INCREASING MACROLIDE RESISTANCE IN STAPHYLOCOCCAL ISOLATES FROM CYSTIC FIBROSIS PATIENTS TREATED WITH AZITHROMYCIN: DOES IT MATTER?

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Abstract Number: 285
CATEGORY: INFECTION/MICROBIOLOGY
SUBCATEGORY: Antibiotics (Pharmacokinetics/Treatment)
KEYWORDS: Azithromycin, *Staphylococcus aureus*, bacteria, clinical microbiology

ABSTRACT:
The successful clinical trials of azithromycin in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa* (Pa) pulmonary infections have led to increasing use of azithromycin as chronic therapy. (1) Many CF patients are also infected with *Staphylococcus aureus* (Sa) and inducible resistance to macrolides in Sa can occur via a number of molecular mechanisms.(2,3) We reviewed the prevalence of macrolide resistance in CF patients colonized with Sa and other gram-positive organisms and treated with chronic azithromycin therapy at Northern New England CF centers. In a sample of 270 CF patients from 3 centers, 58 (21%)were treated with azithromycin as chronic therapy for Pseudomonas and were also colonized with Sa or *Streptococcus pneumoniae* (Sp). Of this group, there were 47(81%) who had either resistant or intermediate sensitivities to erythromycin. Thirty-two of the 46 Sa strains were methicillin-sensitive but 14 had methicillin-resistant Sa (MRSa) also resistant to erythromycin. In CF patients infected with Sa but not receiving azithromycin, resistance was seen in 7-32% of gram-positive isolates at the three centers. In addition to Sa, one patient had transient *S. pneumoniae* resistant to macrolides in the azithromycin group but 4/10 (40%) resistant strains were seen in untreated patients. Our data indicate that CF patients with Sa receiving chronic azithromycin have a high rate of resistance and should receive antibiotics other than macrolides for Sa coverage in acute exacerbations. Whether chronic azithromycin has a role in the CF patient with Sa alone as chronic therapy is not clear. The anti-inflammatory and anti-adhesion effects of azithromycin may provide a rationale for continuing chronic azithromycin in Sa-infected patients but it is unknown whether Sa biofilm formation is susceptible to macrolides, particularly in resistant strains. Increasing resistance to macrolides may also have infection control implications for siblings, given the frequent use of macrolides in community-acquired infections.

1. Saiman,L.,Marshall, BC, Mayer-Hamblett, N et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. JAMA 290:1749-56,2003.2. Prunier, A-L,Malbruny, B, Tande,D et al. Clinical isolates of *Staphylococcus aureus* with ribosomal mutations conferring resistance to macrolides. Antimicrob Agents Chemother 46:3054-56,2002. 3. Volokhov, D, Chizhikov, V, Chumakov, L et al. Microarray determinants of erythromycin resistance determinants. J Appl Micro 95:787-98,2003.

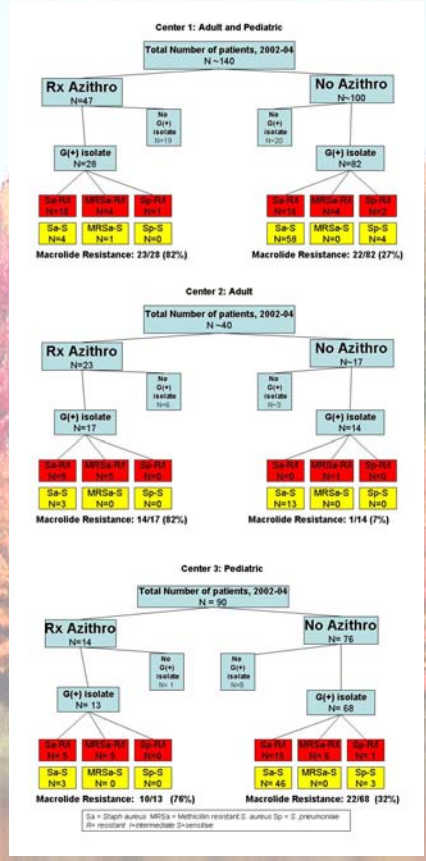
Introduction

The successful clinical trials of azithromycin in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa* (Pa) pulmonary infections have led to increasing use of azithromycin (AZ) as chronic therapy.[1] Many CF patients also have infections with *Staphylococcus aureus* (Sa) and other Gram positive organisms and inducible resistance to macrolides can occur in Sa via a number of molecular mechanisms.[2,3]

1. Saiman,L.,Marshall, BC, Mayer-Hamblett, N et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. JAMA 290:1749-56,2003.
2. Prunier, A-L,Malbruny, B, Tande,D et al. Clinical isolates of *Staphylococcus aureus* with ribosomal mutations conferring resistance to macrolides. Antimicrob Agents Chemother 46:3054-56,2002.
3. Volokhov, D, Chizhikov, V, Chumakov, L et al. Microarray determinants of erythromycin resistance determinants. J Appl Micro 95:787-98,2003.

Goal

To determine the prevalence of macrolide resistance in Sa and other gram-positive isolates from CF patients treated with chronic AZ therapy at three Northern New England CF centers and compare to macrolide resistance in Sa isolates from patients not on chronic AZ.



Methods

Patients receiving chronic macrolide therapy for greater than 3 months were identified through PORTCF at three Northern New England CF Centers. We reviewed all sputum and throat cultures for these patients since 2002 and identified those with clinically significant gram-positive isolates (*Staphylococcus aureus* and *Streptococcus pneumoniae*). We also used to PORTCF to identify patients not receiving AZ who also had gram-positive isolates to determine the rate of macrolide resistance in this group.

Results

In a sample of 270 CF patients seen at three centers, 58 (21%) were treated with AZ as chronic therapy (most with Pa) and were also infected with Sa or Sp. Of this group, there were 47 (81%) who had either resistant or intermediate sensitivities to erythromycin. The rate of resistance in AZ-treated patients was 76, 82 and 82% in the three centers. Thirty-two of the 46 Sa strains were methicillin-sensitive but 14 had methicillin-resistant Sa (MRSa) also resistant to erythromycin. In CF patients infected with Sa but not receiving AZ, resistance was seen in 7-32% of gram-positive isolates at the three centers. In addition to Sa, one patient had transient *S. pneumoniae* resistant to macrolides in the azithromycin group but 4/10 (40%) resistant strains were seen in untreated patients, reflecting the high baseline community resistance rates in Sp.

Conclusion

Our data indicate that CF patients receiving chronic AZ develop a high rate of resistance. Whether chronic AZ has a role in the CF patient who only cultures only Sa is not known. The anti-inflammatory and anti-adhesion effects of AZ may provide a rationale for continuing chronic AZ in Sa-infected patients but it is unknown whether Sa biofilm formation is susceptible to macrolides, particularly in resistant strains. Increasing resistance to macrolides in gram-positive isolates may also have infection control implications for siblings, given the frequent use of macrolides in community-acquired infections.

The Northern New England Cystic Fibrosis Consortium

The NNECFC is a regional, voluntary consortium of more than 80 clinicians and researchers from the CF care centers in Maine, New Hampshire and Vermont.

The mission of the group is to improve CF care and patient outcomes.