

Reduction of corticosteroid use in outpatient treatment of exacerbated COPD – Study protocol for a randomized, double-blind, non-inferiority study (The “RECUT”-Trial)

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Abstract

Background Chronic obstructive pulmonary disease (COPD) is a major public health issue affecting approximately four to seven percent of the Swiss population. According to current inpatient guidelines, systemic corticosteroids are important in the treatment of acute COPD exacerbations and should be given for five to seven days. Several studies suggest that corticosteroids accelerate the recovery of the FEV1 (forced expiratory volume in one second), enhance oxygenation, decrease duration of hospitalization and improve clinical outcome. However, the additional therapeutic benefit on FEV1 recovery appears to be most apparent in the first three to five days. No data are available on the minimal necessary corticosteroid dose and treatment duration in primary care patients with acute COPD exacerbations. Given that many COPD patients are treated on an outpatient basis, there is an urgent need to improve evidence about COPD management in this setting. The aim of this study is to investigate whether a three-day treatment with orally administered corticosteroids is non-inferior to a five-day treatment in acute exacerbations of COPD in a primary care setting. **Methods** The proposed study is a prospective, double-blind, randomized controlled trial conducted in a primary care setting, including an anticipated number of 470 patients with acutely exacerbated COPD. Participants are randomised to receive systemic corticosteroid treatment of 40 mg prednisone daily for five days (conventional arm, n = 235), or for three days, followed by two days of placebo (experimental arm, n = 235). Antibiotic treatment for seven days is given to all patients with CRP \geq 50 mg/l, known diagnosis of bronchiectasis, or presenting with Anthonisen Type-I exacerbation. Additional treatment after inclusion is left at the discretion of the treating general practitioner. Follow-up visits are performed on days three and seven by the treating general practitioners, followed by telephone interviews on days 30, 90 and 180 after inclusion into the study. Primary endpoint is the time to next exacerbation during a six-months follow-up period, which includes re-exacerbation during index exacerbation. **Discussion** This study is designed to assess whether a three-day course of corticosteroid treatment is not inferior to the current conventional five-day treatment course in outpatients with exacerbated COPD regarding time to next exacerbation. Depending on the results, this trial might lead to a further reduction of cumulative corticosteroid dose in COPD patients.

Background

In Switzerland, approximately four to seven percent of the total population suffer from chronic obstructive pulmonary disease (COPD), which is characterized by irreversible airflow obstruction and inflammation of the respiratory tract (1). It is a progressive disease and its acute exacerbations are associated with increased morbidity and mortality, which turns it into a major public health issue (2). The general practitioner-based Swiss COPD cohort demonstrated that approximately one in four COPD patients per year require pharmacological treatment for an acute exacerbation of COPD (AECOPD) (3, 4). Furthermore, a Spanish cross-sectional study found a median number of two exacerbations per patient per year in a population of 1001 COPD patients treated in general practice (5). According to current guidelines, inhalation of short acting beta-adrenergic agonists and anticholinergic agents, as well as systemic glucocorticoids (GC) are considered to be the standard therapy of AECOPD with a

recommended daily treatment dose of 40 mg prednisone over five days (6, 7). Several studies suggest that GCs accelerate the recovery of FEV1, decrease duration of hospitalization, reduce treatment failure and improve clinical outcome (8–14). The additional therapeutic benefit on FEV1-recovery, however, seems to be most apparent during the first three to five days of GC treatment (8, 9).

Side effects of long-term GC treatment are well known, but even short-term treatment may cause adverse effects, such as secondary infections, hyperglycemia or psychiatric symptoms (15). Furthermore, repeated short-term applications of GCs result in high cumulative doses in the long term, which are associated with a higher vertebral fracture risk (16) and muscle weakness (17). Altogether, there is strong evidence for beneficial effects of GCs in the treatment of AECOPD. However in the context of potential serious adverse effects of GCs, coupled with a population base with frequent COPD exacerbations, a reduction in GC administration may be beneficial.

In our previously performed hospital-based REDUCE study we found that a short five-day treatment with systemic steroids was not inferior with regard to re-exacerbation, when compared to a conventional 14-day treatment in patients presenting to emergency departments with AECOPD (6). These findings have led to revisions of international guidelines (7). However, even though many patients with AECOPD are treated in an outpatient setting, no data are available about the minimal necessary corticosteroid treatment duration in a primary care setting. Shorter treatment duration may be advantageous in reducing long-term corticosteroid related side effects, as well as potentially being more cost-effective.

Rationale

With this research project, we focus on the optimization of AECOPD treatment in primary care, where the majority of patients are treated. The primary objective of this study is to investigate whether a three-day treatment with orally administered systemic corticosteroids is non-inferior to a five-day treatment in AECOPD in a primary care setting. The primary endpoint is time to re-exacerbation. The study also aims to evaluate whether it is possible to minimize the cumulative dose of systemic glucocorticoid in patients suffering from AECOPD, without depriving them of the benefits of an optimal medication. A secondary objective is to evaluate differences between the two corticosteroid treatment durations regarding effectiveness and safety. Parameters to be evaluated as secondary endpoints are cumulative steroid dose, side effects and complications of glucocorticoid treatment, change in FEV1, clinical course assessed through the CAT-questionnaire, need for hospitalization during index exacerbation or during follow-up, and death from any cause.

Methods And Design

Study design and setting

The RECUT trial is a prospective, randomized, double-blind, placebo-controlled, non-inferiority trial in a primary care setting. The study is conducted in collaboration with general practitioners (GP) in

Northwestern and Central Switzerland, as well as in the Innsbruck area, Austria. Based on a sample size calculation, a total of 470 patients shall be enrolled, with a 1:1 allocation ratio to the experimental and conventional arm. Participating GPs assess patients with AECOPD for their eligibility criteria and perform diagnostic tests of their choice. Patients who fulfill the eligibility criteria and who are willing to participate receive 40 mg of oral prednisone per day for either five days (standard treatment group) or three days, followed by two days of placebo (experimental group). Antibiotics (amoxicillin/clavulanic acid, 625 mg 3/d, for seven days) are administered to all patients with a serum CRP (C-reactive protein) ≥ 50 mg/l at any of the study visits, or known diagnosis of bronchiectasis, as well as patients presenting with Anthonisen-type-I exacerbation (18). Additional initial treatment and further treatments during follow-up time are determined and documented by the treating GP. Participants are assessed with respect to primary and secondary endpoints after three and seven days by their treating GPs. The coordinating study center contacts patients by phone for further evaluation at days 30, 90, and 180. In cases where patients cannot give sufficient information with regard to the endpoints in the phone interview, their GP is interviewed in addition.

Patient characteristics

The first patient was enrolled in the study in August 2015 and recruitment is expected to conclude by September 2021. Enrolled patients must meet the following inclusion criteria (see also Table 1): age ≥ 40 years, history of ten or more pack-years of smoking (past or present smokers), airway obstruction (defined as FEV1/forced vital capacity (FVC) ratio $\leq 70\%$), and current AECOPD. The latter is defined by the presence of at least two of the following symptoms: change of baseline dyspnea, change of cough, change of sputum quantity or purulence. Key exclusion criteria include asthma/COPD overlap syndrome with predominant asthma component, initial necessity of hospitalization, known severe immunosuppression, and severe coexisting disease with a life expectancy of less than six months. Women who are pregnant or breastfeeding, premenopausal women with insufficient contraception, and patients with diagnosis of tuberculosis are also excluded from the study.

Blinding and Randomization

Identical looking blister packs with daily doses of 40 mg prednisone for either five days (standard treatment arm) or three days, followed by two days of placebo (interventional arm), are packed in a 1:1 ratio in the hospital pharmacy of the University Hospital Basel, Switzerland, in a GMP (Good Manufacturing Practice) regulated environment. Each blister pack is labelled with a computer-generated random alphanumeric code. A concealed envelope marked with this alphanumeric code on the outside contains group allocation and is kept safe at the study center until analysis of the final data. Depending on the expected number of eligible patients, each recruiting GP receives a certain number of the pre-randomized blister packs and hands them out to participating patients. Trial participants, general practitioners, outcome assessors and data analysts are blinded to group allocation.

Study intervention and assessments

The schedule of enrollment, interventions and assessments is presented in Fig. 1. On day one (inclusion visit), patients presenting with AECOPD to their GP are checked for eligibility criteria, give written informed consent, and undergo a general clinical assessment including vital signs, dyspnea assessment (mMRC) and COPD assessment test (CAT). A blood sample for CRP, plasma glucose, and leucocyte cell count is taken and FEV1 and FEV1/FVC are assessed through spirometry. Additional newly started exacerbation medication besides the study medication will be documented by the GP.

The follow-up visits will take place on day three (+/- one day) and day seven (+/- one day) and consist each of a general clinical assessment, a blood sample, and an assessment of clinical course regarding treatment failure and need for hospitalization. Furthermore, any changes in medication (including COPD baseline medication and exacerbation medication), cumulative GC dose, other interventions such as COPD self-management and smoking cessation, as well as clinically manifested side effects of GCs will be documented. During the second follow-up visit on day seven, the detailed medical history with regard to COPD is recorded and a spirometry is performed additionally.

Participants are further followed-up by phone on days 30, 90, and 180 after inclusion into the study (+/- seven days each). The phone interviews include dyspnea (mMRC) and COPD assessment (CAT) questionnaires, as well as questions regarding sputum, cough, any change in medication, and hospitalizations in the intervening time in order to assess re-exacerbation.

Outcomes

The primary endpoint is time to next exacerbation during a six month follow-up period, which includes re-exacerbation during the index exacerbation (i.e. treatment failure). Exacerbation is defined as acute-onset worsening of the patient's condition beyond day-to-day variations requiring interaction with a healthcare provider (19). We chose time to next exacerbation as our first endpoint in order to evaluate effectiveness of the shorter steroid treatment. According to the studies by Leuppi et al. (6), Niewoehner et al. (9), and Aaron et al. (10), who investigated treatment failure rates, relapse rate, and time to relapse in AECOPD patients under GC, time to next exacerbation (which includes treatment failure) seems to be a valid measurement for effectiveness.

Secondary study outcomes are cumulative GC dose, GC side effects and complications, change in FEV1, hospitalization rate during index exacerbation and during follow-up, clinical outcome assessed by CAT and mMRC, as well as overall mortality. Cumulative GC dose and GC side effects are assessed in order to investigate safety of short-term and standard steroid treatment duration. Furthermore, change in FEV1, hospitalization rate during index exacerbation and during follow-up time, as well as clinical outcome and overall mortality are evaluated to compare effectiveness of different durations of systemic corticosteroid treatment.

Statistical Analysis

It is hypothesized that the experimental treatment (three days corticosteroid treatment) is non-inferior to the conventional treatment (five days corticosteroid treatment) with regard to the primary endpoint. For this, a Cox proportional hazards regression model will be fitted to the data. Non-inferiority will be concluded if the two-sided 95% confidence interval of the hazard ratio between the experimental and the control arm lies entirely below the critical hazard ratio defined as

[Due to technical limitations, this equation is only available as a download in the supplemental files section.]

where t is a fixed point of time, λ_e and λ_c are the hazard rates, π_{et} and π_{ct} are the proportions of event-free patients at time t in the experimental and conventional arm respectively, and m is the non-inferiority margin, expressed as the additional proportion of patients having had an event in the experimental arm, assuming that the occurrence of events follows an exponential distribution (20). This approach is partly based on the methodology described in a previously performed study of our research group (6, 21). Following the recommendations of the CHMP (Committee for Medicinal Products for Human Use), a two-sided 95% confidence interval is used to assess non-inferiority (22).

Sample size calculation

For the estimation of necessary sample size, we assumed an exacerbation rate of 30 to 40 percent following an exponential distribution, and a 15 percent drop-out rate evenly distributed within the six months follow-up period, for both the interventional and the conventional arm. The non-inferiority margin was defined as a 15% increase of exacerbation rate within six months, the significance level was chosen to be 5%, and the desired power 80%. A simulation and a cox proportional hazards regression model were used to determine hazard ratios and 95% confidence intervals for the simulated data sets, which led to a sample size of $N = 466$ (95 % CI 461 to 471) for an exacerbation rate of 30%, and $N = 464$ (95 % CI 459 to 469) for an exacerbation rate of 40%, respectively. Therefore, we aim to include $N = 470$ patients into the study.

Sample size will be re-estimated after approximately half of the initially estimated number of patients have reached the six month follow-up. If necessary, the sample size will be increased. We will re-estimate the exacerbation rates in a blinded manner, based on the overall observed exacerbation rate as described by Friede et al. (23). Since no hypothesis test is performed, no p-value adjustment to control the type-I-error rate is needed.

Discussion

The treatment of COPD, and especially the management of AECOPD, remains a challenge in a primary health care setting. Practitioners aim to provide their patients with the most effective, yet safe and

economical therapy option, preferably with fewest side effects. There is sufficient evidence that GCs have a positive effect on recovery from and clinical outcome of AECOPD (10–14), with the current guidelines suggesting a prednisone pulse of 40 mg daily for five days (6, 7). However, the minimal effective duration of a GC pulse in AECOPD has not yet been determined; this has relevance since GCs may cause relevant long-term side effects, and repeated short-term treatments have an impact on the cumulative dose. In cases of AECOPD treated in an outpatient setting, which can be assumed to be generally less severe than in an in-hospital setting, a shorter GC treatment duration might be just as effective, yet lower in side effects. A reduction in standard treatment duration could lead to significantly lower cumulative GC doses, especially in individuals with frequent exacerbations, and decrease short- and long-term side effects. Furthermore, COPD related health care cost could be reduced.

The high prevalence and mortality of COPD and its great impact on quality of life implies the need for not only prevention and new treatment options, but also for optimization of established treatment strategies to reduce its overall burden. This fact strongly underlines the clinical relevance and importance of the RECUT trial. Furthermore, despite the availability of international guidelines, studies showed sub-optimal adherence to evidence-based COPD treatment strategies by GPs (3, 24). When advocating the use of guidelines in primary care, these need to be verified within and optimized for this specific setting in order to increase acceptability among practitioners and to ensure best evidence-based treatment for patients. The innovative design in a primary care setting is one of the key strengths of this project. It may also enhance awareness of current guidelines and therefore improve adherence to evidence-based treatment strategies among participating GPs. Further strengths of the study include its prospective, randomized, placebo-controlled, and double-blind design, as well as its relatively straight-forward process. Even though a randomized approach was chosen, treating GPs retain control by deciding over additional initial and follow-up treatment in accordance with the protocol, which helps readiness for collaboration.

Trial status

The first patient was enrolled into the study in August 2015. The study is currently ongoing with active recruitment under protocol Version 5, dated March 14th, 2019. Recruitment is anticipated to be complete by September 2021.

List Of Abbreviations

AECOPD: acute exacerbation of chronic obstructive pulmonary disease

CAT: COPD assessment test

CHMP: Committee for Medicinal Products for Human Use

CI: confidence interval

COPD: chronic obstructive pulmonary disease

CRP: C-reactive protein

EKNZ: Ethics Committee for the Region of Northwestern and Central Switzerland

FEV1: forced expiratory volume in 1 second

FVC: forced vital capacity

GC: glucocorticoid

GMP: Good Manufacturing Practice

GOLD: Global Initiative for Chronic Obstructive Lung Disease

GP: general practitioner

mMRC: modified British Medical Research Council

SNF: Swiss National Science Foundation

Declarations

Ethics approval and consent to participate

Ethics approval to conduct this trial with the coordinating study center in Liestal has been first granted by the local Ethics Committee for the Region of Northwestern and Central Switzerland (EKNZ, Project-ID: 2015–017) on January 31st 2015. Four amendments regarding financial compensation for recruiting GPs, structural changes of the case report forms, and the archiving of study documents have been approved by the EKNZ between April 2015 and January 2017. The study was first extended from the greater Basel area to the cantons of Luzern, Aargau, Solothurn, and later to the canton of Zurich with approval of the cantonal ethics committee Zurich in May 2017. Approval for an extension to the greater Innsbruck area from the ethics committee of the University of Innsbruck was given in September 2018. Furthermore, we are currently awaiting ethics approval for another extension to the canton of Bern.

The trial will meet the criteria and principles of the Declaration of Helsinki and has been registered in the [Clinicaltrials.gov](https://clinicaltrials.gov) database (Trial registration number: NCT02386735, Registered on 12 March 2015).

Informed consent to participate in the trial is obtained by the recruiting GPs from all patients prior to study entry. Each patient will be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time with no need of justification, and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. Furthermore, the patient will be informed on an obligatory basis that his/her medical records may be examined by authorized individuals other than their treating physician. All patients are covered by liability insurance for the total study duration.

Consent for publication

Not applicable

Availability of data and materials

Trial information can be found at [ClinicalTrials.gov](https://clinicaltrials.gov), NCT02386735. A completed SPIRIT checklist is available in additional file 1.

Competing interests

The authors declare that they have no competing interests with regard to this study.

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Authors' contributions

JDL had the initial idea for the study and is broadly involved in the conception, design, and organizational supervision in his role as the Principal Investigator. PU wrote the original study protocol and participated intensely in the revision of this manuscript. MB drafted, revised and finalized this manuscript. KA is responsible for protocol-conform implementation and coordination, follow-up calls, documentation, and recruitment support for GPs. MC provided sample size calculation, randomization schedule and designed the statistical analysis plan. AZ is Co-Principal Investigator. AZ and TD are involved in the design and implementation of the study and have participated in reviewing this manuscript. HB, SM, OS, CM, SE, EU, and MS support recruitment and coordinate local activities in their role as local project leaders. All authors read and approved the final manuscript.

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Table 1

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
- Age \geq 40 years	- Initial necessity of hospitalization
- Informed consent as documented by signature	- Previous enrollment into the current study
- History of \geq 10 pack-years of smoking (past or present smokers)	- Asthma/COPD overlap syndrome with a predominant asthma component
- Airway obstruction, defined as FEV1/FVC \leq 70%	- Diagnosis of tuberculosis
- Current acute exacerbation of COPD by clinical criteria, defined by the presence of at least two of the following: <ul style="list-style-type: none"> × Change of baseline dyspnea × Change of cough × Change of sputum quantity or purulence 	- Severe coexisting disease with life expectancy < 6 months
	- Known severe immunosuppression or immunosuppression after solid organ or stem cell transplantation
	- Inability to follow study procedures, e.g. due to language problems, psychological disorders, dementia, etc. of the participant
	- Participation in another study involving an investigational drug
	- Women who are pregnant or breast feeding
	- Premenopausal women with insufficient contraception and anamnestic risk for pregnancy

FEV1: forced expiratory volume in one second. FVC: forced vital capacity. COPD: chronic obstructive pulmonary disease.

Figures

	Enrollment	Post-allocation					
	Day 1	Day 3	Day 5	Day 7	Day 30	Day 90	Day 180
ENROLLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation	X						
INTERVENTIONS:							
Experimental arm: Prednisone 40mg/d		◆	◆				
Conventional arm: Prednisone 40mg/d		◆					
ASSESSMENTS:							
Baseline parameters ¹⁾	X						
Outcome parameters on study visits ²⁾		X		X			
Outcome parameters on follow-up calls ³⁾					X	X	X
Other parameters ⁴⁾		X		X	X	X	X

Figure 1

Summary of the RECUT Trial assessments performed at different points in time. Legend: 1) Sex, age, weight, height, nationality, detailed medical history, CRP, plasma glucose, leucocyte cell count, respiratory rate, heart rate, blood pressure, pulse oximetry, body temperature, spirometry, mMRC, CAT, quality and quantity of sputum and cough. 2) All variables as in 1) except demographic variables, as well as treatment failure, hospitalization, mortality, change in medication, cumulative GC dose, clinically manifest side effects of GC or other medication. (CAT only on day 7). 3) mMRC, CAT, quality and quantity of sputum and cough, re-exacerbation, hospitalization, mortality, change in medication, cumulative GC dose, clinically manifest side effects of GC or other medication. 4) Intervention (COPD self-management, smoking cessation), comments, lost to follow up.

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