The Adjunctive Therapy Preferences of Adults with Classic Congenital Adrenal Hyperplasia: A Discrete Choice Experiment

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BACKGROUND

- Classic congenital adrenal hyperplasia (CAH) is a rare autosomal recessive condition (1)
- Glucocorticoid treatments (e.g. hydrocortisone, prednisolone, methylprednisolone, prednisone, dexamethasone) aim to limit androgen-driven symptoms and impacts, often at supraphysiologic doses (beyond what is needed to correct cortisol deficiency), by reducing androgen excess (2-4)
- Adults with classic CAH may have short stature and experience hirsutism, acne, irregular menstruation, fertility problems, osteopenia/osteoporosis and obesity as a result of under- or over-treatment with glucocorticoids (1-4)
- An unmet need exists for a novel therapy that can provide better androgen control with lower, more physiologic doses of glucocorticoids (3)

OBJECTIVE

- To understand the preferences of adults with classic CAH for the benefits of a potential new adjunctive therapy that could provide better androgen control with lower glucocorticoid doses via an online DCE

Table 1: Patient-reported sample demographics, health history and treatment

Characteristic	Qualitative interviews (N=8)	DCE survey (N=118)
Age in years, mean (SD); median [range]	42.4 (17.1); 40.5 [19.0–67.0]	38.6 (14.6); 34.5 [19.0–69.0]
Gender, n (%)		
Female	4 (50.0)	89 (75.4)
Male	4 (50.0)	28 (23.7)
Non-binary	-	1 (0.8)
Race/ethnicity, n (%)[†]		
White	6 (75.0)	104 (88.1)
Asian	2 (25.0)	5 (4.2)[‡]
Of Hispanic, Latino or Spanish origin	-	5 (4.2)
American Indian or Alaskan Native	-	2 (1.7)
Black or African American	-	4 (3.4)
Other: Middle Eastern	-	1 (0.8)
Prefer not to say	-	1 (0.8)
Highest level of education completed, n (%)		
Up to high school diploma or equivalent	3 (37.5)	27 (22.9)
Associate's degree or Bachelor's degree	2 (25.0)	56 (47.5)
Graduate/ post-graduate's degree	2 (25.0)	32 (27.1)
Other: Some college	1 (12.5)	3 (2.5)
Age of classic CAH diagnosis, n (%)		
At birth	6 (75.0)	62 (52.5)
After birth, up to 1 year	-	36 (30.5)
≥2 years old	2 (25.0)	20 (16.9)
Form of classic CAH, n (%)		
Salt-wasting	5 (62.5)	102 (86.4)
Simple virilizing (or non salt-wasting)	3 (37.5)	14 (11.9)
Unsure/do not know	-	2 (1.7)
Current height in feet and inches, mean (SD); median [range]	5'5" (0'2"); 5'5" [5'1"–5'7"][¶]	5'3" (0'3); 5'3" [4'4"–6'0"]
Body mass index (BMI), mean (SD); median [range]	29.0 (10.1); 27.1 [18.8–50.1][¶]	30.9 (8.0); 28.7 [17.2–54.8]
Number of different types of glucocorticoid treatments currently received, n (%)		
1	4 (50.0)	98 (83.1)
2	4 (50.0)	18 (15.3)
3	-	2 (1.7)
Currently receiving mineralocorticoids (fludrocortisone), n (%)		
Yes	7 (87.5)	104 (88.1)
No	1 (12.5)	13 (11.0)
Unsure/do not know	-	1 (0.8)
Level of classic CAH control, n (%)		
Well controlled	8 (100.0)[§]	88 (74.6)
Neither well controlled nor poorly controlled	-	27 (22.9)
Poorly controlled	-	3 (2.5)
Satisfaction with current CAH medication regimen, n (%)		
Completely satisfied	-	36 (30.5)
Somewhat satisfied	-	44 (37.3)
Neutral	-	13 (11.0)
Somewhat dissatisfied	-	20 (16.9)
Completely dissatisfied	-	5 (4.2)

[†] In the DCE survey, N=4 chose multiple: American Indian or Alaskan Native and White (n=2), White and Of Hispanic, Latino, or Spanish origin (n=1), Asian and White (n=1); ‡ No respondents reported Japanese descent; § N=7 because one participant declined to provide height and weight; ¶ Interview participants were asked if their CAH was 'Well controlled' or 'Not well controlled'. Body Mass Index was calculated using converted participant-reported height and weight: weight in kg / (height in cm/100)^2.

METHODS

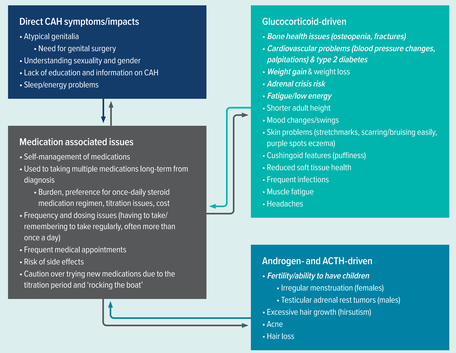
- Industry guidance (5, 6) informed a robust, multi-stage development process for the online DCE survey
  - Stage 1: Information gathering
    - Existing sponsor (Neurocrine Biosciences) data/literature were reviewed, a hand search (PubMed, Google Scholar and Google) for qualitative CAH literature in the past 10 years was performed and 60-minute, semi-structured, web-assisted/telephone qualitative interviews were conducted with eight adults with classic CAH to inform DCE attributes and levels
  - Stage 2: Refinement
    - DCE survey content was reviewed by two endocrinologists (EAI and MS), the study sponsor and research team
    - Cognitive testing was conducted in which three adults with classic CAH completed a draft version of the online DCE survey in their own time and then participated in a 30-minute, web-assisted cognitive interview about the survey
  - Stage 3: Final DCE survey
    - The final DCE survey choice set was designed using a d-optimal algorithmic approach in Ngene software and used a three-block design with 42 unique choice tasks
    - Participants were asked to make a series of 16 choices between two medications in which the attribute levels varied (14 unique choice tasks and two consistency/logic choice tasks)
    - Choice set data were analyzed using conditional logit regression after removal of erroneous data (e.g. duplicate participants, multiple completes from same IP address)

RESULTS

STAGE 1: INFORMATION GATHERING

- Existing data/literature informed the content of qualitative interviews with eight adults with classic CAH (see Table 1 for sample characteristics)
- Qualitative interviews revealed that medication management was the main daily impact of classic CAH and varying participant experience and awareness of the potential attributes (Figure 1)
  - Participants' ranking of their top five attributes that were most important for a new medication to address informed which attributes were considered for inclusion in the DCE
  - Participants prioritized attributes that either affected them at their current age or that they were concerned could affect them in future
  - Most (n=5/7) participants were interested in taking an additional, twice-daily medication that would address the five attributes most important to them
- Stage 1 resulted in the decision to use fixed adjunctive therapy attributes that were unlikely to change/vary to frame the DCE survey and consideration of six attributes that an adjunctive therapy could affect for inclusion in the DCE choice set

Figure 1: Conceptual model of the treatment experience of adults with classic CAH developed from Stage 1 qualitative interviews (N=8)



Bold and italicized glucocorticoid-driven and androgen-/ACTH-driven attributes were considered for inclusion in the DCE as interview participants ranked them as most important for a new medication to address

STAGE 2: REFINEMENT

- The research study team and sponsor drafted seven attributes with 2–3 levels, refining the output of stage 1
- Endocrinologist feedback resulted in changes to improve participant understanding and improve clinical relevance/accuracy
- Cognitive testing with three adults with classic CAH (age 21–63 years, 66.7% female, 100% white, 66.7% educated to Associate's degree or higher) indicated that the adjunctive therapy attributes and levels were well understood with only minor updates made to improve clarity/ understanding of descriptive text
- Stage 2 resulted in seven adjunctive therapy attributes that were included in the final DCE survey (Table 2)

Table 2: DCE survey description and adjunctive therapy attributes and levels

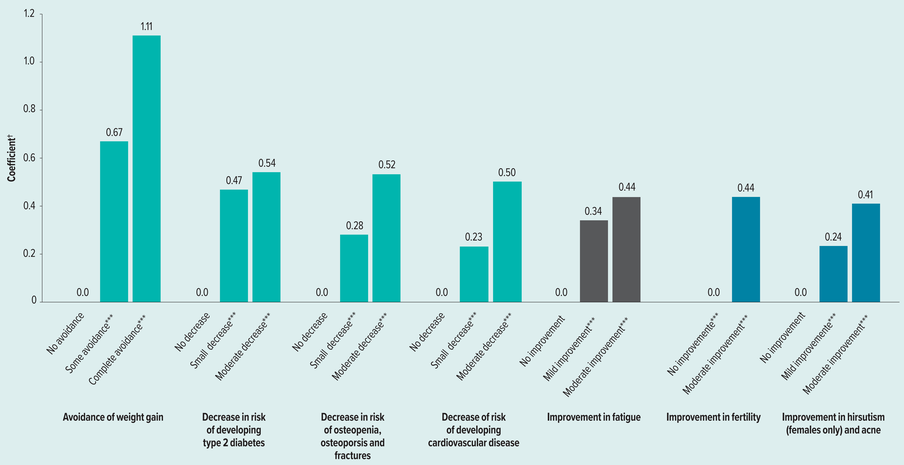
- Introductory text informed participants that the potential new medication:
  - Was not a steroid
  - Worked by providing better control of androgens with lower steroid doses
  - Would need to be taken twice daily in addition to all of their current CAH medications (including steroids)
  - Would not increase or decrease their chance of having an adrenal insufficiency crisis
  - Had a low chance of mild side effects (such as headache, dizziness and upset stomach or feeling nauseous)

	Attribute	Level
Glucocorticoid-driven	Decrease in risk of osteopenia, osteoporosis and fractures from long-term steroids	No decrease
		Small decrease
		Moderate decrease
	Decrease in risk of developing type 2 diabetes from long-term steroids	No decrease
		Small decrease
		Moderate decrease
	Decrease of risk of developing cardiovascular disease from long-term steroids	No decrease
		Small decrease
		Moderate decrease
	Avoidance of weight gain from steroids	No avoidance
		Some avoidance
		Complete avoidance
	Improvement in fatigue	No improvement
		Mild improvement
		Moderate improvement
Androgen-driven	Improvement in hirsutism (females only) and acne	No improvement
		Mild improvement
		Moderate improvement
	Improvement in fertility	No improvement
		Moderate improvement

STAGE 3: FINAL DCE SURVEY

- A pilot launch (N=10 completes) indicated the survey was functioning and randomization was working well
  - Completion time was generally short but participants appeared to have understood and were engaged in the survey (these findings persisted in the full sample)
- Data from 118 adults with classic CAH were analyzed (see Table 1 for sample characteristics)
- All preferences were statistically significant and ordered as expected with higher preferences for the greatest level of benefit for each attribute (Figure 2)
  - Avoidance of weight gain was the most important treatment attribute
    - The coefficient estimate for best level (complete avoidance) in comparison to worst level (no avoidance) was twice the magnitude compared to other attributes indicating its major contribution to overall preferences
  - Moderate decrease in risk of the three glucocorticoid-driven health conditions (osteopenia, osteoporosis and fractures; type 2 diabetes; cardiovascular disease) had similar preference magnitudes
  - Similar preferences were observed for improvement in fatigue and androgen-driven impacts (hirsutism/acne and fertility)
    - Preferences for fatigue and androgen-driven impacts were lower in magnitude than avoiding weight gain and the three glucocorticoid-driven health condition risks

Figure 2: Discrete choice experiement preference patterns



[†]Higher coefficient suggests higher preference; ***p<0.001

LIMITATIONS

- The qualitative sample that informed the selection of attributes was small and may not be representative of the broader classic CAH population
- Highly educated white women comprised a majority of the final DCE survey sample; survey findings may not be generalizable to other demographic or socioeconomic groups
  - Future surveys conducted in other populations or countries could be used to confirm the results of this study

CONCLUSIONS

- This robustly developed DCE survey study appears to be the first to examine adjunctive medication preferences of individuals with classic CAH
  - Iterative study phases identified treatment attributes that were important to patients and ensured the DCE survey was relevant and comprehensible
- All seven attributes significantly influenced choice
  - Results indicated that patients with classic CAH would most highly value a medication that helps them avoid glucocorticoid-related weight gain
  - A medication that reduces risk of glucocorticoid-driven health conditions (type 2 diabetes; osteopenia, osteoporosis and fractures; cardiovascular disease) may also be valued more than one that improves fatigue and androgen-driven symptoms (fertility; hirsutism [females only] and acne)
- The preference results can be used to help guide and inform patient preferences regarding new therapy decisions

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