Patterns of On-demand Medication Use in Patients With Hereditary Angioedema Treated Long-term With Prophylactic Subcutaneous C1-Inhibitor

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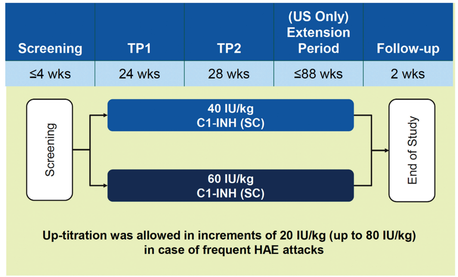
INTRODUCTION

- Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is characterized by recurrent edema of the face, limbs, and trunk, and submucosal tissues of the gastrointestinal, genitourinary, and upper respiratory tracts.[1,2] Attacks may be disfiguring, painful, and, in the case of upper airway involvement, potentially fatal.[3,4]
- International HAE treatment guidelines recommend that all acute attacks be considered for immediate (on-demand) treatment.[5] Recommended medications for on-demand treatment include C1-INH (plasma-derived or recombinant); ecallantide, a kallikrein inhibitor; and icatibant, a bradykinin-2-receptor antagonist.[5]
- HAE prophylactic therapy has the potential to reduce the need for on-demand treatment by decreasing the frequency and severity of attacks, which may in turn improve the cost-effectiveness of overall therapy.
- Subcutaneous C1-inhibitor (C1-INH [SC] 60 IU/kg, HAEGARDA®, CSL Behring) is indicated for routine prophylaxis to prevent attacks in adolescent and adult patients with HAE.[6] Efficacy and safety of C1-INH (SC) was demonstrated in a placebo-controlled phase III trial (COMPACT) and an open-label extension (OLE) of this trial, in which patients were treated for up to 2.7 years.[7,8] In these studies, patients were permitted to use on-demand rescue medication for the treatment of acute attacks.[7,8]
- In this analysis, we examined patterns of on-demand medication use in patients treated with C1-INH (SC) 60 IU/kg in the OLE.

METHODS

- The OLE of the COMPACT trial was a multicenter, randomized, parallel-arm study. Eligible patients (age ≥6 years with ≥4 attacks over 2 consecutive months) were randomly assigned to receive C1-INH (SC) at 40 IU/kg or 60 IU/kg twice weekly for 52 weeks. Patients in the United States were eligible to continue treatment for up to 140 weeks (**Figure 1**).
- Throughout the study, patients were permitted to use on-demand medication for treatment of any HAE attacks, including plasma-derived C1-INH, recombinant C1-INH, icatibant, ecallantide, and fresh frozen plasma.

Figure 1. *COMPACT Open-label Extension Study Design*



- The use of on-demand medication for the treatment of HAE attacks was an exploratory endpoint.
- An attack was considered treated if use of on-demand medication was recorded in the electronic case report form between the start and end date of the HAE attack.

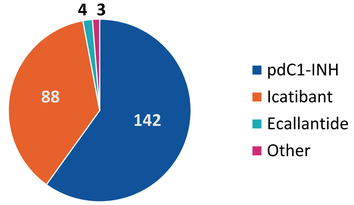
RESULTS

- A total of 126 patients were randomized to treatment (40 IU/kg: n=63; 60 IU/kg: n=63). Data for the FDA-approved 60 IU/kg dose are presented.
- Of the 63 patients in the 60 IU/kg treatment arm, 24 (38.1%) had at least 1 treated attack.
- The mean (SD) and median (range) numbers of treated HAE attacks per month were 0.27 (0.66) and 0.00 (0.00–3.87), respectively.
- In the 60 IU/kg treatment arm, a total of 371 HAE attacks were reported, of which 229 (61.7%) were treated with on-demand medications. Of the 229 attacks, 83.8% (192/229) were treated with only 1 dose of on-demand medication (**Table 1**).
- The majority of treated attacks were treated with plasma-derived C1-INH (IV) or icatibant (**Figure 2**). No attacks were treated with recombinant C1-INH or fresh frozen plasma.
- Of the 229 attacks that were treated, 113 (49%) were severe, 89 (39%) were moderate, and 27 (12%) were mild. The mean (SD) severity of treated attacks was 1.97 (0.58) (1=mild, 2=moderate, 3=severe).

Table 1. *Treated HAE Attacks During Prophylaxis With C1-INH (SC) 60 IU/kg*

Uses of Rescue Medication, n	Patients With Treated Attacks (N=63), n (%)	Treated Attacks (N=229), n (%)
1	24 (38.1)	192 (83.8)
2	6 (9.5)	25 (10.9)
3	4 (6.3)	7 (3.1)
>3	1 (1.6)	5 (2.2)

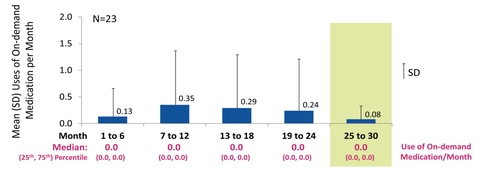
Figure 2. *Number of Attacks Treated with On-demand Medication (Treated Attacks, N=229)*



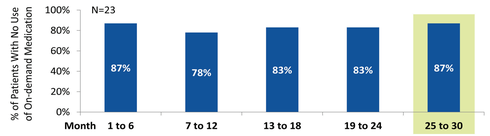
- Post-hoc analysis of annualized on-demand medication use showed that 39 patients (61.9%) treated with C1-INH (SC) 60 IU/kg did not use on-demand medication; 66.7% used on-demand medication less than once per year (mean [SD]: 3.8 [9.6] uses/year; median: 0.0 uses/year).
- The use of on-demand medication remained consistently low throughout the study. An analysis of the subgroup of US patients treated with C1-INH (SC) 60 IU/kg for more than 2 years in the OLE trial showed that between months 25 and 30, 87% (20/23) did not use any on-demand medication. The mean number of uses of on-demand medication per month was 0.08 during this time period, or approximately 1 use per year, and the median was 0.0 uses per month (**Figure 3A, 3B**).
- Consistent with these results, 83% of patients (19/23) treated with C1-INH (SC) 60 IU/kg for more than 2 years were completely attack-free between months 25 and 30. During this period, the mean attack rate was 0.08 attacks/month (approximately 1 attack per year), a reduction of 97% compared with the pre-study period.

Figure 3. *Use of On-Demand Medication Over Time in Patients Treated With C1-INH (SC) 60 IU/kg for >2 Years**

A. Use of on-demand medication per month



B. Percentage of patients without any on-demand medication use



* Five patients had exposure to C1-INH (SC) 60 IU/kg for more than 30 months.

CONCLUSIONS

- The use of on-demand medication was consistently low during prophylactic therapy with C1-INH (SC) 60 IU/kg in this long-term, open-label study.
  - Nearly 40% of the attacks that occurred were not treated with on-demand medication.
  - Only 38% of patients had an attack that was treated with on-demand medication.
  - Two-thirds of patients used on-demand medication less than once per year.
  - Among patients with >2 years of C1-INH (SC) 60 IU/kg exposure, 87% did not use any rescue medication during months 25 to 30.
- The potential for marked reductions in on-demand medication use should be considered in cost-effectiveness analyses of HAE prophylactic therapies.

Sponsor: CSL Behring

Presented at the 2019 National Association of Specialty Pharmacy Annual Meeting, Washington, DC, September 9-12, 2019.

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