Long-term Prophylaxis For Hereditary Angioedema: Treatment Use, Patterns, And Gaps In A US Claims Database

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Background and Objectives

- Hereditary angioedema (HAE) is a genetic disorder characterized by recurrent episodes (attacks) of severe swelling, most commonly on the limbs, face, intestinal tract, and airway, often occurring without a known trigger.[1]
- Existing long-term prophylaxis (LTP) treatments are effective in reducing attacks, but patients still report breakthrough attacks.[2]
- Adherence, treatment gaps, or treatment switches in LTP could impact treatment outcomes. Proportion of days covered (PDC) ≥80% is considered adherent for most chronic medications.[3]
- The objectives of this study using a United States (US) administrative claims database were to:
  - Evaluate the impact of real-world adherence to LTP among patients with HAE
  - Describe LTP treatment patterns and explore clinical outcomes associated with LTP usage in the real world

Methods

- This was a retrospective, longitudinal study of patients with HAE who received LTP ("LTP-treated HAE") based on claims data (2015 to 2024) using the US administrative claims in the IQVIA PharMetrics Plus Enhanced database.
- Clinical outcomes i.e., comorbidities and HAE attacks[4] were defined with International Classification of Diseases, 10th Revision diagnosis codes.
  - Attacks were defined by diagnosis codes for HAE symptoms with/without on-demand therapy (ODT) use; severe HAE attacks required an emergency department (ED) visit or hospitalization with/without ODT use. Claims within 5 days of each other were counted as one attack.

Figure 1. Patient identification criteria

01. ≥2 non-androgen LTP claims between 2021 and 2023
02. Aged ≥16 at index date
03. Continuous coverage for 6 months pre- and post-index date
04. No concomitant claims for LTP, androgen, or tranexamic acid at index date
05. No claim for index LTP in the 3 months before index date

OVERALL ANALYSIS COHORT
LTP-treated HAE patients

ADHERENCE ANALYSIS COHORT
≥12 months on index LTP

Adherent: No prescription gap (>30 days for other LTPs; >60 days for lanadelumab) after supplied days

Non-adherent: ≥1 prescription gap (>30 days for other LTPs; >60 days for lanadelumab) after supplied days

PERSISTENCE ANALYSIS COHORT
Persistence to index LTP

Continued LTP use: Ongoing index LTP claims with last recorded claim in the observation period, and without claims of non-index LTP

Switched LTP: ≥1 non-index LTP claim during observation, regardless of prescription gaps

Discontinued LTP: ≥1 prescription gap after supplied days and no further LTP claims during observation

Abbreviations: HAE, hereditary angioedema; LTP, long-term prophylaxis

Results: LTP-treated HAE patients continued to experience HAE attacks during follow-up.

- In total, 538 LTP-treated HAE patients were eligible for inclusion in the analysis **[Figure 2]**.
- Over a mean follow-up of ~2.4 years, LTP-treated HAE patients stayed on their index LTP for a mean (standard deviation [SD]) of 1.2 (1.0) years.
- Lanadelumab was the most common index LTP **[Table 1]**.
  - Patients averaged >1 claim per month of their index LTP in a year.
- LTP-treated HAE patients had a mean (SD) of 5.3 (5.6) total attacks and a mean (SD) of 0.8 (1.8) annualized severe attacks.

Figure 2. Overall cohort

IQVIA PharMetrics Plus Enhanced database HAE-treated sample (2015–2024); (N = 2,343)

HAE patients with ≥2 claims of non-androgen LTP between 2021 and 2023; (n = 1,640)

Continuous medical and pharmacy coverage (no allowable gaps) for 6 months before and post-index date (inclusive, any plan allowed); (n = 1,052)

No concomitant LTP use at index date; (n = 1,048)

Aged ≥16 at index date; (n = 954)

No recent use of the index LTP, defined as no claim for the index LTP in the 3 months prior to index date; **LTP-treated HAE patients (n = 538)**

Abbreviations: HAE, hereditary angioedema; IV, intravenous; LTP, long-term prophylaxis; SC, subcutaneous

Table 1. Baseline characteristics and treatment use

Baseline characteristics and treatment use	LTP-treated HAE patients (N = 538)
Index LTP, n (%)	
Lanadelumab	252 (46.8%)
Berotralstat	148 (27.5%)
SC C1-INH	112 (20.8%)
IV C1-INH	26 (4.8%)
Follow-up time after index date, years, mean (SD)	2.4 (1.0)
Age at index, years, mean (SD)	40.6 (15.9)
Female sex, n (%)	385 (71.6%)
Comorbidities (>20% of patients)	
Depression or anxiety	201 (37.4%)
Hypertension	128 (23.8%)
Time on index LTP, mean (SD)	1.2 (1.0)
Annualized number of index LTP claims, mean (SD)	12.3 (7.7)
Patients with ≥1 ODT claim while on index LTP, n (%)	367 (68.2%)

Abbreviations: C1-INH, C1 inhibitor; HAE, hereditary angioedema; IV, intravenous; LTP, long-term prophylaxis; ODT, on-demand therapy; SC, subcutaneous; SD, standard deviation

Adherence cohort – About 40% of patients were not adherent to their index LTP.

- Around 40% of LTP-treated HAE patients had adherence issues resulting from treatment gaps; adherence issues were more likely for patients receiving C1 inhibitors **[Figure 3]**.
- Among the adherent group, PDC was 90% compared with 64% in the non-adherent group **[Table 2]**.
- Total and severe HAE attack rates and ODT use were similar between the adherence cohorts, also consistent with the attack rates among the overall cohort of LTP-treated HAE patients **[Table 2]**.

Figure 3. Treatment use and clinical characteristics by adherence status

LTP-treated HAE patients, N = 538

Claim for index LTP ≥12 months after index date, **n = 301 (55.9%)**

Adherent, n = 183 (60.8%)

Index LTP	Percent of those on each LTP
Lanadelumab	115 / 172 (66.9%)
Berotralstat	47 / 79 (59.5%)
SC C1-INH	18 / 42 (42.9%)
IV C1-INH	3 / 8 (37.5%)

Non-adherent, n = 118 (39.2%)

Index LTP	Percent of those on each LTP
Lanadelumab	57 / 172 (33.1%)
Berotralstat	32 / 79 (40.5%)
SC C1-INH	24 / 42 (57.1%)
IV C1-INH	5 / 8 (62.5%)

Abbreviations: C1-INH, C1 inhibitor; HAE, hereditary angioedema; IV, intravenous; LTP, long-term prophylaxis; PDC, proportion of days covered; SD, standard deviation; SC, subcutaneous

Table 2. Clinical characteristics by adherence status

Clinical Characteristics	Adherent (n = 183)	Non-adherent (n = 118)
Follow-up time, years, Mean (SD)	2.1 (0.9)	2.5 (0.8)
Time on index LTP, years, Mean (SD)	1.9 (0.8)	1.6 (0.8)
PDC, Mean (SD)	90.0% (8.0%)	64.0% (21.0%)
HAE Attacks, Mean (SD)		
Annualized number of total HAE attacks	5.3 (4.9)	4.7 (4.8)
Annualized number of severe HAE attacks	0.6 (1.2)	0.7 (1.5)
HAE treatment use, mean (SD)		
Annualized number of ODT refills while on index LTP	3.9 (11.8)	2.2 (3.4)

Abbreviations: HAE, hereditary angioedema; LTP, long-term prophylaxis; PDC, proportion of days covered; SD, standard deviation

Persistence cohort – Patients who switched from their index LTP experienced more HAE attacks and higher ODT refills

- Patients were most likely to continue on lanadelumab as their index LTP and switch/discontinue if they were on C1 inhibitors as their index LTP **[Figure 4]**.
- Patients who switched from their index LTP had annualized attack rate of 7.4 vs. 4.8 in continued LTP users and 4.5 among those who discontinued LTP completely. ODT refills were also much higher among switchers: 10.2 vs. 2.6 (continued LTP users) / 3.8 (discontinued LTP) **[Table 3]**.

Figure 4. Persistence to index LTP

LTP-treated HAE patients, N = 538

Continued Index LTP (n = 227; 42.2%)

Index LTP	Percent of those on each LTP
Lanadelumab	134 / 252; 53.2%
Berotralstat	62 / 148; 41.9%
SC C1-INH	27 / 112; 24.1%
IV C1-INH	4 / 26; 15.4%

Switched LTP (n = 121; 22.5%)

Index LTP	Percent of those on each LTP
Lanadelumab	35 / 252; 13.9%
Berotralstat	41 / 148; 27.7%
SC C1-INH	35 / 112; 31.3%
IV C1-INH	10 / 26; 38.5%

Discontinued LTP completely (n = 190; 35.3%)

Index LTP	Percent of those on each LTP
Lanadelumab	83 / 252; 32.9%
Berotralstat	45 / 148; 30.4%
SC C1-INH	50 / 112; 44.6%
IV C1-INH	12 / 26; 46.2%

Abbreviations: C1-INH, C1 inhibitor; HAE, hereditary angioedema; IV, intravenous; LTP, long-term prophylaxis; SC, subcutaneous

Table 3. Clinical characteristics by persistence status

Clinical Characteristics	Continued index LTP (n = 227)	Switched LTP (n = 121)	Discontinued LTP completely (n = 190)
Follow-up time, years, mean (SD)	2.2 (1.0)	2.7 (0.9)	2.4 (1.0)
Time on index LTP, years, mean (SD)	1.9 (0.9)	0.8 (0.7)	0.8 (0.7)
HAE attacks, mean (SD)			
Annualized number of total HAE attacks	4.8 (4.8)	7.4 (6.8)	4.5 (5.4)
Annualized number of severe HAE attacks	0.5 (1.2)	0.9 (1.4)	0.9 (2.4)
HAE treatment use, mean (SD)			
Annualized number of ODT refills while on index LTP	2.6 (5.2)	10.2 (22.1)	3.8 (7.5)

Abbreviations: HAE, hereditary angioedema; LTP, long-term prophylaxis; ODT, on-demand therapy; SD, standard deviation

Switch cohort – Nearly a quarter of patients switched their index LTP, of whom 44% switched more than once over mean follow-up of 2.7 years.

- Time to first switch from index LTP varied (mean: 7.5 months), although it was slightly higher than the overall time to switch (mean: 6.1 months) **[Table 4]**.
- A subset of patients (28.1%) continue to switch between the treatment options (2–5 switches).
  - About 16% of patients with >5 switches had claims for non-androgen or androgen LTP use simultaneously over the follow-up period, due to concomitant use of LTP.
- About 80% of patients switched from their index LTP in less than a year.
- Patients post the initial switch from index LTP had a reduction in total and severe attacks **[Table 5]**.

Table 4. LTP switching patterns

Switch Patterns	Switched LTP (n = 121)
Number of treatments for those who switch, mean (SD)	2.1 (0.4)
Time to any switch, months	
Mean (SD)	6.1 (7.1)
Time to first switch from index LTP, months	
Mean (SD)	7.5 (7.6)
Number of switches over follow-up period, n (%)	
1 switch	68 (56.2%)
2–5 switches	34 (28.1%)
>5 switches	19 (15.7%)
Proportion of patients with switch in time period, n (%)	
≤12 months from index date	98 (81.0%)
13–24 months from index date	17 (14.1%)
25–36 months from index date	6 (5.0%)

Abbreviations: HAE, hereditary angioedema; LTP, long-term prophylaxis; SD, standard deviation

Table 5. Clinical characteristics for patients post switching index LTP

Switch Patterns	Before 1st Switch from index LTP	After 1st Switch from index LTP
Follow-up time, years, mean (SD)	0.6 (0.6)	2.1 (1.0)
HAE attacks, mean (SD)		
Annualized number of total HAE attacks	10.7 (9.9)	6.8 (6.7)
Annualized number of severe HAE attacks	1.7 (3.0)	0.8 (1.4)

Abbreviations: HAE, hereditary angioedema; LTP, long-term prophylaxis; SD, standard deviation

Limitations

- Data were generally deemed high quality, but limitations inherent to claims analyses, such as the inability to confirm HAE attacks, use of ODT, and concomitant use of LTP exist.
- These findings highlight heterogeneity in real-world LTP use and residual disease burden, although claims data cannot establish the reasons for switching/discontinuation or lack of adherence/persistence. These analyses also cannot establish any causal relationships between treatment patterns and clinical outcomes.

Conclusions

- In this US-based claims analysis, approximately 40% of long-term LTP users were non-adherent with PDC lower than considered adherent, about a quarter switched their index LTP, and about 35% completely discontinued LTP.
- Patients with HAE continued to experience breakthrough attacks regardless of LTP adherence; while patients who switched their LTP had higher annualized number of HAE attacks and ODT utilization that those who stayed on or discontinued index LTP.
- Suboptimal treatment outcomes in the real-world can pose significant burden to patients and healthcare practices. Patients may experience anxiety and require additional medical attention straining healthcare practices as they seek sustained and complete control of their HAE while being managed with LTP.

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