Factors Possibly Associated with Reduced Response to Subcutaneous C1-Inhibitor in Patients with Hereditary Angioedema

H. Henry Li,[1] Henrike Feuersenger,[2] Ingo Pragst[2]

[1]Institute for Asthma and Allergy, Chevy Chase, Maryland, USA; [2]CSL Behring, Marburg, Germany

INTRODUCTION

- The efficacy and safety of subcutaneous C1-inhibitor (C1-INH [SC], HAEGARDA®, CSL Behring) in the prophylactic treatment of hereditary angioedema (HAE) have been demonstrated in the phase 3 COMPACT trial and an open-label extension (OLE) of this trial.[1,2]
- In the OLE, 93% of subjects (113/122 evaluable subjects) were classified as responders, achieving ≥50% reduction in attacks versus the pre-study period. A total of 9 subjects were classified as non-responders, with an attack rate reduction of <50%.[2]
- We assessed these 9 subjects for possible factors contributing to the attenuated response.

METHODS

- In the OLE, eligible subjects (≥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. Subjects in the United States could continue treatment for an additional 88 weeks.
- The percentage of responders (patients with ≥50% reduction in attacks versus the pre-study period) was a secondary efficacy endpoint.
- A qualitative comparison of responders versus non-responders was performed and patient profiles of non-responders were reviewed.

RESULTS

- Qualitative comparison of non-responders with responders revealed a few potential differences (**Table 1**).
  - Mean age of the non-responders was higher than that of responders (52.6 vs 39.0 years).
  - The number of attacks/month pre-study was less in the non-responders group than in the responders group (mean, 2.4 vs 4.5 attacks/month; median, 2.0 vs 3.3 attacks/month).
  - Mean duration of exposure to C1-INH (SC) was 49.7 weeks in non-responders compared with 78.0 weeks in responders.
- Of the 9 non-responders, 3 were C1-INH (SC)-naïve and 6 had been treated with C1-INH (SC) in the placebo-controlled COMPACT trial. Four patients were on 40 U/kg and 5 were on 60 U/kg during the OLE.

Table 1. *Demographic and clinical characteristics of non-responders and responders in the OLE*

Characteristic	Non-responders (n=9)	Responders (n=113)
Age, mean (SD) years	52.6 (17.3)	39.0 (15.0)
Sex (female/male)	6/3	69/44
BMI, mean (SD) kg/m^2	30.2 (5.9)	28.9 (7.3)
Weight, mean (SD) kg	86.2 (24.9)	84.3 (23.6)
No. of pre-study attacks/month, mean (SD)	2.4 (1.3)	4.5 (3.1)
Duration of C1-INH exposure, days (weeks)	348 (49.7)	546 (78.0)

OLE = open-label extension.

Table 2. *Demographic and clinical characteristics of non-responders and responders in the OLE*

Subject	Age, years	Sex	BMI, kg/m^2	Exposure, weeks (dose)	C1-INH (SC) treatment status	Previous prophylaxis
1	63	F	29.9	9 (40)	Naïve	C1-INH (IV)
2	27	F	24.2	24 (40)	Naïve	None
3	45	F	38.6	119 (40)	Naïve	C1-INH (IV)
4	62	M	31.2	53 (40)	Previously treated	None
5	71	F	24.7	52 (60)	Previously treated	Danazol, C1-INH (IV)
6	36	F	26.6	37 (60)	Previously treated	Danazol
7	33	F	21.3	9 (60)	Previously treated	None
8	68	M	27.8	8 (60)	Previously treated	C1-INH (IV)
9	68	M	43.4	80 (60) + 55 (80)	Previously treated	C1-INH (IV)

- All 9 non-responders required use of rescue medication for treatment of acute attacks. Mean attack severity was mild or moderate in 7 patients while 2 patients had mean attack severity as moderate or severe during treatment.
- Six of the 9 non-responders (67%) had received prophylactic treatment with intravenous C1-INH or danazol before enrollment in COMPACT or the OLE.
- Five subjects classified as non-responders (56%) had discontinued the study prematurely (after 8, 9, 9, 24, and 37 weeks of exposure) (**Table 2**).
- Subjects 1, 2, and 8 voluntarily withdrew and subjects 6 and 7 discontinued due to an adverse event (treatment-related headache and arthralgia, respectively).
- No subjects discontinued the study due to lack of efficacy.

CONCLUSIONS

- Ninety-three percent of subjects in the OLE were classified as responders (defined as ≥50% reduction in attacks versus the pre-study period).
- Five subjects withdrew from the study (none due to lack of efficacy).
- The mean age of non-responders was greater than that of responders.
- Non-responders had shorter duration of exposure to C1-INH (SC) which may have contributed to attenuated response (<50% reduction in attacks vs pre-study).

Presented at the AAAAI Annual Meeting, March 13-16, 2020, Philadelphia, Pennsylvania, USA.

Funding: CSL Behring

References: **1.** Longhurst H, Cicardi M, Craig T, et al; for the COMPACT Investigators. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *N Engl J Med.* 2017;376(12):1131-1140. **2.** Craig T, Zuraw B, Longhurst H, et al; COMPACT Investigators. Long-term outcomes with subcutaneous C1-inhibitor replacement therapy for prevention of hereditary angioedema attacks. *J Allergy Clin Immunol Pract.* 2019;7(6):1793-1802.

CSL Behring