CORTICO-COP (The Corticosteroid reduction in COPD) trial

Study protocol

A Clinical Randomized Trial testing the effect of reduced corticosteroid treatment on clinical outcome in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD)

Primary Committee

Ethics Committees of all participating sides (VEK No: H-15012207)

Scientific Project Sponsor

Chronic Obstructive Pulmonary Disease Trial Network: COP: TRIN - A network of independent COPD researchers in Denmark: www.coptrin.eu.
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Table of Contents

1 Background

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a major cause of hospitalization and is associated with increased risk of mortality. AECOPD contributes to long-term decline in lung function and physical activity, impairs quality of life and causes high socioeconomic costs[1].

An exacerbation of COPD is an acute incident characterized by worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and which leads to change in medication[2].

For a long time, the usage of systemic corticosteroids, along with inhaled bronchodilators and oxygen therapy has been a cornerstone in relation to treatment of AECOPD. However, the optimal approach as regards dosage (low/moderate/high), administration (oral/intravenous) and duration of treatment is unknown[3].

As far as duration of treatment, REDUCE found that in patients with AECOPD, five days of treatment with systemic corticosteroid is noninferior to a 14-day treatment with respect to reexacerbation, length of hospital stay, lung function and mortality[4]. Based on these results, the GOLD guidelines recommend five days of corticosteroid treatment to patients with AECOPD[2].

In terms of administration, oral treatment is found to be non-inferior to intravenous treatment with respect to treatment failure, reexacerbation rate and mortality[5].

As for the dosage, there is consensus that 40 mg (37½ mg in Denmark) prednisolone for the treatment of patients with AECOPD is appropriate, although there is no clear evidence for this.

A more recent Cohrane review has shown that systemic corticosteroids to AECOPD patients (compared to placebo) reduces the risk of treatment failure (OR 0.48 [0.35; 0.67] and NNT = 9 [7, 14]). Treatment failure was defined as patients who within 30 days requiried hospitalization or

emergency room visits or patients with a need to intensify pharmacological treatment. The risk of reexacerbation of AECOPD was also reduced within the first month (HR 0.78 [0.63; 0.97]). This difference was not present in the period 1 to 4 months.

Lung function measured up to 72 hours after treatment showed significant improvement of FEV_1 in the corticosteroid group (140 mL [90; 200]). However, the improvement could not be observed later in the process. Mortality was unaltered (OR 1.0 [0.60; 1.66]). The total length of hospital stay was shorter in the corticosteroid group (-1.2 days [-2.3, -0.2]), whereas there was no difference in the length of hospital stay in intensive care unit (ICU). The risk of steroid induced side effects was more than doubled (OR 2.33 [1.59; 3.43]) in the corticosteroid group compared with the control group; NNH = 6 [4, 10]. At the same time, the proportion of side effects in the corticosteroid group (48.1%) was significantly higher than the control group (28.2%). The risk of hyperglycemia was significantly increased (OR 2.79 [1.86; 4.19]) and the absolute risk was 28.2%[5]. Others have pointed out and documented severe mental (depression, mood swings, psychosis) and somatic side effects (cataracts, hypertension, stomach ulcers, myopathy, adrenal insufficiency, diabetes, osteoporosis and increased risk of fractures) [6-8].

Earlier, the inflammatory process in patients with AECOPD was believed to be homogeneous, primarily neutrophilic. However, recent studies have shown that both inflammation [8, 9] and ethiology [10–12] are heterogeneous. It has been demonstrated that a subgroup of patients with AECOPD have eosinophilic inflammation [13]. Specific attention on biological clusters and biomarkers of these have resulted in an increased understanding of the differentiated inflammatory mechanisms that exist in AECOPD [14]. Examinations of sputum from the airways in smokers have increased this understanding further [15]. The economic consequences of the treatment of fractures, iatrogenic pneumonia and other infections, rehabilitation measures, diabetes treatment, cataracts, glaucoma and psychiatric side effects are not systematically eliminated - but are probably a significant part of the high costs in health care and in the municipalities for this group of vulnerable patients.

A small randomized study (n = 109) of COPD patients with moderate exacerbations has indicated that blood eosinophil-guided corticosteroid treatment might reduce the use of systemic corticosteroids in exacerbations by 49% without simultaniously worsening of symptoms and increasing risk of treatment failure compared with standard care [17]. Furthermore, patients with initial low eosinophil count more often experienced treatment failure if they had received corticosteroid therapy rather than if they had not (15% treatment failure in prednisolone group, 2% treatment failure in corticosteroid-saving group, p = 0.04). However, the study had no impact on current recommendations due to the limited sample size. Larger cohort studies documented that diagnosed COPD patients with daily symptoms have more than 3- fold increased risk for AECOPD if they have an eosinophil count $\geq 0.34 \times 10^{\wedge}9$ cells/L [18] and this conclusion is supported by a less elderly but well-studied study [19].

The most important question is thus whether the clinical effects achieved by systemic corticosteroid treatment in AECOPD patients can be achieved by targeted and individualized eosinophil-controlled treatment over the current one-size fits all 5-day treatment. Additionally, if you save on corticosteroid treatment, you can reduce some of the serious side effects that occur during this treatment. No randomized clinical studies with clinically relevant power calculations have so far examined these questions. We want to do this.

(not relevant for the RCT)

Another goal is to identify genetic variants that can help to organize the corticosteroid treatment of AECOPD more individually adapted to the patient based on a specific genetic profile. In this way, the therapeutic effect may be increased and the risk of side effects reduced. Based on the above review of literature, we know that most patients with COPD have a deficient response to corticosteroids resulting in only a few temporary clinical effects. This is due, inter alia, to individual variations of corticosteroid sensitivity, which are genetically conditioned. Since it is the glucocorticoid receptor (GR) that is crucial to the effect of corticosteroids, it is essential to investigate this.

There are described about 50 polymorphisms in the GR gene that can be associated with altered sensitivity to corticosteroids [20]. However, there are only 4 polymorphisms in the GR gene

(NR3C1) which have been shown to be clinically relevant. The polymorphisms N363 S and BclI are associated with increased corticosteroid sensitivity, and the polymorphisms ER22 / 23EK and 9β for decreased corticosteroid sentivity [21].

The first two polymorphisms appear to be predicts for overweight, dyslipidemia and hypertension [22, 23]. BclI has been associated with low BMD [24], hyperglycaemia, increased insulin secretion and abdominal obesity [25]. N363S has been associated with metabolic syndrome, diabetes mellitus type 2 and cardiovascular disease [26], while ER22 / 23EK and 9β appear to be associated with a more favorable metabolic profile [27]. Increased expression of 9β has been described in patients with steroid-resistant asthma [28]. The clinical significance of these polymorphisms for COPD patients in corticosteroid therapy is still unknown.

It is therefore important to investigate which of the 4 polymorphisms in the GR gene associated with the development of an adverse genetic profile (higher BMI, dyslipidemia, hyperglycemia, bone mineral loss, diabetes mellitus type 2, hypertension, depression, etc. [29]) in patients with COPD. And whether it can be used to identify groups of risk patients with AECOPD who need an individually adapted corticosteroid treatment [30].

2 Objectives

The project aims to study:

1) Whether a reduction of the accumulated dosage of systemic corticosteroid therapy in patients with AECOPD, compared with AECOPD patients on standard treatment, is non-inferiority

2) Whether there is a difference in treatment respons in AECOPD patients with eosinophilic airway inflammation (eosinophil count in the blood $\geq 0.3\ 10^9$ cells/ l) compared to AECOPD patients with non-eosinophilic airway inflammation (eosinophil count in the blood $<0.3\ 10^9$ cells/ L).

3) Whether lower accumulated dosage corticosteroid may be associated with fewer corticosteroid induced adverse events in patients with AECOPD.

(not relevant for the RCT)

4) Whether patients with GR polymorphisms associated with increased glucocorticoid sensitivity have an adverse genetic profile after corticosteroid treatment than a) wild type patients and b)

patients with the GR polymorphisms associated with reduced glucocorticoid sensitivity and vice versa.

3 Hypotheses

1) A reduction of the dose of systemic corticosteroids for AECOPD – compared to ”standard care” – does not lead to inferior treatment effect in regards to:
   Days alive and out of hospital within 14 days after recruitment,
   COPD re-exacerbation within 30 days,
   FEV_1 on day 3, after 1 month and 3 month
   180 day mortality rate
   “Treatment failure” (defined as COPD re-exacerbation resulting in emergency room visits, re-admittance to hospital or need to intensify pharmacological treatment, all within 30 days).
2) COPD exacerbation patients with a low eosinophil count ($< 0{,}3 \times 10^9$ cells/L) compared to patients with higher eosinophil count ($\geq 0{,}3 \times 10^9$ cells/L):
   Achieve less treatment response assessed on day 3 FEV_1,
   Re-exacerbation within 30 days
   “Treatment failure” (defined above)
3) Reduced accumulated dosage of corticosteroid for COPD exacerbation will lead to fewer and less serious corticosteroid-induced side-effects / adverse events as compared to ”standard care” treatment (composite adverse endpoint).

(not relevant for the RCT)

4) Genetic differences in corticosteroid-sensitivity (4 defined polymorphisms) has a significance for the development of secondary adrenal insufficiency in patients who suffer from COPD exacerbations.

4 Search strategy

The following databases have been searched: PubMed, Embase and Cohrane Libary.

A combination of the following keywords has been sought: Pulmonary Disease, Chronic Obstructive Pulmonary Disease, COPD, prednisone, prednisolone, glucocorticoid and adverse effects.

The following MeSH searches have been made:

• ((((((("Lung Diseases, Obstructive"[Mesh:noexp]) OR "Pulmonary Disease, Chronic Obstructive"[Mesh:noexp]) OR "Pulmonary Emphysema"[Mesh])) OR ((COPD OR AECOPD OR Chronic obstructive pulmonary disease*)))) AND ((((((("Dexamethasone"[Mesh]) OR "Prednisone"[Mesh]) OR "Glucocorticoids"[Mesh]) OR "Hydrocortisone"[Mesh]) OR "Prednisolone"[Mesh:noexp]) OR "Methylprednisolone"[Mesh])) OR ((Dexamethasone OR Prednisone OR Glucocorticoids OR Hydrocortisone OR Prednisolone OR Methylprednisolone OR "corticosteroids")))

• ((((((("Lung Diseases, Obstructive"[Majr:noexp]) OR "Pulmonary Disease, Chronic Obstructive"[Majr:noexp]) OR "Pulmonary Emphysema"[Majr])) OR ((COPD OR AECOPD OR Chronic obstructive pulmonary disease*)))) AND ((((((("Dexamethasone "[Majr]) OR "Prednisone"[Majr]) OR "Glucocorticoids"[Majr]) OR "Hydrocortisone "[Majr]) OR "Prednisolone"[Majr:noexp]) OR "Methylprednisolone"[Majr])) OR ((Prednisone OR Prednisolone OR Methylprednisolone OR "corticosteroids"))) NOT asthma

• (("Pulmonary Disease, Chronic Obstructive"[Mesh]) AND "Glucocorticoids"[Mesh]) AND "adverse effects" [Subheading]

5 Method

5.1 Study design

A multi-center randomized, controlled, open-label trial

The study will be conducted as a prospective, randomized, "open label" multi-center study in patients with AECOPD. 318 patients are expected to be included in the project within 24 months.

That is, 159 patients allocated to each of the two groups (control group: “standard care” vs. intervention group: “eosinophilic guided corticosteroid-sparing therapy” , see below). Stratified block randomization will be used to ensure equal distribution of patients on site and age.

Patients will be randomized to one of two treatment groups:

a) Control group: Standard of care treatment: Intravenous Solu-Medrol 80 mg on the first day followed by 37.5 mg of prednisolone tablets (1 x 25 mg plus 1 x 12.5 mg) daily for 4 days.

b) Intervention group: Intravenous Solu-Medrol 80 mg, followed by prednisolone tablet 37.5 mg daily (maximum of 4 days in all) if the eosinophil count in the blood $\geq 0.3\ 10^9$/ l. Eosinophil count in the blood $<0.3\ 10^9$/ L results in no treatment with prednisolone. If the patient is discharged during the treatment period given treatment from last measured eosinophil count the remaining days.

(not relevant for the RCT)

Epidemiological study

In a nationwide epidemiological study, to investigate whether systemic corticosteroid therapy is an independent predictor of corticosteroid-induced adverse events (<12 months after prednisolone). Stratify for age, inhalation steroid and lung function (multivariate regression analysis). Endpoints: pneumonia requiring hospitalization, diabetes requiring hospitalization, GI bleeding, osteoporosis diagnosis (= Bisphosphonate / Prolia treatment <12 months). Records for COPD patients are used (Danish Register for COPD: http://www.kcks-vest.dk/klinisk-kvalitetsdatabase) that is linked to data from PERSIMUNE Data warehouse.

(not relevant for the RCT)

Observational prospective study

Genetic study: Gen test performed in patients in the standard arm of the randomized study will be genotyped for the 4 functional GR polymorphisms BclI (rs41423247), 9β (rs6198), N363S and ER22 / 23EK.

The purpose is to investigate which of the 4 clinically relevant polymorphisms in the glucocorticoid receptor gene, which is an independent predictor for the development of an adverse genetic profile including secondary adrenal insufficiency, bone mineral loss and type 2 diabetes mellitus in glucocorticoid-treated patients with AECOPD.

5.2 Randomization

Randomization to standard treatment or eosinophil guided treatment with corticosteroids will take place via a Web-based system. The user of the Web-based system cannot predict or change the outcome of randomization.

5.3 Enrollment & Inclusion

At each center, consecutive screening of patients admitted with AECOPD is performed. Patients admitted with AECOPD at the Emergency Department or at the Pulmonology Department will be screened for inclusion. If a patient is considered as a candidate, the patient will be invited to participate in the project, and informed consent will be obtained. The primary investigator and subinvestigators at each center take part in the inclusion. It is expected that 318 patients will be included, almost equally distributed over four centers: 80 patients from the Department of Pulmonology, Herlev and Gentofte University Hospital,, 78 patients from the Department of Respiratory Medicine, Bispebjerg University Hospital, 80 patients from the Department of Pulmonary and Infectious Diseases, North Zealand University Hospital, Hilleroed and 80 patients from the Department of Pulmonary Medicine, Hvidovre University Hospital. The primary investigator of each of the four departments will be responsible for teaching staff, patient inclusion and data collection. Since pregnancy is an exclusion criterion, all fertile women must have performed pregnancy tests (measurement of urine hCG) prior to inclusion in the trial.

5.4 Inclusion criteria

• Hospitalized patients with AECOPD
• Age ≥ 40 years
• Spirometry-verified COPD (defined as FEV1 / FVC ≤ 70%)

• GOLD Class C or D

5.5 Exclusion Criteria

• Known asthma diagnosis

• Life expectancy less than 30 days

• Severe COPD exacerbation requiring invasive ventilation or ICU

• Allergy to systemic corticosteroids

• Severe mental illness which is not controlled by medication

• People who are detained under the act on the use of coercion in psychiatry

• Severe language difficulties or inability to provide written informed consent

• Pregnancy and lactation

• Systemic fungal infections

5.6 Clinical tests

Table 1 Data collected at baseline and follow-up visits

Data collected	Study period		
	Baseline	1-month	3-month
Demographics	X		
Daily blood glucose measurements	X		
Daily leukocyte differential count[a]	X		
Arterial blood gases and Chest X-ray	X		
Testing for diabetes (HbA1c)	X	X	
Spirometry	X (day 1+day 3)	X	X
Height measurement & vital signs	X		
Weight measurement	X	X	X
Vitamin D and PTH levels	X		X
COPD Assessment Test (CAT)	X	X	X
Medical Research Council Dyspnoea Scale	X	X	X
Bone Turnover Markers (CTX, P1NP)	X	X	X
Questionnaire on general health condition		X	X
Pregnancy test	X		

[a]Completed by patients in the intervention group only.

If the patient does not attend the follow-ip visit, the patient will be contacted for a new follow-up or - if not able to meet for an appointment at the hospital - a home visit by a doctor assigned to the project.

5.7 Research Plan and Data Acquisition

Inclusion of patients, data collection, processing, statistical analysis, and publishing the data will be performed by doctor, Ph.d. student Pradeesh Sivapalan in cooperation with supervisors and members of the steering comittee. Therefore, there is a high possibility that the project will be implemented. The project is expected to start with inclusion of patients from 10th of August 2016 and the last patient is expected to be included by end of July 2018. Data collection ends in December 2019. The Ph.d. student will be responsible for completing blood sampling, questionnaires and the different examinations in scheduled time. Decisions of medical issues are done by a doctor only.

The coordinating investigator (Ph.d. student) is responsible for proper handling (including storage) and delivery of the medication in cooperation with the investigators of the four centers. The investigator on each center keeps accounts of medicine (reception, delivery, return and destruction documented).

Also, an agreement with GCP unit at the University of Copenhagen has been signed in order to monitor the trial of the four centers.

Collected data will be treated confidentially by the staff assigned to the project. Data will be reported in electronic case report forms (e-CRF) specifically for each patient. The data includes demographic data, health status, current illnesses, side effects and whether the various examinations are conducted. E-CRF is kept in the archives of the departments involved for 15 years. Data in e-CRF is entered by the investigator at each center.

5.8 Establishment of research biobank

The purpose of setting up a research biobank is partly to investigate the frequency of prednisolone-induced side effects in different treatment groups and also to organize the work of analyzing the samples as appropriately as possible.

A research biobank with blood samples for patients with AECOPD is being established. All participants will be requested to provide blood samples at inclusion and during follow-up. The biobank will only be used for blood tests. A total of 40 ml of blood will be collected from each patient from inclusion to completion at 3 months follow-up. All blood samples are stored in a freezer in a locked room at each of the four pulmonary departments for analysis before the end of the project. The samples are stored in anonymous form and the material is destroyed upon completion of the project.
The Ethics Committee and the Danish Data Protection Agency have approved the establishment of a biobank. The biobank can only be used for other research projects if there is a separate approval from the Ethics Committee.

6 Statistical considerations and power calculation

Data will be analysed using intention-to-treat (ITT) principles, including all the data available regardless of whether the intervention is completed. The aim of the ITT analysis is also to provide unbiased comparisons among groups and avoid the effects of dropout and handle patients who deviates from the protocol, e.g. intubated patients during their hospitalization.
Patients in SC will be compared to patients with eosinophil guided prednisolone sparing therapy (Intervention group). The mean LOS ($\mu = 8$) and standard deviation ($\sigma = 3.81$ days) after a hospitalization for AECOPD is estimated based on previous studies comparing systemic corticosteroids versus placebo [3, 19]. A two-sided 95%-confidence interval will be computed for the difference in LOS in the intervention group minus standard care group. We will accept a null hypothesis if the LOS in the intervention group does not exceed 1.2 days of the average LOS in the SC arm. The probability that the study will detect a treatment difference is 80% at a two-sided 5% significance level. This provides a sample size of 318 subjects. Samplesize calculation has been performed by using SAS software (version 9.4). The results are expressed in mean (days) and SD if data is normally distributed, or as median (IQR). Data will be analysed using SAS software. The detailed statistics plan is written in a separate document - Statistical Analysis Plan (SAP) from 2nd April 2017.

Planned analyzes of safety and efficacy data (Interim Analysis) will be evaluated when 116 and 210 of patients have completed the study (completed 1 month follow-up). These assessments will be made by an independent Data and Safety Monitoring Board (DSMB). Data on primary and secondary endpoints will be used for this. DSMB will review the protocol, monitoring guideline, evaluate the attempts to recruit participants, participants' risk and on the basis of interim analyzes, make recommendations to investigators as to whether or not to continue the study. In addition, DSMB may at any time require an extraordinary interrim analysis

6.1 Primary endpoint

• Days alive and out of hospital within 14 days after recruitment (defined as the time from hospital discharge and days without hospitalization up to 14 days from recruitment where the patient is alive)

6.2 Secondary endpoints

• Treatment failure (COPD re-exacerbation resulting in emergency room visits, re-admittance to hospital or need to intensify pharmacological treatment, all within 30 days)
• Change in lung function (ΔFEV1) on day 3, after 1 month and 3 month from recruitment
• Mortality rate 360 days
• Infection requiring antibiotic treatment within 180 days after the index of AECOPD
• The period between index AECOPD and the next AECOPD exacerbation. This endpoint will be anlyzed as:

a. Readmission with AECOPD or death within 30 days
b. Time to readmission with AECOPD or death within 30 days

• Cumulative corticosteroid dosage at baseline, 1 and 3 months of follow-up. This endpoint will be anlyzed as:

a. Proportions of patients using corticosteroids during hospitalization (day 1 to day 5) between treatment arms
b. Mean total cumulative dose from recruitment to 3-month follow-up

• Hyperglycemia during admission

• One or more of the following adverse effects at 1 and 3 months follow-up after the index AECOPD

o Change in bone marker levels (Serum P1NP, Serum CTX)

o Dyspepsia, start-up/increase in PPI doses or ulcer complications (gastrointestinal bleeding) 90 days (verified by gastroscopy)

o New onset or worsening of diabetes mellitus during the study period (defined as HbA1c ≥ 48 mmol/mol or initiation / intensification of anti-diabetic treatment) 30 days

o Increase in Body Mass Index (kg / m2)

• Changes in health-related quality-of-life measured by COPD Assessment Test (CAT) between hospitalization, at 30 days, and 3-month follow-up

• Changes in level of dyspnea using the Medical Research Council (MRC) Dyspnoea Scale between hospitalization, at 30 days and 3-month follow-up

• Changes in PTH and Vitamin D status between hospitalization and 3-month follow-up

• Osteoporotic fractures at 360 days

STAGE II

Long-term outcome to be assessed in 1, 2 and 5 years follow-up

Based on the results of the interim analyzes, the study group has decided, for better statistical strength (power, 1-β), to investigate the following endpoints:

Defined secondary long-term endpoints will be published when long-term follow-up is available (after due time) in a separate publication.

- Mortality
- Hospitalization or death
- Changes in Bone Turnover Markers (C-terminal telopeptide of type 1 collagen (CTX) and procollagen type 1 N propeptide (P1NP)) between hospitalization and follow-up
- Osteoporotic fractures
- Infections requiring antibiotic treatment after the index of AECOPD
- Hospital admissions with infections
- New onset or worsening of diabetes mellitus

This is, due to the fact, that the study group in parallel with this randomized clinical trial has conducted a national epidemiological study that has concluded that courses with corticosteroids to patients with COPD may increase the risk of death for up to several years after the exposure.

Since the CORTICO-COP RCT investigates a strategy to reduce the accumulated dose of corticosteroids, it is important that we follow the long-term mortality rate.

Upon completion of the study (after recruiting of the planned 318 patients), the primary endpoint and the short-term follow-up secondary endpoints will be analyzed. Thereafter, post-conditional power calculation will be made to clarify, whether there is need to recruit more patients in a stage II of CORTICO-COP study.

Of course, this does not change the fact that the primary results of the study, as indicated in the original protocol, will be analyzed and published when the 3 months follow-up period of the 318 planned patients is completed.

Stage II of the study is completed after the expected recruitment of another 150 patients - the exact number of patients will be based on the above post conditional power calculation.

When the above has been clarified, we will notify the Ethics Committee of the exact number of patients expected to be recruited at stage II of the study.

6.3 Data analysis

The two treatment groups are compared to endpoints - at the time of hospitalization, 1 and 3 months follow-up - with standard statistical tests, eg t-test or Mann-Whitney U test depending on data distribution. We will use log-rank test for survival analyzes. Hazard ratios are calculated using Cox regression.

In relation to glucocorticoid sensitivity, single-sided ANOVA or nonparametric ANOVA is used, depending on the distribution of the data. Correlation analyzes are performed with either parametric correlation analyzes or Spearmann's Rho.

7 Risks, Events and Side Effects

As subjects are exposed to a smaller dose compared to patients receiving standard treatment, risk and side effects for the intervention group are considered to be less.

According to www.pro.medicin.dk:

Very common (> 10%): Edema. Leukocytosis, leukopenia, lymphopenia, thrombocytosis. Adrenal insufficiency, hypokalaemia, sodium retention, impaired glucose tolerance, growth retardation. Myopathy, Osteoporosis. Infections, Inflammation of infections. Increased intraocular pressure, Cataract.

Common (1-10%): Cardiac insufficiency, Hypertension. Hypercholesterolemia, Hypercorticism, Hypertriglyceridemia. Depression, Euphoria, Psychosis. Dermatitis, Erythema, Hudatrophy, Hududslæt, Purpura, Striae, Wound healing complications, Teleangiectasis, Increased sweating. Hypogonadism (seen as menstrual disturbances in women), Nykturi.

Uncommon (0.1-1%): worsening of diabetes, manifestation of latent diabetes mellitus. Osteonecrosis. Hallucinations, Mania, Personality Disorders.
Allergic reactions. Urolithiasis.

Rare (0.01-0.1%): thrombosis. Tendon rupture. Glaucoma.

Very rare (<0.01%): Pancreatitis. Exophthalmus, Ketoacidosis, Porphyria.
Favorable intracranial pressure increase, Epileptic seizure. Stevens-Johnson syndrome, Toxic epidermal necrolysis.
Anaphylactic reaction.

The Summary of Product Characteristics is used as a reference document when assessing whether a seriously related adverse event (SAR) is unexpected / expected and may thus become a SUSAR. Side effects to the synacthen test are minimal. It is stated that mild nausea may occur after injection (not relevant for the RCT).

In blood sampling there is a small risk of infection or blood collection at the injection site. In addition, the examination may be associated with discomfort when inserting the needle. In the case of X-ray of lungs, a radiation dose of about 0.1 millisievert (mSv) is exposed. This is to be compared with the average background radiation in Denmark of approx. 3 mSv per year. There are no documented side effects in the literature of the radiation dose received by the X-ray of the lungs. Therefore, we consider that the study is not associated with risks or side effects.

The investigator must report any serious events (Serious Adverse Events) to the sponsor as soon as possible. Thereby, the sponsor can report in duly time to the Danish Medicines Agency and The Ethics Committee, if it is estimated that it is a SUSAR.
The sponsor must ensure that all lethal or life threatening information about SUSARs is recorded and reported to the Danish Medicines Agency as soon as possible and within 7 days after the sponsor becomes aware of such a suspected adverse reaction. Within 8 days after the report, the sponsor must notify the Danish Medicines Agency of all relevant information about the follow-up of the sponsor and investigator to the report. All other SUSAR must be reported to the Danish Medicines Agency no later than 15 days after the sponsor has become aware of these. At the same time, investigators are advised at the other centers. The participants are followed up to 3 months after completion of trial medication. Adverse drug reactions are recorded up to 20 hours (5 x half-life) after the last prednisolone tablet.
An annual list of all SUSARs that occurred during the trial period and a report on the subjects' safety are submitted to the Danish Medicines Agency. In addition, all adverse events and events at the end of the trial are reported in the final report to the Danish Medicines Agency.

8 Withdrawal of study

In general, no subject should be removed from the study for a protocol violation prior to confirmation by the coordinating investigator. A patient is only to be withdrawn from the study if the participant explicitly asks for withdrawal.

9 Funding

The study is financed by a grant from Danish Regions (Regionernes Medicinpulje) and The Danish Council for Independent Research and by the participating sites.

Initiative for the project is the Steering Committee for COP: TRIN. The project is budgeted for DKK 3,508,342. This includes wages for one PhD. student, enrollment of PhD student at the University of Copenhagen, project nurse for data collection, GCP Monitoring. Laboratory and

Diagnostic Testing expenses, Database / Website Creation, Maintenance, and Medical Expenses and Dosage Packaging from Glostrup Pharmacy.

The members of the project group have no financial interest in the investigated problem. The study is not supported by pharmaceutical companies or other organizations of economic interest in the investigation.
Department of Pulmonology, Gentofte Hospital, Senior Leader Niels Seersholm (Co-supervisor) has accepted that the PhD study and the randomized intervention study may be startet from the department. The necessary physical frameworks and IT solutions etc. is present.

10 Availability of information

It is the Board's conviction that knowledge sharing contributes to more and better scientific results. Requests for knowledge sharing from other groups will be submitted to the steering committee, and if the hypothesis to be investigated is not intended to be investigated by our group, we will allow the use of our data. However, it should be emphasized that data can be used for a particular purpose, not for future purposes in general.

11 Publication of test results

The project is part of a Ph.D. thesis. The test results will be published regardless of whether they are positive, negative or in-conclusive. Publication in international peer-reviewed scientific journals is planned accompanied by parallel publications in Danish Medical Journal. This includes at least one publication in a scientific journal with a high impact factor (10+).

12 Science ethical statement

Patients with COPD fear acute exacerbations as it increases dyspnea, cough, sputum and is often accompanied by anxiety. AECOPD is associated with significant morbidity and mortality.
This indicates that the repeated systemic corticosteroid therapy in patients with AECOPD causes serious adverse effects, e.g. new infection, diabetes, osteoporosis, adrenal insufficiency and mental

symptoms, etc. Taking into account that prednisolone treatment only has "temporary" beneficial effects on endpoints in patients with AECOPD and no effect at any endpoint one month after discontinuation of treatment, it is relevant to investigate whether the temporary clinical effects may be offset by side effects for corticosteroid treatment.

We believe that the clinical trial is scientifically ethical and, overall, greater gains for the subjects compared to the disadvantages in connection with the participation in the study. The participants will not be exposed to unforeseen risks.
We believe that the study will help to provide relevant information on how to treat patients with AECOPD in the future.
The research project will be carried out in accordance with the present trial protocol, ICH-GCP guideline, applicable government requirements, and in accordance with the Helsinki Declaration and latest revision. The study will be registered in the U.S. Clinical Trials database (www.clinicaltrials.gov), based on guidelines defined by The Food and Drug Administration. The protocol is written from The CONSORT statements 2010 for RCT studies [31].

13 Informed consent

Participation in the trial is voluntary. Informed consent of the participants of the trial is obtained. Executive Order No. 1149 of 30 September 2013 on information and consent to participation in health science research projects and on the notification and supervision of health science research projects. The subjects are protected in accordance with the Personal Data Processing Act. The trial is reported to the The Ethics Committee, The Danish Medicines Agency and the Danish Data Protection Agency

14 Information on compensation or compensation schemes

Patients who consider participating in injury may seek compensation, cf. Legislative Decree No. 1113 of 7 November 2011 on complaints and compensation for healthcare.

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