Successful long-term control of lanadelumab-refractory type 2 hereditary angioedema with berotralstat

Controlo de longo prazo eficaz com berotralstat em angioedema hereditário tipo 2 refratário ao lanadelumab

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Joana Guimarães[1], João Marcelino[1,2,3], Irina Didenko[1], Elza Tomaz[1]

[1] Department of Allergy and Clinical Immunology, Unidade Local de Saúde da Arrábida, Setúbal, Portugal
[2] Charité–Universitätsmedizin Berlin, Berlin, Germany
[3] Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Berlin, Germany

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ABSTRACT

Type 2 hereditary angioedema (HAE-C1INH-Type2) is a rare, potentially life-threatening disorder characterized by functional impairment of C1-esterase inhibitor (C1-INH). Responses to long-term prophylactic (LTP) therapies are variable. We describe a case of HAE-C1INH-Type2 refractory to tranexamic acid, danazol, C1-INH concentrate, and lanadelumab, successfully controlled with berotralstat. A 47-year-old woman with HAE-C1INH-Type2 experienced recurrent facial, extremity, and laryngeal angioedema attacks. Danazol 400 mg/day provided initial control but caused severe dyslipidemia and transaminase elevation. Sequential interventions (tranexamic acid, lanadelumab, C1-INH concentrate) resulted in suboptimal control, with recurrent laryngeal attacks requiring frequent icatibant. Berotralstat 150 mg/day achieved complete and sustained remission with improvement in Angioedema control Test *(AECT),* Angioedema Quality of Life *(AE-QoL) and* Treatment Satisfaction Questionnaire for Medication II *(TSQM-II) scores. Despite sharing therapeutic*

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targets, berotralstat achieved superior disease control and quality of life in this patient compared to previous LTP treatments, representing a highly effective alternative following lanadelumab failure.

Keywords: *Berotralstat, Long-term prophylaxis, plasma kallikrein inhibitor, refractory angioedema, type 2 hereditary angioedema.*

RESUMO

O angioedema hereditário tipo 2 (AEH-C1INH-Tipo2), caracterizado por disfunção do inibidor da C1-esterase, é uma doença rara, potencialmente fatal e com resposta variável à profilaxia de longa duração. Descrevemos um caso de AEH-C1INH-Tipo2 refratário ao ácido tranexâmico, danazol, concentrado de C1-inibidor, e lanadelumab, controlado com berotralstat. Mulher de 47 anos com AEH-C1INH-Tipo2 com episódios recorrentes de angioedema facial, laríngeo e das extremidades, controlado inicialmente com danazol 400 mg/dia, mas com subsequente hipercolesterolemia grave e elevação das transaminases. Intervenções sequenciais com ácido tranexâmico, lanadelumab e concentrado de C1-INH obtiveram apenas controlo parcial. Tentativas de reduzir a medicação resultaram em crises de angioedema laríngeo recorrentes com necessidade de icatibant. O berotralstat 150 mg/dia alcançou remissão completa sustentada, com melhoria nas escalas *Angioedema control Test* (AECT), *Angioedema Quality of Life* (AE-QoL) e *Treatment Satisfaction Questionnaire for Medication II* (TSQM-II). Apesar de alvos terapêuticos similares, o berotralstat proporcionou o melhor controlo e qualidade de vida nesta doente, constituindo uma alternativa eficaz valiosa após falência do lanadelumab.

Palavras-chave: Angioedema hereditário tipo 2, angioedema refratário, berotralstat, inibidores da calicreína plasmática, profilaxia de longa duração.

INTRODUCTION

Hereditary angioedema (HAE) is a rare, autosomal dominant disorder characterized by recurrent episodes of subcutaneous and submucosal swelling, due to bradykinin-mediated increased vascular permeability (1). Comprising approximately 15-20% of HAE cases, HAE-C1INH-Type2 is characterized by a dysfunctional but quantitatively normal C1 esterase inhibitor (C1-INH). Long-term prophylactic (LTP) therapies such as lanadelumab (a monoclonal antibody) and berotralstat (a small-molecule inhibitor) directly target the dysregulated bradykinin pathway. Nonetheless, clinical responses vary, and some patients remain symptom-

atic despite treatment (2, 3), emphasizing the importance of personalized therapeutic strategies in managing refractory HAE.

CASE DESCRIPTION

A 47-year-old white woman first presented at 31 years of age with recurrent angioedema (AE) attacks involving the face, upper and lower extremities, and more frequently affecting the tongue and larynx. The patient experienced monthly attacks requiring frequent emergency visits. These episodes were refractory to standard therapy (adrenaline, corticosteroids, antihistamines), significantly impacting her quality of life. At age 34, following referral to our center, HAE-C1INH-Type2 was diagnosed based on laboratory findings of normal C1-INH levels (30.6 mg/dL), but severely reduced functional activity (2-15%).

LTP with danazol 400 mg/day was initiated and improved HAE-C1INH-Type2 control, evidenced by an AECT score increase from 6 to 9, a reduction in laryngeal AE episodes, and a decrease in monthly attack frequency. Despite achieving reasonable control, the treatment led to significant hypercholesterolemia (total cholesterol 336 mg/dL, LDL 292 mg/dL) and transaminase elevation (alanine aminotransferase - ALT and aspartate aminotransferase - AST between 40 and 100 U/L). A dose reduction to 100 mg/day resulted in weekly breakthrough attacks.

During pregnancy and lactation, danazol was suspended and intravenous (IV) C1-INH concentrate 1500 Units (U) was initiated twice a week (subcutaneous C1-INH concentrate was not available). After lactation, the pre-pregnancy regimen of danazol 200 mg/day (600 mg/day during attacks) was reintroduced but later discontinued due to hypercholesterolemia.

At age 43, tranexamic acid was introduced at 500 mg/day (maximum 1500 mg/day), resulting in reduced attack intensity but not frequency.

At age 44, weekly laryngeal episodes required frequent icatibant rescue therapy.

At age 45, lanadelumab 300 mg every two weeks was initiated but was ineffective after three months; addition of tranexamic acid 500 mg/day achieved partial upper airway control, but daily peripheral attacks persisted. Weekly IV C1-INH concentrate (2500U) provided reasonable control, with end-of-interval breakthrough symptoms.

At age 46, treatment with berotralstat 150 mg/day was initiated, achieving complete symptom control within four weeks. Furthermore, validated Patient-Reported Outcome Measures (PROMs) (Angioedema Control Test (AECT) and Angioedema Quality of Life (AE-QOL) and Treatment Satisfaction Questionnaire for Medication II (TSQM-II)) demonstrated superior disease control, quality of life, and treatment satisfaction with berotralstat compared to all previous therapies (Figure 1).

DISCUSSION

This report illustrates several clinically relevant aspects of HAE-C1INH-Type2 management. First, it demonstrates inter-treatment variability in clinical response, even among plasma kallikrein inhibitors with similar molecular targets. Second, it provides real-world evidence that failure of one inhibitor does not preclude success with another. Third, it emphasizes the value of validated PROMs in guiding personalized treatment strategies.

Although both lanadelumab and berotralstat target plasma kallikrein, the differential clinical responses can be explained by their distinct binding mechanisms. Lanadelumab, a fully human monoclonal antibody, binds to the surface of plasma kallikrein, sterically blocking substrate access to the catalytic site. In contrast, berotralstat, a small-molecule inhibitor (molecular weight 590 Da), binds deep within the active site through covalent interaction. These different binding locations may result in

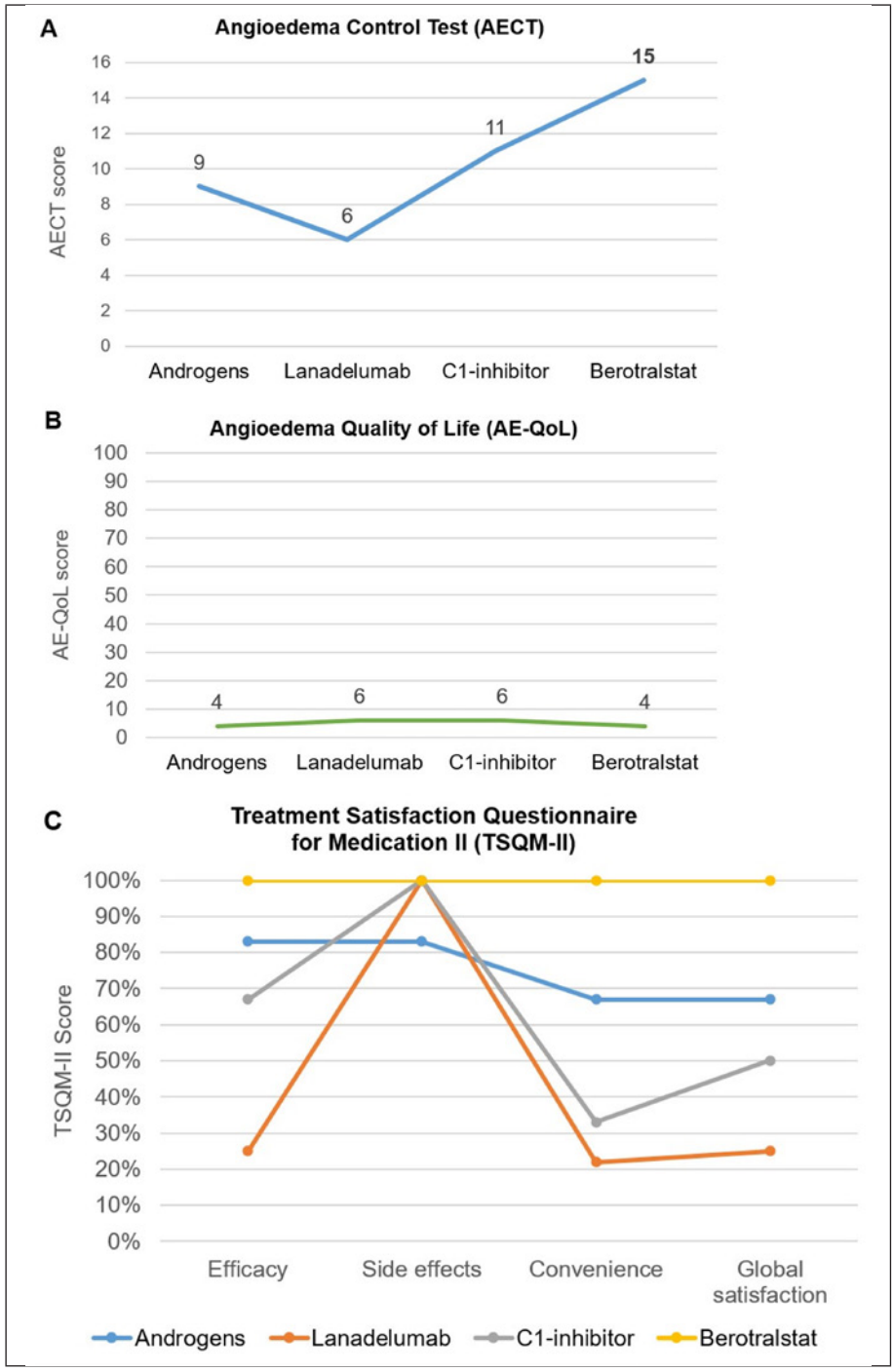

Figure 1. Comparison of patient-reported outcome measures (PROMs) for the treatments used (including androgens, lanadelumab, C1-inhibitor, and berotralstat). (A) Angioedema Control Test (AECT) scores across the different therapeutic lines. (B) Angioedema Quality of Life (AE-QoL) total scores. (C) Treatment Satisfaction Questionnaire for Medication II (TSQM-II) dimension scores expressed as percentages for androgens, lanadelumab, C1-inhibitor, and berotralstat.

variable therapeutic responses among patients due to individual molecular or genetic factors affecting drug-target interactions (2-4).

Real-world evidence supports the efficacy of berotralstat in patients with inadequate responses to other LTP therapies. A Canadian retrospective study of eight patients with HAE-C1-INH (including two with HAE-C1INH-Type2) reported a 52% reduction in attack frequency following berotralstat initiation, with four patients successfully transitioning from plasma-derived C1-INH, and a median AECT improvement of 5 points (5). A practical guide from two international Angioedema Centers of Reference emphasizes that failure to respond to lanadelumab should not preclude the use of berotralstat, given their different kallikrein-binding mechanisms (6). Similarly, recent real-world data from multiple countries consistently demonstrate berotralstat's effectiveness, with attack reductions ranging from 44-79% in extension studies (7).

Notably, while network meta-analyses suggest that lanadelumab may demonstrate statistically superior efficacy compared to berotralstat in population-level analyses, these comparisons have inherent limitations due to differences in study designs, patient populations, and statistical methodology (8). More importantly, our case demonstrates that population-level data may not predict individual patient response. The patient's AECT score of 15 with berotralstat (compared to 6 with lanadelumab) represents a clinically meaningful improvement exceeding the minimal clinically important difference of 3 points, underscoring the importance of individualized therapy selection over generalized population-based evidence (5).

As a single-patient report, this case has inherent limitations, including inability to establish causality and limited generalization. Additionally, variations in treatment duration may influence comparative assessments. Nevertheless, the dramatic and sustained clinical improvement observed with berotralstat following multiple treatment failures provides valuable real-world evidence supporting its role in refractory HAE-C1INH-Type2, particularly after lanadelumab lack of efficacy.

This case report shows that berotralstat can achieve superior disease control in patients with HAE-C1INH-Type2 who remain refractory to multiple LTP options, including lanadelumab. The patient's significant clinical improvement with berotralstat, evidenced by an AECT score increase from 6 to 15 and complete symptom control, underscores the importance of individualized treatment approaches in HAE management. This response exceeds predictions from population-level network meta-analyses, highlighting that statistical comparisons at the population level may not reliably predict individual patient outcomes.

Our findings support the principle that failure of one plasma kallikrein inhibitor should not preclude a trial of another, given their distinct mechanistic differences. Clinicians managing refractory HAE should consider berotralstat as an effective alternative when lanadelumab or other LTP therapies prove inadequate. The use of validated PROMs, including AECT and AE-QoL, remains valuable in objectively assessing and comparing treatment responses across different therapeutic modalities.

This case adds to the growing real-world evidence supporting berotralstat´s efficacy in challenging HAE presentations and reinforces the importance of personalized medicine. Future studies should explore predictive biomarkers to guide optimal selection among available plasma kallikrein inhibitors.

Conflicts of interest

The authors disclose they have no conflicts of interest.

ORCID

Joana Guimarães 0009-0008-7128-7332
João Marcelino 0000-0001-8462-8847
Irina Didenko 0000-0002-4466-4680
Elza Tomaz 0000-0001-8880-9629

Corresponding Author
Joana Guimarães
Department of Allergy and Clinical Immunology
Unidade Local de Saúde da Arrábida, Setúbal, Portugal
E-mail: joanamarquesguimaraes@gmail.com

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