-INH) deficiency (HAE Type 1) or quantitative normal but non-functional C1-INH (HAE Type 2), although other forms of HAE with normal levels and function of C1-INH have been described (HAE-nC1INH)[1,2]. Patients with HAE suffer recurrent attacks of swelling due to the failure to adequately control the contact system and the accumulation of bradykinin[1].

Long-term prophylaxis (LTP) can reduce the burden of HAE by preventing or attenuating its attacks, and should be considered in symptomatic patients, depending on the activity of the disease, the frequency of attacks, the 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 attack[4]. Subcutaneous (SC) formulation was developed and approved for LTP in order to facilitate technical concerns of IV C1-INH and has also shown to be effective[5].

We report 22 patients with C1-INH HAE who started SC C1-INH replacement treatment as LTP during the COVID19 pandemic. Laboratory tests and clinical data were prospectively collected during one or more visits before starting the LTP with SC C1-INH, and in a follow-up visit, at least 8 weeks after switching to it. Patients reported QoL using a visual analogue scale (VAS) before and after the switch and using AE-QoL after the switch. All patients and paediatric patient parents gave their written informed consent for publication of this report

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Age, gender, HAE type, weight, BMI, co-morbidities and/or other conditions, and HAE treatment during the previous year are presented in supplementary material 1 (SM1). Previous C1-INH antigenic levels and C1-INH activity are presented in SM1 as a unique number or, when values from different visits were available, as a range. Before SC C1-INH LTP, 13 patients were suffering 1 or more attack per week and 7 patients, less than 1 attack per week but more than 1 per month. The majority of attacks were classified as severe in 20 patients, one patient had moderate but frequent attacks and one paediatric patient had mild but frequent.

Doses, frequency of administration of SC C1-INH and follow-up periods are presented in supplementary material 2(SM2). C1-INH activity of the 22 patients after receiving SC C1-INH prophylaxis ranged from 2% to 81%. Patient 10, who had the lowest value, had a severe course of the disease but presented a clear improvement in the number and severity of attacks. Overall, the frequency of attacks was reduced (- or 0/ month) after the follow-up period (Table 1)

Eight patients remained asymptomatic, and 12 patients presented less than one mild attack per month. Patient 2 suffered an isolated severe attack, and patient 9, 13 and 18, an isolated mild attack; some of them in the context of a skipped dose or a trauma as triggering factor.

Median (Q1, Q3) self-reported QoL was 5 (2, 5) before the switch and 9 (9, 10) after the follow-up period (supplementary material 3-SM3). Improvements were perceived in all patients, with the exception of one patient who could not respond due to cognitive impairment, and another who reported no changes.

SC C1-INH has been an effective prophylactic treatment in a series of patients with HAE most of whom treated with doses below 40 UI/kg. Patients were evaluated individually and selected for SC C1-INH LTP due to the severity of the attacks and the lack of control with previous treatment. Improvement was observed in terms of frequency and severity of attacks. In line with this findings, the administration of SC C1-INH twice weekly has shown to reduce the rate of attacks and the need for rescue medication in a pivotal study [5]. Moreover, a *post hoc* exploratory analysis showed a preventive effect of SC C1-INH in all patients independently of the variable location of the attacks [6].

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The majority of the presented patients had been previously treated with IV C1-INH, which is an effective and safe option for preventing HAE attacks[4]. However, some disadvantages can be attributed to the IV administration such as the loss venous access [2], which make patients generally prefer SC administration[7]. This may impact the adherence to treatment and the QoL of the patients. Also it has been suggested that the switch from IV to SC C1-INH LTP can derive in a clinically significant benefit in terms of reduction of the rate of attacks [8].

The efficacy and safety of a fixed dose of SC C1-INH *versus* placebo has been previously demonstrated [9]. In our series, most of the patients(n18) were treated with a fixed dose of 2000 IU twice weekly, and the administered doses ranged from 14 to 38 IU/kg *per* dose. The paediatric patient 21 was treated with 61 IU/kg twice weekly and patients 10,11 and 14 with weight higher than 100 kg after period of twice weekly 2000U/ SC C1 INH switched to tree times weekly 2000U/ SC C1 INH. Thus, we hypothesize that the effect of SC C1-INH prophylaxis might have been even higher if doses from 40 IU/kg to 60 IU/kg had been used in all patients. We have also observed that prolonged stability is achievable and maintainable with lower doses, with the precaution of availability of IV C1INH in case of an unpredictable attack.

All adult patients and parents of the paediatric patients were trained in self - administration in the abdominal area. The two pregnant patients(17,22) were suggested to use also quadriceps area in second and third trimester of pregnancy.

In addition to the clinical improvement, self-administered SC C1-INH has shown to positively impact on QoL, and the degree of satisfaction with the treatment compared to on-demand treatment[10]. In the current series, an improvement in the patient's QoL was also observed(SM3). The use of SC C1-INH reduced the economic costs and the burden of the disease, by the reduction of the number and severity of attacks, the use of rescue medication, and the healthcare resources and complications derived from IV administration.

SC C1-INH is an effective prophylactic treatment in a series of patients with HAE treated with doses below 40 UI/kg. Although it is a small series of patients , it is relevant in a rare disease as HAE and confirms previously suggested clinical data during the follow-up period.

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Conflict of Interest

Dr. Krasimira Baynova and Dr. Stefan Cimbollek declare having received speaker's fees from Takeda, CSL Behring and Novartis. The rest of the authors declare no conflicts of interest.

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Table 1. Follow- up data after switch to SC C1INH LTP

Case N	**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																						
	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 (UI/kg)																						
	25	24	29	31	38	31	38	24	33	18	15	25	31	20	33	22	31	37	24	31	61	32
C1 (21-39mg/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/month																						
	-	-	-	-	0	0	-	-	-	-	0	+	-	0	-	-	+	-	0	0	0	0

C1-INH- C1-esterase inhibitor.- / months of treatment -twice/ 3 times weekly. Dosis adjusted due to weight> 100kg, to 2000U/ every 48 h

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