HEALTH-RELATED QUALITY OF LIFE OF PATIENTS WITH CUSHING'S DISEASE TREATED WITH OSILODROSTAT – MIXED-EFFECTS REGRESSION ANALYSIS

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INTRODUCTION

Cushing's syndrome (CS) is a rare endocrine disorder characterized by cortisol overproduction. Cushing's disease (CD) is the most common form of CS (occurring in 70.0%–85.0% of all cases) and is caused by an ACTH-secreting pituitary corticotroph adenoma. Chronic exposure to hypercortisolism has a major impact on patient health, with patients experiencing a substantial impairment in health-related quality of life (HRQoL), most likely due to the multitude of comorbidities including hypertension, diabetes, obesity and depression and symptoms manifestation e.g. weight gain, skin thinning, striae, bruising[1,2].

The 2021 Pituitary Society guideline recommends surgery as the first-line treatment for CS. If surgery is not feasible or successful, pharmacological therapy including steroidogenesis inhibitors, is one of the preferred second-line treatments[3]. According to the guidelines[3], the primary treatment goal is to normalize cortisol concentrations (biochemical control), which may lead to improvements in symptoms and subsequently in HRQoL[4,5].

OBJECTIVES

The objective is to estimate the Health Utility Values (HUV) in biochemically controlled and uncontrolled patients based on the two randomized phase III studies, LINC-3[6] and LINC-4[7], where patients with CD were treated with osilodrostat or placebo. These HUV estimates can be useful in cost-effectiveness evaluations and can inform the decision-making process and healthcare resource allocation.

METHODS

The EQ-5D is a self-administered, generic utility instrument developed by the EuroQoL Group in 1990[8]. EQ-5D-5L values were available in the phase III studies of osilodrostat for the treatment of Cushing's disease, LINC-3 and LINC-4 (see Table 1). LINC-3 was a phase III, prospective, multicentre, double-blind, randomized withdrawal study with a 48 core period followed by a 48 weeks extension phase. After 24 weeks of open-label osilodrostat treatment, patients with normalized mean urinary free cortisol (mUFC) and no dose uptitration between weeks 12-24 were randomized to continue osilodrostat or switch to placebo for 8 weeks[6,9]. LINC-4 was a phase III, multicentre, 48-week study consisting of an upfront 12-week, randomized, double-blind, placebo-controlled phase followed by an 36-week, open-label osilodrostat treatment phase and an 48 week optional open label extension[7,10].

Table 1: Data used to build regression models.

CHARACTERISTIC	LINC-3	LINC-4
No. of patients	137 patients	72 patients
Number of observations per patient (median)	12	7
Timepoints	Baseline and weeks 4, 8, 12, 24, 26, 28, 30, 32, 34, 48, 72, 96 and EOT	Baseline and weeks 12, 14, 26, 36, 48, 72 and EOT
Included population	Population receiving active treatment*	
Constraints	Lacking representative population of patients with long-time biochemically uncontrolled disease** (patients uncontrolled mainly at baseline)	
Dose titration	At a faster pace	At a slower pace
mUFC enrolment criteria	>1.5 times ULN	>1.3 times ULN
Mean (SD) baseline mUFC level	1,006 (1,590)	432 (389)

*Measurements between 0-12 weeks for patients receiving placebo in the LINC-4 study were not included in the dataset; Measurements from the placebo arm in the LINC-3 study in the randomised period of weeks 26-34 were included due to randomised withdrawal setting of the study

**biochemically uncontrolled disease defined as mUFC > upper limit of normal =138 nmol/24 h

Key: EOT, end of treatment; mUFC, mean urinary free cortisol; ULN, upper limit of normal =138 nmol/24 h; SD, standard deviation

EQ-5D-3L values, which are the preferred utility measure of health states, were obtained by mapping with the NICE DSU[11] method as illustrated below.

The utility scores were first estimated using the NICE DSU mapping function to map EQ-5D-5L data to the EQ-5D-3L[11]. The combination of domain scores, age and sex gave each patient a domain ID that corresponds with an estimated EQ-5D-3L utility score.

The main aim of this analysis was to establish the relation between mUFC and HRQoL in order to estimate utility values of patients who achieve and do not achieve biochemical disease control over time. As other variables were available, the model could be adjusted with additional predictors, which were identified first in univariate analysis. Multiple linear mixed-effects regression models were fitted to assess patients' HRQoL, considering the longitudinal cohort type of the data. Models considered various combinations of the potentially relevant covariates e.g. age, sex, BMI, any grade hypocortisolism-related adverse events (HAEs), HAEs grade 3+, duration of cortisol normalization and mUFC value[12,13].

RESULTS

The following patient characteristics were available in the LINC-3 and LINC-4 studies (Table 2). HAEs were also included as potentially relevant to HRQoL. Only parameters that were statistically significant at the level of 0.05 (in bold) were included in the selection of best models. These were continuous predictors: mUFC, treatment duration, time since diagnosis, BMI and binary variables: occurrence of any HAEs and g3+ HAEs.

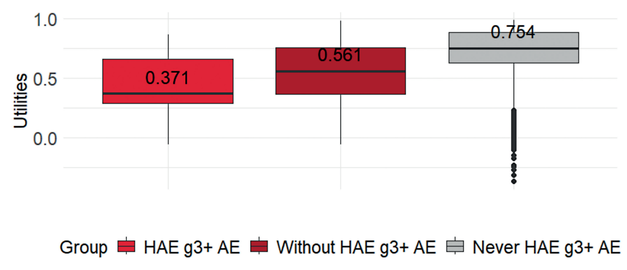
Table 2: Univariate analysis results.

VARIABLE NAME	P-VALUE
Sex	0.214
mUFC	**<0.005**
Treatment time	**<0.005**
Age	0.0642
mUFC at baseline	0.710
Time since diagnosis	**<0.005**
BMI	**<0.005**
Has HAE g3+	**<0.005**
Has HAE any grade	**<0.005**

Key: mUFC, mean urinary free cortisol; HAE g3+, hypocortisolism related adverse event with toxicity grade of 3 or higher; BMI, body mass index

As presented in the boxplot below, the inclusion of the HAEs variable was supported by considerable differences in utilities for affected patients in months of event occurrence.

Figure 1: Comparison of utilities by occurrence of grade 3+ events in patient groups.



Key: HAE g3+, hypocortisolism-related adverse events of toxicity grade 3+

HRQoL values were higher for the patients with no HAE grade 3+ events. The highest scores were observed in the group that never experienced this type of AE. The prevalence of HAE grade 3+ events in the included dataset of LINC-3 and LINC-4 studies was 0.04% and the median duration of the events was 11 days with a standard deviation of 10.8 days.

The final model was selected based on the information criterion (AIC and BIC), with emphasis on the former to avoid favouring simpler models that might omit the significant HRQoL predictors. The three best models were presented, along with two scenario models additionally presented for validation purposes (Table 3).

The first validation model was similar to the base case model (best information criterion) however it included only the LINC-3 dataset. Due to the relatively low number of patients in the LINC-4 study there was no regression model scenario where observations solely from this trial were utilized. The additional validation scenarios included age and sex as potentially relevant parameters for HRQoL according to the literature[14].

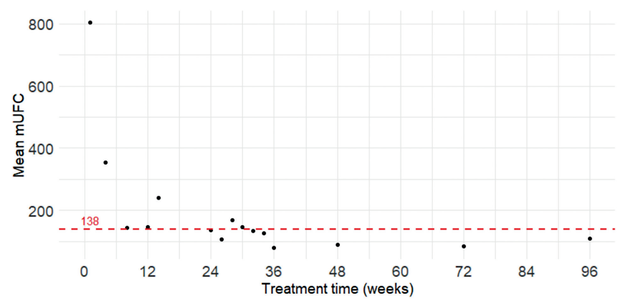
Table 3: Best models basing on AIC information criterion.

TYPE OF MODEL	MODEL STRUCTURE	NO. OF OBSERVATIONS	NO. OF PATIENTS	AIC (BIC)
Model AIC 1	Treatment time + mUFC+ BMI+ has_HAE_g3	1931	209	-2002 (-1963)
Model AIC 2	Treatment time + mUFC+ has_HAE_g3	1931	209	-1998 (-1965)
Model AIC 3	Treatment time + mUFC+ BMI+ has_HAE + has_HAE_g3	1931	209	-1998 (-1953)
SCENARIO MODELS				
Model AIC 1 on LINC-3 only	Treatment time + mUFC+ BMI + has_HAE_g3	1444	137	-1348 (-1311)*
Best model age, sex and mUFC	Treatment time + mUFC + age + sex + BMI + has_HAE_g3	1931	209	-1987 (-1937)

*not comparable to other information criterion as model built on different dataset

Key: HAE g3+, hypocortisolism related adverse event with toxicity grade of 3 or higher; mUFC, mean urinary free cortisol; BMI, body mass index; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Figure 2: Mean mUFC values reported in LINC-3 and LINC-4 studies.



The dashed line in Figure 2 indicates the biochemical control of disease defined as mUFC values below the ULN (138 nmol/24 h). It shows that after week 32 no mean mUFC value exceeds the ULN. A decrease in mUFC levels was accompanied by an increase in the quality of life, as shown in Figure 3.

Figure 3: Mean utility values observed during LINC-3 and LINC-4 studies.

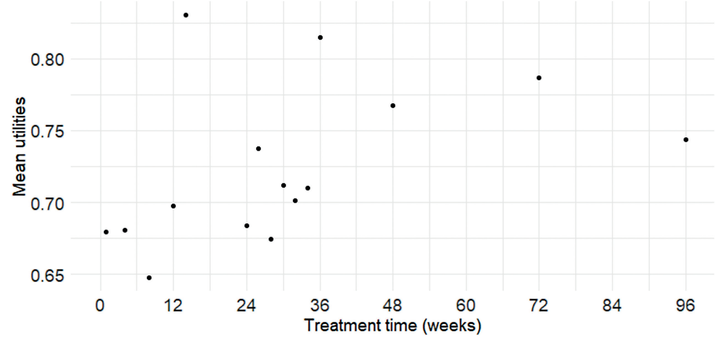
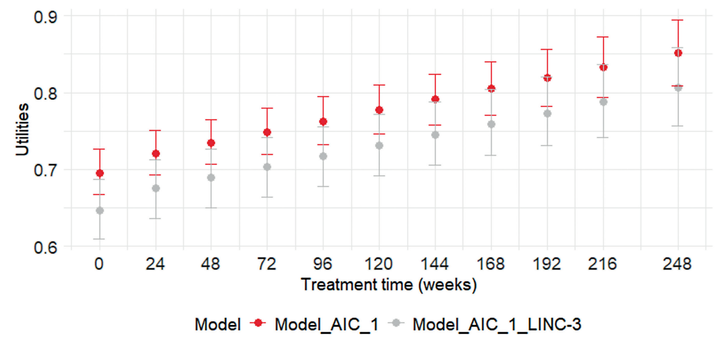


Figure 4: Predictions for EQ-5D-3L utilities from Model 1 AIC with 95% confidence intervals.



Only the predictions of the best fitted model (AIC 1 on two different datasets) were shown. For the other models tested the predictions were almost identical to those for Model AIC 1 on the full dataset, validating the stability of base case estimation. Reference population norms for EQ-5D-3L values, matched to CS patients by age, range from 0.85 to 0.97[15]. These are similar to those which were obtained from regression models for CS patients with stable, long-term biochemical disease control.

Table 4: Predictions for all fitted models.

TREATMENT TIME (WEEKS)	MODEL AIC 1	MODEL AIC 2	MODEL AIC 3	MODEL AIC 1 LINC-3	MODEL AGE & SEX
0	0.696	0.696	0.696	0.646	0.697
48	0.735	0.734	0.735	0.689	0.735
96	0.762	0.763	0.762	0.717	0.763
204	0.825	0.826	0.824	0.780	0.825
248	0.851	0.852	0.849	0.806	0.851

CONCLUSIONS

There is a significant difference in HUVs between biochemically controlled and uncontrolled CS patients. HRQoL improves with mUFC reduction and lower BMI and declines with hypocortisolism-related AEs. HRQoL also increases with the duration of cortisol normalization suggesting that patients' health status may improve with effective biochemical control. The prognosis of the regression model is stable, which was validated by numerous other models employing different parameters sets. Scenario where the results are generated based on the LINC-3 dataset only confirms the general trend of utilities improving with disease control. Estimated values are slightly lower which can be explained with the lower baseline mUFC values for patients in the LINC-3 study as compared to the LINC-4 study. To our knowledge, this is the first study to present the relationship between biochemical control in patients with Cushing's syndrome and EQ-5D estimates.

BIBLIOGRAPHY

1. Bride et al Research Clinical Endocrinology & Metabolism. 2021; 35(1), 101505.
2. Huguet et al. European Endocrinology. 2015; 11(1), 34.
3. Fleseriu et al. Lancet Diabetes Endocrinol. 2021; 9(12):847-75
4. Valassi et al. European Journal of Endocrinology. 2018; 178(4), 399–409.
5. Santos et al. European Journal of Endocrinology. 2012; 167(3), 337–342.
6. Pivonello et al. The Lancet Diabetes & Endocrinology. 2020; 8(9), 748–761.
7. Fleseriu et al. European Journal of Endocrinology. 2022; 187(4), 531–541.
8. EuroQol Research Foundation. EQ-5D-3L User Guide. 2018
9. Gadelha et al. The Journal of Clinical Endocrinology & Metabolism. 2022; 107(7).
10. Gadelha et al. The Lancet. 2023; 402(10418), 2237–2252.
11. NICE Health Technology Evaluation Manual. 2022
12. Sarkis et al. Annales d'Endocrinologie. 2019; 80(1), 32–37.
13. Claessen et al. Pituitary Tumors. 2021; 617–637.
14. Wailoo et al. 2023 NICE DSU Technical Support Document 22
15. Ara et al. Value in Health. 2008;11:1131–43

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