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The effect of oral clarithromycin on health status and sputum bacteriology in stable COPD

D. Banerjee[a,b,1], O.A. Khair[a], D. Honeybourne[b,*]

[a]*Department of Respiratory Medicine, City Hospital, Birmingham, UK*
[b]*Department of Respiratory Medicine, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK*

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Summary *Background*: Chronic obstructive pulmonary disease (COPD) is characterised by airway inflammation, poor health status and recurrent infective exacerbations. Macrolide antibiotics have been shown to improve symptoms and exacerbation rate in chronic lung disease, particularly cystic fibrosis (CF) and diffuse pan-bronchiolitis. The effect of long-term oral clarithromycin on health status, sputum bacterial numbers and exacerbation rate in subjects with clinically stable COPD is undetermined.

Methods: Subjects with moderate-to-severe COPD were recruited into a prospective, double-blind, randomised-controlled trial of 3-months oral clarithromycin (Klaricid XL) or placebo once-daily. The effect of clarithromycin on health status (St. George respiratory and Short Form-36 questionnaires), sputum quantitative bacterial numbers and exacerbation rate were investigated.

Results: Sixty-seven subjects (46 males) were recruited; 31 and 36 subjects received clarithromycin and placebo, respectively. There were 7(10%) withdrawals. Compared to placebo, clarithromycin did not significantly improve health status, sputum bacterial numbers, or exacerbation rate.

Conclusions: Three months of oral clarithromycin given to subjects with stable COPD does not improve health status, sputum bacterial numbers or exacerbation rate. Treatment of COPD with clarithromycin during the clinical stable state yields no clinical advantages and therefore cannot be recommended as means of eliminating sputum bacteria or preventing infective exacerbations.

*Corresponding author. Tel.: +44-121-424-2000; fax: +44-121-772-0292.
E-mail address: david.honeybourne@heartsol.wmids.nhs.uk (D. Honeybourne).
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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic, slowly progressive disorder characterised

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by airflow obstruction that does not change markedly over several months and is a major cause for morbidity and mortality.[1] COPD is characterised by airway inflammation, impaired health status, exercise limitation, and recurrent infective exacerbations. Macrolide antibiotics have been shown to exhibit both anti-inflammatory and anti-bacterial properties.[2] Macrolides, such as clarithromycin, have been commonly used in the treatment of acute infective exacerbations of COPD, showing adequate clinical symptom and bacteriological improvement.[3–5] Macrolides have also an important clinical role in the treatment of diffuse panbronchiolitis with recognised improvements in mortality,[6] symptoms[7] and spirometry;[8] and cystic fibrosis (CF) with evidence for improved health status, spirometry and exacerbation rates.[9,10] More recently, there have been data suggesting that oral azithromycin may improve spirometry in lung transplant recipients suffering from bronchiolitis obliterans syndrome.[11]

The use of prophylactic antibiotics to eliminate bacteria from the bronchial airways and prevent infective exacerbations of COPD whilst in the clinical stable state remains controversial. Routine therapy at present is not recommended,[12] but this statement is based on trials conducted over 30 years ago where antibiotic sensitivity and the range of antibiotics available may have been different. The prescribing of antibiotics, continuously or intermittently, in such subjects, however, remains commonplace. As yet, there have been no published randomised, placebo-controlled trials looking at the effect of macrolide antibiotics on health status, quantitative sputum bacterial loads, and infective exacerbation rates in subjects with COPD during the stable clinical state. The aim of the study was to determine whether 3 months oral clarithromycin (Klaricid XL 500 mg once daily) improves health status, diminish sputum bacterial numbers and reduce exacerbation rates in such subjects compared to placebo.

Methods

Patients

Subjects were recruited from the City Hospital, Birmingham and Birmingham Heartlands Hospital clinics and lung function units. All subjects entering the trial gave written informed consent and had the diagnosis of moderate-to-severe COPD according to the British Thoracic Society (BTS) guidelines.[1] Thus, all subjects had a history of chronic progressive symptoms (cough and/or wheeze and/or breathlessness) and post-bronchodilator objective evidence of airways obstruction by spirometric testing. All subjects had a FEV_1/VC ratio of less than 70%, FEV_1% predicted of less than 60% (i.e. moderate-to-severe) and a less than 200 ml or 15% (of baseline) increase in FEV_1 to a beta-agonist bronchodilator. Current smokers were regarded as those individuals who had smoked regularly over at least 6 months before the recruitment date. Subjects with any previous documented allergies to macrolide antibiotics, a recent infective exacerbation within the last 6 weeks or a clinical history of asthma, bronchiectasis, lung cancer and uncontrolled ischaemic heart disease or diabetes mellitus were excluded. Based on observations that many moderate-to-severe patients in clinical practice are on inhaled corticosteroids and that there is growing evidence that withdrawal of these may have a detrimental effect on clinical state,[13,14] it was decided that only those subjects taking inhaled corticosteroids would be recruited.

Study design

The subjects underwent a run-in period of 2 weeks to ensure stability of disease. Subjects were then block randomised into a prospective, double-blind controlled study of oral clarithromycin (Klaricid XL) 500 mg once daily (Abbott UK Ltd., Maidenhead, UK) or placebo once daily for 3 months. Patients were randomised by the Birmingham Heartlands Hospital pharmacy department, independent of trial staff. The trial was approved by the City Hospital, Birmingham and Birmingham Heartlands Hospital ethics committees. Subjects continued to take their baseline medications as prescribed by their primary care physician. All subjects were regularly in contact to encourage full compliance, with tablet counts and documentation of adverse events. Subjects were asked to report changes in symptoms suggestive of an infective exacerbation.[15] The primary endpoint was health status and secondary endpoints included sputum bacterial quantitative load, infective exacerbation rate, shuttle walk test and serum C-reactive protein levels (CRP). These were assessed initially after 2 weeks of the run-in i.e. day 1 and then 3 months later during the last week of treatment. Analyses of parameters were conducted on an intention to treat basis.

Assessments

Spirometry (FEV_1, FVC and FEV_1/FVC) was measured using a MIR Spirobank electronic device