

BTS guideline on long-term macrolides in adults with respiratory disease: not quite a panacea

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ABSTRACT

The British Thoracic Society (BTS) guideline on the use of long-term macrolides in adults with respiratory disease has been published. It indicates where there is evidence to support the use of long-term low-dose macrolides and where there is not. It discusses the potential benefits of such therapy for patients and also describes the potential risks to individuals and wider populations. It seeks to provide a pragmatic approach for clinicians considering long-term macrolide therapy for their patients. This guideline has also acted as a learning exercise for the BTS in introducing the Grading of Recommendations Assessment, Development and Evaluation approach to guideline development, which will be used going forwards.

INTRODUCTION

The British Thoracic Society (BTS) guideline on the use of long-term macrolides in adults with respiratory disease, using GRADE methodology, reports the clinical efficacy and safety of macrolide antibiotics in the long-term management of patients.¹ Macrolide antibiotics have been used in clinical practice since the early 1950s when erythromycin became commercially available. Clarithromycin and azithromycin followed some 30 years later and remain among the most popular antibiotics for respiratory infections. The potential of macrolides as immunomodulatory agents has been investigated since their reported efficacy in treating diffuse panbronchiolitis in Japan in the late 1980s.² Noted effects include alterations in airway secretions via ion transport and mucus production, modification of the inflammatory process through changes in cytokine production, adhesion molecule expression and the function of inflammatory, airway and other cells. Sublethal effects on bacteria include disruption of biofilms, interference with quorum sensing and reduced bacterial adherence, toxin production and

mobility.³ Early RCTs reporting macrolides in cystic fibrosis appeared in 2002 and have been followed by studies in a wide range of chronic inflammatory lung conditions including asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, bronchiolitis obliterans, chronic rhinosinusitis, cryptogenic organising pneumonia and chronic cough. Alongside this widespread use concerns have been raised for the safety of individual patients and for the effect on bacterial resistance in populations.^{4 5} Against this background, the BTS guideline was commissioned.

KEY RECOMMENDATIONS FOR MACROLIDE USE

The BTS guideline group emphasised the need to optimise conventional therapies prior to considering the use of long-term macrolides in any condition.

The best evidence for long-term macrolides was in bronchiectasis where the combination of three RCTs from the Netherlands, Australia and New Zealand (BAT, BLESS and EMBRACE)⁶⁻⁸ enabled the guideline group to make a strong recommendation for offering macrolides to reduce exacerbations in those with three or more exacerbations each year.

In asthma, two randomised controlled trials (RCTs) aimed at exacerbation rate (AZIZAST and AMAZES)^{9 10} allowed a conditional recommendation to consider macrolides in adults with symptoms despite 80% adherence to high-dose inhaled steroids (>800 µg/day) and at least one exacerbation requiring steroids in the past year.

For COPD, nine RCTs were included in the examination of evidence.¹ A conditional recommendation to consider macrolides for patients with more than three exacerbations including one hospital admission per year to reduce exacerbation rate was made.

In the highly specialised field of lung transplantation the guideline group supported the recommendations of the International Society for Heart and Lung Transplantation/American Thoracic Society/European Respiratory Society clinical practice guideline in making a conditional recommendation for azithromycin

to treat bronchiolitis obliterans syndrome (BOS).¹¹ The guideline group also recommended considering azithromycin to prevent the occurrence of BOS postlung transplantation.

The BTS guideline group did not find sufficient evidence to recommend the use of long-term macrolides for chronic cough or organising pneumonia.

PATIENT SAFETY ISSUES

Gastrointestinal side effects are common but rarely serious. Patients should be warned of the possibility of such side effects, which may be ameliorated by dose reduction (although this may also reduce clinical efficacy). A low rate (1%–5%) of asymptomatic elevation of serum aminotransferase levels of a mild to moderate degree is known to occur with macrolides. Dose modification or discontinuation is rarely required. A more serious cholestatic picture can occur. Monitoring liver function at the start of therapy is recommended.

Prior to initiating long-term macrolide therapy, patients should be asked if they have a history of hearing or balance difficulties. Such patients should be made aware of the potential for a further, almost always reversible deterioration in hearing or balance with macrolide therapy. Patients with pre-existing hearing or balance difficulties who wish to proceed with treatment should be asked to report any change in hearing or balance promptly.

Macrolides, along with many other drugs, have the potential to interfere with conduction in cardiac tissue and cause dangerous cardiac arrhythmias. Before starting macrolide therapy, patients should be asked if they have a history of heart disease, previous hypokalaemia, bradycardia, a family history of sudden death or known long QT syndrome. Patients with such a history should not receive macrolide therapy without careful consideration and counselling of the increased risk of adverse cardiac effects. A drug history detailing the agents that may prolong QT interval should be sought. Prior to therapy, an ECG should confirm a normal QTc interval. This should be repeated a month after initiating therapy. A prolonged QTc interval at any point precludes the use of long-term macrolides.

Patients should be asked if they have a history of previous or current nontuberculous mycobacterial (NTM) infection or disease. Current disease precludes macrolide monotherapy, successfully treated disease does not. If there is any clinical suspicion of NTM disease, this

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needs to be excluded prior to initiating macrolide monotherapy.

Long-term macrolide therapy in chronic lung disease increases the rate of macrolide resistance but the clinical impact of the presence of a macrolide resistant respiratory pathogen such as *Streptococcus pneumoniae*, in an individual patient, at least in the short term, is not clear.^{12–14} The global rise in antimicrobial resistance is of national and international concern.^{15 16} Both azithromycin and clarithromycin are positioned in the ‘Watch’ group of antibiotics by WHO indicating that they are of higher resistance potential than antibiotics in the ‘Access’ group and should be prioritised as key targets for stewardship programmes.¹⁷ Clinicians should discuss with patients the uncertainties surrounding antimicrobial resistance and the use of long-term macrolides as part of the decision-making process.

None of the macrolides has a product licence in the UK for use as a long-term immunomodulatory agent. Their prescription in this context is thus off-label. Clinicians should make patients aware of this. GMC guidance states that decisions should be made in collaboration with the patient by discussing the options with them and ensuring that they have sufficient information about the medicine to allow them to make an informed decision.¹⁸

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