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ORIGINAL ARTICLE

Management of glucocorticoid replacement in adrenal insufficiency shows notable heterogeneity – data from the EU-AIR

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Summary

Context and objective Treatment for adrenal insufficiency (AI) remains suboptimal. Despite glucocorticoid replacement, patients with AI have reduced life expectancy and quality of life. This study aimed to describe the spectrum of management of glucocorticoid replacement in patients with AI enrolled in the European Adrenal Insufficiency Registry (EU-AIR).

Design, setting and patients EU-AIR is a prospective, multinational, multicentre, observational study initiated in August 2012 to monitor the long-term safety of glucocorticoid replacement in routine clinical practice in Germany, the Netherlands, Sweden and the UK (ClinicalTrials.gov identifier: NCT01661387). This analysis included 1166 patients with primary and secondary AI (mean disease duration 16·1 ± 11·6 years) receiving long-term glucocorticoid replacement therapy.

Main outcome measure Glucocorticoid type, dose, frequency and treatment regimen were examined.

Results Most patients (87·4%) were receiving hydrocortisone. The most common dose range, taken by 42·2% of patients, was 20 to <25 mg/day; however, 12·6% were receiving doses of ≥30 mg/day. Hydrocortisone was being taken once daily by 5·5%, twice daily by 48·7%, three times daily by 43·6% and four times daily by 2·1%. Patients with primary AI received higher replacement doses than those with secondary AI (23·4 ± 8·9 and 19·6 ± 5·9 mg/day, respectively). Twenty-five different regimens were being used to deliver a daily hydrocortisone dose of 20 mg.

Conclusions We have shown significant heterogeneity in the type, dose, frequency and timing of glucocorticoid replacement in real-world clinical practice. This reflects dose individualization based on patient symptoms and lifestyle in the absence of data supporting the optimal regimen.

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EU-AIR Investigators details in Appendix A

Introduction

Adrenal insufficiency (AI) is a life-threatening, rare disease resulting from failure of glucocorticoid secretion in patients with secondary AI and additionally mineralocorticoid secretion in the less common case of primary AI (Addison's disease). Left untreated, acute adrenal failure can result in dehydration, hypotension and hypovolemic shock, and can be fatal, particularly during times of intercurrent illness.[1] AI was first described by Thomas Addison during his work at Guy's Hospital, London in 1855. Despite recognition of the condition, AI remained invariably fatal until the 1930s owing to the lack of any disease-specific treatment.[2] It was at this time that the first clinical evidence that extracts of animal adrenocortical tissue could counteract the adverse sequelae of AI in humans became available. Cortisone was first successfully used as a steroid replacement therapy in 1948.[3] Six more synthetic glucocorticoids became available for the treatment of AI during the mid-1950s.

With the development of steroid replacement, it was generally assumed that individuals with Addison's disease could expect to have a relatively normal lifespan, provided that they manage their daily medication appropriately, including taking intercurrent illnesses and stresses into consideration. Current glucocorticoid replacement therapy undoubtedly extends the life expectancy of patients with AI; however, two large registry-based studies in patients with Addison's disease have shown that the relative risk of death for these patients is more than double that

of the background population, despite glucocorticoid replacement.[4–6] Furthermore, these individuals report impaired quality of life, reduced perception of general health and an adverse impact on physical activity, and family, social and work life (including absenteeism from work).[7,8]

Current treatment of AI entails the use of one of the several oral glucocorticoids, usually administered in multiple small doses throughout the day, with the aim of mimicking the normal diurnal cortisol secretion pattern. For patients with primary AI, the addition of mineralocorticoid replacement is also important. The lack of a suitable biomarker for optimizing glucocorticoid replacement means that treatment is guided by subjective health status and clinical assessment of signs and symptoms of glucocorticoid over- and under-replacement. There are a number of variables to consider when using glucocorticoid replacement therapy, including the type of glucocorticoid, total daily dose, number of individual doses that the total daily dose is split into, and the timing of the individual doses. We aimed to establish current patterns of glucocorticoid usage within specialist endocrinology centres, by interrogation of data from the European Adrenal Insufficiency Registry (EU-AIR).

Methods

Study design

EU-AIR is a prospective, multinational, multicentre, observational study sponsored by Shire. It was initiated in August 2012 to monitor the long-term safety of both modified-release hydrocortisone and conventional glucocorticoid replacement therapies during routine clinical practice in patients with chronic AI (ClinicalTrials.gov identifier: NCT01661387). The study focuses on determining the frequency of intercurrent illnesses, adrenal crises and serious adverse events. Data are currently being collected from endocrinology centres in the UK, Germany, the Netherlands and Sweden (Figure S1).

All patients with a diagnosis of AI [primary AI, secondary AI or congenital adrenal hyperplasia (CAH)] who are receiving long-term glucocorticoid replacement therapy are eligible for inclusion in the study. All treatment decisions are made by the registry physician and/or patient, and 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 into the database at subsequent clinic visits. Comprehensive baseline data are collected at enrolment, as described previously.[9]

Ethics

The study has been approved by the appropriate local research ethics committees for all participating centres and is being conducted in accordance with the Declaration of Helsinki. Written informed consent/assent is provided by each patient and/or their parent(s)/legal guardian(s) before enrolment in EU-AIR.

Data collection and analysis

This descriptive analysis was performed on baseline data from patients with primary or secondary AI receiving conventional glucocorticoid replacement therapy, who were enrolled in the EU-AIR between 8 August 2012 and 13 May 2015. As patients with CAH frequently receive greater than physiological glucocorticoid doses, these individuals were excluded from the current analysis. Additionally, patients receiving modified-release hydrocortisone were excluded, as this subcohort predominantly comprised patients from the pivotal study of efficacy of this formulation,[10] and therefore were unlikely to be receiving treatment representative of current clinical practice.

Patients were categorized according to the drug they were receiving at baseline: hydrocortisone, prednisolone, cortisone acetate or dexamethasone. The dose, frequency and times at which patients were taking hydrocortisone and prednisolone were examined. Patients taking other glucocorticoid replacement therapies, and those taking more than one medication at baseline, were counted in a category labelled 'others'. Each patient was represented only once within a particular drug category.

To ensure that the treatment at baseline was not related to emergency/temporary use of medication, a 28-day period after the date of enrolment was examined. Exposure records with a duration of <28 days were excluded. Patients reporting multiple dosing records for their therapy within 28 days after enrolment were counted only at the highest dosage and the highest frequency associated with that dosage.

Descriptive statistics were used to analyze data; these included the number and percentage of observations, median, mean and standard deviation (SD).

Results

In total, 1462 patients with AI who were receiving conventional glucocorticoid replacement therapy were enrolled between initiation of the study and the data-cut on 13 May 2015. Patients with CAH ($n = 71$) and patients receiving modified-release hydrocortisone ($n = 202$) were excluded from the current analysis. A further 23 individuals who had received glucocorticoids for <28 days were excluded to be certain all patients analyzed had a definite diagnosis of chronic AI. The study cohort thus consists of 1166 patients: 364 (31·2%) with primary AI; 801 (68·7%) with secondary AI; and 1 (0·1%) in whom AI aetiology was not documented.

Patient demographics

The overall study cohort was of mean ± SD age 54·3 ± 16·0 years, 52·5% female, with an average disease duration of 16·1 ± 11·6 years from diagnosis (Table 1). The mean age was similar for patients with primary (52·0 ± 15·8 years) and secondary AI (55·2 ± 16·0 years). Patients with primary AI showed a slight female preponderance (65·1%), whereas those with secondary AI showed a similar proportion of females (46·7%) and males. Patients with primary AI had slightly longer

Table 1. Demographic parameters of patients enrolled into the EU-AIR

	Primary AI	Secondary AI	Overall
Patient number, *n*	364	801	1166
Female, *n* (%)	237 (65·1)	374 (46·7)	612 (52·5)
Age, years, mean ± SD	52·0 ± 15·8	55·2 ± 16·0	54·3 ± 16·0
Disease duration, years, *n* (mean ± SD)	364 (17·6 ± 12·8)	800 (15·4 ± 10·9)	1164 (16·1 ± 11·6)
BMI, kg/m^2, *n* (mean ± SD)	321 (26·2 ± 4·8)	695 (28·8 ± 5·1)	1016 (27·0 ± 5·2)
Diabetes, *n* (%)	51 (14·0)	94 (11·7)	145 (12·4)
Hypertension, *n* (%)	92 (25·3)	263 (32·8)	355 (30·4)

AI, adrenal insufficiency; BMI, body mass index; EU-AIR, European Adrenal Insufficiency Registry; SD, standard deviation.

mean duration of disease than those with secondary AI (17·6 ± 12·8 years and 15·4 ± 10·9 years, respectively).

Glucocorticoid replacement therapy

Hydrocortisone was the most frequently used glucocorticoid replacement therapy, with 87·4% of all patients receiving this steroid; 5·1% patients were receiving prednisolone; 4·0% cortisone acetate; and 0·1% were receiving dexamethasone. Data on glucocorticoid use were missing for 2·7% of patients, and 0·7% of patients were receiving other glucocorticoids or more than one type of glucocorticoid concurrently. Hydrocortisone was the most commonly utilized glucocorticoid replacement therapy in patients with both primary (84·9%) and secondary AI (88·5%) [difference: 3·6%; 95% confidence interval (CI) = −0·7% to 7·9%]. Of the patients not receiving hydrocortisone, a greater proportion were from the Netherlands, and fewer from the UK, when compared with those receiving hydrocortisone. The mean hydrocortisone dose equivalent was also lower in those who were not receiving hydrocortisone (14·1 ± 11·9 mg *vs* 20·7 ± 7·2 mg, respectively; Table S1).

Hydrocortisone-treated patients

In patients receiving hydrocortisone, the daily dose varied widely, ranging from 5 mg to >45 mg. The most common dose range taken by patients with AI was 20 to <25 mg/day (Fig. 1), which was being taken by 42·2% of patients. Doses of 15 to <20 mg/day were being taken by 22·9% of patients, and doses of 25 to <30 mg/day by 15·2% of patients. Therefore, 80·3% of patients were receiving a daily hydrocortisone dose of 15 to <30 mg. In total, 12·6% of patients were receiving hydrocortisone doses of 30 mg/day or more. A greater proportion of patients with primary AI were receiving hydrocortisone doses of 30 mg/day or more compared with those with secondary AI [21·4% *vs* 8·8%, respectively (difference: 12·6%; 95% CI = 7·6–17·6%)]. Patients with primary AI received higher mean daily hydrocortisone doses compared with those with secondary AI [23·4 ± 8·9 and 19·6 ± 5·9 mg/day, respectively (difference: 3·8 mg/day; 95% CI = 2·9–4·8 mg/day)]. Overall, doses of hydrocortisone differed depending on the frequency of dosing (Fig. 2): median of 10 mg for once daily (*n* = 56), 20 mg for twice daily (*n* = 496), 20 mg for three times daily (*n* = 444) and 25 mg for four times daily regimens (*n* = 21).

Hydrocortisone was being taken once daily by 56 patients (5·5%), twice daily by 496 patients (48·7%), three times daily by 444 patients (43·6%) and four times daily by 21 patients (2·1%). Two patients (0·2%) were taking hydrocortisone at a higher frequency. Patients with primary AI were more likely to be receiving hydrocortisone three times daily than those with secondary AI [53·7% *vs* 39·2%, respectively (difference: 14·5%; 95% CI = 7·9–21·1%); Fig. 3]. Conversely, patients with secondary AI were more likely to be taking hydrocortisone twice daily than those with primary AI [52·9% *vs* 38·8%, respectively (difference: 14·1%; 95% CI = 7·5–20·6%)].

The timing at which patients received their glucocorticoids [morning (05:01–11:00 h), midday (11:01–15:00 h), afternoon (15:01–18:00 h), evening (18:01–20:00 h), bedtime (21:01–00:00 h) and overnight (00:01–05:00 h)] was recorded. Using these data, we examined the variation in how a daily hydrocortisone dose of 20 mg was delivered. Twenty-five different regimens were being used to deliver a daily dose of 20 mg hydrocortisone; the most common regimen (used by 28·2% of patients) was 10 mg administered in the morning, 5 mg at midday and 5 mg in the evening (Fig. 4). The second most frequent regimen was use of hydrocortisone as a twice-daily regime: 10 mg in the morning and a further 10 mg at midday (18·0%). The third most common regimen was 10 mg administered in the morning, 5 mg at midday and 5 mg in the afternoon (17·2%), differing only from the most common regimen by taking the last hydrocortisone dose earlier. These three most common regimens account for 63·3% of the regimens used to deliver 20 mg hydrocortisone within this cohort.

Discussion

In this study, we observed considerable heterogeneity in the current management of AI in terms of dosage, frequency of administration, dose regimen and type of glucocorticoid used. Notably, the majority of patients with primary and secondary AI were treated with hydrocortisone, with a daily dosage of 15 to <30 mg, and administered using a twice- or thrice-daily regimen. Greater divergence was observed, however, in the regimen by which the glucocorticoid was administered, as exemplified by

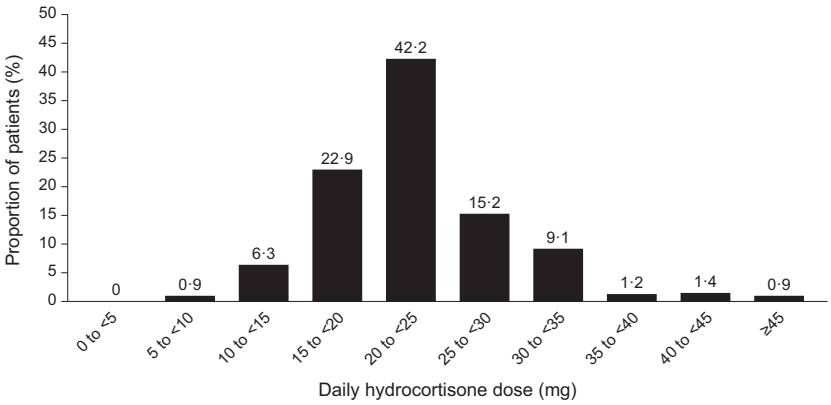

Fig. 1 Proportion of patients enrolled into the EU-AIR receiving different doses of hydrocortisone at baseline. EU-AIR, European Adrenal Insufficiency Registry.

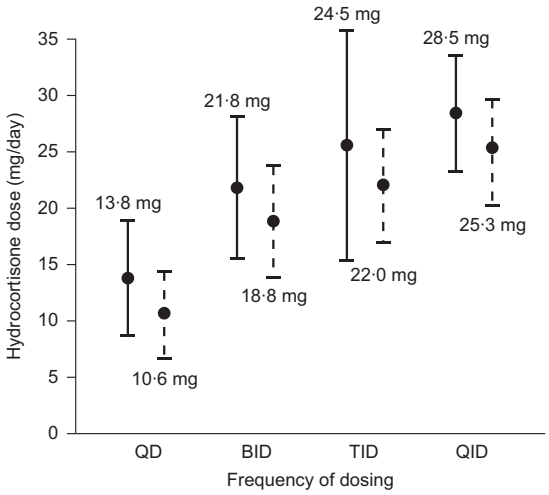

Fig. 2 Mean hydrocortisone doses according to the frequency of administration. Solid line – primary adrenal insufficiency: Dashed line – secondary adrenal insufficiency. Data are presented as mean ± standard deviation. BID, twice daily; QD, once daily; QID, four times daily; TID, three times daily.

our examination of patients receiving a daily hydrocortisone of 20 mg. Within this latter group, we identified 25 different regimens with which the therapy was administered. Although the daily doses of hydrocortisone used by clinicians in real-world practice varied widely from doses considered subtherapeutic (5 mg) to *supra*-physiological (>45 mg), the majority of patients received a daily dosage within the range of 15 to <30 mg.

The prevalence of primary AI in Western Europe is estimated to be 93–140 per million,[11,12] and that of secondary AI to be 290–455 per million population.[13] Due to the low prevalence of AI, adequately powered controlled studies of glucocorticoid regimens, whether comparing different glucocorticoid types or doses, are difficult to perform. Placebo-controlled studies are plagued with difficulty because of potential confusion over the management of increases in glucocorticoids during periods of intercurrent illness. It is unlikely that adequately powered prospective studies based upon the hard end-points of mortality, fracture rates and rates of adrenal crisis will be performed. Therefore, what few studies there are depend on the surrogate measurement of bone density, body composition, metabolism, surrogates of vascular risk, and quality of life. Therefore, data relating to optimal glucocorticoid replacement regimens to date have been derived from open and observational studies including small numbers of patients.[14–17] In contrast, the EU-AIR is a large, multinational registry for patients with AI, which is prospectively collecting observational data on the current management of AI, metabolic parameters and patient outcomes.[9] Analysis of these data will, over time, provide powerful evidence on which to base controlled studies, with the aim of determining best practice for the management of AI. The present analysis imparts considerable knowledge on how AI is currently managed, and the significant variability in the approaches taken.

The intention of current treatment regimens is to mimic the normal circadian pattern of endogenous plasma cortisol. However, in the absence of a specific biomarker to guide glucocorticoid replacement, treatment is guided by the subjective health

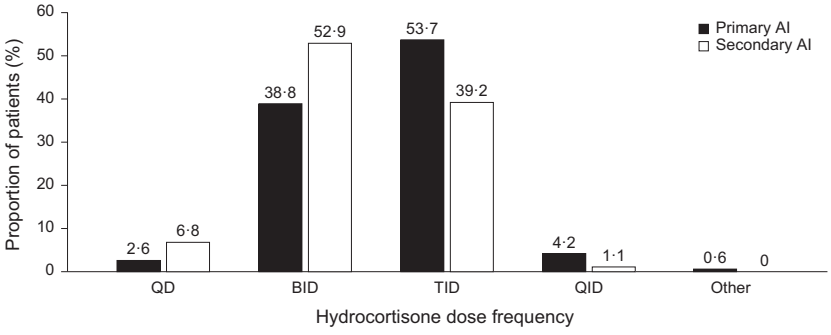

Fig. 3 Proportion of patients enrolled in the EU-AIR receiving different hydrocortisone dose frequencies at baseline. AI, adrenal insufficiency; BID, twice daily; QD, once daily; QID, four times daily; TID, three times daily.

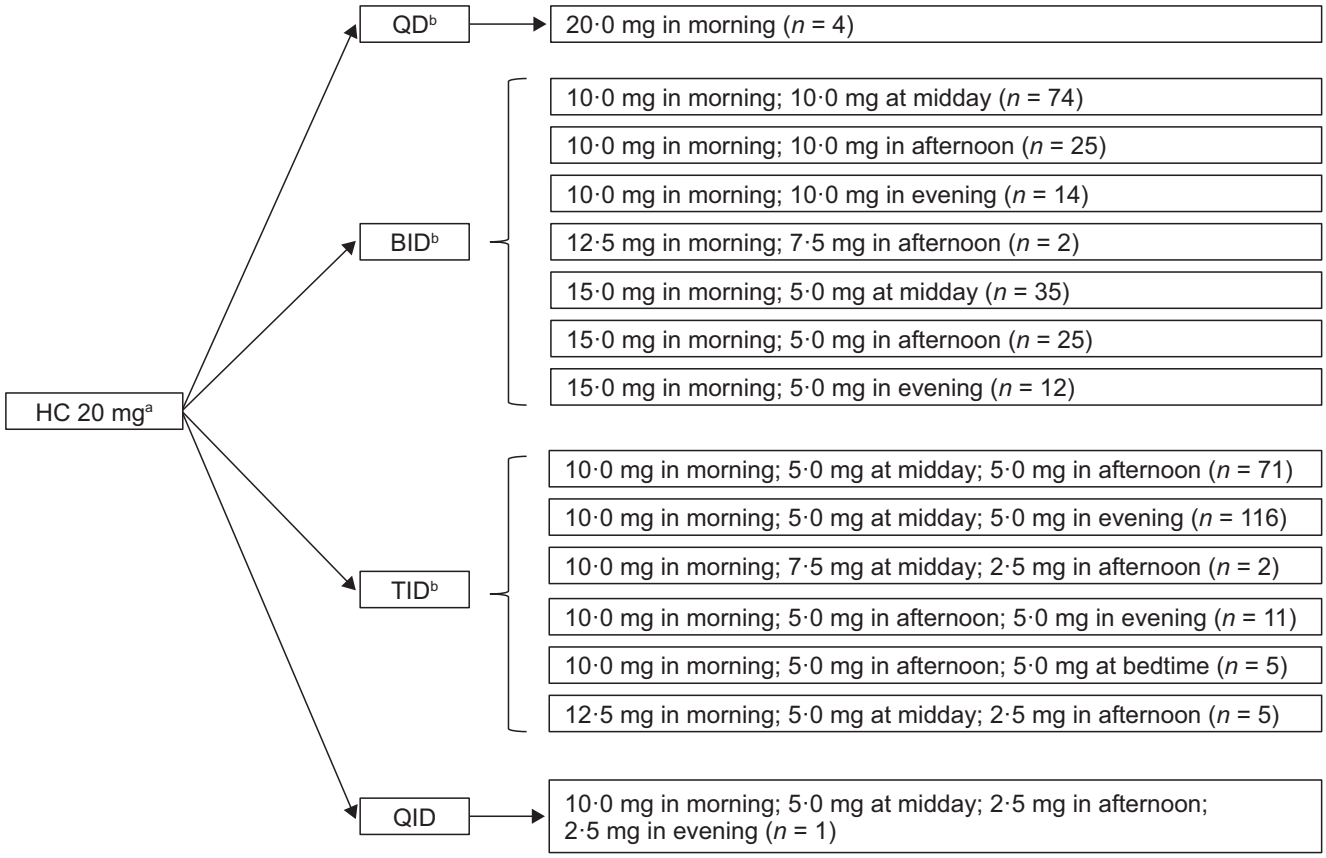

Fig. 4 Dosing regimens used to administer a total daily dose of 20 mg of hydrocortisone. BID, twice daily; HC, hydrocortisone; QD, once daily; QID, four times daily; TID, three times daily. [a]Data were available for 412 patients in total. [b]Two further QD, three further BID regimens and five further TID regimens were used by one patient each.

status of the individual, alongside clinical assessment of signs and symptoms of glucocorticoid over- or under-replacement. These variables lead to individualization of glucocorticoid replacement regimens. This analysis highlights that a multitude of different regimens, in terms of dosage, frequency, dose regimen and glucocorticoid type, are utilized.

From stable isotope dilution and deconvolution analyses, cortisol production rates are estimated to be 5·7–7·4 mg/m^2 per day, which translates to an equivalent daily hydrocortisone dose of 15–20 mg for cortisol replacement.[18–20] In this study, the majority of patients (80%) were taking daily doses of 15 to <30 mg. This would be in keeping with the recent Endocrine Society Clinical Practice Guideline for the diagnosis and treatment of primary AI, which recommends a daily hydrocortisone dose of 15–25 mg.[21] Notably, however, around one in eight (12·6%) patients was receiving hydrocortisone doses of 30 mg/day or more. A substantial proportion of patients within our cohort therefore appear to be over-replaced, increasing the risk of reduced bone mineral density, cardiovascular disease and an adverse metabolic profile.[1,14,18,22,23]

The cardiometabolic profile of the patients in this analysis suggests the possibility of glucocorticoid over replacement, in that mean body mass index (BMI) was elevated, and a substantial proportion had diabetes or hypertension. However, in the absence of a matched control group, it is difficult to make firm conclusions in this regard. In hypopituitary patients, both BMI and serum cholesterol levels are positively correlated with glucocorticoid doses.[22] Furthermore, glucocorticoid over replacement may impact on quality of life; patients taking hydrocortisone doses of 30 mg/day or more experience greater impairment of health-related quality of life compared with those taking lower doses.[24]

At the other end of the spectrum, inadequate glucocorticoid replacement also has important clinical consequences. In this study, 7·2% of patients were receiving hydrocortisone doses of <15 mg/day. This dosage may be sufficient in some patients with secondary AI with partial adrenocorticotropic hormone deficiency. While metabolic end-points in patients receiving daily hydrocortisone equivalent doses of <20 mg do not differ from patients who are glucocorticoid replete,[22] under-replacement has been associated with symptoms of fatigue, nausea, myalgia and joint stiffness, and an increased risk of adrenal crisis. In a study of 53 patients with AI, adrenal crises were most frequently due to glucocorticoid dose reduction or a lack of stress-related dose adjustment.[1]

In addition to the total amount of cortisol produced daily, it is intuitive to expect that the diurnal variation in cortisol levels is important. The frequency and regimen with which patients

take glucocorticoid replacement may therefore also be of clinical significance.[25] The majority of patients within our study who were receiving hydrocortisone were receiving this treatment twice or three times daily. Similar to the previously commented-upon recommended hydrocortisone dose, our observation on dosing frequency is in keeping with the recent recommendations within the Endocrine Society Clinical Practice Guideline for the diagnosis and treatment of primary AI, which recommends that the daily dose is applied in two to three doses.[21] Nevertheless, there was considerable heterogeneity in the frequency of administration and the regimen used to administer the divided doses. As an example, we described 25 different regimens used to deliver a daily hydrocortisone dose of 20 mg. The majority of these regimens provide a larger dose on waking, followed by one or two smaller doses throughout the day to approximate the physiological cortisol secretion profile.[26] How glucocorticoid replacement is delivered is of importance, as it can result in nonphysiological spikes and troughs in cortisol levels and nighttime cortisol exposure. The well-being of patients with AI is improved by closer mimicking of the normal cortisol secretion pattern, by either administering hydrocortisone more frequently or using continuous subcutaneous hydrocortisone infusions.[27–29] A recent study showed that patients prefer four times daily dosing to twice daily dosing when comparing equivalent overall doses of hydrocortisone.[27] Patients on four times daily dosing reported less fatigue, feeling more alert during the day and a less varied treatment effect. A caveat to interpreting these data, however, is that for a given dose of hydrocortisone, the relative bioavailability increases with the frequency of dosing.[27,30]

It has been shown that glucocorticoid replacement regimens that result in exposure to exogenous glucocorticoids late in the day, when physiological levels would normally be low, worsen carbohydrate handling compared with regimens where the dosage is delivered earlier.[25] The cortisol exposure profile, determined by the frequency and timing of glucocorticoid doses, may therefore be important in determining patient outcomes, in addition to the total daily dose. Further data are, however, needed to fully understand the impact of glucocorticoid replacement regimens on metabolism and long-term patient outcomes.

It is noteworthy that patients with primary AI were receiving higher mean daily doses of hydrocortisone than those with secondary AI. This may reflect the fact that patients with secondary AI frequently retain some residual cortisol secretion, whereas this is much less frequent in patients with primary AI.[1] On a similar note, patients with primary AI most frequently received hydrocortisone three times daily, in contrast to patients with secondary AI, who most frequently received twice daily doses. The assumption here is also that patients with secondary AI have sufficient residual cortisol secretion between doses to allow less frequent dosing without adverse effects on subjective well-being. In addition, it might be the case that in primary AI, too low fludrocortisone doses are used and are compensated by higher hydrocortisone doses.[31]

In addition to the uncontrolled nature of databases such as EU-AIR, it must be recognized that the centres participating in this study could all be considered as providers of tertiary care to patients with AI. It is therefore not possible to fully generalize the findings to those of less specialist centres where doses of glucocorticoids and their delivery may differ significantly from those described here.

In summary, we have shown significant heterogeneity in the type, dose, frequency and timing of glucocorticoid replacement therapy used in real-world clinical practice. This likely reflects dose individualization based on patient symptoms and lifestyle. We have additionally highlighted that many patients are receiving *supra*-physiological glucocorticoid doses that may, at least in part, be responsible for the adverse cardiometabolic profile of these individuals. The EU-AIR has the potential to provide data from large numbers of patients with AI, which will help determine 'best practice' in the management of these patients.

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Conflict of interest

MQ, BE, PZ and RDM have received honoraria for talks and consultancy fees from ViroPharma/Shire. CM and SU are employees of Shire.

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Appendix A
Collaborators

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Supporting Information

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