ORIGINAL ARTICLE

Clinical experience with berotralstat in patients with hereditary angioedema: an Italian case series from the ITACA cohort

Andrea Zanichelli[1], Francesco Arcoleo[2], Vincenzo Montinaro[3,4], Massimo Triggiani[5], Donatella Bignardi[6], Dario Cattaneo[7,8], Antonio Gidaro[9], Marica Giliberti[10], Maria Domenica Guarino[11], Francesca Perego[12], Angelica Petraroli[13], Alessandra Vultaggio[14,15], Mauro Cancian[16]

[1]University of Milan Internal Medicine Department, Angioedema Center, IRCCS Policlinico San Donato, San Donato, Milan, Italy

[2]Clinical Pathology and Immunology Unit, A.O.R. "Villa Sofia-Cervello of Palermo, Palermo, Italy

[3]Department of Medicine, LUM University "Giuseppe Degennaro", Casamassima, Bari, Italy

[4]Division of Nephrology, "Miulli" General Hospital, Acquaviva delle Fonti, Bari, Italy

[5]Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy

[6]SSD Allergy Unit, IRCCS Azienda Ospedaliera Metropolitana, Genoa, Italy

[7]Departmenf of Biomedical Sciences, Humanitas University, Pieve Emanuele, Pavia, Italy

[8]IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

[9]Division of Internal Medicine, Luigi Sacco Hospital, University of Milan, Milan, Italy

[10]University Nephrology Unit, Reference Center for Hereditary Angioedema, University Hospital "Policlinico" of Bari, Bari, Italy

[11]Allergy Unit, Hospital of Civitanova Marche, Civitanova Marche, Italy

[12]Department of Internal Medicine, IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy

[13]Division of Internal Medicine and Clinical Immunology, University of Naples Federico II, Naples, Italy

[14]Immunoallergology Unit, Careggi University Hospital, Florence, Italy

[15]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy.

[16]Department of Systems Medicine, University Hospital of Padua, Padua, Italy

Summary

Background. Recent advancements in hereditary angioedema (HAE) management have focused mainly on long-term prophylaxis (LTP), aiming to achieve total disease control and normalize patients' lives. The latest international guidelines recommend as first-line options for LTP plasma-derived C1-INH, lanadelumab, and berotralstat. Berotralstat is a highly selective inhibitor of plasma kallikrein and the first licensed oral therapy for HAE, to be taken once daily. Given the limited clinical experience with berotralstat in Italy, members of the Italian Network for Hereditary and Acquired Angioedema (ITACA) here present and discuss some representative clinical cases treated with berotralstat in their institutions to provide practical guidance for the use of this medication. **Methods.** Three main topics were identified, (I) the switch from injectable medications to new oral therapies, with a focus on shared decision-making, (II) the switch from androgens to berotralstat, and (III) the management of comorbid patients, with a focus on polypharmacy. **Results.** The Italian experience to date indicates that (I) the decision on LTP should be always shared with patients and, given the importance for patients of administration route, berotralstat should always be considered and

proposed; (II) an overlap period between androgens and berotralstat, with progressive tapering of androgens, is the more appropriate strategy when planning this shift; (III) potential drug-drug interactions must be evaluated in patients on multiple medications, with berotralstat showing a good safety profile in this perspective. **Conclusions.** Patient engagement, awareness of androgen risks, transition strategies and drug-interaction evaluation are essential to guide individualized LTP choices.

Key words

Hereditary angioedema; berotralstat; switch from other treatments; shared decision making; drug-drug interactions.

Impact statement

Recent guidelines in hereditary angioedema (HAE) management focus mainly on long-term prophylaxis, aiming to achieve total disease control and normalize patients' lives. Among recommended first-line options, berotralstat is the first oral therapy.

Introduction

Hereditary angioedema (HAE) is a rare and debilitating condition, which affects 1-2 individuals per 100,000 people worldwide (1). It is primarily caused by a deficiency or reduced activity of the enzyme C1 inhibitor (C1INH). This leads to excessive production of bradykinin, which increases the permeability of blood vessels in the subcutaneous tissues and gastrointestinal and respiratory mucosa, resulting in tissue swelling. The disorder is marked by recurring episodes of swelling in the face, upper airways, abdomen, genitals or limbs, typically without hives or itching (2, 3). Different forms of HAE have been recognized in recent years, both related to C1INH deficiency and with normal C1INH. In HAE with C1 inhibitor

deficiency (C1-INH-HAE) the synthesis of C1INH is impaired, with circulating levels of C1INH usually less than 50% of normal, whilst HAE with normal C1 inhibitor (nC1-INH-HAE) is characterized by normal production of a dysfunctional protein. Diagnosing HAE is mainly based on clinical suspicion, usually raised by recurrent, asymmetric, non-itchy, subcutaneous angioedema, which may alternate or being associated with severe abdominal colics. Urticaria is absent, whereas genital swelling or, more rarely, bladder, muscle, or joint swelling may also occur (2, 4). Although laryngeal episodes account for only 0.9% of all the attacks, over 50% of patients experience life-threatening laryngeal episodes in their lifetime (5). Given its rarity, and some similarities with allergic disorders, hereditary angioedema may remain unrecognized for years and even decades (6). Laboratory testing is required to confirm diagnosis, with C1 esterase inhibitor functional activity representing the gold standard. Low C4 can be useful as a screening test, but its sensitivity is only around 90%.

The evolution of the guidelines for HAE treatment has been influenced by the introduction of new treatment options and by the increased attention on patients' quality of life (QoL). The latest international guideline developed by the World Allergy Organization and the European Academy of Allergy and Clinical Immunology (WAO/EAACI) (7) provides recommendations for on demand therapy, short-term prophylaxis and long-term prophylaxis (LTP), with treatment goals aiming not only to reduce the frequency, severity, and duration of attacks but also to achieve total disease control and normalize patients' lives (8). Recent advancements have focused mainly on LTP, and multiple prophylactic therapies have become available, although direct comparisons between them are still lacking. For LTP, three treatments are currently recommended as first-line options: plasma-derived C1-INH, lanadelumab and berotralstat, all with evidence level A and more than 80% agreement.

Berotralstat was licensed by the U.S. Food and Drug Administration (FDA) in 2020 and by European Medicines Agency (EMA) in 2021 as the first oral therapy for LTP in adult patients and adolescents aged 12 years and above (9). In the APeX-2 phase 3 randomized trial program, once-daily oral berotralstat for prophylaxis of HAE attacks led to sustained improvements in attack rates and patient-reported outcomes up to 96 weeks of treatment. Berotralstat was generally well tolerated throughout the 48 weeks, with most treatment-emergent adverse events (TEAEs) being mild or moderate and no serious drug-related TEAEs reported (10-12). The most frequent side effects observed in APeX-2 were gastrointestinal symptoms, such as abdominal discomfort and diarrhea, which tended to resolve overtime (13). Real-world studies conducted in different countries have confirmed these findings (14-17).

Due to its delayed availability (2023), the clinical experience with berotralstat is still limited In Italy. To address the still limited clinical experience with this drug and provide practical guidance for the use of this medicine, the Italian Network for Hereditary and Acquired Angioedema (ITACA) has discussed some representative clinical cases treated with berotralstat, which are reported here as case series.

Methods

ITACA is a network that promotes medical-scientific research and the advancement of knowledge in the field of angioedema. Its Board of Directors identified three topics of particular interest – (I) the switch to new oral therapies, with a focus on patient empowerment and the implementation of shared decision-making, (II) the switch from androgens (AAs) to berotralstat, and (III) the complex patient, with a focus on concomitant diseases and polypharmacy – and engaged some clinicians from ITACA centers to select representative

clinical cases among their patients treated with berotralstat. The cases selected for each topic were presented and discussed by ITACA members during a series of three webinars, conducted between January and May 2025, and were then commented on and discussed to reach a shared clinical conclusion.

Results

I. Drivers of therapeutic choice and patient engagement for a successful therapeutic path (Table I, cases 1, 2 and 3)

Managing HAE presents significant challenges due to the currently wide range of therapeutic options and the potential for severe morbidity and even mortality associated with the condition. It has been recognized that this complexity highlights the need for shared decision-making aids or tools to enhance collaboration between healthcare providers and patients during the decision-making process (18). Brief instruments for assessing the patient's perspective of the shared decision making (SDM) process during his/her clinical encounters with a HAE specialist/allergist have been developed to help determine the best management options for patients with HAE (19). An analysis conducted on patients and HAE specialists of the APeX study revealed that the use of validated HAE-specific treatment decision aids can facilitate successful implementation of SDM in HAE and that patients engaged in SDM are more likely to proactively request a treatment switch (20). The three cases presented on this first topic are summarized in **Table I**.

A survey of 12 physicians from eight German angioedema centers revealed that shared decision-making with the patient is considered essential, and that the most important steps in the process are (i) the opportunity for the patient to proactively express his/her preferences and (ii) the physician's presentation of all possible treatment options before making a

treatment recommendation (22). Needle phobia (both for intravenous and subcutaneous therapy) is a particularly felt problem among younger patients, such as adolescents, and balances the fear of changing therapy.

With these premises it is no longer possible today to think that the patient does not have a role in the therapeutic decision (23,24); on the other hand, it would be an insufficiently responsible attitude to consider the patient's choice as the most important element in the treatment decision. In all these three cases, a reasoned discussion was undertaken with the patients to reach a shared decision. Given that patients suffered from this fear, it was considered that this could contribute to poor adherence, delays in administration, and a significant therapeutic burden, negatively impacting the efficacy of the therapy and the patient's QoL. After extensive discussion, the decision to initiate LTP with berotralstat was agreed upon with the patients, with good efficacy and patient satisfaction.

II. Therapeutic evolution in HAE: switch from AAs to new therapeutic options (Table II, cases 4 and 5)

According to the EAACI/WAO 2021 guidelines, the use of AAs is recommended only as second-line LTP (7). Major adverse effects are commonly associated with AAs, both in females and males. Moreover, in children and adolescents, they have potential effects on bone development and carry potential risk of early puberty (**Figure 1**) (11, 24-26). An Italian survey, involving adult patients with HAE referred to Milan and Padua angioedema centers in the period 1979-2021 undergoing LTP with AAs compared to patients not receiving LTP, showed a greater incidence of hypertension, hypercholesterolemia, diabetes mellitus, hepatic angioma, and focal nodular hyperplasia in patients taking AAs (27). The two cases presented on this second topic (case 4 and 5) are summarized in **Table II**.

So far, the optimal approach for switching from AAs to berotralstat prophylaxis has not been identified. It is suggested to consider factors such as transition times, dosing schedules, specific patient preferences, and characteristics that may influence AA transition and withdrawal (28). Abrupt discontinuation of the AA immediately prior to the initiation of berotralstat is not recommended by EMA. Conversely, berotralstat was effectively administered alongside AA therapy, with a gradual tapering of the AA dosage (29). A very recent study demonstrated that suddenly stopping long-term danazol therapy can lead to temporary, self-resolving hepatitis, with liver function returning to normal within 17 weeks (30). Furthermore, it has been suggested that minimizing the period without prophylaxis by gradually tapering AA therapy, rather than abruptly discontinuing it, could enhance the initial experience with berotralstat (28). The different approaches that have been proposed are summarized in **Figure 2**. During the discussion, overlapping of the two drugs with subsequent progressive tapering of the AA was considered an option based on positive experience of physicians participating in the discussion.

As an effective and prudent solution, in both the presented cases it was proposed to overlap the two therapies, gradually reducing the AA. In case 4, berotralstat 150 mg/day together with danazol 50 mg/day was prescribed for two weeks, then 50 mg every other day for two weeks, followed by complete withdrawal. The frequency of attacks during the transition is illustrated in **Figure 3.** In case 5, several difficulties have been encountered in convincing the patient to switch therapy, given that the potential side effects of prolonged AA therapy are typically not perceived, as they only become apparent over the long term. In the end, he refused danazol decalage but accepted the switch to berotralstat, with good clinical control. Interestingly, not only patients but also physicians are concerned about discontinuing AA therapy. In a survey conducted among physicians involved in the management of HAE, regarding approaches to

transitioning from AAs to other therapies (31), three major concerns were reported in relation to the discontinuation, particularly abrupt discontinuation, of attenuated AAs: (I) in many patients, AA withdrawal may be associated with an increase in HAE attacks; (II) abrupt discontinuation of attenuated AAs may be associated with adverse events, including psychological and somatic symptoms, and abnormal blood tests; (III) patients may experience increased stress when symptom-controlling therapy is discontinued despite a switch to a new treatment approach. However, in our experience, it may be concluded that drugs overlapping with slow AA decalage has been proven to be effective and safe.

III. Management of the complex HAE patient with comorbidities and polytherapy (Table III, cases 6 and 7)

Managing a HAE patient with comorbidities and polytherapy poses the additional challenge to weigh the relevance of drug-drug interactions (DDIs), which is crucial but not always simple (32). For this reason, it is important to know which factors need to be considered in managing potential DDIs in daily clinical practice. The first question to ask is which patients are most at risk of DDIs. It is intuitive that these are the elderly patients who take more drugs, and a Sicilian epidemiological study (33) has shown that there is a direct correlation, at least up to 70-80 years of age, between the patient's age and the number of drugs taken, with a progressively increased risk of DDIs. Additionally, physiological and pharmacokinetic changes associated with aging—such as alterations in drug absorption, distribution, metabolism, and elimination—can impact the safety profile of medications in this population, increasing their susceptibility to treatment-related adverse events.

Another type of complex-to-manage HAE patients are those undergoing surgical or dental procedures. In these cases, short-term prophylaxis, typically with danazol or C1-INH, is generally indicated for HAE patients before the procedure (34).

It is worth remembering that the latest international WAO/EAACI guideline for the management of HAE recommends "to achieve total control of the disease and to normalize patients' lives" (# 13), which can currently only be achieved by LTP, and "to use AAs only as second-line LTP" (# 18) (7). The side effects associated with the use of AAs, especially at high doses and for prolonged periods, such as weight gain, virilization, myalgia, liver problems with possible development of hepatic adenomas, psychiatric conditions such as depression, and cardiovascular complications, are all well known in clinical practice. Alterations in laboratory tests are also common, including hypercholesterolemia, erythrocytosis, increase in hepatic enzymes and amylases (35). In case 6, the attention was focused on the patient's polypharmacy (defined by the concomitant administration of ≥5 drugs), suspecting possible DDIs, with particular attention to atorvastatin, which she had been taking for a long time. Consulting the *Drugs.com* platform, it emerged that berotralstat may increase the blood levels of atorvastatin, which can increase the risk of liver or muscle damage. It was therefore necessary to review the pharmacological therapy as a whole, considering the possibility of suspending berotralstat, or atorvastatin, or both, or rather making no therapeutic changes. It was decided to stop atorvastatin, sharing the decision with the patient's general practitioner (GP). A very recent study by the ITACA group evaluated the possible drug interactions of danazol and berotralstat by consulting free tools such as INTERcheck web, Medscape Drug Interactions Checker, and UpToDate, identifying drug-drug-interaction as red, orange or yellow flags (32). For berotralstat, statins were identified as red flags and clopidogrel as yellow flag. If we review the data from the APeX 2 clinical trial, only one patient in the 150 mg berotralstat

arm discontinued therapy due to asymptomatic elevation of transaminase levels, and only 1 grade 3 or 4 laboratory abnormality was reported by the investigator as an adverse event (AE) during berotralstat therapy: an asymptomatic grade 4 elevation of alanine aminotransferase level (in the 150 mg berotralstat arm, reported as a grade 1 adverse event, possibly related) in a patient with prior AA exposure who discontinued the study drug (13). It is worth noting that in a recent article on berotralstat safety profile, the increase in transaminases and the development of drug-induced hepatitis were below 3% of the total reported side effects, therefore representing a very rare event (17).

Overall, when managing HAE patients with comorbidities who are on multiple medications, it is important to note that berotralstat generally presents a lower risk of potential DDIs compared to danazol, which has historically been widely used for LTP in Italy and continues to be commonly prescribed in regions with limited access to newer, targeted prophylactic therapies (32). Carefully evaluating potential DDIs can help in making more informed decisions when choosing the most suitable prophylactic treatment for patients with HAE-C1INH.

In case 7, the issue was rather the need or not for a periprocedural short-term prophylaxis during LTP with berotralstat on the occasion of cataract surgery. In the recent past, periprocedural planning was considered important for patients to reduce the incidence of acute attacks (7). Awareness of short-term prophylaxis options was considered mandatory to enable physicians to develop an appropriate action plan for their patients (34). However, it was decided not to prescribe any short-term prophylaxis, partly because of the goal of no longer using IV C1-INH therapy within 24 hours before a procedure in patients under LTP, and partly because the procedure was considered minimally invasive. When contacted by telephone one week after the procedure, the patient reported having had no attacks. In

conclusion, berotralstat was shown to be rapidly effective and to maintain its efficacy over time. Furthermore, no pre-procedural prophylactic therapy was required.

Discussion and conclusions

Significant progress has been achieved in the development of oral therapies for HAE, with berotralstat standing out as the sole oral option among the three first-line choices for LTP (9). Given the still limited clinical experience with berotralstat in Italy, ITACA, the Italian network for HAE, proposed this small case series for discussion to a panel of HAE experts, addressing 3 issues that were considered of particular interest, i.e., a correct shared decision-making process in choosing the LTP, the transition from AAs to berotralstat, and the management of the complex HAE patient with comorbidities and polipharmacy, with an extensive focus on the management of DDIs. A short list of suggestions for LTP with berotralstat, derived from clinical experience is provided hereafter.

A. When choosing an LTP pathway for a patient with HAE, a shared decision with the patient is essential to achieve patient's satisfaction and long-term adherence (18,19). The route of administration was shown to be an important driver of therapeutic choice for patients. In these cases, it may be appropriate to propose berotralstat, which is the first oral drug available.

B. When transitioning from androgens to berotralstat, the best approach is to allow for a period of overlap between the two drugs with progressive tapering of the androgen, to reduce the risk of rebound and subsequent onset of attacks (28).

C. In patients with comorbidities and multiple medications, potential DDIs must be considered. DDIs between berotralstat and other treatments were shown to be rarely clinically relevant (32).

The key message regarding patient engagement and shared decision-making is that, following the availability of an oral formulation in the first-line LTP portfolio for HAE, it has become crucial to discuss and share with patients the type of therapeutic formulation best suited to their needs/lifestyle (36). While its clinical value is increasingly acknowledged in practice, shared decision-making has not yet been formally validated in this specific disease compared to other approaches, and its applicability may be context-dependent across different care settings (7).

Regarding AAs, this hormonal treatment carries a significant risk of adverse events in terms of hypertension, diabetes mellitus, and dyslipidemia, the prevalence of which is higher than in a population not treated with AAs (27); however, not all patients perceive these risks, especially when they are satisfied with the clinical disease control. It is therefore important to highlight the adverse effects of AAs and clearly present the therapeutic alternatives currently available. For transition modalities, the best approach is to adopt a period of drug overlapping to reduce the risk of rebound and subsequent onset of attacks (26). Finally, in comorbid and polytreated patients, careful assessment of potential DDIs can help inform the selection of the most appropriate LTP treatment (27).

Fundings

Biocryst Italy Srl, a Neopharmed Gentili Company, provided unconditional support for the overall project.

Contributions

AZ, FA, VM, MT, MC: project administration and supervision. All authors equally contributed to the manuscript data curation, drafting, review and validation. All authors read and approved the final version of the manuscript.

Conflict of interests

AZ reports personal fees from Astria, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, Takeda. FA reports speaker and consultancy fees from CSL Behring, Takeda, BioCryst, Otsuka, Kalvista. VM reports speaker and consultancy fees from CSL Behring, Takeda, BioCryst, Otsuka, GSK, Astellas, Astra Zeneca, Bayer, CSL Vifor, Kiowa Kyrin, Menarini, Amgen. MT reports personal fees from CSL Behring, BioCryst, Takeda (Advisory Board). DB reports personal fees from BioCryst. DC reports personal fees from MSD, Gilead, Pfizer, Menarini, Angelini, Viatris, Biocryst. AG reports personal fees from CSL Behring, Biocryst, Shire-Takeda. MG reports personal fees from Takeda, Biocryst, Sanofi, Chiesi, Kyowa Kirin, CSL Behring, AstraZeneca, Alnylam. MDG reports Speakers for CSL Behring, Takeda, BioCryst. FP reports granted by Takeda for clinical trial, Liberal donation by CSL Behring and Biocryst, Advisory board for Biocryst, Takeda, and CSL Behring, Otsuka. AP reports speaker honoraria from Biocryst, grant from Takeda. AV reports personal fees from GSK, AstraZeneca, Sanofi, Firma, Biocryst (Advisory Board, lecture, congress), GSK (Research Grant). MC reports Grant research support and/or speaker/consultancy fees from BioCryst, Chiesi, CSL Behring, Kalvista, Novartis, Otsuka, Pharming, Pharvaris, Sanofi and Takeda.

Acknowledgments

The authors would like to thank Biocryst Italy Srl, a Neopharmed Gentili Company, Havas Life Milan S.r.l for its supervision of the project and Renata Perego, MD, Havas Life S.r.l. Italy, for her help in drafting the manuscript.

References

1. Fisch SA, Rundle AG, Neugut AI, Freedberg DE. Worldwide Prevalence of Hereditary Angioedema: A Systematic Review and Meta-Analysis. Int Arch Allergy Immunol. 2025:1-9. doi: 10.1159/000543321.
2. Busse PJ, Christiansen SC. Hereditary Angioedema. N Engl J Med. 2020;382(12):1136-48. doi: 10.1056/NEJMra1808012.
3. Zafra H. Hereditary Angioedema: A Review. WMJ. 2022;121(1):48-53.
4. Sinnathamby ES, Issa PP, Roberts L, Norwood H, Malone K, Vemulapalli H, et al. Hereditary Angioedema: Diagnosis, Clinical Implications, and Pathophysiology. Adv Ther. 2023;40(3):814-27. doi: 10.1007/s12325-022-02401-0.
5. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol. 2012;130: 692-7. doi: 10.1016/j.jaci.2012.05.055.
6. Pagnier A, Dermesropian A, Kevorkian-Verguet C, Bourgoin-Heck M, Hoarau C, Reumaux H, et al. Hereditary angioedema in children: Review and practical perspective for clinical management. Pediatr Allergy Immunol. 2024;35(12):e14268. doi: 10.1111/pai.14268.
7. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – The 2021 revision and update. Allergy. 2022;77(7):1961-90. doi: 10.1111/all.15214.
8. Branco Ferreira M, Baeza ML, Spínola Santos A, Prieto-García A, Leal R, Alvarez J, Caballero T. Evolution of Guidelines for the Management of Hereditary Angioedema due to C1 Inhibitor Deficiency. J Investig Allergol Clin Immunol. 2023;33(5):332-62. doi: 10.18176/jiaci.0909.

9. BioCryst Pharmaceuticals Inc. ORLADEYO™ (berotralstat) capsules, for oral use—prescribing information. Durham, NC: BioCryst Pharmaceuticals, Inc.; 2023.
10. Farkas H, Stobiecki M, Peter J, Kinaciyan T, Maurer M, Aygören-Pürsün E, 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. doi: 10.1002/clt2.12035.
11. Wedner HJ, Aygören-Pürsün E, Bernstein J, Craig T, Gower R, Jacobs JS, 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):2305-14.e4. doi: 10.1016/j.jaip.2021.03.057.
12. Kiani-Alikhan S, Gower R, Craig T, Wedner HJ, Kinaciyan T, Aygören-Pürsün E, et al. Once-Daily Oral Berotralstat for Long-Term Prophylaxis of Hereditary Angioedema: The Open-Label Extension of the APeX-2 Randomized Trial. J Allergy Clin Immunol Pract. 2024;12(3):733-43.e10. doi: 10.1016/j.jaip.2023.12.019.
13. Zuraw B, Lumry WR, Johnston DT, Aygoren-Pursun E, Banerji A, Bernstein JA, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial. J Allergy Clin Immunol. 2021;148:164–72.e9. doi: 10.1016/j.jaci.2020.10.015.
14. Srinivasan C, Ritchie B, Adatia A. Berotralstat in hereditary angioedema due to C1 inhibitor deficiency: first real-world evidence from a Canadian center. Front Immunol. 2024;15:1339421. doi: 10.3389/fimmu.2024.1339421.
15. Ahuja M, Dorr A, Bode E, Boulton APR, Buckland M, Chee S, et al. Berotralstat for the prophylaxis of hereditary angioedema-Real-world evidence data from the United Kingdom. Allergy. 2023;78:1380–3. doi: 10.1111/all.15641.

16. Johnson F, Stenzl A, Hofauer B, Heppt H, EV E, Wollenberg B, et al. A retrospective analysis of long-term prophylaxis with berotralstat in patients with hereditary angioedema and acquired C1-inhibitor deficiency-real-world data. Clin Rev Allergy Immunol. 2023;65(3):354–64. doi: 10.1007/s12016-023-08972-2.
17. Donadoni M, La Cava L, Bizzi E, Popescu Janu V, Meschia A, et al. Hereditary Angioedema Prophylaxis Therapy: Berotralstat and Lanadelumab Safety Profile. Medicina. 2025;61(11):1897. doi: 10.3390/medicina61111897
18. Settipane RA, Bukstein DA, Riedl MA. Hereditary angioedema and shared decision making. Allergy Asthma Proc. 2020;41(Suppl 1):S55-S60. doi: 10.2500/aap.2020.41.200057.
19. Odin R, Anderson J, Jacobs J, Jones D, Li HH, Lumry W, et al. The utility of shared decision making in the management of hereditary angioedema. Allergy Asthma Proc. 2024;45(6):434-7. doi: 10.2500/aap.2024.45.240071.
20. Riedl MA, Neville D, Cloud B, Desai B, Bernstein JA. Shared decision-making in the management of hereditary angioedema: An analysis of patient and physician perspectives. Allergy Asthma Proc. 2022;43(5):397-405. doi: 10.2500/aap.2022.43.220050.
21. Levy D, Caballero T, Hussain I, Reshef A, Anderson J, Baker J, et al. Long-Term Efficacy of Subcutaneous C1 Inhibitor in Pediatric Patients with Hereditary Angioedema. Pediatr Allergy Immunol Pulmonol. 2020;33(3):136-141. doi: 10.1089/ped.2020.1143.
22. Greve J, Lochbaum R, Trainotti S, Ebert EV, Buttgereit T, Scherer A, et al. The international HAE guideline under real-life conditions: From possibilities to limits in daily life - current real-world data of 8 German angioedema centers. Allergol Select. 2024;8:346-357. doi: 10.5414/ALX02530E.

23. Banerji A, Anderson J, Johnston DT. Optimal Management of Hereditary Angioedema: Shared Decision-Making. J Asthma Allergy. 2021;14:119-25. doi: 10.2147/JAA.S284029.
24. Riedl MA. Critical appraisal of androgen use in hereditary angioedema: a systematic review. Ann Allergy Asthma Immunol. 2015;114(4):281-8.e7. doi: 10.1016/j.anai.2015.01.003
25. Banerji A, Sloane DE, Sheffer AL. Hereditary angioedema: a current state-of-the-art review, V: attenuated androgens for the treatment of hereditary angioedema. Ann Allergy Asthma Immunol. 2008;100(1 Suppl 2):S19-22. doi: 10.1016/s1081-1206(10)60582-0.
26. Maurer M, Magerl M, Aygören-Pürsün E, Bork K, Farkas H, Longhurst H, et al. Attenuated androgen discontinuation in patients with hereditary angioedema: a commented case series. Allergy Asthma Clin Immunol. 2022;18(1):4. doi: 10.1186/s13223-021-00644-0.
27. Zanichelli A, Senter R, Merlo A, Gidaro A, Popescu Janu V, et al. Comorbidities in Angioedema Due to C1-Inhibitor Deficiency: An Italian Survey. J Allergy Clin Immunol Pract. 2024;12(4):1029-36. doi: 10.1016/j.jaip.2023.12.046.
28. Peter JG, Desai B, Tomita D, Collis P, Stobiecki M. Assessment of HAE prophylaxis transition from AA therapy to berotralstat: A subset analysis of the APeX-S trial. World Allergy Organ J. 2023;16(11):100841. doi: 10.1016/j.waojou.2023.10084.
29. Garcez T. Safe and Effective Introduction of Berotralstat in an Attenuated AA-Treated HAE Patient. Presented at: EAACI Hybrid Congress. Prague: Czech Republic; July 1-3, 2022.
30. de Lange M, Takkenberg RB, Verheij J, Cohn DM. Transient hepatitis as a Novel Withdrawal Phenomenon After Danazol Discontinuation in Hereditary Angioedema. J Allergy Clin Immunol Pract. 2025;S2213-98(25)01014-1. doi: 10.1016/j.jaip.2025.10.027.

31. Johnston DT, Henry Li H, Craig TJ, Bernstein JA, Anderson J, Joseph K, Riedl MA. AA use in hereditary angioedema: A critical appraisal and approaches to transitioning from AAs to other therapies. Allergy Asthma Proc. 2021;42(1):22-9. doi: 10.2500/aap.2021.42.200106.
32. Zanichelli A, Cattaneo D, Gidaro A, Senter R, Arcoleo F, Accardo P, et al. Assessment of potential drug-drug interactions in patients with hereditary angioedema from the ITACA cohort: simulations from a real-life dataset considering danazol versus berotralstat. Front Pharmacol. 2025;16:1550133. doi: 10.3389/fphar.2025.1550133.
33. Scondotto G, Pojero F, Pollina Addario S, Ferrante M, Pastorello M, Visconti M, et al. The impact of polypharmacy and drug interactions among the elderly population in Western Sicily, Italy. Aging Clin Exp Res. 2018;30(1):81-7. doi: 10.1007/s40520-017-0755-2.
34. Williams AH, Craig TJ. Perioperative management for patients with hereditary angioedema. Allergy Rhinol (Providence). 2015;6(1):50-5. doi: 10.2500/ar.2015.6.0112.
35. Konrad Bork, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. Ann Allergy Asthma Immunol. 2008;100(2):153-61. doi: 10.1016/S1081-1206(10)60424-3.
36. Magerl M, Martinez-Saguer I, Schauf L, Pohl S, Brendel K. The current situation of hereditary angioedema patients in Germany: results of an online survey. Front Med (Lausanne). 2024;10:1274397. doi: 10.3389/fmed.2023.1274397.

Table I. Drivers of therapeutic choice and patient engagement for a successful therapeutic path

Case 1: From injectable to oral drug: the importance of shared decision making (SDM) in long-term prophylaxis (LTP)	
A 27-year-old female	
Family history	Positive for C1-INH-HAE (8 affected family members).
2019	Diagnosis at age 22 following the occurrence of two attacks, one peripheral and one abdominal.
2020-21	No attacks
2022	1 attack
2023, 1st therapy	Intensification of attacks (up to 4/month). Treatment with icatibant on demand.
2024, 2nd therapy	The patient complains about frequent attacks and disrupted QoL. LTP is proposed: • with lanadelumab (1 vial SC Q2W, refused by the patient due to fear of injections or needle phobia) • with berotralstat, preferred for its route of administration
Follow-up	During treatment with berotralstat from October 2024 to March 2025, no further attacks occurred. Compliance to berotralstat was total. The patient reported high level of satisfaction with the treatment. Some episodes of nausea occurred during the first week of treatment and spontaneously disappeared.
Case 2: The burden of treatment in the adolescent patient	
A 12-year-old girl with recent menarche	
Family history	Mother and grandmother affected.
March 2023	Diagnosis of HAE at 12 years of age, after menarche.
2023 – 1st treatment	Icatibant 30 mg, 1 vial subcutaneously, on demand. The patient, who is needle phobic with a low pain threshold, complains intense local pain after icatibant injection.
2023 – 2nd treatment	Tranexamic acid, 1 g x 3/daily orally. However, tranexamic acid is no longer indicated.
2023 – 3rd treatment	Lanadelumab (1 vial SC every other week, then every 4 weeks), considered less painful and therefore better accepted than icatibant. However, after each administration, the pain is reported to be similar than that experienced with icatibant.
2023 - 4th treatment	Weight-based SC pd-C1-INH, for which no pain at the injection site is reported (21), at a dose of 4000U (2 vials of 2000U) every 4 days.
December 2023	Angioedema attack treated with on demand parenteral therapy. Good disease control is achieved, albeit with a high therapeutic burden.

2024 - 5th treatment	The girl's weight has increased to 65 kg. Switch to berotralstat, with good control of the disease, high patient satisfaction and adherence to the treatment.
Case 3: Normalizing patient's life by switching from on demand therapy to LTP	
A 72-year-old woman with delayed HAE diagnosis	
1963 - Age of 10	Sporadic episodes of abdominal pain associated with abdominal meteorism, nausea, and diarrhea, treated with symptomatic drugs.
1968/71 - Age 15-18	Recurrence of abdominal colic and suspected milk allergy for which she started a milk-free diet.
1977 and 1979 - Age 24 and 26	Two full-term pregnancies that proceeded without complications. During the same period, episodes of edema involving the limbs and/or face lasting 48 hours, which did not improve with steroid and antihistamine therapy, occurred with a monthly or bimonthly frequency.
2000 - Age 47 - 1st treatment	Diagnosis of C1-INH-HAE. Daughter and grand-daughter received HAE diagnosis. On-demand therapy with IV plasma-derived C1INH.
2000/03 - Age 47-50	Reduction of attacks, resolved after IV treatment with C1INH.
2003 - Age 50	Diagnosis of breast cancer, subsequent surgery and hormone therapy with no relapse.
Following years	Increase of HAE attacks, primarily affecting the abdomen, indicating the need to switch to LTP. Daughter and granddaughter began LTP with lanadelumab, achieving good disease control.
2nd treatment	Refused SC treatment with lanadelumab or C1INH due to compliance issues and local effects at the injection site.
March 2024 - 3rd treatment	Berotralstat (150 mg/day). Up to now she has experienced reduction in attacks until complete disappearance. Initially, experienced gastric disorders, resolved with antacids and taking the drug during the main meal.

C1-INH-HAE: hereditary angioedema with C1 inhibitor deficiency; HAE: hereditary angioedema; LTP: long-term prophylaxis; pd-C1-INH: plasma-derived C1 inhibitor; Q2W: every two weeks; QoL: quality of life; SC: subcutaneously; SDM: shared decision making.

Table II. Therapeutic evolution in hereditary angioedema (HAE): switch from androgens (AAs) to new therapeutic options

Case 4. Switch from androgen (AA) to berotralstat	
66-years-old woman with delayed diagnosis and long term treatment with AA	
Family history	Negative for HAE
Early childhood	Episodes of subcutaneous angioedema localized to the face and limbs.

Adolescence	Severe abdominal attacks with profuse vomiting and diarrhea initially interpreted as colic, with prolonged hospitalizations and diagnosis of psychosomatic disease.
1981 (22 years old)	First episode of severe glottis edema, which induces suspicion of C1-INH deficiency. Diagnosis of angioedema due to C1-INH deficiency.
1st treatment	C1-INH for acute abdominal and laryngeal attacks. Weekly attacks persist.
1986	Diagnosis of HCV hepatitis, with mild fibrosis and normal portal flow.
1989: 2nd treatment	The patient starts AA therapy
1992	Attempts are made to suspend or reduce the dose of danazol with immediate resumption of attacks
1994	Danazol discontinued for pregnancy planning
1996	Pregnancy without attacks, delivery at week 32 by caesarian section, no complications related to angioedema. The daughter is affected by HAE.
2004	Danazol treatment is resumed with progressive achievement of the minimum effective dose of 50 mg/d
Since 2009	Icatibant on demand
2022	In view of HCV eradication treatment, danazol is tapered (50 mg/d), with intake on alternate days and then at longer intervals until discontinuation. Rapid relapses occurred with severe and close episodes, including a laryngeal episode, for which treatment with danazol at 50 mg/d has to be resumed.
2024	SC LTP is proposed but rejected pending the availability of oral treatment. Between April and May 2024, 6 severe attacks occur. On 14/05/2024, she starts LTP with berotralstat 150 mg. The switch was managed by administering berotralstat alongside AA, with a gradual tapering of the AA dosage.
Follow-up	No more attacks have occurred since September 2024. Tolerability was good, with the appearance of gastrointestinal symptoms characterized by abdominal cramps, predominantly in the morning, of moderate severity, which disappeared after about a month. Complete clinical control was achieved.
Case 5. Switch from androgen (AA) requires effective doctor-patient communication and appropriate transition	
58-year-old man, truck driver, heavy smoker	
Age 17	Onset of recurrent angioedema episodes affecting face, hands and feet, abdomen, and genitals.
Age 43	Diagnosis of nC1-INH-HAE. Starts therapy with danazol 200 mg/day
Age 50	Reduction of danazol to 100 mg/day

Age 50-58	Despite the high "burden of disease" (about 2-3 abdominal episodes/month), the patient shows poor adherence to control visits (<1/year) and to treatment. He does not treat acute events (needle-phobia) with consequent delay in remission of the attack. He shows frequent interpersonal difficulties in interacting with most healthcare professionals.
Age 58	Onset of intermittent claudication (IIA), with hypercholesterolemia, hypertriglyceridemia, arterial hypertension, mood disorder.
May 2024	Oral LTP with berotralstat is proposed, with treatments overlapping and slow danazol decalage. However, the patient abruptly discontinued danazol treatment on his own initiative. Nonetheless, he reported no side effects and maintained good adherence to berotralstat, achieving effective clinical control.

AAs: androgens; C1-INH: C1 inhibitor; HAE: hereditary angioedema; HCV: Hepatitis C virus; LTP: long-term prophylaxis; nC1-INH-HAE: HAE with normal C1 inhibitor; SC: subcutaneously.

Table III. Management of the complex hereditary angioedema (HAE) patient with comorbidities and polytherapy

Case 6. Comorbidity and polytherapy in an elderly patient with hereditary angioedema (HAE)	
76-year-old women with comorbidities	
Childhood	Recurrent episodes of angioedema
Age 36	Diagnosis of HAE
1st treatment	Starts LTP with danazol 200 mg/day + human C1-INH 1500 IU IV on demand
Comorbidities	Type 2 diabetes mellitus Arterial hypertension Dyslipidemia
In 2022	Stroke, for which she underwent thrombolysis.
Concomitant medications	Metformin 1000 mg x 2/day Atorvastatin 40 mg/day Clopidogrel 75 mg/day Pantoprazole 20 mg/day Bisoprolol 1.25 mg/day Cholecalciferol 25,000 1 vial/week
2nd treatment, December 2023	To prevent side effects associated with long-term use of AAs, switching to one of the currently recommended drugs, lanadelumab, C1-INH, or berotralstat, is proposed. The latter is preferred due to its oral administration route.
Switch from AA to berotralstat	With drugs overlapping and progressive tapering of danazol.

	Angioedema attacks that had the frequency of about 1 per month on danazol reduction to 0 from December 2023 with the start of berotralstat.
January 2024	Worsening of markers of hepatocellular cytolysis and cholestasis is observed, in the absence of any clinical problem, likely due to polypharmacy and AA discontinuation. Abdominal ultrasound and ECG were normal. No more HAE attacks since start of berotralstat. The statin was discontinued, resulting in a progressive improvement in liver function tests, which persisted even after the statin was reintroduced.
Case 7. Optimizing therapy in a poor compliant patient undergoing surgical procedure	
56-year-old man, with poor compliance with HAE management	
2004	Diagnosed with HAE at 35 years of age.
1st treatment	Danazol, discontinued due to intolerance.
2nd treatment	3-4 attacks per month, always abdominal, treated with icatibant on demand.
QoL	Heavy burden of HAE attacks on his work activities, free time, and social relationships, especially due to their unpredictability. Frequent difficulties concentrating and sleeping. His main concern is that frequency of attacks may increase.
3rd treatment	In December 2023, LTP with berotralstat is started compassionate use program. Addition of probiotics to control potential gastrointestinal side effects of berotralstat
2024	2 attacks in 2 months, controlled with icatibant. No side effects of berotralstat
April 2025	Cataract surgery on April 22; no short-term prophylaxis was deemed necessary. No postoperative attacks.

AAs: androgens; C1-INH: C1 inhibitor; ECG: electrocardiogram; HAE: hereditary angioedema; LTP: long-term prophylaxis.

Figure 1. Common adverse effects associated with androgens

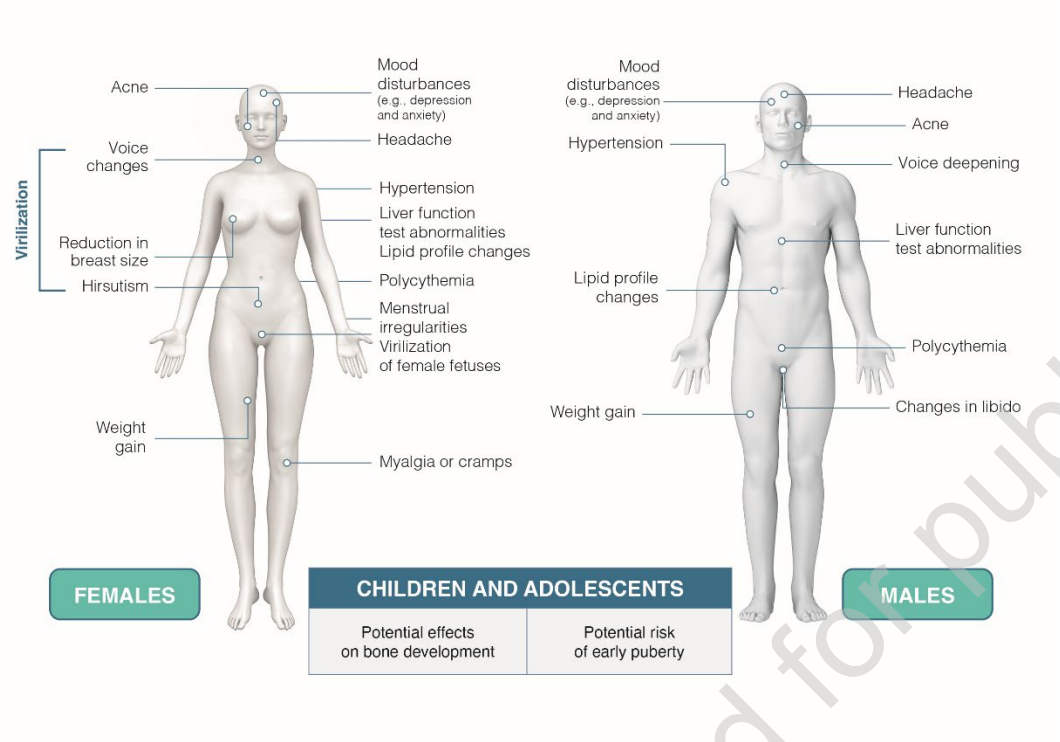

Figure 2. Androgen discontinuation and transition management - AAs: androgens

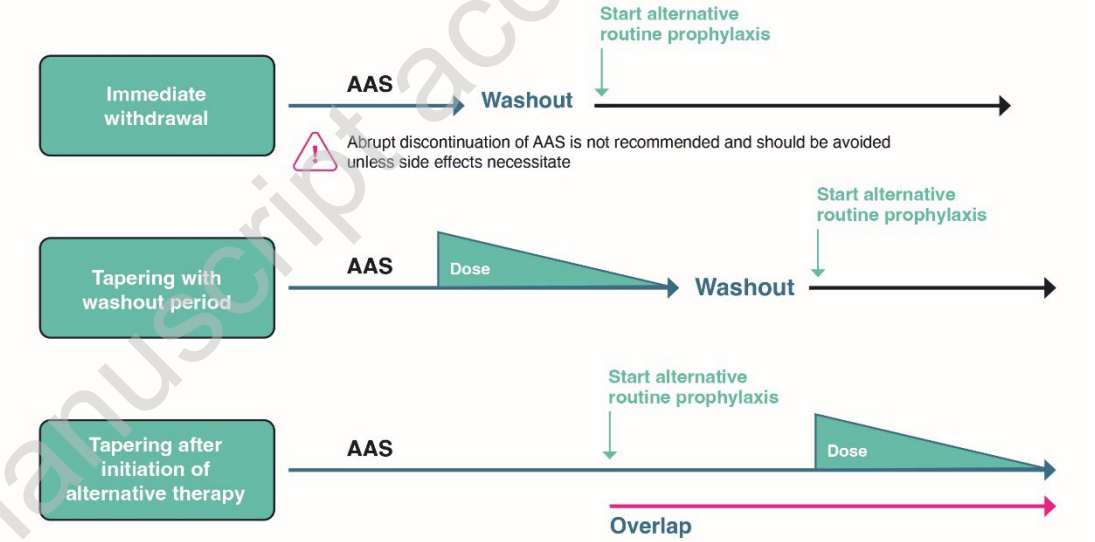

Figure 3. Patient N 4 hereditary angioedema (HAE) acute attacks during the transition from danazol to berotralstat