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Hereditary Angioedema Attacks in Patients Receiving Long-Term Prophylaxis: A Systematic Review

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Background

- Hereditary angioedema (HAE) is a rare genetic disease, most commonly caused by deficiency (type I) or dysfunction (type II) of the C1-inhibitor protein (HAE-C1INH) and subsequent uncontrolled activation of the kallikrein kinin system, resulting in attacks of tissue swelling[1-3]
- Non-androgen and androgen long-term prophylaxis (LTP) reduces the frequency of HAE attacks.[4] In pivotal phase 3 trials, a ≥70% reduction in the frequency of attacks from baseline was reported in 50% of patients who received berotralstat,[5] 76%-89% of patients who received lanadelumab,[6] and 92% of patients who received garadacimab[7]; a ≥70% reduction was reported in 67%-83% of patients who received subcutaneous plasma-derived C1 inhibitor (sc-pdC1INH, Berinert or Haegarda; CSL Behring) as opposed to placebo[8]
- Patients with HAE-C1INH who receive LTP may still experience unpredictable and severe attacks that can be life threatening[9]
  - The characteristics of these attacks and use of on-demand treatment are not well understood

Objective

- This systematic review aimed to describe the population of patients with HAE-C1INH who experienced attacks while receiving LTP and the characteristics of these attacks—including attack severity, duration, location—and on-demand treatment use

Methods

- A systematic search was conducted in PubMed to identify randomized controlled trials (RCTs), open-label extension (OLE), and real-world evidence (RWE) studies that reported LTP use in patients with HAE-C1INH. LTP agents included pdC1INH (intravenous Cinryze [Takeda] or subcutaneous Berinert), lanadelumab, berotralstat, garadacimab, androgens (eg, danazol), or antifibrinolytics (eg, tranexamic acid [TA])
  - Search procedures were established a priori in an operational protocol and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines
- The initial search was conducted May 17, 2022, and was limited to articles published in English from January 1, 2002, onward. The search was updated on May 15, 2023, using the same search criteria
  - Studies that did not clearly report on HAE-C1INH (type I/II) or that reported patients taking only on-demand therapy or only short-term prophylaxis were excluded
- Assessments for risk of bias were performed for included studies using the Risk of Bias 2 tool for RCTs10 and the Newcastle-Ottawa Scale11 for cohort studies
- Supplementary content of this poster is accessible through a QR code at the bottom of this poster and includes the bibliography. Reference numbering is continuous across poster and supplementary materials

Results

Study characteristics

- The initial PubMed search returned 2612 records, and the updated search identified 179 additional records
  - Of these, 58 publications that described 45 primary study results published between January 1, 2002, and May 15, 2023, met inclusion criteria (composed of 13 RCTs, 7 OLEs, and 25 RWE studies). Please scan the QR code to view the PRISMA flow diagram (**Figure 1**)

Proportion of attack-free patients who received LTP

- No active-comparator RCTs between pdC1INH (Berinert/Cinryze), lanadelumab, berotralstat, and garadacimab were identified
- The proportions of attack-free patients in RCTs, OLEs, and RWE studies evaluating LTP with pdC1INH (Cinryze or Berinert), lanadelumab, berotralstat, garadacimab, androgens, and antifibrinolytics are shown in **Table 1**
- No RCTs that reported attack-free rates were identified for patients who received LTP with attenuated androgens or TA; however, in observational studies, 24%-38% of patients who received danazol and ≤20% of patients who received TA for ≥1 year were attack free[12-15] (**Table 1**)

Results (continued)

Table 1. The proportion of patients who received LTP who were attack free

Study identifier	Study design	Duration of treatment	Study population	Number of patients	LTP agent and comparator	Proportion of patients attack free
C1INH replacement						
NCT00462709 (CHANGE 3)[16-18]	Open-label, single arm study	248 days (median)	Children aged ≥1 year and adults[16]	146	Cinryze 1000 U every 3-7 days	35%
			Subgroup: children aged ≥6 to <18 years[17]	23	Cinryze 1000 U every 3-7 days	22%
			Subgroup: pregnant women[18]	11	Cinryze 1000 U every 3-7 days	55%
NCT02052141[19]	Randomized crossover trial	2 x 12-week treatment periods	Children aged ≥6 to <12 years	12	Cinryze 500 U every 3-4 days	25%
					Cinryze 1000 U every 3-4 days[a]	33%
NCT01912456 (COMPACT)[3]	Randomized, placebo-controlled crossover trial	2 x 16-week treatment periods	Adolescents aged ≥12 years and adults	90	Berinert 40 IU/kg twice weekly	38%
					Berinert 60 IU/kg twice weekly	40%
					Placebo (Group 1)	9%
					Placebo (Group 2)	0%
NCT02316353 (COMPACT OLE)[20-22]	Open-label, randomized, parallel-arm study	≥52 weeks – 140 weeks	Children aged ≥6 years and adults[b,21]	63	Berinert 60 IU/kg twice weekly	44%
			Subgroup: adults aged ≥65 years[20]	10	Berinert 40 or 60 IU/kg twice weekly	30%
			Subgroup: children aged ≥6 to <18 years[22]	10	Berinert 40 or 60 IU/kg twice weekly	10%
Japanese study[23]	Open-label, single-arm study	16 weeks	Adolescents aged ≥12 years and adults	9	Berinert 60 IU/kg twice weekly	67%
Lanadelumab						
NCT02093923[24]	Randomized, placebo-controlled trial	14 days[c]	Adults aged ≥18 years	37	Lanadelumab 300 mg Q2W (2 doses)	100%
					Lanadelumab 400 mg Q2W (2 doses)	82%
					Placebo	27%
NCT02586805 (HELP)[6,25]	Randomized, placebo-controlled, parallel-arm trial	26 weeks	Adolescents aged ≥12 years and adults[6]	125	Lanadelumab 150 mg Q4W	39%
					Lanadelumab 300 mg Q4W	31%
					Lanadelumab 300 mg Q2W	44%
					Placebo	2%
			Adolescents aged ≥12 years and adults (post hoc analysis of steady state [Day 70 to Day 182])[6,25]	125	Lanadelumab 150 mg Q4W	54%
					Lanadelumab 300 mg Q4W	45%
					Lanadelumab 300 mg Q2W	77%
					Placebo	3%
NCT02741596 (HELP OLE)[26]	Open-label, single-arm study	33 months (median)	Adolescents aged ≥12 years and adults	212	Lanadelumab 300 mg Q2W[e]	37%
Canadian study[27]	Retrospective chart review	12 months	Patients aged 24-74 years commencing lanadelumab	12	Lanadelumab 300 mg Q2W[f]	25%
Single-center study[28]	Retrospective chart review	36 weeks (median)	Patients aged 21-55 years commencing lanadelumab	9	Lanadelumab 300 mg Q2W or Q4W	56%
Berotralstat						
NCT02870972 (APeX-1)[29]	Randomized, placebo-controlled, parallel-arm trial	28 days	Adults aged 18 to 70 years	77	Berotralstat 62.5 mg QD	0%
					Berotralstat 125 mg QD	43%
					Berotralstat 250 mg QD	21%
					Berotralstat 350 mg QD	39%
					Placebo	9%
Attenuated androgens and TA						
US-HAEA[31]	Patient survey	NR	Patients from the US-HAEA registry	344[j]	Attenuated androgens[k]	26%[j]
Chinese study[14]	Retrospective cohort	1 year	Patients aged ≥11 years of age from China	74	Danazol[k]	34%[j]
German study[13]	Retrospective chart review	11 years (mean)	Patients aged 15-74 years from Germany/Denmark	118	Danazol[k]	24%
Swiss study[12]	Retrospective cohort	1 year	Patients aged ≥5 years from Switzerland	26	Danazol[k]	38%
				10	TA[k]	20%
CREAK study[15]	Retrospective chart review	6 months	Patients aged ≥16 years from France	12	TA[k]	8%
Investigational LTP agents						
NCT03712228[30]	Randomized, placebo-controlled parallel-arm trial	12-week SC administration[g]	Adults aged 18-65 years	32	Garadacimab 75 mg Q4W[h]	56%
					Garadacimab 200 mg Q4W[h]	88%
					Garadacimab 600 mg Q4W[h]	43%
					Placebo[h]	0%
NCT04656418[7]	Randomized, placebo-controlled parallel-arm trial	6 months	Adolescents aged ≥12 years and adults	64	Garadacimab 200 mg QM[i]	62%
					Placebo	0%

C1INH, C1 inhibitor; CREAK, National Reference Centre for Angioedema (France); IV, intravenous; LTP, long-term prophylaxis; NR, not reported; OLE, open-label extension; Q2W, every 2 weeks; Q4W, every 4 weeks; QD, once daily; QM, once monthly; SC, subcutaneous; TA, tranexamic acid; US-HAEA, United States Hereditary Angioedema Association.
[a]Cinryze 1000 U every 3 or 4 days exceeds the recommended dose for children younger than 12 years of age. [b]Post hoc analysis in patients randomly assigned to the Berinert 60-IU/kg treatment arm. [c]Efficacy analyses were assessed from days 8-50. [d]Four dose groups of lanadelumab were administered (30 mg, 100 mg, 300 mg, and 400 mg) in a staggered, dose-escalating fashion; however, the prespecified efficacy analyses were only performed for the lanadelumab 300-mg and 400-mg groups compared with placebo. [e]In rollover patients, a single dose of lanadelumab 300 mg was received at study entry and until the patient experienced their first attack, following which the patient received lanadelumab 300 mg Q2W. Nonrollover patients received lanadelumab 300 mg Q2W from study entry onward. [f]One patient was switched from lanadelumab 300 mg Q2W to Q4W. [g]Efficacy analyses were reported for the 12-week SC treatment period. [h]All patients received an initial IV loading dose on day 1 of placebo or garadacimab 40 mg, 100 mg, or 300 mg, followed by SC treatment with placebo or garadacimab 75 mg, 200 mg, or 600 mg on day 6 and Q4W thereafter for 12 weeks. [i]Patients received a 400-mg SC loading dose on day 1. [j]Percentage of attack-free patients among 344 patients who received attenuated androgens at the time of the survey. [k]The dosage and dosing frequency of each LTP agent was variable or was not reported. [l]The study results showed the outcome as the proportion of patients who had ≤1 attack/year rather than the proportion of patients who were attack free.

Attack severity, duration, and location in patients who received LTP

- The difference compared with placebo in the mean attack severity score was reported in phase 3 trials of pdC1INH[8,32] (**Table 2**; please scan QR code to view Table 2)
  - Phase 3 trials for lanadelumab and garadacimab reported a significant reduction in the number of moderate to severe attacks; however, the average severity of attacks occuring in the presence of LTP was not reported[6,7]
  - A statistically significant reduction in attack duration compared with that for placebo was reported in a phase 3 trial of pdC1INH with Cinryze (P=0.002)[32] but not with lanadelumab in the phase 3 HELP trial[6] or SC Berinert in the phase 3 COMPACT trial[33]
  - None of the placebo-controlled RCTs reported a significant reduction in attack severity or attack duration from baseline for any LTP
- Findings from OLEs and observational RWE studies generally supported a reduction in attack severity with LTP use[23,26,31,34-39] (**Table 3**; please scan QR code to view Table 3)
- RCTs and OLE and RWE studies showed that attacks at all locations continued to occur in patients who received LTP, including laryngeal attacks[5,6,8,12,13,22,26,36,37,40,41]
  - Interventional and observational studies reported that laryngeal attacks accounted for 2%-7% of all attacks in patients who received LTP with pdC1INH, lanadelumab, danazol, or TA (not reported for berotralstat)[5,6,22,26,36]
  - Substantially lower rates of peripheral attacks were reported with lanadelumab[6,24] and berotralstat[5,29] (compared with placebo)

On-demand therapy use for attacks in patients who received LTP

- Study results showed that most attacks in patients who received LTP were treated with on-demand therapy[6,21,22,24,30,33,36,37,42] (**Table 4**)
  - In phase 3 studies, 49%-68% of attacks in patients who received Berinert,[33] 65%-83% of attacks in patients who received lanadelumab,[6] and 82% of attacks in patients who received berotralstat[42] were treated with ≥1 dose of an on-demand therapy. The on-demand agent and dosage administered varied across studies and included icatibant, ecallantide, C1INH replacement (plasma-derived or recombinant), or fresh frozen plasma[6,33,42]
  - Results of observational studies suggest that the proportion of attacks treated with on-demand therapy may be higher in real-world settings than the proportion reported in clinical trials[36,37]
- A small proportion of attacks in patients who received LTP were treated with ≥2 doses of on-demand therapy[21,33,36]

Table 4. Proportion of attacks treated with on-demand therapy in patients who received LTP

First author, date of publication	Study details	Number of patients	LTP agent and comparator	Attacks treated with on-demand therapy, n/N (%)	Treated attacks requiring 2 doses of on-demand therapy, n/N (%)	Treated attacks requiring ≥3 doses of on-demand therapy, n/N (%)
Li, 2019[33]	Phase 3 RCT (COMPACT)	90	Berinert 40 IU/kg twice weekly	99/145 (68)	7/99 (7)	0/99 (0)
			Berinert 60 IU/kg twice weekly	35/71 (49)	0/35 (0)	0/35 (0)
			Placebo[a]	779/975 (80)	60/779 (8)	29/779 (4)
Craig, 2022[21]; Levy, 2020[22]	Phase 3 OLE	63[21]	Berinert 60 IU/kg twice weekly	229/371 (62)	25/229 (11)	12/229 (5)
		10[b,22]	Berinert 40 or 60 IU/kg twice weekly	16/38 (42)	NR	NR
Banerji, 2017[24]	Phase 1b RCT	37	Lanadelumab 300 mg Q2W[c]	0[d]	NR	NR
			Lanadelumab 400 mg Q2W[c]	2/3 (67)	NR	NR
			Placebo	22/24 (92)	NR	NR
Banerji, 2018[6]	Phase 3 RCT (HELP)	125	Lanadelumab 150 mg Q4W	55/84 (65)	NR	NR
			Lanadelumab 300 mg Q4W	87/105 (83)	NR	NR
			Lanadelumab 300 mg Q2W	38/46 (83)	NR	NR
			Placebo	506/572 (88)	NR	NR
Farkas, 2021[42]	Phase 3 OLE (APeX-S)	227	Berotralstat 150 mg QD[e]	82%[f]	NR	NR
Craig, 2022[30]	Phase 2 RCT	32	Garadacimab 75 mg Q4W[g]	11/12 (92)	0/11 (0)	0/11 (0)
			Garadacimab 200 mg Q4W[g]	1/1 (100)	0/1 (0)	0/1 (0)
			Garadacimab 600 mg Q4W[g]	3/8 (38)	0/3 (0)	0/3 (0)
			Placebo[g]	89/95 (94)	6/89 (7)	6/89 (7)
Aberer, 2017[36]	Prospective registry	448	LTP (C1INH, androgens,TA)[h]	≥90% of 973 attacks[i]	9% of 973 attacks[i]	1% of 973 attacks[i]
			On-demand treatment only	≥92% of 2255 attacks[i]	8% of 2255 attacks[i]	1% of 2255 attacks[i]
Rasmussen, 2016[37]	Prospective cohort	6	Cinryze 1000 U twice weekly	63/67 (94)	NR	NR

C1INH; C1 inhibitor; IV, intravenous; LTP, long-term prophylaxis; OLE, open-label extension; NR, not reported; Q2W; every 2 weeks; Q4W; every 4 weeks; QD, once daily; QM, once monthly; RCT, randomized controlled trial; SC, subcutaneous; TA, tranexamic acid.
[a]Placebo calculated by combining two placebo groups. [b]Pediatric subgroup analysis of children aged ≥6 to <18 years. [c]Two doses given 2 weeks apart. [d]No attacks occurred in the treatment arm during the treatment period. [e]The study was initially designed to evaluate berotralstat 150 mg QD, but the protocol was amended to include a berotralstat 110 mg QD in selected patients. [f]The absolute number of attacks and of treated attacks was not reported. [g]All patients received an initial IV loading dose on day 1 of placebo or garadacimab 40 mg, 100 mg, or 300 mg, followed by SC treatment with placebo or garadacimab 75 mg, 200 mg, or 600 mg on day 6 and Q4W thereafter for 12 weeks. [h]The dosage and dosing frequency of LTP was not reported. The study reported the proportion of patients who treated attacks with 1 dose, 2 doses, and ≥3 doses of on-demand therapy. The absolute number of treated attacks was not reported.

Limitations

- Limitations of this systematic review include the restriction of articles published from 2002 onward and articles published in English
  - Studies published before 2002 reporting the efficacy of attenuated androgens, TA, and pdC1INH were not included in this review
- Other limitations are the inconsistency in clinical endpoint reporting between studies, differences in study populations, and lack of reporting on attack characteristics at baseline

Conclusions

- **This systematic review confirmed that long-term (≥6 months) attack-free rates are generally low (<45%) with pdC1INH, berotralstat, danazol, and TA and are higher with the monoclonal antibody–based agents lanadelumab (44% for lanadelumab 300 mg Q2W [77% in a post hoc analysis from Day 70 to Day 182]) and garadacimab (62%)**
- **Although use of LTP results in significant reductions in attack frequency, interventional and observational study results show that patients continue to experience attacks in all anatomic locations, with potentially life-threatening laryngeal attacks accounting for 2%-7% of all attacks (regardless of the LTP agent)**
- **Although reductions in attack severity vs placebo were reported in pdC1INH, lanadelumab, and garadacimab phase 3 trials (using various severity assessments), no placebo-controlled RCT reported significant reductions in attack severity or attack duration from baseline for any LTP agent**
- **Most attacks that occurred in patients who received LTP were treated with ≥1 dose of an on-demand therapy, and access to a safe and effective on-demand therapy is essential for all people with HAE-C1INH, including patients receiving LTP**

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Fig.1 PRISMA flow diagram of included studies

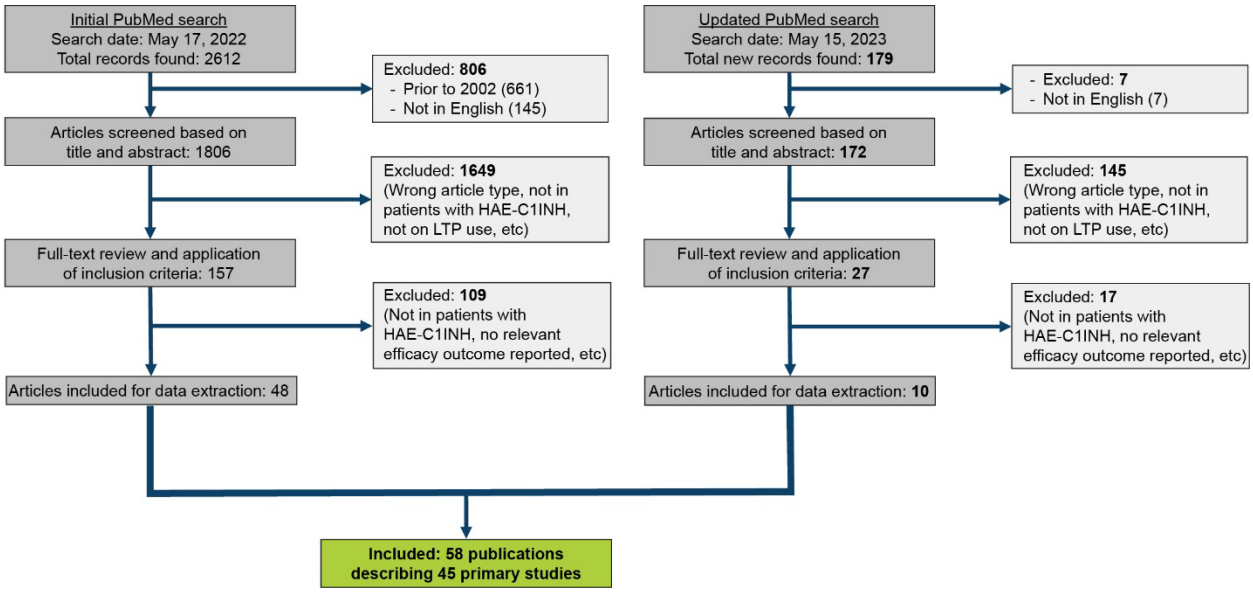

Table 2. Attack severity and attack duration in patients who received LTP in placebo-controlled phase 3 trials

First author, year of publication	Duration of treatment	Number of patients	Assessment of attack severity	LTP agent and dose	Attack severity, mean (SD) or n (%)			Attack duration, mean (SD)		
					LTP	Placebo	*P* value	LTP	Placebo	*P* value
Zuraw, 2010[32]	2 x 12-weeks	24	Attack severity score, mean (SD)[a]	Cinryze 1000 U every 3-4 days	1.3 (0.9)	1.9 (0.4)	<0.001	2.1 (1.1) days	3.4 (1.4) days	0.002
Longhurst, 2017[8]; Li, 2019[33]	2 x 16-weeks	90	Attack severity score, mean (SD)[a]	Berinert 40 IU/kg twice weekly	1.8 (0.6)	2.0 (0.5)	NR	1.8 (1.1) days	2.1 (1.2) days	NR
				Berinert 60 IU/kg twice weekly	1.6 (0.6)	1.9 (0.5)	NR	1.6 (1.0) days	1.6 (0.7) days	NR
Banerji, 2018[6]	26 weeks	125	Patients with a maximum attack severity of 'severe', n (%)[b]	Lanadelumab 150 mg Q4W	5 (18)	14 (34)	0.18	35.6 (24.9) hours	33.5 (23.4) hours	0.770
				Lanadelumab 300 mg Q4W	4 (14)	14 (34)	0.09	26.0 (21.1) hours	33.5 (23.4) hours	0.222
				Lanadelumab 300 mg Q2W	2 (7)	14 (34)	0.02	26.6 (22.7) hours	33.5 (23.4) hours	0.330
Craig, 2023[7]	6 months	64	Patients with a maximum attack severity of 'severe', n (%)[c]	Garadacimab 200 mg QM[d]	5 (13)	10 (42)	NR	NR	NR	NR

CI, confidence interval; LTP, long-term prophylaxis; NR, not reported; Q2W, every 2 weeks; Q4W, every 4 weeks; QM, once monthly; SD, standard deviation.[a]Attack severity score was based on a 3-point scale, with 1 indicating mild; 2, moderate; and 3, severe. [b]The difference from placebo was analyzed using Fisher exact test.[c]Proportions were calculated with the number of patients in the treatment period for ≥30 days as the denominator (n=39 for garadacimab and n=24 for placebo). [d]Patients received a 400-mg SC loading dose of garadacimab or placebo on day 1.

Table 3. Attack severity and attack duration in open-label extension and observational studies

First author, year of publication	Study design	Number of patients	Assessment of attack severity	LTP agent	Attack severity, mean (SD)			Attack duration, mean (SD)		
					Baseline	On LTP treatment	*P* value	Baseline	On LTP treatment	*P* value
Aygören-Pürsün, 2019[19]	Non-controlled pediatric trial	12	Attack severity score[a]	Cinryze	7.2 (6.0)	2.0 (2.9)[b]	NR	NR	NR	NR
Rasmussen, 2016[37]	Prospective cohort	6	Attack severity score[a]	Cinryze	2.1	2.3	NR	38.7 hours	20.0 hours	NR
Fukuda, 2023[23]	Open-label study (Japanese patients)	9	Time-normalized relative reduction in moderate-to-severe attacks	Berinert	NR	88.8% relative reduction	0.008	NR	NR	NR
Dorr, 2023[43]	Retrospective chart audit	62	Number of severe attacks per month	Lanadelumab	7.2 (7.2)	0.4 (1.4) 6 months 0.3 (0.7) 12 months	NR	NR	NR	NR
Hahn, 2020[34]	Prospective cohort	12	Reduction in the number of mild, moderate, and severe attacks per month	Lanadelumab	NR[c]	Mild: Moderate: Severe:	0.008 <0.0001 0.0001	NR	NR	NR
Banerji, 2022[26]	Open-label extension	212	Number of moderate or	Lanadelumab	2.03	0.2	NR	NR	NR	NR

			severe attacks per 4 weeks							
Ahuja, 2023[35]	Patient survey	54	Attack severity score[e]	Berotralstat	3.5 (0.8)	2.3 (1.2)	<0.0001	NR	NR	NR
Zuraw, 2016[31]	Patient survey	334[d]	Attack severity score[e]	Attenuated androgens	4.3 (0.1)	2.5 (0.1)	<0.0001	NR	NR	NR

First author, year of publication	Study design	Number of patients	Assessment of attack severity	LTP agent	Attack severity, proportion of attacks (%)			Attack duration, median		
					On-demand therapy only	On LTP treatment	*P* value	On-demand therapy only	On LTP treatment	*P* value
Aberer, 2017[36]	Prospective registry (Icatibant Outcome Survey)	448	Proportion of attacks rated as severe/very severe	Any LTP agent	NR	NR	NR	9.0 hours	8.0 hours	0.543
				C1-INH	53%	46%	0.193	9.0 hours	4.0 hours	0.041
				Androgens	53%	69%	0.043	9.0 hours	8.0 hours	0.984
				TA	53%	53%	0.989	9.0 hours	11.6 hours	0.016
Katelaris, 2023[38]	Prospective cohort	49	Proportion of attacks rated as severe or significant	C1-INH (SC)	22%	35%	NR	NR	NR	NR
				C1-INH (IV)	22%	23%	NR	NR	NR	NR
				Danazol	22%	23%	NR	NR	NR	NR
				TA	22%	18%	NR	NR	NR	NR

				Lanadelumab	22%	0%	NR	NR	NR	NR
Zanichelli, 2011[39]	Prospective cohort	103	NR	Attenuated androgens	NR	NR	NR	1.7 days	1.5 days	NR
				Antifibrinolytics	NR	NR	NR	1.7 days	1.6 days	NR

C1-INH, C1 inhibitor; IV, intravenous; LTP, long-term prophylaxis; NR, not reported; SC, subcutaneous; SD, standard deviation; TA, tranexamic acid. [a]Attack severity score was based on a 3-point scale, with 1 indicating mild; 2, moderate; and 3, severe. [b]Presented data are limited to the IV pdC1INH 500 U dose as it is the approved dose for children aged 6 to <12 years.[44] [c]The data were shown graphically by baseline; however, mean and SD values were not reported for LTP. [d]Mean (SD) baseline and on LTP treatment attack severity score among 344 patients receiving attenuated androgens at the time of the survey. [e]Attack severity score was based on a 5-point scale, with 1 indicating very mild; 2, mild; 3, moderate; 4, severe; and 5, very severe.

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