Efficacy and safety of oral corticosteroids to treat outpatients with acute exacerbations of COPD in primary care: a multicentre pragmatic randomised controlled study

Jean-Laurent Thebault[1], Nicolas Roche[2], Hendy Abdoul[3], Alain Lorenzo[4], Thomas Similowski[5,6] and Christian Ghasarossian[1]

[1]Département de Médecine Générale, Université Paris Cité, Paris, France. [2]AP-HP, Centre – Université Paris Cité, Cochin Hospital and Institute (INSERM UMR1016), Respiratory Medicine, Paris, France. [3]Unité de Recherche Clinique Centre d'Investigation Clinique, Paris Descartes Necker/Cochin, Hôpital Tarnier, Paris, France. [4]Département de Médecine Générale, Sorbonne Université, Paris, France. [5]Sorbonne Université, INSERM, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France. [6]AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Département R3S (Respiration, Réanimation, Réadaptation respiratoire, Sommeil), Paris, France.

Corresponding author: Jean-Laurent Thebault (jean-laurent.thebault@u-paris.fr)

Shareable abstract (@ERSpublications)
Oral prednisone did not show any advantage in patients with COPD exacerbation in primary care. Significantly higher respiratory-related treatment failure in the prednisone group warns against the use of corticosteroids in this setting. https://bit.ly/3NwoEr2

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Abstract

Aim To compare prednisone and placebo for the treatment of outpatients treated for acute exacerbations of chronic obstructive pulmonary disease (COPD) in a primary care setting.

Methods A multicentre, parallel, double-blind, pragmatic randomised controlled trial was performed in France. A total of 66 general practitioners included patients aged ⩾40 years with cumulative smoking of ⩾10 pack-years and a diagnosis of certain or likely acute exacerbation of COPD. Oral prednisone (40 mg) or placebo were administered daily for 5 days. The main outcome was treatment failure at 8 weeks, defined as a composite criterion based on the occurrence of at least one of the following: unplanned visit to an emergency department or to a practitioner in the ambulatory setting, hospital admission or death. The planned sample size was 202 patients per group.

Results 175 patients were included from February 2015 to May 2017 (43% of the planned sample). All-cause 8-week treatment failure rate was 42.0% in the prednisone group and 34.5% in the placebo group (relative risk 1.22, 95% CI 0.87–1.69, p=0.25). Respiratory-related 8-week treatment failure rate was 27.6% in the prednisone group and 13.6% in the placebo group (relative risk 2.00, 95% CI 1.15–3.57, p=0.015).

Conclusion Although the planned sample size was not achieved, the study does not suggest that oral corticosteroids are more effective than placebo for the treatment of an acute exacerbation of COPD in a primary care setting.

Introduction

Chronic obstructive pulmonary disease (COPD) has a major health impact that is continuing to increase worldwide. This impact can be seen from both individual (patient outcome) and collective (resource burden) perspectives. It relates mainly to acute exacerbations and handicap due to impaired exercise performance. The impact of exacerbations can be both immediate and long term. They impair health status and, in severe cases, are associated with premature death with in-hospital mortality reaching 7.5%. In the long term, repeated exacerbations of COPD are associated with an accelerated decline in lung function and health status, increased mortality, aggravation of comorbidities and increased direct (healthcare) and indirect (decreased productivity) costs [1, 2].

The pharmacological management of COPD exacerbation relies mostly on three families of drugs: bronchodilators (to relieve dyspnoea), antibiotics (when sputum is purulent) and oral corticosteroids [3, 4]. Most efficacy evaluations of oral corticosteroids in COPD exacerbation have been conducted in hospitalised patients and in patients visiting emergency departments who were subsequently discharged without being admitted. In these populations, efficacy has been demonstrated with a brief improvement of lung function and gas exchange and a reduction of length of hospitalisation and risk of treatment failure [5], with short-term treatment (5 days, 40 mg·day^{-1}) being as effective as longer-term treatment (14 days) [6]. In the ambulatory setting, the American Thoracic Society/European Respiratory Society guideline taskforce identified only three studies evaluating oral corticosteroids in COPD patients (conducted in a total of 204 patients), which failed to demonstrate an effect on mortality or treatment failure, despite a favourable effect on lung function [2]. The conclusions that can be drawn from this meta-analysis are limited owing to the heterogeneity of the recruitment setting (primary care or emergency room), the absence of some important clinical outcomes and the small number of events and patients [7–9]. Overall, most guidelines recommend oral corticosteroids for all patients with COPD exacerbation [10], despite the lack of evidence on their efficacy and safety for outpatients in primary care and the need to perform studies specifically in primary care. To address this issue, a randomised double-blind pragmatic clinical study was performed in the primary care setting comparing prednisone to placebo in patients treated for an acute COPD exacerbation.

Methods

Study design, investigators and treatment

The BECOMEG study was a multicentre, parallel, double-blind, pragmatic randomised controlled study in a primary care setting. A total of 800 general practitioners (GPs), members of the French national college of teachers in general practice, covering the whole of metropolitan France were contacted by email. Of these, 247 were recruited and 66 included at least one patient over a period of 27 months from February 2015 to May 2017. Patients were randomised 1:1 by centre with blocks of four receiving oral prednisone (40 mg, 5 days) or placebo. Investigators could prescribe any treatment (including antibiotics) for the exacerbation of COPD except oral corticosteroids.

Patients

To be included, patients had to fulfil the following conditions: age ⩾40 years, cumulative smoking ⩾10 pack-years and diagnosis of certain or likely acute exacerbation of COPD. Acute exacerbation was defined by the onset or worsening of a least two of the four following symptoms: cough, sputum volume, sputum purulence and dyspnoea. The diagnosis of acute exacerbation of COPD was considered certain in patients with a known spirometry-based diagnosis of COPD reporting an acute increase in respiratory symptoms. The diagnosis was considered probable in patients reporting exertional dyspnoea in their daily life (modified Medical Research Council (mMRC) dyspnoea grade of ⩾1) that could not be explained by any known or suspected underlying chronic respiratory or cardiovascular disease other than COPD. In the context of a pragmatic study, exclusion criteria were kept to a minimum. Patients were not included if hospitalisation was planned or when alternative diagnoses were suspected based on clinical presentation (pneumonia, pulmonary oedema) (table 1). Other exclusion criteria included treatment with prednisone in the last 7 days and contraindications to prednisone [11, 12].

The study was approved by the appropriate French authorities. It received ethical approval from the Comité de Protection des Personnes Ile de France 3 (decision #3192) and was publicly registered before the first patient was included at www.clinicaltrials.gov (NCT02330952). All patients provided written informed consent before inclusion.

Intervention

Patients and investigators were blinded to the assigned treatment. Treatment units were numbered according to a randomisation list drawn up by the project's lead methodologist. At the start of the study, each GP investigator received four treatment units in numbered and sealed cases containing 10 tablets of 20 mg of prednisone or placebo of the same appearance. If needed, the investigators could receive more treatment units after the two first inclusions. The GP dispensed an interventional medical product (IMP) to the patient during the inclusion visit and noted the IMP's number in the electronic case report form (e-CRF) in order to identify the allocation arm at the end of the study. GPs who made home visits were advised to bring the first available IMP on their list with them during their visits to include a patient if necessary. Inclusion, randomisation and dispensation of treatment were therefore done simultaneously.

TABLE 1 Inclusion and exclusion criteria

Inclusion	Exclusion
Age ⩾40 years	Known or suspected chronic respiratory disease other than COPD (*e.g.* asthma, bronchiectasis)
Past or current smoking ⩾10 pack-years	Suspicion of pneumonia or acute heart failure
Diagnosis of certain or likely acute exacerbation of COPD	Fever not related to the acute exacerbation of COPD
Patients who gave informed and written consent to participate in the study	Hospitalisation required
	Ongoing oral corticotherapy or stop for <1 week
	Risk of noncompliance
	Scheduled moving within 8 weeks after inclusion
	No public health insurance or social aid insurance
	Patient already included in BECOMEG trial
	Patients with a contraindication to prednisone according to the summary of product characteristics[#]

COPD: chronic obstructive pulmonary disease. [#]: uncontrolled arterial hypertension, unbalanced diabetes, deep infection site, history of untreated tuberculosis, untreated peptic ulcer, untreated wound, ulcerative colitis, patients allergic to corticosteroids, any severe or uncontrolled infectious state not falling within the indications specified in the summary of product characteristics, hepatitis, evolving genital herpes, chickenpox, shingles in progress, recent or scheduled live or attenuated vaccine, psychotic state not yet controlled by treatment, hypersensitivity to prednisone or to one of the excipients of Cortancyl, in particular lactose intolerance.

Collected data and outcomes

Patient inclusion and follow-up were organised as follows. An inclusion visit was made by the GP (at their office or at the patient's home) comprising a check of inclusion and exclusion criteria, collection of informed consent, randomisation and treatment delivery. Telephone contact was made by a research assistant at 1 week and 4 weeks. An end-of-study visit at 8 weeks was made by the GP (in their office, at home or by telephone) with collection of the primary outcome.

The following data were collected at inclusion: demographics, anthropometric characteristics, COPD and history of COPD exacerbation, usual symptoms and treatments, comorbidities and their treatments, clinical features including mMRC dyspnoea grade and COPD Assessment Test (CAT) score.

The main outcome was treatment failure at 8 weeks, defined as a composite criterion by the occurrence of at least one of the following: self-medication with corticosteroids or antibiotics following an action plan, any cause of an unplanned visit to an emergency department or to a practitioner in the ambulatory setting, hospital admission or death.

The following secondary outcomes were defined: respiratory-related treatment failure at 8 weeks, defined as an impairment of the respiratory status leading to one or more of self-medication with corticosteroids or antibiotics following an action plan, unplanned visit to an emergency department or to a practitioner in the ambulatory setting, hospital admission or death; each individual component of the main composite outcome, analysed separately; health status (CAT score) and dyspnoea grade (mMRC scale) at 1 week, 4 weeks and 8 weeks; wellbeing score (general feeling of wellbeing during the last week rated from 0 "As good as it could be" to 6 "As bad as it could be") at 1 week, 4 weeks and 8 weeks [13]; adverse events; and quality-adjusted time without symptoms and toxicity (Q-TWiST) [14]. Overall survival (OS) was classified using three distinct states: Tox (time with toxicity), TWiST (time without symptoms or toxicity) and Rel (time with relapse or recurrence). Quality-adjusted time survival for each group was calculated using the following equation:

$$\text{Q-TWiST}=\text{UTox}\times\text{Tox}+\text{TWiST}+\text{URel}\times\text{Rel}.$$

Tox was defined as the presence of any adverse event during the follow-up period. UTox was the utility coefficient attributed by the scientific committee to the Tox period according to the quality of life associated with it, from 0 to 1 (0 for death and 1 for perfect health) (supplementary table S1). Rel duration was set at 8 days, based on the average duration of exacerbations [15]. URel was the utility coefficient assigned to the Rel period according to the same quality of life scale as UTox. A utility of 0.7 was set for all exacerbation by the scientific committee.

Statistical methods and sample size calculation

To detect a 30% relative difference in the main outcome with a reference rate of treatment failure of 20% in the control group [16–18], with a 5% alpha risk and 80% power, 507 patients were required in each group. The sample size requirement was subsequently amended following the publication of new data on treatment failure rate and the effects of oral corticosteroids in hospitalised patients [5, 19]. The new (conservative) estimations were 40% for reference treatment failure rate and 37.5% for relative risk reduction. With an alpha risk of 5% and 90% power, sample size requirement was amended to 202 per group.

Treatment failure rate at 8 weeks in each group was compared. Rate difference and adjusted rate ratio were estimated using a generalised estimating equations Poisson model with an exchangeable correlation structure to take into account the correlation within patients from the same centre. The same analysis strategy was used for respiratory-related treatment failure and each individual component of the main composite outcome was analysed separately.

Wellbeing score at 8 weeks was compared between groups using a longitudinal analysis. The model was a linear mixed-effects model with wellbeing score at each visit (week 1, week 4, week 8) as outcome; randomisation arm, visit and randomisation arm × visit interaction as fixed effects; and patient and centre as random effects. The same analysis strategy was used for CAT score and mMRC scale.

For the Q-TWiST analysis, mean duration of each state was determined using the Kaplan–Meier method in each group. Mean duration for time with toxicity (Tox) and OS were determined using the area under the corresponding Kaplan–Meier curve. Mean duration without exacerbation (NoEx) was calculated with OS and a predetermined duration of exacerbation (8 days). Mean TWiST duration was calculated with NoEx and Tox (TWiST=NoEx−Tox) and mean Rel duration was calculated with OS and NoEx (Rel=OS−NoEx). Mean duration of each health state and Q-TWiST were compared using z-tests, with bootstrap calculation of standard error distribution and normal approximation of 95% confidence intervals.

Adverse events and severe adverse events were described for each randomisation arm and proportions were compared using Fisher exact tests.

All analyses were performed on the intention-to-treat population.

Results

Patients and adherence to study medication

The study flow diagram is presented in figure 1. Patient characteristics at inclusion are summarised in table 2 and were similar between groups. A total of 175 patients were included. Recruitment was halted after an extended recruitment period of 2 years owing to the accretion rate being too slow to reach the target population size before the expiry date of the experimental treatments. Mean±SD age of the patients was 62±11 years and 61.7% were men. The mean±SD cumulative smoking was 38±21 pack-years. 34% had spirometry-confirmed airflow obstruction. The 14 patients with spirometry but without airflow obstruction performed spirometry between 2 and 6 years before their inclusion in the study. The most prevalent airways obstruction severity stage was Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2. 62.9% had maintenance therapy and 89.1% had at least one other chronic disease. Adherence to medications as estimated by counting of remaining treatments was excellent (100% for 90% of patients in both groups).

Outcomes

All-cause 8-week treatment failure rate was 42.0% in the prednisone group and 34.5% for placebo, with a risk ratio of 1.22 (95% CI 0.87–1.69, p=0.25) (table 3).

Respiratory-related treatment failure was significantly higher in the prednisone than in the placebo group, with a risk ratio of 2.00 (95% CI 1.15–3.57, p=0.015) (table 3). Accordingly, the number of days spent in relapse, a component of Q-TWiST, was significantly higher in the prednisone group (3.76 days *versus* 1.78 days, p=0.044) (table 4). Although the number of unplanned visits to a GP and visits to the emergency department was numerically higher in the prednisone than the placebo group (31 *versus* 24 visits, and eight *versus* four visits, respectively), the difference between groups did not achieve statistical significance (table 3). Q-TWiST as a whole was similar between groups (figure 2, table 4), as were wellbeing, CAT score and mMRC dyspnoea grade (table 5).

In the subgroup of patients with spirometry-confirmed airflow obstruction (n=61), treatment failure rate was higher in the prednisone group than the placebo group (51.4% *versus* 34.6%), as was respiratory

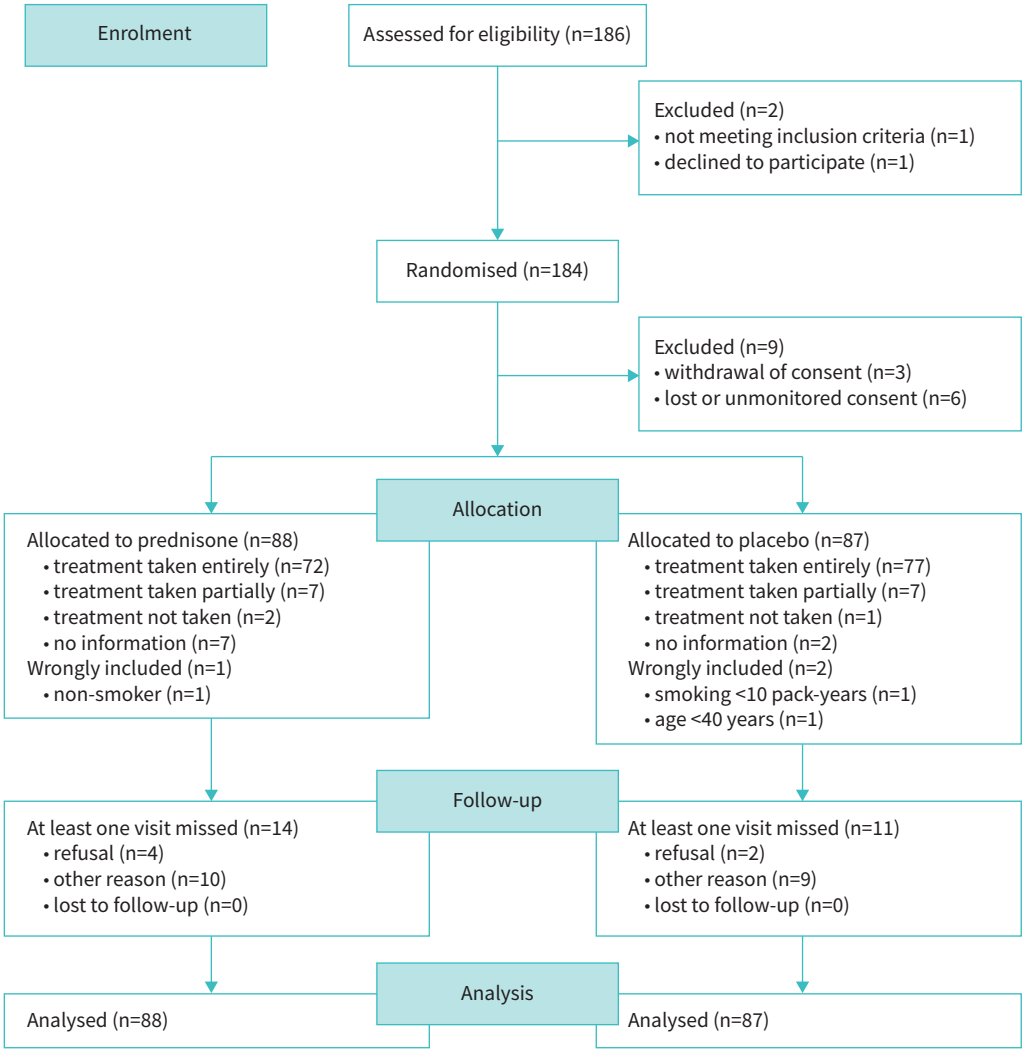

FIGURE 1 Flow chart.

treatment failure (34.3% *versus* 15.4%) (supplementary table S2). When excluding patients with a forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio >70% (14 patients included in the study), treatment failure rate was higher in the prednisone group than the placebo group (43.0% *versus* 35.8%), as was respiratory treatment failure (27.8% *versus* 14.8%) (supplementary table S3).

Adverse events

Adverse event did not differ between groups (table 6), with 56.8% and 54.0% of patients experiencing an adverse event in the prednisone and placebo groups, respectively (p=0.76). Four adverse events (<5%) were categorised as severe in each group. There were no deaths in either group.

The number of non-respiratory infections was similar between the prednisone group (two infections) and placebo group (three infections). No hyperglycaemia, fluid retention or digestive disorder was observed in the prednisone group. The main adverse events in each group are shown in table 7.

Discussion

Key findings

This pragmatic randomised study compared prednisone treatment to placebo in patients treated for an acute exacerbation of COPD in an ambulatory setting. The study was terminated without having reached the target sample size due to slow recruitment and as a result was statistically underpowered. The frequency of treatment failure (primary outcome) was not significantly different in the prednisone and placebo groups,

TABLE 2 Baseline demographic and clinical characteristics

	Prednisone	Placebo
Subjects (n)	88	87
Age (years)	61±11	64±11
Sex (male)	57 (64.8)	51 (58.6)
Occupation		
Farmer	1 (1.2)	0 (0.0)
Shopkeepers and craft workers	8 (9.3)	10 (11.8)
Managers and higher intellectual professions	15 (17.4)	10 (11.8)
Intermediate white-collar workers	11 (12.8)	16 (18.8)
Office, sales and service workers	30 (34.9)	23 (27.1)
Blue-collar workers	14 (16.3)	22 (25.9)
Other	7 (8.1)	4 (4.7)
BMI ($kg \cdot m^{-2}$)	26.5±4.4	27.2±5.4
Characteristics of the acute exacerbation of COPD		
Increased sputum volume	80 (90.9)	82 (94.3)
Increased purulence of sputum	65 (73.9)	64 (73.6)
Increased cough	87 (98.9)	85 (97.7)
Increased dyspnoea	74 (84.1)	72 (82.8)
Presence of the four exacerbation criteria	53 (60.2)	51 (58.6)
mMRC scale at baseline	2.1±0.9	2.1±0.9
Medical history		
Cumulative smoking (pack-years)	39±21	37±22
Patients with previous spirometry	43 (48.9)	32 (36.8)
with FEV_1/FVC<70%	35 (89.7)	26 (89.7)
GOLD grade		
GOLD 1	5 (12.8)	4 (14.3)
GOLD 2	27 (69.2)	16 (57.1)
GOLD 3	7 (17.9)	8 (28.6)
GOLD 4	0 (0)	0 (0)
Chronic cough with sputum	66 (75.0)	68 (78.2)
Ongoing or past inhaled maintenance therapy	57 (64.8)	54 (62.1)
LABA+LAMA+ICS	11 (19.3)	9 (16.7)
LABA+ICS	8 (14.0)	8 (14.8)
LABA+LAMA+ICS+SABA	8 (14.0)	6 (11.1)
LABA+ICS+SABA	4 (7.0)	8 (14.8)
LAMA	3 (5.3)	6 (11.1)
LABA+LAMA	5 (8.8)	3 (5.6)
SABA	6 (10.5)	2 (3.7)
LABA	4 (7.0)	3 (5.6)
LABA+ICS+SABA+SAMA	3 (5.3)	3 (5.6)
ICS	0 (0)	2 (3.7)
LAMA+ICS	1 (1.8)	1 (1.9)
ICS+SABA	0 (0)	1 (1.9)
LABA+ICS+LAMA+SABA+SAMA	0 (0)	1 (1.9)
LABA+LAMA+SABA	1 (1.8)	0 (0)
LABA+SABA	1 (1.8)	0 (0)
SABA+LAMA	1 (1.8)	0 (0)
SABA+SAMA+LAMA	1 (1.8)	0 (0)
SAMA+LABA	0 (0)	1 (1.9)
Number of suspected acute exacerbations of COPD over the last 12 months		
0	19 (21.6)	20 (23.3)
1	29 (33.0)	18 (20.9)
2	19 (21.6)	24 (27.9)
⩾3	21 (23.9)	24 (27.9)
Comorbidities		
At least one comorbidity	79 (89.8)	77 (88.5)
Arterial hypertension	37 (42.0)	35 (40.2)
Obesity	24 (27.3)	24 (27.6)
Diabetes	12 (13.6)	10 (11.5)
Ischaemic heart disease	11 (12.5)	10 (11.5)

Continued

TABLE 2 Continued

	Prednisone	Placebo
Exacerbation management		
Antibiotics	67 (76.1)	65 (74.7)
Increased dose of inhaled maintenance therapy	6 (6.8)	7 (8.0)
Addition of another inhaled treatment	12 (13.6)	17 (19.5)
Nebulisers	6 (6.8)	2 (2.3)
Chest X-ray	13 (14.8)	12 (13.8)
Blood test	13 (14.8)	11 (12.6)

Data are presented as mean±SD or n (%). BMI: body mass index; COPD: chronic obstructive pulmonary disease; mMRC: modified Medical Research Council; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LABA: long-acting β-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroids; SABA: short-acting β-agonist; SAMA: short-acting muscarinic antagonist.

but was numerically higher in the prednisone group. There were no differences between groups for healthcare resource utilisation, patient-related outcomes or adverse events. However, respiratory-related treatment failure rate and the number of days spent in relapse were significantly higher, and unplanned visits were numerically higher in the steroid group than in the placebo group.

Context of the study

To our knowledge, this is the first randomised study assessing the effect of prednisone on clinical outcomes and healthcare resource utilisation in COPD exacerbation in a pure outpatient primary care setting. The topic is important because most COPD exacerbations are managed in primary care, even if the knowledge of the epidemiology of these events in outpatients is less accurate than for hospitalised exacerbations, which currently represent about 130 000 events in France each year [20]. In addition, oral corticosteroids are widely used in an ambulatory setting despite a lack of robust evidence for efficacy. In Spanish and French observational studies, 40% of outpatients with exacerbations received oral corticosteroids [21–23]. Systemic corticosteroids have known systemic side-effects and their cumulative intake appears to be associated with an increase in mortality and a decrease in the effectiveness of important measures such as nutritional support [24].

Several studies have been conducted to determine the effect of oral corticosteroid therapy in COPD exacerbations [5, 25, 26]. Most involved inpatients or patients discharged from emergency departments. In this situation, corticosteroid therapy reduced the duration of hospital stay, treatment failures at 1 and 3 months and an improvement in FEV_1. In outpatients, a small study published by Thompson *et al.* [7] in 1996 included 27 patients and found an accelerated improvement in arterial blood gases and lung function with prednisone, together with a reduction in treatment failure rate and an improvement in dyspnoea. Another study in outpatients published by Aaron *et al.* [8] in 2003 recruited 147 patients in the emergency department and was therefore not performed in a pure outpatient setting. Improvements were found in terms of rate of relapse, FEV_1 and dyspnoea. Altogether, the available body of evidence summarised above supports the use of systemic corticosteroids in patients hospitalised or discharged from emergency departments, but does not provide sufficient information in outpatients, which was the main justification of our study.

TABLE 3 Efficacy of intervention at 8 weeks

Event	Prednisone, n (%)[#]	Placebo, n (%)[¶]	Risk ratio (95% CI)	Risk difference (%) (95% CI)
Primary end-point				
Treatment failure at 8 weeks	37 (42.0)	30 (34.5)	1.22 (0.87–1.69)	7.6 (−5.2–20.4)
Secondary end-points				
Respiratory-related treatment failure at 8 weeks	24 (27.6)	12 (13.6)	2.00 (1.15–3.57)	13.7 (−2.9–24.5)
Unplanned visit to a practitioner in the ambulatory setting	31 (35.6)	24 (27.6)	1.30 (0.88–1.89)	8.4 (−3.9–20.8)
Unplanned visit to an emergency department	8 (9.2)	4 (4.6)	2.08 (0.58–7.14)	4.6 (−3.1–12.3)
Hospital admission	7 (8.0)	6 (6.9)	1.20 (0.42–3.45)	1.3 (−6.1–8.7)

[#]: n=88; [¶]: n=87.

TABLE 4 Comparison of the average duration of the different states in the two groups

	Duration (days)		Difference (95% CI)	p-value
	Prednisone[#]	Placebo[¶]		
OS	48.00	48.0	0.00	
NoEx	44.24	46.22	−1.98 (−3.90– −0.05)	0.044
Rel	3.76	1.78	1.98 (0.05–3.90)	0.044
Tox	3.97	4.39	−0.42 (−3.23–2.83)	0.77
TWiST	40.28	41.83	−1.55 (−5.06–1.95)	0.39
Q-TWiST	46.06	46.57	−0.51 (−1.35–0.34)	0.24

OS: overall survival time; NoEx: average duration without exacerbation; Rel: time with exacerbation; Tox: time with toxicity; TWiST: time without symptoms or toxicity; Q-TWiST: quality-adjusted time without symptoms and toxicity. [#]: n=88; [¶]: n=87.

Interpretation of results

Because the study failed to achieve its planned sample size, the statistical analysis was underpowered and so the results must be interpreted with caution. Nevertheless, the observations were consistent across all the outcomes studied and none of the between-group comparisons were in favour of oral steroids. The rate of treatment failure was numerically higher in the prednisone group than in the placebo group, but not significantly (risk ratio 1.22, 95% CI 0.87–1.69, p=0.25). In other words, there is a very low (*i.e.* 13%) level of confidence that oral corticosteroid treatment can decrease the risk of treatment failure at 8 weeks compared to placebo [27]. The discrepancy between this finding and the positive results found in hospital-based or emergency department-based studies could be explained by the difference in the severity of the underlying disease and/or the acute episode or differences in the underlying mechanisms. The significantly higher frequency of respiratory-related treatment failure with steroids as compared to placebo comes as a surprise. We cannot rule out that it occurred by chance given that this was a secondary outcome that should be considered as exploratory in the context of small sample size, lack of adjustment for multiple comparisons and the absence of hierarchy in the statistical analysis. However, in 2009, a French observational study also found that patients in primary care with an exacerbation of COPD that was treated with oral corticosteroids had a significantly increased risk of having a new exacerbation within

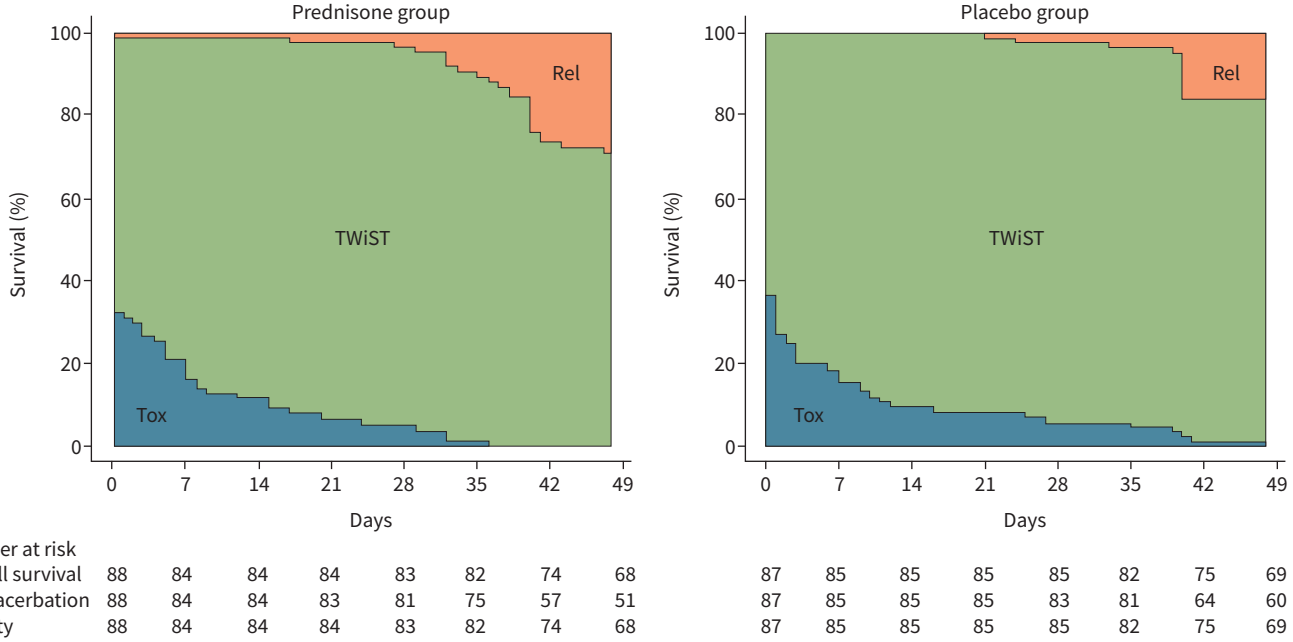

FIGURE 2 Quality-adjusted time without symptoms and toxicity. Rel: time with exacerbation; Tox: time with toxicity; TWiST: time without symptoms or toxicity.

TABLE 5 Evolution of well-being, COPD Assessment Test (CAT) score and modified Medical Research Council (mMRC) scale between week 1 (W1) and week 8 (W8) in each group

	Prednisone				Placebo				Mean difference (95% CI) at 8 weeks
	Baseline	W1	W4	W8	Baseline	W1	W4	W8	
Wellbeing scale (0–6)		n=75 2.8±1.3	n=75 2.3±1.5	n=58 1.7±1.3		n=81 2.7±1.4	n=76 2.0±1.5	n=58 1.7±1.4	0.1 (−0.4–0.6)
CAT score (0–40)		n=76 16.3±7.5	n=77 14.0±8.7	n=70 10.7±6.9		n=81 15.9±7.2	n=78 13.2±8.2	n=70 10.3±7.0	0.3 (−1.9–2.5)
mMRC scale (0–4)	n=88 2.1±0.9	n=76 1.2±1.0	n=77 1.2±1.1	n=75 1.1±0.9	n=86 2.1±0.9	n=81 1.3±1.2	n=80 1.3±1.1	n=75 1.1±1.0	0.1 (−0.2–0.3)

Data are presented as mean±SD, unless otherwise stated. W: week.

3 months, which seems to be in the same direction as the result of our study [23]. A negative effect on the lung microbiome favouring further infection could also be hypothesised, but we had no way to test this hypothesis [28]. Furthermore, only patients with a high eosinophil count may benefit from treatment with prednisone [29], but eosinophil level was not measured in our study. Whatever its mechanisms, this observation also calls for caution regarding the wide use of oral steroids in patients treated for acute exacerbations of COPD in primary care. Because COPD is a heterogeneous condition, point-of-care testing to help characterise patient phenotypes and exacerbations could help better target patients likely to respond to oral corticosteroids.

Strengths and weaknesses

The main strength of this study was that it was performed in a primary care setting using a pragmatic design. Most patients with COPD exacerbations are cared for in an ambulatory setting, but there is a huge gap in our knowledge on the effect of oral corticosteroids in this population. The study design followed the recommendations for conducting a pragmatic trial: recruitment at the usual care setting by the usual GP, with low-restrictive selection criteria, and outcomes of clinical interest for patients [30]. Another strength is that no patient was lost to follow-up. Finally, adherence to medications was excellent.

The main limitation of the study was the reduced sample size compared to that which was initially planned. Only 27% of investigators recruited at least one patient. A qualitative study was carried out with a sample of investigators in order to identify obstacles to inclusion [31]. The first reason cited was the difficulty in identifying exacerbations of COPD, due to nonspecific symptoms and underdiagnosis of the underlying disease. The other reasons identified were related to the organisation of the research (administrative burden, lack of communication and training) and the difficulty of integrating research into current clinical activity (lack of practice, unsuitable procedure).

Another limitation was the lack of formal confirmation of the diagnosis of COPD in most patients. This can, however, also be perceived as a strength because it corresponds to the real-life situation in France, as in many other countries, where primary care practitioners often do not have access to previous lung function measurements for these patients. Although this should improve with the use of protected electronic medical files owned by the patient and shared with all healthcare providers, several surveys

TABLE 6 Patient-reported adverse events in both groups

	Prednisone	Placebo	p-value
Subjects (n)	88	87	
At least one adverse event or severe adverse event	50 (56.8)	47 (54.0)	0.76
Severe adverse event	4 (4.5)	4 (4.6)	0.99
Number of adverse events			
None	38 (43.2)	40 (46.0)	
1	23 (26.1)	31 (35.6)	
2	17 (19.3)	10 (11.5)	
>2	10 (11.4)	6 (6.9)	

Data are presented as n (%), unless otherwise stated.

TABLE 7 Main adverse events in both groups

Prednisone[#]	Events	Placebo[¶]	Events
Sleep disorder	8 (8.51)	Transit disorder	9 (11.54)
Headache	7 (7.45)	Abdominal pain	8 (10.26)
Transit disorder	7 (7.45)	Dizziness or malaise	6 (7.69)
Dizziness or malaise	7 (7.45)	ENT infection	5 (6.41)
Muscle or tendon pain	5 (5.32)	Mood disorder	5 (6.41)
ENT infection	5 (5.32)	Joint pain	3 (3.85)
Fever or infection not specified	4 (4.26)	Muscle or tendon pain	3 (3.85)
Itch	4 (4.26)	Sleep disorder	3 (3.85)
Abdominal pain	3 (3.19)	Anxiety	2 (2.56)
Joint pain	2 (2.13)	Epitaxis	2 (2.56)
Mood disorder	2 (2.13)	Fatigue	2 (2.56)
		Fever or infection not specified	2 (2.56)
		Urinary tract infection	2 (2.56)
		Nausea	2 (2.56)
		Itch	2 (2.56)

Data are presented as n (%). ENT: ear, nose and throat. [#]: n=94; [¶]: n=78.

found that many patients with probable COPD do not undergo lung function testing. Interestingly, while it has been reported that only 30% of patients followed for COPD in primary care have a diagnosis confirmed by spirometry, 35% of the population included in our study had available lung function tests [32]. Thus, while being suboptimal in terms of diagnostic certainty, this study mimicked real-life conditions in the setting of interest, which was the goal pursued when designing this pragmatic study. As such, the results are likely to be applicable in general terms to primary care practice in France.

Self-medication with corticosteroids or antibiotics following an action plan was one of the criteria in the protocol and should be one of the possible events of the primary endpoint "treatment failure". Unfortunately, this question was omitted from the e-CRF due to a technical issue that was not captured during preliminary checks.

For calculation of the Q-TWiST, the duration of Rel, *i.e.* the time spent with exacerbation-related symptoms after an unplanned visit to an emergency department or to a practitioner in the ambulatory setting or hospital admission, was set at 8 days, due to the absence of information on the actual duration of the relapse. The actual duration likely varied depending on the severity of the exacerbation. In the literature, the duration until remission of an exacerbation also varies from 10 days to 6 weeks, depending on the criteria chosen and the setting [33, 34]. We chose a short relapse duration because of the mild-to-moderate nature of the exacerbations treated in primary care.

The final limitation was that the corticosteroid-free delay required to include patients (7 days) was relatively short. We had no information concerning corticosteroid use in the previous month, which could increase the risk of treatment failure. However, the proportion of patients with an oral corticosteroid therapy before the previous 7 days should be balanced between groups and the exacerbation history in the previous 12 months was similar in the two groups (table 1).

In conclusion, with all due caution regarding the lack of statistical power, this study provides a signal that suggests that prednisone might not be necessary when used to treat suspected COPD exacerbations in primary care and could possibly have detrimental effects. Additional studies should be conducted to verify these findings with adequate power. Meanwhile, we believe the results of this study are sufficient to warn against the unconsidered use of oral corticosteroids in the primary care management of suspected COPD exacerbations, particularly those suspected to be of infectious origin.

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References

1 Anzueto A. Impact of exacerbations on COPD. *Eur Respir Rev* 2010; 19: 113–118.
2 Wedzicha JA, Miravitlles M, Hurst JR, *et al.* Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2017; 49: 1600791.
3 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2019. Available from https://goldcopd.org/
4 Jouneau S, Dres M, Guerder A, *et al.* Management of acute exacerbations of chronic obstructive pulmonary disease (COPD). Guidelines from the Société de pneumologie de langue française (summary). *Rev Mal Respir* 2017; 34: 282–322.
5 Walters JA, Tan DJ, White CJ, *et al.* Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014; 9: CD001288.
6 Walters JAE, Tan DJ, White CJ, *et al.* Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014; 3: CD006897.
7 Thompson WH, Nielson CP, Carvalho P, *et al.* Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med* 1996; 154: 407–412.
8 Aaron SD, Vandemheen KL, Hebert P, *et al.* Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 2003; 348: 2618–2625.
9 Bathoorn E, Liesker JJW, Postma DS, *et al.* Anti-inflammatory effects of combined budesonide/formoterol in COPD exacerbations. *COPD* 2008; 5: 282–290.
10 Laue J, Reierth E, Melbye H. When should acute exacerbations of COPD be treated with systemic corticosteroids and antibiotics in primary care: a systematic review of current COPD guidelines. *NPJ Prim Care Respir Med* 2015; 25: 15002.
11 Kotz D, Nelemans P, van Schayck CP, *et al.* External validation of a COPD diagnostic questionnaire. *Eur Respir J* 2008; 31: 298–303.
12 Price DB, Tinkelman DG, Halbert RJ, *et al.* Symptom-based questionnaire for identifying COPD in smokers. *Respir Int Rev Thorac Dis* 2006; 73: 285–295.
13 Paterson C. Measuring outcomes in primary care: a patient generated measure, MYMOP, compared with the SF-36 health survey. *BMJ* 1996; 312: 1016–1020.

14 Porcher R, Lévy V, Fermand JP, *et al.* Evaluating high dose therapy in multiple myeloma: use of quality-adjusted survival analysis. *Qual Life Res* 2002; 11: 91–99.
15 Seemungal T, Harper-Owen R, Bhowmik A, *et al.* Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1618–1623.
16 Adams SG, Melo J, Luther M, *et al.* Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. *Chest* 2000; 117: 1345–1352.
17 Beauchesne M-F, Julien M, Julien L-A, *et al.* Antibiotics used in the ambulatory management of acute COPD exacerbations. *Int J Chron Obstruct Pulmon Dis* 2008; 3: 319–322.
18 Dewan NA, Rafique S, Kanwar B, *et al.* Acute exacerbation of COPD: factors associated with poor treatment outcome. *Chest* 2000; 117: 662–671.
19 Rohde GGU, Koch A, Welte T, *et al.* Randomized double-blind placebo-controlled study to demonstrate that antibiotics are not needed in moderate acute exacerbations of COPD – the ABACOPD study. *BMC Pulm Med* 2015; 15: 5.
20 Molinari N, Chanez P, Roche N, *et al.* Rising total costs and mortality rates associated with admissions due to COPD exacerbations. *Respir Res* 2016; 17: 149.
21 Miravitlles M, Mayordomo C, Artés M, *et al.* Treatment of chronic obstructive pulmonary disease and its exacerbations in general practice. *Respir Med* 1999; 93: 173–179.
22 Murio C, Soler X, Pérez M, *et al.* Acute exacerbation of chronic obstructive pulmonary disease in primary care setting in Spain: the EPOCAP study. *Ther Adv Respir Dis* 2010; 4: 215–223.
23 Laporte C, Huas D. Etude observationelle de la stratégie thérapeutique de prise en charge de l'exacerbation aigeü de BPCO [Observational study of the therapeutic strategy of management of acute exacerbation of COPD]. *Exercer La Revue Francophone de Médecine Generale* 2010; 21: 24S–25S.
24 Creutzberg EC, Wouters EFM, Mostert R, *et al.* Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. *Nutrition* 2003; 19: 120–127.
25 Niewoehner DE, Erbland ML, Deupree RH, *et al.* Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1999; 340: 1941–1947.
26 Dobler CC, Morrow AS, Beuschel B, *et al.* Pharmacologic therapies in patients with exacerbation of chronic obstructive pulmonary disease. *Ann Intern Med* 2020; 172: 413–422.
27 Shakespeare TP, Gebski VJ, Veness MJ, *et al.* Improving interpretation of clinical studies by use of confidence levels, clinical significance curves, and risk-benefit contours. *Lancet* 2001; 357: 1349–1353.
28 Huang YJ, Sethi S, Murphy T, *et al.* Airway microbiome dynamics in exacerbations of chronic obstructive pulmonary disease. *J Clin Microbiol* 2014; 52: 2813–2823.
29 Ramakrishnan S, Jeffers H, Langford-Wiley B, *et al.* Point of care blood eosinophil guided oral prednisolone for COPD exacerbations: a multi-centre double blind randomised controlled trial (the STARR2 trial). *Eur Respir J* 2022; 60: 4728.
30 Ford I, Norrie J. Pragmatic trials. *N Engl J Med* 2016; 375: 454–463.
31 Cascio R, Thebault J, Gasperini F, *et al.* Déterminants de l'inclusion de patients dans une étude thérapeutique randomisée en soins primaires: une question de temps, de temporalité et de relationnel [Inclusion of patients in a randomised controlled trial in primary care: a matter of time, timing and relationship]. *Exercer La Revue Francophone de Médecine Generale* 2020; 168: 466–472.
32 Herrera AC, de Oca MM, Varela MVL, *et al.* COPD underdiagnosis and misdiagnosis in a high-risk primary care population in four Latin American countries. A key to enhance disease diagnosis: the PUMA study. *PLoS One* 2016; 11: e0152266.
33 Ramakrishnan S, Janssens W, Burgel P-R, *et al.* Standardisation of clinical assessment, management and follow-up of acute hospitalised exacerbation of COPD: a Europe-wide consensus. *Int J Chron Obstruct Pulmon Dis* 2021; 16: 321–332.
34 Mathioudakis AG, Ananth S, Bradbury T, *et al.* Assessing treatment success or failure as an outcome in randomised clinical trials of COPD exacerbations. A meta-epidemiological study. *Biomedicines* 2021; 9: 1837.