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LETTER

Berotralstat for the prophylaxis of hereditary angioedema—Real-world evidence data from the United Kingdom

To the Editor,

Berotralstat is an oral plasma kallikrein inhibitor, used for routine prevention of attacks of hereditary angioedema (HAE) Type 1 and Type 2. It became available in the UK in November 2020.[1–5] Our objective was to evaluate the real-world clinical outcomes of using this medication. We sent out a patient survey (Appendix S1) to obtain information on an estimated 100 UK patients taking berotralstat 150 mg daily. We received 54 responses from 12 UK centres. We collected information on treatment, adverse events, attack frequency and disease severity, using a questionnaire (Appendix S1) beginning 3 months prior to commencing berotralstat and repeated at 3- and 6-month intervals. This included the validated tool for patient-reported outcome measures, the Angioedema Control Test (AECT).[6]

BASELINE PROPHYLAXIS

Most patients (32, 59.3%) were receiving prophylaxis prior to starting berotralstat. 50% (16) were on attenuated androgens, 37.5% (12) on tranexamic acid (TA) and 6.35% (2) were on both. 6.35% (2) were on C1 inhibitor concentrate. Eight patients (18.6%) had prior prophylactic treatment overlapping with initiation of berotralstat.

EFFICACY

A mixed-effect model analysis showed statistically significant reductions in the number of attacks over 6 months during treatment compared with 3 months prior to treatment with berotralstat (6.21 ± 7.07 attacks for months 1–3 of treatment, 4.54 ± 5.49 attacks for months 4–6 vs. 12.91 ± 7.94 attacks for the 3 months prior to treatment; $p < 0.0001$, $n = 28–33$, Figure 1A). This corresponded to a 51.9% and 64.9% reduction for months 1–3 and 4–6, respectively.

AECT SCORES

AECT scores showed significant improvement in scores from the 3 months prior to treatment compared with 98.6% and 123.8% increases at 1–3- and 4-6-month–post-treatment, respectively (9.79 ± 4.53 at 1–3 months and 11.03 ± 3.14 at 4–6 months, vs. 4.93 ± 3.42 at baseline; $p < 0.0001$, $n = 32–43$, Figure 1B).

SYMPTOM SEVERITY

Analysis of patient-reported severity scores (1 = very mild, 2 = mild, 3 = moderate, 4 = severe and 5 = very severe) showed significant improvement over 6 months of treatment compared with 3 months prior to treatment (2.50 ± 1.21 attacks for months 1–3 of treatment, 2.34 ± 1.17 attacks for months 4–6 vs. 3.47 ± 0.79 attacks for the 3 months prior to treatment; $p < 0.0001$, $n = 38–49$, Figure 1C).

ADVERSE EFFECTS

In our survey, 22 patients (40.7%) reported abdominal adverse effects (cramps, nausea, diarrhoea and vomiting) and 3 patients reported headaches whilst taking berotralstat. In patients that continued treatment, symptoms were mild or had resolved by the 6-month survey.

TREATMENT FAILURE

Twelve (22%) patients in the survey stopped treatment before the 6-month analysis compared to 3% reported in the trials.[1,3,4] Nine of these patients stopped treatment due to adverse side effects. Three patients stopped treatment due to a lack of efficacy. Although there are no specific monitoring requirements for this medication in the UK,[2] 1 patient who had recently discontinued androgens discontinued berotralstat treatment due to deranged liver function tests. A further 6 patients (not otherwise included in this project) were reported by the submitting centres to have stopped treatment before the first data point collection.

The real-world data provides additional evidence for the efficacy and tolerability of berotralstat as the first oral prophylactic medication designed specifically for the treatment of HAE. Our findings are comparable with previous APeX trials[4] where 58% of the patients had a ≥50% reduction in their HAE attack rates compared with baseline vs. 25% of placebo patients. However, our data suggest a higher

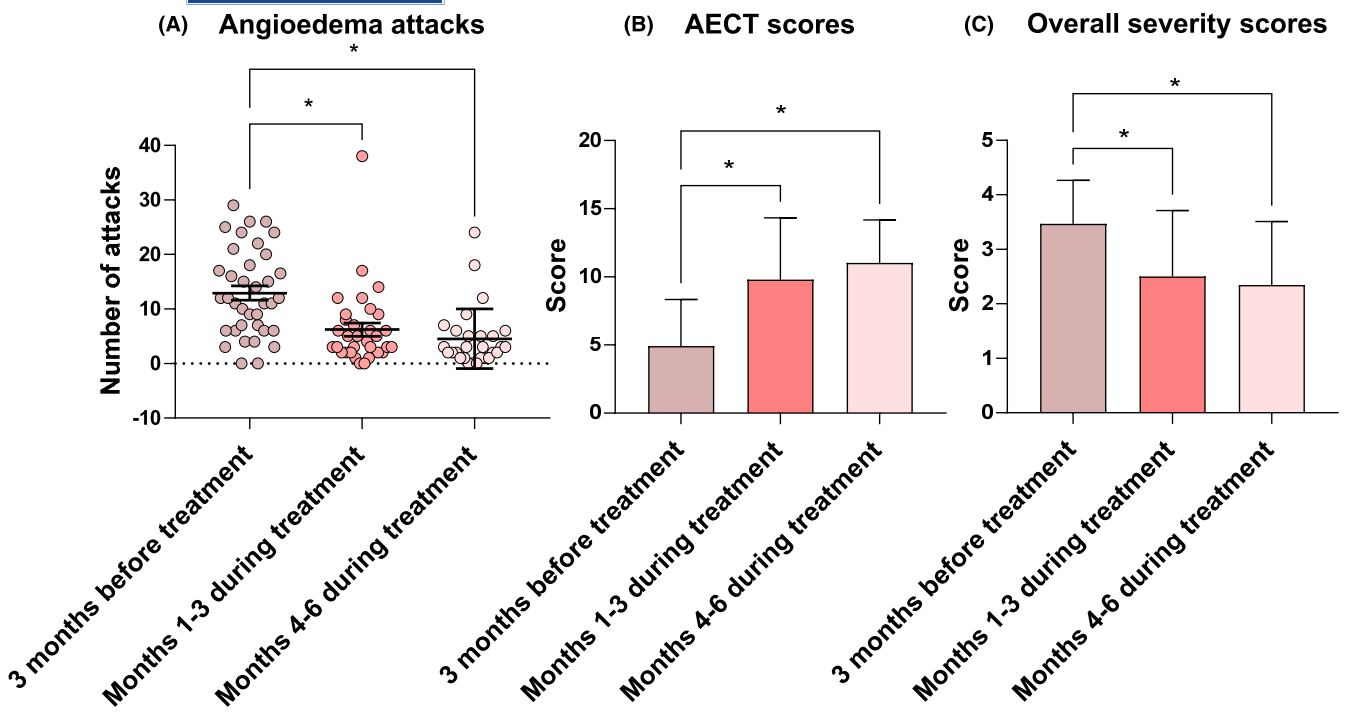

FIGURE 1 (A) HAE attack frequency for 3 months prior to initiation of berotralstat treatment and at 1–3 and 4–6 months during treatment. Black lines denote mean ± SD. *$p < 0.0001$ vs. baseline; $n = 28–33$. (B) Overall AECT scores for 3 months prior to initiation of berotralstat treatment and at 1–3 and 4–6 months during treatment. Black lines denote mean ± SD. *$p < 0.0001$ vs. baseline; $n = 32–43$. (C) HAE overall severity scores (1–5 with 1 = very mild, 2 = mild, 3 = moderate, 4 = severe and 5 = very severe) for 3 months prior to initiation of berotralstat treatment and at 1–3 and 4–6 months during treatment. Black lines denote mean ± SD. *$p < 0.0001$ vs. baseline; $n = 38–49$.

rate of reported adverse events compared to 21% of patients who reported abdominal pain and 14% reporting diarrhoea in the trials. Further studies are needed to evaluate long-term outcomes and requirement for monitoring blood tests when initiating berotralstat and discontinuing other prophylactic medications.

CONFLICT OF INTEREST

Manisha Ahuja received honoraria for advisory boards and attending educational events from Takeda and Biocryst. Anthony Dorr received an honorarium from Takeda. Anne Pacita Rosillo Boulton received expenses to attend educational meeting from Biotest. Shuayb Elkhalifa received funds as part of an Advisory Board or expert consultation from BioCryst, CSL and Takeda Pharmaceutical Companies. Tariq El-Shanawany received educational support, speaker fees and/or advisory board fees from Allergy Therapeutics, CSL, Novartis, Octapharma, Takeda, Thermo Fisher and Viatris. Archana Herwadkar received support for expenses to attend meetings and conferences from BioCryst, CSL Berhing, Pharming, Takeda (previously Shire) and Octapharma. Tomaz Garcez (Chair of NHS England Clinical Reference Group for immunology and allergy) received honoraria from BioCryst, CSL Berhing, Octapharma, Pharming and Takeda (previously Shire) for advisory board and speaking services and expenses to attend meetings and conferences from BioCryst, CSL Berhing, Pharming and Takeda (previously Shire). Sofia Grigoriadou participated in the APEX-2 clinical trial and received expenses to attend conference by Biocryst. Rashmi Jain received funding for attending educational events and for being on advisory board from CSL and Takeda. Lorena Lorenzo received educational grants from Biotest and CSL, had advisory and consulting activity with Pharming and received speaker's fees from Takeda and Biocryst. Leman Mutlu received honoraria for an education event from Biocryst. Catherine Stroud received honoraria for education and advisory boards from Biocryst, CSL, Pharming and Takeda. Patrick Yong participated in APEX-2 clinical trial and received honoraria from Biocryst, CSL Behring, Pharming and Takeda for educational support, speaker fees and/or advisory boards. Sorena Kiani-Alikhan participated in APEX-2 clinical trial and received honoraria from Biocryst for education and advisory boards.

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REFERENCES

1. Farkas H, Stobiecki M, Peter J, et al. Long-term safety and effectiveness of berotralstat for hereditary angioedema: the open-label APeX-S study. *Clin Transl Allergy*. 2021;11(4):e12035.
2. [Withdrawn] Berotralstat: Treatment protocol: Information for healthcare professionals [Internet]. GOV.UK. 2022 [cited 10 April 2022]. https://www.gov.uk/government/publications/berotralstat-in-the-treatment-of-hereditary-angioedema/berotralstat-treatment-protocol-information-for-healthcare-professionals
3. Johnston D, Banerji A, Riedl M, et al. P154 berotralstat improves patient-reported quality of life through 48 weeks in the phase 3 apex-2 trial. *Ann Allergy Asthma Immunol*. 2020;125(5):S22.
4. Wedner H, Aygören-Pürsün E, Bernstein J, et al. Randomized trial of the efficacy and safety of berotralstat (BCX7353) as an oral prophylactic therapy for hereditary angioedema: results of APeX-2 through 48 weeks (part 2). *J Allergy Clin Immunol Pract*. 2021;9(6):2305-2314.e4.
5. Bernstein J, Zuraw B, Aygoren-Pursun E, et al. Oral prophylaxis with berotralstat (BCX7353) reduces use of standard of care (SOC) on-demand medication in patients with hereditary angioedema (HAE): APeX-2 study results. *J Allergy Clin Immunol*. 2020;145(2):AB106.
6. Weller K, Donoso T, Magerl M, et al. Validation of the angioedema control test (AECT)—a patient-reported outcome instrument for assessing angioedema control. *J Allergy Clin Immunol*. 2020;8(6):2050-2057.e4.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.