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# Impact of Anabolic Androgens on The Response to C1 Inhibitor Prophylaxis in Patients with HAE

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**ABSTRACT**

**Background:** Nanofiltered C1 inhibitor (C1INH-nf) has been shown to be effective for the long-term prophylaxis of hereditary angioedema (HAE). Due to increasing concerns about the safety of anabolic androgens, many patients previously receiving anabolic androgens for long-term prophylaxis are being switched to C1INH-nf. Little is known about the impact of existing anabolic androgen treatment on the efficacy of C1INH-nf prophylaxis or whether it is appropriate to discontinue anabolic androgens in patients being started on C1INH-nf.

**Objective:** To assess the impact of existing anabolic androgen prophylaxis on the efficacy of subsequent C1INH-nf prophylaxis.

**Methods:** This is a retrospective analysis of the data from two prior trials of C1INH-nf, including the phase 3 double-blind randomized trial and the open-label extension trial of C1INH-nf for the prevention of hereditary angioedema attacks

**Results:** C1INH-nf was effective for long-term prevention of HAE even in patients who had previously been on anabolic androgens. The effectiveness of C1INH-nf was not diminished even after discontinuation of anabolic androgens.

**Conclusion:** The decision to use long-term prophylaxis should be based on a comprehensive individualized management plan for each patient. Long-term prophylaxis with C1INH-nf can be initiated irrespective of the past history of androgen use, and anabolic androgens can be discontinued without reducing the efficacy of C1INH-nf.

## INTRODUCTION

Hereditary angioedema due to C1 inhibitor (C1INH) deficiency (HAE) is characterized by recurrent episodes of angioedema that may be associated with significant morbidity and mortality.[1] Because of this, many HAE patients have been managed with prophylactic treatment designed to prevent attacks from occurring. Until 2008, the only drugs available for HAE prophylaxis were antifibrinolytic agents and 17α-alkylated androgens (anabolic androgens).[2,3] Because anabolic androgens were recognized to be more effective than antifibrinolytics,[4] most patients on long-term prophylaxis used anabolic androgens. Randomized and open-label studies of a nanofiltered plasma-derived C1-inhibitor concentrate (C1INH-nf, Cinryze, Shire plc) provided evidence that C1INH-nf was safe and effective for the long-term prophylaxis of HAE. In 2008, C1INH-nf was licensed for HAE prophylaxis.

Many HAE patients have been switched from anabolic androgens to C1INH-nf prophylaxis because of the safety and efficacy profile of C1INH-nf [5-8] as well as the side effects from anabolic androgens.[9] Little is known, however, regarding the efficacy of prophylactic C1INH-nf in HAE patients who discontinue use of anabolic androgens. Since anabolic androgens are typically used in patients with relatively severe HAE, it is possible that patients taking anabolic androgens would experience reduced efficacy of C1INH-nf compared to patients not taking anabolic androgens. Since discontinuation of anabolic androgens may result in a worsening of attack frequency and severity, the safety of stopping anabolic androgens to start prophylactic C1INH-nf is also an important question that needs to be clarified.

Neither the randomized nor the open-label C1INH-nf long-term prophylaxis trials excluded concomitant use of anabolic androgens. We were able to address, therefore, how the use of anabolic androgens impacted the outcomes of study patients. We analyzed the efficacy of C1INH-nf in patients who were using anabolic androgens at the time they enrolled in either the randomized or open-

label C1INH-nf studies whether they continued, discontinued or tapered the anabolic androgens. We observed that C1INH83 nf was equally effective in patients not using androgens as it was in patients who were taking androgens, and that discontinuation of androgens did not reduce the efficacy of C1INH-nf.

## METHODS

This is a retrospective analysis of the data from the phase 3 double-blind randomized [6] and open-label [5] trials of C1INH-nf for the prevention of hereditary angioedema attacks. The phase 3 double-blind randomized trial was a crossover study involving 22 subjects with 12-week C1INH-nf (1,000 units twice weekly) or placebo arms. The open label C1INH-nf study involved 146 subjects taking C1INH-nf (1,000 units every 3-7 days) for up to 2.6 years. Each study was approved by the Institutional Review Board for each participating site. Data analysis was performed by the first author.

## STATISTICS

Results are reported as mean ± standard error of the mean (SEM) or median with interquartile range (IQR). Statistical analysis of differences between groups was performed using the Wilcoxon signed-rank test. Bivariate regressions were analyzed by analysis of variance (ANOVA). A P value of less than 0.05 was considered statistically significant. Statistical analyses were performed using JMP 9 (SAS, Cary, NC).

## RESULTS

### *Impact of anabolic androgens in the randomized C1INH-nf study*

Eight of 22 subjects (36.4%) were using an anabolic androgen at the screening visit (prior to study entry) in the C1INH-nf randomized prophylactic trial. Five of the 8 subjects chose to discontinue their anabolic androgens during the run-in phase, and the remaining 3 subjects continued the same dose of androgens throughout the entire study. The anabolic androgens used as well as their doses and the subjects' historical attack rates (determined at the screening visit) are shown in **Table 1**. Subjects taking anabolic androgens at the time of the screening visit had a median of 12 (11.3,15.0) attacks per 12 weeks, compared to 10.5 (6.0,12.0) attacks per 12 weeks in subjects not taking anabolic androgens.

We observed a significant correlation between the patient reported historical attack rate and the attack rate observed during the placebo arm ($R^2$=0.20; p=.034). Subjects who were not using anabolic androgens had similar historical (10.5 [6.0,12.0]) and placebo (11.0 [8.2,14.2]) attack rates. Subjects who discontinued anabolic androgens experienced an increase in attack rate from the historical rate of 12.0 (11.3,15.0) to a placebo arm rate of 16.4 (11.9,19.3). The 3 subjects who continued their anabolic androgens at the same dose also reported an increase in attack rate from a historical median of 12.0 (10.5,18.0) to 15.6 (14.0,16.2) during the placebo period.

**Table 1. Subjects in randomized trial using androgens**

| Group | Anabolic Androgen | Dose | Historical Attack Rate * | Placebo Attack Rate ** |
|---|---|---|---|---|
| Discontinued | Danazol | 150 mg/day | 6 | 8.2 |
| Discontinued | Danazol | 100 mg/day | 12 | 11.9 |
| Discontinued | Danazol | 100 mg/day | 12 | 19.3 |
| Discontinued | Stanozolol | 2 mg qd-tid | 12 | 16.4 |
| Discontinued | Stanozolol | 2 mg qd-tid | 24 | 19.5 |
| Continued | Oxandrolone | 2.5 mg/day | 9 | 12.5 |
| Continued | Oxandrolone | 2.5 mg qod | 12 | 15.6 |
| Continued | Oxandrolone | 10 mg/day | 24 | 16.8 |

* Attacks per 3 months based on patient report at screening visit

** Attacks per 3 months during placebo arm, normalized to 12 weeks

**Table 2** shows the impact of C1INH-nf on the median number 123 of attacks per 12 weeks in the subjects by anabolic androgen status. As initially reported, there was a 53% decrease in the median number of attacks per 12 weeks during the C1INH-nf arm compared to the placebo arm (12.9 [8.5,16.2] to 6.1 [2.0,11.0]).[6] Prophylactic C1INH127 nf decreased the median number of attacks by 64% in patients who were not using androgens at entry (11.0 [8.2,14.2] to 4.0 [1.3,8.0]). Patients who stopped their anabolic androgens reported a 87% decrease in the attack frequency while on C1INH compared to placebo (16.4 [11.9,19.3] to 2.1 [2.0,13.5]) while subjects who continued their anabolic androgens reported a 27% decrease in attack frequency on C1INH relative to placebo (15.6 [14.0,16.2] to 11.4 [9.3,11.9]). **Figure 1** shows the mean ± SEM attack rates during the C1INH and placebo arms stratified by anabolic androgen usage.

We also assessed the impact of C1INH-nf on attack severity and days of swelling (**Table 3**). Prophylactic treatment with C1INH-nf reduced the median severity score and median days of swelling in each group.

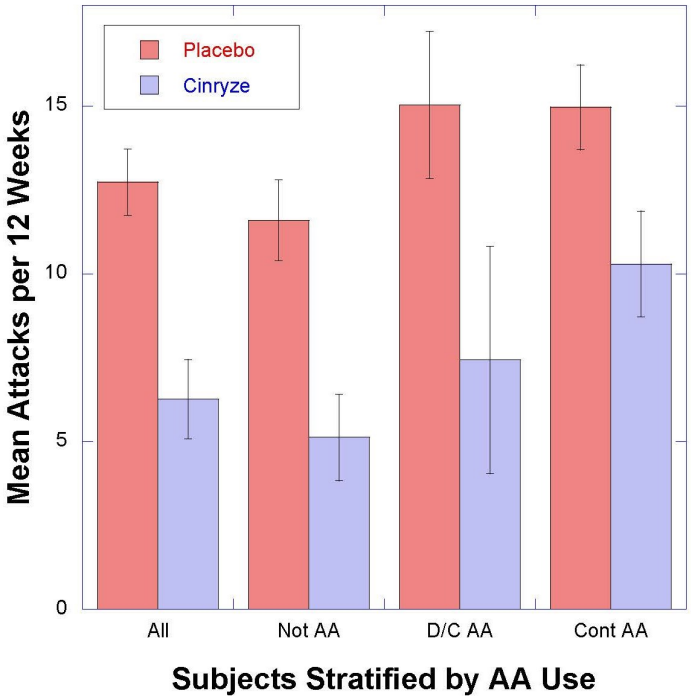
**Table 2.** Impact of anabolic androgens on efficacy of C1INH-nf in randomized trial

| Group (number) | Historical Attack Rate* | Placebo Attack Rate** | C1INH-nf Attack Rate** | Reduction in Attack Rate |
|---|---|---|---|---|
| All subjects (22) | 12 (6.75, 12) | 12.9 (8.5, 16.2) | 6.1 (2.0, 11.0) | 53% |
| Not using AA (14) | 10.5 (6,12) | 11.0 (8.2, 14.2) | 4.0 (1.3, 8.0) | 64% |
| Discontinuing AA (5) | 12 (12,12) | 16.4 (11.9, 19.3) | 2.1 (2,13.5) | 87% |
| Continuing AA (3) | 12 (10.5, 18) | 15.6 (14.0, 16.2) | 11.4 (9.3, 11.9) | 27% |

* Median attacks (IQR) per 3 months based on patient report at screening visit

** Median attacks (IQR) per 3 months during placebo or C1INH-nf arm, normalized to 12 weeks

**Figure 1.** Mean ± SEM attack rates during the C1INH and placebo arms stratified by anabolic androgen usage.



Compared to the entire group or the subjects not using anabolic androgens, subjects who discontinued androgens appeared to obtain more benefit from C1INH-nf while subjects who continued to use anabolic androgens showed less benefit from C1INH-nf.

## IMPACT OF ANABOLIC ANDROGENS IN THE OPEN- LABEL STUDY

In the Cinryze open-label study, a total of 146 subjects received prophylactic C1INH-nf[5] with 42 (28.8%) of these taking androgens at the time of entry into the study. Twenty-three of the 42 subjects taking anabolic androgens (54.8%) discontinued their anabolic androgens upon enrollment; 11 subjects (26.2%) reduced but did not stop the anabolic androgens; and 8 subjects (19.0%) continued their anabolic androgens at the same dose. **Table 4** shows the anabolic androgens used by these subjects at the time of enrollment.

**Table 5** shows the median attack rate (number of attacks per month) in the subjects stratified by anabolic androgen use, as well as the mean length of their participation in the open-label study. C1INH-nf was highly effective in reducing the attack rate irrespective of whether the subjects were taking anabolic androgens or not. In addition, there was little difference seen whether they discontinued, reduced or continued their anabolic androgens. **Figure 2** shows the impact of C1INH-nf on mean attack rate among the subjects.

**Table 3.** Impact of anabolic androgens on attack severity and days of swelling per period in C1INH-nf randomized trial

| Group (number) | Median (IQR) Severity Score* | | Median (IQR) Days Swelling | |
|---|---|---|---|---|
| Arm: | Placebo | C1INH-nf | Placebo | C1INH-nf |
| All subjects (22) | 1.9 (1.7, 2.0)** | 1.3 (1.0,1.8) | 28.1 (16.6, 38.6) | 6.6 (2.9,15.8) |
| Not using AA (14) | 1.9 (1.7, 2.0) | 1.3 (1.0, 1.9) | 26.6 (12.8, 41.6) | 5.0 (2.0,11.9) |
| Discontinuing AA (5) | 1.9 (1.7, 2.0) | 1.2 (1.0, 1.7) | 37.9 (21.7, 38.5) | 5.2 (3.0,19.7) |
| Continuing AA (3) | 1.7 (1.6, 1.9) | 1.4 (1.3, 1.6) | 27.6 (22.1, 31.1) | 13.3 (10.2, 15.0) |

* Subjects rated their attacks as mild (=1), moderate (=2) or severe (=3).

**Table 4.** Anabolic androgen use in patients enrolled in open-label trial (n=146)

| Group (number) | Danazol | | Stanozolol | | Oxandralone | | Methyltestosterone | |
|---|---|---|---|---|---|---|---|---|
| | n | Dose* (mg/day) | n | Dose* (mg/day) | n | Dose* (mg/day) | n | Dose* (mg/day) |
| No AA (89) | 0 | n/a | 0 | n/a | 0 | n/a | 0 | n/a |
| PRN during trial (9) | 6 | Variable prn | 2 | Variable prn | 1 | Variable prn | 0 | n/a |
| Discontinued AA (23) | 17 | 174 ± 28 | 3 | 1.67 ± 0.33 | 2 | 6.25 ± 1.25 | 1 | 30 |
| Reduced AA (11) | 9 | 211 ± 39 | 2 | 5.5 ± 3.5 | 0 | n/a | 0 | n/a |
| Same AA (8) | 4 | 300 ± 58 | 2 | 3.5 ± 0 | 2 | 2.5 ± 0 | 0 | n/a |
| PRN before and during the trial (6) | 5 | Variable prn | 1 | Variable prn | 0 | n/a | 0 | n/a |

* Mean ± SEM dose at time of enrollment

## DISCUSSION

We analyzed the C1INH-nf randomized study dataset to elucidate how anabolic androgen use impacted the efficacy of prophylactic C1INH-nf. We found that the efficacy of prophylactic C1INH-nf was essentially identical whether patients were using anabolic androgens or not. The overall median number of attacks per 3 months in the 22 subjects decreased from 12.9 (8.5,16.2) during the placebo arm to 6.1 (2.0,11.0) during the C1INH-nf arm, a 53% reduction. In 14 subjects not using anabolic androgens at the time of the screening visit, the attack rate decreased from 11.0 (8.2,14.2) during the placebo arm to 4.0 (1.3,8.0) during the C1INH-nf arm, a 64% reduction. Surprisingly, the median attack rate decreased 87% from 16.4 (11.9,19.3) during the placebo arm to 2.1 (2.0,13.5) during the C1INH-nf arm in the 5 subjects who chose to discontinue their anabolic androgens between the screening visit and enrollment visit. There was a more modest 27% decrease in attack frequency observed in the 3 subjects who maintained their anabolic androgens throughout the study (15.6 171 [14.0,16.2] to 11.4 [9.3,11.9]).

The reason for the smaller reduction of attacks during the C1INH-nf arm in the 3 subjects who continued to take anabolic androgens is not clear. Interestingly, this group also showed less benefit from C1INH-nf on the median severity of attacks and the median number of swelling days. We know of no mechanism that would suggest that anabolic androgens would interfere with the *in vivo* activity or clearance of C1INH-nf, and it is possible that this result is due to random noise in the very small subject group. Two of the subjects who continued anabolic androgens were using low to very low-dose oxandrolone while the third was using a relatively high dose of oxandrolone. This finding raises a question about the utility of using additional full 180 or low-dose anabolic androgens to improve outcomes in patients taking prophylactic C1INH-nf. In contrast, those subjects who discontinued their anabolic androgens showed an excellent response to C1INH-nf with the greatest reduction in the attack rate, days of swelling, and attack severity.

Because the numbers of subjects were limited in the randomized study, we also analyzed the dataset from the 146 subject open-label C1INH-nf extension study. As previously reported, the median number of attacks per month fell from a historical rate of 3 (2,4) to 0.19 (0,0.64) during C1INH-nf prophylaxis,[5] a 94% reduction. We found that 42 of the 146 subjects (28.8%) were taking androgens at the time of entry into the study, and 23 of these subjects (54.8%) discontinued their anabolic androgens upon enrollment while 11 subjects (26.2%) reduced but did not stop the anabolic androgens, and 8 subjects (19.0%) continued their anabolic androgens at the same dose. The overall reduction in median attacks per month was 93% in subjects not using androgens (0.22 attacks/month), 100% in subjects who discontinued

**Table 5.** Impact of anabolic androgen use on C1INH-nf efficacy in open-label study

| Group | Days in OL Study* | Historical Attack Rate° | C1INH-nf Attack Rate‡ | Reduction in Attack Rate |
|---|---|---|---|---|
| All subjects (146) | 340 ± 21 | 3 (2,4) | 0.19 (0,0.64) | 94% |
| Not using AA (89) | 324 ± 25 | 3 (2,4) | 0.22 (0,0.66) | 93% |
| None before & PRN during trial (9) | 595 ± 104 | 3.5 (3,4) | 0.44 (0.09, 0.79) | 87% |
| Discontinuing AA (23) | 257 ± 45 | 3 (1.25,11) | 0 (0,0.31) | 100% |
| Reduced AA (11) | 411 ±79 | 2 (2,3) | 0.24 (0067) | 88% |
| Same dose AA (8) | 401 ± 99 | 3.5 (2.8,5) | 0.26 (0.06, 0.71) | 93% |
| PRN before and during trial (6) | 301 ± 100 | 2 (2,3) | 0.24 (0,0.67) | 88% |

* Mean ± SEM duration in study
° Median (IQR) attacks per month based on patient report at screening visit
‡ Median (IQR) attacks per month during open-label C1INH-nf

their anabolic androgens (0 attacks/month), 88% in subjects who reduced their androgens (0.24 attacks/month), and 93% in subjects who continued the same dose of their androgens (0.26 attacks/month). These data corroborate and extend the results from the randomized study showing that C1INH-nf was efficacious in patients taking anabolic androgens. Once again we observed that subjects who discontinued use of anabolic androgens obtained undiminished efficacy from C1INH-nf prophylaxis. In contrast, C1INH-nf remained highly effective in the group who continued taking anabolic androgens at the same dose, suggesting that the results from the randomized study may be an anomaly due to the very small sample size.

The significant correlation between the reported historical attack rate and the placebo arm attack rate in the randomized study ($^{R}2$=0.20; p=0.034) suggests that historical estimation of attack rates by subjects can be used to estimate disease severity. We also found that discontinuation of androgens resulted in a modest increase in attack frequency during the placebo arm from 12.0 (11.3,15.0) attacks per 12 weeks to 16.4 (11.9,19.3) attacks per 12 weeks despite the fact that the anabolic androgens were being used at typical dosages (average of 100 mg/day of danazol or 3.3 mg/day of stanozolol). In contrast, the attack rates in subjects not taking anabolic androgens was almost unchanged, going from a historical rate of 10.5 (6.0,12.0) to 11.0 (8.2,14.2) during the placebo arm. These results suggest that anabolic androgens were having relatively poor efficacy in this group of severely affected subjects, but that this same severely affected group responded well to C1INH-nf.

In conclusion, we found that C1INH-nf was effective for long-term prevention of HAE even in patients who had previously been on anabolic androgens. The effectiveness of C1INH-nf was not diminished even after discontinuation of anabolic androgens. While it would be useful to know whether the anabolic androgens can be abruptly discontinued or else must be tapered, this study does not directly address that issue. Recent evidence-based HAE guidelines[10-14] recommend that treatment of HAE, including the decision on whether to use long-term prophylaxis or not, should be based on a comprehensive individualized management plan for each patient. This study shows that long-term prophylaxis with C1INH-nf can be initiated irrespective of the past history of androgen use.

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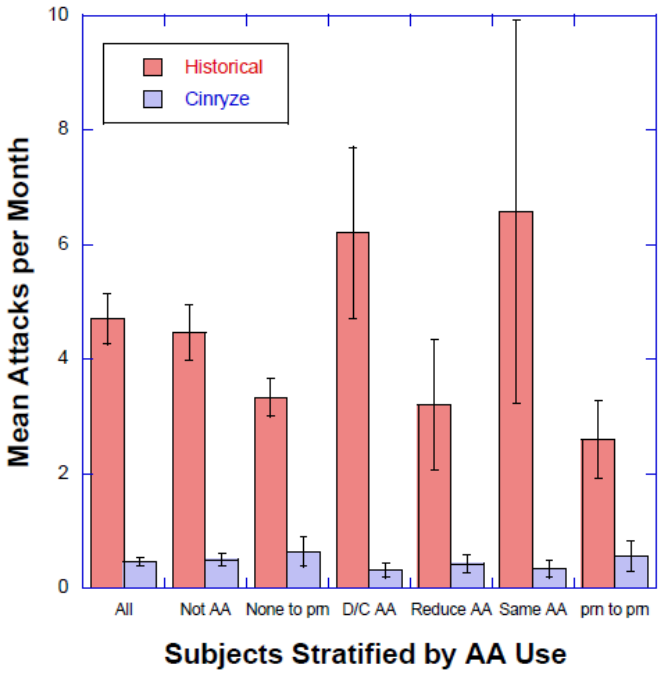
**Figure 2.** Efficacy of C1INH-nf during open-label 300 extension study. Error bars show SEM.



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