SHORT COMMUNICATION

A pilot study of low-dose erythromycin in bronchiectasis

K.W.T. Tsang*, P.-I. Ho**, K.-n. Chan[+], M.S.M. Ip*, W.-k. Lam*, C.-s. Ho*, K.Y. Yuen**, G.C. Ooi[++], R. Amitani[§], E. Tanaka[§]

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ABSTRACT: Patients with bronchiectasis suffer from sputum production, recurrent exacerbations, and progressive airway destruction. Erythromycin is effective in diffuse panbronchiolitis, another suppurative airway disorder, although its efficacy is unknown in idiopathic bronchiectasis.

A double-blind placebo-controlled study was therefore conducted to evaluate the effects of 8-week administration of low dose erythromycin (500 mg *b.i.d.*) in steady-state idiopathic bronchiectasis.

Patients in the erythromycin group (n=11, 8 female, mean age 50±15 yrs), but not the placebo group (n=10, 8 female, mean age 59±16 yrs) had significantly improved forced expiratory vol-ume in one second, forced vital capacity and 24-h sputum volume after 8 weeks (p<0.05). There was no parallel improvement in sputum pathogens, leukocytes, interleukin (IL)-1α and IL-8, tumour necrosis factor-α, or leukotriene B_4.

The results of this pilot study show that low-dose erythromycin improves lung function and sputum volume in bronchiectasis. Further studies are indicated to evaluate the efficacy of long-term erythromycin therapy in bronchiectasis.
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Bronchiectasis is a common condition in the Chinese, and affected patients suffer from regular sputum production punctuated by recurrent infective exacerbations. Different pro-inflammatory mediators particularly interleukin (IL)-1, IL-8, and tumour necrosis factor (TNF)-α, and leukotriene (LT)B_4 [1–3] contribute to mucus secretion and recruitment of neutrophils to the inflamed airways which degranulate and release harmful products such as neutrophil elastase [4, 5]. Erythromycin (EM) is clinically effective in reducing sputum production in patients with bronchorrhoea [6] and diffuse panbronchiolitis (DPB) which, similar to bronchiectasis, is characterized by copious sputum production, rhinosinusitis, progressive airway destruction, and chronic *Pseudomonas aeruginosa* infection of the airways [7, 8]. Although low-dose EM is used frequently in the treatment of chronic bronchiectasis in Japan and many parts of Asia, the possible efficacy of EM in idiopathic bronchiectasis has not been studied in a controlled manner. This double-blind placebo-controlled pilot study was therefore performed to evaluate the effects of 8-week administration of low-dose EM (500 mg *b.i.d.*) in steady-state bronchiectasis.

Methods

Patient selection

Patients with proven bronchiectasis, diagnosis by high-resolution computed tomography (HRCT), were recruited from the outpatient clinics of the University of Hong Kong. Inclusion criteria included: 24-h sputum volume >10 mL; absence of unstable systemic diseases; and "steady-state" bronchiectasis (<10% alteration of 24-h sputum volume, forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), and in the absence of deterioration in cough, dyspnoea, wheezing, fever, or chest pain at baseline visits). Exclusion criteria included: unreliable clinic attendance, adverse reaction to macrolides, and females who were lactating. Written informed consent was obtained, and the study protocol had approval from the institutional ethics committee. Patients were assessed at 0 and 8 weeks after commencement of therapy.

Clinical and laboratory assessment

At each visit, each patient was examined fully. Laboratory assessment included: 24-h sputum volume, sputum leukocyte density (per mL); sputum pathogenic density (colony forming unit (cfu)·mL^{-1}); and sputum (sol phase) IL-1α, TNF-α and LTB$_4$. Spirometry was measured between 10:00 and 11:00 h, using standard protocols, with a SensorMedics 2200 (SensorMedics, Yorba Linda, CA, USA) package. The number of bronchiectatic lung lobes was determined using thin-cut HRCT, within 12-months of the assessment in the supine position [9]. The aetiology of bronchiectasis was determined after history taking, examination, and investigations including nasal respiratory ciliary beat frequency assessment [10]. Evaluation of serum immunoglobulin (Ig)G, IgA, and IgM; auto antibody

titres (for rheumatoid factor, anti-nuclear factor, and IgG against Ro, La, Jo-$_1$, mitochondrial, and smooth muscle); serum IgG subclasses; α_1-antitrypsin level; viral titres (measles, mumps, influenza, para-influenza, respiratory syncytial, adeno-, rota-, and entero-viruses); blood CD4/CD8 lymphocyte ratio; IgG against *P. pseudomallei*, *Legionella pneumophilia*, *Chlamydia psittaci*, and *Mycoplasma pneumoniae*; aspergillus precipitins; serum cold haemagglutinin; complements 3 and 4; and sputum microbiology (routine aerobic and anaerobic, mycobacterial and fungal cultures) was performed at the Biochemistry, Haematology, Clinical Immunology, and Microbiology Departments of the University of Hong Kong.

Sputum collection and assessment for physical characteristics

The methodology on sputum collection and assessment of 24-h sputum volume has been described previously [11]. Briefly, 24-h sputum collection was made at home in clear sterile plastic (60-mL) pots, and fresh sputum was obtained within 1 h following 15 min of expectoration-aiding physiotherapy (or until no further sputum was obtained). Sputum leukocyte density, performed on five randomly selected aliquots of a fresh specimen, was assessed within 2 h using light microscopy and haemocytometry [11].

Sputum microbiology

Standard microbiological and dilutional techniques were employed to identify all the sputum pathogens (*P. aeruginosa*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and Gram-negative bacilli) and to determine their densities in sputum using enriched and selective media (blood agar (Oxoid CM271 (Oxoid, Basingstoke, UK), with 5% defibrinated horse blood), chocolate agar supplemented with 18.9 U·mL^{-1} bactracin (Sigma, St. Louis, MO, USA), mannitol salt agar (Oxoid CM85) and cetrimide-nalidixic acid agar (Oxoid CM559 and SR102)) incubated at 37°C in 5% CO_2 [11].

Measurement of sputum pro-inflammatory cytokine and LTB$_4$ concentrations

Fresh sputum was stored at -70°C within 15 min of collection until ultracentrifugation (100,000 × *g* for 30 min at 4°C) was used to obtain the sol phase needed for enzyme-linked immunoabsorbent assay of cytokine and LTB$_4$ levels performed in commercially available 96-well plates (R&D Systems, Minneapolis, MN, USA) [11]. The mean concentration of the cytokines or LTB$_4$ was determined from triplicate measurements.

Data analysis

The primary objective of this study was to evaluate the effects of low-dose EM on sputum volume and lung function indices in steady-state bronchiectasis. Based on the authors' experience, the daily sputum volume might vary by as much as 10% between days in stable bronchiectatic patients. Accepting a type I error of 0.05 and a type II error of 0.20 (power 0.80), a study size for a randomized placebo-controlled study of 20 subjects (10 in each treatment group) would allow detection of 12% change in sputum volume. As the lung function, sputum volume and cytokine concentrations were log-normally distributed, they were logarithmically transformed before analysis. These variables were compared between treatment groups by analysis of variance (ANOVA) with Bonferroni's correction and reported as the geometric mean and 95% confident interval. Within-group changes after treatment were examined with paired Student's t-tests. Data that were highly skewed (sputum bacteriology and leukocyte density) were compared between and within treatment groups by Wilcoxon's rank sum test and reported as median and interquartile range. A p-value of <0.05 was taken as indicative of statistical significance.

Results

Patient demography and clinical details

The patient demography and clinical details are shown in table 1. Between October 1996 and April 1997, 14 and 10 patients, who suffered from idiopathic bronchiectasis, were recruited to receive EM (500 mg twice daily) and identical placebo tablets, respectively. In the EM group, three patients were withdrawn as two were unreliable attenders and one developed a maculopapular rash 5 days after EM therapy. The mean age and number of exacerbations in the previous 12 months were not significantly

Table 1. – Clinical characteristics of patients in the erythromycin and placebo groups at baseline

	Erythromycin group (n=11, 8 F)	Placebo group (n=10, 8 F)
Age yrs*	50±15	59±16
Smoking history		
Never	10	8
Exsmokers	1	2
Number of exacerbations in previous 12 months*	2.1±1.68	2.9±1.2
Number of lung lobes with bronchiectasis*	3.0±1.34	3.2±1.40
Past medical history		
Nil else	8	7
Thrombocytopaenia	1	0
Bone marrow transplant	1	0
Biliary calculi	1	0
Renal transplant	0	1
Hypertension	0	1
Hepatitis B	0	1
Current medications		
Inhaled bronchodilators	6	6
Inhaled steroids	6	3
Nebulized aminoglycosides	2	3
Prednisolone	1	0
Cyclosporin	1	1
Azathioprine	1	0
Diuretic	0	1

Data are presented as number of patients, except where indicated. *: data are mean±SD. F: female. There was no significant difference between the age or number of exacerbations in the previous 12 months between the two groups (p>0.05).

Table 2. – Spirometry, sputum characteristics and pro-inflammatory mediator levels before and after treatment in the patient groups

	Erythromycin		Placebo	
	Before treatment	After treatment	Before treatment	After treatment
Forced expiratory volume in one second L	1.06 (0.77–1.47)	1.20 (0.84–1.73)*	0.99 (0.71–1.39)	0.94 (0.66–1.33)
Forced vital capacity L	1.85 (1.35–2.53)	1.97 (1.38–2.79)*	1.51 (1.17–1.94)	1.51 (1.14–2.00)
24-h volume mL	33.7 (23.0–49.3)	23.8 (15.7–36.1)*	26.2 (18.4–37.4)	22.7 (16.0–32.3)
Bacterial density $\times 10^7$ cfu·mL^{-1+}	1.93 (1.08–5.04)	3.84 (2.20–7.40)	7.66 (0.48–13.4)	1.85 (0.95–3.48)
Commensal bacterial density $\times 10^7$ cfu·mL^{-1+}	0.94 (0.39–2.84)	1.99 (0.80–2.45)	2.41 (0.20–5.00)	1.05 (0.30–2.86)
Pathogen density $\times 10^7$ cfu·mL^{-1+}	0.18 (0.01–1.73)	0.77 (0.01–6.05)	0.10 (0.00–10.4)	0.18 (0.00–1.40)
Leukocyte density $\times 10^7$·mL^{-1+}	0.73 (0.36–10.0)	1.26 (0.17–8.50)	6.76 (0.97–9.50)	2.68 (0.87–12.1)
Interleukin-1α pg·mL^{-1}	6029 (2440–14894)	7395 (3114–17559)	15152 (6205–37001)	15536 (7047–34252)
Interleukin-8 pg·mL^{-1}	17648 (7610–40929)	20858 (11646–37358)	16196 (7713–34006)	18648 (10843–32071)
Tumour necrosis factor-α pg·mL^{-1}	92.9 (38.8–222.2)	98.0 (55.2–173.9)	127.5 (30.4–534.6)	82.0 (18.5–363.3)
Leukotriene B$_4$ pg·mL^{-1}	3090 (992–9621)	2190 (720–6663)	1547 (834–2866)	3309 (1638–6684)

Data are presented as geometric mean with 95% confidence interval in parentheses, unless otherwise indicated. $^+$: median (interquartile range). *: $p < 0.05$ when compared with baseline.

different at baseline between the two groups ($p > 0.05$). No other adverse reactions had been reported in either group. None of the patients in the EM group experienced haemoptysis or exacerbations, whereas two patients in the placebo group had an exacerbation during the "treatment phase" which resolved after 10 days′ treatment with sparfloxacin (200 mg daily). No other alteration in regular medications was made during the study.

Spirometry and sputum indices

The spirometry and sputum indices results are shown in table 2. FEV1, FVC, and 24-h sputum volume improved significantly ($p < 0.05$) in the EM group but not the placebo group. *P. aeruginosa* and *H. influenzae* were isolated from the sputum in, respectively, 10 and one of the EM patients, and *P. aeruginosa*, *H. influenzue*, *Klebsiella pneumoniae*, and *Escherichia coli* isolated in the sputum of six, two, one and one placebo patient, respectively. The sputum pathogenic densities and concentrations of IL-1α, IL-8, TNF-α and LTB$_4$ did not change significantly in either group ($p > 0.05$).

Discussion

The results of this study show that 8-week administration of low-dose EM significantly reduces sputum volume and improves lung function in steady-state severe idiopathic bronchiectasis. However, the *in vitro* parameters showed no significant changes including sputum densities of leukocytes, pro-inflammatory mediators, and pathogens. Not withstanding the small sample size and the short study duration, the EM group appeared to have less infective exacerbations than the placebo group. Despite the lack of statistical significance, the median values of sputum pathogenic and leukocyte densities appeared to have improved after 8 weeks of placebo treatment. This might

have been related to the administration of antibiotics in two patients but might also have occurred by chance as a placebo effect.

There is considerable traffic of neutrophils migrating into the tracheobronchial wall which is probably the result of both host and bacterial factors [12]. Bacterial products induce production of IL-1α and TNF-α which leads to expression of the chemoattractants intracellular adhesion molecule (ICAM)-1 and the CD11/CD18 integrin complex [1, 13]. IL-8 and LTB$_4$ are potent chemoattractants and IL-8 may also degranulate neutrophils in the bronchiectatic airways [2, 5]. This study, being one of the few longitudinal profiles of sputum pro-inflammatory mediators, showed a "static" output of inflammatory mediators after EM therapy. This might simply be a type II error or a reflection of a lack of response at the biochemical level. A previous study also showed that "clinically efficacious" treatment did not alter the levels of sputum IL-1α, IL-8, and TNF-α concentrations after antibiotic treatment which improved sputum purulence and volume in six bronchiectatic patients [14]. Similarly, sputum levels of IL-8, TNF-α, and ICAM-1 do not correlate with clinical status in cystic fibrosis [15, 16].

Low-dose EM treatment improves lung function and prevents disease progression in DPB, an idiopathic chronic suppurative airway disease predominantly seen in Japan. The present authors′ extensive investigations [8] had excluded DPB in all the patients. The mechanism of action of EM in bronchiectasis is not known although it is unlikely to be bactericidal in view of the low dosage and poor tracheobronchial penetration. EM inhibits glycoconjugate release [17] and chloride secretion by airway epithelium [18], and macrophage mucus secretagogue production [19] which might result in decreased sputum water contents and volume. Low dose EM might also affect the bacterial–host interaction *in vivo* [20] by altering bacterial morphology and *P. aeruginosa* exotoxin production [21], neutrophil migration [22], superoxide generation [22], and macrophage production of mucus secretagogue [19].

The results of this preliminary study, which is the first controlled study on the effects of erythromycin in chronic bronchial sepsis, show the efficacy of low dose and moderately long-term administration of erythromycin in steady-state bronchiectasis. Low dose and long-term erythromycin therapy might be a disease modifying treatment for idiopathic bronchiectasis, and further studies should be performed to establish the dose response, appropriate duration of therapy, and criteria for patient selection.

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