Anti-inflammatory therapy

Azithromycin

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Background

Prevention of lung deterioration is one of the most important goals in Cystic Fibrosis therapy, because persistent pulmonary infection and the associated hyperactive inflammatory response cause lung damage. Pseudomonas aeruginosa (P.a.), above all its mucoid phenotype, is considered the most important pathogen in chronic airway infection.

Macrolides are an orally available class of antibiotics with a broad spectrum of action, mainly against gram-positive bacteria and Azithromycin (Az) is the most studied macrolide.

Az has shown the most significant activity against P.a. virulence factors and its efficacy against P.a. has been studied recently in a rat lung infection model (Kumar M, 2021)

Az has demontrated an anti-inflammatory activity (Olveira C, 2017), even if more recently the OPTIMIZE trial (Pittman JE,2022) demonstrated improvement in time to first pulmonary exacerbation in children with new P.a. treated with Az, but no impact has been found in systemic markers of inflammation over 18 months.

Finally ,a possible role in the management and prevention of rhinovirus (RV)-induced CF pulmonary exacerbations (Schögler A·2015) has been speculated

International Guidelines (Mogayzel P. 2013) had affirmed that Az chronic use, above all in patients infected by P.a., is recommended, even if Az administration should be avoided in the presence of severe hepatic or renal involvement. After 6 months of treatment the drug should be discontinued if no observable effects are noted on clinical parameters, exacerbation rate and/or FEV1 values. More recently, (Abely M,2015) a National Consensus in France validated Az use as a long-term anti-inflammatory agent in children aged over 6 years, presenting with the classical form of CF, irrespective of the bacteriological status, except for Non-Tuberculous Mycobacteria (NTM).

No sure adverse events related to Az use are reported in CF patients. In patients affected by other diseases, it has been hypothesized (Ray WA, 2012 that Az may increase the risk of cardiovascular death, above all by severe arrhythmias, but it has been affirmed (Albert RK, 2014), that the large majority of subjects experiencing cardiac arrhythmias from macrolides, have other co-existing risk factors. In 2019 (Avedissian SN ,2019) a retrospective study conducted over a 3-year period in an adult CF Center, did not show any association between chronic Az therapy and longer QTc intervals or significant QTc prolongation. Az long-term use (Magaret A, 2021) has shown no association with QTc prolungation, in children too. Recently (Song Y, 2021) it has been reported an unusual side effect of first degree heart block after 8 months of Az in combination with tezacaftor/ivacaftor CFTR modulator.

In 2022 (Akkermann-Niylan A M, 2022) a study enrolled 72 CF patients using Az for a cumulative period of 364,8 years and observed no renal or hepatic toxicity, nor cardiac arrhythmias for a mean study duration of more than 5 years. even if attention has been reccommended in patients using other QTc-interval prolonging medication.

The hypothesized Az role in increasing the risk for NTM infection (Renna M, 2012), has not been confirmed (Binder AM, 2013). On the contrary, a study (Coolen N, 2015) has suggested that Az may be a primary prophylaxis for NTM infection in CF adults and a more recent study (Cogen JD, 2018), in which data about 26.914 patients from the US CF Foundation Patient Registry, were collected, showed that chronic Az users had a lower risk of acquiring several CF-related respiratory pathogens including NTM. Moreover, In 2021 (Richter W, 2021) low rates of macrolide-resistant Mycobacterium avium complex was shown, despite chronic Az therapy.

Concerns have emerged about the concomitant use of Az and Tobramycin in pulmonary exacerbations (Cogen JD, 2021) and about the Az therapy during pregnancy (Taylor-Coursar J, 2021)

Issues

Azithromycin efficacy in preventing pulmonary deterioration, evaluated as lung function evolution, lung exacerbation frequency, quality of life and survival.

Short-term and long-term azithromycin therapy-associated adverse effects (gastrointestinal symptoms, liver problems, hearing impairment, acquisition of significant CF lung pathogens, change in antibiotic susceptibility pattern, cardiovascular problems).

Optimal therapy administration protocol.

What is known

One CDSR (Southern KW, 2024) included 14 studies (1467 participants) lasting 28 days to 36 months. All the studies assessed azithromycin: 11 compared oral azithromycin to placebo (1167 participants); one compared a high dose to a low dose (47 participants); one compared nebulised to oral azithromycin (45 participants); and one looked at weekly versus daily dose (208 participants). Azithromycin therapy is associated with a small but consistent improvement in respiratory function, a decreased risk of exacerbation and

longer time to exacerbation at six months; but evidence for treatment efficacy beyond six months remains limited. Azithromycin appears to have a good safety profile (although a weekly dose was associated with more gastrointestinal side effects, which makes it less acceptable for long?term therapy), with a relatively minimal treatment burden for people with CF, and it is inexpensive. A wider concern may be the emergence of macrolide resistance reported in the most recent study which, combined with the lack of long?term data, means we do not feel that the current evidence is strong enough to support azithromycin therapy for all people with CF. - Future research should report over longer time frames using validated tools and consistent reporting, to allow for easier synthesis of data. In particular, future trials should report important adverse events such as hearing impairment or liver disease. More data on the effects of azithromycin given in different ways and reporting on our primary outcomes would benefit decision?making on whether and how to give macrolide antibiotics. Finally, it is important to assess azithromycin therapy for people with CF who are established on the relatively new cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies which correct the underlying molecular defect associated with CF (none of the trials included in the review are relevant to this population).

One CDSR, updated November 2012(Southern KW, 2012) included 10 RCT with 959 enrolled CF patients older than 6 years. In 8 studies, azithromycin (Az) was compared with placebo. Only adults were enrolled in one study and only children were enrolled in four, and in one study only P.a.-positive patients were enrolled, whereas in another study only P.a.-negative patients were enrolled. CDSR results suggest that Az, administered at the dosage of 500 mg (250 mg if weight is <40 Kg) three times a week, improves lung function and reduces pulmonary exacerbations, mainly in patients with chronic P.a. lung infection and during the first six months of treatment. With this dose regimen adverse events are uncommon, even if Staphylococcus aureus (S.a.) macrolide resistence increases.

A meta-analysis (Reynaud Q, 2020) about risk factors for nontuberculous mycobacterial isolation has not found Az therapy among them.

In 2018 (Mayer-Hamblett N, 2018) a multicenter, placebo-controlled, trial in children with CF with early Pa.isolation, Az resulted associated with a significant reduction in risk of pulmonary exacerbation and improvement in weight but not with impact on microbiologic outcomes.

In 2019 (Nichols DP, 2019) a retrospective cohort study using the U.S. CF Foundation Patient Registry, showed that, across 3 years, FEV1 %/ year decline was nearly 40% less in those with P. aeruginosa using azithromycin compared to matched controls and that this rate of decline did not differ based on azithromycin use in those without P.a.

In 2020 one RCT (Magaret AS, 2020) about 221 CF children showed that long-term chronic azithromycin use, with a median of 18 months follow-up, was not associated with increased QT prolongation.

In 2021 (Akkerman-Nijland AM, 2021) an observational controlled study observed no renal or hepatic toxicity, nor cardiac arrythmias during azithromycin use in CF patients for a mean study duration of more than 5 years.

In 2022, the COMBACT CF, a phase 3 RCT (StickSM, 2022) demonstrated that Az treatment from CF diagnosis does not reduce the extent of structural lung disease at 36 months of age, but it reduces airway inflammation and pulmonary exacerbations.

A systematic review (Elmegeed AA, 2025) investigate the safety and efficacy of Azithromycin in Cystic fibrosis. It included randomized controlled trials (RCTs) and cohort studies. Cystic fibrosis (CF) patients with chronic lung inflammation and decline. A total of 18 studies comprising 2877 patients were included, with 11 studies meeting the criteria for inclusion in the meta-analysis. AZM significantly reduced the need for new oral antibiotics (RR = 0.77; 95 % CI: [0.66, 0.89]). No significant increase in adverse events was observed. However, lung function (FEV1, FVC, FEF), inflammatory markers, and pulmonary exacerbations remained unchanged. In cuìonclusion, Azithromycin holds promise for managing CF, but further research is needed to fully understand its long-term impact on lung health and resistance patterns.

Unresolved questions

- Efficacy and safety of azithromycin therapy over a more prolonged period of time, mainly in children, above all in pre-symptomatic ones.

No RCT are ongoing

Keywords

Anti-Inflammatory Agents; Macrolides;