CLINICAL INVESTIGATION

Macrolides for bronchiectasis and chronic obstructive pulmonary disease: should we worry about antimicrobial resistance?

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The past 18 months have seen a relative explosion of high-quality publications in non-cystic fibrosis (CF) bronchiectasis (hereafter just termed bronchiectasis), with important data emerging in relation to both airway microbiology [1] and inflammation [2], and their relationships to key clinical markers [1–3]. Randomized controlled trials (RCTs) have proven the efficacy of oral macrolide antibiotics [4] and evidence is emerging of novel inhaled antibiotic formulations with potential efficacy [5]. The benefits of long-term macrolide therapy in this condition have been demonstrated in four high-quality RCTs, using either erythromycin or azithromycin [6].

Macrolide antibiotics have also demonstrated benefits in CF, diffuse panbronchiolitis and chronic obstructive pulmonary disease (COPD) [7] and there are ongoing studies in asthma, creating the impression of macrolides as a panacea for inflammatory airways diseases, with few attendant serious side effects. However, the primary risk related to these agents, the development of population antimicrobial resistance, is largely covert and therefore difficult to appreciate. The majority of clinicians caring for subjects with bronchiectasis or COPD would cite potential macrolide side effects as nausea and gastrointestinal complaints, risk of sudden cardiac death associated with QTc prolongation and possibly ototoxicity and drug interactions. However, I suspect few would genuinely consider antimicrobial resistance a serious potential 'side effect'.

The widespread uptake of maintenance azithromycin for common inflammatory airway diseases (e.g., COPD) poses substantial risks of induction of macrolide resistance in bacterial pathogens in the community [7]. Clinicians recognize the esoteric concept that 'antibiotic use increases resistance', but may have difficulty grasping how that relates to their individual prescribing practices, or do not feel it is of sufficient concern to restrict their own prescription of azithromycin to patients.

In the remainder of this paper, I will use a series of statements and questions, with responses, to address issues around maintenance azithromycin prescription and induction of population-level macrolide resistance.

Patients taking azithromycin do not seem to demonstrate increased complications related to the carriage of macrolide-resistant organisms

Response: The risk posed by macrolide resistance induction is not primarily to the individual patient taking maintenance azithromycin, but rather to the community around the patient.

This statement is indicative of one of the primary problems clinicians have with conceptualizing the real risk of macrolide resistance posed by maintenance macrolide use. The risks of antimicrobial resistance are not primarily to those individuals actually taking the antibiotic long-term, but rather to the community of individuals around them [7,8]. The development of macrolide resistance in bacterial pathogens (e.g., pneumococcus) is unlikely to be a significant clinical problem in the individual bronchiectasis patient being prescribed azithromycin – if this patient develops pneumococcal pneumonia, no clinician

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would treat this with azithromycin, but would utilize an alternative nonmacrolide agent. The risk instead relates to the transmission of macrolide-resistant flora or pathogens to others in this patient's community – if a 6-year-old child (who had never previously received antibiotics) develops sepsis related to a (macrolide-resistant) pneumococcus and is treated initially with azithromycin alone, a poor outcome is likely.

Considered in another way, the widespread use of maintenance azithromycin will result in significant increases in rates of population-level macrolide resistance in a variety of pathogens (e.g., pneumococcus) [7–10] – ultimately, this may render this entire antibiotic class useless for the future treatment of infections.

The bacterial resistance risk that needs to be considered is therefore primarily to the community at large, not to our individual patients.

Clinical trials of macrolide therapy in inflammatory airways disease do not generally show a strong signal of increased macrolide resistance in sputum bacterial pathogens

Response: These clinical trials have not generally employed the optimal methods to assess the effect of macrolides on bacterial resistance.

One factor that confuses clinicians in relation to assessing the risk–benefit of macrolides for chronic airways diseases is that clinical trials of macrolides often do not suggest a strong effect of azithromycin on bacterial resistance rates of pathogens in sputum. However, this is the wrong outcome measure for the question we are asking. First, in performing sputum culture on individuals with COPD or bronchiectasis, often the culture will simply contain 'normal respiratory flora' without any specific pathogen identified for subsequent susceptibility testing – of course this does not mean that azithromycin is having no effect on macrolide resistance in these organisms. Second, even where a pathogen is identified, often the pathogen is an organism that is inherently resistant to macrolides anyhow (e.g., *Pseudomonas aeruginosa*). Third, where the organism is one that is potentially sensitive (e.g., pneumococcus), azithromycin is likely to suppress growth to the extent that it is not able to be cultured in sputum while on treatment. In each of these circumstances, no evidence of induction of macrolide resistance in sputum bacterial pathogens will be identified, but this does not mean that azithromycin is not inducing macrolide resistance.

In order to answer this question properly, a different method is required – for example, by measuring rates of proportional macrolide resistance in a community of bacteria in subjects taking macrolides [9,10]. When assessed in this way, azithromycin can be shown to have very potent and nearly immediate effects on resistance rates, with proportional macrolide resistance in oropharyngeal streptococci of nearly 90% after only three doses of azithromycin in volunteers [11], and 34% after 12 months of erythromycin therapy in bronchiectasis subjects [4].

There is little evidence directly linking my own macrolide prescribing with population-level macrolide-resistance rates

Response: All available data are consistent with the interpretation that azithromycin use drives macrolide resistance, and there are no reliable data that contradict this.

This statement represents the barrier to convincing some clinicians of the importance of rationing of macrolide use – while there is, technically, truth in such a position, it is a specious argument. The concept that macrolide use drives macrolide resistance is supported by biologic plausibility, *in vitro* data, elegant RCTs in individuals [11], and a wealth of published data consistently linking population-level macrolide resistance rates to macrolide use in communities and nations, with azithromycin use particularly implicated (reviewed in [7]).

Are the risks of induction of antimicrobial resistance similar for different macrolides?

Response: Long-acting macrolides (especially azithromycin) have the most potent effects upon induction of macrolide resistance.

All available data suggest that the long-acting macrolides (especially azithromycin, which may remain detectable for up to 30 days [12]) have a much a greater effect upon macrolide resistance rates than short-acting macrolides such as erythromycin [7]. Short-term RCTs show greater induction of resistance in oropharyngeal flora with azithromycin than clarithromycin [11] or erythromycin [13]. Furthermore, numerous epidemiological studies have consistently linked rising rates of population macrolide resistance to azithromycin use in particular [7]. The introduction of azithromycin in the USA in 1992 was temporally associated with substantial, immediate increases in macrolide resistance rates in pneumococci, reaching nearly 30% within 6 years; prior to this time pneumococcal macrolide resistance was almost nonexistent, in spite of the availability of erythromycin since the 1950s [7].

Conclusion

For some of our patients, the potential benefit of macrolide therapy is undoubtedly sufficient to justify the risks to population macrolide-resistance rates. This is

especially true of patients with potentially lethal conditions such as CF and diffuse panbronchiolitis. However, for other patients with more indolent (and far more common) inflammatory airways disease, our approach must be far more circumspect.

The risk of inducing significant population-level macrolide resistance is related to both the proportion of individuals in the community who are being prescribed these agents and the 'resistance-inducing potency' of the specific agent. Hence, clinicians can apply two simple principles. First, where macrolide therapy is indicated, use low-dose erythromycin in preference to azithromycin. Second, consider macrolide therapy only in those subjects with disease of sufficient severity to truly require it, and only when all other potentially reversible contributors to respiratory decline have been addressed (e.g., smoking, aspiration, sinus disease and postnasal drip, among others).

The existing evidence-base is insufficiently robust to precisely define the subgroups of COPD patients for whom erythromycin is most strongly indicated. However, exacerbation reduction is the primary therapeutic intent of macrolide therapy and common sense would therefore suggest targeting its use to subjects with exacerbations requiring hospitalization (I would suggest at least two hospitalizations in the prior 12 months). For subjects with bronchiectasis, data from the BLESS trial suggest that particular benefit upon exacerbations was derived by subjects with *P. aeruginosa* airway infection or those experiencing frequent pulmonary exacerbations (with a cut-point of ≥5 per year in that study) [4]. These simple markers provide a logical starting point for erythromycin therapy as they are also among the strongest predictors of morbidity and mortality in bronchiectasis [14].

Macrolides represent an important addition to the armamentarium for management of chronic inflammatory airways disease; however, their future value as antibacterial agents must also be considered in our decisions around maintenance macrolide prescription. For 'non-CF' inflammatory airways diseases, restricting the use of macrolides to more severe subgroups, combined with the preferential use of erythromycin, represents an approach that attempts to balance the risk of resistance against the demonstrated clinical value of these agents [6].

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