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White Paper

RARE DISEASE

# Is Azithromycin the Answer to Mitigate the Loss of Lung Function in Cystic Fibrosis Due to Pulmonary Acute Exacerbations?

CROMSOURCE is an international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialised in clinical development and staffing solutions.

Acute pulmonary exacerbations, especially those requiring hospitalisation, are a major issue in cystic fibrosis (CF) management due to their association with loss of lung functions beginning in mid-childhood and continuing unabated through life in these patients. By consequence, the ability to prevent such exacerbations is a key priority.

Pseudomonas aeruginosa (Pa) is an important pathogen infecting the lower airways of subjects with CF and its acquisition in early life is associated with a pro-inflammatory response, lower lung function, increased cost of care and decreased survival. Early Pa isolates have distinct phenotypic characteristics including high susceptibility to antibiotic therapy, whereas chronic infection is associated with mucoid phonotype, biofilm formation and increasing antibiotic resistance often refractory to treatment. Thus, understanding the transition from early to chronic infection and developing preventive strategies are central to management of CF lung disease.

Previous studies using low dose macrolides was conducted in adult CF patients chronically infected with Pseudomonas aeruginosa and indicated improvement in clinical parameters and pulmonary function after 6 - 12 months of treatment. Additional trials will be needed to evaluate further the efficacy and safety of prolonged use (>1 year) of macrolide antibiotics in children.

Researchers in clinical trials of azithromycin therapy in CF have universally reported a reduction in acute pulmonary exacerbations in CF and as such this therapy may hold the key to preservation of lung function. However, concerns remain about the duration of benefit and about risk. Risk include side effects and development of antibiotic resistance.

Now, a very recent study has provided a new finding on it. Mayer-Hamblett (Professor, Department of Pediatrics, University of Washington, Seattle Children's Research Institute, Seattle, WA) and colleagues have published in the peer journal AJRCCM the result of the OPTIMIZE (Optimizing Treatment for Early Pseudomonas aeruginosa Infection in Cystic Fibrosis) trail. This is a multicentre, randomized, and controlled, double-blind trial of azithromycin three times per week, administered orally via suspension (approximately 10mg/kg up to a maximum of 500 mg per dose) versus placebo in children with CF with early Pseudomonas acquisition. Study drug was used in combination with inhaled tobramycin that was prescribed to eradicate the Pseudomonas infection.

The 18 months follow-up period is the longest to date in a trial investigating the use of azithromycin for the treatment of CF lung disease.

All randomized children with CF ages 6 months to 18 years with documented new positive oropharyngeal, sputum or lower respiratory tract culture for Pa within 40 days of the baseline visit, received standardised Tobramycin Inhalation Solution (TIS) therapy (TOBI 300 mg bid delivered by inhalation using the PARI LC PLUS nebulizer ) during the first treatment quarter, consisting of a 28-day course of TIS therapy with a second 28-day course for those who remained Pa positive at 21 days.

Subsequently, participants received TIS therapy at the beginning of each quarter (administered as a single 28-day course) only if their quarterly cultures were Pa positive.

Enrolled was stopped early by NHLBI because the trial had reached the pre-specific interim boundary for efficacy.

The primary endpoint was time to protocol-defined pulmonary exacerbation (PEx) requiring oral, inhaled, or intravenous antibiotics, utilizing a pre-specified definition as shown in the following box,

## The Presence Of A Pulmonary Exacerbation Was Established By The Following:

### 1) MAJOR CRITERIA ALONE

1. **Absolute decrease** in $FEV_1$ % predicted of ≥ 10%
2. **Oxygen saturation** < 90% on room air or absolute decrease of ≥ 5%
3. **New lobar infiltrate**(s) or atelectasi(e)s on chest radiograph
4. **Hemoptysis** (more than streaks on more than one occasion in past week)

*One finding alone establishes the presence of a pulmonary exacerbation*

OR

### 2) MINOR SIGNS / SYMPTOMS
AND FULLFILLMENT OF SYMPTOM DURATION

1. **Increase work** of breathing or respiratory rate
2. **New or increased** adventitial sound on lung exam
3. **Weight loss** ≥ 5% of body weight or decrease one major percentile in weight percentile of age in past six months
4. **Increase cough**
5. **Decreased** exercise tolerance of level of activity
6. **Increased** chest congestion or change in sputum

*Two minor signs/symptoms are required in the absence of major criteria. If at least two minor signs/symptoms are present, at least one needs to be three or more days in duration to meet the PE definition*

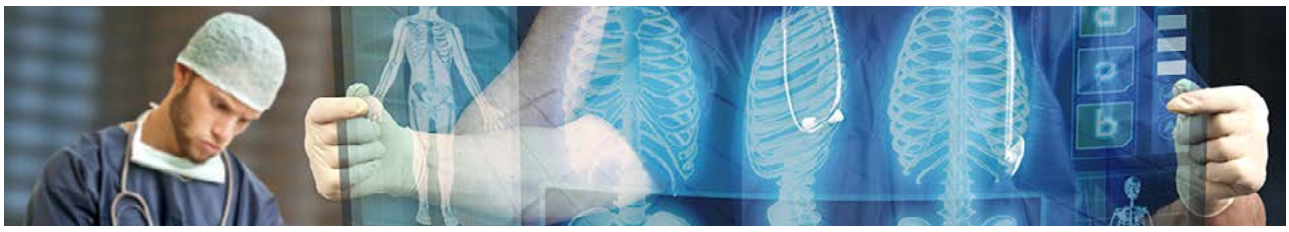
while secondary endpoint was time to *Pa* recurrence, in addition to other clinical and safety outcomes.

In children who received azithromycin, 110 patients out of 221 participants, the risk of PEx was reduced by 44% compared to placebo, (highly significant p=0.004).

The greatest reductions were observed in the youngest age group (6 months -3 years) and females.

Weight increase was by 1,27 kg in the azithromycin group compared to placebo (p=0.046).

No significant differences were seen in microbiological or other clinical or safety endpoints including no evidence of a negative clinical or microbiologic interaction with TIS when used as initial eradication therapy during early *Pa* infection.



The importance of this study lies in the relatively long follow-up period of 18 months and the safety monitoring, which included hearing tests and electrocardiography. Reassuringly, no increased side effects, in particular hearing loss and ECG abnormalities, were detected in the azithromycin group despite the 18 months of treatment. Hence, the risk of serious azithromycin-related side effects appears to be low even when azithromycin is used for extended periods.

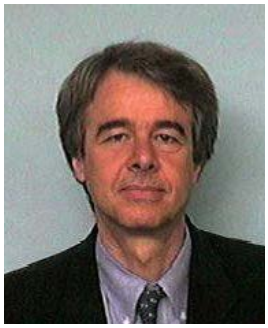
The mechanism through which azithromycin reduces the risk of pulmonary exacerbations in CF is not entirely clear, but it is most likely to be linked to anti-inflammatory activity. CF is known to be a disease of neutrophil-mediated immune dysregulation, and azithromycin ameliorates neutrophilic inflammation through, among others, the nuclear factor-kB pathway.

The evident question is whether regular azithromycin should be routinely prescribed for children with CF. Mayer-Hamblett and colleagues conclude that given the association between exacerbation risk and morbidity over the lifetime of individuals with CF, azithromycin may be a therapeutic option for children with CF and early *Pa* infection.

## References

Mayer-Hamblett N., Retsch-Bogart G., Kloster M., et al.
Azythromycin for early Pseudomonas infection in cystic fibrosis: the OPTIMIZE randomized trial.
Am. J. Respir. Crit. Care med. 2018; 198: 1177 – 1187.

## About The Author



**Renato Testi** graduated from the University of Padua with a degree in Chemistry, before gaining his MD from the University of Verona. After a couple of years at Padua University as an assistant in the Organic Chemistry Department, Renato joined Laboratory Glaxo S.p.A. (Italy) as Head of Chemistry from 1974 to 1979. In 1979 he moved to the Medical Department as a Medical Advisor, subsequently becoming Medical Respiratory Leader in the same company Glaxo Smith Kline SpA (Italy) from 1979 to December 2004. In this role Renato supported clinical development and marketing activities of several drugs in respiratory medicine.

In 2006, Renato became a Clinical Research Physician at Centro Ricerche Cliniche, Policlinico BG Roma, Verona focusing on performing medical activities and screening visits for volunteers involved in clinical trials in Phase I to III. Renato joined CROMSOURCE in 2010 as a Medical Monitor in the Clinical Research division. Here Renato has managed clinical trial activities, medical oversight and monitoring procedures for many international clinical trials in both asthma and COPD.

Renato continues practising as a physician specialised in respiratory medicine.

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## About CROMSOURCE

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