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Azithromycin therapy for neutrophilic airways disease: myth or magic?

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The anti-inflammatory potential of macrolides was first appreciated with the successful use of erythromycin in the treatment of diffuse panbronchiolitis, a disease principally affecting the Japanese, and characterised by a persistent neutrophilic inflammatory infiltrate of the bronchi. While there are only limited data on the efficacy of other macrolides in treating this condition,[1] the observation has generated considerable interest in examining the role of macrolides in other respiratory diseases where chronic airways inflammation is a prominent feature.

Azithromycin (AZM) is a 15-membered macrolactam ring macrolide which, in randomised controlled studies, has demonstrated a beneficial role in the treatment of cystic fibrosis (CF)[2–5] despite its lack of direct bactericidal or bacteriostatic activity against *Pseudomonas aeruginosa*. More recent (albeit smaller) studies have suggested a role for AZM in the treatment of bronchiolitis obliterans syndrome (BOS)[6] and asthma,[7] with a common finding in both being its ability to reduce airway neutrophilia. Such observations have focused attention on understanding how AZM and other macrolides may modulate host-pathogen interactions in chronic lung infection and their role as an immunomodulatory agent in both respiratory and non-respiratory settings. Clinical studies have usually been designed to study an individual macrolide agent, but it is likely that the findings in such trials represent a "class effect". Although some in vitro experiments have suggested subtle differences between individual class members, the in vivo significance of these observations is uncertain.

MODULATION OF HOST-PATHOGEN INTERACTIONS

The direct antimicrobial activity of macrolides against Gram-positive bacteria results from inhibition of bacterial protein synthesis. Although AZM has little direct activity against Gram-negative organisms, it has been shown to modulate bacterial virulence factors and thus affect the outcome of chronic infections with organisms such as *P aeruginosa*. Quorum sensing is a sophisticated mechanism whereby pathogen-derived molecules act as auto-inducers and trigger a variety of biological functions such as biofilm formation and production of virulence factors. AZM reduces the transcription of *lasI* and *rhlI*, two vital components of the quorum sensing system, resulting in reduced generation of the auto-inducer molecule HSL.[8] Furthermore, in vitro studies have shown that AZM-exposed *P aeruginosa* displays impaired mobility and oxidative stress responses,[9] perhaps contributing to the reduced biofilm formation observed in AZM-treated cultures.[10] More recently, sub-MIC concentrations of AZM have also been shown to decrease formation of *Haemophilus influenzae* biofilms.[11]

In CFTR-null mice infected with *P aeruginosa*, AZM suppressed the production of virulence factors, improved the clearance of *P aeruginosa* biofilms and reduced the severity of lung pathology.[12] In a separate study conducted in wild-type mice, AZM failed to affect the pulmonary clearance of *P aeruginosa* embedded in agar beads but dramatically reduced the cellular infiltrate in the lung, with a substantial reduction in neutrophil numbers.[13] The disparity between these studies probably reflects methodological differences, not least the higher dose of AZM used in the former study (500 mg/kg vs 20 mg/kg) and the use of suspension rather than agar-embedded organisms which are more likely to promote biofilm production. Taken together, these studies indicate that AZM is able to antagonise bacterial virulence in the absence of a direct antibacterial effect; however, its beneficial effects in lung inflammation may not be restricted to modulating host-pathogen interactions. This view is supported by findings in mice homozygous for the ΔF508 mutation, where AZM reduced spontaneous and lipopolysaccharide (LPS)-induced inflammatory changes, suggesting that AZM may have direct effects on the immune system.[14]

MODULATION OF CYTOKINE RESPONSES

Several studies have demonstrated the ability of macrolide antibiotics, including AZM, to modulate cytokine responses both in vitro and in vivo. AZM significantly reduced nuclear factor-kappa B (NF-κB) expression, tumour necrosis factor α (TNFα) mRNA levels and TNFα secretion in a CF-derived airway epithelial cell line.[15] In mice treated with intraperitoneal LPS, AZM attenuated the increase in plasma TNFα and increased the survival in animals challenged with intravenous LPS.[16] Together, these studies show that AZM can ameliorate the proinflammatory response to bacterial antigens. This conclusion is supported by work examining the role of AZM in the treatment of bronchopulmonary dysplasia (BPD), which has demonstrated suppression of TNFα-stimulated NF-κB activation in tracheal aspirate cells from preterm infants with the reduction of interleukin (IL)-6 and IL-8 production to control levels.[17] Similarly, in an animal model of BPD, AZM caused decreased IL-6 production, less emphysematous change

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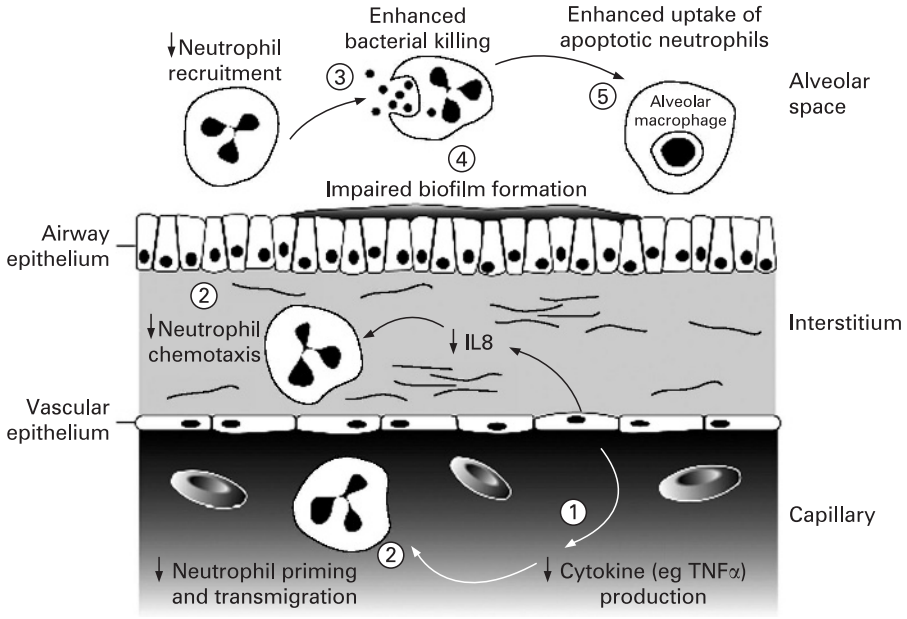

Figure 1 Effects of azithromycin (AZM) on neutrophil accumulation and activation. AZM has the capacity to modulate the cascade of neutrophil recruitment, activation and disposal at several points including (1 and 2) the initial generation and response to chemokines, principally interleukin (IL)-8 and tumour necrosis factor (TNF)α; (3) direct bactericidal or bacteriostatic effects and enhanced intracellular killing of pathogens (supported by the intense concentration of AZM within neutrophils); (4) inhibition of quorum sensing and biofilm formation by *Pseudomonas aeruginosa* and other organisms; and (5) enhanced rates of neutrophil apoptosis and (5) enhanced phagocytic removal by alveolar macrophages.

and improved survival.[18] In a small double-blind randomised placebo controlled study in extremely premature infants, prophylaxis with AZM reduced postnatal steroid requirements and duration of mechanical ventilation, although the incidence of BDP and overall mortality were unaffected.[19]

IL-8 is an inflammatory chemokine which plays a major role in neutrophil recruitment in airway diseases. AZM reduces both IL-8 levels and airway neutrophilia in patients with BOS following lung transplantation,[6] and there is interest in whether such an effect can be replicated in chronic obstructive pulmonary disease (COPD), bronchiectasis and "neutrophilic" asthma. AZM has also been shown to reduce IL-8 production by cultured airway epithelial and smooth muscle cells, perhaps as a result of suppression of mitogen activated protein kinase (MAPK) activity.[15 17 20] Administration of macrolide antibiotics including AZM to patients with nasal polyps and chronic rhinosinusitis[21] was found to reduce both polyp size and IL-8 levels in nasal lavage, again supporting an anti-inflammatory mechanism. However, under certain conditions AZM has been reported to have no effect or even to increase the release of proinflammatory cytokines. For example, a biphasic IL-8 response was demonstrated in a study using LPS-stimulated normal human bronchial epithelium cells in which AZM increased IL-8 release at 24–72 h with a return to control levels after 5 days of exposure.[22] Overall, these studies demonstrate decreased synthesis and release of proinflammatory cytokines in response to prolonged treatment with AZM, with some studies additionally suggesting an initial transient proinflammatory effect. This polyphasic response to AZM could theoretically be helpful in conditions in which infection triggers a beneficial early response with enhancement of bactericidal activity and subsequent anti-inflammatory effects promoting the resolution of airway neutrophilia; it may also complement a similar facilitatory-then-inhibitory effect on neutrophil function as described below.

MODULATION OF INNATE IMMUNITY

AZM accumulates selectively in phagocytic cells, particularly neutrophils and alveolar macrophages.[23] The intracellular concentration of AZM within the neutrophil may be up to 2000-fold that in plasma, potentially favouring antibiotic delivery to phagocytosed bacteria.[24] This could underlie enhanced intracellular killing of micro-organisms by AZM-treated neutrophils, although other mechanisms are possible.[25] It has also been suggested that fibroblasts act as a tissue reservoir for the drug, and may even be involved in the transfer of AZM to phagocytic cells.[26] The subsequent convergence of neutrophils at the site of active inflammation/infection may therefore act as a mechanism for delivering high concentrations of AZM to an inflammatory focus to exert its immunomodulatory and antimicrobial effects.

In addition to reducing the generation of neutrophil chemoattractants, AZM causes a significant reduction in the chemotactic response of both mouse and human neutrophils to chemokines (KC or IL-8) and bacterial-derived peptides (fMLP).[13] This effect was mainly due to inhibition of the ERK-1/2 rather than PI3-kinase pathway. This "double hit" of inhibiting both chemoattractant generation and chemotactic responses may explain the pronounced reduction in airway neutrophilia reported in a range of pulmonary pathologies.[6 7 13]

Interesting but apparently contradictory data have been reported on the direct effects of AZM on neutrophil degranulation and oxidative burst responses. Neutrophils isolated from healthy volunteers treated with AZM exhibit enhanced, unaffected or suppressed respiratory burst activity depending on the stimulus and the time following dosage.[27 28] For example, the responses to phorbol ester and opsonised zymosan particles were enhanced within hours following treatment but reduced after several days of AZM. Differential effects of AZM were also noted on degranulation, with evidence of an initial increase and subsequent decrease in the release of azurophil granules; however, serum elastase activity in healthy volunteers did not change over a 3-day period of AZM treatment.[27]

A study of isolated neutrophils treated with AZM in vitro did not recapitulate the effects of in vivo dosing on the oxidative burst, but instead found that AZM induced early neutrophil apoptosis.[29] Likewise, in vivo dosing with AZM was found to increase marginally the number of apoptotic neutrophils detected in blood smears in healthy volunteers, an effect maximal 28 days after the last AZM dose.[28] A further study examining isolated neutrophils after 24 h with AZM failed to demonstrate any effect on apoptosis, but in co-culture experiments employing A549 airway epithelial cells AZM reduced granulocyte-macrophage colony stimulating factor release, causing an indirect reduction in neutrophil survival.[30] Finally, ingestion of

apoptotic neutrophils and apoptotic bronchial epithelial cells by alveolar macrophages has been reported to be enhanced by AZM;[31] indeed, alveolar macrophages isolated from patients with COPD given AZM demonstrated enhanced phagocytic activity to apoptotic bronchial epithelial cells associated with increased expression of the mannose receptor.[32] Studies on the effects of macrolides on the frequency of exacerbations in COPD are ongoing.[33] These data suggest that AZM may modulate the cytokine environment to curtail neutrophil survival at inflammatory sites and, in addition, it acts to promote clearance of apoptotic cells. The effects of AZM on neutrophil accumulation and activation are summarised in fig 1.

Despite the above effects of AZM on immune cell function, there is only limited information on the intracellular mechanisms through which AZM might act. Several studies have suggested inhibition of the ERK/MAPK pathway leading to reduced IL-8 release from the bronchial epithelium, but the precise level and nature of this effect is uncertain. Other proposed mechanisms by which macrolides may impact on neutrophil signalling include altering intracellular calcium flux and impairing oxidant production due to the macrolide L-cladinose ring interfering with phospholipase D signalling.[34] However, further studies are required to shed light on the precise biochemical mechanisms underlying the immunomodulatory effects of AZM.

ADVERSE EFFECTS OF AZM

The value of medications in chronic disease must always be balanced against the potential for toxicity. Because of the potential to induce cholestasis, AZM is contraindicated in the presence of significant hepatic impairment (which excludes many patients with CF from this treatment modality), and liver and renal function should be monitored. AZM has been reported to cause tinnitus and hearing loss, and audiometry plus advice to discontinue the medication in the event of an effect on hearing may be appropriate. True allergic reactions are rare but necessitate treatment withdrawal; gastrointestinal intolerance is common but may respond to dose reduction or the use of an oral suspension. The provision of long-term antibiotics raises the potential for selection of antibiotic-resistant organisms; of particular concern is the potential for patients with CF to become colonised with atypical mycobacterial species since macrolide resistance in this context is a major clinical and therapeutic problem. Regular screening of such patients for atypical mycobacteria is normal practice, and isolation of such organisms may lead either to the use of full antimycobacterial regimens or withdrawal of macrolide monotherapy.

SUMMARY AND CONCLUSIONS

The usefulness of AZM and other macrolides in treating chronic inflammatory lung disease is likely to reflect a broad spectrum of effects, including direct and indirect antibacterial activity, modulation of systemic and pulmonary cytokine profiles and an inhibitory effect on the over-exuberant innate immune response which characterises these conditions. Further clinical trials in conditions such as BOS, BPD, COPD and asthma are required; a better understanding of the mechanisms underlying the anti-inflammatory properties of these versatile agents may help target appropriate patients for treatment and aid in the development of other immunomodulatory agents.

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Respiratory applications of telemedicine

Christopher B Cooper

Dramatic advances in electronic communications have expanded access to information and contributed vastly to global human knowledge and understanding. At the same time, electronic acquisition, processing, storage and transmission of data is rapidly becoming an integral part of modern health care. The potential seems boundless. The electronic medical record has the ability to improve the reliability and completeness of individual healthcare information and should therefore facilitate continuity of care between healthcare providers and minimise human errors. At the same time, legislators have seen the absolute necessity to respect privacy in handling protected health information.[1]

A promising application of electronic data transmission in healthcare development and delivery is telemedicine.[2] Telemedicine has evolved from the development of synchronous data modalities, through data transfer and storage, towards automated decision making and robotics.[3] One recent review article[4] analysed 104 published articles on telemedicine in order to develop an operational definition. The authors concluded that telemedicine is a branch of e-health that uses communications networks for delivery of healthcare services and medical education from one geographical location to another. Although more than 50% of published articles on telemedicine originate from the USA,[3] telemedicine has the potential to advance healthcare delivery in developing or underserved regions of the world by concentration of expertise in special centres and dissemination of services through information technologies. Teleradiology, for example, enables radiographs and CT scans to be read at remote specialised centres in other countries.[5] Approaches such as this should not only make services more widely accessible, but should also enhance the uniformity of quality of services throughout populations.

As telemedicine finds its way into mainstream medical practice, a number of clinicians and researchers have reported its application in their respective specialties. Advances in telemedicine can benefit general practice networks[6] as well as academic health centres.[7] Several publications have used telemedicine for home monitoring of patients with respiratory diseases,[2] congestive heart failure,[8] psychiatric[9 10] and other chronic illnesses[11] as well as geriatric patients with risk of falling.[12] In conjunction with portable electronic monitoring equipment, telemedicine has been shown to assist in the home monitoring of blood glucose[9] and also pulmonary function.[13] Clinical outcomes must be vigorously studied to provide convincing evidence of success in telemedicine. However, there is already some evidence of benefit in terms of health economics. One comprehensive review has shown reduced resource use, improved compliance and stabilised disease,[14] and another study of ''home telehealth'' reported reduced healthcare costs in chronic disease management.[15]

Potential applications of telemedicine in respiratory disease include home-based clinical diagnosis and monitoring, data interpretation at specialised centres for quality assurance and centralised pulmonary function measurement in clinical trials. The development of electronic spirometers, coupled with advances in telemedicine described above, has already facilitated home spirometric monitoring in patients with various lung diseases.[16] The most extensive experience to date is in home monitoring of asthma.[17] Finkelstein *et al*[18 19] implemented home spirometric monitoring for following asthma severity. The same investigators showed that this approach is well accepted by patients.[20] Home spirometric monitoring is also useful for monitoring patients following lung transplantation where critical falls in vital capacity can be indicative of acute rejection.[21] Other studies in patients following lung transplantation showed satisfactory agreements, within 4% for forced expiratory volume in 1 s and within 6% for mid forced expiratory flow, when comparing home and hospital spirometry.[22 23] A similar potential application of telemedicine is the early detection of exacerbations in chronic obstructive pulmonary disease (COPD). This has particular appeal, knowing the implications of frequent COPD exacerbations on the decline of pulmonary function and quality of life as well as healthcare utilisation. Home physiological monitoring should be explored in the context of collaborative self-management, an approach that has already been shown to substantially reduce exacerbations and healthcare expenditure in COPD.[24] However, despite interesting possibilities, appropriate methods for the detection of COPD exacerbations still need to be worked out.

While home monitoring has proved feasible, caution is probably still needed in evaluating home-based diagnostic tests. First, home physiological monitoring increases healthcare contact and expenditure. Clinically meaningful limits of deviation from an established baseline therefore need to be well worked out, and actions that result from detecting such changes must be rigorously evaluated to make sure they achieve clinically meaningful and cost-effective outcomes. Second, home physiological monitoring could fail to match the sensitivity and specificity of laboratory-based testing. For example, in one study, home-based overnight oximetry tended to underestimate the number of desaturation events in

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