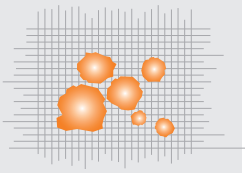

Long-term antibiotics to reduce COPD exacerbations: pros and cons

Linda Bryant MClinPharm, PGDipHospPharmAdmin, PhD, FNZHPA, FNZCP, FPSNZ, MCAPA

KEY POINTS

- Long-term antibiotics for frequent exacerbations of COPD are effective, but need to be balanced against the real risk of resistance to antibiotics.
- Selection of people with very severe COPD for treatment with long-term macrolides should be on a case-by-case basis.
- The decision about initiation of macrolides will usually be made by a respiratory physician.
- General practitioners' role includes awareness and monitoring of potential adverse effects and interactions.

J PRIM HEALTH CARE. 2015;7(1):78–80.

CORRESPONDENCE TO:
Linda Bryant
Clinical Manager, Clinical Advisory Pharmacist,
East Health Trust PHO
PO Box 38248, Howick
Auckland, New Zealand
l.bryant@auckland.ac.nz

The overall two-year case fatality for a person after their first severe exacerbation of COPD is up to 30%.[1] This statistic reinforces the major impact of COPD on morbidity and mortality. Other than smoking cessation, the management of COPD is very much focused on reducing exacerbations, as well as improving functional status and quality of life through such interventions as influenza vaccination and potentially long-term antibiotics in selected people.

There has been growing interest in, and increasing evidence for, the use of long-term continuous antibiotics, particularly macrolides, for reducing exacerbations of COPD. There are still many unknowns that should caution us against routinely adopting the use of long-term macrolides specifically, and antibiotics generally, for people with severe COPD.

What we know

Meta-analyses have found that long-term macrolides, particularly for six to 12 months, reduce the rate of acute exacerbations of COPD by approximately 50%, with a number needed to treat for one person to benefit of approximately eight.[2,3] Possible reduction in hospitalisation ranges from no significant reduction[3] up to 27% reduction in hospitalisation.[4] Although a systematic review reported a statistically significant improvement in respiratory-related quality of life, this improvement was not seen as clinically relevant.[2] Adverse effects reported include significant hearing impairment with azithromycin.

The studies to date have been relatively small, with fewer than 3200 people in total, involving only azithromycin, erythromycin and clarithromycin. It is not possible to compare possible differences between macrolides from these studies. In New Zealand (NZ) the choice of macrolide is restricted to erythromycin, due to the current funding limitations on azithromycin and clarithromycin (as of December 2014). Roxithromycin is subsidised and may be a reasonable alternative, but there are no studies on this to date.

What we don't know

Bacterial resistance

A major concern is the increased risk of bacterial resistance with an increased use of long-term antibiotics, particularly with few new classes of antibiotic in development. Exposure to the antibiotic is not just in the respiratory tract, but also the gastrointestinal tract, urinary tract and other tissues. It is also not just about the individual, but also the community. With antimicrobial stewardship being the responsibility of all prescribers, targeted use of antibiotics for those people most likely to benefit is important.

There is a paucity of information on the emergence and significance of bacterial resistance, but in one large study of long-term azithromycin in COPD, it appeared that people with no previous nasopharyngeal colonisation at baseline were more likely to be colonised with resistant bacteria at the end of the study.[4] Unfortunately, this aspect of the study was not well reported and so the data were very limited.

Which people should be targeted?

We do not know the non-antimicrobial mechanism of action for macrolides in COPD, leading

NUGGETS *of* KNOWLEDGE provides succinct summaries of pharmaceutical evidence about treatment of common conditions presenting in primary care and possible adverse drug reactions.

to limitations for targeting people, which would therefore avoid inappropriate use of antibiotics and risk of bacterial resistance. The benefit of macrolides in COPD is proposed to be an anti-inflammatory effect, immunomodulation and/or a reduction in the bacterial load. Knowing the mechanism is important because this will help target the most suitable subpopulation of people with COPD and reduce the non-beneficial use of antibiotics.

Dose, duration, choice

The six randomised controlled trials of continuous long-term macrolides have used different macrolides, doses and durations of therapy. Again, to reduce excessive use of long-term antibiotics, more studies are required.

Long-term outcomes

The effect on lung function and mortality with long-term use of macrolides in COPD is still unknown, requiring larger and longer-term controlled trials.

What we need to be cautious about

Important common drug interactions

With the limited choice of macrolides in NZ, erythromycin and perhaps roxithromycin are likely to be the macrolides most used if long-term antibiotic therapy is initiated. Erythromycin is a potent inhibitor of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein, resulting in relatively frequent, potentially significant drug–drug interactions. Clarithromycin and roxithromycin

Table 1. Common potential pharmacokinetic drug interactions with macrolides

	Erythromycin	Clarithromycin	Roxithromycin	Azithromycin
Statins	**Avoid**	**Avoid**	Caution	Caution
	Risk mitigation • Advise the patient to report any muscle aches or weakness immediately, and specifically ask about this at every visit. Muscle weakness may include respiratory muscles • Consider statins not metabolised by CYP3A4, such as pravastatin or rosuvastatin if muscle problems occur • Use low dose statins, especially simvastatin, for which 20 mg daily is the recommended maximum dosage if it needs to be continued at all			
Colchicine	**Avoid**	**Avoid**	Caution	Caution
	There are reports of erythromycin and clarithromycin causing colchicine toxicity related to colchicine's metabolism by P-glycoprotein		Lack of reports may be due to limited concurrent use	
	Risk mitigation • Use prednisone or a NSAID for treatment of gout or prophylaxis while introducing allopurinol			
Calcium channel blockers	Caution	Caution	Caution	Caution
	Risk mitigation • Interaction is most likely to occur with erythromycin. Isolated cases reported, more so with felodipine • Monitor blood pressure and for swollen ankles			
Cyclosporin/tacrolimus	**Avoid**	**Avoid**	**Avoid**	**Avoid**
	Risk mitigation • While it is possible to monitor serum concentrations, it is preferable to avoid this combination of medicines. Azithromycin appears less likely to interact			
Digoxin	Caution	Unpredictable	Unpredictable	Unpredictable
	Risk mitigation • Do baseline serum digoxin concentration and repeat in 10 days • Monitor clinically for gastric upset, colour vision disturbance			
Warfarin	Unpredictable	Unpredictable	Unpredictable	Unpredictable
	Risk mitigation • Monitor INR weekly for the first four weeks			

Table 2. Common medicines that potentially have an additive effect for QTc prolongation with macrolides

Medicine	Comment	Action
Amiodarone	Avoid	• Check serum potassium and magnesium. Avoid dehydration • Consider the possibility of drug-induced QTc prolongation in people presenting with new onset syncope, palpitations, seizures or resuscitated cardiac arrest
Domperidone	Avoid. Use alternative prokinetic medicine	
Methadone	Avoid	
Antipsychotics	Includes clozapine, haloperidol, quetiapine, risperidone. Monitor	
Antidepressants	Although some SSRIs, such as escitalopram, citalopram and venlafaxine are more frequently reported, all SSRIs and tricyclic antidepressants (e.g. amitriptyline, mirtazapine) may cause QTc prolongation. Monitor	
Ondansetron	Possible association. Use alternative antinausea agent	

See **www.qtdrugs.org** for a full list.

are less potent inhibitors of CYP3A4, but caution is still recommended. Azithromycin is less likely to cause a significant interaction but there are still reports of, for example, rhabdomyolysis when used in combination with statins. As well as drug interactions involving macrolides increasing the concentration of a concurrent drug, there may be a pure additive effect with other medicines, such as selective serotonin reuptake inhibitors (SSRIs), domperidone and methadone, that can cause QTc prolongation in susceptible people. Tables 1 and 2 provide a summary of common medicines that may potentially interact with macrolides, but are not a complete list.

Adverse effects

The common adverse effect of macrolides, particularly of erythromycin, is gastrointestinal upset due to stimulation of motilin receptors, which increase gastric motility. Other adverse effects to monitor for are QTc prolongation, and skin reactions, from mild to erythema multiforme and Stevens-Johnson syndrome. To reduce the risk of QTc prolongation, as well as not giving a macrolide with other medicines that may cause QTc prolongation, ensure that serum potassium and magnesium concentrations are adequate and that there is no underlying cardiac condition, such as bradycardia.

Bottom line

People with very severe COPD who have had frequent exacerbations requiring hospitalisations in the previous 12 months are potential candidates for long-term macrolides, but this is not necessarily a straightforward decision. The selection of suitable people is on a case-by-case basis. Having had repeated hospitalisations, these people will be under the collaborative care of their general practitioner and respiratory physician who can undertake further investigations. While the respiratory physician will usually make the decision about initiation of long-term macrolides, this will continue in primary care, and awareness and monitoring of the adverse effects and interactions is necessary.

Future possibility

With the recognised benefit of inhaled antibiotics for cystic fibrosis and non–cystic fibrosis bronchiectasis, this will be an area of research for COPD, and may help alleviate some concerns about bacterial resistance.

ACKNOWLEDGEMENTS
The author would like to thank Associate Professor Jeff Garrett, Respiratory Physician, and Dr Wing Cheuk Chan, Public Health Physician, both of The University of Auckland, and Counties Manukau District Health Board, for assistance with this article.

References

1. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax. 2012; 67:957–63.
2. Herath S, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2013 Nov 28;11:CD009764.
3. Donath E, Chaudhry A, Hernandez-Aya L, Lit L. A meta-analysis on the prophylactic use of macrolide antibiotics for the prevention of disease exacerbations in patients with Chronic Obstructive Pulmonary Disease. Respir Med. 2013;10799:1385–92
4. Albert R, Connett J, Bailey W, Casaburi R, Cooper A, Criner G et al. Azithromycin for prevention of exacerbations of COPD. N Eng J Med. 2011;365:689–98.