Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis

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Summary

Background Bronchiectasis guidelines recommend long-term macrolide treatment for patients with three or more exacerbations per year without *Pseudomonas aeruginosa* infection. Randomised controlled trials suggest that long-term macrolide treatment can prevent exacerbations in adult patients with bronchiectasis, but these individual studies have been too small to do meaningful subgroup analyses. We did a systematic review and individual patient data (IPD) meta-analysis to explore macrolide benefit in subpopulations, including those in which macrolide therapy is not currently recommended.

Methods We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science from Jan 1, 2000, to Sept 30, 2018, to identify double blind, randomised, placebo-controlled trials of macrolide antibiotics in adult patients with bronchiectasis. We applied no language restrictions. Randomised controlled trials were eligible if treatment was defined a priori as long term and had a primary or secondary outcome of bronchiectasis exacerbations. Studies in patients with cystic fibrosis bronchiectasis were excluded. The primary outcome of the meta-analysis was frequency of exacerbations requiring treatment with antibiotics. Secondary endpoints were time to first exacerbation, change in quality of life according to the St George's Respiratory Questionnaire (SGRQ), and change in FEV_1. IPD meta-analysis was done using fixed effects models adjusting for age, sex, FEV_1, and trial. We did prespecified subgroup analyses for each of the primary and secondary endpoints using one-step meta-analysis only. Subgroups were defined by age, sex, previous exacerbation frequency, smoking status, inhaled corticosteroid use at baseline, body-mass index at baseline, cause, C-reactive protein at baseline, baseline FEV_1 percentage of predicted, SGRQ total score, and *Pseudomonas aeruginosa* in sputum culture at baseline. The meta-analysis is registered with the PROSPERO international register of systematic reviews, number CRD42018102908.

Findings Of 234 identified studies, we included three randomised controlled trials, and IPD was obtained for 341 participants. Macrolide antibiotics reduced the frequency of exacerbations (adjusted incidence rate ratio [IRR] 0·49, 95% CI 0·36 to 0·66; p<0·0001). We also found that macrolide treatment improved the time to first exacerbation (adjusted hazard ratio 0·46, 0·34 to 0·61; p<0·0001) and was associated with improved quality of life measured by the SGRQ (mean improvement 2·93 points, 0·03 to 5·83; p=0·048). Macrolides were not associated with a significant improvement in FEV_1 (67 mL at 1 year, –22 to 112; p=0·14). Effect estimates in prespecified subgroup analyses revealed a reduced frequency of exacerbations in all prespecified subgroups, including a high level of benefit in patients with *P aeruginosa* infection (IRR 0·36, 0·18–0·72; p=0·0044) and in patients with one to two exacerbations per year (0·37, 0·16–0·88; p=0·025). Studies were rated as low risk of bias across all domains.

Interpretation Long-term macrolide treatment significantly reduces the frequency of exacerbations in patients with bronchiectasis, with similar benefits observed in all subgroups based on patient characteristics. This finding suggests that macrolides might be considered in patients in whom macrolides are not indicated according to the current guidelines, particularly if alternative approaches to reduce exacerbations have been unsuccessful. However, downsides of long-term macrolide treatment must also be taken into account.

Funding European Respiratory Society.

Lancet Respir Med 2019; 7: 845–54

Published Online August 9, 2019 http://dx.doi.org/10.1016/S2213-2600(19)30191-2

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Introduction

Bronchiectasis is a common chronic disease associated with frequent respiratory tract infections, chronic symptoms of cough, and sputum production.[1] The disease has a devastating impact on patients' quality of life.[2] In addition, exacerbations of bronchiectasis, which are characterised by increases in symptoms requiring antibiotic treatment, are a major driver of disease progression and associated mortality.[3,4]

Bronchiectasis is characterised by a vicious vortex of bacterial infection, airway inflammation, and impaired mucociliary clearance, which each interact to promote

Research in context

Evidence before this study

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science from Jan 1, 2000, to Sept 30, 2018, using the search strategy described in the appendix (p 1). No language restrictions were applied. Searches were supplemented with review of reference lists and by reviewing previous meta-analyses and guidelines. Clearly ineligible studies were excluded based on abstract review alone.

We identified 234 unique references, of which three randomised controlled trials compared long-term treatment with macrolide antibiotics (>3 months duration) versus placebo and had reduction of exacerbations as the primary outcome.

We identified several existing aggregate meta-analyses that suggested that macrolides reduce the frequency of exacerbations of bronchiectasis. Neither the individual trials nor the existing meta-analyses reported on the effectiveness of macrolides in different subpopulations. Identifying which patients benefit from macrolides was identified as a key research priority in bronchiectasis. The current European Respiratory Society guidelines suggest consideration of macrolides for patients without *Pseudomonas aeruginosa* infection with a history of at least three exacerbations in the previous year.

Added value of this study

We report the first individual patient data meta-analysis of long-term macrolide therapy in bronchiectasis. Our data, from 341 patients enrolled in randomised clinical trials in the Netherlands, New Zealand, and Australia, suggest that macrolide treatment for 6–12 months results in a reduction in the frequency of exacerbations compared with placebo (adjusted incidence rate ratio 0·49, 95% CI 0·36–0·66). Additional benefits included prolongation of the time to first exacerbation and significant improvements in quality of life measured by the St George's Respiratory Questionnaire. Lung function was not significantly improved. Analyses in prespecified subgroups, including age, sex, disease severity, and baseline microbiology, suggested that macrolides effectively reduced exacerbations across all subgroups of patients. Importantly, macrolides had a significant and clinically meaningful impact in patients in whom macrolides are not currently considered as first-line treatment, including those with P aeruginosa infection and patients with fewer than three exacerbations per year.

Implications of all the available evidence

Our data suggest that macrolide therapy is highly effective in reducing the frequency of exacerbations in bronchiectasis. Given the strong evidence that exacerbations contribute to long-term morbidity and mortality in bronchiectasis, macrolides should be considered in patients with frequent or severe exacerbations. Current bronchiectasis guidelines recommend inhaled antibiotics as first-line treatment for patients with *P aeruginosa* infection and frequent exacerbations. In view of the high level of effectiveness of macrolides in reducing exacerbations in the subgroup with *P aeruginosa* infection, and of equivocal data on the effectiveness of inhaled antibiotics, macrolides could be considered as first-line therapy for patients with *P aeruginosa* infection. The magnitude of benefit was similar in patients with one or two exacerbations per year and in those with three exacerbations per year, in whom macrolides are recommended by international guidelines; this finding suggests an individualised discussion of the risks and benefits of macrolides should be had. Macrolides have important adverse events and the potential to induce antimicrobial resistance, so should be used judiciously. No studies were identified with a treatment duration of more than 1 year and so the longer-term efficacy and safety of macrolides is unknown.

lung damage.[5,6] Few evidence-based treatments exist for bronchiectasis, as reflected in the 2017 European Respiratory Society bronchiectasis management guidelines,[7] which were unable to recommend any pharmacotherapy with a high quality of evidence. Macrolide antibiotics are among the most widely used chronic treatments to prevent exacerbations in bronchiectasis.[8,9] They are particularly attractive because there is evidence that they target each of the key components of bronchiectasis pathophysiology.[10,11] In addition to reducing bacterial burden, macrolides have well established immunomodulatory effects that include suppression of neutrophil-mediated lung damage and enhancement of cilia function to promote mucociliary clearance.[10,12,13]

A few randomised controlled trials[14–17] have shown that the macrolide class of antibiotics significantly reduce exacerbations in bronchiectasis. Meta-analyses[18,19] of these trials based on aggregate data suggest a clear reduction in the frequency of exacerbations with macrolide therapy, along with other benefits. For example, the meta-analysis by Gao and colleagues[18] identified nine trials with 559 participants of which six were conducted in adults. Macrolide therapy reduced the frequency of exacerbations by 58% and the proportion of patients experiencing exacerbations, with slight improvements in FEV_1 and quality of life.[18] Macrolides, however, were associated with increased adverse events, such as diarrhoea and abdominal discomfort, and with an increased risk of antibiotic resistance.[9,14] Hearing loss and cardiovascular effects have been detected in other patient populations but were not observed in bronchiectasis trials.[9,20,21] On the basis of these observations, the most recent Cochrane review called for further research to identify specific patient groups who are most responsive to macrolides.[22] A 2016 consensus statement[23] by the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) of the European Respiratory Society (ERS), based on a survey of over 100 bronchiectasis experts and over 1000 patients, identified "further studies to define the optimal patient population to benefit from

long-term macrolide therapy" as one of the 22 key research priorities in bronchiectasis.

We therefore undertook an individual participant data (IPD) meta-analysis of studies of long-term macrolides in adults, with the objective of identifying responsive patient subgroups.

Methods

Search strategy and selection criteria

We did a systematic review and one-step and two-step meta-analysis of individual participant data. Double-blind, randomised, placebo-controlled trials of macrolide antibiotics in adult patients (≥18 years) with bronchiectasis were eligible for inclusion if they also had long-term treatment (defined a priori as treatment duration of at least 3 months on the basis of the previous ERS guidelines) and had frequency of exacerbations as a primary or secondary outcome.[7] Studies in patients with cystic fibrosis bronchiectasis were excluded to focus solely on patients with primary bronchiectasis.

Two investigators (JDC and MLC) searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science using the search terms listed in the appendix (p 1). Databases were searched from Jan 1, 2000, to Sept 30, 2018. No language restrictions were applied. Searches were supplemented with examination of reference lists and by reviewing previous meta-analyses and guidelines. Clearly ineligible studies were excluded based on abstract review alone. Systematic reviews and meta-analyses are exempt from research ethics committee review in the UK. Findings are reported according to the PRISMA guidelines[24] for IPD meta-analysis. The review protocol was prospectively registered with the PROSPERO, number CRD42018102908.

Outcomes

The primary outcome of the meta-analysis was the frequency of exacerbations requiring treatment with antibiotics. This outcome was selected based on clinical and regulatory opinion that it is the most important clinical endpoint in bronchiectasis studies.[4,25,26] Exacerbation definitions varied across different studies and therefore a-priori definitions were used based on prescription of antibiotics for an increase in respiratory symptoms. Secondary endpoints were time to first exacerbation, change in quality of life according to the St George's Respiratory Questionnaire (SGRQ), and change in FEV_1 (in mL).

Data analysis

Our IPD meta-analysis approach followed published guidelines.[27] Initially, we re-analysed all studies separately to replicate the results of the original reported studies using the methodology described in the respective publications. Any discrepancies were resolved with the original study authors. Studies were assessed using the Cochrane risk of bias tool.

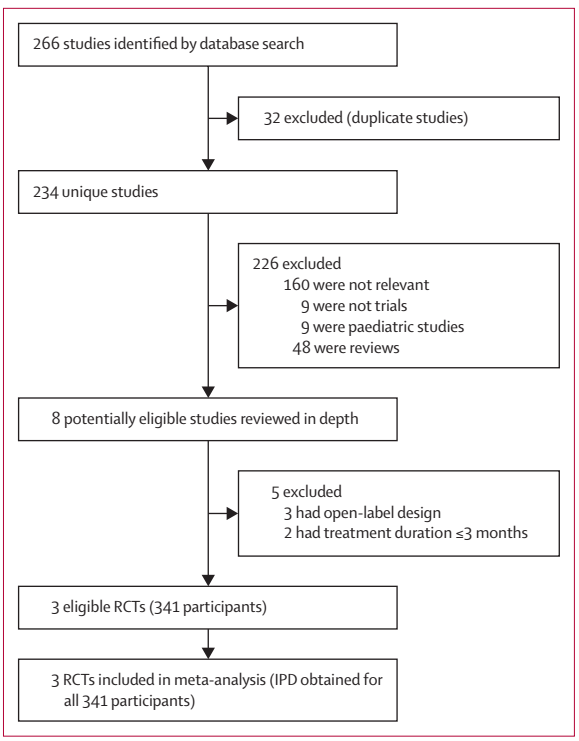

Figure 1: **Study selection**
IPD=individual-patient data. RCT=randomised controlled trial.

See **Online** for appendix

We then performed a one-step and two-step meta-analysis of the primary outcome (exacerbation frequency). We analysed this outcome using a negative binomial model with time in study as an offset. We expressed the primary outcome results as incident rate ratios (IRRs) with associated 95% CIs. For secondary outcomes, we performed one-step meta-analysis only; we modelled IPD from studies with fixed effects adjusting for age, sex, FEV_1 at baseline, and study to obtain the pooled intervention effect estimate. Adjustment for trial as a fixed effect was prespecified after the literature review on the basis of the very similar inclusion criteria, patient characteristics, design, and outcomes used in all studies ultimately included in the meta-analysis. Secondary outcome results were expressed as hazard ratios (HRs) for time to first exacerbation and mean differences for change in SGRQ score and FEV1 % predicted with their associated 95% CIs.

For the sensitivity analysis of the primary outcome, we controlled for study as a random effect. To check the validity of the CIs around the estimates, we did a non-parametric bootstrap. We analysed time to next exacerbation using Cox proportional hazards regression adjusted for age, sex, and FEV_1 at baseline as covariates and with study as a stratification variable. We confirmed the proportional hazards assumption by inspection of log-minus-log plots. We analysed continuous outcomes using a generalised linear model, with the addition of baseline value of the endpoint as an additional covariate.

	Setting	Key inclusion criteria	Age per group (intervention *vs* placebo), years	Number of participants	Macrolide treatment	Number of participants per group (intervention *vs* placebo)	Study duration
Altenburg et al (2013)[14]	14 hospitals in the Netherlands (2008–2010)	≥3 exacerbations; positive sputum culture in the year before baseline	59·9 (12·3) *vs* 64·6 (9·1)	83 (30 men, 53 women)	Azithromycin (250 mg daily)	43 *vs* 40*	12 months with a 3-month run-out period
Serisier et al (2013)[15]	Single centre in Australia (2008–2011)	≥2 exacerbations; daily sputum production	61·1 (10·5) *vs* 63·5 (9·5)	117 (46 men, 71 women)	Erythromycin ethylsuccinate (400 mg twice daily)	59 *vs* 58	48 weeks with a 4-week washout period
Wong et al (2012)[16]	Three centres in New Zealand (2008–2009)	≥1 exacerbation in the previous year	60·9 (13·6) *vs* 59·0 (13·3)	141 (43 men, 98 women)	Azithromycin (500mg three times per week)	71 *vs* 70	6 months of treatment followed by 6 months of observation without treatment

Data are mean (SD), unless otherwise specified. *Two patients in the azithromycin group and four patients in the placebo group were excluded after randomisation before receiving the first dose of drug; these patients were not included in our individual-patient data analysis.

Table 1: **Randomised controlled trials of macrolide use in patients with bronchiectasis**

In addition to the analysis of quality of life as a continuous outcome variable, we did a responder analysis using logistic regression with the response being an improvement of 4 points or more in the SGRQ score (the reported minimum clinically important difference for this score).[25,26]

For the two-step approach to the primary outcome, we analysed the IPD using a negative binomial regression with adjustment for age, sex, and baseline FEV_1 to produce an estimate of treatment effect for each trial. We then did a meta-analysis using the Mantel-Haenszel method, and heterogeneity was reported using the I^2 statistic.

A key objective of this study was to identify subgroups of patients in whom macrolides had a differential effect. We evaluated interactions by including interaction terms in the appropriate models as described. We did prespecified subgroup analyses for each of the primary and secondary endpoints using one-step meta-analysis only. Subgroups were defined as age (<50 years, ≥50 years to <70 years, and ≥70 years); sex (male and female); previous exacerbation frequency (one or two per year, three per year, and four or more per year); smoking status (never and former or current smoker); inhaled corticosteroid use at baseline (yes or no); body-mass index at baseline (<21 kg/m², 21–24·9 kg/m², 25–29·9 kg/m², and ≥30 kg/m²); cause (idiopathic and post-infective or other); C-reactive protein at baseline (<2 mg/L, 2–5 mg/L, 5·1–10 mg/L, and >10 mg/L); baseline FEV_1 percentage predicted (>80%, 50–79%, <50%), SGRQ total score (<30, 30–49, ≥50); and *Pseudomonas aeruginosa* in sputum culture at baseline (positive or negative). Significance was inferred for subgroup effects in which the p value for interaction was less than 0·05.

Analyses were done with R, version 3.4.0, and SPSS, version 22. The two step meta-analysis was done with Review Manager 5.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

234 potentially eligible studies were identified. After exclusion of 231 manuscripts that did not meet the inclusion criteria, three double-blind, randomised, placebo-controlled trials with a total of 341 participants were included (figure 1). We sought IPD for these three trials and obtained data for all eligible participants.

These trials were done in the Netherlands, New Zealand, and Australia. Two trials compared azithromycin versus placebo,[14,16] whereas the third trial compared erythromycin versus placebo.[15] Participants randomly assigned to either treatment or placebo were aged 18–80 years (median 64 years, IQR 57–69) and 222 (65%) of 341 patients were female. Our analyses included 173 patients treated with macrolide and 168 patients treated with placebo (table 1). All randomised controlled trials contributing data to the IPD meta-analysis were assessed as being at low risk of bias (appendix p 2).

In the one-step meta-analysis, long-term macrolide therapy was associated with a marked reduction in frequency of exacerbations (IRR 0·49, 95% CI 0·36–0·66; p<0·0001) compared with placebo (appendix p 2). Sensitivity analyses were performed excluding the adjustment for baseline covariates and removing the offset, which identified similar results. Similarly, controlling for study as a random effect did not impact on the overall conclusions (appendix p 2). A non-parametric bootstrap of the data produced similar confidence intervals to those obtained directly from the model (data not shown).

The two-step meta-analysis identified a similar result to the one-step approach (IRR 0·51, 95% CI 0·37–0·69; p<0·0001), with no heterogeneity (I^2 0%; appendix p 6).

The response to macrolide was significant for most subgroups and none of the subgroup analyses showed significant interactions, with the exception of cause ($p_{interaction}$=0·034; table 2). Please note that in our study

the numerical values of the effect estimates for individual subgroups are more relevant in identifying clinical benefit than their associated measures of significance (p value and 95% CI) because of the high risk of type II error due to the small size of some of the subgroups.

The IRR estimates suggested improved response (ie, reduction in frequency of exacerbations) with increasing age, extremes of body-mass index (BMI), increasing systematic inflammation (baseline concentration of C-reactive protein), and in patients with one to two exacerbations per year but the $p_{interaction}$ values were not significant (table 2).

Focusing in particular on patient groups in which the current guidelines advise to withhold macrolide treatment (ie, patients with less than three exacerbations per year and patients with *P aeruginosa* infection), we found no significant difference in the IRR between different strata of baseline exacerbation frequency ($p_{interaction}$=0·86). Absolute risk reductions in each strata of baseline exacerbation frequency are shown in the appendix (p 3). The number of events that required treatment was 1·0 for patients with four or more exacerbations in the previous year, 1·7 for patients with three exacerbations in the previous year, and 1·5 for patients with a history of one or two exacerbations in the previous year. The response to macrolide was significant in patients both with (IRR 0·36, 95% CI 0·18–0·72; p=0·004) and without (0·53, 0·38–0·74; p<0·0001) *P aeruginosa* infection; however, there was no significant interaction for patients with *P aeruginosa* infection ($p_{interaction}$=0·45; table 2). In a post-hoc analysis, response showed no significant interaction based on sputum culture. *H influenzae* was the second most frequent pathogen and post-hoc analysis of this subgroup showed no differential response (0·40, 0·10–1·69; p=0·21).

Time to first exacerbation was significantly prolonged with macrolide treatment (adjusted hazard ratio 0·46, 95% CI 0·34–0·61; p<0·0001; appendix p 6). The model-derived median time to first exacerbation was 98 days in the placebo groups and 280 days in the macrolide-treated groups (appendix p 6). Table 3 shows the analysis of time to first exacerbation in the prespecified subgroups. Almost all HRs were significant for each individual subgroup, but none of the subgroup interactions were.

We identified a significant improvement in quality of life with macrolide treatment versus placebo (SGRQ score increase 2·93 points, 95% CI 0·03–5·83; p=0·048; appendix p 3). The number of patients achieving more than a 4-point improvement in SGRQ score was also increased with macrolide therapy compared with placebo (odds ratio 1·61, 1·02–2·54; p=0·042). Cause of bronchiectasis (idiopathic or post-infective causes *vs* other causes) was the factor with the strongest association with improvement in quality of life, with a significant interaction (p=0·035; figure 2).

Increasing numerical values of SGRQ scores (indicative of quality-of-life improvement) within subgroup categories were seen in older patients, female participants, former smokers, inhaled corticosteroid users, and patients with BMI greater than 30 kg/m², with C-reactive protein

	Number of participants (intervention *vs* placebo)	Incident rate ratio (95% CI)	p value	$p_{interaction}$ value
Age groups	..	..	..	0·18
<50 years	53 (27 *vs* 26)	0·61 (0·27–1·37)	0·23	..
50–69 years	211 (110 *vs* 101)	0·52 (0·36–0·76)	0·0011	..
≥70 years	77 (36 *vs* 41)	0·36 (0·18–0·71)	0·0032	..
Sex	..	..	..	0·31
Male	119 (59 *vs* 60)	0·59 (0·35–0·99)	0·047	..
Female	222 (114 *vs* 108)	0·43 (0·29–0·62)	<0·0001	..
Previous exacerbations (per year)	..	..	..	0·86
1–2	73 (37 *vs* 36)	0·37 (0·16–0·88)	0·025	..
3	85 (48 *vs* 37)	0·62 (0·32–1·20)	0·072	..
≥4	183 (88 *vs* 95)	0·52 (0·36–0·77)	0·0019	..
Smoking status	..	..	..	0·64
Never	222 (115 *vs* 107)	0·51 (0·35–0·74)	<0·0001	..
Former	112 (56 *vs* 56)	0·44 (0·27–0·73)	0·0024	..
Current	7 (2 *vs* 5)	NE	NA	..
Inhaled corticosteroid use	..	..	..	0·46
Yes	223 (112 *vs* 111)	0·49 (0·34–0·71)	<0·0001	..
No	118 (61 *vs* 57)	0·44 (0·26–0·75)	0·0036	..
BMI at baseline (kg/m²)	..	..	..	0·50
<21	38 (20 *vs* 18)	0·36 (0·13–1·02)	0·054	..
21–24·9	179 (92 *vs* 87)	0·56 (0·37–0·84)	0·0050	..
25–29·9	65 (36 *vs* 29)	0·55 (0·27–1·10)	0·093	..
30 or more	59 (25 *vs* 34)	0·27 (0·12–0·61)	0·0018	..
Cause	..	..	..	0·034
Idiopathic and post-infective	267 (149 *vs* 118)	0·56 (0·39–0·80)	0·0029	..
Other	74 (24 *vs* 50)	0·23 (0·11–0·52)	<0·0001	..
Baseline concentration of C-reactive protein (mg/L)	..	..	..	0·27
<2	98 (49 *vs* 49)	0·60 (0·34–1·03)	0·065	..
2–5	95 (51 *vs* 44)	0·52 (0·30–0·92)	0·023	..
5·1–10	71 (36 *vs* 35)	0·33 (0·15–0·73)	0·0061	..
>10	60 (30 *vs* 30)	0·35 (0·17–0·76)	0·0086	..
Baseline FEV_1 (% predicted)	..	..	..	0·51
≥80	137 (64 *vs* 73)	0·52 (0·32–0·84)	0·0088	..
50–79	144 (82 *vs* 62)	0·43 (0·27–0·70)	0·0015	..
<50	60 (27 *vs* 33)	0·55 (0·27–1·12)	0·10	..
SGRQ total score	..	..	..	0·90
<30	139 (72 *vs* 67)	0·50 (0·29–0·84)	0·0082	..
30–49	123 (64 *vs* 59)	0·45 (0·27–0·74)	0·0024	..
≥50	79 (37 *vs* 42)	0·50 (0·28–0·90)	0·022	..
Pseudomonas aeruginosa infection	..	..	..	0·45
Yes	61 (31 *vs* 30)	0·36 (0·18–0·72)	0·0044	..
No	280 (142 *vs* 138)	0·53 (0·38–0·74)	<0·0001	..

IRR=incident rate ratio. NE=not estimable. NA=not applicable. BMI=body-mass index. SGRQ=St George's Respiratory Questionnaire.

Table 2: **Subgroup analysis of bronchiectasis exacerbation frequency**

	HR (95% CI)	p value	$p_{interaction}$ value
Age group	..	..	0·15
<50 years	0·65 (0·29–1·44)	0·29	..
50–69 years	0·50 (0·35–0·72)	<0·0001	..
≥70 years or more	0·24 (0·11–0·54)	<0·0001	..
Sex	..	..	0·22
Male	0·57 (0·34–0·95)	0·030	..
Female	0·38 (0·27–0·55)	<0·0001	..
Previous exacerbations (per year)	..	..	0·45
1–2	0·40 (0·17–0·96)	0·040	..
3	0·47 (0·25–0·89)	0·020	..
≥4	0·48 (0·34–0·69)	<0·0001	..
Smoking status	..	..	0·34
Never	0·49 (0·34–0·72)	<0·0001	..
Former	0·37 (0·22–0·58)	<0·0001	..
Inhaled corticosteroid use	..	..	0·89
Yes	0·44 (0·31–0·63)	<0·0001	..
No	0·46 (0·27–0·76)	0·0039	..
BMI at baseline (kg/m²)	..	..	0·24
<21	0·22 (0·07–0·70)	0·010	..
21–24·9	0·56 (0·38–0·82)	0·0037	..
25–29·9	0·33 (0·17–0·67)	0·0020	..
≥30	0·26 (0·11–0·59)	0·0019	..
Cause	..	..	0·11
Idiopathic and post-infective	0·53 (0·38–0·75)	<0·0001	..
Other	0·29 (0·15–0·57)	<0·0001	..
Baseline concentration of C-reactive protein (mg/L)	..	..	0·20
<2	0·61 (0·35–1·05)	0·072	..
2–5	0·44 (0·26–0·76)	0·0031	..
5·1–10	0·27 (0·12–0·57)	0·0014	..
>10	0·39 (0·19–0·82)	0·013	..
Baseline FEV_1 (% predicted)	..	..	0·86
≥80	0·49 (0·31–0·77)	0·0023	..
50–79	0·37 (0·23–0·59)	<0·0001	..
<50	0·54 (0·27–1·09)	0·087	..
SGRQ total score	..	..	0·21
<30	0·60 (0·37–0·98)	0·039	..
30–49	0·37 (0·24–0·59)	<0·0001	..
≥50	0·42 (0·23–0·77)	0·0045	..
Pseudomonas aeruginosa infection	..	..	0·47
Yes	0·36 (0·19–0·69)	0·0017	..
No	0·47 (0·34–0·65)	<0·0001	..

HR=hazard ratio. BMI=body-mass index. SGRQ=St George's Respiratory Questionnaire.

Table 3: **Subgroup analysis of time to first bronchiectasis exacerbation**

concentration greater than 10 mg/mL, and with FEV_1 less than 50% of predicted (figure 2 and appendix p 3).

Macrolides were not associated with a significant improvement in FEV_1 (increased by 67 mL at 1 year, 95% CI –22 to 112; p=0·14; appendix p 3). In the analysis of subgroup effects on lung function, only the interaction between idiopathic or post-infective causes and other cause was significant ($p_{interaction}$=0·026; figure 3 and appendix p 3). The greatest numerical improvements in FEV_1 were seen in patients with three exacerbations in the previous year (163 mL, 37 to 290), causes other than idiopathic or post-infective (286 mL, –11 to 583), higher systemic inflammation (253 mL, 119 to 388), and *P aeruginosa* infection at baseline (171 mL, –128 to 469; figure 3 and appendix p 3).

Discussion

This IPD meta-analysis shows that the use of macrolides in patients with bronchiectasis reduces the frequency of exacerbations (IRR 0·49, 95% CI 0·36–0·66) over 6–12 months and is associated with a significant improvement in quality of life measured with the SGRQ score; although this improvement did not exceed the minimum clinically important difference, the proportion of patients who achieved a clinically meaningful improvement in quality of life was increased in participants in the macrolide group versus those in the placebo group. The findings of this study agree with the findings of the original BAT,[14] BLESS,[15] and EMBRACE[16] studies and the results of previous meta-analyses.[18,22] The advantage of IPD meta-analysis is the ability to standardise the analysis and reporting of each trial. Previous meta-analyses[18,22] have been limited in their assessment of frequency of exacerbations, time to first exacerbation, quality of life, and other endpoints because of different methods of reporting in the three studies[14–16] we reviewed. The most recent Cochrane systematic review[22] of macrolide antibiotics in bronchiectasis could not fully analyse the frequency of exacerbations endpoint because of heterogeneous reporting of data and hence limited the analysis to the proportion of patients with one or more exacerbations. Previous estimates[18,19] of the effect of macrolides on quality of life and lung function were also based on incomplete data.

Therefore, our IPD meta-analysis provides a more accurate assessment of the benefits of macrolide treatment in adults with bronchiectasis than previously published studies.[18,22] The most novel aspect of our study, however, is the ability to examine subgroup effects. Subgroup analyses can provide useful information for clinicians who need to decide how to use macrolides in practice but should be treated with caution because of the risks of multiple statistical testing. We found that few of the subgroup analyses showed a significant interaction, indicating a true difference in treatment response. Even though we pooled the results of three randomised controlled trials, the total number of participants (n=341) was probably still insufficient to provide statistical power to detect subgroup effects other than very large ones. With the caveat that such differences are numerical rather than significant, we

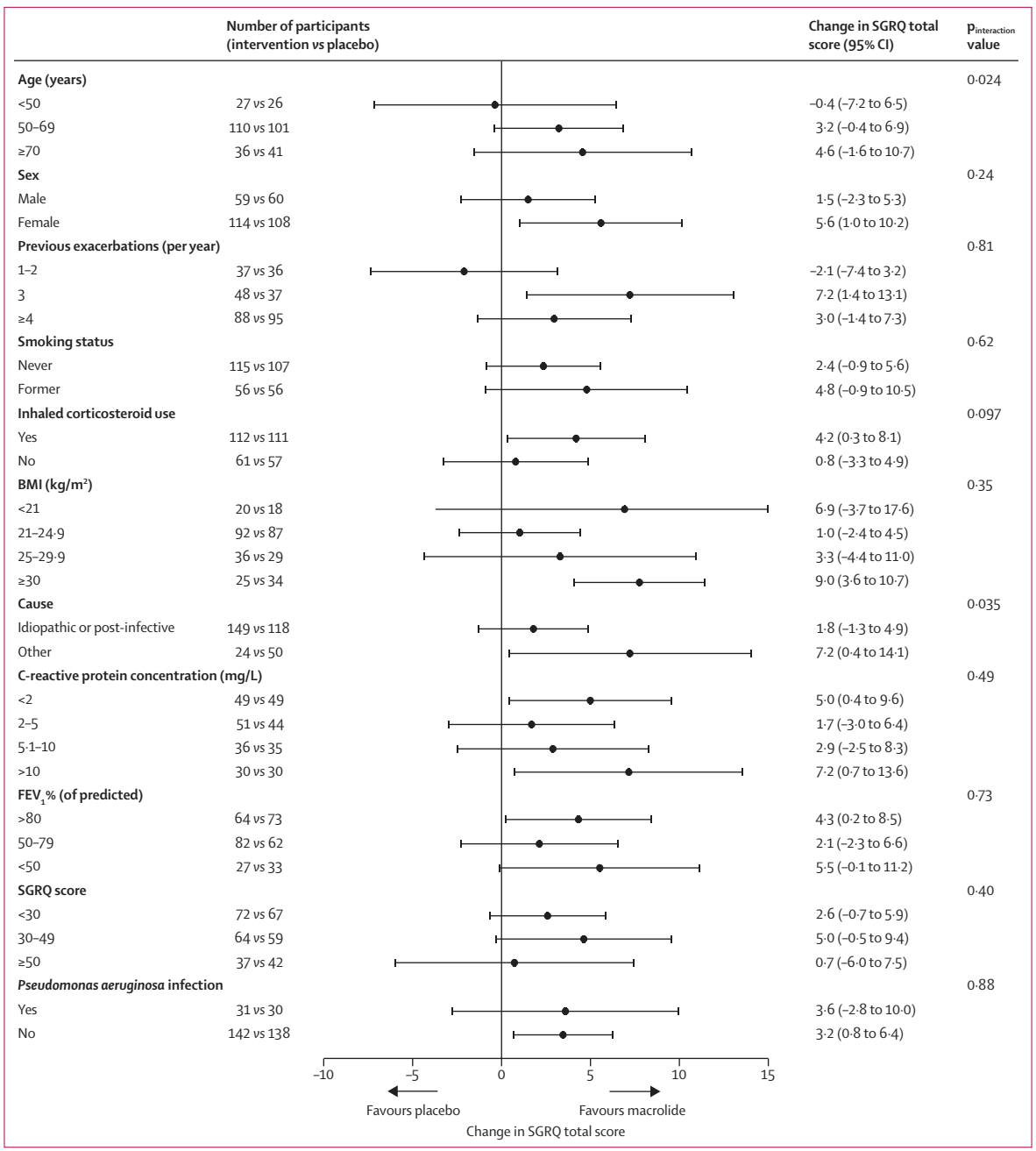

Figure 2: **Forest plot of the effect of macrolide treatment on the change in quality of life**
The change in quality of life was assessed using the SGRQ total score in the one-step meta-analysis between patients in the intervention group (n=173) and in the placebo group (n=168). Values for change in SGRQ score and the associated 95% CIs and p values are also summarised in the appendix (p 3). BMI=body-mass index. NE=not estimable. SGRQ=St George's Respiratory Questionnaire.

observed the largest relative treatment effects with respect to exacerbation in patients older than 70 years, with a history of one to two exacerbations per year, a BMI of 30 kg/m² or higher or lower than 21 kg/m², a high baseline C-reactive protein, *P aeruginosa* infection, and causes other than idiopathic and post infective.

The ERS guidelines[7] recommend consideration of macrolide treatment in patients with three or more exacerbations per year. Our finding of a strong treatment benefit in patients with a lower frequency of exacerbations suggests that macrolides might be considered in patients with one to two exacerbations per year, particularly if alternative approaches to reduce exacerbations have been unsuccessful. No quality-of-life or lung-function benefits were observed in this subgroup, however. We found no evidence that the response to

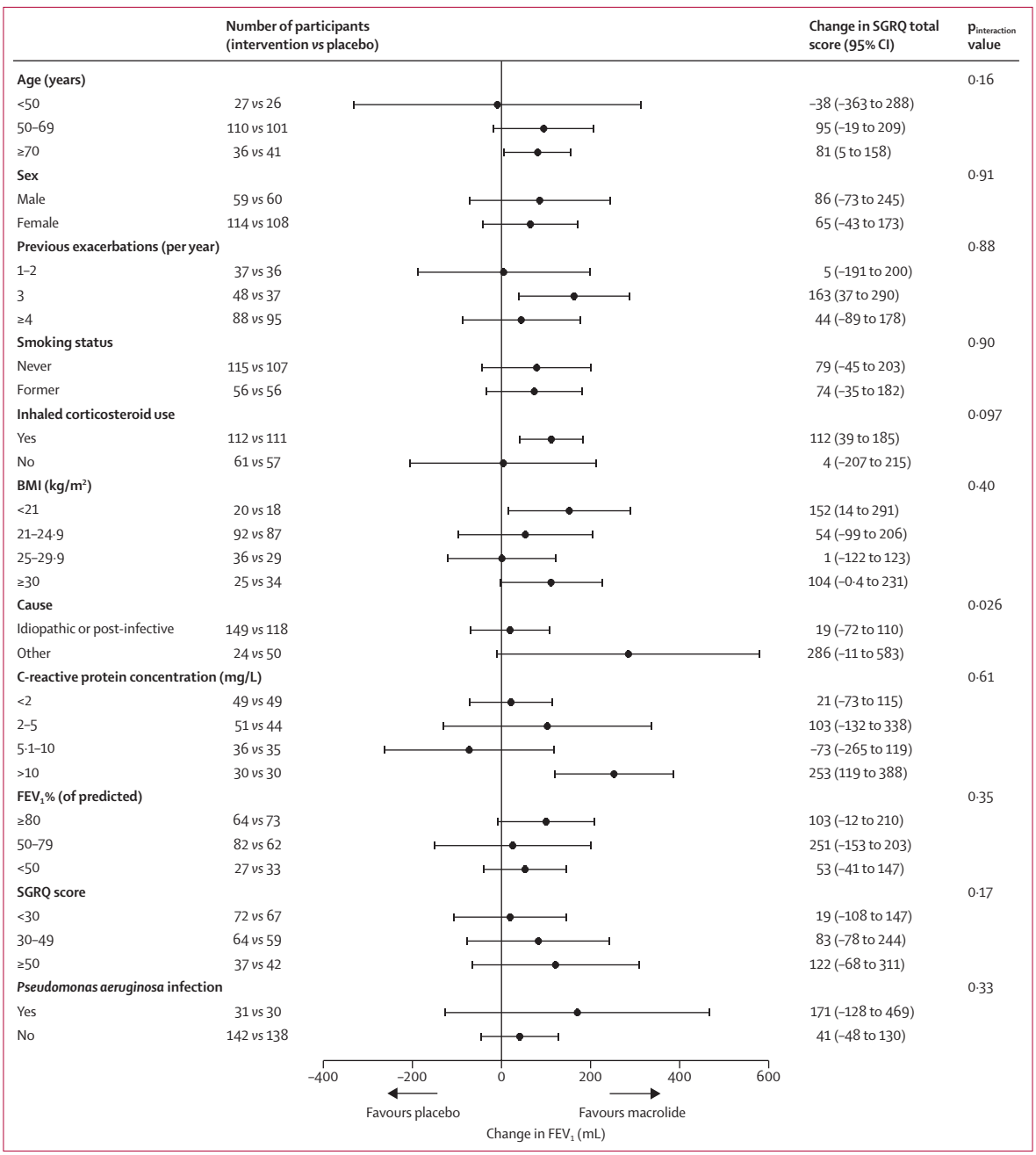

Figure 3: **Forest plot of the effect of macrolide treatment on the change in FEV_1**

The change in FEV_1 was assessed in the one-step meta-analysis between patients in the intervention group (n=173) and in the placebo group (n=168). BMI=body-mass index. Values for change in FEV_1 and the associated 95% CIs and p values are listed in the appendix (p 3). BMI=body-mass index. NE=not estimable.

macrolides was modified by the presence of *P aeruginosa* in sputum. *P aeruginosa* is a key pathogen in bronchiectasis as it is linked to increased frequency of exacerbations, hospital admissions, and risk of mortality.[28] Prophylactic antibiotics are widely used in patients infected with *P aeruginosa* in view of their increased morbidity.[29] Serisier and colleagues reported in the original BLESS trial[15] a possible—albeit not significant—increase in efficacy of erythromycin in patients with *P aeruginosa*. This finding has been misinterpreted by some authors[30,31] to suggest that macrolides are most effective in patients with *P aeruginosa* infection or that macrolides are ineffective in patients without *P aeruginosa* infection. Our study is constrained by sample size as only 61 (18%) of 341 participants had *P aeruginosa* infection, among whom 34 (10%) came from the BLESS trial.[15] Nevertheless, it is

clear that macrolides are effective in patients without *P aeruginosa* with a significant reduction in the frequency of exacerbations (IRR 0·53, 95% CI 0·38–0·74; p<0·0001) and positive effect estimates for quality of life in this subgroup. The estimated effect in patients with *P aeruginosa* infection was a significant reduction in exacerbation frequency (0·36, 0·18–0·72; p=0·0044). We also observed no differential response in the small subgroup of patients with *H influenzae* infection. Current ERS guidelines[7] recommend that inhaled antibiotics should be considered first line for exacerbation reduction in patients with *P aeruginosa* infection. The best estimate of inhaled-antibiotic efficacy in patients with bronchiectasis is an approximate 30% reduction in the frequency of exacerbations and some randomised controlled trials[25,26,32,33] have given mixed or inconsistent results. Our data support the use of macrolides in patients with *P aeruginosa* infection and, in the absence of head-to-head studies, this class of drugs could be an appropriate first-line maintenance antibiotic in selected patients. Our results are consistent with the experience of macrolide treatment in cystic fibrosis, in which it reduces exacerbation frequency in patients both with and without *P aeruginosa* infection.[34,35]

Older patients (≥65 years) with chronic obstructive pulmonary disease were previously identified as a subgroup with an increased response to macrolides and our study suggests this might also be the case for older patients with bronchiectasis.[36] Systematic inflammation is a risk factor for exacerbation in patients with bronchiectasis and the anti-inflammatory effects of macrolides have been shown to reduce systemic inflammation, including concentrations of C-reactive protein.[37] The association between increased age, increased systemic inflammation, and increased efficacy of macrolides is therefore biologically plausible. It is clear, however, that further studies would be required to provide sufficient statistical power to confidently identify these patient groups as more responsive to macrolide treatment.

The strength of our study is the pooling of three high-quality, double-blind, randomised controlled trials, all of which were evaluated as being at low risk of bias. Access to IPD was comprehensive and allowed more detailed analysis than has previously been possible in aggregate meta-analysis. The three studies were done in different regions but showed concordant results across Europe and the Asian and Pacific regions, strengthening confidence that these results will be generalisable. Nevertheless, our study has limitations. First, as outlined by the 2019 European Medicines Agency guidance for interpretation of subgroup analyses of randomised controlled trials, even if a medicine is associated with benefit it will, by chance alone, appear not to work or even to harm in some subgroups of patients if sufficient multiple tests are performed. We did 30 subgroup analyses and so at least one or two associations would be expected purely by chance. Results of subgroups should ideally be confirmed in future randomised studies. Second, many subgroups were small and the effect estimates we obtained in these groups often had very wide CIs, reflecting the small size of the overall patient population. Third, we were unable to evaluate some potential predictors of response—such as disease severity according to multidimensional scoring systems—because some data required to calculate these scores (such as radiological extent of disease) were not collected in the original trial databases. Finally, we pooled two trials of azithromycin[14,16] and one trial of erythromycin.[15] However, our study was not designed to evaluate any differences in efficacy between these two macrolides.

The fact that the favourable effect of macrolides extends beyond patients who have frequent exacerbations, who are the traditional recipients should, however, not serve as a permit to unrestricted use of macrolide maintenance treatment in patients with bronchiectasis. Macrolides have important adverse effects, including direct side-effects, population risk of antimicrobial resistance, induction of resistance in non-tuberculous mycobacteria, cardiovascular effects, and drug–drug interactions.[8] The results of safety evaluation of the three trials[14–16] included in our meta-analysis are extensively reported in the primary publications and subsequent meta-analyses, hence were not the focus of this manuscript. However, the trend to decreased quality of life in younger patients (<50 years) and in those with non-frequent exacerbations (one to two per year), might be a reflection of increased number of side effects in these particular subgroups, which would be consistent with our clinical experience. In each individual patient, the potential benefit should be carefully balanced against the potential long-term effect of macrolide treatment. Therefore, when making the decision to start macrolide maintenance treatment, international guidelines[7,38] recommend that protocols for monitoring of adverse effects and subsequent response evaluation should be in place, aimed at detection of cardiotoxity, ototoxicity, and hepatotoxicity. Recent guidelines[38] recommend to withhold macrolide treatment until active non-tuberculous mycobacteria infection has been excluded and in patients with evidence of a long QT interval on electrocardiogram. The longest trial identified in our search was 12 months and the efficacy and safety of macrolides beyond 12 months is unknown. Ideally, a future RCT should be sufficiently large to prospectively validate some of the responder subgroups identified in this meta-analysis and should have sufficiently long follow-up to establish long-term efficacy and safety.

In conclusion, macrolides significantly reduced the frequency of exacerbations in bronchiectasis, prolonged the time to next exacerbation, and improved quality of life. They did not improve FEV_1. A reduction in the frequency of exacerbations was evident across all patient subgroups, including some patient populations (such as those with *P aeruginosa* infection) for whom current guidelines do not recommend macrolides as first-line treatment.

For the **2019 European Medicines Agency guidance** see https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-confirmatory-clinical-trials_en.pdf

Contributors

JDC, WB, ML, SLT, CW, and JA designed the study. JDC, MLC, and JA searched the literature. WB, LJ, MLC, NK, MLM, LDB, CW, and JA collected the data. JDC, ML, MLC, and JA analysed the data. JDC, WB, ML, SLT, CW, and JA interpreted the data. JDC, ML, and JA wrote the manuscript draft. All authors revised the manuscript and approved it for submission.

Declaration of interests

JDC reports grants and personal fees from Glaxosmithkline, Boehringer-Ingelheim, Astrazeneca, Pfizer, Bayer Healthcare, Grifols, Napp, Aradigm corporation, and Insmed outside of the submitted work. All other authors declare no competing interests.

Acknowledgments

This study was funded by the European Respiratory Society through the EMBARC2 consortium. EMBARC2 is supported by project partners Chiesi, Grifols, Insmed, Novartis, and Zambon. JDC is supported by the GSK/British Lung Foundation Chair of Respiratory Research. The BAT study was funded by Foreest Medical School and an unrestricted grant from GlaxoSmithKline. The BLESS study was funded by the Mater Adult Respiratory Research Trust Fund. The EMBRACE study was funded by the Health Research Council of New Zealand and the Auckland District Health Board Charitable Trust.

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