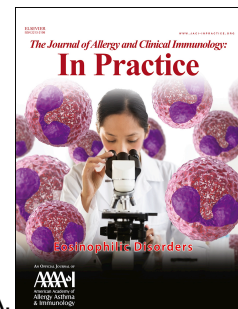


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Treatment Effect of Switching from Intravenous to Subcutaneous C1-inhibitor for Prevention of Hereditary Angioedema Attacks: COMPACT Subgroup Findings

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Clinical Implications

This subgroup analysis of COMPACT trial data suggests that patients with hereditary angioedema using C1-INH(IV) as routine prophylaxis can derive a clinically meaningful benefit when switched to prophylaxis with C1-INH(SC), observable as a further reduction in HAE attacks.

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CSL Behring, Pharming and BioCryst. Dr. M Riedl has served in a research support capacity for BioCryst, CSL Behring, Pharming, and Shire; he has received consulting fees from BioCryst, CSL Behring, Shire, Pharming, Kalvista, and Adverum; he has received honorarium for speaking from CSL Behring, Pharming, and Shire. Dr. M Manning reports grants and personal fees from Shire, grants from Dyax, grants and personal fees from CSL Behring, personal fees from Pharming, grants from BioCryst, outside the submitted work. Dr. A Banerji has received research grants from Shire and BioCryst; she served on advisory boards for Shire, BioCryst, CSL Behring, and Pharming. Dr. R Gower reports grants and personal fees from CSL Behring, grants and personal fees from Shire/Dyax, grants from Biocryst, grants and personal fees from Pharming/Salix, outside the submitted work. Dr. T Caballero has received speaker fees from CSL Behring, Novartis, and Shire; consultancy fees from BioCryst, CSL Behring, Novartis, Octapharma and Shire; funding for travel and meeting attendance from CSL Behring, Novartis, and Shire; and has participated in clinical trials/registries for BioCryst, CSL Behring, Novartis, and Shire. She is a researcher for the IdiPaz program promoting research activities. Dr. H Farkas has received research support from Shire, is on the advisory boards for CSL Behring, Shire, BioCryst and Swedish Orphan Biovitrum (SOBI), has received consultancy fee from CSL Behring, Shire, BioCryst and SOBI and speaker fee from CSL Behring, Pharming Group and SOBI. Dr. H Feuersenger, reports personal fees from employment by CSL Behring (funding company), outside the submitted work. Dr. I Jacobs reports personal fees from employment by CSL Behring (funding company), outside the submitted work. Dr. T Machnig reports personal fees from employment by CSL Behring (funding company), outside the submitted work. Dr. HJ Longhurst has received consultancy fees, educational support and/or research funding from Adverum, BioCryst, CSL Behring, Pharming and Shire, outside the submitted work.

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TO THE EDITOR:

Hereditary angioedema (HAE) is a rare, debilitating, and potentially life-threatening condition typically resulting from deficiency (Type 1 HAE) or dysfunction (Type 2 HAE) of the C1-inhibitor (C1-INH) protein.¹ International HAE management guidelines recommend that all patients be evaluated for long-term (routine) prophylaxis and that human, plasma-derived C1-INH has been cited as a first-line option.¹ Intravenous (IV) human C1-INH (C1-INH[IV]; Cinryze[®], Shire), FDA-approved in 2008,³ was the first C1-INH product specifically indicated for routine prophylaxis and represented a major advancement in HAE management. However, its use entails an ongoing need for venous access and possibility of related complications. In addition, breakthrough attacks are common at the initial FDA approved dose and only a minority of patients are completely attack-free.⁴⁻⁶

A volume-reduced formulation of human C1-INH for subcutaneous (SC) administration (C1-INH[SC]; HAEGARDA[®], CSL Behring)⁷ was FDA-approved in June 2017 for routine prevention of HAE attacks. Twice-weekly administration of C1-INH(SC) significantly reduced HAE attack rate and improved quality-of-life versus placebo in the phase 3 COMPACT trial.^{8,9} While the comparative prophylactic effectiveness of C1-INH(SC) and C1-INH(IV) is of clinical interest, head-to-head data are not available. Thus, an exploratory analysis was performed on a prespecified subgroup of COMPACT study participants who were using C1-INH(IV) for routine prophylaxis prior to the study; pre-study HAE attack rates while using C1-INH(IV) prophylaxis were compared to on-study attack rates while using C1-INH(SC) prophylaxis.

Detailed methods and primary findings of the COMPACT study have been reported elsewhere.⁸ Briefly, the study included a screening period (up to 4 weeks) and a prophylaxis-free run-in period (up to 8 weeks) during which attacks could be treated with rescue HAE therapy, after which subjects were randomized to crossover treatment with either C1-INH(SC) 40 or 60 IU/kg administered twice weekly for 16 weeks, preceded or followed by twice-weekly placebo for 16 weeks. The initial study protocol allowed use of C1-INH(IV) as prophylaxis within 3 months prior to screening; this was later amended to preclude such patients due to Institutional Review Board concerns over potentially

increased attack frequencies when C1-INH(IV) prophylaxis was withdrawn. Eligible participants were individuals ≥ 12 years of age with Type 1 or 2 HAE, with a history of ≥ 4 HAE attacks over any consecutive 2-month period prior to use of prophylactic therapy.

The subgroup for this analysis included 21 patients who entered the COMPACT study after using C1-INH(IV) at variable doses for routine prophylaxis of HAE attacks prior to screening; 13 patients previously used C1-INH(IV) prophylaxis at or above the approved dose and/or frequency of 1000 IU every 3-4 days,³ while 8 patients were using regimens involving lower doses and/or frequency than recommended (**Table 1**). The mean (SD) age was 46.3 (18.2) years, and 71% (n=15) were female. Attack data while using C1-INH(IV) in the 3 months prior to screening were obtained from patients' medical charts. During the study, investigators recorded attack information in electronic case report forms based on patients' daily electronic diaries (eDiaries). Patients recorded any HAE symptoms (regardless of need for treatment) in the eDiaries. Eight patients were randomized to a C1-INH(SC) 40 IU/kg sequence and 13 patients were randomized to a C1-INH(SC) 60 IU/kg sequence.

The mean (SD) time-normalized number of HAE attacks (HAE attack rate per month) was determined prior to screening and during study treatment. The HAE attack rate per month per subject was calculated by dividing the total number of HAE attacks during the period of interest by the number of days of the period, then multiplying the resulting number of attacks per day by 30.4375 to yield the number of attacks per month. The percentage reduction in monthly HAE attack rate for C1-INH(SC) vs C1-INH(IV) was calculated as: $100 * (1 - [\text{time-normalized number of HAE attacks during treatment with C1-INH(SC)} / \text{time-normalized number of HAE attacks pre-study}])$.

The time-normalized number of HAE attacks (primary endpoint in COMPACT study) was lower during on-study use of C1-INH(SC) prophylaxis than during pre-study use of C1-INH(IV) prophylaxis (mean, 1.2 vs 2.7 attacks/month; median, 0.6 vs 2.0 attacks/month) (**Table 2**). There was a 52.1% mean reduction (73.6% median reduction) in HAE attack rate from pre-study use of C1-INH(IV) for routine prophylaxis to

on-study use of C1-INH(SC) for routine prevention. Findings were similar for the 40 IU/kg and 60 IU/kg dose groups individually.

In the absence of prospective head-to-head comparisons of C1-INH(IV) and C1-INH(SC), this post hoc analysis of COMPACT data provides first evidence of the relative effectiveness of C1-INH(SC) compared with recent use of C1-INH(IV). These findings suggest that patients on C1-INH(IV) prophylaxis may experience a clinically meaningful reduction of HAE attacks after switching to C1-INH(SC). On average, attack rates during C1-INH(SC) use were reduced by about half compared with pre-study C1-INH(IV) prophylaxis; the median reduction of attacks per month was almost 74%.

This analysis has several limitations including a small sample size and some dosing disparities. However, previous use of C1-INH(IV) reflected real-world, non-standardized dosing which varied greatly and in some cases was below approved dosing recommendations (**Table 1**).³ While it could be assumed that pre-study, real-world treatment was individualized for optimum efficacy since C1-INH(IV) prescribing recommendations allow for doses up to 2500 IU twice weekly,³ there was no way to confirm such dose/administration frequency optimization for each patient. In this analysis, more than one-third of patients (n=8) used C1-INH(SC) at a dose of 40 IU/kg during the COMPACT study, which is lower than the approved dose of 60 IU/kg,⁷ thus the true treatment difference after switching to approved dosing with C1-INH(SC) (60 IU/kg) may be underestimated by these data. Another limitation is the possibility of patient selection bias, in that patients well-controlled on C1-INH(IV) prophylaxis may have been less likely to enroll in the COMPACT study. Finally, the methodology for identifying HAE attacks during the pre-study period was not systematic but based on medical chart entries and patients' histories, thus, not as methodical as the systematic recording of attacks during the COMPACT study treatment phases.

In summary, within the limitations of this subgroup analysis, we conclude that patients previously using C1-INH(IV) at various doses as routine prophylaxis can experience a substantial and clinically meaningful reduction in HAE attack rate when switching to

180 C1-INH(SC). Additional clinical experience and further studies will be needed to confirm
181 these observations.

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210 **Table 1.** Individual subject data

			Time-normalized Number of HAE Attacks (Number / Month)	
Prior C1-INH(IV) Prophylaxis By subject	Prior C1-INH (IV) dose	C1-INH(SC) Dose	Pre-study	C1-INH(SC) 40 IU/kg or 60 IU/kg BIW
Cinryze®				
1	1000 IU BIW	40 IU/kg	3.67	1.74
2	1500 IU Q3D	40 IU/kg	11.00	1.45
3	1000 IU BIW	40 IU/kg	3.00	1.16
4	1000 IU BIW	40 IU/kg	2.00	0.00
5	500 IU TIW*	40 IU/kg	1.33	0.29
6	1000 IU BIW	40 IU/kg	0.00	0.00
7	1000 IU BIW	60 IU/kg	1.67	0.00
8	1500 IU BIW	60 IU/kg	1.33	0.00
9	1000 IU QW*	60 IU/kg	1.67	1.15
10	1500 IU Q3D	60 IU/kg	1.33	0.60
11	1000 IU QW*	60 IU/kg	1.67	0.70
12	500 IU BIW*	60 IU/kg	2.00	0.62
13	1000 IU BIW	60 IU/kg	8.00	0.29
14	1000 IU BIW	60 IU/kg	1.67	---
15	1000 IU BIW	60 IU/kg	2.00	0.00
Berinert®				
16	1000 IU Q5D*	40 IU/kg	0.00	6.09
17	2000 IU BIW	40 IU/kg	2.33	4.35
18	1000 IU Q4D	60 IU/kg	0.67	1.48
19	2000 IU QW*	60 IU/kg	4.67	0.61
20	500 IU BIW*	60 IU/kg	3.00	0.64
Not Specified				
21	1000 IU QW*	40 IU/kg	2.67	2.90
TOTAL				
Mean (SD)			2.65 (2.57)	1.20 (1.58)
Min, Max			0.00, 11.00	0.00, 6.09
Median			2.00	0.63

211 BIW, twice weekly; QW, once weekly; Q3D/Q4D/Q5D, every 3/4/5 days; TIW, three times
 212 weekly

213 * C1-INH(IV) use at doses lower and/or less frequent than recommended (1000 IU every 3-4
214 days)

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Table 2. Monthly HAE attack rate by study phase and % reduction in attack rate.

Study Phase	Time-normalized number of HAE attacks/month by treatment group		
	All Subjects N=21 ^a	C1-INH(SC) 40 IU/kg n=8	C1-INH(SC) 60 IU/kg n=12
C1-INH(IV) (Pre-study)			
Mean $\pm$ SD (95% CI)	2.7 $\pm$ 2.6 (1.5, 3.8)	2.9 $\pm$ 3.5 (-0.02, 5.9)	2.6 $\pm$ 2.0 (1.3, 3.8)
Median (lower, upper quartile)	2.0 (1.3, 3.0)	2.2 (0.7, 3.3)	1.8 (1.5, 2.8)
C1-INH(SC) ^a			
Mean $\pm$ SD (95% CI)	1.2 $\pm$ 1.6 (0.5, 1.9)	1.9 $\pm$ 2.2 (0.04, 3.7)	0.7 $\pm$ 0.8 (0.2, 1.3)
Median (lower, upper quartile)	0.6 (0.1, 1.5)	1.3 (0.1, 3.0)	0.6 (0.1, 0.9)
% reduction in attack rate, C1-INH(SC) on study vs C1-INH (IV) pre-study			
Mean $\pm$ SD (95% CI)	52.1 $\pm$ 63.6 (20.4, 83.7)	48.8 $\pm$ 68.4 (-23.0, 120.5)	53.7 $\pm$ 64.2 (12.9, 94.6)
Median (lower, upper quartile)	73.6 (52.6, 96.4)	69.8 (52.6, 86.8)	73.8 (43.2, 98.2)

^aN=20 while using C1-INH(SC); 1 subject in the *Placebo* $\rightarrow$ *C1-INH(SC)* sequence discontinued before the C1-INH(SC) period.