LETTER TO THE EDITOR

Hereditary angioedema C1-esterase inhibitor replacement therapy and coexisting autoimmune disorders: findings from a claims database

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Abstract
In this letter to the editor, we present results of claims data analysis. This claims data analysis supports a hypothesis that in patients with hereditary angioedema due to C1-esterase inhibitor (C1-INH) deficiency, the occurrence and/or symptomatology of coexisting autoimmune disease may be positively influenced by a replacement therapy with plasma derived C1-INH.

Keywords: Plasma-derived C1-esterase inhibitor, Hereditary angioedema, Autoimmune disorders, Claims database, Lupus erythematosus

To the editor
In hereditary angioedema (HAE), a mutation in the SERPING1 gene causes either deficiency or dysfunctional C1-esterase inhibitor (C1-INH), resulting in activation of contact-kinin system and increased production of bradykinin leading to episodic angioedema [1]. Deficiency of C1-INH leads to enhanced consumption of C2 and C4, which may predispose for autoimmune disease (AD) [2]. Plasma-derived C1-INH (pdC1-INH) is safe and effective for acute treatment and prevention of HAE attacks [3].

To explore the potential association between the type of treatment for HAE due to C1-INH deficiency (C1-INH-HAE) and ADs, we compared coexisting ADs claims frequencies in C1-INH-HAE patients treated with pdC1-INH versus “Other (non-C1-INH)” treatments.

C1-INH-HAE patients were identified in the IMS Health PharMetrics Plus claims database for the period January 2012 to December 2016 by International Classification of Diseases (ICD) 9/10 diagnosis code, and classified into “pdC1-INH” (Cinryze and Berinert) or “Other (non-C1-INH)” treatment (Firazyr and Kalbitor) groups.

Patients with at least 1 diagnosis code for C1-INH-HAE including ICD-9-CM 277.6 and 277.8 or ICD-10-D84.1 were included. Patients were required to have an initial Cinryze, Berinert, Firazyr, or Kalbitor pharmacy or medical claim for HAE (index date) from 01 January 2012 to 31 December 2015 (the identification period) and to be continuously enrolled in the same health plan for at least 12 months (the follow-up period) through 31 December 2016. For patients using pdC1-INH, the first fill was used as the index date even if other HAE medications had been used previously. Frequency of visit claims for AD was identified by diagnostic codes.

The association between HAE treatment and AD visit frequency was summarized by overall patients and by gender and age group. The prevalence of patients with at least 1 visit for an AD considered in the study were

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reported by treatment group. Mean (95% confidence interval [CI]), standard deviation (SD), and range for the visits per patient per year (PPPY) by treatment group, stratified by gender and age group (< 50 versus ≥ 50 years) were summarized. A 2-sided Wilcoxon rank sum test was used to compare the frequency of AD visits PPPY by treatment group.

A total of 589 C1-INH-HAE patients were identified from the claims database; the majority were female (69%) and 38% aged ≥ 50 years. A total of 313 patients (860 patient years) received pdC1-INH and 276 patients (729 patient years) “Other (non-C1-INH) treatments”. Overall, 76 patients (12.9%) had at least 1 visit for a coexisting AD. Based on coded diagnoses, the most common coexisting ADs were: lupus erythematosus (19 patients [3.2%]), alopecia (13 [2.2%]), rheumatoid arthritis, sicca syndrome, and connective tissue disorders (each 12 patients [2.0%]) (Table 1).

The mean (95% CI) number of visits for ADs PPPY was lower in the pdC1-INH treatment (1.4 [0.562, 2.185]) than the “Other (non-C1-INH) treatments” (2.3 [0.832, 3.727]). Regardless of the treatment and age groups (< 50 and ≥ 50 years), the mean (95% CI) number of visits with ADs PPPY was higher in females than males. In the age group < 50 years, the mean (95% CI) number of AD visits with autoimmune diagnoses PPPY in pdC1-INH groups was 2.0 (0.381, 3.583) in females versus 0 in males, and 4.7 (1.178, 8.243) in females versus 0.6 [−0.213, 1.505] in males for “Other (non-C1-INH) treatments” (Table 2).

C1-INH-HAE may be linked with increased autoimmunity due to consumption of early components of the classical complement pathway and may be analogous to the increase in AD seen in patients with genetic deficiencies of C1 or C2 [4].

The estimated prevalence of ADs is 4.5% in the general population (2.7% in males and 6.4% in females) [5]. Only a few studies have been conducted which evaluated the association of C1-INH-HAE with ADs. In 1986, Brickman et al. systematically evaluated 157 patients with C1-INH-HAE and found that 19 patients (12%) had manifestations of ADs [6]. In 2011, Farkas et al. assessed the prevalence of ADs among 130 C1-INH-HAE and found a prevalence of 11.5% and also an increased severity of angioedema attacks in those with ADs [7].

In this present analysis, the prevalence of AD-related visits among 313 C1-INH-HAE patients treated with pdC1-INH was 13.4%, and prevalence of AD-related visits among 276 C1-INH-HAE patients treated with other (non-C1-INH) treatments was 12.3%. There is only a small difference in the prevalence of AD-related visits between these groups but still consistent with the benefit of the pdC1-INH treatment for reducing AD visits PPPY in C1-INH-HAE patients. Our analysis suggests a hypothesis that pdC1-INH replacement therapy may have a modulating effect on the occurrence and/or

### Table 1  Autoimmune conditions present in at least 1 visit

| AI condition                      | HAE index (%) of patients | Total (N = 589) |
|----------------------------------|---------------------------|-----------------|
|                                  | Cinryze/Berinert          | Firazyr/Kalbitor |
| Any AI condition                 | 42 (7.13)                 | 34 (5.77)       | 76 (12.9) |
| Lupus erythematosus              | 12 (2.04)                 | 7 (1.19)        | 19 (3.23) |
| Alopecia                        | 6 (1.02)                  | 7 (1.19)        | 13 (2.21) |
| Rheumatoid arthritis            | 9 (1.53)                  | 3 (0.51)        | 12 (2.04) |
| Sicca syndrome                  | 6 (1.02)                  | 6 (1.02)        | 12 (2.04) |
| Connective tissue disorders      | 5 (0.85)                  | 7 (1.19)        | 12 (2.04) |
| Crohn disease                   | 3 (0.51)                  | 6 (1.02)        | 9 (1.53)  |
| Celiac disease                  | 6 (1.02)                  | 2 (0.34)        | 8 (1.36)  |
| Raynaud’s disease                | 4 (0.68)                  | 4 (0.68)        | 8 (1.36)  |
| Thyroiditis                     | 3 (0.51)                  | 3 (0.51)        | 6 (1.02)  |
| Psoriasis                       | 2 (0.34)                  | 4 (0.68)        | 6 (1.02)  |
| Antiphospholipid syndrome       | 3 (0.51)                  | 2 (0.34)        | 5 (0.85)  |
| Rheumatism                      | 2 (0.34)                  | –               | 2 (0.34)  |
| Systemic sclerosis (scleroderma) | –                         | 2 (0.34)        | 2 (0.34)  |
| Ulcerative colitis              | –                         | 2 (0.34)        | 2 (0.34)  |
| Nephritic syndrome              | 1 (0.17)                  | –               | 1 (0.17)  |

AI, autoimmune; HAE, hereditary angioedema; N, total number of patients with HAE due to C1-inhibitor deficiency. 
| Any autoimmune condition     | Medication cohort         | Number of patients | Total f/u years | Number of visits | Autoimmune visits | Autoimmune visits per patient per f/u year |
|------------------------------|---------------------------|--------------------|-----------------|-----------------|-------------------|--------------------------------------------|
|                              |                           |                    |                 |                 | Mean (SD) 95% CI LB | 95% CI UB Range | p-value<sup>b</sup> |
| All                          | Other non-C1-INH          | 276                | 729             | 62,864          | 1528              | 2.3 (12.22) 0.832 3.727 0–107.03 0.7369 |
|                              | pdC1-INH                  | 313                | 860             | 85,859          | 1381              | 1.4 (7.30) 0.562 2.185 0–107.08          |
| < 50 years                    |                           |                    |                 |                 |                   |                                            |
| Male                         | Other non-C1-INH          | 56                 | 136             | 6087            | 66                | 0.6 (3.21) −0.213 1.505 0–21.97 0.0733   |
|                              | pdC1-INH                  | 45                 | 120             | 8082            | 0                 | 0.0 (0.00) 0.000 0.000 0.000             |
| Female                       | Other non-C1-INH          | 110                | 286             | 29,465          | 1188              | 4.7 (18.69) 1.178 8.243 0–107.03 0.6410   |
|                              | pdC1-INH                  | 146                | 386             | 44,613          | 1004              | 2.0 (9.79) 0.381 3.583 0–107.08          |
| Lupus                        | All                       | Other non-C1-INH   | 276             | 729             | 62,864            | 324             | 0.6 (6.92) −0.189 1.451 0–105.23 0.375    |
|                              | pdC1-INH                  | 313                | 860             | 85,885          | 357               | 0.4 (2.65) 0.078 0.667 0–26.14           |
| < 50 years                    |                           |                    |                 |                 |                   |                                            |
| Male                         | Other non-C1-INH          | 56                 | 136             | 6087            | 0                 | 0.0 (0.00) 0.000 0.000 0–0 1.0000         |
|                              | pdC1-INH                  | 45                 | 120             | 8082            | 0                 | 0.0 (0.00) 0.000 0.000 0–0               |
| Female                       | Other non-C1-INH          | 110                | 286             | 29,465          | 315               | 1.6 (10.92) −0.499 3.629 0–105.23 0.6040  |
|                              | pdC1-INH                  | 146                | 386             | 44,613          | 236               | 0.5 (2.68) 0.025 0.900 0–25.91           |

<sup>a</sup> 14 patients were missing age (8 females and 6 males)<br><sup>b</sup> Two-sided Wilcoxon rank sum test

pdC1-INH treatment = Cinryze and Berinert and "Other non-C1-INH treatment" = Fizryzr and Kalbitor

C1-INH C1-inhibitor, CI confidence interval, f/u follow-up, LB lower bound, pd plasma-derived, SD standard deviation, UB upper bound
severity of ADs in C1-INH-HAE patients, possibly by increasing C1, C4 and/or C2.

This analysis has several limitations. Retrospective analyses of observational claims data over a limited period of time may be prone to unobserved confounders which can bias the observed associations. Therefore, these results can only be considered as hypothesis generating. The higher AD visit frequency observed for patients using treatments other than pdC1-INH for HAE may be associated with unobserved confounders, such as more severe HAE, or other factors that influenced their treatment decisions. Since claims data are based on professional coding for reimbursement purposes, some diagnoses may be missed, disregarded, or inaccurately applied. The purpose of the visits and reasons for the use of AD codes could not be verified in this study. The study also did not look at mode of treatment for ADs or number of frequency of treatments.

**Conclusion**

Data from this claims database review showed that the C1-INH-HAE patients treated with pdC1-INH replacement therapy have a lower number of visits for coexisting ADs compared to those C1-INH-HAE patients treated with other methods. This provides a potential role of pdC1-INH replacement therapy in reducing or ameliorating the occurrence of AD in patients with C1-INH-HAE. Further research is needed to better understand the impact of pdC1-INH replacement therapy in modulating the severity and risk of concomitant AD in patients with C1-INH-HAE.

**Abbreviations**

AD: Autoimmune disease; C1-INH: C1-esterase inhibitor; C1-INH-HAE: HAE due to C1-INH deficiency; CI: Confidence interval; HAE: Hereditary angioedema; ICD: International Classification of Diseases; pdC1-INH: Plasma-derived C1-INH; PPPY: Per patient per year; SD: Standard deviation.

**Acknowledgements**

Bhawna Basin from Trilogy Writing & Consulting Ltd, Frankfurt, Germany, provided medical writing services on behalf of CSL Behring.

**Authors’ contributions**

MF analyzed and interpreted the data. All authors revised this letter to the editor for intellectual content. All authors read and approved the final manuscript.

**Funding**

This analysis was supported by CSL Behring.

**Availability of data and materials**

All data are contained in the paper.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

HF is a speaker and consultant to CSL Behring, Pharming, Biocryst, Octapharma, and Shire. DL is a researcher, speaker, and consultant to CSL Behring and speaker and consultant to Takeda. MF is a consultant to CSL Behring. DS, MB, and SP are employees of CSL Behring. MB also holds company’s stock.

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**Received: 16 December 2019 Accepted: 18 May 2020**

**Published online: 27 May 2020**

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