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Indirect comparison between human C1-inhibitor (C1-INH) subcutaneous treatment and lanadelumab for routine prevention of hereditary angioedema (HAE) attacks

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INTRODUCTION

- HAE is a rare genetic disease that is classified into two distinct types: type I, caused by a deficiency in C1-INH, and type II, caused by abnormal, non-functional C1-INH[1]
- Approved therapies for the long-term prophylaxis of HAE attacks include the subcutaneous replacement of human C1-INH (C1-INH[SC]) (HAEGARDA; CSL Behring)[2] and lanadelumab (TAKHZYRO), a monoclonal antibody that targets kallikrein[3]
- Both therapies have been investigated in two placebo-controlled Phase 3 trials (COMPACT and HELP)[4,5]
  - COMPACT (NCT01912456) was a Phase 3, multicenter, randomized, double-blind, crossover trial of C1-INH(SC) compared with placebo over two 16-week periods (16 weeks of treatment with C1-INH(SC) followed by 16 weeks of placebo)[4]
  - HELP (NCT02586805) was a Phase 3, multicenter, randomized, double-blind, parallel-group trial of lanadelumab compared with placebo over a 26-week period[5]
- The absence of a head-to-head trial prevents direct comparison of these therapies

OBJECTIVE

- This study aimed to standardize the statistical methods used in the COMPACT and HELP clinical trials, allowing for an indirect comparison of treatments

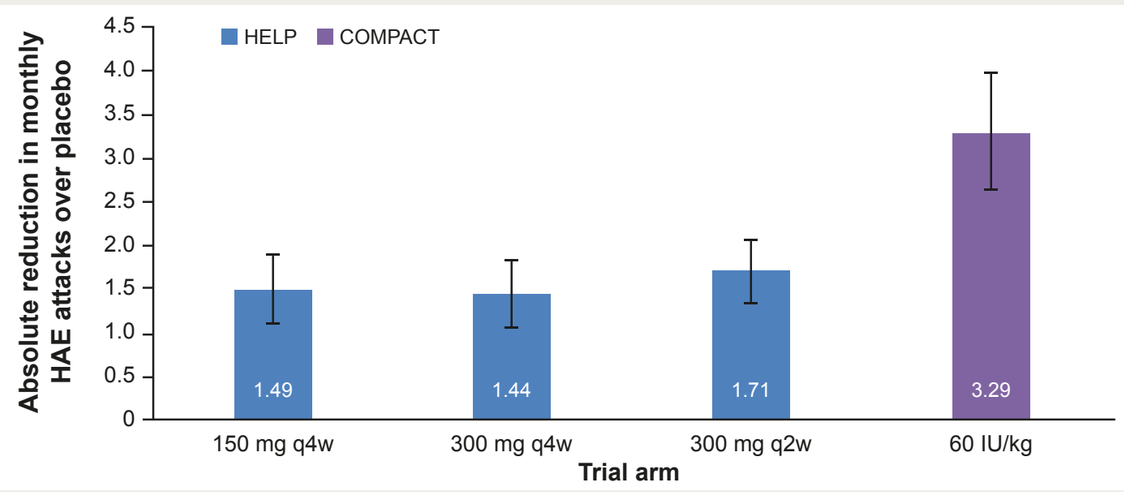
METHODS

- In COMPACT, the number of confirmed HAE attacks was compared between the treatment and placebo periods using a mixed model accounting for the within-patient correlation;[4] whereas in HELP, the primary endpoint for each active treatment group was compared with the placebo group using a Poisson regression model[5]
- To standardize differences in design and methodology, individual patient data from COMPACT were reanalyzed using a generalized estimating equation model for Poisson multiple regression with overdispersion and days of observation as an offset variable, as in HELP. The model was used to account for the within-patient correlation and a 95% confidence interval (CI) bias-correction and acceleration bootstrap estimate was reported for the absolute attack rate reduction over placebo
- Treatment group, period, sequence and normalized run-in period attack rate were used as fixed effects in the model

RESULTS

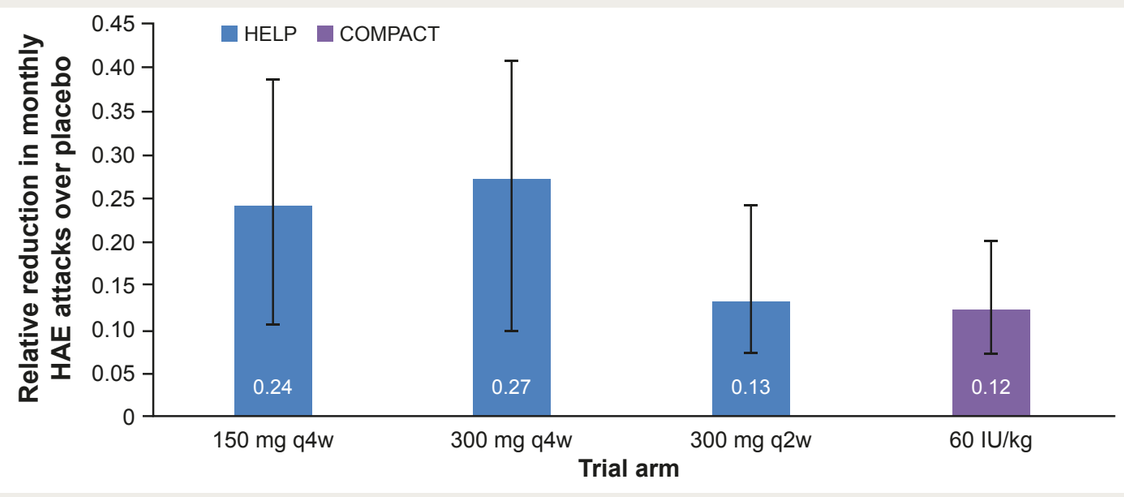
- In the original COMPACT study, the model-based LS mean (95% CI) HAE monthly attack rate was 0.52 (0.00–1.04) for the recommended C1-INH(SC) dose (60 IU/kg, twice weekly) and 4.03 (3.51–4.55) for the placebo group
- The HELP Poisson regression mean (95% CI) HAE monthly attack rates for the lanadelumab arms (150 mg every 4 weeks [q4w], 300 mg q4w, 300 mg every 2 weeks [q2w]) and the placebo arm were 0.48 (0.31–0.73), 0.53 (0.36–0.77), 0.26 (0.14–0.46), and 1.97 (1.64–2.36), respectively
- For the HELP 150 mg q4w, 300 mg q4w, and 300 mg q2w lanadelumab arms, compared with the reanalyzed COMPACT study:
  - Poisson regression mean (95% CI) monthly reduction in absolute attack rates over placebo was 1.49 (1.08–1.90), 1.44 (1.04–1.84), and 1.71 (1.33–2.09) for lanadelumab groups, respectively, versus the regression-based reduction of 3.29 (2.65–3.98) attacks per month for C1-INH(SC) (**Figure 1**)
  - Poisson regression mean (95% CI) reduction in relative attack rates over placebo was 0.24 (0.15–0.39), 0.27 (0.18–0.41), and 0.13 (0.07–0.24) for lanadelumab groups, respectively, versus the regression-based reduction of 0.12 (0.07–0.20) attacks per month for C1-INH(SC) (**Figure 2**)
- The relative reduction in monthly attacks experienced compared with placebo was 0.12 for patients treated with C1-INH(SC) (60 IU/kg) in COMPACT and 0.13 for patients in the lanadelumab 300 mg q2w arm of HELP

Figure 1. Absolute attack rate reduction over placebo



Least square (LS) means (95% CI) were calculated for HELP and COMPACT using a Poisson regression model. HAE, hereditary angioedema; IU, international units; q2w, every 2 weeks; q4w, every 4 weeks.

Figure 2. Relative attack rate reduction over placebo



Incidence rate ratios (95% CI) were calculated for HELP and COMPACT using a Poisson regression model. HAE, hereditary angioedema; IU, international units; q2w, every 2 weeks; q4w, every 4 weeks.

LIMITATIONS

- In spite of the attempt to adjust for potential differences between studies (e.g. rate of run-in attacks, duration of treatment and crossover design factors in COMPACT) and the similarity in inclusion/exclusion criteria between trials, it is possible that other observed and unobserved factors not accounted for in this analysis influenced the outcomes
- Only a direct head-to-head randomized controlled trial can formally establish superiority of one treatment over another

CONCLUSIONS

- The absolute reduction in monthly attacks experienced by patients treated with C1-INH(SC) compared with placebo in COMPACT was substantially higher than that experienced by patients treated with lanadelumab (all doses) compared with placebo in HELP
- The relative reduction in monthly attacks experienced by patients treated with C1-INH(SC) (60 IU/kg) compared with placebo in COMPACT was the same as that for patients in the lanadelumab 300 mg q2w arm in HELP
- These findings may be explained by the higher mean monthly attack rate during the run-in period of patients treated with C1-INH(SC) (60 IU/kg) as part of COMPACT (roughly 4 HAE attacks per month) compared with patients in the placebo arm from Day 0 to 182 in HELP (roughly 2 HAE attacks per month)
- The COMPACT Poisson regression results, which were reanalyzed using methods similar to those used in HELP, confirm that the strong efficacy of C1-INH(SC) is invariant to the statistical method used

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