Weight-based Dosing of Subcutaneous C1-Inhibitor Facilitates Management of Hereditary Angioedema in Obese Patients

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INTRODUCTION

- In a retrospective analysis comparing patients with hereditary angioedema (HAE) and a demographically matched non-HAE cohort, the proportion of patients with obesity was significantly higher in the HAE cohort (22.5% vs 13.9%; *P*<0.0001) (Patel A, unpublished data, August 2019).
- Management of obese patients with HAE may be challenging due to intravenous access issues and the difficulty in achieving adequate concentrations of HAE medications using fixed-dose regimens.[1,2]
- Obese patients have been shown to have a greater burden of disease with more severe attacks.[2]
- In this subgroup analysis, we compared the prophylactic efficacy of subcutaneous C1-inhibitor (C1-INH [SC], HAEGARDA®, CSL Behring) in obese versus non-obese patients treated in an open-label extension (OLE) of the phase 3 COMPACT trial.

METHODS

- In the OLE, eligible patients (≥6 years old with ≥4 attacks over 2 consecutive months before enrollment) were randomized to receive C1-INH (SC) 40 IU/kg or 60 IU/kg twice weekly for 52 weeks (Treatment Period 1 – 24 weeks; Treatment Period 2 – 28 weeks). Patients in the United States could continue treatment for an additional 88 weeks.[3]
- During Treatment Period 1, patients who experienced ≥12 attacks within a 4-week period were eligible for C1-INH (SC) dose increases. During Treatment Period 2, patients who experienced ≥ 3 HAE attacks within an 8-week period were eligible for C1-INH (SC) dose increases.
- Patients in the United States who continued treatment for an additional 88 weeks could have their C1-INH (SC) dose escalated according to the rules outlined for Treatment Period 2.[4]
- C1-INH (SC) dose increases could be made in increments of 20 IU/kg (up to a maximum dose of 80 IU/kg). All CSL830 dose increases were optional and at the sole discretion of the investigator.[3]
- For this analysis, patients were stratified by body mass index (BMI) and classified as obese (≥30 kg/m^2) or non-obese (<30 kg/m^2) based on the World Health Organization's definition of obesity.[5] Efficacy endpoints were compared between these 2 subgroups.

RESULTS

- Of 126 patients in the OLE, 50 (39.7%) were obese. Compared with the non-obese group, obese patients were older, with a predominance of males (**Table 1**).
- The obese group had a higher pre-study median attack rate (3.4 vs 3.0 attacks/month) and mean attack rate (4.7 vs 4.0 attacks/month).
- Of the obese patients, 3 of the 29 randomized to the 40 IU/kg dose and 2 of the 21 randomized to the 60 IU/kg dose had their dose titrated upward.
- The median attack rates during the study on C1-INH (SC) prophylaxis were similar in obese and non-obese patients (0.087 and 0.086 attacks/month, respectively, or ~1 attack/year) (**Table 2**).
- With C1-INH (SC) prophylaxis, 91.3% (42/46) of evaluable obese patients and 93.4% (71/76) of evaluable non-obese patients were classified as responders, with ≥50% reduction in attacks versus pre-study and 81.6% (40/49) of obese patients and 84.2% (64/76) of non-obese patients had <1 attack/4 weeks.
- Although the mean number of uses of rescue medication was similar in obese versus non-obese patients (mean 0.32 vs 0.27 uses/month), 62% (47/76) of the non-obese group did not use any rescue medication versus only 46% (23/50) of obese patients.

Table 1. *Demographic and clinical characteristics of obese vs non-obese patients with HAE*

	Obese (n=50)	Non-obese (n=76)
Age, mean (SD)	46.3 (15.2)	36.8 (14.7)
Sex, no. (%)		
Female	22 (44)	54 (71)
Male	28 (56)	22 (29)
Weight (kg)		
Mean (SD)	107.6 (15.8)	70.4 (14.6)
Median	105.6	68.3
Pre-study attacks/month before randomization		
Mean (SD)	4.7 (3.7)	4.0 (2.7)
Median	3.4	3.0
Dose at randomization, no. of patients		
40 IU/kg	29	34
60 IU/kg	21	42
Up-titrated, no. (%) of patients	5 (10)	4 (5)
Previously treated with C1-INH (SC), no. (%) of patients	25 (50)	39 (51)

Table 2. *Efficacy outcomes in obese and non-obese patients treated on study with C1-INH (SC)*

	Obese (n=50)	Non-obese (n=76)
No. of attacks/month, median	0.087	0.086
No. of attacks/year	1.04	1.03
No. (%) of responders*	42/46 (91.3)	71/76 (93.4)
No. (%) of patients with <1 attack/4 weeks	40/49 (81.6)	64/76 (84.2)
Use of rescue medication/month		
Mean	0.32	0.27
Median	0.03	0
No. (%) of patients with no rescue medication use	23/50 (46)	47/76 (62)

*Four patients in the obese group were not evaluable for the responder analysis. A responder was defined as ≥50% reduction in attacks vs pre-study.

CONCLUSIONS

- Obese patients with HAE may have a greater disease burden than non-obese patients. The attack rate at baseline was numerically higher in the obese group, despite the predominance of male patients who generally have a lower attack rate than female patients.[6] This may be related to hyperestrogenemia seen in obese men.[7] Estrogen is a known trigger of HAE attacks.[8]
- In obese patients with HAE, fixed-dose regimens of C1-INH may not be sufficient to achieve therapeutic C1-INH levels.
- Weight-based dosing and SC administration of C1-INH enable obese patients to effectively prevent HAE attacks with similar attack rates in obese and non-obese patients.

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