An expert panel's review on patients with hereditary angioedema switching from attenuated androgens to oral prophylactic therapy

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ABSTRACT

Background: *Hereditary angioedema (HAE) is a rare condition marked by swelling episodes in various body parts, including the extremities, upper airway, face, intestinal tract, and genitals. Long-term prophylaxis (LTP), prescribed to control recurring HAE attacks, is integral to its management. Previously, attenuated androgens (AAs) were the only oral LTP options. However, in 2020, berotralstat, an oral plasma kallikrein inhibitor, was approved in the United States. A 2018 survey of adults with HAE type I or type II showed that almost all the patients who used prophylactic HAE medication preferred oral treatment (98%) and felt that it fit their lifestyle better than injectable treatment (96%). Still, guidelines lack consensus on transitioning patients from AAs to alternative oral prophylactic therapy.*

Objective: *This paper aims to share expert insights and patient feedback on transitioning from AAs to berotralstat, an alternative oral prophylactic therapy, from the perspective of clinicians with extensive experience in treating patients with HAE.*

Methods: *A panel of five HAE specialists convened for a virtual half-day roundtable discussion in April 2023.*

Results: *Discussions about transitioning from AAs to berotralstat were prompted by routine consultations, patient inquiries based on independent research, ineffective current treatment, or worsening AA-related adverse effects. For patients who switched from AAs, the physicians reported that the decision was influenced by the alternative therapy's ability to prevent HAE attacks, its safety, and the once-daily administration schedule. All expert panel members identified fewer AA-related adverse effects; better quality of life; and less severe, shorter, and less frequent HAE attacks as clinical or patient goals they hoped to achieve through the treatment switch.*

Conclusion: *The emergence of new, highly specific LTP drugs for HAE calls for the development of comprehensive recommendations and guidelines for transitioning from AAs to alternative oral prophylactic therapy. The expert panel highlighted key factors to consider during the development of such guidelines.*

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The primary forms of hereditary angioedema (HAE), type I and type II, are the result of SERPING1 gene mutations, which lead to a decrease in the production or a dysfunction of the C1-esterase inhibitor (C1-INH) protein, respectively.[1,2] An estimated 6,000 individuals are living with HAE type I or type II

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in the United States.[3] HAE attacks, characterized by extensive swelling, are precipitated by a lack of adequate C1-INH function, which leads to decreased control and increased activation of the kallikrein-kinin pathways.[4,5] Moreover, the impaired function of C1-INH contributes to inadequate inhibition of C1s proteases within the classic pathway as well as mannose-binding lectin-associated serine protease 1/2 within the lectin pathway.[6–8] HAE attacks can be unpredictable, life-threatening, and affect any region of the body, including the extremities, upper airway, face, intestinal tract, and genitals.[1,6,9,10]

The management of HAE types I and II involves a combination of therapeutic strategies. These strategies include long-term prophylaxis (LTP) to control recurring attacks and on-demand therapies for acute attacks.[3,11] Short-term prophylaxis can also be used before any events that have the potential to induce an attack (*e.g.*, dental procedures).[3,11] Historically, attenuated androgens (AAs) have been used for LTP.[3,11] However, the global World Allergy Organization/European Academy of Allergy and Clinical Immunology and US HAE Association Medical Advisory Board (US HAEA MAB) guidelines recommend AAs such as danazol or stanozolol as second-line LTP therapy.[3,12] Although some patients find AAs to be effective and tolerable,[13] AAs are not effective for all patients.[2,14] In two different case series studies of patients with HAE ($N = 10$[2] and $N = 118$[14]), some patients (30% [3 of 10][2] and 5.9% [7 of 118][14]) discontinued AAs because of inadequate HAE control.[2,14]

Findings from multiple studies show that patients taking AAs can experience a range of adverse effects.[11,14–18] In addition, AAs are contraindicated during pregnancy and are not recommended for use.[11,19] In a retrospective case series of patients with HAE type I or II who received danazol ($N = 118$)[14], 78.8% experienced one or more adverse effects related to danazol. The adverse effects included weight gain (42.4%), hirsutism (18.6%), menstrual irregularities (14.4%), changes to the voice (14.4%), headaches (13.6%), muscle aches or cramps (12.7%), depression (11.0%), and acne (9.3%).[14] Another study compared patients with HAE who received danazol as LTP with patients with HAE who had not received persistent danazol as LTP and healthy volunteers. Compared with the control groups (patients with HAE not receiving danazol and healthy control subjects), the patients with HAE who were receiving danazol as LTP had increased low-density lipoprotein levels (HAE patients receiving danazol vs. HAE patients not receiving danazol, $p = 0.0060$; HAE patients receiving danazol vs. healthy control subjects, $p < 0.0001$) and reduced high-density lipoprotein levels ($p < 0.0001$ for both comparisons).[17] Moreover, these patients showed increased body mass index (HAE patients receiving danazol vs. HAE patients not receiving danazol, $p = 0.0055$; HAE patients receiving danazol vs. healthy control subjects, $p = 0.0020$) and alanine aminotransferase levels (HAE patients receiving danazol vs. HAE patients not receiving danazol, $p = 0.0298$; HAE patients receiving danazol vs. healthy control subjects, $p = 0.0457$).[17]

In a physician survey study that involved 12 physicians who treat patients with HAE, half of the responding physicians (50.0%) indicated they had patients who experienced adverse effects, including fatigue and changes in mood, as a result of discontinuing AAs.[15] To date, extensive studies on AA withdrawal and strategies for its discontinuation are lacking, which underscores the imperative for additional research in these areas.[2,15]

Recent advancements in HAE treatment have introduced effective and well-tolerated options for LTP.[5] Plasma-derived C1-INH concentrates and plasma kallikrein inhibitors, such as berotralstat and lanadelumab, are available alternatives to AAs.[4] Despite the availability of various novel treatment options over the past 15 years, a number of patients have remained on AAs due to their low cost and oral administration.[5,20]

Shared decision-making (SDM), defined as "an approach in which clinicians and patients share the best available evidence when faced with the task of making decisions, and when patients are supported to consider options, to achieve informed preferences,"[21] is a commonly used approach to facilitating cooperation between physicians and patients in the decision-making process.[3,22] Research has demonstrated that SDM is effective in improving both patient adherence and outcomes.[22] The 2020 US HAEA MAB guidelines3 recommend that all patients with HAE, especially those whose quality of life (QoL) is considerably affected, discuss the potential benefits of LTP with their healthcare provider.[3,23] During these discussions with patients about LTP, the treating clinicians should also consider patient-related concerns, including the route of administration, adverse effects, and patient preferences.[22] For patients with HAE who prefer to avoid daily treatment, injectable LTP with monthly or twice-monthly administration is available as an alternative to AAs.[4] However, this article focuses primarily on alternative oral prophylactic options.[24]

Although the patient and physician may decide that switching from AAs to an alternative oral prophylactic agent is appropriate, the challenge remains that there is currently no consensus in the US HAEA MAB3 or other guidelines on how to make this transition.[12,25] In this article, we present the findings of a roundtable discussion that involved five physicians experienced in treating HAE to (i) share insights into how they incorporate patient preferences and goals into treatment decisions, with a particular focus on the implementation of SDM during this process; (ii) consider the feedback received from patients about HAE and its treatments; and (iii) identify real-world strategies clinicians use when switching patients from AAs to berotralstat.

METHODS

An expert panel that consists of five U.S. HAE specialists with backgrounds in allergy and immunology was convened to discuss and evaluate the real-world experience of patients with HAE who switch from AAs to berotralstat. To prepare for the roundtable, the participating physicians reviewed information from patient charts and collected insights from their patients. This approach ensured that the panel's input during the roundtable would focus on the specialists' experience with treating patients with HAE.

Inclusion Criteria for the Charts Reviewed

- Children (ages 12–17 years) or adults (ages ≥ 18 years) who were diagnosed with HAE type I or type II;
- patients who were currently taking AAs or had previously taken AAs in the past 3 years; and
- patients with a documented history of annual (or more frequent) follow-ups.

Exclusion Criteria for the Charts Reviewed

- Patients with a condition other than HAE that required treatment with AAs;
- patients who did not take AAs in the past 3 years; and/or
- patients with incomplete or unreliable medical records.

Information was recorded by using Qualtrics software (Qualtrics, Provo, UT).[26] Physician responses about HAE treatments were qualitatively compared with the corresponding information from the patients to assess the degree of physician-patient agreement.

Roundtable Discussion

All experts who completed at least one chart review were invited to participate in a virtual half-day roundtable discussion. During the roundtable, the experts reviewed the aggregated data from the chart reviews and information concerning the patient perspective. This discussion focused on two groups of patients: those who were transitioning or had transitioned from AAs to berotralstat and those who remained on AAs. The roundtable encompassed the following topics: the type of patients from the chart review to be discussed, the decision-making process of choosing an LTP, and factors considered when weighing treatment choices. Strategies for transitioning between LTPs were also discussed, including abrupt changes or tapering (*i.e.,* the gradual reduction in dosage over time) and treatment goals associated with such transitions. Finally, the level of agreement between physicians and their patients was qualitatively evaluated.

RESULTS

Expert Panel

A roundtable discussion was held with all the experts who had reviewed at least one patient chart (n = 5). These panel members treated a median of eight patients with HAE per month and had been in practice for a median of 22 years (range of 15–41 years).

Patient Profiles

The patients considered during the discussion fell into two categories: (1) patients who were either transitioning or had already transitioned from AAs to berotralstat (hereafter referred to as "patients who transitioned from AAs"), with completed chart reviews for seven patients and patient-reported data from five patients; and (2) patients who decided to remain on AAs, with completed chart reviews for six patients and patient-reported data from four patients.

Initiating Discussions with Patients about LTP Treatments

Experts agreed that AAs are not typically initiated with patients who are newly diagnosed, and individuals currently taking AAs have likely been on this treatment for decades. It was emphasized that treatment decisions are multifactorial and that no single metric can serve as an indicator that a treatment switch is needed. Several prompts could initiate discussions with patients with regard to the potential shift from AAs to an alternative oral prophylactic agent. Such prompts might include routine consultations, inquiries from patients driven by their independent research on HAE therapies, the lack of effectiveness of a patient's current treatment, or worsening AA-related adverse effects.

Factors Influencing the Decision to Switch and Treatment Choice

For patients who transitioned from AAs (n = 7), the physicians most commonly reported the alternative therapy's ability to prevent HAE attacks (100%), safety (100%), and the once-daily administration schedule (86%) as factors that influenced their decision to switch patients from AAs to berotralstat. There was unanimous agreement among physicians with regard to the goals they hoped to achieve for their patients transitioning from AAs, with all experts (100%) reporting fewer AA-related adverse effect; better QoL; and less severe, shorter, and less frequent HAE attacks as clinical or patient goals that they hoped to achieve. Physicians most commonly cited AA-related adverse effects (100%) and patient preference (86%) as patient factors they considered before deciding to switch patients from AAs to berotralstat.

The expert panel emphasized that patient goals are individual and may evolve, which highlights SDM as a crucial tool to ensure that patient-specific factors are considered in treatment decisions. For patients transitioning from AAs, the majority of physicians (86%) noted that the availability of an oral LTP influenced their decision to recommend discontinuing AAs. After switching from AAs to berotralstat, the patients from the chart review (n = 7) experienced a reduction in the frequency and severity of HAE attacks as well as improved adherence. The panel acknowledged that these chart review findings align with observations from their clinical practice.

AA Tapering Strategies and AA Discontinuation

Several strategies (e.g., tapering or abrupt switching) are available for transitioning patients from AAs to a non-androgen oral prophylactic therapy. The physicians reported that the chosen strategy depends on factors such as patient preference and the level of HAE control (*i.e.,* the frequency, location, severity, and duration of HAE attacks). Among the patients from the chart review who transitioned from AAs to berotralstat (n = 7), tapering was the most common strategy (86%) used to transition the patients (Table 1 presents physician's notes concerning the approach used to taper from AAs to berotralstat). The reasons discussed for a more gradual transition included allowing time for the new treatment to become effective, giving the patient's body time to adjust to AA discontinuation, and accommodating patient preference. The panel agreed that the best strategy would be tailored to each patient's situation because AA discontinuation considerations differ by age. For instance, certain outcomes associated with discontinuing AAs, such as skin changes and menstrual cycle changes, are more relevant for younger individuals.

Choosing to Remain on AAs and the Factors Influencing Treatment Choice

For those who remained on AAs (n = 6), the physicians most commonly reported patient preference (100%) and a lack of perceived adverse effects (83%) as key factors that influence the decision to continue patients on AAs.

The expert panel explained that physicians are responsible for discussing non-androgen alternatives with their patients currently on AAs. However, the panel acknowledged that a substantial change in health status or personal circumstances such as mood, hormone levels, liver function tests, or other life events would likely be required before patients still taking AAs would consider a switch to a different LTP therapy.

Alignment between Patients and Their Physicians

The concordance between physician and patient perspectives was evaluated qualitatively by using the physician-reported data from the chart reviews and patient-reported information collected by the physicians. Physicians and their patients were largely in agreement on several key topics, including treatment goals, factors that influence the decision to discontinue AAs, adherence estimates, treatment-related experiences (*e.g.,* adverse effects, physiologic changes associated with AA discontinuation), and willingness to consider discontinuing AAs in the future (for those who remained on AAs). Overall, the observed concordance underscored the experts' view that SDM is the most appropriate way to determine the best therapy for their patients.

DISCUSSION

Treatment Burden

Beyond addressing the HAE disease burden, which includes physical, psychological, and social effects, the expert panel concurred that clinicians treating patients with HAE also have the crucial task of managing the treatment burden. Long-term use of AAs is generally considered suboptimal for patients' health, which makes non-androgen LTP preferable. Except in special circumstances, AAs typically have not been initiated as LTP since the introduction of HAE-specific treatments.

Table 1 **Physician notes on the tapering approach used (n = 6)***

4 weeks
100 mg daily for 1 week, 50 mg daily for 1 or 2 weeks, 50 mg every 2 days for 1 week, 50 mg every 3 days for 1 week, and 50 mg once a week for a month
100 mg for 1 week, 50 mg for 1 week, 50 mg q.o.d. for 1 week; then stop AAs
50 mg for 2 weeks; then off AAs while on berotralstat
The patient was tapered by consultation with an endocrinologist; the patient's tapering process lasted ~4 months

AA =Attenuated androgen; q.o.d. = every other day.
**Details concerning the tapering process were not provided for one patient.*

A series of surveys between 2010 and 2019 of U.S. physicians treating patients with HAE showed that fewer physicians now prescribe AAs than a decade ago.[27] From a 2018 survey of U.S. adult patients diagnosed with HAE type I or type II, nearly all the respondents who were using prophylactic HAE medication preferred oral treatment (98%) and believed that an oral preventative therapy would integrate better into their lifestyle than an injectable treatment (96%).[28] For the overwhelming majority of patients using prophylaxis who prefer an effective treatment that allows them to avoid needles,[28] an oral LTP treatment, such as berotralstat, could be an alternative to AAs. In addition, patients' commitment and adherence to a therapy, as well as their perception of disease management, can be greatly influenced by the therapy's route of administration.[29]

AA Discontinuation Strategies

Tapering was the most common strategy used by the expert panel for patients from the chart review who switched from AAs to berotralstat. However, the physicians underscored that the most appropriate switching strategy would be unique to each patient and that a gradual approach would only be suitable for specific patients.

SDM

Although physicians typically view non-androgen prophylactic therapies more favorably as a long-term treatment option compared with AAs, it is critical that physicians practice SDM when recommending any LTP. SDM involves presenting all available information to patients, which enables them to make informed decisions about their HAE treatment. The decision to switch from AAs to another treatment is complex, and each patient's life stage and individual context may influence the patient's treatment decision. Overall, the level of agreement between the patient and physician pairs was high, which supports the emphasis placed on SDM during the roundtable discussion.

Future Studies to Consider

Whereas the roundtable discussion focused primarily on patients who switched between oral prophylactic therapies, future discussions could consider all non-androgen prophylactic treatment alternatives, including intravenous and subcutaneous options.

CONCLUSION

The emergence of new, highly specific LTP drugs for HAE calls for the development of comprehensive recommendations and guidelines for transitioning patients from AAs to other oral LTP alternatives. This expert panel discussion highlights factors that should be considered, from both the physician and patient perspective, during the development of future recommendations and guidelines.

In disease areas such as HAE, in which multiple treatment options are available and patient preference is fundamental, SDM is particularly relevant. Results of studies have shown that SDM can profoundly impact care, including the ability of SDM to educate patients, enhance patient adherence, and improve outcomes.[22] Furthermore, the principles of SDM align with the recommendations for HAE management plans,[3] which underscore the need for individualized therapy.[22]

The expert panel agreed that each patient's unique circumstances make the decision-making process for HAE treatment changes complex. These decisions, which may involve switching LTP therapies, selecting a new LTP, or determining the transition strategy from one LTP to another (*e.g.,* abrupt, gradual), require careful consideration of both the disease burden (*e.g.,* follow-up, monitoring, necessary interventions) and treatment burden (*e.g.,* route of administration, adverse effects). Accordingly, SDM is paramount in making optimal medical choices on review of evidence-based data.

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