Author(s):
Date:
Question: Macrolide treatment compared to standard care in asthma affect microbiology
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	macrolide treatment	standard care	Relative (95% CI)	Absolute (95% CI)		
Number of organisms resistant to azithromycin in sputum AMAZES 2017 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	19/39 (48.7%)	12/42 (28.6%)	not estimable		⨁⨁⨁⨁ HIGH	
Chlamydia pneumoniae IgG antibiody titres (follow up: range 6 weeks to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	105	112	-	MD **4 lower** (0 to 0)	⨁⨁⨁⨁ HIGH	

CI: Confidence interval; **MD:** Mean difference

Author(s):
Date:
Question: Macrolides compared to standard care for Asthma
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolides	standard care	Relative (95% CI)	Absolute (95% CI)		
steroid reduction(dichotomous) Evans et al. Cochrane review of trolendomycin 2000												
1	randomised trials	not serious	not serious	not serious	not serious		4/6 (66.7%)	4/5 (80.0%)	not estimable	**1 more per 1,000** (from 0 more to 7 more)	-	IMPORTANT
symptom score: Shoji 1999 roxithromycin (follow up: 8 weeks; assessed with: Oosaki symptom score 0-3; Scale from: 0 to 3)												
1	randomised trials						14	14	-	mean **0.76 lower** (0 to 0)	-	IMPORTANT

CI: Confidence interval

Author(s):
Date:
Question: Macrolides compared to standard care for exacerbation reduction in asthma
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	macrolides	standard care	Relative (95% CI)	Absolute (95% CI)		
Exacerbations requiring hospitalisation Kew et al. 2016 Cochrane Review OR 0.98(0.13-7.23) (follow up: range 4 weeks to 52 weeks)												
2 [1,2]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	2/72 (2.8%)	2/71 (2.8%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Severe Exacerbations requiring OCS Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)												
5 [1,2,3,4,5]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	31/158 (19.6%)	32/132 (24.2%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Exacerbations Evans et al. 2000 Cochrane review troleandomycin (follow up: range 12 weeks to 12 weeks)												
1 [6]	randomised trials	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	6	5	-	MD **7 higher** (50.65 lower to 64.65 higher)	⨁⨁⨁⨁ HIGH	
Exacerbation rate in all participants Bruselle et al. AZISAST study 2013 (follow up: range 26 weeks to 26 weeks)												
1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	55	54	-	**0.92 lower** (0.6 higher to 1.4 higher)	⨁⨁⨁⨁ HIGH	
Severe Exacerbation rate in all participants Bruselle et al. AZISAST study 2013 (follow up: range 26 weeks to 26 weeks)												
1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	55	54	-	Ratio **1.05 lower** (0.63 higher to 1.76 higher)	⨁⨁⨁⨁ HIGH	
Exacerbation rate in severe non-eosinophilic asthma Bruselle et al. AZISAST study 2013 (follow up: range 26 weeks to 26 weeks)												

1 [1]	randomised trials	not serious	not serious	not serious	not serious	none	27	29	-	RR **0.54 fewer** (0.29 fewer to 0.88 fewer)	⨁⨁⨁⨁ HIGH	

Exacerbations AMAZES 2017 (follow up: range 48 weeks to 48 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	213	207	-	IRR **0.59 lower** (0.47 lower to 0.74 lower)	⨁⨁⨁⨁ HIGH	

Exacerbations in non-eosinophilic asthma AMAZES 2017 (follow up: range 48 weeks to 48 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	224		-	IRR **0.66 lower** (0.47 lower to 0.93 lower)	⨁⨁⨁⨁ HIGH	

Exacerbations in eosinophilic asthma AMAZES 2017 (follow up: range 48 weeks to 48 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	196		-	IRR **0.52 lower** (0.29 lower to 0.94 lower)	⨁⨁⨁⨁ HIGH	

Exacerbations in frequent exacerbators AMAZES 2017 (follow up: range 48 weeks to 48 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	140		-	IRR **0.55 lower** (0.41 lower to 0.73 lower)	⨁⨁⨁⨁ HIGH	

Exacerbations in bacteria positive AMAZES 2017 (follow up: range 48 weeks to 48 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	48		-	IRR **0.39 lower** (0.22 lower to 0.69 lower)	⨁⨁⨁⨁ HIGH	

Exacerbations in bacteria negative AMAZES 2017 (follow up: range 48 weeks to 48 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	188		-	IRR **0.61 lower** (0.52 lower to 0.72 lower)	⨁⨁⨁⨁ HIGH	

Severe Exacerbations in non-eosinophilic asthma AMAZES 2017 (follow up: range 48 weeks to 48 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	213	203	-	IRR **0.59 lower** (0.42 lower to 0.83 lower)	⨁⨁⨁⨁ HIGH	

Antibiotic courses for RTI AMAZES 2017 (follow up: range 48 weeks to 48 weeks)

1	randomised trials	not serious	not serious	not serious	not serious		36/213 (16.9%)	64/203 (31.5%)	not estimable		-	

CI: Confidence interval; **MD:** Mean difference

Explanations

a. overall evidence quality very low, high risk of publication bias, inconsistencies in results and indirectness, selective reporting

References

1. al., Bruselle,et. Azithromycin for prevention of exacerbations in severe asthma(AZISAST): A multi-centre randomised double blind placebo controlled trial . Thorax; 2013.
2. al., Amayasu,et. Clarithromycin reduces Bronchial Hyperresponsiveness associated with eosinophilic inflammation in patients with asthma. Annals of Allergy, Asthma and Immunology; 2000.
3. al., Hahn,D,et. Azithromycin for bronchial asthma in adults: an effectiveness trial. Journal of the American Board of Family Medicine; 2012.
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6. al., Kamada,A,et. Efficacy and safety of low-dose troleandomycin therapy in children with severe, steroid-requiring asthma.. Journal of Allergy and Clinical Immunology; 1993.

Author(s):
Date:
Question: Macrolides compared to standard care for lung function improvement in asthma
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	macrolides	standard care	Relative (95% CI)	Absolute (95% CI)		
FEV1(L) (Amayasu et al.200) (follow up: range 8 weeks to 8 weeks)												
1 [1]	randomised trials	not serious	not serious	very serious	not serious	all plausible residual confounding would reduce the demonstrated effect	17	17	-	MD **0.01 l lower** (1.77 lower to 1.75 higher)	⨁⨁⨁◯ MODERATE	
FEV1 (% predicted)(Coeman et al.) Retrospective Observational Cohort (Follow up 3-8 weeks) (follow up: range 3 weeks to 8 weeks)												
1	observational studies	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect dose response gradient	14	47	-	7% **0 %** (0 to 0)	⨁◯◯◯ VERY LOW	
FEV1(l) (Gotfried et al. 2004) (follow up: range 14 weeks to 14 weeks)												
1	observational studies	very serious [b]	very serious [b]	very serious [b]	very serious [b]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	14	0	-	MD **0.04 l higher** (0 to 0)	⨁◯◯◯ VERY LOW	
FEV1 Evans et al. Cochrane review of Troleomycin 2000 (follow up: range 2 weeks to 12 weeks)												
3 [2,3]	randomised trials	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	11	10	-	SMD **0.06 SD higher** (0.8 lower to 0.92 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
FEV1 kew et al. Cochrane review 2016 (follow up: range 4 weeks to 52 weeks)												
9 [1,4,5,6,7,8,9,10,11]	randomised trials	serious [c]	serious [c]	serious [c]	serious [c]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	318	313	-	MD **0.08 L higher** (0.02 higher to 0.14 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Morning PEFR Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)

4 [2,4,8,12]	randomised trials	serious [c]	serious [c]	serious [c]	serious [c]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	147	142	-	MD **2.22 L/Min higher** (9.73 lower to 14.17 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Evening PEFR Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)

3 [2,8,12]	randomised trials	serious [c]	serious [c]	serious [c]	serious [c]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	108	104	-	MD **1.97 l/min higher** (12.68 lower to 16.62 higher)	⨁◯◯◯ VERY LOW	

PEFR Gotfried et al. 2004 (follow up: range 14 weeks to 14 weeks)

1	observational studies	very serious [a]	very serious	very serious [a]	very serious [a]		14	0	-	MD **19.43 l/s higher** (0 to 0)	-	

FEV1(%predicted) Arm A Clarithromycin 250mg BD Kostadima et al. 2004 (follow up: range 8 weeks to 8 weeks)

1 [13]	randomised trials	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	22	21	-	MD **2 % lower** (0 to 0)	⨁⨁⨁⨁ HIGH	

FEV1(%predicted) Arm B Clarithromycin 250mg TDS Kostadima et al. 2004 (follow up: range 8 weeks to 8 weeks)

1 [13]	randomised trials	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	20	21	-	**1 % higher** (0 to 0)	⨁⨁⨁⨁ HIGH	

FEV1 Bruselle et al. AZISAST study 2013 (pre-BD) (follow up: range 26 weeks to 26 weeks)

1 [12]	randomised trials	not serious	not serious	not serious	not serious	none	55	54	-	MD **0.88 %pred higher** (3.44 lower to 5.19 higher)	⨁⨁⨁⨁ HIGH	
Morning PEFR Bruselle et al. AZISAST study 2013 (follow up: range 26 weeks to 26 weeks)												
1 [12]	randomised trials	not serious	not serious	not serious	not serious	none	55	54	-	MD **3.96 higher** (15.4 lower to 23.32 higher)	⨁⨁⨁⨁ HIGH	
Evening PEFR Bruselle et al. AZISAST study 2013 (follow up: range 26 weeks to 26 weeks)												
1 [12]	randomised trials	not serious	not serious	not serious	not serious	none	55	54	-	MD **3.84 higher** (23.1 lower to 30.78 higher)	⨁⨁⨁⨁ HIGH	
FEV1 Sutherland 2010 RCT of clarithromycin vs placebo all partcipants (follow up: range 16 weeks to 16 weeks)												
1 [8]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	47	45	-	MD **0.1 % higher** (1.6 lower to 1.6 higher)	⨁⨁◯◯ LOW	
FEV1 Sutherland 2010 RCT of clarithromycin vs placebo PCR positive (follow up: range 16 weeks to 16 weeks)												
1 [8]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	6	6	-	MD **1 %pred higher** (3.9 lower to 3.9 higher)	⨁⨁◯◯ LOW	
FEV1 Sutherland 2010 RCT of clarithromycin vs placebo PCR negative (follow up: range 16 weeks to 16 weeks)												
1 [8]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	41	39	-	MD **0.2 %pred higher** (1.8 lower to 1.8 higher)	⨁⨁◯◯ LOW	
Morning PEFR Sutherland 2010 RCT of clarithromycin vs placebo (follow up: range 15 weeks to 16 weeks)												
1 [8]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	47	45	-	MD **2.4 SD more** (8.6 more to 0)	⨁⨁◯◯ LOW	
Evening PEFR Sutherland 2010 RCT of clarithromycin vs placebo (follow up: range 16 weeks to 16 weeks)												

1 [8]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	47	45	-	**0.8 sd higher** (9 higher to 0)	⨁⨁◯◯ LOW	
Morning PEFR Sutherland 2010 RCT of clarithromycin vs placebo PCR positive (follow up: range 16 weeks to 16 weeks)												
1 [8]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	41	39	-	MD **9.3 lower** (10.8 higher to 0)	⨁⨁◯◯ LOW	
Morning PEFR Sutherland 2010 RCT of clarithromycin vs placebo PCR negative (follow up: range 16 weeks to 16 weeks)												
1 [8]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	6	6	-	**3.4 higher** (6.4 higher to 0)	⨁⨁◯◯ LOW	
evening PEFR Sutherland 2010 RCT of clarithromycin vs placebo PCR positive (follow up: range 16 weeks to 16 weeks)												
1 [8]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	6	6	-	**1.8 lower** (13 higher to 0)	⨁⨁◯◯ LOW	
evening PEFR Sutherland 2010 RCT of clarithromycin vs placebo PCR negative (follow up: range 16 weeks to 16 weeks)												
1 [8]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	41	39	-	**0.3 lower** (6.6 higher to 0)	⨁⨁◯◯ LOW	
FEV1(L) Shoji et al. 1999 Roxithromycin vs placebo (follow up: range 8 weeks to 8 weeks)												
1 [7]	randomised trials	not serious	not serious	not serious	not serious	none	14	14	-	MD **0.12 higher** (0 to 0)	⨁⨁⨁⨁ HIGH	
FEV1 (% predicted)Simpson et al. 2008 clarithromycin vs placebo (follow up: range 8 weeks to 8 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	23	23	-	MD **0.4 lower** (0 to 0)	⨁⨁⨁⨁ HIGH	
FEV1(?L) Reiter et al. meta-analysis 2013												
8 [1,6,7,8,13,14,15]	randomised trials	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	381		-	SMD **0.05 SD lower** (0.14 lower to 0.25 lower)	⨁⨁⨁⨁ HIGH	
PEFR Reiter et al. meta-analysis 2013 (Children and adults) (follow up: range 3 to 26 weeks)												

4 [2,8,12,16]	randomised trials	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	419		-	MD **6.7 higher** (1.35 higher to 12.06 higher)	⊕⊕⊕⊕ HIGH	

PEFR in adults Reiter et al. meta-analysis 2013 (follow up: range 3 weeks to 26 weeks)

3 [8,12,16]	randomised trials	not serious	not serious	not serious	not serious	none			-	MD **6.68 higher** (1.32 higher to 12.04 higher)	⊕⊕⊕⊕ HIGH	

FEV1(L) Tong et al. 2015 meta-analysis

9 [1,4,5,6,7,8,9,10,11]	randomised trials	not serious	not serious	not serious	not serious	none	619		-	MD **0.11 higher** (0.06 higher to 0.16 higher)	⊕⊕⊕⊕ HIGH	

FEV1 (%Predicted) Tong et al. 2015 meta-analysis

8 [8,9,10,11,12,13,14]	randomised trials	not serious	not serious	not serious	not serious	none	435		-	SMD **0.27 SD higher** (0.05 lower to 0.59 higher)	⊕⊕⊕⊕ HIGH	

PEFR Tong et al. 2015 meta-analysis

7 [4,8,9,10,11,12,16]	randomised trials	not serious	not serious	not serious	not serious	none	786		-	SMD **0.25 SD higher** (0.1 higher to 0.39 higher)	⊕⊕⊕⊕ HIGH	

FEV1 (%predicted) Gotfried et al. 2004

1	observational studies	very serious	very serious [a]	very serious [a]	very serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	14		-	**7.3 % higher** (0 to 0)	⊕◯◯◯ VERY LOW	

Morning PEFR Black et al. 2001 Roxithromycin vs placebo (follow up: range 6 weeks to 6 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	105	114	-	MD **6 l/min higher** (0 to 0)	⊕⊕⊕⊕ HIGH	

Evening PEFR Black et al. 2001 (follow up: range 6 weeks to 6 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	105	114	-	MD **12 l/min higher** (0 to 0)	⨁⨁⨁⨁ HIGH	

Cameron et al. ERJ Morning PEFR 12 weeks Azithromycin 250mg (follow up: range 12 weeks to 12 weeks)

1 [17]	randomised trials	not serious	not serious	not serious	not serious	none			-	MD **10.3 lower** (47.1 lower to 26.4 lower)	⨁⨁⨁⨁ HIGH	

Cameron et al. ERJ FEV1 12 weeks Azithromycin 250mg (follow up: range 12 weeks to 12 weeks) (follow up: 12 weeks)

1 [17]	randomised trials	not serious	not serious	not serious	not serious	none			-	MD **0.03 higher** (0.08 lower to 0.14 higher)	⨁⨁⨁⨁ HIGH	

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference

Explanations

a. retrospective observational study, no blinding and unclear how participants selected or followed up. No given
b. Planned as RCT but analysed as before/after, stopped early due to poor enrolment, clear bias from authors, off protocol analysis
c. considerable uncertainty relating to study methodology, incomplete and selective reporting of results, high risk of publication bias
d. Planned to randomise 1:1 based on PCR positivity but insufficient PCR positive patients so major protocol change and much lower recuitment than planned

References

1. al., Amayasu,et. Clarithromycin reduces Bronchial Hyperresponsiveness associated with eosinophilic inflammation in patients with asthma. Annals of Allergy, Asthma and Immunology; 2000.
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17. al., Cameron,E,et. Randomised Controlled Trial of azithromycin in smokers with asthma. ERJ; 2013.

Author(s):
Date:
Question: Macrolides compared to standard care for reducing bronchial hyper-responsiveness in asthma
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	macrolides	standard care	Relative (95% CI)	Absolute (95% CI)		
Methacholine challenge test log PC20 Amayasu et al. 2000												
1 [1]	randomised trials	very serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	17	17	-	MD **0.36 SD higher** (0.57 higher to 0)	⨁⨁◯◯ LOW	
PD20 Arm A 250mg BD (methacholine challenge) Kostadima et al. ERJ 2004 (follow up: range 8 weeks to 8 weeks)												
1 [2]	randomised trials	very serious	not serious	not serious	not serious	publication bias strongly suspected dose response gradient	22	21	-	MD **1 higher** (0.5 higher to 1.9 higher)	⨁⨁◯◯ LOW	
PD20 ARM B 250mg TDS Kostadima et al. 2004 (follow up: range 8 weeks to 8 weeks)												
1 [2]	randomised trials	serious	not serious	not serious	not serious	publication bias strongly suspected dose response gradient	20	21	-	MD **1.6 higher** (1.1 higher to 1.9 higher)	⨁⨁⨁◯ MODERATE	
PC20 Methacholine Challenge Sutherland et al. 2010 PCR negative for M/C.pneumoniae (follow up: range 13 weeks to 13 weeks)												
1 [3]	randomised trials	serious [a]	not serious	not serious	not serious	none	6	6	-	MD **1.2 higher** (0.7 higher to 1.7 higher)	⨁⨁⨁◯ MODERATE	
PC20 Methacholine Challenge Sutherland et al. 2010 PCR positive for M/C.pneumoniae (follow up: range 13 weeks to 13 weeks)												
1 [3]	randomised trials	serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	41	39	-	MD **1.2 higher** (0.8 higher to 1.7 higher)	⨁⨁⨁◯ MODERATE	
PC20 Methacholine Challenge Sutherland et al. 2010 all participants (follow up: range 16 weeks to 16 weeks)												

1 [3]	randomised trials	serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	47	45	-	MD **1.2 higher** (0.8 higher to 1.7 higher)	⨁⨁⨁◯ MODERATE	

pc20 sulpyrine shoji et al. 1999 (follow up: range 8 weeks to 8 weeks)

1 [4]	randomised trials	very serious [b]	not serious	not serious	not serious	publication bias strongly suspected	14	14	-	**0.03 higher** (0 to 0)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **MD:** Mean difference

Explanations

a. secondary exploratory outcome
b. small japanese study with treatment-naive patients

References

1. al., Amayasu,et. Clarithromycin reduces Bronchial Hyperresponsiveness associated with eosinophilic inflammation in patients with asthma. Annals of Allergy, Asthma and Immunology; 2000.
2. al., Kostadima,E,et. Clairthomycin reduces the severity of bronchial hyperresponsiveness in patients with asthma. ERJ; 2004.
3. al., Sutherland,et. A trial of clarithromycin for the treatment of suboptimally controlled asthma. The journal of allergy and clinical immunology; 2010.
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Author(s):
Date:
Question: Macrolides compared to standard care for reducing markers of inflammation in asthma
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	macrolides	standard care	Relative (95% CI)	Absolute (95% CI)		
Blood eosinophils Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)												
2 [1,2]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	31	31	-	MD **35.5 lower** (36.11 lower to 30.9 lower)	⨁◯◯◯ VERY LOW	
Sputum Eosinophils Kew et al. 2016 Cochrane Review (Unable to pool results due to contrasting results) (follow up: range 4 weeks to 52 weeks)												
3 [1,2,3]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	31	31	-	**0** (0 to 0)	⨁◯◯◯ VERY LOW	
ECP in serum Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)												
2 [1,2]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	31	31	-	MD **12.84 lower** (15.67 lower to 10 lower)	⨁◯◯◯ VERY LOW	
ECP in sputum Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)												
2 [1,2]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	31	31	-	MD **1.45 lower** (1.78 lower to 1.11 lower)	⨁◯◯◯ VERY LOW	
Blood Eosinophils Amayasu et al. 2000 (follow up: range 16 weeks to 16 weeks)												
1 [2]	randomised trials	very serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [b]	17	17	-	MD **33.3 lower** (0 to 0)	⨁⨁◯◯ LOW	

Sputum Eosinophils Amayasu et al. 2000 (follow up: range 16 weeks to 16 weeks)

1 [2]	randomised trials	very serious	not serious	not serious	not serious	publication bias strongly suspected strong association	17	17	-	MD **74 lower** (0 to 0)	⨁⨁◯◯ LOW	

Serum ECP Amayasu et al. 2000 (follow up: range 16 weeks to 16 weeks)

1 [2]	randomised trials	very serious	not serious	not serious	not serious	publication bias strongly suspected strong association	17	17	-	MD **10.1 lower** (0 to 0)	⨁⨁◯◯ LOW	

Sputum ECP Amayasu et al. 2000 (follow up: range 16 weeks to 16 weeks)

1 [2]	randomised trials	very serious	not serious	not serious	not serious	publication bias strongly suspected	17	17	-	MD **1.1 lower** (0 to 0)	⨁◯◯◯ VERY LOW	

FeNO Bruselle et al. AZISAST study 2013 (follow up: range 26 weeks to 26 weeks)

1 [4]	randomised trials	not serious	not serious	not serious	very serious [c]	none	55	54	-	MD **1.6 lower** (0 to 0)	⨁⨁◯◯ LOW	

FeNO Sutherland et al. clarithromycin versus Placebo (follow up: range 16 weeks to 16 weeks)

1 [5]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	47	45	-	**4.6 lower** (4.2 higher to 0)	⨁⨁◯◯ LOW	

FeNO Sutherland et al. clarithromycin versus Placebo PCR positive (follow up: range 16 weeks to 16 weeks)

1 [5]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	6	6	-	**11.4 lower** (11.9 higher to 0)	⨁⨁◯◯ LOW	

FeNO Sutherland et al. clarithromycin versus Placebo PCR negative (follow up: range 16 weeks to 16 weeks)

1 [5]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	41	39	-	**3.4 lower** (4.5 higher to 0)	⨁⨁◯◯ LOW	

Serum eosinophils Shoji et al. 1999 roxithromycin vs placebo (follow up: range 8 weeks to 8 weeks)

1 [1]	randomised trials	very serious [e]	not serious	not serious	not serious	publication bias strongly suspected strong association	14	14	-	**30.4 lower** (2.3 higher to 0)	⨁⨁◯◯ LOW	

serum ECP Shoji et al. 1999 Roxithromycin vs placebo (follow up: range 8 weeks to 8 weeks)

1 [1]	randomised trials	very serious	not serious	not serious	not serious	publication bias strongly suspected strong association	14	14	-	MD **11.2 lower** (1.4 higher to 0)	⨁⨁◯◯ LOW	

Sputum Eosinophils Shoji et al. 1999 Roxithromycin vs placebo (follow up: range 8 weeks to 8 weeks)

1 [1]	randomised trials	very serious	not serious	not serious	not serious	publication bias strongly suspected strong association	14	14	-	**80 higher** (6 higher to 0)	⨁⨁◯◯ LOW	

sputum ecp shoji et al. 1999 roxithromycin vs placebo (follow up: range 8 weeks to 8 weeks)

1 [1]	randomised trials	very serious	not serious	not serious	not serious	publication bias strongly suspected	14	14	-	**1.3 lower** (0.1 higher to 0)	⨁◯◯◯ VERY LOW	

Sputum IL-8 protein Simpson et al. 2008 clarithromycin vs placebo (follow up: range 8 weeks to 8 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected	23	23	-	median **2.7 lower** (0 to 0)	⨁⨁⨁◯ MODERATE	

Sputum Neutrophil Elastase Simpson et al. 2008 clarithromycin vs placebo (follow up: range 8 weeks to 8 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected	23	23	-	median **223.2 lower** (0 to 0)	⨁⨁⨁◯ MODERATE	

MMP=9 (follow up: range 8 weeks to 8 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected	23	23	-	median **4812 lower** (0 to 0)	⨁⨁⨁◯ MODERATE	

									not estimable		-	

Sputum Neutrophils Simpson et al. 2008 clarithromycin vs placebo (follow up: range 8 weeks to 8 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected	23	23	-	median **76.2 lower** (0 to 0)	⨁⨁⨁◯ MODERATE	

Sputum Neutrophils Shoji et al. 1999 roxithromycin vs placebo (follow up: range 8 weeks to 8 weeks)

1 [1]	randomised trials	very serious	not serious	not serious	not serious	publication bias strongly suspected	14	14	-	mean **74 lower** (0 to 0)	⨁◯◯◯ VERY LOW	

sputum IL-8 protein in non-eosinophilic asthma(NEA) Simpson et al. 2008 (follow up: range 8 weeks to 8 weeks)

1	randomised trials	serious [f]	not serious	not serious	not serious	publication bias strongly suspected	14	14	-	median **3.2 lower** (0 to 0)	⨁⨁◯◯ LOW	

sputum neutrophil elastase Simpson et al. 2008 Non-eosinophilic asthma (follow up: range 8 weeks to 8 weeks)

1	randomised trials	serious	not serious	not serious	not serious	publication bias strongly suspected	14	14	-	median **207.4 lower** (0 to 0)	⨁⨁◯◯ LOW	

sputum MMP-9 Simpson et al. 2008 Non-eosinophilic asthma (follow up: range 8 weeks to 8 weeks)

1	randomised trials	serious	not serious	not serious	not serious	publication bias strongly suspected	14	14	-	median **5928 lower** (0 to 0)	⨁⨁◯◯ LOW	

sputum neutrophils Simpson et al. 2008 Non-eosinophilic asthma (follow up: range 8 weeks to 8 weeks)

1	randomised trials	serious	not serious	not serious	not serious	publication bias strongly suspected			-	median **40 lower** (0 to 0)	⨁⨁◯◯ LOW	

Sputum Neutrophil Count Cameron et al. ERJ 12 weeks Azithromycin 250mg (follow up: range 12 weeks to 12 weeks) (follow up: 12 weeks)

1 [6]	randomised trials	serious [g]	not serious	not serious	not serious	publication bias strongly suspected			-	MD **19.2 higher** (24.2 lower to 62.6 higher)	⨁⨁◯◯ LOW	

Sputum Eosinophil Count Cameron et al. ERJ 12 weeks Azithromycin 250mg (follow up: range 12 weeks to 12 weeks) (follow up: 12 weeks)

1 [6]	randomised trials	serious	not serious	not serious	not serious	publication bias strongly suspected			-	MD **1 higher** (0.5 higher to 2 higher)	⨁⨁◯◯ LOW	

FeNo Cameron et al. 2013 ERJ Azithromycin 250mg 12 weeks (follow up: 12 weeks)

1 [6]	randomised trials	serious	not serious	not serious	not serious	publication bias strongly suspected			-	**1.94 lower** (5.97 lower to 2.1 higher)	⨁⨁◯◯ LOW	

CI: Confidence interval; **MD:** Mean difference

Explanations

a. indirectness and inconsistency across studies, selective reporting and high risk of publication bias
b. crossover study of 17 treatment-naive Japanese patients (SABA only).
c. secondary endpoint. not powered. baseline FeNO 18 ppb (i.e. low on average)
d. Planned to randomise 1:1 based on PCR positivity but insufficient PCR positive patients so major protocol change and much lower recuitment than planned
e. crossover study of 14 japanese treatment-naive patients. Same research group as amayasu et al
f. subgroup analysis
g. smokers only

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6. al., Cameron,E,et. Randomised Controlled Trial of azithromycin in smokers with asthma. ERJ; 2013.

Author(s):
Date:
Question: Macrolides compared to standard care for steroid reduction in asthma
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	macrolides	standard care	Relative (95% CI)	Absolute (95% CI)		
Steroid Reduction Evans et al. 2000 Troleandomycin Cochrane Review (follow up: range 2 weeks to 52 weeks)												
3 [1,2,3]	randomised trials	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	40	37	-	SMD **0.29 SD lower** (0.75 lower to 0.17 higher)	⨁⨁⨁⨁ HIGH	
steroid reduction Kew et al. 2016 Cochrane review (results not pooled as not comparable)												
1 [2]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect			-	MD **6.6 lower** (11.88 lower to 1.32 lower)	⨁◯◯◯ VERY LOW	
Steroid reduction Kew et al. 2016 Cochrane Review (results not pooled as not comparable)												
1 [1]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	29	27	-	MD **4.1 lower** (7.7 lower to 0.5 lower)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. publication bias, inconsistency and indirectness across trials, selective reporting

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2. al., Kamada,A,et. Efficacy and safety of low-dose troleandomycin therapy in children with severe, steroid-requiring asthma.. Journal of Allergy and Clinical Immunology; 1993.
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Author(s):
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Question: Macrolides compared to standard care for symptom reduction in asthma
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	macrolides	standard care	Relative (95% CI)	Absolute (95% CI)		
Symptom scale reduction Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)												
4 [1,2,3,4]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	80	76	-	SMD **0.35 SD lower** (0.67 lower to 0.02 lower)	⨁◯◯◯ VERY LOW	
Asthma Control Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)												
4 [2,5,6,7]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	179	174	-	SMD **0.05 SD lower** (0.26 lower to 0.15 higher)	⨁◯◯◯ VERY LOW	
Symptom Score(unique 5 point scale) Gotfried et al. 2004 (follow up: range 14 weeks to 14 weeks)												
1	observational studies	very serious [b]	very serious [b]	very serious [b]	very serious [b]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	14	0	-	MD **0.49 lower** (0 to 0)	⨁◯◯◯ VERY LOW	
Symptom score Coeman et al. 2011 (unique score 0-8) (follow up: range 3 weeks to 8 weeks)												
1	observational studies	serious [c]	serious [c]	serious [c]	serious [c]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	131	0	-	-58% **0** (0 to 0)	⨁◯◯◯ VERY LOW	
Symptom reduction Evans et al, Cochrane review Troleoandomycin 2000 (follow up: range 12 weeks to 12 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	6	5	-	MD **0.1 lower** (1.16 lower to 0.96 higher)	⨁⨁⨁⨁ HIGH	

symptom score Amayasu et al. 2000 (Unique score) (follow up: range 16 weeks to 16 weeks)

1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	17	17	-	MD **0.75 lower** (0 to 0)	⨁⨁⨁⨁ HIGH	

ACQ score Bruselle et al. AZISAST study 2013 (follow up: range 26 weeks to 26 weeks)

1 [5]	randomised trials	not serious	not serious	not serious	not serious	none	55	54	-	MD **0.12 lower** (0.44 lower to 0.21 higher)	⨁⨁⨁⨁ HIGH	

ACQ Asthma control score: Sutherland 2010 RCT of clarithromycin vs placebo (follow up: 16 weeks; assessed with: ACQ score; Scale from: 0 to 7) (follow up: range 16 weeks to 16 weeks)

1 [6]	randomised trials	not serious	serious [d]	not serious	serious [d]	all plausible residual confounding would reduce the demonstrated effect	47	45	-	MD **0.2 lower** (0.2 lower to 0.2 higher)	⨁⨁⨁◯ MODERATE	

ACQ Asthma control score: Sutherland 2010 RCT of clarithromycin vs placebo - PCR Positive for M/C.pneumoniae (follow up: range 16 weeks to 16 weeks)

1 [6]	randomised trials	not serious	serious [d]	not serious	serious [d]	all plausible residual confounding would reduce the demonstrated effect	6	6	-	MD **0.2 lower** (0.2 lower to 0.4 lower)	⨁⨁⨁◯ MODERATE	

ACQ Asthma control score: Sutherland 2010 RCT of clarithromycin vs placebo - PCR negative for M/C.pneumoniae (follow up: range 16 weeks to 16 weeks)

1 [6]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	41	39	-	MD **0.3 lower** (0 to 0.8 lower)	⨁⨁◯◯ LOW	

Symptom score (unique scale 0-4) shoji et al. 1999 roxithromycin vs placebo (follow up: range 8 weeks to 8 weeks)

1 [8]	randomised trials	not serious	not serious	not serious	not serious	none	14	14	-	**0.76 lower** (0 to 0)	⨁⨁⨁⨁ HIGH	

ACQ: Simpson 2008 (follow up: 8 weeks; assessed with: ACQ Juniper; Scale from: 1 to 7) (follow up: range 8 weeks to 8 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	23	23	-	median **0.2 lower** (0 to 0)	⨁⨁⨁⨁ HIGH	

Pooled Symptom scores Reiter et al. 2013 meta-analysis

8 [1,2,3,4,5,6,8,9]	randomised trials	not serious	serious [e]	not serious	serious [e]	all plausible residual confounding would suggest spurious effect, while no effect was observed	478	0	-	MD **0.46 lower** (0.6 lower to 0.32 lower)	⨁⨁⨁◯ MODERATE	
pooled symptom scores Tong et al. 2015 meta-analysis												
11 [1,2,3,5,6,7,8,9,10,11,12]	randomised trials	not serious	not serious	not serious	not serious	none	582	0	-	**0.24 lower** (0.64 lower to 0.16 higher)	⨁⨁⨁⨁ HIGH	
ACQ6 Score AMAZES 2017 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	213	207	-	MD **0.2 lower** (0.34 lower to 0.05 lower)	⨁⨁⨁⨁ HIGH	
Daytime Symptom Score (Unique to study) Black et al. 2001 (follow up: range 6 weeks to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	105	112	-	MD **11 % higher** (0 to 0)	⨁⨁⨁⨁ HIGH	
Nighttime symptoms score (unique to study) Black et al. 2001 (follow up: range 6 weeks to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	105	112	-	MD **12.5 % higher** (0 to 0)	⨁⨁⨁⨁ HIGH	
Symptoms Score (Unique to study) Hahn et al. 2012 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	serious [f]	not serious	serious [f]	none	38	37	-	MD **0.03 lower** (0 to 0)	⨁⨁◯◯ LOW	
ACS Open label Azithromycin group Hahn et al. 2012 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	serious [f]	not serious	serious [f]	none	0	0	-	1.2 **0** (0 to 0)	⨁⨁◯◯ LOW	
Symptom score (likert scale) Hahn et al. 2006 (follow up: range 6 weeks to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	19	17	-	**0.68 higher** (0.05 higher to 1.29 higher)	⨁⨁⨁⨁ HIGH	
ACQ Cameron et al. ERJ 12 weeks Azithromycin 250mg (follow up: range 12 weeks to 12 weeks) (follow up: 12 weeks)												

1 [13]	randomised trials	not serious	not serious	not serious	not serious	none	0	0	-	MD **0.21 higher** (0.11 lower to 0.53 higher)	⨁⨁⨁⨁ HIGH	

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Publication bias, very low quality of evidence, selective reporting, inconsistency and indirectness
b. Clear bias, Planned as RCT but analysed as before/after - off protocol analysis, stopped early due to poor recruitment
c. retrospective observational cohort study, unclear how participants recruited or followed up, variable treatment regimes
d. Planned to randomise 1:1 based on PCR positivity but insufficient PCR positive patients so major protocol change and much lower recuitment than planned
e. Variable symptom scoring systems, studies reporting change from baseline were homogeneous ; studeis reporting final scores were heterogenous; parallel study designs showed no significance but cross-over designs did show significance
f. Combination of RCT with Open label arm as under-recruiting, under-powered

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Author(s):
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Question: Macrolides compared to standard care for symptom reduction in asthma
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	macrolides	standard care	Relative (95% CI)	Absolute (95% CI)		
Symptom scale reduction Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)												
4 [1,2,3,4]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	80	76	-	SMD **0.35 SD lower** (0.67 lower to 0.02 lower)	⨁◯◯◯ VERY LOW	
Asthma Control Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)												
4 [2,5,6,7]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	179	174	-	SMD **0.05 SD lower** (0.26 lower to 0.15 higher)	⨁◯◯◯ VERY LOW	
Symptom Score(unique 5 point scale) Gotfried et al. 2004 (follow up: range 14 weeks to 14 weeks)												
1	observational studies	very serious [b]	very serious [b]	very serious [b]	very serious [b]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	14	0	-	MD **0.49 lower** (0 to 0)	⨁◯◯◯ VERY LOW	
Symptom score Coeman et al. 2011 (unique score 0-8) (follow up: range 3 weeks to 8 weeks)												
1	observational studies	serious [c]	serious [c]	serious [c]	serious [c]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	131	0	-	-58% **0** (0 to 0)	⨁◯◯◯ VERY LOW	
Symptom reduction Evans et al, Cochrane review Troleoandomycin 2000 (follow up: range 12 weeks to 12 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	6	5	-	MD **0.1 lower** (1.16 lower to 0.96 higher)	⨁⨁⨁⨁ HIGH	

symptom score Amayasu et al. 2000 (Unique score) (follow up: range 16 weeks to 16 weeks)

1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	17	17	-	MD **0.75 lower** (0 to 0)	⨁⨁⨁⨁ HIGH	

ACQ score Bruselle et al. AZISAST study 2013 (follow up: range 26 weeks to 26 weeks)

1 [5]	randomised trials	not serious	not serious	not serious	not serious	none	55	54	-	MD **0.12 lower** (0.44 lower to 0.21 higher)	⨁⨁⨁⨁ HIGH	

ACQ Asthma control score: Sutherland 2010 RCT of clarithromycin vs placebo (follow up: 16 weeks; assessed with: ACQ score; Scale from: 0 to 7) (follow up: range 16 weeks to 16 weeks)

1 [6]	randomised trials	not serious	serious [d]	not serious	serious [d]	all plausible residual confounding would reduce the demonstrated effect	47	45	-	MD **0.2 lower** (0.2 lower to 0.2 higher)	⨁⨁⨁◯ MODERATE	

ACQ Asthma control score: Sutherland 2010 RCT of clarithromycin vs placebo - PCR Positive for M/C.pneumoniae (follow up: range 16 weeks to 16 weeks)

1 [6]	randomised trials	not serious	serious [d]	not serious	serious [d]	all plausible residual confounding would reduce the demonstrated effect	6	6	-	MD **0.2 lower** (0.2 lower to 0.4 lower)	⨁⨁⨁◯ MODERATE	

ACQ Asthma control score: Sutherland 2010 RCT of clarithromycin vs placebo - PCR negative for M/C.pneumoniae (follow up: range 16 weeks to 16 weeks)

1 [6]	randomised trials	not serious	serious [d]	not serious	serious [d]	none	41	39	-	MD **0.3 lower** (0 to 0.8 lower)	⨁⨁◯◯ LOW	

Symptom score (unique scale 0-4) shoji et al. 1999 roxithromycin vs placebo (follow up: range 8 weeks to 8 weeks)

1 [8]	randomised trials	not serious	not serious	not serious	not serious	none	14	14	-	**0.76 lower** (0 to 0)	⨁⨁⨁⨁ HIGH	

ACQ: Simpson 2008 (follow up: 8 weeks; assessed with: ACQ Juniper; Scale from: 1 to 7) (follow up: range 8 weeks to 8 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	23	23	-	median **0.2 lower** (0 to 0)	⨁⨁⨁⨁ HIGH	

Pooled Symptom scores Reiter et al. 2013 meta-analysis

8 [1,2,3,4,5,6,8,9]	randomised trials	not serious	serious [e]	not serious	serious [e]	all plausible residual confounding would suggest spurious effect, while no effect was observed	478		-	MD **0.46 lower** (0.6 lower to 0.32 lower)	⨁⨁⨁◯ MODERATE	
pooled symptom scores Tong et al. 2015 meta-analysis												
11 [1,2,3,5,6,7,8,9,10,11,12]	randomised trials	not serious	not serious	not serious	not serious	none	582		-	**0.24 lower** (0.64 lower to 0.16 higher)	⨁⨁⨁⨁ HIGH	
ACQ6 Score AMAZES 2017 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	213	207	-	MD **0.2 lower** (0.34 lower to 0.05 lower)	⨁⨁⨁⨁ HIGH	
Daytime Symptom Score (Unique to study) Black et al. 2001 (follow up: range 6 weeks to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	105	112	-	MD **11 % higher** (0 to 0)	⨁⨁⨁⨁ HIGH	
Nighttime symptoms score (unique to study) Black et al. 2001 (follow up: range 6 weeks to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	105	112	-	MD **12.5 % higher** (0 to 0)	⨁⨁⨁⨁ HIGH	
Symptoms Score (Unique to study) Hahn et al. 2012 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	serious [f]	not serious	serious [f]	none	38	37	-	MD **0.03 lower** (0 to 0)	⨁⨁◯◯ LOW	
ACS Open label Azithromycin group Hahn et al. 2012 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	serious [f]	not serious	serious [f]	none			-	1.2 **0** (0 to 0)	⨁⨁◯◯ LOW	
Symptom score (likert scale) Hahn et al. 2006 (follow up: range 6 weeks to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	19	17	-	**0.68 higher** (0.05 higher to 1.29 higher)	⨁⨁⨁⨁ HIGH	
ACQ Cameron et al. ERJ 12 weeks Azithromycin 250mg (follow up: range 12 weeks to 12 weeks) (follow up: 12 weeks)												

1 [13]	randomised trials	not serious	not serious	not serious	not serious	none			-	MD **0.21 higher** (0.11 lower to 0.53 higher)	⨁⨁⨁⨁ HIGH	

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Publication bias, very low quality of evidence, selective reporting, inconsistency and indirectness
b. Clear bias, Planned as RCT but analysed as before/after - off protocol analysis, stopped early due to poor recruitment
c. retrospective observational cohort study, unclear how participants recruited or followed up, variable treatment regimes
d. Planned to randomise 1:1 based on PCR positivity but insufficient PCR positive patients so major protocol change and much lower recuitment than planned
e. Variable symptom scoring systems, studies reporting change from baseline were homogeneous ; studeis reporting final scores were heterogenous; parallel study designs showed no significance but cross-over designs did show significance
f. Combination of RCT with Open label arm as under-recruiting, under-powered

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Author(s):
Date:
Question: Macrolides compared to standard care in asthma lead to SAE
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	macrolides	standard care	Relative (95% CI)	Absolute (95% CI)		
SAE including Mortality Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)												
7	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected	221	213	-	0.80 **0 Odds ratio** (0.24 higher to 2.68 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Reported AE in Coeman et al. 2011 (rash =1, Diarrhoea =2, dysgeusia =1) (follow up: range 3 weeks to 8 weeks)												
1	observational studies	serious [b]	serious [b]	serious [b]	serious [b]		4/131 (3.1%)		not estimable		-	
AE in Gotfried et al. 2004 (Discontinued due to nausea) (follow up: range 14 weeks to 14 weeks)												
1	observational studies	very serious [c]	very serious [c]	very serious [c]	very serious [c]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	1/15 (6.7%)		not estimable		⨁◯◯◯ VERY LOW	
Nausea AE Reiter et al. 2013 meta-analysis Significantly more nausea when pooled (p=0.012); (follow up: range 3 weeks to 26 weeks)												
3 [1,2,3]	randomised trials	not serious	not serious	not serious	not serious	none			-	2.47 **0** (1.22 higher to 5 higher)	⨁⨁⨁⨁ HIGH	
reversible abnormality in LFTS whilst on macolides Reiter et al,. 2013 meta-analysis (follow up: range 3 weeks to 26 weeks)												
3 [1,3,4]	randomised trials	not serious	not serious	not serious	not serious	none			-	**0** (0 to 0)	⨁⨁⨁⨁ HIGH	
Diarrhoea AE Reiter et al. 2013 meta-analysis (follow up: range 3 weeks to 26 weeks)												
3 [1,2,3]	randomised trials	not serious	not serious	not serious	not serious	none			-	**0.93 higher** (0.53 higher to 1.61 higher)	⨁⨁⨁⨁ HIGH	
Abdominal Pain AE Reiter et al. 2013 meta-analysis (follow up: range 3 weeks to 26 weeks)												
2 [2,3]	randomised trials	not serious	not serious	not serious	not serious				-	**1.06 higher** (0.51 higher to 2.2 higher)	-	

All SAE AMAZES 2017 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	16/213 (7.5%)	26/203 (12.8%)	not estimable		⨁⨁⨁⨁ HIGH	
Diarrhoea AMAZES 2017 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	72/213 (33.8%)	39/203 (19.2%)	not estimable		⨁⨁⨁⨁ HIGH	
QTC prolongation AMAZES 2017 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	1/213 (0.5%)	1/203 (0.5%)	not estimable		⨁⨁⨁⨁ HIGH	
Tinnitus AMAZES 2017 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	2/213 (0.9%)	2/203 (1.0%)	not estimable		⨁⨁⨁⨁ HIGH	
Hearing loss AMAZES 2017 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	6/213 (2.8%)	7/203 (3.4%)	not estimable		⨁⨁⨁⨁ HIGH	
abdominal pain AMAZES 2017 (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	38/213 (17.8%)	30/203 (14.8%)	not estimable		⨁⨁⨁⨁ HIGH	
diarrhoea Black et al. 2001 (follow up: range 6 weeks to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	6/105 (5.7%)	10/112 (8.9%)	not estimable		⨁⨁⨁⨁ HIGH	
nausea Black et al. 2001 (follow up: range 6 weeks to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	13/105 (12.4%)	5/112 (4.5%)	not estimable		⨁⨁⨁⨁ HIGH	
changes in LFTS Black et al. 2001 (follow up: range 6 weeks to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	6/105 (5.7%)	1/112 (0.9%)	not estimable		⨁⨁⨁⨁ HIGH	
Nausea Hahn et al. 2012 (33% Azithromcyi0 vs 9% placebo) (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	serious [d]	not serious	serious [d]	none			-	33% **0** (0 to 0)	⨁⨁◯◯ LOW	
Stomach pain Hahn et al. 2012 (42% Azithromcyin vs 12% placebo) (follow up: range 48 weeks to 48 weeks)												
1	randomised trials	not serious	serious [d]	not serious	serious [d]	none			-	42% **0** (0 to 0)	⨁⨁◯◯ LOW	
Diarrhoea Hahn et al. 2012 (42% Azithromcyin vs 15% placebo) (follow up: range 48 weeks to 48 weeks)												

1	randomised trials	not serious	serious [d]	not serious	serious [d]	none			-	42% **0** (0 to 0)	⨁⨁◯◯ LOW	

CI: Confidence interval

Explanations

a. indirectness, inconsistency between trials, selective reporting and publication bias
b. retrospective observational cohort with no blinding, unclear participant selection and follow up
c. Clear bias, off protocol analysis - planned as RCT but analysed as before/after, stopped early due to poor recruitment
d. RCT and open label combined due to under-recruitment, underpowered, sae outcomes combined RCT and open label groups

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Author(s):
Date:
Question: Should macrolides compared to standard care for quality of life improvement in asthma
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	should macrolides	standard care	Relative (95% CI)	Absolute (95% CI)		
AQLQ Score Kew et al. 2016 Cochrane Review (follow up: range 4 weeks to 52 weeks)												
5 [1,2,3,4,5]	randomised trials	serious [a]	serious [a]	serious [a]	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	198	191	-	MD **0.06 higher** (0.12 lower to 0.24 higher)	⨁◯◯◯ VERY LOW	
QOL (20 point scale Marks et al. 1992) Gotfried et al. 2004 (follow up: range 14 weeks to 14 weeks)												
1	observational studies	very serious [b]	very serious [b]	very serious [b]	very serious [b]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	14	0	-	MD **0.44 higher** (0 to 0)	⨁◯◯◯ VERY LOW	
AQLQ score Bruselle et al. AZISAST study 2013 (follow up: range 26 weeks to 26 weeks)												
1 [3]	randomised trials	not serious	not serious	not serious	not serious	none	55	54	-	MD **0.12 higher** (0.2 lower to 0.44 higher)	⨁⨁⨁⨁ HIGH	
AQLQ score Sutherland 2010 RCT of clarithromycin vs placebo all partcipants (follow up: range 16 weeks to 16 weeks)												
1 [4]	randomised trials	not serious	serious [c]	not serious	serious [c]	none	47	45	-	MD **0.2 higher** (0.2 lower to 0.2 higher)	⨁⨁◯◯ LOW	
AQLQ score Sutherland 2010 RCT of clarithromycin vs placebo PCR Positive (follow up: range 16 weeks to 16 weeks)												
1 [4]	randomised trials	not serious	serious [c]	not serious	serious [c]	none	6	6	-	MD **0.1 lower** (0.6 lower to 0.6 higher)	⨁⨁◯◯ LOW	
AQLQ score Sutherland 2010 RCT of clarithromycin vs placebo PCR negative (follow up: range 16 weeks to 16 weeks)												

1 [4]	randomised trials	not serious	serious [c]	not serious	serious [c]	none	41	39	-	MD **0.2 higher** (0.2 lower to 0.2 higher)	⊕⊕◯◯ LOW	

AQLQ: Simpson 2008 (follow up: 8 weeks; assessed with: AQLQ Juniper; Scale from: 1 to 7) (follow up: range 8 weeks to 8 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	23	23	-	median **0.7 higher** (0 to 0)	⊕⊕⊕⊕ HIGH	

AQLQ: Simpson et al. 2008 Non-eosinophilic asthma (follow up: range 8 weeks to 8 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	14	14	-	median **0.7 higher** (0 to 0)	⊕⊕⊕⊕ HIGH	

AQlQ Reiter et al. meta-analysis 2013

5 [1,2,3,4,6]	randomised trials	not serious	serious [d]	not serious	serious [d]	all plausible residual confounding would reduce the demonstrated effect	346		-	MD **0.18 higher** (0.001 higher to 0.37 lower)	⊕⊕⊕◯ MODERATE	

Pooled QOL Tong et al. 2015 meta-analysis

6	randomised trials	not serious	not serious	not serious	not serious	none	450		-	**0.09 higher** (0.11 lower to 0.29 higher)	⊕⊕⊕⊕ HIGH	

AQLQ AMAZES 2017 (follow up: range 48 weeks to 48 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	213	207	-	MD **0.36 higher** (0.21 higher to 0.52 higher)	⊕⊕⊕⊕ HIGH	

AQLQ Black et al. 2001 (follow up: range 6 weeks to 6 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	105	112	-	MD **0.09 higher** (0 to 0)	⊕⊕⊕⊕ HIGH	

AQL (Juniper) Hahn et al. 2012 (follow up: range 48 weeks to 48 weeks)

1	randomised trials	serious [e]		not serious	serious [e]	none	38	37	-	MD **0.1 higher** (0 to 0)	-	

AQL Open label Azithromycin group Hahn et al. 2012 (follow up: range 48 weeks to 48 weeks)

1	randomised trials	not serious	serious [e]	not serious	serious	none			-	**1.8 higher** (0 to 0)	⊕⊕◯◯ LOW	

AQLQ (Juniper) Hahn et al. 2006 (6 weeks Azithromycin) (follow up: range 6 weeks to 6 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none	19	17	-	**0.25 higher** (0.35 lower to 0.84 higher)	⨁⨁⨁⨁ HIGH	

AQLQ Cameron et al. ERJ 12 weeks Azithromycin 250mg (follow up: range 12 weeks to 12 weeks) (follow up: 12 weeks)

1	randomised trials	not serious	not serious	not serious	not serious	none			-	**0.31 lower** (0.69 lower to 0.07 lower)	⨁⨁⨁⨁ HIGH	

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Publication bias, selective reporting, inconsistency and indirectness
b. bias, planned as RCT but analysed as before/after - off protocol analysis, terminated early due to poor enrolment
c. Planned to randomise 1:1 based on PCR positivity but insufficient PCR positive patients so major protocol change and much lower recuitment than planned
d. studies highly homogeneous
e. Combination of RCT with open label as under-recruiting, underpowered

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