

BMJ Open PlenadrEMA: effect of dual-release versus conventional hydrocortisone on fatigue, measured by ecological momentary assessments: a study protocol for an open-label switch pilot study

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ABSTRACT

Introduction Patients with adrenal insufficiency have impaired health-related quality of life (QoL). The dual-release hydrocortisone preparation, Plenadren, has been developed to mimic the physiological cortisol release more closely than conventional hydrocortisone treatment. Plenadren has been shown to improve QoL, in particular fatigue, in patients with primary adrenal insufficiency. However, the effect has not been investigated in patients with secondary adrenal insufficiency; furthermore, no study has taken the diurnal variation of fatigue into account. To assess diurnal variations, it is necessary to use repeated daily measurements, such as ecological momentary assessments (EMAs). This study aims to evaluate EMAs of fatigue as outcome in future large-scale randomised clinical trials.

Methods and analysis The PlenadrEMA trial is an investigator-initiated open-label switch pilot trial of the effect of Plenadren versus conventional hydrocortisone on fatigue in patients with secondary adrenal insufficiency. The trial will include 30 participants. After 5 weeks on their usual hydrocortisone treatment, patients will be shifted to Plenadren for 16 weeks. Fatigue will be assessed using momentary versions of the Multidimensional Fatigue Inventory (MFI-20). Items will be administered to participants via a smartphone application four times daily during 20 days. Assessments will be performed before treatment shift and repeated after 12.5 weeks on Plenadren. The study will identify the best suited outcome for future randomised clinical trials, and in addition, estimate the variability and difference in fatigue between the two treatments to perform power calculations.

Ethics and dissemination The trial will be conducted in accordance with the Declaration of Helsinki and has been approved by the Regional Scientific Ethical Committee in Copenhagen (ID: H-1-2014-073). All patients will receive written and verbal information about the trial and will give informed consent before enrolment. Findings will be published in peer-reviewed journals and presented at international conferences.

Trial registration number EudraCT201400203932.

Strengths and limitations of this study

- The study employs a novel and innovative measurement technology applicable to many other patient groups.
- The study will become the first to provide an outcome for assessing diurnal variations of fatigue in clinical trials.
- Future power calculations for large-scale randomised clinical trials can be conducted on a well-informed basis.
- Because the study is a pilot study testing the outcomes, technology and measurement properties, it is neither blinded nor randomised.

INTRODUCTION

Adrenal insufficiency is a rare, but life-threatening disease in which the adrenal production of glucocorticoid is reduced. It can be caused by primary adrenal failure or secondary adrenal insufficiency due to impairment of the hypothalamic–pituitary axis. Since the 1950s, patients with adrenal insufficiency have been treated with glucocorticoid replacement, and for the last decades the standard treatment has been hydrocortisone. For treating adults an oral administration of 15–25 mg hydrocortisone per day is recommended.^{1,2} Usually, the replacement regimen is divided into two to three daily doses with a higher dose on waking and the smallest dose in the afternoon/evening, in an attempt to mimic the physiological rhythm of cortisol.^{1,3–5} Despite optimised regimens, it has, however, been clear to most clinicians that this replacement regimen is far from optimal in terms of many factors including mortality and important aspects of quality of

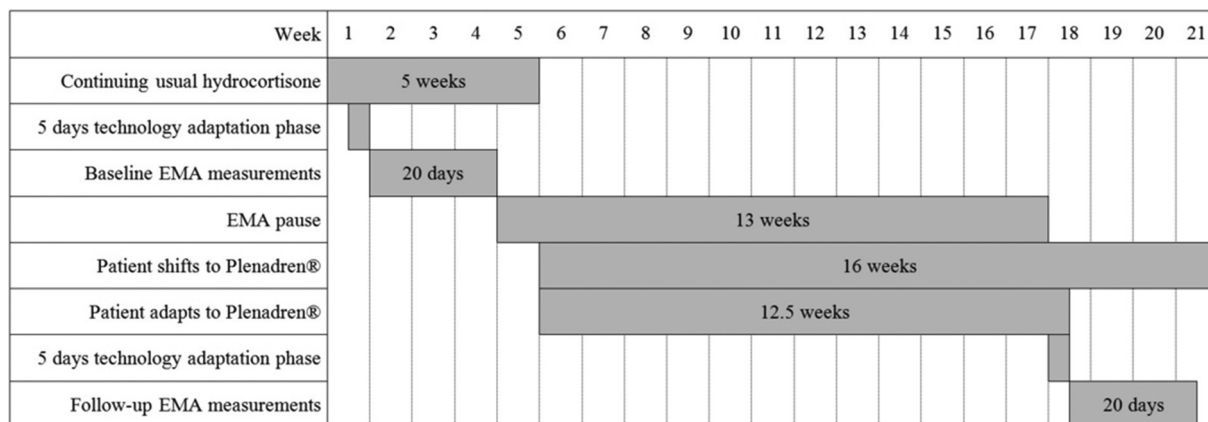


Figure 1 Study period for an individual participant, total duration: 21 weeks. EMA, ecological momentary assessment.

life (QoL) such as fatigue.^{4,6,7} Hydrocortisone has a short plasma half-life of 1.7 hours, often resulting in undetectable levels in the morning and a steep rise after the first dose, followed by very low levels by mid-afternoon. Thus, patients treated with the conventional replacement regimen characteristically have higher fatigue level at certain times during the day. A possible explanation is the suboptimal imitation of the physiological rhythm. Patients often report sleep disturbances, daytime fatigue and early morning fatigue associated with inability to undertake employment.⁴

To mimic the physiological cortisol rhythm more closely a dual-release formulation of hydrocortisone, Plenadren was developed. It has been shown to significantly improve QoL, particularly fatigue, when measured as secondary outcomes of a recent open randomised cross-over trial in patients with primary adrenal insufficiency.⁸ However, it is unknown, if a similar effect can be observed in patients with secondary adrenal insufficiency due to hypopituitarism. Furthermore, no studies have evaluated the effect, taking into account the diurnal variation of fatigue.

Recently, a new method of measuring QoL, including fatigue has emerged: ecological momentary assessments (EMAs). EMA is characterised by repeated sampling of real-time experience in the natural environment of the patient, allowing both between-subject and intersubject analyses including variations over time.⁹ Thus, it has the potential to capture diurnal variations in patient-reported outcomes with a high level of reliability and accuracy.

The present study aims to evaluate EMA as outcome in future large-scale randomised clinical trials of dual-release hydrocortisone, furthermore, to quantify the variability of such EMA measurements in patients with adrenal insufficiency due to hypopituitarism and acquire an estimate of the size of the expected difference in scores, both of which are required for sample size calculations. Finally, the study aims to identify the best suited outcome for a randomised clinical trial, that is, the most informative outcome with the least participant burden. We hypothesise that dual-release hydrocortisone will show similar improvements in QoL in patients with hypopituitarism as shown in patients with primary adrenal insufficiency. Furthermore, we

hypothesise that the EMA method is highly suitable for detecting diurnal variations of fatigue and the changes hereof compared with standard questionnaires.

METHODS AND ANALYSIS

Design

The PlenadrEMA study is an investigator-initiated open-label switch pilot trial. Included patients will be observed for 5 weeks on their usual treatment (two or three times daily hydrocortisone). Assessments of QoL, in terms of EMA assessments, to be used as baseline measurement in the study, will be collected at the beginning of the trial period for 20 days preceded by a 5-day technology adaptation phase (see figure 1), that is, EMA collection will begin on day 6 of the trial period. Thereafter, participants will be shifted to dual-release hydrocortisone (Plenadren) once daily, on an equivalent dose as per Summary of Product Characteristics. Assessments of QoL to be used as primary outcome will be performed 12.5 weeks after initiation of the intervention treatment, in order to take into consideration the period of readjustment of the body after the switch from conventional hydrocortisone to Plenadren. As done at the baseline observation, 20 days of EMA measurements will be preceded by a 5-day technology adaptation phase (figure 1). At the end of the intervention treatment period, the patients will be shifted to their usual hydrocortisone treatment and will be followed at the outpatient clinic according to the standard directives of the clinic.

Study population

All patients with a diagnosis of adrenal insufficiency due to hypopituitarism who are referred to or followed at the Department of Endocrinology at Copenhagen University Hospital Rigshospitalet will be considered for participation in this trial. Patients may enter the PlenadrEMA study if they comply with the inclusion and exclusion criteria.

Inclusion criteria: age ≥ 18 years; diagnosis of adrenal insufficiency due to hypopituitarism; in steady two or three times daily (10–40 mg) hydrocortisone replacement treatment; written informed consent; for women: use of

reliable methods of contraception in clinical trials in accordance with the definition by the Danish Health and Medicines Authority; intrauterine devices or hormonal methods (oral contraceptives, contraceptive implants, transdermal patches, hormonal vaginal devices or injections with prolonged release).

Exclusion criteria: pregnancy; breast feeding; acromegaly; Cushing's disease; diabetes mellitus; other major confounding disease; known or expected hypersensitivity to any of the excipients; lack of compliance (attendance and medication).

Given that the method of EMA measurement of fatigue is novel, power calculations to determine the correct sample size cannot be conducted on a sufficiently informed basis, since the magnitude of the expected change and the variability is unknown. In order to obtain reliable estimates of variability and magnitude of expected differences, a sample size of $N=30$ was decided for this pilot study, after discussion with an experienced biostatistician. Several other pilot studies have investigated EMA for measuring symptoms. These studies have included between 19 and 33 participants,^{10–15} which corresponds well with our chosen sample size.

Intervention

The investigational medicinal product in this study is the dual-release hydrocortisone, Plenadren. It is produced and delivered by Shire in tablets containing 5 mg and 20 mg hydrocortisone and will be stored according to Summary of Product Characteristics. The initial dose of Plenadren is equal to the total daily dose of the patients' usual conventional hydrocortisone. Patients will be instructed to take the Plenadren tablets orally in fasting state in the morning (between 6:00 and 8:00). The duration of the intervention period is 16 weeks, including a run-in period of 12.5 weeks.

The usual hydrocortisone replacement regimen of the patients, that is, conventional hydrocortisone, is used as comparator in the trial. Doses include variable combinations of hydrocortisone 20 mg tablets produced by TAKEDA and an unlicensed preparation of hydrocortisone 5 mg tablets produced by Glostrup Pharmacy. The total dose per day is between 10 and 40 mg and is administered in two to three daily doses. The individual, usual dose of the patient will not be altered on entering the trial unless the patient shows clinical symptoms of insufficient replacement.

Collection of EMA data

In our research group, we have developed a smartphone application for collection of EMA data. It follows state-of-the-art standards for electronic EMA instruments as described in the field of EMA research.¹⁶ This includes, for example, individually adjusted diurnal rhythm, a possibility to delay a data entry for up to 1 hour, and time stamping of data entries in order to evaluate compliance. The EMA application is integrated with the trial management system PROgmatic.¹⁷ The integrated system handles

patient flow, electronic case report forms and collection of EMA data from mobile devices. EMA data are stored on mobile devices and uploaded to a secure, encrypted back-end system each night. From here, data are pulled also on a nightly basis to PROgmatic, where data completeness can be surveyed in real-time, enabling appropriate action to secure data quality, that is, avoid missing data. The system is approved by the Danish Data Protection Agency (local identifier at Rigshospitalet: 30–1233).

Outcome measures

The primary outcome of the study is variability and difference in fatigue between conventional and dual-release hydrocortisone treatment. Fatigue is measured by the standardised, validated fatigue instrument: Multidimensional Fatigue Inventory (MFI-20),¹⁸ which will be adapted to EMA. The MFI-20 is formulated in a way that makes it relatively easy to convert into an EMA-measure. Four times daily, at semi-randomised time points, the participants are prompted by the EMA application to respond to eight brief questions from the MFI-20. Four items from the General Fatigue scale are administered every day during the observation period as well as four items from one of the four remaining scales (Physical Fatigue, Mental Fatigue, Reduced Activity and Reduced Motivation). The reason for administering only one of the four specific scales per day is to reduce response burden; thus, these scales are administered in cycles of 4 days: Physical Fatigue on day 1, Mental Fatigue on day 2, Reduced Activity on day 3 and Reduced Motivation on day 4.

Secondary outcome assessment is specified in [table 1](#) and includes the standardised, validated questionnaires: Fatigue Impact Scale, Addison Disease-specific QoL questionnaire and the Short Form Health Survey, all of which will be administered on visit 2 and 4. Furthermore, blood samples, dual-energy X-ray absorptiometry primarily for evaluation of body composition, 24 hours blood pressure, salivary cortisol and recording of adverse events (AEs) will be assessed as part of the safety evaluation of Plenadren on visit 2 and 4. Patients will be asked to pause their hydrocortisone treatment and blood samples will be collected at least 12 hours after last hydrocortisone dosage. Blood samples consist of cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting blood glucose, glycated haemoglobin, C reactive protein, electrolytes, fibrinogen, plasminogen activator inhibitor-1, cortisol, adrenocorticotropic hormone, cortisol binding globulin, serum type 1 procollagen and collagen type 1 cross-linked C-telopeptide, osteocalcin, receptor activator of nuclear factor kappa-B ligand, osteoprotegerin and sclerostin.

Biobank

A research biobank of serum and plasma will be established for analysis of biochemical markers specified in the outcome measures section and for future use. Participants are informed orally and in writing, and will consent

Table 1 Timing of data collection

Variable	Information visit	Visit 1 (0–1 weeks)	Visit 2 (5 weeks)	Visit 3 (17 weeks)	Visit 4 (21 weeks)
Informed consent	x	x			
Baseline information on current illness and medical history		x			
Screening blood samples*		x			
Start-up EMA		x		x	
Shift to Plenadren			x		
QoL questionnaire: Fatigue Impact Scale AddiQoL SF-36			x		x
DEXA-scan			x		x
24 hours blood pressure			x		x
Blood samples			x		x
Salivary cortisol (3 days)			x		x
Recording of adverse events, adverse reactions and the need for rescue medication		x	x	x	x

*Screening blood samples corresponds to the annual biochemical assessment in pituitary patients at the Department of Endocrinology, Copenhagen University Hospital Rigshospitalet. Fasting is not necessary.

AddiQoL, Addison Disease-specific quality of life; DEXA, dual-energy X-ray absorptiometry; EMA, ecological momentary assessment; QoL, quality of life; SF-36, Short Form Health Survey.

to the withdrawal and storing of biological material. Blood samples for the biobank are collected at visit 2 and 4. Access to material of the biobank for further analysis, not included in the study protocol, will require a specific authorisation from the Committees of Health Research Ethics. The material will be stored according to requirements of the Danish Data Protections Agency.

Monitoring

The trial will be monitored by the Good Clinical Practice unit at Copenhagen University Hospital.

Data and statistical analysis

For each of the two EMA reporting periods, four diurnal fatigue profiles are generated for each participant. Each diurnal fatigue profile consists of four daily measurement points. One diurnal profile summarises General Fatigue responses during the day across all 20 days. For each of the other four scales, a profile summarising the responses during the day across the 5 days they were administered is generated. Scale means will be calculated for conventional treatment versus dual-release hydrocortisone by mixed models for repeated measures. The scale with the largest change in score will be selected as the best suited EMA outcome, of which difference in mean and SD will be used for sample size calculations for future randomised clinical trials. Diurnal curves will be generated for the General Fatigue scale and inspected as well as statistically tested for temporal patterns (mixed models), by dividing the day into 3-hour blocks and testing for significant

variation in scores.¹⁹ All analyses will be conducted as intention-to-treat analyses, with two-sided significance level at 5%.

Patient safety and AE recording

Independent of treatment period, in case of intercurrent illness or physical or mental stress, participants will be instructed to take additional substitution of immediate release hydrocortisone tablets (rescue medication) according to current guidelines. The need for rescue medication will be assessed at trial visits according to table 1. Participants are questioned about AEs according to table 1. In addition, participants are instructed to contact their trial contact person if they experience symptoms suggestive of AEs. Any identified AE will be registered in the case report form of the patient and will be reported to the Regional Research Ethics Committee and the Danish Health and Medicines Authority according to the Good Clinical Practice regulations. When a possible serious adverse event (SAE), serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR) is identified, the event will be followed up by the sponsor-investigator or delegated (medically qualified). Details about the event will be sought from the patient's medical record and through direct contact with the patient or relatives (in case of an event leading to death or incapacitation of the participant). The event will be assessed for causality between Plenadren and the event by the sponsor-investigator or delegated based on a clinical evaluation. Any SAE, SAR or SUSAR will be reported as an outcome measure.

ETHICS AND DISSEMINATION

The study will be performed in compliance with the Declaration of Helsinki. Inclusion of patients will only be carried out after informed consent is obtained. At the information visit sponsor–investigator or qualified delegate will provide written and verbal information about the study. Participants are given the opportunity of reflection for up to 1 week before giving their consent. The original signed written informed consent forms are archived at the trial site and a copy is given to the participant.

A patient who no longer wishes to participate in the trial, can withdraw informed consent at any time without need of further explanation, and this will have no consequence on the patient's further treatment. To conduct intention-to-treat analyses, with as little missing data as possible, the investigator or delegate, may ask the patient which aspects of the trial he or she wishes to withdraw from. This could involve the trial intervention (Plenadren), participation in EMA measurement of fatigue, use of already collected data in the data analyses or assessment of safety variables. The sponsor–investigator shall discontinue a patient from the trial intervention at any time, if the patient becomes pregnant, experiences intolerable adverse reactions or is diagnosed with a major confounding disease during the trial period. Dropouts and patients withdrawn from the trial by sponsor–investigator will be shifted to their usual hydrocortisone treatment and standard follow-up at the outpatient clinic. Subjects will not be replaced in the trial. Furthermore, in the event that new knowledge about Plenadren may be published that would raise profound uncertainty about the safety of the patients, the trial will be stopped immediately. Due to the short half-life of hydrocortisone, specific follow-up for dropouts and patients withdrawn from the trial are not required.

The results of this study will be presented at national and international conferences as well as to patients and clinicians. Results will be submitted for publication in peer-reviewed journals.

DISCUSSION

Previous studies have shown improvements in fatigue and QoL in patients with primary adrenal insufficiency treated with Plenadren.^{8 20} However, the effect has not yet been studied in patients with secondary adrenal insufficiency due to hypopituitarism. Furthermore, the effect has not been investigated taking the diurnal variation of fatigue into account. The present study is designed as a pilot study with the aim of evaluating feasibility of the EMA method for assessing diurnal variations of fatigue, quantifying variability and expected difference in EMA scores to perform sample size calculations and finally, to identify the best suited EMA outcome measure for future large-scale randomised clinical trials.

Until the measurement properties have been clarified and sample size calculations can be performed on a sufficient foundation, an open-label switch format has been chosen instead of conducting a blinded and randomised

trial. This format has limitations regarding the interpretation of QoL data. To avoid potential placebo effects, future studies should be blinded. However, we believe the format is well suited to examine diurnal variations for this pilot study. Since hydrocortisone replacement is vital to patients with adrenal insufficiency washout before treatment switch is not possible. The lack hereof may result in carryover effects. However, by including a run-in period of 12.5 weeks before collection of EMA and 16 weeks before secondary outcomes assessment we aim to minimise such effects.

The coexistence of untreated deficiencies of other pituitary axes could influence the outcome of fatigue during treatment of adrenal insufficiency. Most patients in the potential study group have verified insufficiencies on multiple pituitary axes and receive replacement therapy according to common practice. Patients are followed at the endocrine outpatient clinic where they are regularly tested for pituitary insufficiencies and replacement treatment is initiated if needed. In the present study, the inclusion criteria are not restricted to specific pituitary axes (except for adrenal insufficiency), since we aim to investigate Plenadren and EMA measurements of fatigue in a broad patient group rather than to limit the findings to a specific subgroup. However, it is recognised that changes in replacement therapy during the trial period can affect our results, why stable treatment is favoured. In order to increase comparability within the patient group, patients receiving only the most common hydrocortisone dosages, for example, 15–25 mg per day, could be included in the study. However, to avoid being unable to reach the sample size of 30, the span of daily dosage has been widened to 10–40 mg per day.

Surveillance of replacement therapy and adjustment of doses remain a great challenge for patients and physicians. Because no objective assessment has proven reliable, monitoring treatment effect is mainly based on clinical ground.^{2 3} An important aspect of the clinical assessment of replacement quality includes evaluation of the patients' subjective well-being, that is, QoL. As described, a major complaint in patients treated for adrenal insufficiency is fatigue. Thus, fatigue is central to assess in the clinical evaluation of treatment effect. It is, though, a subjective and quite variable concept which can be difficult to measure. Fatigue, as experienced by patients with chronic diseases, has been defined as 'a general feeling of debilitating tiredness or loss of energy'.²¹ Scientifically, fatigue has been conceptualised as a multidimensional and subjective construct with a range of aspects, such as physical, mental, affective and behavioural.²²

For decades, effort has been made to develop responsive instruments in order to assess QoL.^{18 23 24} However, a sophisticated and feasible method responsive to changes over short time, such as diurnal variation, is still warranted. The EMA method has a great potential for assessing such diurnal variation with a high level of sensitivity and reliability. Collecting EMA data electronically through a smartphone application is an innovative and

novel technology within the field of QoL research and to our knowledge no previous study has used this technology to assess EMA of fatigue as a primary outcome. A great advantage of the application is that it can be installed on the patient's own smartphone, and thus, can easily be implemented in everyday life. Fatigue has been shown to have substantial impact on patients' overall QoL. Thus, a specific and sensitive instrument is needed to assess the effect of interventions with the aim of reducing fatigue in patients with chronic diseases. The application possibilities of this EMA method for other patient groups are wide. Especially, in monitoring subjective health status and treatment effect in other patient groups with diurnal variations of fatigue such as patients with rheumatoid arthritis, multiple sclerosis, chronic cancer, ischaemic heart diseases or renal diseases, this method has great potential.

Trial status

The first patient visit is scheduled for September 2017. Last patient's last visit is expected in March 2019.

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Contributors TC, TW, MK, SWB and UFR designed the study and contributed to the development of the study protocol. VBB and TC drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Regional Scientific Ethical Committee in Copenhagen (ID: H-1-2014-073).

Provenance and peer review Not commissioned; externally peer reviewed.

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