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The Efficacy and Safety of Azithromycin for Patients with Cystic Fibrosis: A Systematic Review

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A B S T R A C T

Azithromycin has antimicrobial, immunomodulatory, and anti-inflammatory effects for chronic inflammatory processes in cystic fibrosis (CF). This systematic review evaluates the effectiveness and safety of azithromycin as a potential therapy for CF patients. The authors assessed the efficacy of azithromycin using the FEV1 and the drug's safety by comparing adverse effects. Furthermore, we also reviewed secondary outcomes, consisting of Forced vital capacity (FVC) values and pro-inflammatory indicators. In addition, they consist of exacerbations, bodyweight gain, and quality of life. The authors searched the published literature using online databases PUBMED and Cochrane Library published until March 9, 2021. The keywords were "Azithromycin" and "Cystic fibrosis" with the Boolean operator "AND" with no restrictions in publication year and research design. We conducted a critical study using the Critical Appraisal Skills Program (CASP) and Jadad score to minimize bias. Findings from eight journals showed that five studies reported increased mean FEV1 after giving azithromycin in patients with CF. Three studies notified increased FVC, and four research reported decreased pro-inflammatory indicators, namely CRP, IL-8, and neutrophils. Two papers reported a significant weight gain. Two studies informed improved the patients' quality of life. In addition, three publications did not report any significant or severe side effects. The most common adverse effect informed by the other four studies were rash in two studies, diarrhea in two studies, nausea, and fever in two studies. In conclusion, we consider azithromycin administration for CF patients is relatively safe and well-tolerated.

INTRODUCTION

Cystic fibrosis (CF) is the most life-threatening autosomal recessive disease in the United States. It is the primary cause of pulmonary and gastrointestinal system morbidity in children, leading to death in young adults (Farrell *et al.*, 2017). CF can cause an abnormality in the liver, gastrointestinal system, and male reproductive system. However, lung disease is the primary cause of morbidity and mortality in this disease. Almost every patient has an obstructive pulmonary disease associated with a chronic infection which causes progressive loss of lung function (Rafeeq and Murad, 2017). The disrupted gene in CF is chromosome 7, which codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Cystic fibrosis transmembrane conductance regulator functions as an ion channel and controls the movement of salt and water in and out of epithelial cells. More than 1,000 mutations in the CF gene have been identified. The most common mutation is delta F508, where there is a deletion of three base pairs at position 508 (De Boeck, 2020).

At least one of 4,000 newborns in the United States has CF, and it seems that the incidence is increasing in European countries (Farrell *et al.*, 2017). Until recently, cystic fibrosis is rarely found in the non-Caucasian population. Data about the prevalence of cystic fibrosis in Indonesia has not been documented

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in the literature yet. Still, the estimated cystic fibrosis incidence in Southeast Asians is 1: 9.000 to 1: 40.0000 in the Southeast Asian population living in Canada and the United States (Ahmed *et al.*, 2020).

CTFR gene regulates the ability of the normal sweat duct epithelium to absorb chloride. Mutation of the CFTR gene will cause a disruption of chloride transport in the epithelium, causing an increase of chloride in the sweat – therefore, clinical diagnosis to establish CF is the sweat chloride test. At the same time, the airway epithelium and the gastrointestinal tract require CFTR for chloride secretion. The inability to secrete chloride into the lumen, accompanied by the increased sodium absorption, leads to water osmotic resorption from the lumen and dehydration of the mucus layer that covers the mucosal cells. Mucociliary dysfunction and accumulation of very thick secretion will eventually block the activity of the "defensin" antibacterial substances produced by the epithelium. This condition predisposes the patient to recurrent infections. Patients with a homozygous F508 delta mutation (or one of the combinations of the two severe mutations) render CFTR dysfunctional. Further, it causes CF's severe clinical manifestation (classic cystic fibrosis) and an early pancreatic insufficiency with varying degrees of lung damage (Savant and McColley, 2019).

Babies with CF mostly have moderately severe respiratory symptoms, and some of them even need to be hospitalized. Cough, tachypnea, rhonchi, and wheezing are the most common clinical symptoms. Abnormalities in lung function initially indicate a pattern of obstruction, reduced flow rate, and increased lung volume. As the disease progresses, the total lung capacity is also impaired. The incidence of airflow reactivity in CF is estimated at 25-50%, several times higher than the incidence in the general population. At first, there was a *Staphylococcus aureus* colonization, but *Pseudomonas aeruginosa* became the predominant pathogen in most people. Mucus produced from the *Pseudomonas* pathogen is associated with a rapid decline in lung function. The earliest involved lesions are hyperplasia of the mucous glands in the bronchial epithelium, mucosa, and submucosal cellular. Then there are infiltrates with dilatation of the airways. Bronchiolectasis and bronchiectasis sometimes occur afterward (Klimova *et al.*, 2017; Savant and McColley, 2019).

Treatment for CF is drugs to improve cellular processing and facilitate chloride movement across ion channels. In addition, there is gene therapy capable of delivering functional CFTR directly to the lungs. Currently, antibiotics are still the most effective way to reduce clinical signs and symptoms of disease in most CF patients. Macrolide antibiotic is one of the antibiotics used in the long term. One of them is azithromycin (Rafeeq and Murad, 2017).

Azithromycin can inhibit bacterial growth by attaching to 23S RNA at the 50S unit of the bacterial ribosome to prevent the growth of bacterial polypeptides (Acosta *et al.*, 2021). It is an immunomodulator and anti-inflammatory drug. It increases the immune system against infection and reduces the inflammatory response triggered by internal and external factors in CF patients. It modulates host defense

and reduces inflammation by interacting with structural cells such as epithelial cells, smooth muscle cells, fibroblasts, neutrophils, and mononuclear leukocytes. It ensures transepithelial integrity and resistance to permeability induced by *P.aeruginosa* virulence factors. In addition, it reduces mucin secretion and attenuates inflammatory cytokine expression. Azithromycin inhibits interleukin-8 (IL-8) release in airway smooth muscle cells and attenuates fibroblast growth factor induced by vascular endothelial growth factor (Fonseca *et al.*, 2020; Thornton, Chin and Somayaji, 2021).

Azithromycin is one of the most potent drugs in treating CF patients. It is due to its pharmacological properties. This literature review study evaluates the effectiveness and safety of azithromycin as a potential therapy for CF patients. In this study, the authors assessed the efficacy of azithromycin using the FEV1 and the drug's safety by comparing adverse effects. FEV1 is a forced expiratory volume in the first second. Furthermore, we also reviewed secondary outcomes, consisting of Forced vital capacity (FVC) values and pro-inflammatory indicators. In addition, they consist of exacerbations, bodyweight gain, and quality of life. This systematic review can contribute to the more efficient use of therapy in managing CF, especially azithromycin as one of the regimens in CF management.

METHOD

The authors searched the published literature using online databases PUBMED and Cochrane Library published until March 9, 2021. The keywords were "Azithromycin" and "Cystic fibrosis" with the Boolean operator "AND" with no restrictions in publication year and research design. Selection criteria were publication with randomized control trial (RCT), involved CF patients of all ages, and compared placebo with azithromycin. We conducted a critical study using the Critical Appraisal Skills Program (CASP) and Jadad score to minimize bias. The data analysis was presented in descriptive narrative and tabular form.

RESULT

The results revealed the Jadad score (Table 1), demographic data of the research population (Table 2), research design (Table 3), summary of literature review findings (Table 4), and therapeutic safety (Table 5). Table 1 shows that six studies are considered high quality (Jadad scale ≥4 points) (Equi *et al.*, 2002; Wolter *et al.*, 2002; Saiman *et al.*, 2003; Clement *et al.*, 2006; Mayer-Hamblett *et al.*, 2018; Steinkamp *et al.*, 2018). Meanwhile, one study is relatively low quality (Jadad Score ≤3) (Jaffe *et al.*, 1998).

Table 1 The Jadad Score on each study

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No	Author	Year	Randomization	Blinding	Withdrawal/Dropout	Jadad Score
1	Jaffe et al	1998	2	0	0	2
2	A Equi et al	2002	2	2	0	4
3	Wolter et al	2002	2	2	0	4
4	Saiman et al	2003	2	2	1	5
5	Clement et al	2006	2	2	1	5
6	Steinkamp et al	2008	2	2	1	5
7	Mayer-Hamblett et al	2018	2	1	1	4

There was a total of 616 patients assessed from seven RCT studies evaluating the effect of azithromycin on CF patients ranging from 1998 to 2018 (Jaffe *et al.*, 1998; Equi *et al.*, 2002; Wolter *et al.*, 2002; Saiman *et al.*, 2003; Clement *et al.*, 2006; Mayer-Hamblett *et al.*, 2018; Steinkamp *et al.*, 2018). Most participants in two studies (Jaffe *et al.*, 1998; Wolter *et al.*, 2002) were females, while most respondents in one study (Mayer-Hamblett *et al.*, 2018) were males. The participants' age ranged from 6 months old to 18 years old. However, four studies did not mention the participants' age (Equi *et al.*, 2002; Saiman *et al.*, 2003; Clement *et al.*, 2006; Steinkamp *et al.*, 2018) (Table 2).

Table 2 Demographic data of the research population

No	Author	Year	Intervention	Total Participants/participants who completed the study	Sex (Male/Female)	Age Range (Year)	Mean ± standard deviation or median age of the Participant (Year)
1	Jaffe et al	1998	azithromycin and placebo	7/7	3/4	6-18 years old	12,1
2	A Equi et al	2002	azithromycin and placebo	41/41	Not mentioned	8-18 years old	13,8
3	Wolter et al	2002	azithromycin and placebo	60/60	M: 29 people F: 31 people	18-44 years old	27,9
4	Saiman et al	2003	azithromycin and placebo	185/184	Not mentioned	6 years old - adult (19 subjects aged < 13 years old)	Not mentioned
5	Clement et al	2006	azithromycin and placebo	82/72	Not mentioned	>6 years old	11,0 ± 3.3
6	Steinkamp et al	2008	azithromycin and placebo	40/31	Not mentioned	>8 years old	23.7
7	Mayer-Hamblett et al	2018	azithromycin and placebo	227/221	M: 117 people F: 104 people	6 months-18 years old	Group azithromycin: 7.1±5.1 Group placebo: 6.8±5.0

Furthermore, the duration of azithromycin therapy ranges from 8 weeks to 18 months. The dose of azithromycin given varies in each study; one of the considerations was participants' age (Jaffe *et al.*, 1998; Equi *et al.*, 2002; Wolter *et al.*, 2002; Saiman *et al.*, 2003; Clement *et al.*, 2006; Mayer-Hamblett *et al.*, 2018; Steinkamp *et al.*, 2018).

Table 3 Research Design

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No	Author	Year	Intervention	Washout Period	Duration of Azithromycin Therapy	Dose (D) Time (T) of Azithromycin Administration
1	Jaffe et al	1998	azithromycin and placebo	Not mentioned	Not reported	Not reported
2	A Equi et al	2002	azithromycin and placebo	Two months	Six months	D: 40 kg bodyweight: 250 mg daily, >40 kg bodyweight: 500 mg daily T: once a day
3	Wolter et al	2002	azithromycin and placebo	Not mentioned	Three months	D: 250 mg T: once a day
4	Saiman et al	2003	azithromycin and placebo	Not mentioned	Six months	D: 500 mg (bodyweight>40 kg), 250 mg (bodyweight<40 kg) T: 3 times a week (Monday, Wednesday, and Friday)
5	Clement et al	2006	azithromycin and placebo	Not mentioned	12 months	D: 500 mg (bodyweight>40 kg), 250 mg (bodyweight<40 kg) T: 3 times a week
6	Steinkamp et al	2008	azithromycin and placebo	Not mentioned	Eight weeks	D: (20-29 kg bodyweight: 500 mg, 30-39 kg bodyweight: 750 mg, 40-49 kg bodyweight: 1000 mg, and ≥50 kg bodyweight: 1250 mg) T: Once a week
7	Mayer-Hamblett et al	2018	azithromycin and placebo	Not mentioned	18 months	D: 10 mg/kg bodyweight, maximum 500 mg T: 3 × a week

Five studies (71,4%) reported increased mean FEV1 after giving azithromycin in patients with CF (Jaffe et al., 2018; A Equi et al., 2002; Wolter et al., 2002; Saiman et al., 2003; Clement et al., 2006). Three studies notified increased FVC (Jaffe et al., 2018; A Equi et al., 2002; Wolter et al., 2002), while the three others did not include FVC as the study result (Clement et al., 2006; Steinkamp et al., 2008; Mayer-Hamblett et al., 2018). Four studies informed a decrease in pro-inflammatory indicators, namely CRP, IL-8, and neutrophils (A Equi et al., 2002; Wolter et al., 2002; Clement et al., 2006; Steinkamp et al., 2008). In addition, two studies reported a significant weight gain in the azithromycin group (Saiman et al., 2003; Mayer-Hamblett et al., 2018). Furthermore, two studies reported improving the patients' quality of life by receiving Azithromycin treatment (Wolter et al., 2002; Steinkamp et al., 2008) (Table 4).

Table 4 Summary of literature review findings

No	Author	Publication Year	No. of Participant/No. of Participant who completed the study	Findings	Significance value (*p*)
1	Jaffe et al	1998	7/7	• The median increase in FEV_1 in the azithromycin group was 11% (3.6 - 13.4) • The median increase in FVC in the azithromycin group was 11.3% (-5.5 – 24.7) • Increased oxygen saturation in the azithromycin group from 65% to 93%	< 0.03* < 0.03* No report in *p*-value

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2	A Equi et al	2002	41/41	• Increased mean FEV_1 in the azithromycin group	0.031*
				• Increased FVC in the azithromycin group	0.032*
				• Decreased use of additional antibiotics in the azithromycin group	0.005*
				• The median absolute value of IL-8 in the azithromycin vs. placebo group was 9041 g/g sputum (95% CI – 70 889 – 73 800)	>0.05
				• Neutrophil estalase (95% CI -12 – 6)	>0.05
3	Wolter et al	2002	60/60	• Increased FEV1 % pred in the azithromycin group	0.047*
				• Increased FVC of Azithromycin	0.001*
				• Reduced days on providing intravenous antibiotics when acute exacerbations in the azithromycin group	0.009
				• Reduced days of intravenous antibiotic use at home in the azithromycin group	0.037*
				• Median CRP values in the azithromycin group were lower	<0.001*
				• Improved quality of life in the azithromycin group	0.042*
4	Saiman et al	2003	185/184	• Increased mean FEV_1 on day-168 in the azithromycin group 0.094 L 95% CI, 0.023-0.165	0.009*
				• Decreased exacerbation in the azithromycin group (hazard ratio 0.65; 95% CI, 0.44-0.95)	0.03*
				• Weight gain in the azithromycin group was 0.7 kg more than the placebo group (95% CI, 0.44-0.95)	0.03*
5	Clement et al	2006	82/72	• Changes in FEV_1 % were predicted after 12 months in the azithromycin and placebo groups (mean SD -4.3 (17.9) % vs. -1.5 (5.4) %	No report in *p*-value
				• Decreased exacerbation in the azithromycin group (95% CI, 0.32-0.79)	< 0.005*
				• Reduced use of oral antibiotics in the azithromycin group (95% CI, 0.36-0.85)	< 0.01*
6	Steinkamp et al	2008	40/31	• Changes in the mean absolute FEV_1 from the baseline in the two groups were not significantly different	0.708
				• FEV_1 decreased by 4.4% (SD 14.1%) in the azithromycin group and 5.2% (SD 11.2%) in the placebo group	0.826
				• Improvement of serum CRP values in the azithromycin group (+0.9µg/ml)	0.019*
				• Improved quality of life in the azithromycin group (weight gain, respiratory symptoms, and eating disorders)	<0.05*
7	Mayer-Hamblett et al	2018	227/221	• Change in mean FEV_1% pred at 18 months (95% CI -7,76,4,34)	0.384
				• Decreased exacerbations in the azithromycin group (95% CI 0.37, 0.83)	0.004*
				• Weight gain of 1.27 kg in the azithromycin group (95% CI 0.01-2.52)	0.046*

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Table 5 indicates the adverse events of azithromycin. One study did not report any side effects (Jaffe *et al.*, 1998), and two studies did not report any significant or severe side effects (Equi *et al.*, 2002; Mayer-Hamblett *et al.*, 2018). The most common adverse effect reported by the other four studies were rash in two studies (Wolter *et al.*, 2002; Clement *et al.*, 2006), diarrhea in two studies (Saiman *et al.*, 2003; Clement *et al.*, 2006), nausea, and fever in two studies (Clement *et al.*, 2006, Steinkamp *et al.*, 2008).

Table 5 Therapeutic Safety

No	Author	Year	Therapeutic Safety
1	Jaffe et al	1998	Not reported
2	A Equi et al	2002	No side effects appeared during the study
3	Wolter et al	2002	Urticaria, neutropenia, rash
4	Saiman et al	2003	Nausea, diarrhea, and wheezing
5	Clement et al	2006	Headache, diarrhea, nausea, rash, and fever
6	Steinkamp et al	2008	Pain, fever, nausea, and sneezing
7	Mayer-Hamblett et al	2018	There were no severe side effects

DISCUSSION

Cystic fibrosis (CF) is a fatal autosomal recessive genetic disease that mainly affects the lungs and digestive system (Fonseca *et al.*, 2020). A hereditary mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) causes this disease. As a result, there are impaired sodium and bicarbonate ion transporters, causing an increase in pH and mucus viscosity (Patel, Bono, and Rowe, 2020). Increased mucus viscosity causes impaired mucociliary action and the accumulation of very thick secretion that prevents the activity of antibacterial substances produced by the epithelium. Most infants with CF have respiratory problems, so adequate therapy is needed to reduce respiratory symptoms (Rafeeq and Murad, 2017). Azithromycin is a therapy that has been used for a long time by clinicians to reduce bothersome respiratory symptoms in CF patients. Azithromycin has microbiological, immunomodulatory, and anti-inflammatory effects. After giving azithromycin, the improvement in lung function is assessed by the mean value of FEV_1 (Fonseca *et al.*, 2020).

This systematic review showed that most studies were conducted outside of Asia. It may be because the prevalence of CF in non-Caucasian populations is not widely reported (Ahmed *et al.*, 2020). In addition, six journals were conducted more than ten years ago, and only one study in 2018. Furthermore, five (71.4%) publications reported an increase in mean FEV_1 after giving azithromycin to patients with CF (Jaffe *et al.*, 2018; A Equi *et al.*, 2002; Wolter *et al.*, 2002; Saiman *et al.*, 2003; Clement *et al.*, 2006).

Inflammation is a significant focus in the pathogenesis of lung disease in CF. Therefore, preventing the overproduction of inflammatory factors is the primary strategy to improve lung function and survival rates. One of the most common worldwide prescribed anti-inflammatory drugs is azithromycin. Azithromycin is an anti-inflammatory agent. It inhibits the release of pro-inflammatory mediators, prevents neutrophil

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aggregation, regulates mucus secretion, and prevents the formation of the *P.aeruginosa* biofilm matrix. In addition, there are reports that azithromycin in vivo can restore chloride efflux function in CF patients (Samson *et al.*, 2016).

The Cochrane study demonstrated that giving low-dose azithromycin for 6-12 months could improve lung function. In addition, it reduced exacerbations, the need for antibiotics, and gained weight in CF patients. Furthermore, five-year survival increased to 95% in patients with diffuse panbronchiolitis (Samson *et al.*., 2016). This efficacy of azithromycin is used as CF therapy to improve lung function. However, our findings revealed no significant change in mean FEV1 in the azithromycin group in the two studies. It may be due to the small number of samples studied (<60) and the wide variation in FEV1 assessments (Steinkamp *et al.*, 2008; Mayer-Hamblett *et al.*, 2018).

This literature review also assessed several secondary outcomes. One of them was the value of forced vital capacity (FVC). Three studies found a significant increase in FVC in the azithromycin group (Jaffe *et al.*, 2018; A Equi *et al.*, 2002; Wolter *et al.*, 2002). Meanwhile, another research did not include the FVC test (Clement *et al.*, 2006; Steinkamp *et al.*, 2008; Mayer-Hamblett *et al.*, 2018). In addition, four studies showed a significant reduction in the need for intravenous and oral antibiotics in the azithromycin group. In addition, they revealed decreased (c-reactive protein) CRP, Interleukin-8 (IL-8), and neutrophils in the azithromycin group. Furthermore, they found reduced recurrence/exacerbation rates in the azithromycin group (A Equi et al., 2002; Wolter et al., 2002; Clement et al., 2006; Steinkamp et al., 2008). Two studies demonstrated significant weight gain and quality of life in the azithromycin group (Saiman et al., 2003; Mayer-Hamblett et al.; 2018). The last secondary outcome evaluated was the quality of life. Two studies described the improved quality of life in CF patients receiving azithromycin intervention. Quality of life assessment consisted of respiratory disorders, eating disorders, and emotional complaints (Wolter et al., 2002; Steinkamp et al.; 2008).

This research also indicated that azithromycin had good therapeutic safety to improve lung function in CF patients. In all studies reviewed, three studies (42.8%) did not report any significant adverse events from using azithromycin (Jaffe et al., 1998; A Equi et al., 2002; Mayer-Hamblett et al., 2018). Meanwhile, other publications informed that the adverse events were urticarial and neutropenia. Its adverse events were also gastrointestinal disturbances, wheezing, fever, and rash (Wolter et al., 2002; Saiman et al., 2003; Clement et al., 2006; Steinkamp et al., 2008).

CONCLUSION

In conclusion, we consider azithromycin administration for CF patients is relatively safe and well-tolerated. Further research should evaluate the long-term effects of Azithromycin in CF patients.

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