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Clinical Research Article

A Retrospective Study on Weaning Glucocorticoids and Recovery of the Hypothalamic–Pituitary–Adrenal Axis

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Abstract

Context: Glucocorticoids suppress the hypothalamic–pituitary–adrenal (HPA) axis, resulting in tertiary adrenal insufficiency (AI). When weaning patients off glucocorticoids there is no consensus on whether to maintain patients on prednisolone or convert to hydrocortisone.

Objective: To investigate HPA axis recovery in patients on long-term prednisolone and assess outcome after hydrocortisone conversion.

Methods: This was a retrospective cohort study at an outpatient endocrine steroid clinic. Patients were on long-term prednisolone and referred for HPA axis testing between 2015 and 2022. The main outcomes measured were (1) HPA axis recovery rate in patients on prednisolone demonstrated by a normal adrenocorticotrophic hormone (ACTH) stimulation test (AST) and (2) HPA axis recovery rate subanalysis of dose-matched patients with confirmed tertiary AI on prednisolone or hydrocortisone were measured.

Results: In total, 206 patients on prednisolone were tested for tertiary AI. Of these, 176 remained on prednisolone while 30 were converted to hydrocortisone. The overall HPA axis recovery rate for patients on prednisolone after interval testing was 137/206 (66.5%). The HPA axis recovery rate in dose-matched prednisolone and hydrocortisone conversion groups was 7/10 (70%) and 2/13 (15%) ($P = .008$), respectively. There was no difference in mean (SD) age (67.1 [12.2] vs 63.4 [11.1] years; $P = .464$) and baseline cortisol (5.3 [4.2] vs 4.6 [3.1] µg/dL; $P = .648$) and median [interquartile, IQR] glucocorticoid duration (1213 [1114] vs 2316 [4808] days; $P = .693$) and baseline ACTH (20.5 [29.0] vs 16.3 [14.8] ng/L; $P = .905$) between dose-matched prednisolone and hydrocortisone groups. Follow-up duration in the prednisolone group was significantly lower (median [IQR] 348 [975] vs 667 [884] days; $P = .012$).

Conclusion: Patients with glucocorticoid-induced AI maintained on once-daily prednisolone can recover HPA axis function when weaning. There is no apparent advantage to recover HPA axis function in converting to multiple-dosing hydrocortisone.

Key Words: prednisolone, hydrocortisone, hypothalamic–pituitary–adrenal axis, glucocorticoids

Abbreviations: ACTH, adrenocorticotrophic hormone; AI, adrenal insufficiency; AST, ACTH stimulation test; HPA, hypothalamic–pituitary–adrenal; IQR, interquartile range.

Glucocorticoids are frequently used in the treatment of inflammatory conditions and malignancies (1). It is estimated that 1% to 3% of the general population is taking systemic glucocorticoids (2, 3), and in some countries the prevalence could be even higher due to inappropriate use (4, 5). Adrenal insufficiency (AI), or more appropriately adrenal suppression, may result from the use of exogenous glucocorticoids, and a metanalysis has estimated that up to 50% of patients on oral steroids are at risk of adrenal suppression (1). Hypothalamic–pituitary–adrenal (HPA) axis suppression may occur when glucocorticoids are administered at doses of >5 mg per day of prednisolone or equivalent glucocorticoid dose for 4 weeks or longer (6, 7). Tertiary AI can occur with glucocorticoid administration via any route of administration and the risk rises with increasing cumulative dosage and longer duration of treatment (1).

Glucocorticoids cause a wide range of adverse effects when taken at supraphysiological doses (8). For this reason, anti-inflammatory doses of glucocorticoids are tapered down as soon as possible after disease control is achieved. Once the glucocorticoid dose is weaned down to a physiological replacement dose, it is helpful to assess for HPA axis suppression (6). This can be done clinically, without hormone measurement; however, formal biochemical assessment can be undertaken by measuring a morning serum cortisol before glucocorticoid administration. If the result indicates possible adrenal suppression, this is then followed by the 250-µg adrenocorticotrophic hormone (ACTH) stimulation test (AST), also known as the short Synacthen test (9-11). Recently, waking salivary cortisone has shown promise to be a useful adjunct in assessment of adrenal function and also has the advantage of being carried out at home (12).

Tertiary AI is usually reversible with time. Individuals are maintained on the lowest physiological doses and tested at frequent intervals (1, 6, 13). International consensus suggests converting prednisolone to hydrocortisone to facilitate

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weaning (14). Prednisolone has higher glucocorticoid receptor occupancy and a longer plasma half-life than hydrocortisone (120-360 minutes vs 90 minutes) (15-17). The biological half-lives of hydrocortisone and prednisolone are 8 to 12 hours and 18 to 36 hours, respectively, leading to prednisolone usually being administered once a day (18-21) while hydrocortisone is usually prescribed either twice or thrice daily, with the highest dose in the morning (22). The supposition is that the hydrocortisone regimen is less likely to cause continuous suppression and therefore offers more physiological weaning, potentially encouraging reactivation of the HPA axis more quickly than prednisolone. Some consider prednisolone to be a better glucocorticoid for replacement in general (23), believing that the multidose hydrocortisone regimens result in peaks that may perseverate adrenal axis suppression (22, 24, 25). However, during the weaning process, there is no evidence to support either strategy.

The primary aim of this study was to examine HPA axis recovery in patients who remained on long-term prednisolone throughout the weaning process. The secondary aim was to assess the recovery rates in retrospectively dose-matched patients with confirmed tertiary adrenal insufficiency either on prednisolone or converted to hydrocortisone from prednisolone.

Materials and Methods

Study Design

This was a retrospective observational cohort study of all adult patients diagnosed with tertiary AI attending a dedicated endocrine steroid clinic between September 2015 and April 2022 at Sheffield Teaching Hospitals NHS Foundation Trust, UK. For the study, we first identified all patients who underwent an AST, using our AST database. Then we identified all those who had an AST for suspected tertiary AI secondary to oral and/or inhaled glucocorticoids and excluded all other patients who had an AST for any other indication. Patients on oral glucocorticoids other than prednisolone at the start of the study (hydrocortisone, dexamethasone, or budesonide) were not included. Patients with known protein-losing disorders, known severe liver disease, on estrogens, or pregnant were not included, as salivary cortisone was used to make decisions on adrenal status in these patients instead. Patients who had been on nightshift work within the previous week and those with active infections were excluded from undergoing ASTs. Tertiary AI was defined as a failed AST (30-minute cortisol <430 nmol/L or <15.6 µg/dL) performed after the glucocorticoid dose was weaned down to a physiological replacement dose of prednisolone ≤5 mg/day (26, 27). All patients had been on supraphysiological prednisolone doses for at least 3 months.

Following a first failed AST, we followed up patients with interval ASTs every 6 to 12 months until HPA axis recovery (defined as a subsequent normal AST; 30-minute cortisol ≥430 nmol/L or ≥15.6 µg/dL) or study end date (April 30, 2022), whichever came first. During follow-up, an expert endocrinologist managed these patients in the endocrinology steroid clinic, maintaining them on the lowest possible physiological replacement dose. If the subsequent AST(s) failed, patients on prednisolone were maintained on the same glucocorticoid. However, if they were symptomatic (steroid withdrawal syndrome or adrenal insufficiency symptoms), they were converted to hydrocortisone. Patients with confirmed adrenal insufficiency were given standardized education on steroid sick day rules and given a steroid emergency card (25). For prednisolone, once the patients subsequently passed their AST, the glucocorticoid doses were weaned down by 1 mg every 3 to 4 weeks until completely stopped. All patients who came off their glucocorticoid were advised to monitor their symptoms and given an emergency glucocorticoid prescription to cover intercurrent illness for 6 to 12 months after stopping glucocorticoids (28).

Outcomes

The primary outcome of the study was defined as the percentage of patients who were only on long-term prednisolone ± glucocorticoid inhalers at the start of the study period and throughout follow-up, who demonstrated recovery of the HPA axis biochemically by a normal AST (30-minute cortisol post – Synacthen ≥430 nmol/L or ≥15.6 µg/dL). The secondary outcome was the comparison of HPA axis recovery rates between patients with confirmed tertiary AI who were either maintained on prednisolone or converted to hydrocortisone during the study period. In order to reduce confounding bias due to lack of randomization in observational studies (29), in this subanalysis we dose matched our patients on prednisolone who were on 4 to 5 mg/day with patients converted to hydrocortisone 20 mg/day. A safety analysis was also performed to determine the total number of hospital admissions including admissions related to adrenal crisis, as evidenced by the presence of hypotension (systolic blood pressure <100 mmHg) ± hyponatremia requiring parenteral hydrocortisone during the follow-up period.

ACTH Stimulation Test Protocol

Endocrine nurse specialists carried out all ASTs on a dedicated investigation unit in the hospital. The protocol for the AST included standard administration of intravenous or intramuscular injection of 250 µg of Synacthen (Atnahs Pharma UK Limited, Essex, UK) and measurement of plasma adrenocorticotrophic hormone ACTH and serum cortisol at 0 minutes and serum cortisol at 30 minutes. Patients on prednisolone were advised to omit the dose on the day of test until completion of the AST, while patients on hydrocortisone were advised to omit the preceding evening dose in addition to the morning dose on the day of test. Those on inhaled corticosteroids were also asked to omit the dose the evening before and on the day until the test was complete. Measurement of blood markers was conducted using the Elecsys Cortisol II assay (Roche Diagnostics GmbH, Mannheim, Germany) (Cobas interassay precision coefficient of variation 1.1-5.5%) for cortisol and Siemens Immulite 2000 and chemiluminescent assay (Siemens, Frimley, UK, interassay precision coefficient of variation 6.1% to 10.0%) for ACTH.

Data/Statistics

Data for all those in the study were extracted from patient case notes. In addition to age and sex, data on other potential confounding factors (length of weaning period to HPA activation, length of follow-up, underlying etiology, baseline serum cortisol, baseline plasma ACTH, opioid use, and duration of glucocorticoids) were also collected. All the data were recorded in a password-protected Excel spreadsheet and stored securely on a hospital computer in line with national governance protocols. Continuous variables are represented as mean and SD

for normally distributed data, and as median and interquartile range [IQR] for non-normally distributed data, while categorical variables are represented by the number of cases (n) and a percentage (%) of the total. Continuous variables were analyzed using the paired t test and Mann–Whitney U test for normally and non-normally distributed data, respectively, and categorical variables using the chi-squared (χ^2) test. Analyses were conducted in SPSS version 27 and in all analyses; $P < .05$ was considered to be statistically significant.

Approvals

The study was registered with Sheffield Teaching Hospitals Clinical Effectiveness Unit (reference number 10195) as an institutional case note review. All data were collected as part of this project reflected routine clinical care and therefore formal ethics approval was not required. No funding was required. The study has been reported in line with the STROBE statement for observational studies (30).

Results

Eight hundred and thirty-seven patients underwent an AST during the study period of 6 years and 8 months. After excluding those who underwent an AST for another indication, a total of 276 patients on long-term glucocorticoids suspected of having tertiary AI remained: 254 on oral glucocorticoids ± glucocorticoid inhalers and 22 on inhaled glucocorticoids only (Fig. 1). After excluding the patients on glucocorticoids other than prednisolone ± steroid inhalers at the start of the study, there were 206 patients who were included in the study. The baseline demographics and clinical parameters for these patients are summarized in Table 1 below.

Primary Outcome

Of the patients on prednisolone ± steroid inhalers at the start of the study (n = 206), 176 remained on prednisolone throughout the study period while 30 symptomatic patients, who all failed their first AST, were converted to hydrocortisone. In total, 112/176 patients on prednisolone passed their first AST and were successfully weaned off glucocorticoids within the study period. Of the remaining 64 patients, 41 patients underwent a second AST, after which another 18 patients recovered their HPA axis. A further 10 patients underwent subsequent short Synacthen tests and 7 were successfully weaned off glucocorticoids. Only 3 patients did not recover their HPA axis after having ≥3 ASTs. The remaining 36 patients were awaiting a subsequent AST, lost to follow-up, or had died before the subsequent AST. Thus, the overall HPA axis recovery rate for all those patients who were on prednisolone ± glucocorticoid inhalers at the study start and who remained on prednisolone throughout the study period was 137/206 (66.5%) (Fig. 1). When excluding patients

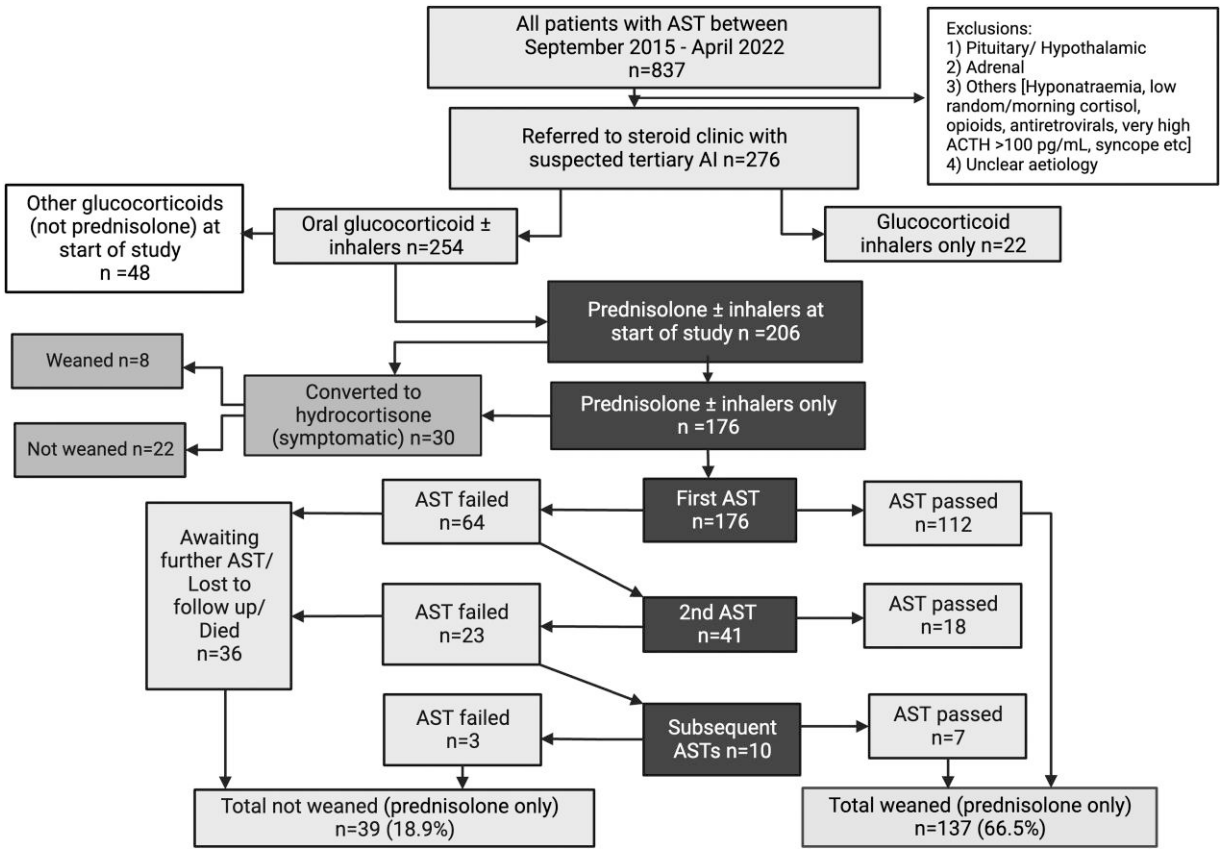

Figure 1. Consort diagram outlining study methodology and primary outcome (created with biorender.com). Abbreviations: ACTH, adrenocorticotrophic hormone; AI, adrenal Insufficiency; AST, ACTH stimulation test. Patients on prednisolone ± inhaled glucocorticoids (n = 206) were included in the study. Of these, 30 were converted to hydrocortisone due to symptoms, while the remaining 176 were still taking prednisolone as their oral glucocorticoid. The patients on prednisolone underwent testing with serial ASTs until they passed the AST. Thirty-six patients were still either waiting further ASTs at the end of the study or were lost to follow-up or died. The overall weaning rate for patients on prednisolone only throughout the study period was 137/206 (66.5%).

Table 1. Demographic and clinical parameters of all patients on prednisolone at start of the study

	Prednisolone n = 206
Median (IQR) age (years)	63.3 (20.5)
Sex n (%)	Females = 129 (62.6%)
	Males = 77 (37.4%)
Etiology	Respiratory = 105 (51%)
	Rheumatology = 50 (24.3%)
	Hematology = 28 (13.6%)
	Malignancy = 5 (2.4%)
	Dermatology = 6 (2.9%)
	Gastroenterology = 3 (1.5%)
	Others = 6 (2.9%)
Inhaled glucocorticoids n (%)	68 (33%)
	High dose = 62%[a]
	Medium or low dose = 38%
Mean (SD) baseline cortisol at first AST	228 (120) nmol/L
	8.27 (4.4) μg/dL
Median (IQR) baseline ACTH at first AST[b]	20.4 (20.0) ng/L (n = 190)
	4.5 (4.4) pmol/L
Median (IQR) duration of glucocorticoids (days)	853 (1273) n = 201
Median (IQR) follow-up duration in patients with >1 ASTs (days)	357 (405) (n = 71)
Mean (SD) duration for weaning prednisolone from testing (days)	141 (192) (n = 137)

Abbreviations: ACTH, adrenocorticotrophic hormone; AST, ACTH stimulation test; IQR, interquartile range.
[a]Dose calculated as per National Institute of Clinical Excellence (NICE) clinical knowledge summaries (available via link: https://cks.nice.org.uk/topics/asthma/prescribing-information/inhaled-corticosteroids/#:~:text=More%20than%20800%20micrograms%20budesonide, be%20considered%20a%20low%20dose). High-dose inhaled glucocorticoids defined as beclometasone dipropionate pressured metered dose or dry power >1000 μg/day or extrafine >500 μg/day, budesonide >1000 μg/day, fluticasone propionate >500 μg/day, or fluticasone furoate >100 μg/day.
[b]13/206 (6.3%) patients fully suppressed ACTH (<5 ng/L) at first AST (baseline).

who were converted to hydrocortisone there were 137/176 (77.8%) of the patients on prednisolone ± steroid inhalers who reactivated their HPA axis.

Secondary Outcome

During the study period, there were 161 patients who had failed an AST and therefore had confirmed tertiary AI. Of these, there were 71 patients on prednisolone ± glucocorticoid inhalers at the start of the study and underwent subsequent testing with AST(s). To assess whether conversion to hydrocortisone influenced recovery outcome, 10 and 13 patients on dose-matched prednisolone (4-5 mg) and hydrocortisone (20 mg), respectively, were analyzed (Fig. 2). The recovery rate in the prednisolone group was 70%, while in those patients converted to hydrocortisone it was 15% ($P = .008$). Results were similar for reactivation of the HPA axis in all adrenally suppressed patients who underwent subsequent testing. Prednisolone ≤5 mg/day; n = 41 vs hydrocortisone ≤25 mg/day; n = 30% and 61% vs 27%; $P = .004$, recovered, respectively (Supplementary Table (31)).

Analysis of Confounding Factors

A comparison of demographic and clinical factors between the 2 dose-matched groups showed that there was no difference in age, indication for glucocorticoid treatment, or duration of glucocorticoids between the 2 groups. There were more females in the hydrocortisone group, albeit the difference fell short of statistical significance ($P = .074$). However, there was significantly higher use of opioids in the prednisolone group ($P = .034$). The mean baseline cortisol (0 minutes) and median ACTH at first AST was not different between the 2 groups. The mean number of ASTs per patient was significantly fewer and the follow-up duration time in the prednisolone group was significantly shorter than in the hydrocortisone group (Table 2).

Hospital Admissions Comparison Between Prednisolone and Hydrocortisone Groups

There were no hospital admissions due to adrenal crisis in the prednisolone group while there were 2 patients in hydrocortisone group who had at least 1 hospital admission due to adrenal crisis (5 in 1 patient) during the study period. There was no inpatient mortality during any of the admissions. The total number of admissions for any indication was 14 in the prednisolone group and 26 in the hydrocortisone converted group.

Discussion

This retrospective study found that most patients on long-term prednisolone have normal HPA axis function when referred for dynamic testing. When tertiary AI is confirmed, the weaning rate was high, and the process was short in most patients on low-dose daily prednisolone throughout the weaning process, with only 1.7% of patients remaining on prednisolone after 3 or more failed ASTs. Conversion from prednisolone to hydrocortisone did not seem to enhance HPA axis recovery in those who were converted. There were no hospital admissions for adrenal crisis in the patients weaned from prednisolone and 6 in those on hydrocortisone. These results question the rationale for converting patients to a hydrocortisone replacement regimen to enhance HPA axis reactivation when weaning patients from anti-inflammatory glucocorticoids.

Our findings show that most patients on long-term prednisolone (≥12 weeks) do not have tertiary AI when tested at 3 to 5 mg per day, and, therefore, can be weaned further. The absolute risk of tertiary AI due to oral glucocorticoids reported in a meta-analysis from 74 studies is 48.7% (95% CI 36.9-60.6) (1). This is higher than the 33.5% (69/206) rate reported in this study. The difference may be explained by heterogeneity in the methodology, reporting, assays, glucocorticoid type, or testing in the studies included in the metanalysis. Also, the rate of tertiary AI in our study cohort has been only reported in those who underwent dynamic testing. The metanalysis also showed good rates of further HPA axis recovery in patients when they are managed by review and retesting, similar to our findings.

To our knowledge, there is only 1 study comparing reactivation of the HPA axis between patients on prednisolone and hydrocortisone (32). Although comparison of the weaning success between the 2 glucocorticoids was not the primary aim of their study the authors reported a recovery rate in the prednisolone group higher than hydrocortisone (71% vs 27%).

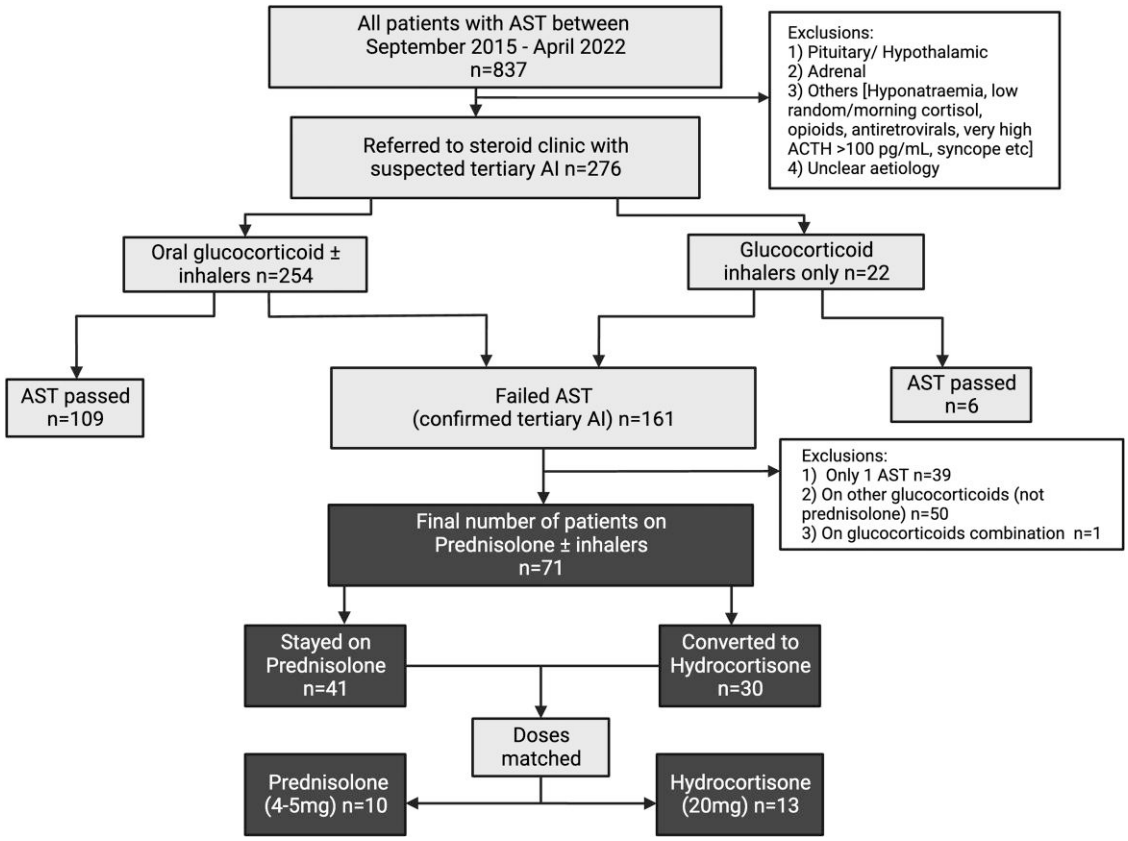

Figure 2. Consort diagram outlining study methodology and secondary outcome (created with biorender.com). Abbreviations: ACTH, adrenocorticotrophic hormone; AI, adrenal Insufficiency; AST, ACTH stimulation test. Of all patients referred to the steroid clinic who underwent AST testing, 161 failed the AST and had confirmed tertiary AI. Of these, only patients who were on prednisolone only and who underwent further AST testing (n = 71) were included in this analysis. Of these, 30 were converted to hydrocortisone due to symptoms while the rest (n = 41) remained on prednisolone. The patients in both groups were dose matched and recovery rates compared.

However, it was a retrospective study of rheumatology patients who were not matched for glucocorticoid doses and the mean baseline cortisol in hydrocortisone group was lower than the prednisolone group, limiting the direct comparison between the 2 glucocorticoids. In addition, little information was provided on potential confounding factors. In our study, we questioned whether converting patients on long-term prednisolone, who were symptomatic on physiological dosing and who failed their AST to hydrocortisone had any impact on their rate of recovery. In our dose-matched analysis between these patients and those on long-term prednisolone converting to hydrocortisone did not improve recovery rate, irrespective of there being no difference in duration of glucocorticoids, underlying etiology, or mean baseline cortisol/ACTH between the groups. There were more females (non-significant) in the hydrocortisone group; however, this is unlikely to have impacted on tertiary AI rate recovery as there is no such reported association in the literature (1). We also found that there was a statistical difference in the use of opioids between the groups, but all the users were in our prednisolone rather than hydrocortisone group. Nonetheless our analysis is retrospective, and these data cannot establish for certain which is the best glucocorticoid for HPA axis recovery. In addition, some patients do not recover from adrenal suppression, 15% after 3 years from cessation (33), possibly contributing to the lower rate of recovery in patients converted to hydrocortisone. A randomized controlled trial is needed to prospectively assess this.

Despite a paucity of evidence, experts recommend conversion to hydrocortisone in the weaning process. In a recently published Delphi study (14), which included 131 experts from pulmonology, endocrinology, rheumatology, and patient advocacy organization representatives from all over the world, 65% supported the statement that "the prednisolone to hydrocortisone conversion aids in the tapering process." Although this statement did not reach final consensus (<70% agreement), it is noteworthy that only 8% experts disagreed with the statement that patients should be converted to hydrocortisone when weaning patients off prednisolone. Conversion to hydrocortisone may have the advantage of avoiding other physicians inadvertently stopping prednisolone with no clinical monitoring or biochemical assessment for adrenal suppression. Conversely, we have shown that maintaining patients with glucocorticoid induced adrenal suppression on once daily low-dose prednisolone allows reactivation of the HPA axis in most patients.

The mechanism allowing HPA recovery is not clear, but the assumption is that once glucocorticoid levels fall to or below physiological levels the HPA axis will start to recover. Identifying the most appropriate glucocorticoid replacement dose in a patient with tertiary adrenal insufficiency is not straightforward. No formal glucocorticoid biomarkers are available to help titrate dosing, therefore in most cases conventional guidelines used in the treatment of patients with adrenal insufficiency are followed (21). The total physiological

Table 2. Comparison of various demographic and clinical parameters between dose matched prednisolone and hydrocortisone groups in the subanalysis

	Prednisolone n = 10	Hydrocortisone n = 13	*P* value
Mean (SD) age (years)	67.1 (12.2)	63.4 (11.1)	.464
Sex, n (%)	Females = 5 (50%)	Females = 11 (85%)	.074
	Males = 5 (50%)	Males = 2 (15%)	
Etiology, n (%)	Respiratory = 4 (40%)	Respiratory = 10 (76%)	.150
	Rheumatology = 4 (40%)	Rheumatology = 1 (8%)	
	Malignancy = 1 (10%)	Hematology = 1 (8%)	
	Dermatology = 1 (10%)	Gastroenterology = 1 (8%)	
Mean (SD) baseline cortisol at first AST	145 (115) nmol/L 5.3 (4.2) µg/dL	126 (86) nmol/L 4.6 (3.1) µg/dL	.648
Median (IQR) baseline ACTH at 1st AST[a]	20.5 (29.0) ng/L (n = 9) 4.5 (6.4) pmol/L	16.3 (14.8) ng/L (n = 10) 3.6 (3.3) pmol/L	.905
Median (IQR) duration of glucocorticoids (days)	1213 (1114)	2316 (4808)	.693
Number of patients on opioids, n (%)	3 (30%)	0 (0%)	**.034**
Median (IQR) number of ASTs per person	2 (2)	3 (1)	**.042**
Median (IQR) follow-up duration (days)	348 (975)	677 (884)	**.012**

P values in bold indicates statistical significance.
Abbreviations: AST, ACTH stimulation test ACTH, adrenocorticotrophic hormone; IQR, Interquartile range.
[a]In prednisolone group 3/10 patients had a suppressed ACTH at first AST (baseline). None of the patients had a suppressed ACTH at first AST in the hydrocortisone group.

adult dose equivalent of hydrocortisone recommended by guidelines is 15 to 25 mg per day in 2 to 3 divided doses (21, 34). Converting to hydrocortisone did not appear to allow faster reactivation of the HPA axis. A possible explanation for delayed recovery when converting to multiple dosing hydrocortisone is that peaks of hydrocortisone result in excess glucocorticoid exposure over at least 12 hours of the day from waking. Recently, once-daily administered modified-release hydrocortisone preparations with longer half-lives have become available, but their role in recovery of HPA axis remains unknown.

Adrenal crisis resulting from hypocortisolemia is a potentially life-threatening complication and results in mortality in approximately 6% of cases (35). Despite treatment, 6% to 8% of patients with AI suffer a crisis annually (36). We had 6 hospital admissions with adrenal crisis in this glucocorticoid cohort during the study period, none resulting in serious harm. The risk of adrenal crisis in tertiary AI is lower than in primary AI, possibly due to some residual cortisol secretion and aldosterone sufficiency (37, 38). Nonetheless, education on sick day rules and supply of parenteral glucocorticoids should be ensured in these patients as standard (25).

Our study is mainly limited by its retrospective design and a prospective study is needed to verify the findings. The rate of tertiary AI is reported for patients who underwent dynamic testing and does not include patients who were weaned off glucocorticoids, without testing, or were tested with unstimulated cortisol or salivary cortisone (12). Cumulative dosing was difficult to collect in view of retrospective study design limitations and therefore this was not considered in the analysis. Another limiting factor is that patients were converted to hydrocortisone by a clinician due to symptoms and therefore this selection was not random. On the other hand, baseline cortisol and ACTH between prednisolone and hydrocortisone groups and doses were matched in the subanalysis indicating similar adrenal suppression, albeit in small numbers of patients. There was a difference in the duration of glucocorticoids in the 2 groups, which was statistically not significant; however, this difference was not observed in the overall study population (median [IQR] duration of steroids in prednisolone n = 176: 832 [1205] days vs hydrocortisone n = 30: 1199 [1530] days; *P* = .305). Symptoms were either secondary to adrenal insufficiency or to withdrawal syndrome; these were precipitated by weaning to lower prednisolone doses. Nonetheless, we have established that converting a patient on prednisolone who has symptomatic adrenal suppression or withdrawal syndrome to hydrocortisone does not enhance the adrenal recovery rate, although some patients might get symptomatic benefit. An alternative approach for symptomatic patients on prednisolone could be a change to a slower wean.

We conclude that prednisolone allows HPA axis recovery in patients being weaned off glucocorticoids and can be considered as an appropriate option to continue long-term while awaiting recovery with periodic clinical and biochemical assessments at frequencies decided by physicians depending on adrenal status (13). A prospective randomized study to determine the optimal weaning regimen comparing different treatment regimens is needed in larger patient numbers.

Disclosures

John Newell-Price: Research income and consultancy paid to the University of Sheffield from Diurnal, Crinetics, Recordati, HRA Pharma. Richard Ross: Consultant to Diurnal Plc.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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