

Tolerability and Effectiveness of 17- α -Alkylated Androgen Therapy for Hereditary Angioedema: A Re-examination



Bruce L. Zuraw, MD^{a,b}, Donna K. Davis, BA^c, Anthony J. Castaldo, MPA^c, and Sandra C. Christiansen, MD^a La Jolla and San Diego, Calif; and Honolulu, Hawaii

What is already known about this topic? 17- α -Alkylated androgens have been widely used for prophylactic treatment of hereditary angioedema (HAE) to reduce attack frequency and severity. Relatively little is known about the variability in clinical responses or degree of side effects they cause.

What does this article add to our knowledge? In the largest cohort ever reported, we show that androgen effectiveness is extremely variable and that many subjects continue to swell even on high doses. Reported side effects are extremely frequent, severe, and dose related.

How does this study impact current management guidelines? Androgens should not be used for most patients with HAE. When tried, androgens should be given at the lowest possible dose. If ineffective, patients should be switched to an alternative rather than increasing the androgen dose.

BACKGROUND: Hereditary angioedema (HAE) is a genetic disorder clinically characterized by recurrent attacks of subcutaneous and mucosal swelling. 17- α -Alkylated androgens (AA) have been used prophylactically to reduce HAE severity, but there are many questions about the efficacy and tolerability of AA.

OBJECTIVE: The objective of this study was to investigate the tolerability and effectiveness of AA therapy in a large cohort of patients with HAE.

METHODS: We performed a retrospective cross-sectional study on 650 subjects with HAE utilizing a one time, anonymous, web-based survey. Based on an initial questionnaire, patients were

routed to one of the following questionnaires: currently using AA, previously used but discontinued AA, or never used AA. **RESULTS:** Statistical analysis revealed that androgens decreased attack frequency and severity in previous AA users ($P < .0001$) and current AA users ($P < .0001$). Substantial variability in the effectiveness was observed. Users who discontinued AA reported significantly lesser benefit. No dose effect was seen for the beneficial effect of AA; however, almost all users reported frequent side effects that were dose related and often severe. **CONCLUSIONS:** AA therapy is usually effective for the treatment of HAE although a substantial fraction of patients with HAE do not achieve adequate benefit. In contrast, the side effects of AA are seen in almost all subjects who take the medicines. If used, AA should only be recommended in the lowest effective and tolerated dose for carefully selected patients. © 2016 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:948-55)

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Hereditary angioedema (HAE) with low C1 inhibitor (C1INH) is clinically characterized by recurrent swelling episodes. The frequency and severity of angioedema attacks in patients with HAE is highly variable.^{1,2} It has been estimated that the average untreated patient with HAE will swell approximately every 10-14 days, with individual attacks typically lasting 3-4 days before resolving.³⁻⁵ Attacks are almost equally likely to involve the skin and the abdomen.⁶ Abdominal attacks are often associated with severe pain and emesis, not infrequently being misdiagnosed as a surgical abdomen and resulting in unnecessary

^aDepartment of Medicine, University of California, San Diego, La Jolla, Calif

^bMedicine Service, VA San Diego Healthcare System, San Diego, Calif

^cUnited States Hereditary Angioedema Association, Seven Waterfront Plaza, Honolulu, Hawaii

US HAEA conducted the online survey.

Conflicts of interest: B. L. Zuraw has received consultancy fees from Alnylan, Arrowhead, BioCryst, CSL Behring, Dyax, Ionis, Nektar, Shire, and Salix; and has received travel support from US Hereditary Angioedema Association (HAEA). A. J. Castaldo has received travel support from Shire, ViroPharma, and CSL Behring; and declares that the US HAEA receives nonrestricted educational grants from BioCryst, CSL Behring, and Shire (which now owns Dyax and ViroPharma, which also provided nonrestricted educational grants). The rest of the authors declare that they have no relevant conflicts.

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Corresponding author: Bruce L. Zuraw, MD, University of California, San Diego, 9500 Gilman Dr., Mail code 0732, La Jolla, CA 92093-0732. E-mail: bzuraw@ucsd.edu.

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Abbreviations used

AA- 17- α -Alkylated androgens
C1INH- C1 inhibitor
HAE- Hereditary angioedema
HAE-nl-C1INH- HAE with normal C1 inhibitor
pdC1INH- Plasma-derived C1 inhibitor
US HAEA- United States HAE Association

abdominal surgery. Most patients with HAE report that their disease has had a substantial negative impact on their lives, including school, work, social life, and sleep.^{7,8} Additionally, laryngeal attacks carry a substantial risk of mortality secondary to asphyxiation.⁹ Given the cumulative burden of suffering endured by patients with HAE, it could clearly be considered a catastrophic disease.⁵ The substantial risk of morbidity and mortality associated with this disease requires effective strategies to protect patients with HAE.

Before 2008, there was no reliably effective acute treatment for attacks of HAE available in the United States. Because of this, a substantial fraction of patients with HAE were managed on prophylactic regimens to decrease the frequency and severity of attacks. Prophylactic options up to that time were limited to 17- α -alkylated androgens (AA) or antifibrinolytics.¹ Although both modalities were shown to be beneficial,^{10,11} each is associated with significant risk of side effects. AA were used most frequently (except in children and pregnant women in whom they are relatively contraindicated) because of their increased efficacy relative to antifibrinolytics.¹² Since 2008, 5 new (4 on-demand drugs and 1 prophylactic drug) have been approved for the treatment of HAE. These drugs have been transformational in the approach to treatment of HAE with demonstration of high efficacy and minimal side effects^{3,13-16} as well as significant reductions in the burden of HAE disease.^{8,17} Although these new drugs appear highly effective and safe, issues have been raised regarding their relative expense and difficulties in administration compared with orally available AA.¹⁸ It is crucial to recognize, however, that large randomized controlled studies of AA have never been performed. Therefore, it remains important to better understand the efficacy, safety, and tolerability of AA to reasonably discuss their potential role in the management of HAE. The purpose of this investigation was to evaluate the effectiveness, safety, and tolerability of AA therapy in a very large cohort of patients with HAE.

METHODS

Study design

The United States HAE Association (US HAEA) conducted a survey of adult patients in the United States with self-reported HAE. All subjects reported a history of physician-diagnosed HAE. The survey was performed in 2008. The Western Institutional Review Board approved this study. After subjects signed informed consent, they were given a password for access to an online set of questionnaires. Subjects were identified in the database only by a random code.

The screening questionnaire gathered baseline subject demographic information as well as whether subjects either were currently taking or ever had taken AA. After completing the screening questionnaire, subjects were divided into 3 groups, based on their androgen usage: (1) subjects who had never used androgens;

(2) subjects who had previously used androgens but were not currently using (discontinued) androgens, or (3) subjects currently using androgens. Each subject was asked to fill out a second detailed questionnaire specific to his or her assigned group. Information from the questionnaire was collected in an online database. Subjects were identified only by a random code. The questionnaires are available in [Figures E1-E4](#) in this article's Online Repository at www.jaci-inpractice.org.

Inclusion/exclusion criteria

All patients who reported a physician diagnosis of HAE were eligible for inclusion. Because the inclusion criteria of physician diagnosis of HAE were based on subject report, we used 3 exclusion criteria to attempt to limit the analysis to subjects with HAE due to C1INH deficiency. First, we excluded patients who reported a history of HAE with normal C1 inhibitor (HAE-nl-C1INH) because of the lack of robust diagnostic criteria for that disease.¹⁹ Second, we excluded patients reporting a history of being treated with corticosteroids for their angioedema, which is known to be ineffective for this condition.¹ Third, we excluded patients who reported that their first episode of swelling occurred after the age of 30 unless they participated in one of the HAE type I/II clinical drug trials. The vast majority of HAE due to C1 inhibitor deficiency patients become symptomatic before the age of 20, and almost all patients manifest swelling by the age of 30.⁶

Statistical analysis

Parameters are reported either as mean $\pm$ standard error of the mean for normally distributed data or median (25%-75% interquartile range). Statistical analyses used, as indicated in the text, were the nonparametric Wilcoxon or Kruskal-Wallis test, the Pearson χ^2 test, and logistic regression. In all cases, a *P* value of $\leq .05$ was considered significant. Statistical analysis was performed using JMP 11.2 (SAS Institute, Cary, NC).

RESULTS

Study population

Approximately 1000 US HAEA members were contacted, and a total of 731 subjects completed the questionnaires. Of these, 81 subjects were excluded from final analysis based on meeting one of the exclusion criteria as follows: (1) diagnosis of HAE-nl-C1INH (*n* = 60); (2) first symptom of HAE occurred after the age of 30 (*n* = 15); and (3) treated with corticosteroids for their angioedema (*n* = 6).

The remaining 650 subjects were divided into the 3 groups based on androgen usage history and analyzed. There were 126 subjects who had never used androgens (group 1, never AA); 180 subjects who had previously used androgens but had discontinued and were not currently using them (group 2, prior AA); and 344 current androgen users (group 3, current AA).

Demographics

[Table 1](#) shows that the 3 groups were significantly different. Subjects on androgens (groups 2 and 3) were significantly older, began swelling at a younger age, and more likely to be male. Because the age of first symptom has been shown to correlate with overall disease severity,^{6,20} the androgen-treated subjects in groups 2 and 3 may have selected for more severe HAE compared with the subjects in group 1.

We compared the attack frequencies as well as emergency department (ED) visits and hospital admissions for HAE attacks

TABLE I. Baseline characteristics of subjects

	All (650)	Never AA (126)	Prior AA (180)	Current AA (344)	P-value*
Age (y)	42.6 ± 0.5	37.4 ± 1.1	41.5 ± 0.9	45.1 ± 0.7	<.0001
Gender F:M (%F)	462:188 (71%)	102:24 (81%)	140:40 (77.8%)	220:124 (64%)	.0001
Age at first symptom	12.2 ± 0.3	14.0 ± 0.7	12.1 ± 0.6	11.6 ± 0.4	.0052
Age at diagnosis	22.4 ± 0.5	25.9 ± 1.2	22.5 ± 0.9	21.1 ± 0.7	.0023
HAE I:II:unknown (% type II)	251:65:334 (20.6%)	32:10:84 (23.8%)	78:20:82 (20.4%)	141:35:168 (19.9%)	.004
Age at first AA	27.3 ± 0.5	NA	27.2 ± 0.9	27.4 ± 0.6	.8410
Attacks/y off AA	18 (8, 36)	12 (6, 48)	24 (8.5, 48)	18 (8, 36)	.3655
ED/y off AA	0 (0, 3) [3.5 ± 0.4]	0 (0, 0) [0.8 ± 0.2]	1 (0, 4) [4.0 ± 0.8]	0.5 (0, 3) [3.2 ± 0.5]	<.0001
Admit/y off AA	0 (0, 0) [1.3 ± 0.2]	0 (0, 0) [0.3 ± 0.1]	0 (0, 1) [1.9 ± 0.4]	0 (0, 0) [0.9 ± 0.2]	<.0001

AA, 17- α -alkylated androgens; ED, emergency department; HAE, hereditary angioedema.

Bold type indicates statistical significance ($P < .05$).

*Difference in groups analyzed by a contingency table with the Pearson test (gender, HAE type) or Wilcoxon/Kruskal-Wallis (age, age at first symptom, age at diagnosis, age at first AA, attacks/y, ED visits/y, admissions/y). Data are expressed as median (interquartile range), mean ± standard error of the mean, or percentage.

during times when the subjects were not taking AA. **Table I** confirms that the numbers of attacks off AA were higher in the AA-treated subjects (groups 2 and 3), but this did not reach statistical significance. In contrast, there was a statistically significant increase in ED visits in groups 2 and 3 compared with group 1, as well as a statistically significant increase in HAE admissions in group 2 versus groups 1 and 3.

17- α -Alkylated androgens reduce the number and severity of HAE attacks

A total of 524 subjects in groups 2 and 3 reported using AA at some point. Median AA dose was 200 (71,400) [178 ± 9] mg/day danazol equivalent in group 2 and 100 (55,200) [256 ± 22] mg/day danazol equivalent in group 3. Treatment with AA resulted in a significant decrease in the frequency and severity of attacks (**Table II**). Overall, attacks decreased from 24 (9, 36) before AA to 4 (1, 18) on AA ($P < .0001$). The median severity of attacks also decreased from 4 (4, 5) to 3 (1, 4) ($P < .0001$). Corroborating this improvement, the number of ED visits per year, hospital admissions due to HAE, and days using narcotic pain medicines per year also significantly decreased on AA ($P < .0001$ in each case). Finally, subjects reported that the impact of HAE on their life significantly improved during the time that they used AA ($P < .0001$). The relative frequency of attacks at different locations was not impacted by AA therapy and was consistent across groups and treatments (see **Tables E1** and **E2** in this article's Online Repository at www.jaci-inpractice.org).

We compared these outcomes in subjects who remained on AA (group 3) versus those who discontinued AA (group 2). Both groups experienced improvements in each of these outcomes, but subjects who remained on AA (group 3) reported a significantly greater magnitude of improvement in attack frequency, attack severity, ED visits, days of narcotic pain use, and HAE effect on life ($P < .0001$ in each case). In contrast, there was no significant difference in hospitalizations due to HAE. There was a statistically significant difference in the overall perception of the effectiveness of AA, with group 3 rating AA much more effective, 4 (3.5) [3.73 ± 0.06], than group 2, 2 (1, 3) [2.33 ± 0.10] ($P < .0001$) (**Figure 1**). Subjects in group 3 were queried about their eagerness to stop AA once effective alternative medicines were available, using a 5-point scale (1 = no, 5 = yes). Despite the perceived effectiveness of AA, 186 subjects (54.7%) indicated "yes" that they would stop their AA, 64 (18.6%) indicated that

they would probably stop the AA, and 68 (19.8%) indicated that they would possibly stop AA. Only 9 (2.6%) indicated that they would not stop AA, and 17 (4.9%) indicated that they probably would not stop AA.

The percentage of subjects who reported experiencing no attacks on AA was 23% in the entire population, 19% in group 2, and 26% in group 3. A significant number of subjects continued to experience frequent attacks, with >12 attacks per year reported in 29% of the entire population, 45% of group 2, and 20% of group 3. **Figure 2** shows the number of attacks per year while on AA for the entire cohort as well as for groups 2 and 3. Subjects in group 3 reported substantially fewer angioedema attacks on AA than subjects in group 2.

Subjects in group 2 were asked why they stopped taking AA. Subjects could check more than 1 reason, so the total number of responses is greater than the number of subjects. The reasons given for stopping androgens were side effects (104); lack of efficacy (80); enrollment in a clinical trial (39); no continuing need for prophylaxis (39); pregnancy (10); switched to home plasma-derived C1 inhibitor (pdC1INH) (10); lack of availability (5); cost (4); and unwillingness to take a regular medicine (2). The attack rate in those subjects who discontinued AA significantly increased from 12 (2, 30) to 18 (5, 41) ($P < .0001$). The attack frequency after stopping AA was not significantly different from that before starting AA ($P = 0.1913$).

Tolerability of 17- α -alkylated androgen therapy

Subjects were asked to rate multiple potential side effects of AA using a 5-point scale (1 = no problem, 3 = moderate, and 5 = very severe problem) (**Table III**). The side effect with the highest percentage of subjects reporting moderate or worse symptoms was weight gain at 59%. Anxiety, menstrual abnormalities, increased facial hair, sadness, depression, aggressiveness, acne, difficulty sleeping, and headaches were all reported as being at least moderate in severity in more than 1/3 of subjects. The frequency and severity of reported side effects were remarkably similar between subjects in group 2 and group 3 (**Figure 3**). No statistically significant differences were seen between the groups other than elevated cholesterol levels, which was more of a problem in group 3 than group 2.

The vast majority of subjects reported side effects from AA. On average, subjects reported 5.2 ± 0.2 side effects that were

TABLE II. AA decrease attack frequency and severity, ED visits, HAE hospitalizations, and narcotic pain medicine usage

	Combined: Groups 2, 3 (524)			Prior AA: Group 2 (180)			Current AA: Group 3 (344)		
	Before AA	On AA	P-value*	Before AA	On AA	P-value*	Before AA	On AA	P-value*
Attacks/y	24 (9, 36)	4 (1, 18)	<.0001	24 (8.5, 48)	12 (2, 30)	<.0001	18 (8, 36)	4 (0, 12)	<.0001
Severity†	4 (4, 5) [4.2 ± 0.04]	3 (1, 4) [2.7 ± 0.1]	<.0001	4 (3, 5) [3.9 ± 0.1]	3 (2, 4) [3.1 ± 0.1]	<.0001	4 (4, 5) [4.3 ± 0.1]	3 (1, 3) [2.5 ± 0.1]	<.0001
ED/y	0.6 (0.1, 3) [3.6 ± 0.5]	0.1 (0, 1.1) [2.4 ± 0.4]	<.0001	1 (0.2, 3.6) [4.1 ± 0.8]	0.5 (0, 4) [4.2 ± 0.9]	.2040	0.5 (0.1, 3) [3.3 ± 0.5]	0.1 (0, 1) [1.4 ± 0.5]	<.0001
Admits/y	0.1 (0, 0.5) [1.4 ± 0.2]	0 (0, 0.2) [1.1 ± 0.2]	<.0001	0.1 (0, 1.2) [1.9 ± 0.4]	0 (0, 1) [1.5 ± 0.3]	.0916	0.1 (0, 0.4) [1.1 ± 0.2]	0 (0, 0.1) [0.9 ± 0.2]	<.0001
Days pain meds/y	2 (0, 20) [25.6 ± 2.7]	0 (0, 10) [19.6 ± 2.5]	<.0001	3 (0, 23.3) [27.7 ± 4.5]	0 (0, 15) [25.8 ± 4.7]	.0459	2 (0, 18) [24.4 ± 3.4]	0 (0, 5) [16.3 ± 2.8]	<.0001
Affect life (1-5 scale)†	4 (3, 5) [3.9 ± 0.04]	3 (2, 4) [2.8 ± 0.1]	<.0001	4 (3, 5) [3.7 ± 0.1]	3 (2.25, 4) [3.3 ± 0.1]	<.0001	4 (3, 5) [4.0 ± 0.1]	2 (2, 3) [2.6 ± 0.1]	<.0001

AA, 17- α -alkylated androgens; ED, emergency department; HAE, hereditary angioedema.

Bold type indicates statistical significance ($P < .05$).

*Paired groups analyzed using the Wilcoxon test.

†5-point scale (1 = very mild to 5 = very severe).

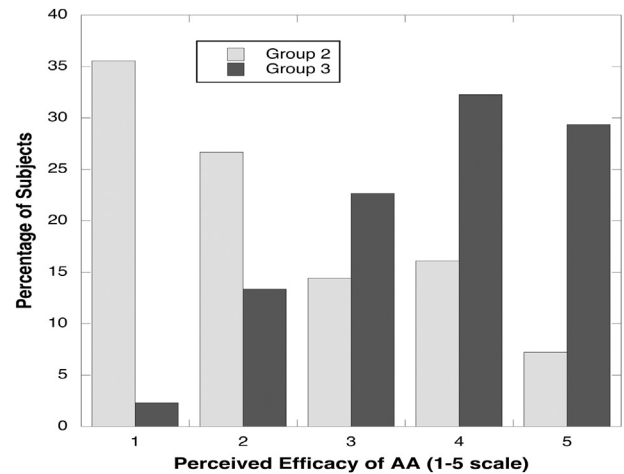


FIGURE 1. Patients remaining on 17- α -alkylated androgens (AA) (group 3) perceive the effectiveness of AA to be much greater than do patients who stopped using AA (group 2). Effectiveness is rated on a 5-point scale from 1 = not effective to 5 = highly effective.

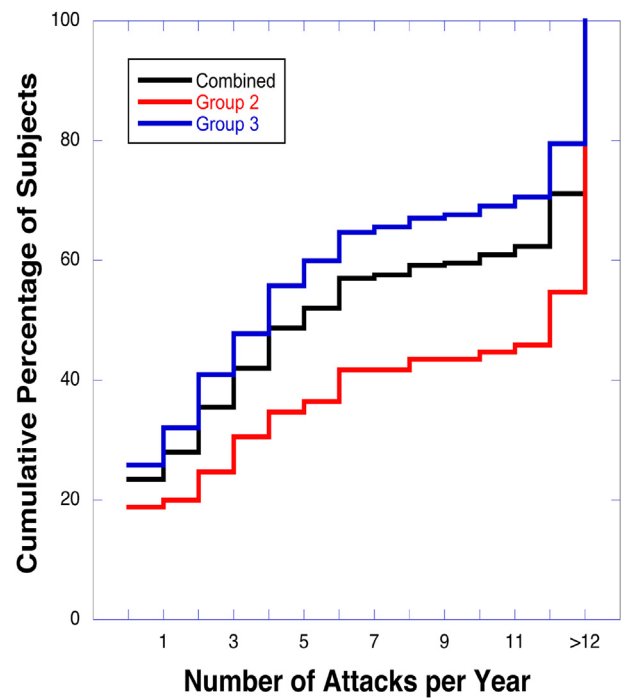


FIGURE 2. Distribution of the number of attacks per year while on 17- α -alkylated androgens (AA). The cumulative percentage of subjects with the indicated number of attacks per year is shown for the entire AA-treated population, subjects in group 2, and subjects in group 3. Although not directly comparable, the distribution of attacks per year while on plasma-derived C1 inhibitor (pdC1INH) is also shown.

moderate or worse and 2.8 ± 0.2 side effects that were severe or very severe. The percentage of subjects reporting at least one side effect varied with the severity of the side effect and was 85.9% for

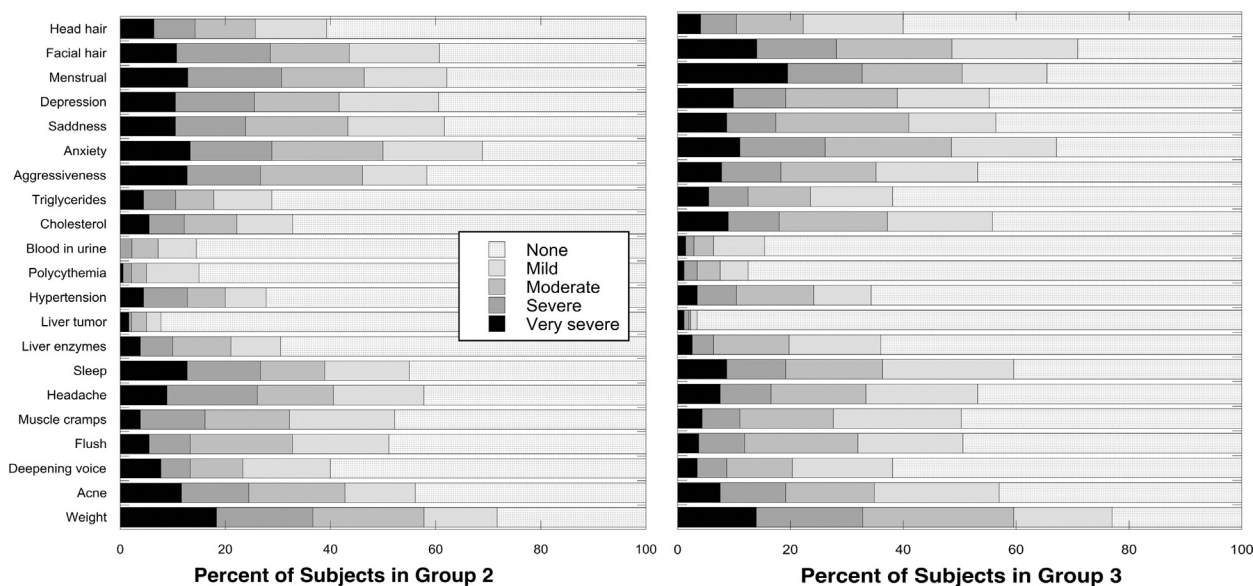
TABLE III. Side effects from AA

	Combined (524)	Prior AA (180)	Current AA (344)	Group 2 vs 3 <i>P</i> -value
Weight gain*	3 (2, 4), 2.84 ± 0.06, 59%	3 (1, 4), 2.84 ± 0.11, 58%	3 (2, 4), 2.83 ± 0.07, 60%	.2589
Anxiety	2 (1, 4), 2.56 ± 0.06, 49%	3 (1, 4), 2.61 ± 0.10, 50%	2 (1, 4), 2.53 ± 0.07, 49%	.9463
Menstrual abnormalities (women only)	2 (1, 4), 2.62 ± 0.08, 49%	2 (1, 4), 2.52 ± 0.12, 46%	3 (1, 4), 2.68 ± 0.10, 50%	.4059
Increased facial hair (women only)	2 (1, 4), 2.55 ± 0.07, 47%	2 (1, 4), 2.44 ± 0.12, 44%	2 (1, 4), 2.62 ± 0.09, 49%	.1507
Sadness	2 (1, 3), 2.29 ± 0.06, 42%	2 (1, 3), 2.39 ± 0.10, 43%	2 (1, 3), 2.24 ± 0.07, 41%	.2708
Depression	2 (1, 3), 2.28 ± 0.06, 40%	2 (1, 4), 2.38 ± 0.10, 42%	2 (1, 3), 2.23 ± 0.07, 39%	.2344
Aggressiveness	2 (1, 3), 2.25 ± 0.06, 39%	2 (1, 4), 2.44 ± 0.11, 46%	2 (1, 3), 2.15 ± 0.07, 35%	.0986
Acne or oily skin	2 (1, 3), 2.24 ± 0.06, 38%	2 (1, 3), 2.35 ± 0.11, 43%	2 (1, 3), 2.19 ± 0.07, 35%	.1065
Difficulty sleeping	2 (1, 3), 2.27 ± 0.06, 37%	2 (1, 4), 2.33 ± 0.11, 39%	2 (1, 3), 2.24 ± 0.07, 36%	.0760
Headaches	2 (1, 3), 2.19 ± 0.06, 36%	2 (1, 4), 2.33 ± 0.10, 41%	2 (1, 3), 2.11 ± 0.07, 33%	.0787
Elevated cholesterol	1 (1, 3), 2.04 ± 0.06, 32%	1 (1, 2), 1.73 ± 0.06, 22%	2 (1, 3), 2.27 ± 0.07, 37%	<.0001
Flushing	2 (1, 3), 2.00 ± 0.05, 32%	2 (1, 3), 2.03 ± 0.09, 33%	2 (1, 3), 1.98 ± 0.06, 32%	.9242
Muscle cramps	2 (1, 3), 1.97 ± 0.05, 29%	2 (1, 3), 2.04 ± 0.09, 32%	2 (1, 3), 1.93 ± 0.06, 28%	.3113
Head hair (women only)	1 (1, 2), 1.80 ± 0.06, 24%	1 (1, 3), 1.86 ± 0.11, 26%	1 (1, 2), 1.77 ± 0.07, 22%	.5924
High blood pressure	1 (1, 2), 1.70 ± 0.05, 23%	1 (1, 2), 1.65 ± 0.09, 20%	1 (1, 2), 1.72 ± 0.06, 24%	.1763
Elevated triglycerides	1 (1, 2), 1.73 ± 0.05, 22%	1 (1, 2), 1.62 ± 0.08, 18%	1 (1, 2), 1.80 ± 0.07, 24%	.3143
Deepening of the voice	1 (1, 2), 1.75 ± 0.05, 21%	1 (1, 2), 1.84 ± 0.09, 23%	1 (1, 2), 1.71 ± 0.06, 20%	.3045
Elevated liver enzymes	1 (1, 2), 1.65 ± 0.05, 20%	1 (1, 2), 1.66 ± 0.08, 21%	1 (1, 2), 1.65 ± 0.05, 20%	.1352
Too many RBC	1 (1, 1), 1.24 ± 0.03, 7%	1 (1, 1), 1.25 ± 0.05, 5%	1 (1, 1), 1.25 ± 0.04, 8%	.2101
Blood in urine	1 (1, 1), 1.25 ± 0.03, 7%	1 (1, 1), 1.25 ± 0.05, 7%	1 (1, 1), 1.26 ± 0.04, 6%	.3848
Liver tumors	1 (1, 1), 1.12 ± 0.03, 3%	1 (1, 1), 1.17 ± 0.05, 5%	1 (1, 1), 1.09 ± 0.03, 2%	.0667

AA, 17- α -Alkylated androgens; *IQR*, interquartile range; *RBC*, red blood cells; *SE*, standard error of the mean.

Bold type indicates statistical significance ($P < .05$).

*5-point scale (1 = no problem, 3 = moderate, and 5 = very severe problem); Data is median (*IQR*), mean $\pm$ SE, % ≥ 3 (moderate to severe). Analyzed by contingency table with Pearson test.

FIGURE 3. Side effect profile of 17- α -alkylated androgens (AA) in groups 2 and 3.

moderate or worse, 68.9% for severe or worse, and 42.6% for very severe. Groups 2 and 3 were again similar. In group 2, 83% experienced at least a moderate side effect, whereas 69% experienced a severe or very severe side effect. The average numbers of moderate and severe/very severe side effects among subjects in group 2 were 6.7 ± 0.5 and 3.9 ± 0.4 . In group 3, 87%

experienced at least a moderate side effect, whereas 69% experienced a severe or very severe side effect. The average numbers of moderate and severe/very severe side effects among subjects in group 3 were 6.3 ± 0.3 and 3.2 ± 0.2 .

When asked whether the side effects from AA outweighed their benefits, 77.9% of the subjects agreed, with 38.4% stating

TABLE IV. Relationships* between AA dose or exposure and reported side effects

	Relationship to AA dose		Relationship to AA treatment years	
	χ^2	P-value	χ^2	P-value
Weight gain*	9.28	.0544	6.90	.1411
Acne	11.83	.0186	8.81	.0661
Voice change	4.73	.3162	1.22	.8749
Flushing	3.88	.4232	13.18	.0104
Cramps	21.44	.0003	8.58	.0724
Headaches	18.44	.0010	17.34	.0017
Trouble sleeping	12.92	.0117	7.84	.0976
LFT elevations	11.00	.0265	22.78	.0001
Liver tumors	4.29	.3678	8.12	.0873
Elevated BP	21.63	.0002	16.96	.0020
Anemia	12.97	.0114	8.88	.0642
Blood in urine	2.40	.6630	13.44	.0093
Cholesterol	5.85	.2107	43.56	<.0001
Triglycerides	3.60	.4630	20.20	.0005
Aggressiveness	16.40	.0025	2.83	.5875
Anxiety	15.30	.0041	0.95	.9180
Sadness	19.34	.0007	4.19	.3814
Depression	22.97	.0001	5.31	.2570
Menstrual	19.47	.0006	6.24	.1818
Facial hair	4.77	.3113	22.53	.0002
Head hair	5.43	.3653	5.56	.3518

AA, 17- α -Alkylated androgens; LFT, liver function tests.Bold type indicates statistical significance ($P < .05$).

*Analyzed by logistic regression.

that this was true to a significant extent and 39.5% stating that this was true to a moderate or slight extent. Among subjects who stopped AA, 73.3% felt that the adverse effects outweighed the benefits with 42.2% stating that this was true to a significant extent. In subjects who remained on AA (group 3), 80.2% felt that the adverse effects outweighed the benefits with 36.3% stating that this was true to a significant extent.

Dose response effects

We then examined how the exposure to AA influenced effectiveness or tolerability, assessing both the dose of AA and the number of years of AA treatment. We found no evidence that a higher AA dose was associated with improved effectiveness (see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org). In fact, there was a small but nonsignificant inverse relationship ($R^2 = 0.0004$; $P = .3730$). Similarly, there was no relationship between AA dose and ED visits, hospitalizations, attack severity, or effect of HAE of life. We also observed no relationship between the duration of AA exposure and effectiveness parameters. In contrast, a significant correlation was observed between the AA dose and several of the side effects (Table IV). Among the strongest relationships were increasing mental health measures (anxiety, depression, sadness, aggressiveness), headaches, and hypertension with increased AA dose. Elevated cholesterol levels did not show a relationship with AA dose, but did with AA duration of exposure. Several side effect (liver function tests, hypertension, and headache) values were significantly related to both AA dose and exposure duration and

models incorporating both dose and length of exposure resulted in a stronger relationship.

DISCUSSION

Until late 2008, treatment of HAE in the United States was severely limited. AA were the primary drugs used for prophylactic treatment of HAE, and no reliably effective on-demand medicines were available to treat HAE attacks. Over the last 7 years, 5 new drugs have been approved for the treatment of HAE, and more are currently in clinical trials. The plethora of options now available require that physicians be able to make informed decisions about the optimal strategies for treating HAE patients. Continuing use of AA for HAE prophylaxis has remained controversial, with markedly different patterns of AA use observed between different countries and even between different HAE physicians. Physician opinions regarding the benefits and risks of AA can also be markedly disparate. It is clearly important and necessary to better define the underlying assumptions about the benefits and risks of AA. Although AA have been widely used to treat HAE for more than 40 years, relatively little known about their efficacy and tolerability. Much of the confusion about AA is attributable to the fact that HAE is an ultrarare disease.¹ Thus, it has been difficult to impossible for a single center to conduct adequate studies to address the role of AA for HAE prophylaxis. Only 2 randomized controlled studies of AA have been reported. One was an innovative crossover design that studied the effect of using 600 mg danazol per day in a total of 9 patients with HAE.¹⁰ The other was also a crossover design that studied the effect of using 10 mg methyltestosterone per day in a total of 4 patients with HAE.²¹ The largest previous study was a retrospective case study involving 118 AA exposed patients with HAE that reported the efficacy and side effects of AA therapy, but did not evaluate the impact of dose or compare different groups.²² In this report, we were able to assess the impact of AA in a cohort of 650 patients with HAE that included 524 patients who had used AA. The results provide a detailed picture of the benefits and risks of AA treatment in HAE, and may help guide decisions if and when AA use should be considered.

There is widespread agreement that AA reduce HAE attacks. Two small-randomized clinical studies, multiple mostly small open-label reports, and wide clinical experience have reported that AA reduce attack frequency in HAE.²³ Our data confirm the effectiveness of AA in reducing HAE attacks. Median attack frequency decreased from 24 (9, 36) before AA to 4 (1, 18) on AA ($P < .0001$). This 83% reduction in attack frequency is in close agreement with the 84% reduction found in the retrospective case series of 118 patients with HAE who took a mean dose of 171.2 mg danazol per day.²² We also found highly significant improvements in median severity of attacks, number of ED visits per year, hospital admissions due to HAE, and days using narcotic pain medicines. Furthermore, subjects reported that a significant lessening of the negative impact of HAE on their lives while taking AA.

For comparison purposes, we reanalyzed the patient-reported results from the previously published open-label extension of pdC1INH in 146 patients with HAE,²⁴ converting the data into the cumulative percentage of subjects with 0 to ≥ 12 attacks per year. At every attack number, there were a higher percentage of pdC1INH patients who achieved a response than either group 2 or group 3 of the AA treated subjects. It should also be noted that

almost half of the subjects were using pdC1INH at less than the recommended 1000 units twice/week dose (2000 units/week), and the average weekly dose of pdC1INH used in the 146 subjects was 1386 ± 34 units. As the open-label pdC1INH extension study was prospective, whereas the AA study was retrospective, we cannot statistically compare the patient-reported outcomes between these 2 studies. Despite these limitations, there does appear to be a larger percentage of subjects in both AA-treated groups who continue to have frequent attacks compared with the pdC1INH-treated subjects.

There is less agreement about the extent to which AA cause side effects, with some open-label studies suggesting that they are safe and well tolerated^{25,26} and others suggesting that they cause frequent side effects.²² We found that AA use was associated with reports of side effects in the vast majority of exposed subjects. At least 1 side effect that was of moderate or worse severity was attributed to AA in 86% of the subjects, and the average number of reported side effects that were moderate severity or worse was 5.2 ± 0.2 . The prior study by Bork in Germany reported that 78% of subjects experienced side effects, but the severity of these side effects was not reported. We found that 180 of the 524 AA-treated subjects (34%) discontinued AA. This is somewhat smaller than the percentage in Bork's study where 58 of 118 patients (49%) discontinued AA; however, pdC1INH was widely available in Germany while it was only available in clinical trials for our US subjects during the time frame of the investigation.

Critically, relatively little is known about the variability of individual patient responses to AA treatment. This study assessed this variability as well as the factors that contributed to the decisions on whether to continue or discontinue AA treatment. The 2 most commonly cited reasons for stopping AA in our study were lack of efficacy and side effects. Although AA did demonstrate effectiveness both in subjects who continued AA (group 3) and those who discontinued AA (group 2), the degree of effectiveness was significantly reduced in group 2 compared with group 3 despite the fact that the median AA dose was 100 mg/day of danazol in group 3 and 200 mg/day of danazol in group 2. Although our study was not designed to assess AA effectiveness dose responses, we did observe that a substantial subgroup of patients continued to swell despite taking high doses of AA. In contrast, there was a clear significant dose-dependent increase in side effects as the AA dose increased. Although group 2 subjects reported modest increases in the severity for most side effects, these did not reach statistical significance. Thus, it was the relatively reduced effectiveness rather than increased side effects that appeared to be the driver in the decision to stop AA treatment. The desire of the vast majority of subjects in group 3 who perceived substantial benefit from AA to discontinue AA once effective alternative medicines were available likely reflects the high prevalence of side effects in this group.

The decision to use AA for long-term prophylaxis needs to consider both efficacy and tolerability. HAE attacks can result in significant morbidity and mortality, and the goal of treatment needs to be restoring a normal life. When AA were one of the major available and FDA-approved options to accomplish this goal, patients would tolerate the risk and side effects as the benefit of AA therapy outweighed the risks. In today's environment, however, the risk to benefit ratio needs to account for the very high prevalence of moderate and severe side effects associated with AA use. Because of these side effects, AA are generally

considered contraindicated in pregnant or breastfeeding women, and are relatively contraindicated in children.²⁷⁻³⁰ A recent consensus paper by the US HAEA Medical Advisory Board urged caution in the use of AA for women in general.³¹ Although low-dose AA may be more acceptable in men, it is incumbent on the physician to closely monitor for side effects. The overall approach to the management of HAE has also shifted with the availability of effective on-demand treatments. The ability to manage HAE attacks using on-demand medicines means that many patients who previously would select long-term prophylactic treatment with AA despite their side effects now have other options.

Currently, the 2 major HAE prophylactic medicines are AA and pdC1INH. The lack of head-to-head comparisons between different HAE medicines makes it difficult to assess relative benefits and risks. We used data from the previously published patient-reported open-label pdC1INH prophylaxis study²⁴ to compare with AA prophylaxis. As graphically displayed in Figure 2, pdC1INH provided similar if not superior reduction in attack frequency compared with AA. High efficacy for pdC1INH was also reported even in patients who continued to have frequent HAE attacks on AA.³² Although we did not have comparable tolerability data, the high incidence of multiple severe side effects in the AA treated patients compared with the low incidence of reported side effects in the pdC1INH study is striking.

As shown in Figure 2, a minority of AA-treated patients achieved complete or near complete reduction in attacks. Considering that there was no obvious relationship between AA dose and effectiveness, whereas there was a clear dose relationship with side effects, it is worth speculating whether there could be an AA dose low enough to still provide benefit but without side effects in a select subgroup of patients with HAE. This question could not be addressed in this study and has not been explicitly studied in other reports. In this study, there were 48 subjects in group 3 (currently taking AA) who were using less than 50 mg/day equivalent of danazol. Although the number and severity of side effects was reduced, 73% of them reported having >12 attacks/year, whereas the remaining 27% reported no attacks. Considering that the mechanism(s) by which AA reduce attack frequency and severity in HAE are unknown, it is difficult to predict how many patients might benefit from this type of approach, but our data suggest that it is a very small subset. Given the inability to predict which patient may benefit from low-dose AA without experiencing significant side effects, our data would suggest considerable caution in recommending AA to patients.

Our study does have limitations. This was a cross-sectional retrospective. We cannot, therefore, address recall or selection bias and the study would not be expected to be sensitive to dynamic changes from changes in AA dose. Furthermore, there was a significant overrepresentation of female subjects. Finally, there are inherent issues with patient-reported data, particularly related to lack of certainty concerning the correct HAE diagnosis. We attempted to use stringent inclusion and exclusion criteria to limit the study to subjects with type I/II HAE, but acknowledged the difficulty in knowing if any subjects with other types of angioedema were inappropriately included in the analysis. The large size of the subject population and the use of patient-reported outcomes are strengths of the approach help mitigate the limitations. Although there are issues of reporting accuracy and recall bias associated with patient reporting, physician reporting of patient attack data may also be subject to significant

accuracy concerns due to incomplete data as well as the tendency of patients to underreport attacks to physicians. We recently reported that results from a large retrospective patient-reported study yielded results that were almost identical with outcomes of a prospective analysis using the identical burden of disease questions, thus underscoring the value of the patient centric approach.¹⁷ It is also striking how closely our data parallel the retrospective case series of the effects of AA in HAE.²²

In summary, we show that the effectiveness of AA prophylactic treatment for HAE is highly variable, and that side effects are very common and dose related. In addition, our results highlight that the side effects experienced by patients using AA are usually multiple and severe. Our data suggest that physicians should exercise caution before increasing the AA dose in patients who fail to respond well to low or standard doses (≤ 200 mg/day of danazol). In view of the dose-related side effects of AA, these patients may be better managed using an alternative strategy. Considering the improved benefit and safety of pdC1INH relative to AA, we suggest that women and children not be treated with AA, and that AA therapy in male patients if considered at all be limited to the lowest effective dose, but not exceeding danazol 200 mg/day (or equivalent). Men who experience side effects from low-dose AA should be switched to an alternative management program. It is essential that the physician have an informed dialog with any patient about the potential benefits and risks of the treatments before selection of a prophylactic therapy. With the improved safety and efficacy profile of pdC1INH, the availability of effective on-demand treatments, and the promise of new more convenient long-term prophylactic options, the role of AA in the overall management of HAE will likely continue to decline.

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Questionnaire #1: Background

1-1) I am a (please check one)

☐ male ☐ female

1-2) How old are you? (in years)

1-3) To the best of your recollection, how old (in years) were you when you first began to have HAE symptoms?

1-4) How old (in years) were you when your HAE was first diagnosed by a physician?

1-5) I was diagnosed with (check one)

☐ Type I HAE ☐ Type II HAE ☐ don't know

1-6) Are you currently receiving treatment for you attacks at a clinical trial center?

☐ Yes ☐ No

if yes:

Which clinical trial?

Pharming C1 Inhibitor

Lev Pharma C1 Inhibitor

Jerini's Icatibant

Dyax Corporation DX-88

CSL Behring C1 Inhibitor

if no:

Are you currently being treated at home with imported C1 inhibitor ?

☐ Yes ☐ No

1-7) Have you ever used anabolic androgens (also known as androgens) such as

Danazol (danocrine), Winstrol (stanozolol), Oxandrin (oxandrolone), or

Methyltestosterone to treat your HAE?

☐ Yes ☐ No (if no, go to questionnaire #4: "Never used androgens")

1-8) To the best of your recollection, how old (in years) were you when you first began taking androgens to treat your HAE?

1-9) Are you still taking androgens?

☐ Yes ☐ No (if yes, go to questionnaire #2: "Currently using androgens"; If no go to questionnaire #3 "Previously used androgens")

FIGURE E1. Online background questionnaire. All subjects completed the background questionnaire first. Based on responses to this questionnaire, subjects were then routed to 1 of the 3 additional questionnaires.

Questionnaire 2: Currently using androgens

2-1) Which androgen are you currently using? (pick list as below]

Danazol (danocrine)

Winstrol (stanozolol)

Oxandrin (oxandrolone)

Methyltestosterone)

Other (list): _____

2-2) What is the dose of the androgen you are currently using? Indicate either the number of mg (preferred) or the number of tablets.

2-2a) How often do you take your androgen? (*every day; less often than daily*)

2-2b) If you take androgen less often than daily, how many days between doses?

2-3) As best you can recall, how many years have you been using androgens of any type?

2-4) Did you have a HAE attack in the year before you began taking androgens? (*yes; no*)

2-5) To the best of your recollection, please estimate how often, on average, you had HAE attacks in the year before you began taking androgens?

2-5a) Focusing on the attacks that you had in the year before taking androgens, how often do you estimate your attacks involved the following body parts: (*1, all of the time; 2, most of the time; 3, some of the time; 4, a little of the time; 5, none of the time*):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

2-6) Did you have a hereditary angioedema attack during the last 12 months while you've been taking androgens? (*yes; no*)

FIGURE E2. Online questionnaire for subjects who reported that they were currently taking 17- α -alkylated androgens at the time they filled out the background questionnaire.

2-7) To the best of your recollection, please estimate how often, on average, you had HAE attacks during the last 12 months while you have been taking androgens

2-7a) Focusing on the attacks that you had in the past, during the last 12 months while you've been taking androgens, how often do you estimate your attacks involved the following body parts: (1, *all of the time*; 2, *most of the time*; 3, *some of the time*; 4, *a little of the time*; 5, *none of the time*):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

2-8) Overall, how severe would you consider your hereditary angioedema attacks? Please rate the severity on a scale of 1 to 5, with 1 being very mild and 5 being very severe?

In the year before you began taking androgens

During the last 12 months while you've been taking androgens

2-9) Have you ever gone to the emergency room to seek treatment for attacks of hereditary angioedema? (*yes*; *no*)

2-9a) Please provide an estimate of the number of times you have gone to the emergency room to seek treatment for attacks of hereditary angioedema.

When you were not taking androgens

During the time while you've been taking androgens

2-10) Regardless of whether you were seen in the emergency room, have you ever been admitted to the hospital because of an attack of hereditary angioedema? (*yes*; *no* – *if no skip to 2-14*)

2-10a) Were you admitted to the hospital for attacks of hereditary angioedema during the time when you were not taking androgens? (*yes*; *no* – *if no, skip to 2-12*)

2-11) Please provide an estimate of the number of times you have been admitted to the hospital for attacks of hereditary angioedema, when you were not taking androgens.

FIGURE E2. (CONTINUED).

2-11a) Focusing on the admissions to the hospital that you have had in the past, when you were not taking androgens, how often would you estimate your admissions involved swelling of the following body parts: (1, *all of the time*; 2, *most of the time*; 3, *some of the time*; 4, *a little of the time*; 5, *none of the time*):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

2-12) Were you admitted to the hospital for attacks of hereditary angioedema during the time while you have been taking androgens? (*yes*; *no – if no, skip to 2-14*)

2-13) Please provide an estimate of the number of times you have been admitted to the hospital for attacks of hereditary angioedema, during the time while you've been taking androgens.

2-13a) Focusing on the admissions to the hospital that you have had in the past, during the time while you've been taking androgens, how often would you estimate your admissions involved swelling of the following body parts: (1, *all of the time*; 2, *most of the time*; 3, *some of the time*; 4, *a little of the time*; 5, *none of the time*):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

2-14) Have you ever been intubated (tube inserted in your throat to help you breathe) for an attack of laryngeal angioedema? (*yes*; *no – if no skip to 2-15*)

2-14a) How many times have you been intubated for laryngeal angioedema in your lifetime? (1-*none*; 2-*once*; 3-*twice*; 4-*>2times*)

When you were not taking androgens

FIGURE E2. (CONTINUED).

During the time while you've been taking androgens

2-14b) Have you ever had an emergency tracheostomy (surgical incision in the neck to open an airway in the windpipe so you could breathe) for an attack of laryngeal angioedema? (yes, no - if no, skip to 2-15)

2-14c) How many times have you had a tracheostomy for laryngeal angioedema in your lifetime? (1-none; 2 - once; 3-twice; 4 - >2times)

When you were not taking androgens

During the time while you've been taking androgens

2-15) Have you ever had abdominal surgery for what you now know was a hereditary angioedema attack? (yes; no)

2-16) Have you ever taken prescription pain medication for an attack of hereditary angioedema? (yes; no - skip to 2-17)

2-16a) How many days in a year would you estimate that you require prescription pain medications for your hereditary angioedema

When you were not taking androgens

During the time while you've been taking androgens

2-16b) Which pain medications have you used for hereditary angioedema attacks? (check all that apply)

Morphine, Codeine, Hydrocodone, Fentanyl, Methadone, Percocet, Vicodin, Other: ____

2-17) To what degree has your HAE affected your life? (1, no effect; 2, mild effect; 3, moderate effect; 4, severe effect; very severe effect)

In the year before you began taking androgens

During the last 12 months while you've been taking androgens

2-18) How would you rate the overall effectiveness of androgens in preventing your HAE attacks on a scale of 1 to 5 with 1 being not effective at all and 5 being highly effective?

2-19) Please rate the extent to which you have experienced any of the following side effects from taking androgen medications: (1, no problem; 2, some problem; 3, moderate problem; 4, severe problem; 5, very severe problem)

FIGURE E2. (CONTINUED).

Weight gain; Acne or oily skin; Deepening of the voice; Flushing; Muscle cramps; Headaches; Difficulty sleeping; Elevated liver enzymes; Liver tumors; High blood pressure; Too many red blood cells (polycythemia); Traces of blood in urine; Elevated cholesterol levels; Elevated triglycerides; Aggressiveness; Anxiety; Sadness; Depression

2-19a) Additional possible side effects for females: (1, no problem; 2, some problem; 3, moderate problem; 4, severe problem; 5, very severe problem)

Changes in menstrual cycle; Unnatural hair growth; Thinning hair (on the head)

2-19b) Please list and rate any other side effects from taking androgen medications, that were not included in the previous list. (1, no problem; 2, some problem; 3, moderate problem; 4, severe problem; 5, very severe problem)

2-20) Overall, do you feel that the side effects from taking androgens outweigh the benefits from taking androgens?

1- absolutely; 2- to significant extent; 3- to moderate extent; 4- to slight extent; 5- not at all

The next three questions ask you to provide your opinion on what you might choose to do if new HAE medicines were approved in the United States.

2-21) If an effective therapy for HAE attacks were approved and available, I would want to stop taking the androgen medication I now use to control swelling attacks

1- not at all; 2- probably not; 3- possibly; 4- probably; 5- absolutely

2-22) If an effective therapy for HAE attacks were approved and available, I would want to reduce the amount of androgens I use to control swelling attacks.

1- not at all; 2- probably not; 3- possibly; 4- probably; 5- absolutely

2-23) If an effective therapy for HAE attacks were approved and available, I would want to continue to take my androgen medication at the same dose I now use to control swelling attacks and use the new medicine to treat any breakthrough attacks.

1- not at all; 2- probably not; 3- possibly; 4- probably; 5- absolutely

Are there any other comments you would like to make regarding the long term use of androgens for preventing HAE attacks?

FIGURE E2. (CONTINUED).

Questionnaire 3: Previously used androgens but not currently using androgens

3-1) Which androgens did you use in the past? (pick all that apply)

Danazol (danocrine)

Winstrol (stanozolol)

Oxandrin (oxandrolone)

Methyltestosterone

Other (list): _____

3-2) Which androgen did you use most recently? (pick one)

Danazol (danocrine)

Winstrol (stanozolol)

Oxandrin (oxandrolone)

Methyltestosterone

Other (list): _____

3-3) What was the dose of the last androgen that you used? Indicate either the number of mg (preferred) or the number of tablets.

3-3a) How often do you take your androgen? (*every day; less often than daily*)

3-3b) If you take androgen less often than daily, how many days between doses?

3-4) When did you stop taking this androgen? (*month, year*)

3-5) What were the main reasons that caused you to stop using androgens? (check all that apply)

___ *They were not effective enough*

___ *Their side effects were too severe*

___ *I enrolled in a clinical trial*

___ *I began home treatment with imported CI inhibitor*

___ *I reduced my dose and did not have attacks, so I completely went off the medicine*

___ *Other, please explain:* _____

FIGURE E3. Online questionnaire for subjects who reported that they had previously taken 17- α -alkylated androgens but had stopped at the time they filled out the background questionnaire.

3-6) Did you have any HAE attacks before taking androgens? (yes; no – skip to 3-8)

3-7) To the best of your recollection, please estimate how often you had HAE attacks before you began taking androgens.

3-7a) Focusing on the attacks that you had in the past, before taking androgens, how often do you estimate your attacks involved the following body parts: (1, all of the time; 2, most of the time; 3, some of the time; 4, a little of the time; 5, none of the time):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

3-8) Did you have any HAE attacks while you were taking androgens? (yes; no – skip to 3-10)

3-9) To the best of your recollection, please estimate how often you had HAE attacks while you were taking androgens.

3-9a) Focusing on the attacks that you had in the past, while you were taking androgens, how often do you estimate your attacks involved the following body parts: (1, all of the time; 2, most of the time; 3, some of the time; 4, a little of the time; 5, none of the time):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

3-10) Have you had any hereditary angioedema attacks since you have stopped taking androgens? (yes; no – skip to 3-12)

3-11) To the best of your recollection, please estimate how often you have had HAE attacks since you have stopped taking androgens.

FIGURE E3. (CONTINUED).

3-11a) Focusing on the attacks that you had in the past, since you have stopped taking androgens, how often do you estimate your attacks involved the following body parts: (1, *all of the time*; 2, *most of the time*; 3, *some of the time*; 4, *a little of the time*; 5, *none of the time*):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

3-12) Overall, how severe would you consider your angioedema attacks? Please rate the severity on a scale of 1 to 5, with 1 being very mild and 5 being very severe

a) Before you took androgens:

b) While you were taking androgens:

c) Since you stopped taking androgens:

3-13) Have you ever gone to the emergency room to seek treatment for attacks of hereditary angioedema? (*yes, no – skip to 3-14*)

3-13a) Please provide an estimate of the number of times you have gone to the emergency room to seek treatment for attacks of hereditary angioedema.

a) Before you took androgens:

b) While you were taking androgens:

c) Since you stopped taking androgens:

c) Since you stopped taking androgens:

3-14) Regardless of whether you were seen in the emergency room, have you ever been admitted to the hospital because of an attack of hereditary angioedema? (*yes, no – skip to 3-21*)

3-15) Were you ever admitted to the hospital because of an attack of hereditary angioedema before you took androgens? (*yes, no – skip to 3-17*)

3-16) Please provide an estimate of the number of times you have been admitted to the hospital for attacks of hereditary angioedema, before you took androgens.

FIGURE E3. (CONTINUED).

3-16a) Focusing on the admissions to the hospital that you have had in the past, before you took androgens, how often would you estimate your admissions involved swelling of the following body parts: (1, *all of the time*; 2, *most of the time*; 3, *some of the time*; 4, *a little of the time*; 5, *none of the time*):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

3-17) Were you ever admitted to the hospital because of an attack of hereditary angioedema while you were taking androgens? (*yes, no – skip to 3-19*)

3-18) Please provide an estimate of the number of times you have been admitted to the hospital for attacks of hereditary angioedema, while you were taking androgens.

3-18a) Focusing on the admissions to the hospital that you have had in the past, while you were taking androgens, how often would you estimate your admissions involved swelling of the following body parts: (1, *all of the time*; 2, *most of the time*; 3, *some of the time*; 4, *a little of the time*; 5, *none of the time*):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

3-19) Were you ever admitted to the hospital because of an attack of hereditary angioedema since you stopped taking androgens? (*yes, no – skip to 3-21*)

3-20) Please provide an estimate of the number of times you have been admitted to the hospital for attacks of hereditary angioedema, since you stopped taking androgens.

FIGURE E3. (CONTINUED).

3-20a) Focusing on the admissions to the hospital that you have had in the past, since you stopped taking androgens, how often would you estimate your admissions involved swelling of the following body parts: (1, *all of the time*; 2, *most of the time*; 3, *some of the time*; 4, *a little of the time*; 5, *none of the time*):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

3-21) Have you ever been intubated (tube inserted in your throat to help you breathe) for an attack of laryngeal angioedema? (*yes*; *no – if no skip to 3-22*)

3-21a) Please provide an estimate of the number of times you have been intubated for laryngeal angioedema in your lifetime. (1-*none*; 2 – *once*; 3-*twice*; 4 - *>2times*)

a) Before you took androgens:

b) While you were taking androgens:

c) Since you stopped taking androgens:

3-21b) Have you ever had an emergency tracheostomy (surgical incision in the neck to open an airway in the windpipe so you could breathe) for an attack of laryngeal angioedema? (*yes*; *no – if no skip to 3-22*)

3-21c) How many times have you had a tracheostomy for laryngeal angioedema in your lifetime? (1-*none*; 2 – *once*; 3-*twice*; 4 - *>2times*)

a) Before you took androgens:

b) While you were taking androgens:

c) Since you stopped taking androgens:

3-22) Have you ever had abdominal surgery for what you now know was a hereditary angioedema attack? (*yes*, *no*)

3-23) Have you ever taken prescription pain medication for an attack of hereditary angioedema? (*yes*; *no – skip to 3-24*)

FIGURE E3. (CONTINUED).

3-23a) How many days in a year would you estimate that you require prescription pain medications for your hereditary angioedema?

a) Before you took androgens:

b) While you were taking androgens:

c) Since you stopped taking androgens:

3-23b) Which pain medications have you used for hereditary angioedema attacks? (check all that apply)

Morphine, Codeine, Hydrocodone, Fentanyl, Methadone, Percocet, Vicodin, Other: ____

3-24) To what degree has your HAE affected your life? (*1, no effect; 2, mild effect; 3, moderate effect; 4, severe effect; very severe effect*)

a) Before you took androgens:

b) While you were taking androgens:

c) Since you stopped taking androgens:

3-25) How would you rate the overall effectiveness of androgens in preventing your HAE attacks on a scale of 1 to 5 with 1 being not effective at all and 5 being highly effective?

3-26) Please rate the extent to which you have experienced any of the following side effects from taking androgen medications: (*1, no problem; 2, some problem; 3, moderate problem; 4, severe problem; 5, very severe problem*)

Weight gain; Acne or oily skin; Deepening of the voice; Flushing; Muscle cramps; Headaches; Difficulty sleeping; Elevated liver enzymes; Liver tumors; High blood pressure; Too many red blood cells (polycythemia); Traces of blood in urine; Elevated cholesterol levels; Elevated triglycerides; Aggressiveness; Anxiety; Sadness; Depression

3-26a) Additional possible side effects for females: (*1, no problem; 2, some problem; 3, moderate problem; 4, severe problem; 5, very severe problem*)

Changes in menstrual cycle; Unnatural hair growth; Thinning hair (on the head)

3-26b) Please list and rate any other side effects from taking androgen medications, that were not included in the previous list. (*1, no problem; 2, some problem; 3, moderate problem; 4, severe problem; 5, very severe problem*)

3-27) Overall, do you feel that the side effects from taking androgens outweigh the benefits from taking androgens?

1- absolutely; 2- to significant extent; 3- to moderate extent; 4- to slight extent; 5- not at all

Are there any other comments you would like to make regarding the long term use of androgens for preventing HAE attacks?

FIGURE E3. (CONTINUED).

Questionnaire 4: Never used androgens

4-1) To the best of your recollection, please estimate how often, on average, you have HAE attacks in the past 12 months.

4-1a) Focusing on the attacks that you had in the past 12 months, how often do you estimate your attacks involved the following body parts: (1, *all of the time*; 2, *most of the time*; 3, *some of the time*; 4, *a little of the time*; 5, *none of the time*):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

4-2) Overall, how severe would you consider your hereditary angioedema attacks? Please rate the severity on a scale of 1 to 5, with 1 being very mild and 5 being very severe?

4-3) Have you ever gone to the emergency room to seek treatment for attacks of hereditary angioedema? (yes; no – skip to 4-4)

4-3a) Please provide an estimate of the number of times you have gone to the emergency room to seek treatment for attacks of hereditary angioedema.

4-4) Regardless of whether you were seen in the emergency room, have you ever been admitted to the hospital because of an attack of hereditary angioedema? (yes; no – if no skip to 4-6)

4-5) Please provide an estimate of the number of times you have been admitted to the hospital for attacks of hereditary angioedema.

4-5a) Focusing on the admissions to the hospital that you have had in the past, how often would you estimate your admissions involved swelling of the following body parts: (1, *all of the time*; 2, *most of the time*; 3, *some of the time*; 4, *a little of the time*; 5, *none of the time*):

Extremities (arms/legs/hands/feet)

Trunk (buttocks/flank (side)/back/chest)

Genitourinary (scrotal/vaginal)

Abdominal (stomach)

FIGURE E4. Online questionnaire for subjects who reported that they had never taken 17- α -alkylated androgens at the time they filled out the background questionnaire.

Facial (cheeks/neck/lips/eyes)

Oropharynx (mouth/throat)

4-6) Have you ever been intubated (tube inserted in your throat to help you breathe) for an attack of laryngeal angioedema? (*yes; no – if no skip to 4-7*)

4-6a) How many times have you been intubated for laryngeal angioedema in your lifetime? (*1-none; 2 – once; 3-twice; 4 - >2times*)

4-6b) Have you ever had an emergency tracheostomy (surgical incision in the neck to open an airway in the windpipe so you could breathe) for an attack of laryngeal angioedema? (*yes, no – if no, skip to 4-7*)

4-6c) How many times have you had a tracheostomy for laryngeal angioedema in your lifetime? (*1-none; 2 – once; 3-twice; 4 - >2times*)

When you were not taking androgens

During the time while you've been taking androgens

4-7) Have you ever had abdominal surgery for what you now know was a hereditary angioedema attack? (*yes; no*)

4-8) Have you ever taken prescription pain medication for an attack of hereditary angioedema? (*yes; no – skip to 4-9*)

4-8a) Over the past 12 months, how many days in a year would you estimate that you require prescription pain medications for your hereditary angioedema

4-8b) Which pain medications have you used for hereditary angioedema attacks during the past 12 months? (check all that apply)

Morphine, Codeine, Hydrocodone, Fentanyl, Methadone, Percocet, Vicodin, Other: ____

4-9) To what degree has your HAE affected your life? (*1, no effect; 2,mild effect; 3, moderate effect; 4, severe effect; very severe effect*)

Are there any other comments you would like to make regarding the long term use of androgens for preventing HAE attacks?

FIGURE E4. (CONTINUED).

TABLE E1. Impact of AA dose on attack frequency

AA dose	Group	Number of attacks per year					
		0	1	2-3	4-6	7-12	>12
All doses	All (505)*	23.56	4.55	14.06	15.05	14.26	28.51
	Group 2 (168)	19.05	1.19	10.71	11.31	13.10	44.64
	Group 3 (337)	25.82	6.23	15.73	16.91	14.84	20.47
≤50 mg/d	All (114)	21.05	7.02	14.04	17.54	21.05	19.3
	Group 2 (31)	12.90	0.00	12.90	22.58	19.35	32.26
	Group 3 (83)	24.10	9.64	14.46	15.66	21.69	14.46
≤100 mg/d	All (123)	28.46	1.63	18.70	16.26	15.45	19.51
	Group 2 (31)	22.58%	0.00%	19.35%	16.13%	12.90%	29.03%
	Group 3 (92)	30.43%	2.17%	18.48%	16.30%	16.30%	16.30%
≤200 mg/d	All (136)	18.38	8.09	14.71	16.18	13.24	29.41
	Group 2 (35)	8.57	2.86	11.43	14.29	20.00	42.86
	Group 3 (101)	21.78	9.90	15.84	16.83	10.89	24.75
>200 mg/d	All (104)	21.15	1.92	8.65	12.5	8.65	47.12
	Group 2 (45)	11.11	2.22	2.22	2.22	8.89	73.33
	Group 3 (59)	28.81	1.69	13.56	20.34	8.47	27.12

AA, 17- α -Alkylated androgens.

*Among the 505 subjects in groups 2/3, 477 were able to provide the AA dose.

TABLE E2. Location of swelling

	Extremities	Trunk	GU	Abdomen	Face	Airway
Attacks before AA						
Combined	2 (2, 3)*	4 (3, 5)	4 (3, 4)	2 (1, 3)	4 (3, 5)	4 (4, 5)
Group 2	2 (2, 3)	4 (3, 5)	4 (3, 4)	2 (1, 3)	4 (3, 4)	4 (3, 5)
Group 3	2 (2, 3)	4 (3, 5)	4 (3, 5)	2 (1, 3)	4 (3, 5)	4 (3, 5)
Attacks on AA						
Combined	2 (2, 3)	4 (3, 5)	4 (3, 5)	2 (1, 3)	4 (3, 5)	5 (4, 5)
Group 2	2 (2, 3)	4 (3, 5)	4 (3, 4)	2 (2, 3)	4 (3, 5)	4 (3, 5)
Group 3	2 (2, 4)	5 (3, 5)	4 (3, 5)	2 (1, 4)	5 (4, 5)	5 (4, 5)
Attacks off AA						
Combined	2 (2, 3)	4 (3, 5)	4 (3, 5)	2 (2, 3)	4 (3, 5)	4 (3, 5)
Group 2	2 (2, 3)	4 (3, 5)	4 (3, 5)	2.5 (2, 3)	3 (2, 4)	4 (3, 5)
Group 3	2 (1.5, 3)	4 (3, 5)	4 (3, 4)	2 (1, 3)	4 (3, 5)	4 (3, 5)

AA, 17- α -Alkylated androgens; GU, genitourinary.

*5-point scale, where 1 = all of the time, 2 = most of the time, 3 = some of the time, 4 = rarely, and 5 = never.

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