Randomised controlled trial of azithromycin in smokers with asthma

To the Editor:

Smokers with asthma have poor symptom control, accelerated decline in lung function and an attenuated response to corticosteroids compared to nonsmokers with asthma [1]. There is an unmet need for alternative or additional drugs for smokers with asthma who are unable to stop smoking [2]. Macrolide antibiotics have anti-inflammatory activity [3] and in clinical studies there is good evidence for efficacy in the treatment of diffuse pan-bronchiolitis and cystic fibrosis, as well as in preventing chronic rejection after lung transplantation [4, 5]. In asthma, chronic treatment is associated with a reduction in bronchial hyperreactivity in mild-to-moderate asthma [6] and in exacerbation rates in non-eosinophilic severe asthma [7]. To date, no studies have examined the efficacy of macrolide antibiotics exclusively in current smokers with asthma.

A randomised double-blind parallel-group trial compared azithromycin, 250 mg per day, with placebo for 12 weeks. All subjects were aged 18–70 years, were current smokers ($\geqslant$5 pack-years history) with chronic asthma (>1 year duration; defined by international criteria [8]) and had to be free of exacerbation and respiratory tract infection for a minimum 6-week period prior to randomisation. A baseline visit was performed following a 4-week run-in period on inhaled corticosteroid (ICS) therapy equivalent to 400 μg beclometasone $\pm$ a long-acting β_2-agonist (LABA). Ethical approval was obtained and all subjects provided written informed consent. Study visits were performed at 4, 8 and 12 weeks. Clinic visit peak expiratory flow (PEF) after 12 weeks treatment was the primary outcome measure. A sample size of 68 was calculated to have an 80% power to detect a mean difference of 25 $L \cdot min^{-1}$ in change from baseline to 12 weeks in morning PEF, the primary end-point [9], assuming a standard deviation of changes of 36 $L \cdot min^{-1}$ using a two-sample t-test with a 5% two-sided significance level. Recruitment of 80 patients was planned to ensure that 68 patients completed the study. 77 subjects were randomised with 71 completing the study. Other measures of airway responsiveness PC_{20} (provocation concentration of methacholine causing a 20% fall in forced expiratory volume in 1 s (FEV_1)), inflammation (exhaled nitric oxide fraction at 50 $mL \cdot s^{-1}$ (F_{ENO50})/induced sputum/blood and sputum supernatant biomarkers), symptom control (Asthma Control Questionnaire (ACQ) [10] and Leicester Cough Questionnaire (LCQ) [11]) and quality of life (Asthma Quality of Life Questionnaire (AQLQ) [10]) were assessed during the study. PEF was recorded using Piko-1 electronic peak flow meters (nSpire, Hertford, UK) and symptoms were recorded in a validated diary card [10]. Bacteriological and virological analysis of induced sputum was also undertaken. All statistical tests were two-sided and used a significance level of 5%. All data was analysed using SAS (version 9.2; SAS Institute, Cary, NC, USA). QTc was also measured at baseline and 12 weeks.

Baseline demographic data and clinical characteristics of the patients were comparable and the two groups were well balanced. Placebo *versus* azithromycin groups: age 42.8$\pm$9.4 years *versus* 46.4$\pm$8.8 years; male sex 17 (44.7%) *versus* 20 (51.3%); smoking history 23.6$\pm$15.8 pack-years *versus* 28.6$\pm$16.4 pack-years; duration of asthma 24.6$\pm$12.6 years *versus* 18.8$\pm$12.5 years; atopic 23 (60.1%) *versus* 27 (69.2%); median (interquartile range) total IgE 103 (38–291) $IU \cdot mL^{-1}$ *versus* 165 (48–254) $IU \cdot mL^{-1}$; use of ICS at screening 31 (81.6%) *versus* 35 (89.7%); equivalent beclomethasone dose at screening 709$\pm$564 μg *versus* 603$\pm$457 μg; use of LABA at randomisation 18 (47.4%) *versus* 15 (38.5%); pre-bronchodilator FEV_1 81.0$\pm$16.8% predicted *versus* 78.3$\pm$16.4% pred; post-bronchodilator FEV_1 89.0$\pm$15.1% pred *versus* 86.8$\pm$15.2% pred; FEV_1 11.3$\pm$9.8% reversibility *versus* 12.3$\pm$10% reversibility; geometric mean PC_{20} 1.06$\pm$4.10 $mg \cdot mL^{-1}$ *versus* 1.07$\pm$3.13 $mg \cdot mL^{-1}$.

At the final study visit (12 weeks) the change in mean morning clinic PEF (primary outcome), as compared with baseline, did not differ substantially between the azithromycin and placebo treatment groups (mean difference -10.3 (95% CI 47.1–26.4 $L \cdot min^{-1}$), p=0.58) (table 1). There was no difference in either pre- or post-albuterol FEV_1 at 4, 8 or 12 weeks between the two groups (table 1). No differences were evident for PC_{20} (baseline to 12 week comparison) between the azithromycin or placebo groups (table 1). None of the self-reported diary card recordings (ACQ, AQLQ or LCQ score) demonstrated any significant differences between the two groups at 4, 8 or 12 weeks. Noninvasive measures of inflammation, *i.e.* induced sputum, sputum supernatant cytokines, peripheral blood cytokines and F_{ENO50}, did not demonstrate any substantial improvements after 12-weeks of treatment with azithromycin (table 1). Bacterial colony counts did not

TABLE 1 Clinical outcomes and sputum cell counts after azithromycin treatment or placebo

Variables	Baseline		4 weeks		Treatment difference#, azithromycin minus placebo (95%CI)	8 weeks		Treatment difference#, azithromycin minus placebo (95%CI)	12 weeks		Treatment difference#, azithromycin minus placebo (95%CI)
	Placebo	Azithromycin	Placebo	Azithromycin		Placebo	Azithromycin		Placebo	Azithromycin	
Morning clinic PEF L·min^{-1}	411.1±124.3	390.5±114.5	412.9±110.6	384.2±143.5	-4.2 (-30.6–22.2), p=0.75	406.0±120.4	394.6±150.7	1.2 (-28.1–30.5), p=0.94	416.7±122.7	394.2±156.3	-10.3 (-47.1–26.4), p=0.58
FEV_1 pre-albuterol L	2.54±0.77	2.43±0.72	2.48±0.74	2.37±0.76	0.08 (-0.06–0.23), p=0.25	2.47±0.77	2.42±0.75	0.03 (-0.08–0.14), p=0.55	2.46±0.75	2.41±0.77	0.03 (-0.08–0.14), p=0.62
FEV_1 post-albuterol L	2.80±0.80	2.68±0.73	2.73±0.72	2.59±0.74	0.04 (-0.08–0.17), p=0.50	2.72±0.80	2.68±0.74	0.04 (-0.04–0.12), p=0.34	2.70±0.79	2.66±0.77	0.04 (-0.06–0.14), p=0.41
Reliever inhaler puffs per 24 h	2.8±2.9	2.9±4.4	2.5±2.7	3.1±4.4	-0.1 (-0.8–0.6), p=0.78	2.5±2.6	2.4±2.8	0.3 (-0.5–1.0), p=0.50	2.7±2.5	3.0 [4.0	-0.3 (-1.3–0.7), p=0.55
7-point ACQ score	1.76±0.88	1.73±0.74	1.64±0.90	1.74±0.85	0.12 (-0.18–0.42), p=0.43	1.69 ±1.03	1.86±0.99	0.21 (-0.14–0.55), p=0.23	1.58±0.96	1.75±0.83	0.21 (-0.11–0.53), p=0.20
logPC_{20} mg·mL^{-1}	0.07±1.14	0.06±1.41	ND	ND		ND	ND		0.19±1.29	0.20±1.52	-0.02 (-0.49–0.45), p=0.93
Total LCQ score	16.90±3.49	16.31±3.53	ND	ND		ND	ND		17.51±3.55	16.01±3.02	-1.06 (-2.16–0.05), p=0.06
Total AQLQ score	5.09±0.99	5.25±1.18	ND	ND		ND	ND		5.42±1.31	5.20±1.06	-0.31 (-0.69–0.07), p=0.11
F_{ENO50} ppb	15.6±21.2	11.5±8.9	ND	ND		ND	ND		16.2±20.1	11.0±7.9	-1.94 (-5.97–2.10), p=0.34
Total sputum cell count ×10^4	644±240	626±245	ND	ND		ND	ND		714±326	668±211	1.0 (0.9–1.2), p=0.75
Neutrophil ×10^4	150±123	172±103	ND	ND		ND	ND		141±96	162±97	19.2 (-24.2–62.6), p=0.38
Neutrophil %	33.1±24.3	39.0±22.5	ND	ND		ND	ND		31.0±19.9	34.4±18.6	3.0 (-5.9–11.8), p=0.50
Eosinophil ×10^4	4.9±6.4	6.9±9.3	ND	ND		ND	ND		6.8±13.9	10.3±20.1	1.0 (0.5–2.0), p=0.89
Eosinophil %	1.1±1.5	1.6±2.3	ND	ND		ND	ND		1.5±3.1	1.6±3.0	-0.4 (-1.8–1.0), p=0.55

Data are presented as mean±SD, unless otherwise stated. PEF: peak expiratory flow rate; FEV_1: forced expiratory volume in 1 s; ACQ: Asthma Control Questionnaire; PC_{20}: provocation concentration of methacholine causing a 20% fall in FEV_1; LCQ: Leicester Cough Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; F_{ENO50}: exhaled nitric oxide fraction at 50 mL·s^{-1}; ND: not done. #: treatment difference from ANCOVA analysing change from baseline and adjusting for baseline value.

demonstrate any treatment difference between the placebo and azithromycin groups (p=0.66, data not shown). PCR for *Mycoplasma pneumonia* and *Chlamydophila pneumoniae* were negative at both baseline and 12 weeks. QTc was unchanged following 12 weeks of treatment with azithromycin.

No suspected unexpected serious adverse events occurred during the reporting period of the study. Compliance assessed by capsule count was >90% in each group.

In the first randomised controlled study of azithromycin in smokers with asthma we found that there were no clinically important improvements in both the primary end-point and morning PEF, and in a range of secondary clinical outcomes including ACQ score, AQLQ score, spirometry and airway responsiveness, as well as measures of airway inflammation after 12 weeks of treatment. The median ACQ score of the participants recruited to the study was raised at 1.7 indicating that they had poorly controlled disease and scope for clinical improvement. We believe that the choice of a different macrolide from azithromycin or a different dose of azithromycin is unlikely to have altered our findings. This study was powered to test the hypothesis on the primary end-point, PEF. We exceeded our minimum recruitment target ensuring adequate numbers completed the study. The lack of response to treatment was such that recruiting greater numbers would be unlikely to affect either the primary end-point or the majority of secondary analyses. Taken together these findings indicate that short-term therapy with azithromycin does not improve lung function or other indices of current asthma control of smokers with mild-to-moderate asthma who are already receiving treatment with inhaled corticosteroids. This is supported by a recent study where 6 months of treatment with azithromycin in nonsmokers with severe asthma did not improve lung function [7].

Recently published data reported that azithromycin administered over 1 year reduced the rate of exacerbations in chronic obstructive pulmonary disease (COPD), although this benefit was not found in current smokers with COPD, and bronchiectasis was not an exclusion [12, 13]. Moreover, a 6-month study with azithromycin in nonsmokers with severe asthma powered to measure exacerbation frequency did not find any statistical difference between treatment and placebo groups [7], although a beneficial effect of azithromycin on reducing exacerbations was reported in patients with non-eosinophilic asthma [7]. The smokers with asthma in our study had non-eosinophilic asthma, but did not respond to azithromycin, although the duration of treatment was not long enough to assess the effects of azithromycin on exacerbations.

In conclusion, we have studied the effects of 12 weeks of azithromycin in smokers with asthma, an understudied patient group, and provide clear evidence demonstrating lack of efficacy in both clinical and laboratory outcomes. Further randomised clinical trials exploring new therapies in smokers with asthma who are unable to stop smoking are required.

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Daily azithromycin is ineffective in improving indices of asthma control and airway inflammation in smokers with asthma http://ow.ly/nQjyn

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Use of household cleaning products, exhaled nitric oxide and lung function in children

To the Editor:

The application of domestic cleaning agents increases the risk of asthma and respiratory symptoms in adults [1], in particular when products are applied in spray form [2]. Despite the associations observed in adults, the potential effects of passive exposure on children's respiratory health have not been extensively explored. Analyses of data from birth cohorts have suggested that frequent use of cleaning agents and their use in spray form increased the risk of wheezing and lower respiratory tract infections (LRTIs) during the first year of life [3, 4] and the risk of persistent wheezing at school age [5, 6]. By contrast, a cross-sectional study reported protective effects of using bleach at home on the prevalence of asthma and allergic sensitisation at school age [7]. Our study investigates the effects of the use of 10 common cleaning products on exhaled nitric oxide fraction (F_{ENO}) and on lung function (forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1)) during childhood in a population-based birth cohort in Menorca, Spain [8].

Recruitment was performed during pregnancy and 482 children were enrolled at birth. Written informed consent was obtained from all participants and the study was approved by a committee on ethical practice. Questionnaires on wheezing, asthma, treatment and allergies (rhinitis, eczema or hay fever) were administered by the mother repeatedly from birth until the age of 10 years. At the age of 10–13 years, F_{ENO} (NIOX MINO; Aerocrine AB, Solna, Sweden) and forced spirometry (EasyOne; ndd Medical Technologies, Inc., Andover, MA, USA) testing was carried out. In addition, an interviewer-led questionnaire on the frequency of use of 10 different cleaning products (bleach, ammonia, polishes or waxes, acids, solvents, furniture sprays, glass cleaning sprays, degreasing sprays, air freshening sprays, and air freshening plug-in devices) was carried out. A total of 295 individuals completed the 10-year follow-up visit and the cleaning products questionnaire and performed the F_{ENO} and/or the lung function test.

For statistical analyses, we computed a combined spray variable incorporating the four sprays (furniture, glass cleaning, degreasing and air freshening sprays) and a semiquantitative total score for cleaning product use. The means of the reported days of use per week (never=0, <1 day per week=0.5, 1–3 days per week=2 and 4–7 days per week=5.5) for each product were summed providing a score ranging from 0 (no exposure) to 55 (exposed to all 10 products used 4–7 days per week). Multivariable linear regression models were developed to predict log-transformed F_{ENO} concentration and non-transformed levels of FVC and FEV_1. Models were adjusted for sex, age, maternal education, parental smoking indoors, asthma medication, season of respiratory test measurement, and for height and weight for lung function measurements only. The coefficients obtained from the log-transformed F_{ENO} models were back-transformed