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

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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.

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Introduction

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

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 pan-bronchiolitis 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

(accuracy $\pm 3\%$, flow range $\pm 16\,l/s$). Reversibility of FEV_1 was assessed by repeating spirometric tests 20 min after inhalation of salbutamol (400 μg) given through a volume spacer by a trained member of the lung function department. Static lung volumes were measured at the City Hospital, Birmingham lung function unit by body box and gas transfer using single breath carbon monoxide method (V6200 Autobox, Sensormedics, USA). Health status was measured using the St. George respiratory questionnaire (SGRQ) as a disease-specific assessment of symptoms, activity and impact. The Short-Form 36-item questionnaire (SF-36) was also used as a general health measure covering eight health concepts; physical functioning, social functioning, physical role limitation, emotional role limitation, mental health, pain index, vitality and general health perception. The shuttle walk test was used to assess functional capacity as previously described and validated.[16] Hypertonic (3%) saline induction using a De Vilbiss ultrasonic nebuliser (output 2.2 ml/min) via a mouth piece was undertaken to obtain sputum samples for quantitative bacterial assays. The nebulisation procedure was stopped if the patient wished to do so or if the FEV_1 fell by more than 20% compared to baseline after the first nebulisation period with the judgement (made by the operator) that it would be unsafe to continue.

Quantitative bacterial culture measurements on the sputum were carried out as previously described by Pye et al..[17] The sputum sample was homogenised using an equal volume of Sputasol (Oxoid Ltd., Basingstoke, UK; containing 100 μg/ml dithiothreitol), diluted in sterile saline (0.9% NaCl) and inoculated onto chocolate, blood, and MacConkey agar plates. All plates were incubated at 36 °C in an atmosphere of 5% CO_2 in air and examined for bacterial growth after 24 and 48 h. Colonies on the plates were counted and the viable bacterial numbers present were expressed as colony-forming units (cfu)/ml of the original sputum. Sputasol has been shown not to affect bacterial viability.[17] Bacterial pathogens recovered were regarded as potential pathogenic microorganisms (PPMs) or non-potential pathogenic microorganisms (non-PPMs). In the current study, PPMs included the respiratory bacterial pathogens e.g. *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Mycobacterium catarrhalis*, *Haemophilus parainfluenzae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and the following were regarded as non-PPMs: *S.viridans*, *Neisseria* spp, *Corynebacterium* spp, *Candida* spp, *Enterococcus* spp, and coagulase-negative staphylococcus. These studies

were carried out by the appropriate technical support.

Statistical analysis

Statistical analyses were performed using a SPSS version 10.0 (Chicago, USA) package. To determine whether the distributions of all continuous data were normal, a Kolmogorov–Smirnov test was performed. Where such an assumption could not be met, the data were summarised in terms of medians and interquartile ranges (IQR) rather than means and standard errors (SE). In order to compare data of a parameter before and after an intervention, the mean change in the parameter in the active group was compared to the mean change in the parameter in the placebo group using parametric (non-paired two-independent group t-test) or non-parametric (Mann–Whitney U-test) testing where appropriate. Analysing the change in the parameter value eliminated any pre-treatment discrepancies between the placebo and clarithromycin groups. Bacterial numbers i.e. cfu were log transformed in order to normalise the data. Two-tailed tests were used and the level of significance was taken as $P < 0.05$. Any statistical significant findings or findings of relevance are presented as a size of effect i.e. mean difference with 95% confidence intervals (95% CI). A sample size of 50 (25 in each group) was required to detect a difference of 0.8SD (standardised difference) in the mean change of health status score in the clarithromycin group compared to the placebo group. With an allowance for a 25% patient drop out/exclusion rate or missing data, 66 subjects were necessary assuming these exclusions. These calculations were based on an $\alpha = 0.05$, $\beta = 20\%$ hence a power of 80%.

Results

Patients

Sixty-seven subjects (46 males) screened for the trial were entered and randomised to receive clarithromycin ($n = 31$) and placebo ($n = 36$). Both groups were similar for age, body mass index (BMI), smoking history and lung function. Table 1 shows the baselines values for lung function, shuttle walk distance, health status scores and CRP levels for both groups. SGRQ total, impact, symptom, SF-36 physical functioning, bodily pain and physical role limitation scores were significantly different between the two groups at the outset. All subjects

Table 1 Baseline demographic, lung function, shuttle walk distance, health status scores and CRP for the clarithromycin and placebo groups.

Parameter	Clarithromycin ($n = 31$)	Placebo ($n = 36$)	P value
Age (years)	65.1 (1.4)	68.1 (1.2)	NS
BMI (kg/m^2)	24.7 (0.9)	24.3 (1.0)	NS
Current smoker	45%	64%	NS
Cigarette pack-years	58 (5.6)	59 (3.8)	NS
FEV$_1$ observed (l)	1.12 (0.07)	1.13 (0.07)	NS
FEV$_1$ % predicted	42.5 (2.0)	43.9 (2.0)	NS
FVC observed (l)	2.57 (0.15)	2.53 (0.14)	NS
FVC % predicted	78.4 (2.9)	76.8 (2.8)	NS
FEV$_1$/FVC observed	43.8 (1.6)	45.5 (2.1)	NS
TLC % predicted	112 (2.4)	119 (2.2)	NS
RV % predicted	177 (10.5)	162 (5.7)	NS
RV/TLC % predicted	154 (5.7)	144 (3.7)	NS
DLCO % predicted	52 (3.2)	50 (2.5)	NS
KCO % predicted	70 (3.2)	67 (3.0)	NS
Shuttle walk distance (m)	179 (24.4)	223 (21.7)	NS
Total SGRQ	57 (3.9)	47 (2.5)	0.03
SGRQ impact	45 (3.2)	34 (2.7)	0.01
SGRQ symptom	69 (3.2)	60 (3.3)	0.04
SGRQ activity	73 (2.1)	65 (3.3)	NS
SF-36 general health perception	31 (2.5)	41 (3.5)	NS
SF-36 physical functioning	31 (2.5)	47 (3.8)	0.01
SF-36 bodily pain	52 (3.3)	69 (4.0)	0.01
SF-36 vitality	34 (2.4)	42 (3.8)	NS
SF-36 physical role limitation[*]	0 (0–12)	12 (0–81)	0.03
SF-36 emotional role limitation[*]	100 (33–100)	100 (33–100)	NS
SF-36 social functioning[*]	75 (25–100)	100 (46–100)	NS
SF-36 mental health[*]	68 (48–82)	78 (56–88)	NS
CRP (mg/dl)	8.7 (1.7)	9.6 (1.4)	NS

BMI = body mass index, FEV$_1$ = forced expiratory volume in 1 s, FVC = forced vital capacity, TLC = total lung capacity, RV = residual volume, DLCO = gas transfer, KCO = corrected gas transfer, SGRQ = St. George respiratory questionnaire, SF-36 = short form-36. CRP = C − reactive protein, NS = not significant.
[*]Denotes non-parametric data and are presented as median (IQR), parametric data are presented as mean (SE).

tolerated saline sputum induction and there were no abandonments from this procedure.

All subjects recruited were taking an inhaled corticosteroid, 12 (18%) were taking long-acting beta-2 agonists and 42 (63%) were taking inhaled anticholinergics. There were equal proportions of those taking long-acting beta-2 agonists and anticholinergics in both groups. Seven subjects (10%) were lost to follow-up without completing the course and hence were regarded as missing data (five from the clarithromycin group and two from the placebo group). One patient from the clarithromycin group had a gastrointestinal upset and did not wish to complete the course. Four subjects (three from the clarithromycin group and one from the placebo group) were unable to attend follow-up due to continued poor health following an infective exacerbation and two (one from each group)

admitted poor compliance and both withdrew voluntarily. In total, 26 subjects receiving clarithromycin and 34 receiving placebo completed the course and intention to treat analyses were therefore performed on a total of 60 patients.

Health status, shuttle walk distance, spirometry, and CRP

In general, clarithromycin did not show any advantageous trends in health status scores when compared to placebo. There was a significant improvement in the SGRQ symptom score (mean difference (95%CI)=10.2 (1.6–18.7) units, $P = 0.04$). Improvement was not seen in any other SGRQ domains. There was no overall significant improvement in the SF-36 health status scores except for

SF-36 physical functioning score (mean difference (95%CI)=12.9 (3.1–22.6) units, $P = 0.01$). Compared to placebo, 3 months of clarithromycin did not significantly improve shuttle walk distance, spirometry or CRP levels.

Exacerbations and sputum quantitative bacterial assessment

In total, there were five infective exacerbations in the clarithromycin group and two in the placebo group during 3 months of treatment. This difference was not significantly different ($P = 0.24$). *H.influenzae* (12 isolates), *S.pneumoniae* (nine isolates) and *M.catarrhalis* (seven isolates) species accounted for 90% of the total number of bacterial isolates at the outset. *S.aureus*, *K.pneumoniae*, *P.aeruginosa*, Coliform spp. and Acinetobacter spp. accounted for the other 10%. Some subjects had more than one PPM in their sputum. After 3 months of clarithromycin, the number of subjects with sputum PPMs increased from 12 to 15 and the number of bacterial isolates[16] did not change. In the placebo group, the number of subjects with sputum PPMs increased from 10 to 16 and the number of bacterial isolates increased from 15 to 25. Clarithromycin, when compared to placebo, did not significantly reduced the mean number of *H.influenzae*, *S.pneumoniae*, or *M.catarrhalis* cfu (log)/bacterial isolate (Table 2). No multi-resistant gram-negative organisms emerged in the clarithromycin group. When all the PPM isolates were taken together as a group, clarithromycin did not significantly change the mean cfu (log) number per bacterial isolate compared to placebo. These findings are shown by means of a scatter plot (Fig. 1).

Discussion

This randomised-controlled trial in stable subjects with moderate-to-severe COPD found that 3 months
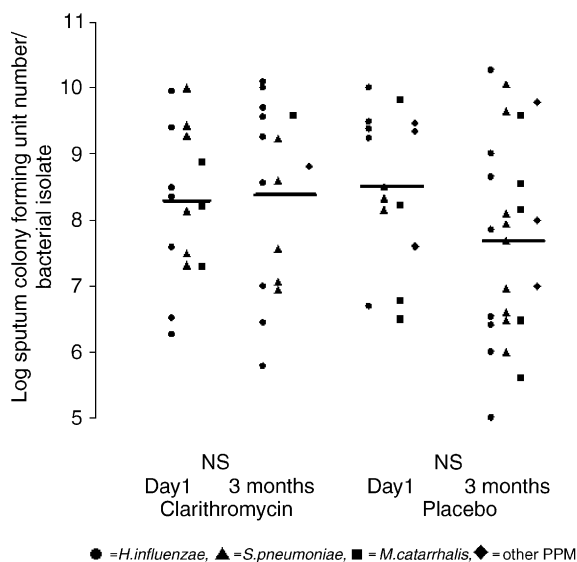

Figure 1 The effect of clarithromycin and placebo on sputum cfu numbers/bacterial (PPM) isolate. Cfu numbers are logged. Weighted bars indicate the mean for the whole group. There was no statistically significant difference between pre- and post- cfu numbers for both clarithromycin and placebo groups. NS indicates not significant.

Table 2 The effect of clarithromycin and placebo on the sputum mean (SE) colony forming unit (cfu) numbers (log)/bacterial isolate.

		Clarithromycin Mean (log) cfu (SE)/isolate	Placebo Mean (log) cfu (SE)/isolate
H.influenzae	Pre-	8.06 (0.52) $n = 7$	8.96 (0.58) $n = 5$
	Post-	8.46 (0.54) $n = 9$	7.46 (0.62) $n = 8$
	P value	NS	NS
S.pneumoniae	Pre-	8.61 (0.40) $n = 6$	8.33 (0.09) $n = 3$
	Post-	7.88 (0.44) $n = 5$	7.71 (0.47) $n = 9$
	P value	NS	NS
M.catarrhalis	Pre-	8.13 (0.46) $n = 3$	7.82 (0.76) $n = 4$
	Post-	9.59 $n = 1$	7.16 (0.54) $n = 5$
	P value	NS	NS
All PPMs	Pre-	8.28 (0.29) $n = 16$	8.50 (0.30) $n = 15$
	Post-	8.38 (0.35) $n = 16$	7.69 (0.29) $n = 25$
	P value	NS	NS

Cfu numbers were logged to normalise the data. NS indicates not significant.

of oral clarithromycin (Klaricid XL) did not significantly change health status, sputum bacteriology or exacerbation rate. There were no changes in spirometry, shuttle walk test or CRP levels as well. To our knowledge from the available literature, this is the first study investigating the effect low dose 3-months oral clarithromycin on health status, bacteriology and exacerbation rate in patients with COPD during the clinical stable state.

Although, two health status domains in this current study were significantly improved in clarithromycin group, their clinical significance is unclear in the absence of any other positive changes. The clinical role of macrolides in other chronic lung diseases has been investigated elsewhere. Long-term low-dose erythromycin in panbronchiolitis has been shown by Nagai et al. to demonstrate a significant reduction in dyspnoea and cough[7] and by Kudoh et al. to show an improved survival.[18] The mechanism is thought to be anti-inflammatory rather than antibacterial.[19] In subjects with CF, 3 months of oral azithromycin detected improvements in dyspnoea, fatigue, and total health status scores using the Chronic Respiratory Disease Questionnaire.[10] This latter study also showed a small improvement in spirometry and a reduction in the exacerbation rate when compared to placebo. The improvement in symptoms may be due to an improvement in spirometry and exacerbation rate. However, other trials in CF have not shown similar improvements in spirometry or bacteriology,[20,21] although one of these trials implied a reduced need for multiple antibiotic courses.[20] A recent Cochrane review on the role of macrolides in stable CF concluded that the exact role of these antibiotics in this condition remains unclear and that more clinical trials are needed before widespread usage is recommended.[22] There has been no similar review of the use of macrolides in COPD.

The choice of clarithromycin was made on the basis of its better side-effect profile compared to other macrolides, especially erythromycin. Clarithromycin also comes as an extended release form (Klaricid XL 500 mg) which allows once daily dosing. Once daily dosing of clarithromycin has been shown to result in adequate drug levels in the plasma and bronchial epithelial lining fluid.[23] It was believed that these factors would encourage good compliance. In general, clarithromycin was well tolerated with very few side effects and only one withdrawal (gastrointestinal upset) directly related to this drug. Subjects enrolled into this study typified the heterogeneous nature of COPD, i.e. differing smoking histories and therapeutic regimens. Although, all subjects in this trial with moderate-to-severe COPD were taking inhaled corticosteroids, inhaled corticosteroids are not currently regarded as mandatory treatment for those with moderate COPD only. How differing smoking histories and inhaler usage may have influenced the endpoint results are unknown. However, it was felt that the 67 subjects enrolled would typically reflect the type of subject with COPD that primary and secondary care physicians would commonly encounter in their practice. In this present study, however, the results for 60 subjects were available for full analysis and a larger study may give more meaningful outcomes.

The length of treatment in this study was 3 months. Although the trial resulted in no positive outcomes, the effect of long-term i.e. more than 3 months, clarithromycin on parameters such as health status, bacteriology, exacerbation rates and spirometry is unclear and hence further longer studies may be necessary to determine this. Any clinically meaningful improvements in spirometry and exacerbation rate may only be seen after long-term therapy, although it is doubtful that long-term therapy would lead to significant sputum bacteriological clearance that was not achieved in the present study after 3 months. A further long-term follow-up in this trial, however, may have detected a beneficial effect.

The lack of effect of clarithromycin on bacterial colony numbers in sputum in subjects with stable COPD is interesting, as this would contradict previous studies of clarithromycin in subjects with acute exacerbations of chronic bronchitis or COPD. These trials have shown adequate bacterial eradication in between 70% and 95% of patients.[3,4] *H.influenzae*, *S.pneumoniae* and *M.catarrhalis* contribute to the majority of bacterial exacerbations, but in this current work clarithromycin did not affect the number of these bacterial isolates nor the mean cfu number per isolate whilst in the clinical stable state. It may be possible that an absence of effect of antibiotic on bacterial numbers may be a result of a lack of compliance in this trial. However, regular checks of compliance were carried out by the trial team, and only two subjects were deemed as insufficient compilers. It has been suggested that in vitro tests underestimate the clinical utility of this drug because of the added antibacterial effects of clarithromycin and its 14-hydroxy metabolite.[24] The minimum inhibitory concentration-90 (MIC_{90}) of clarithromycin for *H.influenzae* is higher than other bacterial species, e.g. *M.catarrhalis*, suggesting reduced susceptibility.[25] This current study did not measure MIC_{90} which may be useful in any further similar antibiotic trials to detect changes in antibiotic

susceptibility or resistance with time. This is particularly important if oral antibiotics are considered as prophylactic measures long term. There was no emergence of multi-drug-resistant gram-negative bacterial species in those subjects taking clarithromycin. Other trials assessing the effect of other antibiotics, such as penicillins or cephalosporins, given continuously during the stable state using a similar design to the current study may be worthwhile as it is possible that any positive effect on health status, bacteriology and exacerbation rate may be found in other antibiotic groups and not clarithromycin.

In conclusion, this randomised-controlled trial has shown that oral clarithromycin given for 3-months in subjects with moderate-to-severe stable COPD, had no advantageous effect on health status, sputum bacteriology or exacerbation rate. Therefore, the treatment of subjects with stable COPD with clarithromycin to obtain an improvement in health status, achieve sputum bacterial clearance, and reduce the number of infective exacerbations may need further larger long-term studies.

Acknowledgements

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