CLINICAL MANAGEMENT OF ADRENAL INSUFFICIENCY (AI) SHOWS NOTABLE HETEROGENEITY – DATA FROM THE EUROPEAN AI REGISTRY (EU-AIR)

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INTRODUCTION

- Adrenal insufficiency (AI) is a life-threatening, rare disease resulting from failure of corticosteroid hormone secretion. Characteristic signs and symptoms of AI include fatigue, anorexia, weight loss, nausea and vomiting.[1]
- Over the past 50 years, the mainstay of treatment for patients with AI has consisted of conventional glucocorticoid (GC) replacement therapy given orally two or three times daily; however, there are no consensus guidelines regarding the optimal GC regimen in AI.
- Despite conventional replacement therapy, AI is associated with unfavourable metabolic effects, some of which are dose-dependent,[2–4] and life expectancy remains reduced compared with the general population.[1,5]
- Patients with AI who are receiving conventional GC replacement therapy also report impaired quality of life and the condition impacts on physical activity, and family, social and work life (including absenteeism from work).[6,7]

AIMS

- The aim of this analysis was to describe the current management of AI in patients receiving conventional GC therapy who are enrolled in the European Adrenal Insufficiency Registry (EU-AIR).

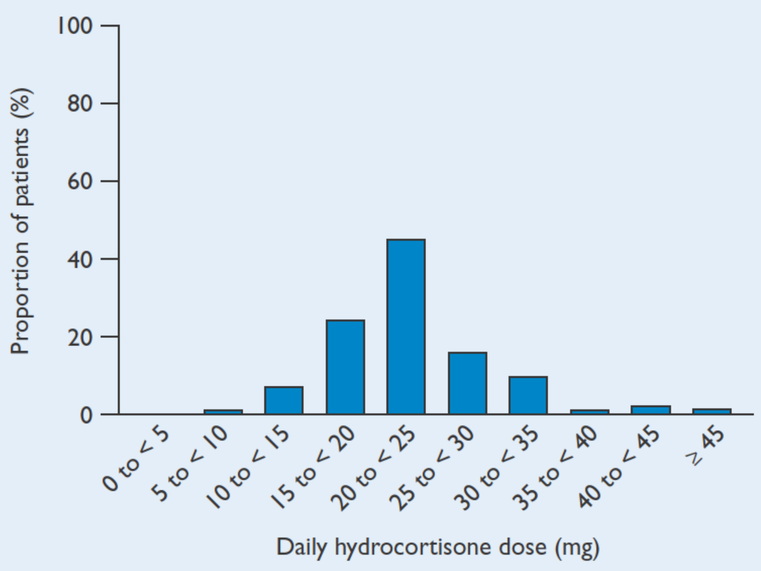
METHODS

- EU-AIR is a prospective, multinational, multicentre, observational study that was initiated in August 2012 to monitor the long-term safety of modified-release hydrocortisone and conventional GC replacement therapy during routine clinical practice in patients with chronic AI (ClinicalTrials.gov identifier: NCT01661387). The registry is sponsored by Shire.
- Written informed consent/assent is provided by each patient and/or their parent(s)/legal guardian(s) before enrolment in EU-AIR.
- All patients with a diagnosis of AI (primary AI, secondary AI or congenital adrenal hyperplasia) who are receiving modified-release hydrocortisone or other GC replacement therapies are eligible for inclusion in the study. All treatment decisions are made by the treating physician and/or patient.
- Routine visits occur every 6–12 months. Patient diaries are used to record intercurrent illnesses and illness-related dose changes between visits; this information is entered in the database at subsequent clinic visits.
- Data collection and entry are conducted as described previously.[8]
- This descriptive analysis included data collected between 8 August 2012 and 5 November 2014 from patients with primary or secondary AI receiving conventional GC replacement therapy for 28 days or longer. Individuals may have received more than one GC replacement therapy and/or received a single GC therapy at different doses during this time period. Patients with congenital adrenal hyperplasia and those receiving dual-release hydrocortisone were not included in the analysis. Exposure records with a duration of less than 28 days were excluded, as were data on dosage and/or dose frequency that appeared to be temporary (for emergencies).

RESULTS

- In total, 946 patients with AI who were enrolled in EU-AIR had received conventional GC replacement therapy for a duration of 28 days or more between 8 August 2012 and 5 November 2014 (510 [53.9%] female; 310 [32.8%] with primary AI, 634 [67.0%] with secondary AI and 2 [0.2%] with unknown AI aetiology). Mean (± standard deviation [SD]) age at the time of analysis was 54.6 ± 16.4 years. Mean body mass index was 28.0 ± 5.5 kg/m^2. Patients came from 18 centres in four countries.

Figure 1. Proportion of patients exposed to different doses of hydrocortisone between 8 August 2012 and 5 November 2014 (minimum exposure = 28 days).[a]

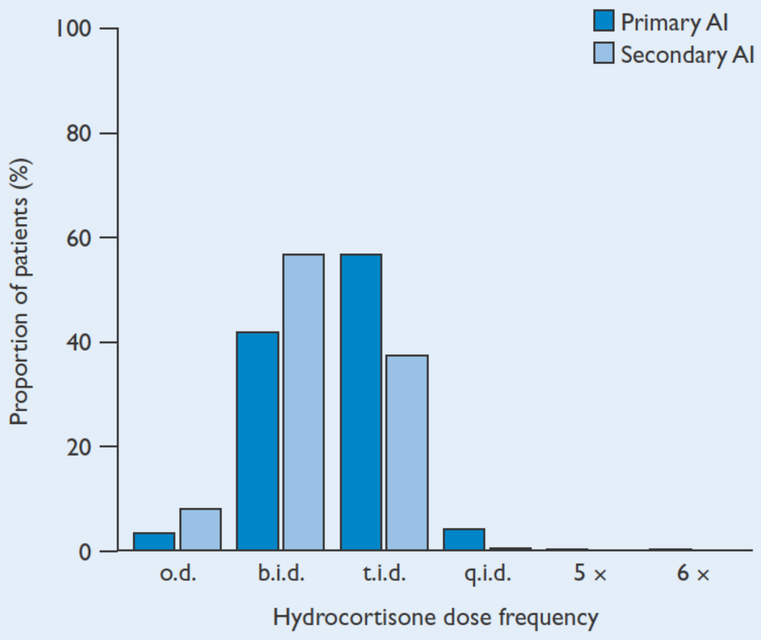


- Hydrocortisone was the most frequently used GC replacement therapy (91.8% of all patients with AI), and 6.8% had received prednisolone, 1.6% cortisone acetate, 0.1% dexamethasone and 0.3% had received another treatment.[a]

Hydrocortisone-treated patients

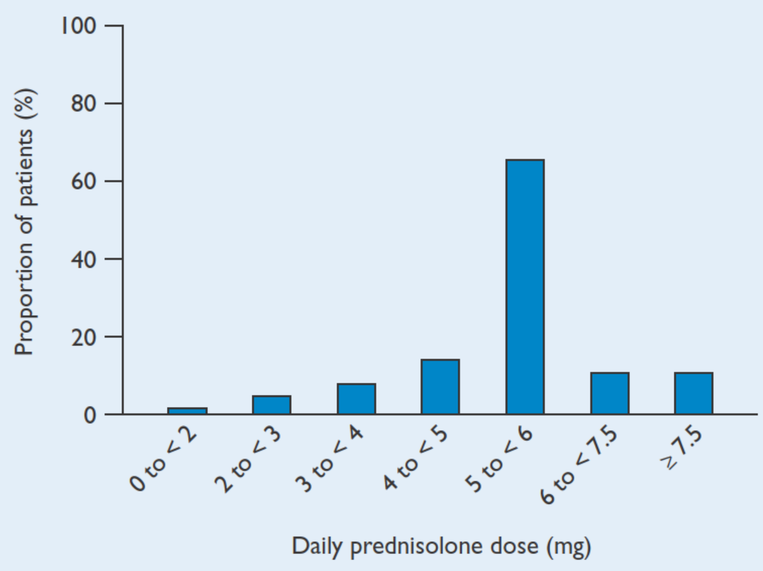
- Based on records of hydrocortisone use in EU-AIR, daily doses ranged from 5 to > 45 mg. The dose range that had been received by the most patients during the analysis period was 20 to < 25 mg/day (Figure 1), which was received by 44.9% of patients.[a] Doses of 15 to < 20 mg/day were received by 24.3% of patients and doses of 25 to < 30 mg/day by 16.0% of patients at some time during the study period. In total, 15.0% of patients had received hydrocortisone doses of ≥ 30 mg/day.
- Hydrocortisone had been taken once daily by 58 patients (6.7%), twice daily by 452 patients (52.1%), three times daily by 381 patients (43.9%), four times daily by 16 patients (1.8%), five times daily by 1 patient (0.1%) and six times daily by 1 patient (0.1%).[a] Patients with primary AI were more likely to have received hydrocortisone three times daily at some point in time during the study than those with secondary AI (56.9% versus 37.6%, respectively; Figure 2); conversely, patients with secondary AI were more likely to have received twice-daily dosing, at some time during the study, than those with primary AI (42.0% versus 56.9%, respectively).

Figure 2. Proportion of patients exposed to different hydrocortisone dose frequencies between 8 August 2012 and 5 November 2014 (minimum exposure = 28 days).[a]



AI, adrenal insufficiency; b.i.d, twice daily; o.d, once daily; q.i.d., four times daily; t.i.d., three times daily; 5 ×, five times daily; 6 ×, six times daily.

Figure 3. Proportion of patients exposed to different doses of prednisolone between 8 August 2012 and 5 November 2014 (minimum exposure = 28 days).[a]



- Patients with primary and secondary AI received mean (± SD) daily hydrocortisone doses of 23.3 (± 10.0) and 19.3 (± 5.9) mg/day, respectively.[b] Overall, median daily doses of hydrocortisone differed depending on the frequency of dosing: 10 mg for once daily (n = 59), 20 mg for twice daily (n = 476), 20 mg for three times daily (n = 411) and 25 mg for four times daily (n = 21). However, care should be taken in the interpretation of and decisions made regarding data from small numbers of patients (i.e. n < 30 patients).

Prednisolone-treated patients

- Based on records of prednisolone use, the daily doses ranged from < 2 to > 7.5 mg. The dose range received by the most patients during the study period was 5 to < 6 mg/day, which was used at some time by 65.6% of patients (Figure 3).[a]
- Prednisolone had been taken once daily by 47 patients (73.4%), twice daily by 19 patients (29.7%) and three times daily by 1 patient (1.6%).[a]
- Overall, median daily doses of prednisolone did not vary depending on the frequency of daily dosing: 5 mg for once daily (n = 54) and twice daily (n = 20) dosing.[b] However, care should be taken in the interpretation of and decisions made regarding data from small numbers of patients (i.e. n < 30 patients).

CONCLUSIONS

- The results of this analysis demonstrate that there is considerable heterogeneity in the current management of AI in terms of the type of GC used, and the dosage and frequency of administration.
- These findings probably reflect the real-world practice of dose individualization in the absence of robust data supporting an optimal treatment regimen for long-term outcomes.
- Variability in GC dosing may have clinical consequences for patients. It is already known that some of the adverse effects of GC therapies are dose-dependent.[3,4] Furthermore, GC over-replacement may lead to iatrogenic Cushing's syndrome, while under-replacement carries the risk of adrenal crisis.[9]
- This descriptive analysis highlights the need for clinical treatment guidelines for GC use and monitoring in patients with AI.

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[a]An individual patient may appear in more than one category. Each patient will be represented only once within a particular category.
[b]An individual patient may appear more than once within a particular category (e.g. a patient who has received 10 mg and 5 mg doses twice daily will be counted twice within the twice daily category), as well as in more than one category (e.g. a patient who has received treatment once and twice daily will appear in each category). Each combination of dose and frequency is represented only once.

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Study support: EU-AIR is funded by Shire. Medical writing support was provided by Harriet Crofts and Katie Pillidge at Oxford PharmaGenesis Ltd, Oxford, UK, and was funded by Shire.

Poster EP-39 presented at the 17th European Congress of Endocrinology, 16–20 May 2015, Dublin, Ireland.