Oral or IV Prednisolone in the Treatment of COPD Exacerbations*

A Randomized, Controlled, Double-blind Study

Ynze P. de Jong, MD; Steven M. Uil, MSc; Hans P. Grotjohan, MD, PhD; Dirkje S. Postma, MD, PhD; Huib A.M. Kerstjens, MD, PhD; and Jan W.K. van den Berg, MD, PhD, FCCP

Background: **Treatment with systemic corticosteroids for exacerbations of COPD results in improvement in clinical outcomes. On hospitalization, corticosteroids are generally administered IV. It has not been established whether oral administration is equally effective. We conducted a study to demonstrate that therapy with oral prednisolone was not inferior to therapy with IV prednisolone using a double-blind, double-dummy design.**

Methods: **Patients hospitalized for an exacerbation of COPD were randomized to receive 5 days of therapy with prednisolone, 60 mg IV or orally. Treatment failure, the primary outcome, was defined as death, admission to the ICU, readmission to the ICU because of COPD, or the intensification of pharmacologic therapy during a 90-day follow-up period.**

Results: **A total of 435 patients were referred for a COPD exacerbation warranting hospitalization; 107 patients were randomized to receive IV therapy, and 103 to receive oral therapy. Overall treatment failure within 90 days was similar, as follows: IV prednisolone, 61.7%; oral prednisolone, 56.3% (one-sided lower bound of the 95% confidence interval [CI], −5.8%). There were also no differences in early (*ie*, within 2 weeks) treatment failure (17.8% and 18.4%, respectively; one-sided lower bound of the 95% CI, −9.4%), late (*ie*, after 2 weeks) treatment failure (54.0% and 47.0%, respectively; one-sided lower bound of the 95% CI, −5.6%), and mean (± SD) length of hospital stay (11.9 ± 8.6 and 11.2 ± 6.7 days, respectively). Over 1 week, clinically relevant improvements were found in spirometry and health-related quality of life, without significant differences between the two treatment groups.**

Conclusion: **Therapy with oral prednisolone is not inferior to IV treatment in the first 90 days after starting therapy. We suggest that the oral route is preferable in the treatment of COPD exacerbations.**

Trial registration: **Clinicaltrials.gov Identifier: NCT00311961.**

(CHEST 2007; 132:1741–1747)

Key words: COPD; exacerbation; IV prednisolone; oral prednisolone

Abbreviations: CCQ = Clinical COPD Questionnaire; CI = confidence interval; GOLD = Global Initiative for Chronic Obstructive Lung Disease; MCID = minimal clinically important difference; SGRQ = St. George Respiratory Questionnaire

COPD is a major health problem worldwide, and both morbidity and mortality are rising.[1] Characteristic of the clinical course of COPD are acute episodes of deterioration in symptoms and respiratory function called *exacerbations*. These exacerbations frequently require hospitalization, which also constitutes the largest component of total healthcare costs for COPD.[2] Systemic corticosteroids have been demonstrated to be beneficial in the treatment of COPD exacerbations.[3,4] Systemic corticosteroid

For editorial comment see page 1728

treatment leads to shorter hospital stays and quicker recovery of FEV_1.[5] It also leads to a decrease in treatment failure and reduces the relapse rate in

thefirst 1 to 3 months after initial treatment.[6,7] These and other smaller studies[8–14] vary considerably in corticosteroid dosage and length of treatment. Even though current guidelines suggest that the oral route of administration is preferable, the optimal route of administration of systemic corticosteroids in the treatment of exacerbations of COPD has not been rigorously studied. Moreover, the preferred route of administration varies markedly between countries. Many hospitals routinely administer the corticosteroids IV, at least initially. A good rationale for this route lacks, since there is close to 100% bioavailability of prednisolone following oral administration under normal conditions.[15]

Oral corticosteroids are more convenient to administer because there is no need for IV access, fewer personnel are required for starting and monitoring therapy, and material costs are smaller. We hypothesized that oral administration is not inferior to IV administration of prednisolone in the treatment of patients hospitalized for an exacerbation of COPD. We therefore conducted a prospective, randomized, double-blind, double-dummy, placebo-controlled, parallel-group clinical study with treatment failure as the primary outcome.

Materials and Methods

Patients

Patients referred to the Isala klinieken hospital for an exacerbation of COPD were enrolled in the study from June 2001 to June 2003. Inclusion criteria were an age of > 40 years, a history of at least 10 pack-years of cigarette smoking, and evidence of airflow limitation. Airflow limitation was defined as an FEV_1/FVC ratio of $< 70\%$ and an FEV_1 of $< 80\%$ predicted (at least Global Initiative for Chronic Obstructive Lung Disease [GOLD] severity stage II).[16,17] An exacerbation of COPD was defined as a history of increased breathlessness and the presence of at least two of the following symptoms for at least 24 h: increased cough frequency or severity; increased sputum volume or purulence; and increased wheeze. Excluded were patients who had signs of a very severe exacerbation on hospital admission (arterial pH < 7.26 or $Paco_2 > 9.3$ kPa), with significant or unstable comorbidity, who had a history of asthma, had participated in another study within the 4 weeks before hospital admission, were previously randomized into this study, had clinically significant findings on chest radiography other than fitting with signs of COPD, a known hypersensitivity to prednisolone, or who were known to be totally noncompliant. The study was approved by the hospital medical ethics committee, and all patients gave written informed consent.

Study Design

Patients were randomized using a computer minimization program[18] for the following 10 parameters: use of oral prednisolone; use of inhaled corticosteroids; theophylline use 30 days before hospital admission; admission to the hospital because of an exacerbation of COPD in the last year; age (< 65 or ≥ 65 years); gender; smoking history (< 50 or ≥ 50 pack-years); use of supplemental oxygen at home; Pco_2 (< 5.4 or ≥ 5.4 kPa); and time since the diagnosis of COPD (*ie*, < 5, 5 to 10, 10 to 15, or > 15 years, or unknown). Patients received either a 5-day course of IV or oral prednisolone, 60 mg, together with placebo medication. Active and placebo medication had a similar appearance. After 5 days, all patients received oral prednisolone in a dosage of 30 mg once daily, which subsequently was tapered with 5 mg daily to 0 mg or a prior maintenance dosage. All patients received nebulized ipratropium bromide and albuterol four times daily together with oral amoxicillin/clavulanate. In case of allergy to this regimen, doxycycline was prescribed. Spirometry was measured on days 1 and 7.[19] On the same days, health status was measured using the St. George Respiratory Questionnaire (SGRQ),[20] a change in score of ≥ 4 points, constituting the minimal clinically important difference (MCID).[21] Health-related quality of life was measured daily in the first week using the 24-h version of the Clinical COPD Questionnaire (CCQ),[22] with a change of ≥ 0.4 points constituting the MCID.[23] The respiratory physician decided the date of hospital discharge and was free to intensify pharmacologic therapy if clinical improvement was not satisfactory. Patients were free to withdraw at any time. The follow-up period was 90 days with outpatient visits at days 42 and 90.

Study End Points

The primary outcome was treatment failure, defined as death from any cause, admission to the ICU, readmission to the hospital because of COPD, or the necessity to intensify pharmacologic treatment. The intensification of pharmacologic treatment was defined as the prescription of open-label corticosteroids, theophylline, or antibiotics. Treatment failure was subdivided into early failure, the first 2 weeks after randomization, and late failure, from 2 weeks to 3 months. When patients received additional medication, as mentioned above, from their general practitioner, this was also labeled as treatment failure. Secondary outcomes were changes from days 1 to 7 in FEV_1, SGRQ scores, CCQ scores, and length of hospital stay.

Statistical Analysis

The study was designed as a noninferiority study. The planning committee decided that if results with IV prednisolone were $> 15\%$ better (that is, produced a treatment failure rate that was 15% lower) than the rate with oral prednisolone, then clinicians would judge that the benefits of IV therapy clearly outweigh the advantages of oral administration. A difference in the rate of treatment failure of $\leq 15\%$ was deemed to be sufficient to accept that oral corticosteroids were not inferior to IV therapy in patients admitted to the hospital with COPD. In total, 256 patients were required to have 80% power with a one-sided α-statistic of 5% and an expected treatment failure rate of 37%.[6] To determine noninferiority in accordance with the study design, the lower bound of a one-sided 95% confidence interval (CI) for differences was used.

*From the Department of Pulmonology (Drs. de Jong, Grotjohan, and van den Berg, and Mr. Uil), Isala Klinieken, Zwolle, the Netherlands; and the Department of Pulmonology (Drs. Postma and Kerstjens), University Medical Center Groningen, Groningen, the Netherlands.
The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Manuscript received January 23, 2007; revision accepted May 30, 2007.

Correspondence to: Ynze P. de Jong, MD, Isala klinieken, Pulmonology, PO Box 10500, Zwolle 8000 GM, the Netherlands; e-mail: y.p.de.jong@isala.nl
DOI: 10.1378/chest.07-0208