European Adrenal Insufficiency Registry (EU-AIR): a comparative observational study of glucocorticoid replacement therapy

Ekman B,[1] Fitts D,[2] Marelli C,[3] Murray RD,[4] Quinkler M,[5] Zelissen PMJ[6]

1. Department of Medicine and Health Sciences, Linköping University, Linköping, Sweden; 2. ViroPharma Inc., Exton, PA, USA; 3. ViroPharma SPRL, Maidenhead, UK; 4. Department of Endocrinology, St James's University Hospital, Leeds, UK; 5. Department of Clinical Endocrinology, University of Medicine, Berlin, Germany; 6. Department of Internal Medicine and Endocrinology, University Medical Center Utrecht, Utrecht, Netherlands

INTRODUCTION

- Adrenal insufficiency (AI) is a rare, life-threatening disease caused by the failure of corticosteroid hormone secretion; it is characterized by signs and symptoms that include weakness, fatigue, anorexia, weight loss, nausea and vomiting.[1]
- Prevalence of primary AI (Addison's disease) in Western Europe is estimated to be 90–160 per million inhabitants,[1–4] whereas the prevalence of secondary AI (pituitary insufficiency) has been reported to be 150–280 per million inhabitants.[1]
- There has been very little progress in the treatment of AI over the past 50 years. Despite treatment with conventional glucocorticoid (GC) replacement therapy, AI is still associated with high mortality and morbidity including increased hospitalizations due to infections, and unfavourable metabolic effects on blood pressure, weight, lipid profile and bone mineral density.[1,5] Patients with AI also report an impaired quality of life and a negative impact on physical activity and on family, social and work life.[5,6]
- PLENADREN® (hydrocortisone modified-release tablets) is a novel, once-daily, dual-release formulation of hydrocortisone that has been developed to mimic physiological cortisol secretion more closely than conventional GC replacement therapy in the management of patients with AI.
- The European Adrenal Insufficiency Registry (EU-AIR) was initiated in August 2012 as a multinational, observational study of patients with primary or secondary AI. This study will provide opportunities to characterize and evaluate current therapeutic approaches to controlling AI, as well as to collect long-term safety data related to the use of PLENADREN®.
- Here, we describe the protocol for EU-AIR, highlight the early enrolment of patients into the study and present preliminary demographic results.

METHODS

- EU-AIR is being conducted at clinics in Germany, the UK, Sweden and the Netherlands (Figure 1). All clinics must obtain informed consent from their patients before submitting data.
- Main endpoints of the study are the incidences of intercurrent illness, adrenal crisis events and other serious adverse events (SAEs), as well as the duration of SAEs and changes in dose of GC replacement therapy related to SAEs.
- At baseline, demographic information is collected for each patient, together with the relevant medical history (including type of AI and year of diagnosis). Other data recorded at baseline and at routine clinic visits (approximately every 6 months) are shown in Table 1. Relevant additional data (e.g. dual-energy X-ray absorptiometry) and information from patient diaries are also recorded.
- At participating clinics, all patients with a diagnosis of AI who are receiving chronic GC replacement therapy are eligible for inclusion in the study. In Germany, only adult patients are eligible. Any patient participating in an interventional clinical study must wait for 3 months after completion of that study before enrolment in EU-AIR.
- The EU-AIR protocol offers no guidance or instructions for patient management. All decisions regarding treatment and patient care are made by the physician and patient.
- The target sample size is 3600 patient-years of exposure (i.e. 1800 patient-years each on conventional GC and PLENADREN®).
  - This level of exposure is assumed to provide 80% power to demonstrate non-inferiority of PLENADREN® relative to conventional GC replacement therapy.
  - This assumption will be evaluated after 50% of the target exposure has been achieved.
- When the registry reaches the target sample size, the null hypothesis that the incidences of intercurrent illness and adrenal crises in patients with AI are higher with PLENADREN® than with other GC replacement therapies will be tested.
- Reports from the registry will be provided to the European Medicines Agency on a regular basis.

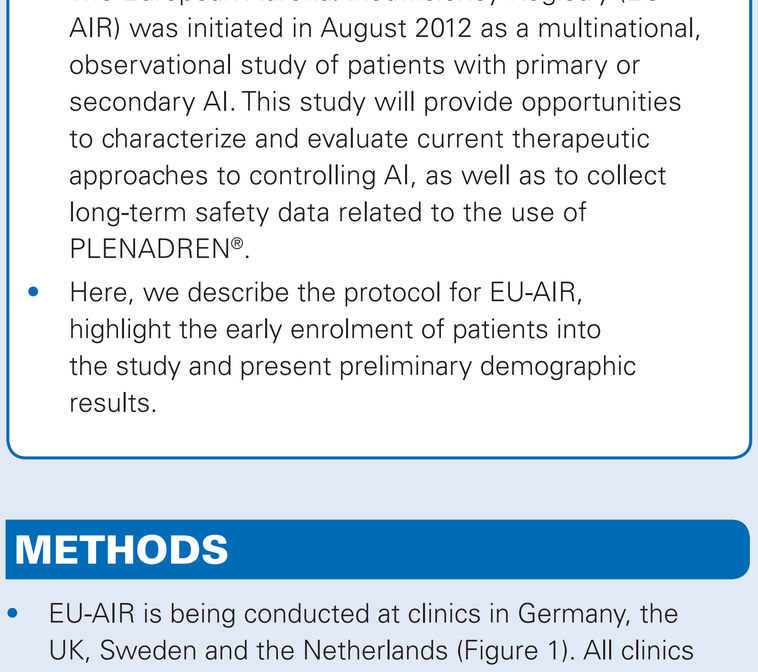

Figure 1. Overview of the EU-AIR study design

[a]Primary analysis will occur after 1800 patient-years of exposure in each group (i.e. after 3600 patient-years).
EMA, European Medicines Agency.

Table 1. Data collection and laboratory assessments at both baseline and routine clinic visits

Data collected at both baseline and routine clinic visits
- Relevant concomitant disease[a]
- GC replacement therapy[b]
- Concomitant medication
- Physical examination[c]
- Vital signs[d]
- Pregnancy status[e]
- DEXA[f]

Laboratory assessments at both baseline and routine clinic visits (as available)
- Fasting plasma glucose
- Fasting insulin
- Glycated haemoglobin A_{1c}
- Serum triglycerides
- Cholesterol
- High-density lipoprotein
- Low-density lipoprotein
- Apolipoprotein B/apolipoprotein A1
- Serum sodium
- Serum potassium
- Serum renin
- Serum osteocalcin
- Serum procollagen I N-terminal propeptide

Routine visits occur approximately every 6 months; patients who experience complications (e.g. adrenal crisis) or who require changes in GC replacement therapy may be followed more frequently by their physician.
[a]Diabetes mellitus, hypertension, other hormone deficiencies, renal/hepatic impairment, disorders/diseases of gastrointestinal emptying/motility. [b]PLENADREN® or other; data collected on dosing regimen and start/stop dates. [c]Height (baseline only), body weight and waist circumference. [d]Blood pressure (systolic and diastolic) and heart rate. [e]Recorded at baseline, if available; as applicable post-baseline. [f]Recorded in the electronic case report form at baseline in patients identified as being at high risk of osteoporosis at centres routinely performing DEXA; performed during routine clinic visits (every 2–3 years in patients identified as being at high risk of osteoporosis).
DEXA, dual-energy X-ray absorptiometry; GC, glucocorticoid.

RESULTS

- The increase in the number of patients enrolled in EU-AIR since August 2012 is shown in Figure 2. By March 2013, the patient count had reached 293. Baseline demographics of these patients are presented by AI type in Table 2.
- The mean age (standard deviation) of the enrolled patients at baseline was 52.5 (17.2) years.
- Approximately 39% (114/293) of the enrolled patients have been identified as having primary AI.

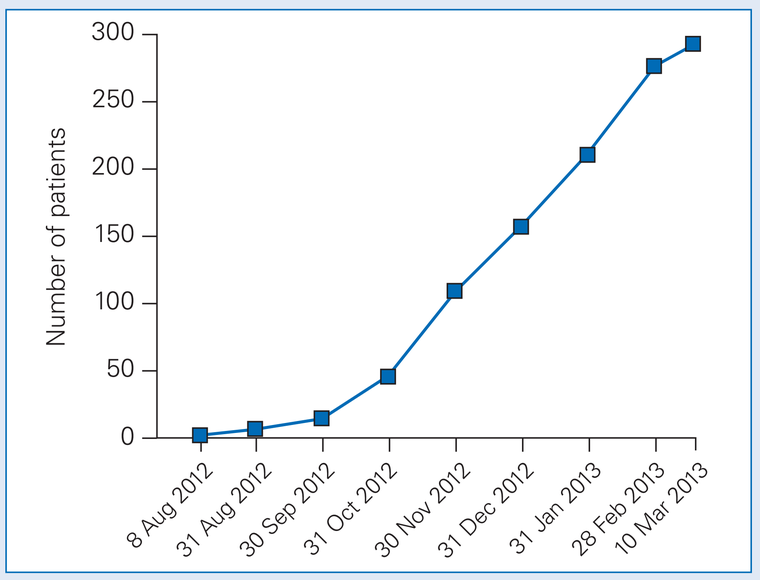

Figure 2. Cumulative enrolment of patients in EU-AIR from August 2012 to March 2013

Table 2. Baseline patient demographics (enrolment as of March 2013)

	All AI	Primary AI	Secondary AI
Number of patients enrolled, n (%)	293	114[a] (38.9)	140[a] (47.8)
Female, n (%)	138[a] (53.7)	78[a] (68.4)	59[a] (42.1)
Male, n (%)	119[a] (46.3)	36[a] (31.6)	81[a] (57.9)
Age, years	52.47 (17.18)	49.9 (16.87)	55.05 (16.98)
n	257[a]	114[a]	140[a]
BMI, kg/m²: female	27.76 (5.95)	26.61 (5.09)	29.62 (6.72)
n	125[a]	74[a]	52[a]
BMI, kg/m²: male	29.42 (11.86)	26.54 (4.43)	30.85 (13.89)
n	108[a]	34[a]	73[a]

[a]Owing to the lag between enrolment and data entry at study sites, some demographic data are currently unavailable.
Data are presented as mean (standard deviation) unless otherwise indicated.
AI, adrenal insufficiency; BMI, body mass index.

CONCLUSIONS

- The number of patients enrolled in EU-AIR has increased steadily every month since the start of the study.
- It is anticipated that EU-AIR will become a valuable source of information on treatment approaches to AI. The data collected will be used to evaluate the long-term safety and tolerability of both PLENADREN® and conventional GC replacement therapy.
- Data from EU-AIR should therefore help to inform and improve clinical practice in the treatment of AI.

REFERENCES

1. Arlt W, Allolio B. *Lancet* 2003;361:1881–93.
2. Kong MF, Jeffcoate W. *Clin Endocrinol (Oxf)* 1994;41:757–61.
3. Willis AC, Vince FP. *Postgrad Med J* 1997;73:286–88.
4. Løvås K, Husebye ES. *Clin Endocrinol (Oxf)* 2002;56:787–91.
5. Bergthorsdottir R *et al. J Clin Endocrinol Metab* 2006;91:4849–53.
6. Hahner S *et al. J Clin Endocrinol Metab* 2006;92:3912–22.

Poster P49 presented at the 15th European Congress of Endocrinology, 27 April–1 May 2013, Copenhagen, Denmark.

The study was funded by ViroPharma SPRL, Maidenhead, UK.