CENTRE OF EXCELLENCE IN
SEVERE ASTHMA

Innovative solutions for severe asthma

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CLINICAL RECOMMENDATIONS FOR THE USE OF AZITHROMYCIN IN SEVERE ASTHMA IN ADULTS

NOTE: The use of macrolide antibiotics, including azithromycin, for the treatment of asthma is off-label

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Note: *An overview video on macrolide treatment for asthma is available on the Centre of Excellence website:* ***https://www.severeasthma.org.au/macrolides-severe-asthma/***

Azithromycin Treatment for Severe Asthma

WHAT IS AZITHROMYCIN?

A MACROLIDE ANTIBIOTIC THAT IS:

Anti-bacterial and **Anti-inflammatory**

WHAT IS THE EFFECT OF TREATMENT ON SEVERE ASTHMA?

- Reduced asthma attacks
- Improved quality of life
- Reduced bronchitis episodes
- Improved asthma symptom scores

Improvements in lung function (e.g. FEV_1) have also been reported

WHO SHOULD MACROLIDES BE USED IN?

In patients with severe asthma who fail to achieve symptom control treatment should be initiated in specialist care

Note: The use of macrolide antibiotics for the treatment of asthma is off-label in Australia

TREATMENT APPROACH:

1 SCREENING

Patients should be excluded based on the following:

- Prolonged QTc interval (>480 ms)
- Cardiac arrhythmia
- Caution should be considered in people with hearing loss

2 DOSING

500 mg (3x per week)

OR

250 mg daily

For up to 12-months

3 MONITORING

DIARRHOEA: Increased rates were observed in a clinical trial (34% vs. 19% placebo). If diarrhoea occurs the dose can be adjusted and a probiotic co-administered.

RHABDOMYOLYSIS: Interactions have been reported between macrolides and statins. Discontinue use if myopathy symptoms occur.

ANTIBIOTIC RESISTANCE: Emergence of resistant pathogens may occur. Breaks in chronic therapy may be considered to reduce resistance. *Note: detection of antibiotic resistance should not automatically result in treatment discontinuation*

References: Reiter, J. 2013 Allergy, Gibson, P.G. 2017. Lancet, GINA Pocket Guide 2018, Hiles S.A. 2019 ERJ

Developed as part of the: SEVERE ASTHMA TOOLKIT
toolkit.severeasthma.org.au

ABOUT THE TREATMENT

INTRODUCTION

Macrolides have a broad range of biological activities including antibacterial, antiviral and anti-inflammatory effects (1). Macrolides are used to treat infections by Gram-positive bacteria and some Gram-negative bacterial species, including some respiratory tract infections. Due to their immunomodulatory effects, macrolides are also used for the treatment of inflammation associated with diffuse panbronchiolitis, bronchiectasis, chronic rhinosinusitis, COPD, and cystic fibrosis (1). Clinical trials have also demonstrated benefits of long-term azithromycin on asthma outcomes (2).

MECHANISM OF ACTION

Macrolides have a diverse range of effects on numerous cell types. Effects are mediated by modulation of intracellular signalling via multiple pathways, including intracellular calcium regulation, MAPK (mitogen-activated protein kinase) signalling pathways and modulation of transcription factor function (1).

Macrolides directly inhibit bacterial growth by reducing adherence, virulence factor production, biofilm formation and quorum sensing (1).

The anti-inflammatory effects of macrolides include reduced pro-inflammatory cytokine expression, reduced adhesion molecule expression on immune cells, reduced chemical mediator release and reactive oxygen species (ROS) production, increased apoptosis, and increased efferocytosis (1). Macrolide antibiotics also limit mucus secretion and ion transport in the airways and increase mucociliary function of epithelial cells (1).

PHARMACODYNAMICS

For full details on azithromycin characteristics, indications and safety considerations consult the Azithromycin Tablet Product Information Document (see Resources Used for link)

Azithromycin is absorbed from the gastrointestinal tract, with an absolute bioavailability of 37% and maximal serum concentrations achieved 2-3 hours after oral administration (3). Serum levels of azithromycin decline in a polyphasic pattern, with an average terminal half-life of 68 hours. Food intake, including high fat meals, has no significant effect on bioavailability. Pharmacokinetics are largely unaltered in elderly patients and no dosage adjustment is necessary based on patient age.

Azithromycin is distributed throughout the body, moving rapidly from blood into tissues. As a result, azithromycin levels are significantly higher in tissue than in plasma, reaching levels up to approximately 100 times those observed in plasma (3). Azithromycin appears to localise intracellularly in tissues, including in white blood cells (e.g. neutrophils, monocytes, lymphocytes and alveolar macrophages). Studies have assessed intracellular concentrations of azithromycin in white blood cells following azithromycin treatment (3 daily doses of 500mg). Mean intracellular azithromycin concentrations of 17mg/L in neutrophils and 21mg/L in monocytes and lymphocytes 10 days were observed after treatment, compared to <0.05mg/L in serum (4). Azithromycin persists in the lung after administration (3 daily oral doses of 500mg), with a terminal half-life of approximately 132 hours in lung tissue and 74 hours in bronchial washings (5).

CLINICAL BENEFIT ON ASTHMA OUTCOMES

Systematic reviews and meta-analyses of clinical trials data have demonstrated beneficial effects of macrolide antibiotic treatment (including azithromycin) on asthma outcomes (2, 6-8). Improvement in some measures of lung function (e.g. FEV1) have been demonstrated following treatment (6, 7). Improvements in asthma symptom scores, quality of life and airway hyper-responsiveness may occur following ongoing treatment with macrolides for more than 3 weeks (8).

The primary benefit of long-term azithromycin treatment in clinical trials is reduced rates of asthma exacerbations (2, 9, 10). In the AMAZES trial, 48 weeks of azithromycin treatment reduced asthma exacerbations (1.07 per patient year) compared with placebo control (1.86 per patient-year; incidence rate ratio 0.59 [0.47-0.74] p<0.0001) (10). The proportion of patients experiencing at least one exacerbation during the study period was also reduced compared with placebo control (44% vs. 61%; p<0.0001) (10). Azithromycin treatment also improved asthma-related quality of life (QoL) (10). Improvements were observed regardless of inflammatory phenotype, in patients with both eosinophilic and non-eosinophilic asthma (10). An individual patient data meta-analysis confirmed these results (2).

DOSAGE

Recommended dosing for azithromycin for asthma is 500mg per dose, 3 times per week (10) or 250mg daily (9).

A pre-determined duration of treatment should be defined prior to treatment initiation. In clinical trials, azithromycin treatment for <3 months failed to improve asthma outcomes (9, 10) and no evidence was identified to support seasonal treatment approaches.

Recommended duration of treatment is 12 months.

SCREENING

Initiation of maintenance macrolide treatment for asthma should occur by specialist only, with a pre-determined period of treatment defined at the outset.

All patients should undergo screening prior to initiation of treatment.

Patients should be excluded from macrolide treatment based on the following:

- Prolonged QTc interval > 0.48 sec, assessed by electrocardiogram (ECG). Consider the risk of QT prolongation (which can be fatal) when weighing the risks and benefits of azithromycin for at-risk groups (as described in **Safety Profile** below)
- Cardiac arrhythmia
- Caution should be considered in people with hearing loss

MONITORING

DIARRHOEA

Increased rates of diarrhoea were observed following azithromycin treatment in clinical trials (10). If diarrhoea occurs, treatment dose may be modulated, for example reducing the dose or the dosing frequency. Another approach is co-administration of a probiotic.

RHABDOMYOLYSIS

Case reports suggest a drug interaction between statins and azithromycin in the development of rhabdomyolysis (11). However, a limited evidence base is currently available on this potential interaction. Among the macrolide antibiotics, azithromycin has the least risk of adverse events when co-administered with statins (12). Patients currently taking statin medications should be counselled about the risks of myopathy and encouraged to report muscle pain, tenderness or weakness. If rhabdomyolysis is identified, azithromycin treatment should be discontinued.

CYTOCHROME P450 INTERACTIONS

Some macrolides (e.g. erythromycin, clarithromycin) inhibit the cytochrome P450 isoenzyme 3A4 (CYP3A4). Inhibition increases the blood concentration of some statins, which are substrates for this enzyme, including simvastatin and atorvastatin. As a result, concomitant administration of some macrolides and statins have been reported to cause significant drug interactions and toxicity (12). This can be managed by using a macrolide that does not inhibit CYP3A4 (e.g. azithromycin) and a statin that is not a substrate for CYP3A4 (e.g. rosuvastatin, fluvastatin or pravastatin).

ANTIBIOTIC RESISTANCE

Long-term azithromycin treatment has the capacity to increase antibiotic resistance in the individual patient and broader community (13). The emergence of macrolide-resistant pathogens should be considered in the individual patient. **However, detection of antibiotic resistance in sputum culture should not automatically result in treatment discontinuation.**

SAFETY PROFILE

In clinical trials assessing azithromycin treatment in people with severe asthma, treatment was generally well tolerated (2). In the AMAZES trial, 48 weeks of azithromycin treatment had no effect on the overall rate or type of serious adverse events, compared with placebo treatment (10). Azithromycin treatment was associated with increased diarrhoea compared with placebo (34% vs. 19% of patients; p=0.01) (10). There was no significant difference in other drug-related adverse events. Adverse events due to diagnosed infection were reduced in patients treated with azithromycin compared with placebo (20% vs. 36%; p<0.001) (10), with a significant reduction in respiratory infections requiring antibiotics.

Concern has been raised about the risk of increased antimicrobial resistance associated with long-term macrolide use as a treatment for inflammatory airway diseases (13). Azithromycin treatment increases macrolide resistance in respiratory-tract organisms. There is concern that widespread use may increase macrolide resistance at a population level. A non-statistically significant increase in pathogen antibiotic resistance was observed in the AMAZES trial (10), which may be clinically relevant. This risk should be carefully considered against the potential benefit of treatment for the individual patient.

Detailed information on azithromycin precautions and adverse effects are available in product information and consumer medicine information documents, available on the PBS website (**https://www.pbs.gov.au/medicine/item/4115N-5616N-6221K-8200N-8201P-8336R**; Accessed 06 June 2019).

PRECAUTIONS

For full details on azithromycin characteristics, indications and safety considerations consult the Azithromycin Tablet Product Information Document (see Resources Used for link)

HYPERSENSITIVITY

Rare, serious allergic reactions have been reported in patients on azithromycin therapy. Treatment should be discontinued if an allergic reaction occurs, and alternative appropriate therapy should be commenced. Reappearance of allergic symptoms may occur when symptomatic therapy of allergic reactions is discontinued. Emergence of allergic symptoms requires prolonged observation and symptomatic treatment. The potential relationship of these incidents to the long tissue half-life of azithromycin and exposure to allergen / antigen is unknown.

PROLONGATION OF THE QT INTERVAL

Azithromycin treatment has been associated with ventricular arrhythmias with prolonged QT interval, including ventricular tachycardia and torsades de pointes. Screening for prolonged QT interval (QTc > 0.48s) should be performed prior to treatment initiation. Use with care in patients with coexisting cardiac arrhythmias, and where concomitant medication use may prolong QTc.

Prescribers should consider the potential for QT prolongation when assessing the risks and benefits of azithromycin treatment in at-risk groups. Risk considerations may include:

- Patients predisposed to QT interval progression;
- Patients receiving medications that prolong the QT interval (e.g. Class IA / II antiarrhythmics, antipsychotics, antidepressants and fluoroquinolones);
- Patients with electrolyte disturbance (particularly in hypokalaemia and hypomagnesemia);
- Elderly patients, who may be more susceptible to drug-associated effects

DRUG INTERACTIONS

Ergotism may result following co-administration of some macrolide antibiotics in patients concomitantly prescribed ergot derivatives. There are no specific data on interactions between ergot and azithromycin. However, azithromycin should not be administered concomitantly with ergot due to the theoretical possibility of ergotism.

Co-ingestion of antacids with azithromycin reduces peak serum levels of azithromycin (14). Antacids should not be concomitantly administered with azithromycin.

Concomitant administration of digoxin and azithromycin may alter drug metabolism resulting in raised serum digoxin levels. Monitoring and measurement of serum digoxin levels may be necessary during and after azithromycin treatment.

Cyclosporin requires dosage adjustment when administered concomitantly with azithromycin.

USE IN PREGNANCY

No studies have been carried out in pregnant women and azithromycin treatment should only be used during pregnancy if clearly needed.

USE IN LACTATION

There are no data on the secretion of azithromycin into breast milk. Azithromycin should only be used in lactating women where alternatives are not available and treatment is clearly needed.

ADVERSE EFFECTS

For full details on azithromycin characteristics, indications and safety considerations consult the Azithromycin Tablet Product Information Document (see Resources Used for link)

Most of the adverse events reported in clinical trials of azithromycin treatment were mild to moderate in severity and reversible on discontinuation of the drug. In a meta-analysis of clinical trials assessing azithromycin therapy for lower respiratory tract infections only 23 of 3487 total patients (0.7%) discontinued treatment due to adverse effects (15). Most adverse events leading to treatment discontinuation affected the gastrointestinal tract (e.g. nausea, vomiting, diarrhoea or abdominal pain). Potentially serious, adverse events were rare, and included 1 case of angioedema and 1 case of cholestatic jaundice.

Hearing impairment has been reported, typically following higher dose treatments for prolonged periods of time. The majority of these events resolve with treatment cessation.

Following multiple-dose regimens of azithromycin, most adverse events also relate to the gastrointestinal system, with diarrhoea/loose stools (5%), nausea (3%) and abdominal pain (3%) most frequently reported. No other side effects occurred with a frequency >1%, in patients on the multiple-dose regimen.

Serious adverse events are shown in the Table below, reported from the AMAZES trial (10):

	Placebo (n=207)	Azithromycin (n=213)
Total serious adverse events	31; 26 (13%)	26; 16 (8%)
Cardiac	8; 6 (3%)	7; 5 (2%)
Gastrointestinal tract	5; 4 (2%)	5; 5 (2%)
Other health issue	10; 8 (4%)	9; 3 (1%)
Possible infectious serious adverse events	8; 8 (4%)	5; 3 (1%)
Study withdrawal (treatment discontinuation due to adverse event)	10 (5%)	15 (7%)

Data presented as number of events; number of people (%).

Treatment-related adverse events are shown in the Table below, reported from the AMAZES trial (10):

	Placebo (n=207)	Azithromycin (n=213)
Nausea	20 (10%)	31 (15%)
Diarrhoea	39 (19%)	72 (34%)
Abdominal pain	30 (15%)	38 (18%)
Other gastrointestinal tract	7 (3%)	7 (3%)
Headache	6 (3%)	6 (3%)
Vertigo	0	1 (<1%)
Tinnitus	2 (1%)	2 (1%)
Hearing loss	7 (9%)	6 (6%)
Oral thrush	2 (1%)	7 (3%)
Allergy	0	1 (<1%)
Rash	10 (5%)	11 (5%)
Other adverse event	27 (13%)	41 (19%)

Data presented as number of events (%).

LABORATORY ABNORMALITIES

Laboratory abnormalities have been reported in clinical trials of azithromycin treatment. Abnormalities observed in >1% of treated patients include elevated serum creatinine phosphokinase, potassium, alanine aminotransferase (ALT; SGPT), gamma glutamyltransferase (GGT) and aspartate aminotransferase (AS; SGOT), lymphocyte and neutrophil numbers or decreased neutrophil numbers. Abnormalities reported in <1% of treated patients include leukopenia, neutropenia, thrombocytopenia, elevated serum alkaline phosphatase (ALP), bilirubin, blood urea nitrogen (BUN), creatinine, blood glucose, lactate dehydrogenase (LDH), phosphate, monocytes, basophils, bicarbonate and decreased sodium or potassium. Changes in laboratory tests appeared to be reversible upon follow-up.

Laboratory abnormalities are shown in the Table below, reported from the AMAZES trial (10):

	Placebo (n=207)	Azithromycin (n=213)
Abnormal liver function tests	3 (1%)	1 (<1%)
QTc prolongation	2 (3%)	5 (5%)

Data presented as number of events (%).

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RESOURCES USED

APO-Azithromycin Tablets Product Information – Australia Document; Updated 22 April 2016
https://medicines.org.au/files/txpazith.pdf
Accessed 06 June 2019)

The AMAZES Study Protocol Research Protocol: Asthma and Macrolides – The Azithromycin Efficacy and Safety Study
(**https://www.severeasthma.org.au/wp-content/uploads/2017/04/AMAZES-Protocol-V15-25.02.14-final.pdf**;
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