Continuous Subcutaneous Hydrocortisone Infusion Therapy in Addison’s Disease: A Randomized, Placebo-Controlled Clinical Trial

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Context: Patients with Addison’s disease (AD) report impaired subjective health status (SHS). Since cortisol exhibits a robust circadian cycle that entrains other biological clocks, impaired SHS may be due to the noncircadian cortisol profile achieved with conventional glucocorticoid replacement. Continuous subcutaneous hydrocortisone infusion (CSHI) reproduces a circadian cortisol profile, but its effects on SHS have not been objectively evaluated.

Objective: The aim of this study was to determine the effect of CSHI on SHS in AD.

Setting and Design: This was a multicentre, double-blind, placebo-controlled trial of CSHI vs oral glucocorticoid therapy. Participants received in random order 4 weeks of: CSHI and oral placebo, and subcutaneous placebo and oral hydrocortisone, separated by a 2-week washout period. SHS was assessed using the Short-Form 36 (SF-36), General Health Questionnaire (GHQ-28), Fatigue Scale (FS), Gastrointestinal Symptom Rating Scale (GSRS); and Addison’s Quality of Life Questionnaire (AddiQoL). Participants were asked their (blinded) treatment preference. Twenty-four hour urine free cortisol (UFC) and diurnal salivary cortisol collections compared cortisol exposure during each treatment.

Results: Ten participants completed the study. Baseline SHS scores (mean ± SE) were consistent with mild impairment: SF-36 physical component summary 48.4 ± 2.4, mental component summary 53.3 ± 3.0; GHQ-28 18.1 ± 3.3; GSRS 3.7 ± 1.6, and AddiQoL 94.7 ± 3.7. FS was similar to other AD cohorts 13.5 ± 1.0 (P = 0.82). UFC between treatments was not different (P = 0.87). The salivary cortisol at 0800 h was higher during CSHI (P = 0.03), but not at any other time points measured. There was no difference between the treatments in the SHS assessments. Five participants preferred CSHI, four oral hydrocortisone, and one was uncertain.

Conclusions: Biochemical measurements indicate similar cortisol exposure during each treatment period, although a more circadian pattern was evident during CSHI. CSHI does not improve SHS in AD with good baseline SHS. This casts some doubt on the potential benefit of circadian cortisol delivery on SHS in AD. (J Clin Endocrinol Metab 99: 4149–4157, 2014)
Primary adrenal insufficiency (Addison’s disease, AD), described by Thomas Addison in 1855, is most frequently due to autoimmune destruction of the adrenal cortex (1, 2). The widespread availability of glucocorticoid replacement in the 1950s improved survival of this otherwise fatal disease (3). Physical and mental fatigue, stress, anxiety, depression, and impaired concentration (“L’encephalopathie addisonienne”) have long been recognized, and despite modern-day treatment, these symptoms, and impaired subjective health status (SHS), in this patient group persist (4–10). Specific impairments are in general health and vitality; mental and physical fatigue, reduced stress tolerance, and gastrointestinal (GI) symptoms are also reported (5–7). Impaired SHS is clinically relevant as it may result in work disability (5).

In healthy individuals, cortisol secretion follows a light-entrained circadian rhythm, in which cortisol levels reach nadir at midnight, begin to increase at approximately 0200 h, peak within 30 minutes of waking (cortisol-awakening response), and then gradually decrease throughout the day (11, 12). The circadian rhythm is derived from a dynamic ultradian rhythm comprising discrete pulses of glucocorticoid secretion, which follow adrenocorticotropin hormone (ACTH) pulses (13, 14). Superimposed is the pulsatile secretion of cortisol in response to psychological and physical stressors and other stimuli (eg, protein-containing mid-day meal) (15–17).

Conventional glucocorticoid replacement comprises intermittent oral dosing, which produces peaks and troughs in serum cortisol quite unlike the circadian variation (18). It has been hypothesized that impaired SHS in AD is due to nonphysiological glucocorticoid replacement (19). This has provided the impetus for the development of circadian glucocorticoid delivery systems: modified-release oral hydrocortisone (OHC) and continuous subcutaneous hydrocortisone infusion (CSHI) therapy using proprietary insulin pumps (20, 21). Anecdotal data and open-label studies suggest that SHS is improved, but placebo-controlled trials have not been performed (21–23).

We performed a randomized, double-blind, placebo-controlled clinical trial to determine whether CSHI improves SHS in AD compared with standard best practice: thrice daily OHC (24).

### Subjects and Methods

#### Patients and Methods

**Subjects and design**

This was a multicenter randomized, double-blind, placebo-controlled clinical trial (Therapeutic Goods Administration Clinical Trials Notification Scheme [Drugs], Trial Number 2008/217), conducted between 2008 and 2013. We obtained site-specific Human Ethics Committee approval (Royal Adelaide Hospital [RAH], Princess Alexandra Hospital [PAH] and Sir Charles Gairdner Hospital [SCGH]). Potential participants were identified by their Endocrinologist and referred to the site-specific principal investigator (PI; L.G., W.J.I., or D.E.H.). The inclusion criterion was an Endocrinologist-certified diagnosis of autoimmune AD. The exclusion criteria were: age <18 years, bilateral adrenalectomy, secondary adrenal insufficiency, hypopituitarism, type 1 diabetes, celiac disease, pregnancy, disturbed sleep-wake cycle (eg, shift workers), current treatment for a major psychiatric disorder, and any other disorder which, at the discretion of the investigators, could influence SHS or limit study participation. Safety considerations required that participants were living within the metropolitan area of the study site.

After a screening visit and providing written, informed consent, participants attended a practical session with a credentialed diabetes nurse educator on subcutaneous pump management following which written instructions were provided.

#### Interventions

The Pharmacy Department, RAH, performed the randomization and prepared the hydrocortisone and placebo capsules and reservoirs for all sites but had no direct contact with the study participants. Participants underwent two treatment periods each of 4 weeks duration and separated by a 2-week washout period (Figure 1). They received in random order: 1) CSHI and oral placebo, 2) OHC and placebo infusion. Double blinding of the randomization allocation was maintained until all participants had completed the study.

Hydrocortisone sodium succinate (Solu-Cortef; Pfizer Australia) was diluted in sterile water for injection to a concentration of 50 mg/ml. The placebo infusion was normal saline. The infusions were delivered by a MiniMed insulin pump (model 712; Medtronic Australasia). The infusion apparatus was applied as for an insulin pump. Participants were instructed to clean the injection site with an alcohol swab before cannula insertion and replace the reservoir and other disposable infusion apparatus (cannula and lines) every three days.

The OHC and oral placebo (lactose tablet) had identical encapsulations and were prescribed thrice daily (0800, 1200, and 1600 h). The total daily OHC dose was equivalent to the participant’s usual treatment. Infusion rates were derived from previously published data, our dose-response evaluation in one volunteer with AD and determined so as to be comparable with the ±10% the total daily OHC dose (21).

In addition to the basal infusion, participants self administered a bolus on waking, with lunch, and with the experience of a “daily life psychic stress.” The bolus doses used were based on data from our pilot study of hydrocortisone bolus administration in one volunteer with AD, with serial monitoring of salivary and serum cortisol and plasma ACTH at 20-minute intervals for the two hours following each bolus. This volunteer did not participate in the main part of the trial. On the evening prior to evaluation, the evening dose of hydrocortisone was replaced with 0.25 mg dexamethasone to permit safe omission of both the evening and following morning doses of hydrocortisone, which would otherwise confound the analyses. We evaluated bolus doses of hydrocortisone of 0.09, 0.18, 0.36, 0.72, 2.16 and 2.88 mg. Together, the waking and lunchtime bolus doses were 30–50% of the total daily basal dose. To prevent excessive hydrocortisone administration, participants were allowed a maximum of two “stress” boluses per day. For the purposes of the study, we
defined “daily life psychic stress” as “an episode of increased emotional tension, often associated with symptoms such as a rapid heartbeat, sweating, tummy rumbling. The episode must last longer than two minutes and often follows a socially challenging situation.” Participants were asked to record all boluses administered, and to describe the experience that preceded, and the perceived efficacy of, the “stress” bolus. Basal infusion rates, bolus doses, and OHC dosing schedules are presented in Table 1.

During weeks 2 and 4 of each treatment participants performed a 24-hour urine free cortisol (UFC) collection and a diurnal (collected at 0800, 0830, 0900, 1200, 1230, 1300, 1600, and 2100 h) salivary cortisol profile.

### Safety considerations

In the event of an intercurrent illness, participants suspended all study drugs, increased their glucocorticoid dose, sought medical assistance in accordance with their usual practice, and notified the study site PI.

### Assays

**Plasma ACTH**

ACTH was measured using the Immulite 2000 assay (Siemens Medical Solutions Diagnostics). The coefficient of variation for the assay was 9.4% at 32 ng/L.

**UFC, serum, and salivary cortisol**

These were assayed using the Roche Elecsys Cortisol Electrochemiluminescence Immunoassay on a Roche e601 analyzer (Roche Diagnostics). The coefficient of variation for the UFC assay was 12% at 91 nmol/L, and for the serum cortisol assay, 7% at 70 nmol/L. The sensitivity of the salivary cortisol assay was 8.5 nmol/L and cross-reactivity with cortisol was 0.3%.

### Subjective health status questionnaires

These were completed prior to and at the end of each treatment. We used the Short Form 36 Health Survey (SF-36), the Fatigue Scale (FS), the General Health Questionnaire-28 (GHQ-28), and Gastrointestinal Symptom Rating Scale (GSRS) (25–28). The SF-36 is the most widely used generic instrument to assess quality of life (QOL) (25). It consists of eight multi-item domains representing physical functioning (PF), role functioning physical (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role functioning emotional (RE), and mental health (MH). The domain scores range from 0–100 with higher values indicating better QOL. SF-36 scores are reported as absolute values. We compared baseline SF-36 scores of study participants with data from an Australian reference population and Norwegian and United Kingdom (UK) AD cohorts (5, 7, 26). The FS is an 11-item questionnaire developed to measure the severity of fatigue (27). We compared baseline FS scores of study participants with data from a Norwegian AD cohort (5). The GHQ-28 is a 28-item survey that screens for psychiatric disorders (28). It evaluates for severe depression, anxiety/stress and somatic symptoms. GI symptoms were evaluated using the GSRS (29). Higher scores with the FS, GHQ-28, and GSRS reflect more severe fatigue, psychiatric distress and GI symptoms, respectively. Participants entering the trial after the Addison’s Quality of Life Questionnaire (AddiQOL), a validated 30-item questionnaire for assessing health-related quality of life in AD, became available also completed this (n = 5) (30). Higher scores reflect better QOL.
the end of the study, participants were asked in a free response questionnaire whether and why they had a preference for either treatment.

**Statistical analysis**

Continuous variables are summarized as mean (±SEM). The comparison of means and ANOVA for two-period, repeated-measures, crossover design studies, were performed using Statistica (99 Edition, Statsoft). All other analyses were performed using GraphPad Prism version 6 for Mac OS X (GraphPad Software). We used the Student’s t test for all statistical tests with 2-sided P < 0.05 considered statistically significant.

**Results**

**Participant characteristics**

Forty-two individuals expressed an interest in participating in this study. Fifteen individuals fulfilled exclusion criteria, 12 did not consent and five withdrew from the study after consenting, but prior to commencing the study. Ten individuals completed the study and their characteristics (mean ± SD) are shown in Table 2.

**Pilot study**

Serum and salivary cortisol were undetectable after bolus doses of 0.09 and 0.18 mg hydrocortisone. Bolus doses of 0.36, 0.72, 2.16 and 2.88 mg produced peak increments in serum cortisol of 20, 50, 100 and 200 nmol/L, respectively, with the peak measured cortisol on each occasion occurring 40 minutes following bolus administration. There was no detectable change in salivary cortisol for bolus doses of 0.36 and 0.72 mg of hydrocortisone. The salivary cortisol increments after 2.16 and 2.88 mg of hydrocortisone were 18 nmol/L and 8 nmol/L, respectively, occurring 40 minutes following bolus administration. Plasma ACTH levels were not suppressed by any bolus dose. Based on these data, participants were given 3–5 mg hydrocortisone self administered a 10-U bolus of hydrocortisone.

**Glucocorticoid levels**

The mean total daily dose of OHC was not significantly different between the two treatments (21.76 ± 1.82 mg and 21.7 ± 2.22 mg for CSHI and OHC, respectively; P = 0.98). The 24 h UFC during CSHI and OHC treatments was not significantly different (189.8 ± 69.4 nmol/24 h, 200.3 ± 42.4 nmol/24 h, respectively; P = 0.87; Figure 2). Salivary cortisol was significantly higher at 0800 h during CSHI (19.4 ± 4.1 nmol/L) than during OHC (8.16 ± 1.7 nmol/L).

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**Table 1. Oral, Sc Basal, and Sc Bolus Infusion Doses for Each Study Participant**

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<td>36.36</td>
<td>20.6</td>
<td>21.57</td>
<td>22.68</td>
<td>13.64</td>
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<td>10</td>
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<td>10</td>
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<td>8</td>
<td>2.5</td>
<td>8</td>
<td>4</td>
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<td>4</td>
<td>10</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>2.5</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
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<td>40</td>
<td>20</td>
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<td>20</td>
<td>13</td>
<td>22</td>
<td>20</td>
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</table>

For ease of dose comparison between treatments, infusion doses are given in mg of hydrocortisone. The concentration of hydrocortisone in the infusion set was 50 mg/mL. The infusion pump was set to deliver hydrocortisone in “units per hour.” This conversion was made as follows: 1 U = 0.5 mg hydrocortisone (based on a hydrocortisone concentration of 50 mg/mL and the conventional insulin concentration of 100 U/mL). Thus, a participant administering 5 mg of hydrocortisone self administered a 10-U bolus of hydrocortisone.

Abbreviations: TDD, total daily dose.

* Basal plus waking and lunch bolus doses.
nmol/L; \( P = 0.03 \)) treatment (Figure 2). At all other collection times there was no difference in salivary cortisol levels between the treatment groups (\( P > 0.05 \) for all comparisons).

**Stress boluses**

These were infrequently used. Four participants administered “stress” boluses during the trial. Two administered a total of six boluses while receiving placebo infusion, and four administered a total of five boluses while receiving CSHI.

**Subjective health status: Baseline**

Baseline SF-36 scores were not significantly different from an Australian Household survey (Figure 3) (26). Our participants had better RP, SF and MH and a trend to better VT and RE than a UK AD cohort (Figure 3) (7). The mean baseline SF-36 and FS scores were not significantly different from a previously reported cohort of Norwegian patients with AD, although there was a nonstatistically significant trend (\( P = 0.1 \)) to better SF in our study participants (Figure 3) (5). Comparison of the UK and Norwegian AD cohort data revealed significantly higher scores in RP, RE, and MH domains (\( P = 0.02, 0.03, \) and 0.03, respectively) in the Norwegian AD cohort. The mean GHQ-28 score was 18.1 (±3.3), with two participants (20%) recording scores above 23, consistent with emotional distress (31). Four participants reported no GI symptoms at baseline, whereas two, three, four, and five participants reported abdominal pain, dyspeptic syndrome, indigestion syndrome, and bowel dysfunction syndrome symptoms, respectively. The median baseline AdDiQoL score was 99.

**Change in subjective health status following each treatment period**

The mean change in SF-36 domains during each treatment period is shown in Figure 4. Although there were greater improvements in GH, VT and MCS during CSHI than during OHC, the differences were not statistically significant. The mean change in FS score following OHC was \(-0.4 (±1.1); \text{range } -6 \to 7\) and following CSHI was \(-1.9 (±1.2); \text{range } -10 \to 2; P = 0.43\) (Figure 4). The mean change in GHQ-28 score following OHC was \(-4.56 (±2.6); \text{range } -18 \to 5\) and following CSHI, was \(-2.78 (±0.9); \text{range } -7 \to 1; P = 0.44\) (Figure 4). Of the two participants with a GHQ-28 score consistent with emotional distress at baseline, one continued to report such scores at all times during the study, whereas the other had pretreatment, but not post-treatment scores consistent with emotional distress. The mean change in GSRS score follow-
ing OHC was \(-1.0 (\pm 1.2; \text{range } -10 \text{ to } 4)\) and following CSHI was \(-1.6 (\pm 0.8; \text{range } -7 \text{ to } 1; P = 0.54)\) (Figure 4). There was no significant difference in the change in any of the subjective health status questionnaires between the two treatments \((P > 0.05 \text{ for all comparisons})\). ANOVA of SHS scores revealed no interaction between treatment and time \((P = 0.1 \text{ for all comparisons, data not shown})\).

**Treatment preference**

Four participants preferred OHC, five CSHI, and one participant did not have a preference.

**Discussion**

This is the first randomized, double-blind, placebo-controlled clinical trial evaluating the effect of CSHI on SHS in patients with AD. UFC measurements suggested that overall cortisol exposure during blinded CSHI was akin that of intermittent OHC, the standard care comparator. Salivary cortisol day curves suggested that higher morning cortisol levels were achieved with CSHI. Using a number of SHS assessments, we found that in individuals with a good baseline level of SHS, CSHI does not provide further improvement. Participants did not express a treatment preference for either OHC or CSHI.

Impaired SHS has been reported in a number of AD cohorts, suggesting a disease-specific deficit \((5, 7)\). Furthermore, using the SF-36, the RP, GH, VT and RE domains were most consistently impaired \((5, 7)\). In contrast, our participants had similar SF-36 scores to a reference Australian population \((26)\). Comparison with a UK AD cohort revealed better RP, SF and MH, and a trend to better VT and RE in our study participants, but no significant differences with a Norwegian cohort \((5, 7)\). This may be explained by statistically significant differences between the UK and Norwegian AD cohorts for RP and MH \((5, 7)\). There was a nonsignificant trend \((P = 0.1)\) to higher SF in our study participants compared with the Norwegian cohort \((5)\). Fatigue is also commonly reported in AD; our study participants had comparable fatigue levels to a Norwegian AD cohort \((5)\). The GHQ-28 detected a mental health illness prevalence of 20% in our study, similar to the prevalence of 19.5% in a large South Australian survey \((32)\). Our participants had baseline AddiQoL scores (median 99) higher than another AD cohort (median = 87, \(n = 99\)), and comparable with reference population data (median = 97, \(n = 462\)) \((33)\). Thus, overall, our study participants had relatively good SHS prior to entry into the trial.

There was no significant difference between changes in SHS with CSHI compared with conventional OHC. In contrast with our findings, an open-label crossover study of CSHI found significant improvements in SHS as measured by AddiQoL, suggesting an improvement in fatigue and in the PF domain of the SF-36 \((23)\). However, as acknowledged by the study’s authors, the open-label design renders the results prone to bias. The double-blind, placebo-controlled design of our study was devised to eliminate such bias. Although we found no improvement in SHS with CSHI, our study participants had relatively good SHS prior to entry into the trial. It could be that these individuals were already optimally replaced with glucocorticoid prior to enrolment, such that there could be no further improvement with CSHI. Our study protocol evaluated four weeks of CSHI, in contrast with the three
months evaluated by the open-label study (23). It is possible that four weeks of CSHI is too brief to document an improvement in SHS.

Although efforts to improve SHS in AD have focused on the development of modalities for circadian cortisol delivery, recent in vitro and rodent studies highlight the importance of the ultradian rhythm of cortisol in signal transduction (34). Rodent studies have demonstrated behavioral differences in response to continuous and pulsatile corticosterone delivery (35). Thus, the absence of ultradian variation in cortisol with conventional glucocorticoid replacement may account for impaired SHS, which cannot be improved with CSHI. A pulsatile CSHI, which replicates physiological circadian and ultradian rhythmicity, has recently been validated in healthy volunteers, and it will be of interest ultimately to examine the effects of this delivery system, on SHS in AD (36).

The better baseline SHS in our study participants compared with other AD cohorts is not surprising, given that our study group was largely self-selected. Our study protocol was intensive since safety considerations in this double-blind study required that participants use both the pump and the oral medication during each treatment as though each contained the active drug. Thus, the study design demanded a focus from participants such that perhaps only those with a good baseline SHS volunteered to be involved. Similarly, the participants in the open-label study had better SHS than previous cross-sectional studies (23).

Our measurements of cortisol during OHC and CSHI showed no difference in overall cortisol exposure between the treatments as 24-hour UFC was not significantly different. This is in contrast to the open-label study in which 24-hour UFC was significantly higher during CSHI than during OHC treatment (23). This discrepancy could be explained by similar daily hydrocortisone doses during the two treatments in our study (21.76 ± 1.82 mg, 21.7 ± 2.22 mg, with CSHI and OHC, respectively; P = 0.98) and significantly higher hydrocortisone doses during CSHI in the open-label study (22.59 mg ± 0.98, 18.9 ± 0.91 mg, with CSHI and OHC, respectively; P = 0.0082) (23). In our study, salivary cortisol was significantly higher at 0800 h during CSHI, but not at any other time points. This is expected as during CSHI participants were receiving hydrocortisone at the time of sample collection, whereas during the OHC treatment, participants collected the sample immediately prior to medication administration. Similarly, the open-label study found comparable salivary cortisol levels to those during OHC treatment at all time points except 0600 h (23). These data reflect the difficulty in producing a detectable circadian variation with CSHI, using salivary cortisol measurements, even when an open-label design allows initial dose adjustments (23). Dose considerations are relevant as there has been a trend toward lower glucocorticoid replacement doses in light of revised estimates of normal cortisol secretion rates being on the order of 5.7 mg/m² (37). Thus, fatigue in AD may be secondary to hypocortisolism, whereas higher cortisol replacement doses may also impair SHS (9).

Salivary cortisol is a measure of free (unbound) cortisol, which accounts for approximately 5% of total circulating cortisol. The parotid gland tissue harbors 11β-hydroxysteroid dehydrogenase 2, which metabolizes cortisol to cortisone (38). Thus, salivary cortisol concentrations are determined not only by unbound serum cortisol, but also by parotid gland metabolism of cortisol to cortisone. In contrast, salivary cortisone is largely derived from enzymatic conversion of plasma cortisol by the salivary glands (39). Preliminary data suggest salivary cortisone may be a better biomarker of free cortisol in certain clinical situations, including hydrocortisone administration (40). It may be that measurement of salivary cortisone would have allowed a more easily detectable circadian variation in cortisol, but this testing is not available in clinical practice (23).

A unique aspect of our study was the administration of hydrocortisone boluses on waking, with lunch and with a defined “psychic stress” to mimic the pulsatile secretion of cortisol in response to these stimuli. Our pilot study demonstrated peak cortisol levels approximately 40 minutes after bolus administration, which is similar to when endogenous cortisol peaks following these stimuli in healthy individuals (15–17). Few study participants reported administering stress boluses. This may reflect a perceived stigma to acknowledging the experience of stress.

A limitation of our study is the small number of study participants. The expected effects of CSHI were not known prior to this study, such that power calculations were difficult. The limited number of study participants implies the potential for insufficient statistical power to detect a difference between the treatments. Moreover, the good baseline SHS of the participants may have further impaired our ability to detect a difference between the treatments. Another limitation is that the AddiQoL was not available at the commencement of this study, and thus only the five participants entering the study after it became available, also responded to this questionnaire. This is likely to be too few respondents to have detected any difference between the treatments using the AddiQoL.

The high rate of nonconsent and withdrawal from this study calls into question the acceptability of CSHI to the AD patient population. CSHI involves invasive procedures (cannula insertion) foreign to most patients with AD. Unlike patients with type 1 diabetes mellitus in whom
conventional insulin treatment is with multiple daily injections, and hence who might find cannula replacement twice or thrice weekly comparatively appealing, standard treatment for AD is intermittent oral therapy. The need for self injection and wearing of an external device that may interfere with work and social activities, as well as serve as a constant reminder of their illness, may render CSHI unacceptable to most patients with AD. Ancillary data suggest a benefit of CSHI in patients with AD and impaired SHS (21). Our efforts suggest that studies of CSHI in AD are unlikely to recruit those individuals with the greatest impairments in SHS and in whom therefore the greatest benefit with CSHI might be demonstrated. This study, together with those of others, suggests that CSHI is safe, and thus an open-label therapeutic clinical trial could be performed in an individual patient with impaired SHS, whilst acknowledging the limited evidence for benefit (21, 23).

This is the first randomized, double-blind, placebo-controlled trial of CSHI compared with standard oral intermittent glucocorticoid replacement in patients with AD. Our data suggest that in patients with good baseline SHS, CSHI does not provide further improvement.

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