Antiinflammatory Therapies for Cystic Fibrosis: Past, Present, and Future

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Inflammation is a major component of the vicious cycle characterizing cystic fibrosis pulmonary disease. If untreated, this inflammatory process irreversibly damages the airways, leading to bronchiectasis and ultimately respiratory failure. Antiinflammatory drugs for cystic fibrosis lung disease appear to have beneficial effects on disease parameters. These agents include oral corticosteroids and ibuprofen, as well as azithromycin, which, in addition to its antimicrobial effects, also possesses antiinflammatory properties. Inhaled corticosteroids, colchicine, methotrexate, montelukast, pentoxifylline, nutritional supplements, and protease replacement have not had a significant impact on the disease. Therapy with oral corticosteroids, ibuprofen, and fish oil is limited by adverse effects. Azithromycin appears to be safe and effective, and is thus the most promising antiinflammatory therapy available for patients with cystic fibrosis. Pharmacologic therapy with antiinflammatory agents should be started early in the disease course, before extensive irreversible lung damage has occurred.

Key Words: cystic fibrosis, inflammation, antiinflammatory, corticosteroid, ibuprofen, macrolide, azithromycin, antioxidant, antiprotease, nutrition.

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OUTLINE

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Cystic fibrosis is the most common lethal, genetically inherited disorder among Caucasians.[1] The clinical features of cystic fibrosis occur as a result of mutations in the cystic fibrosis transmembrane conductance regulator gene.[2] Consequently, the cystic fibrosis airway is exposed to a vicious cycle of obstruction, infection, and inflammation, all intimately linked.[3] Airway inflammation begins early in the disease course, with notable neutrophil infiltration present in infants as young as 4 weeks.[4–11] The inflammatory process persists throughout the patient's life and, if left unchecked, irreversibly damages the airways, leading to bronchiectasis and progressive decline in lung function.[10] Pulmonary disease accounts for most of the morbidity and mortality in patients with cystic fibrosis. Therefore,

interrupting this cycle with antiinflammatory agents may slow disease progression, improve quality of life, and delay respiratory failure.[12] However, less than 50% of pulmonary practitioners prescribe specific antiinflammatory agents, and only 25% of patients with cystic fibrosis receive such therapy.[13]

The safety and efficacy of numerous anti-inflammatory therapies have been studied for treatment of cystic fibrosis. Several agents have proved beneficial, particularly in younger patients with mild disease. However, safety concerns have limited the utility of certain drugs.

Characteristics of Pulmonary Inflammation in Cystic Fibrosis

Inflammation plays a pivotal role in the progression of lung destruction in patients with cystic fibrosis. The cystic fibrosis airway is characterized by persistent infiltration of vast numbers of neutrophils which, when present in excess, produce more harm than good (Figure 1).[1, 3, 4, 6, 8, 9, 11, 14–24] Bacterial infection and continuing colonization are the primary stimuli for inflammation in the cystic fibrosis airway.[1] However, pulmonary inflammation has been observed in young children without identifiable infection.[4, 6, 8, 11] If these children were truly without infection, one might speculate that the lack of functional cystic fibrosis transmembrane conductance regulator in the epithelial lining of the cystic fibrosis lung may contribute to the inflammatory process.[23] Regardless of whether infection precedes or supersedes inflammation, the two become closely integrated in cystic fibrosis lung disease.[24]

Therapies with Proven Antiinflammatory Effects

Corticosteroids

The therapeutic efficacy and safety of several oral and inhaled corticosteroids have been evaluated in children with cystic fibrosis, but the

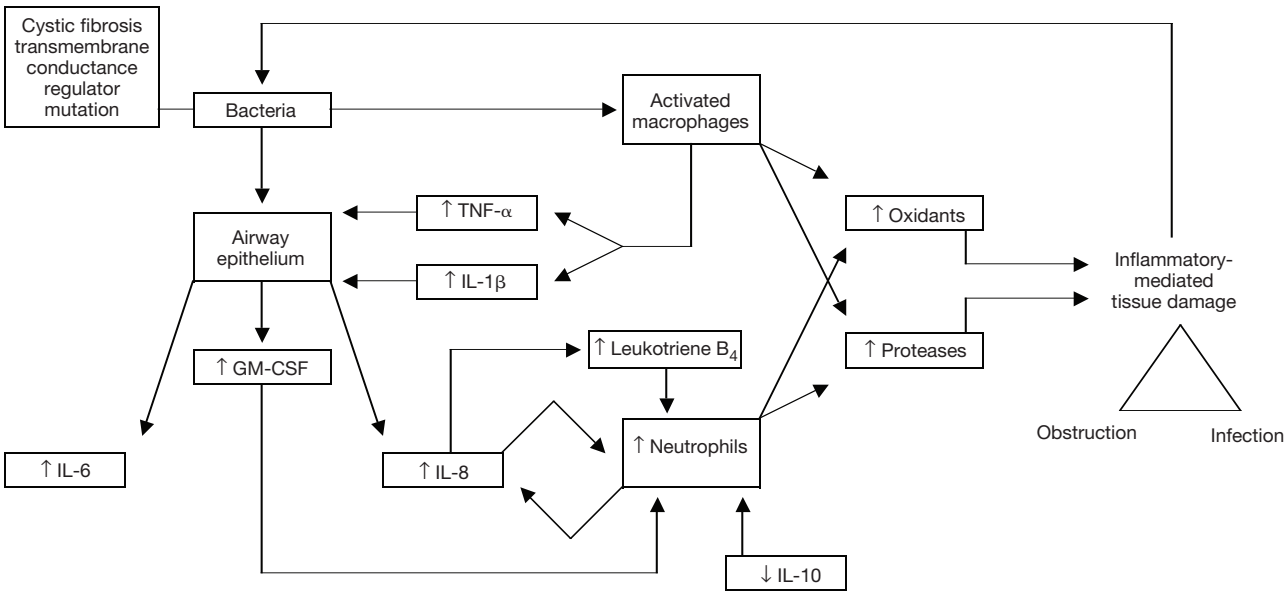

Figure 1. Pathophysiology of cystic fibrosis airway inflammation and potential targets of antiinflammatory therapy. The inflammatory process is initiated through interaction of the epithelium with bacteria or bacterial products. Then interleukin (IL)-8, IL-6, and possibly granulocyte-macrophage colony-stimulating factor (GM-CSF) are produced directly and indirectly through stimulated macrophage production of IL-1β and tumor necrosis factor (TNF)-α. The latter two inflammatory mediators stimulate the epithelium to produce IL-8, IL-6, and GM-CSF in excess. In addition, concentration of the antiinflammatory cytokine IL-10 is reduced in the cystic fibrosis airway, eliminating the inhibitory effect on production of IL-8 and TNF-α. The IL-8 recruits neutrophils into the airway, which subsequently release neutrophil elastase and additional IL-8 and leukotriene B_4, leading to further neutrophil influx. Neutrophils release large amounts of oxidants and proteases, which subsequently overwhelm the deficient antioxidant and dysfunctional antiprotease defenses of the cystic fibrosis airway, leading to direct tissue damage. In addition, neutrophil elastase, a major protease in the cystic fibrosis lung, may indirectly cause harm to the epithelium by increasing airway obstruction, contributing to the persistence of infection and promoting the generation of chemoattractants. (From references 1, 3, 4, 6, 8, 9, 11, 14–24.)

precise mechanism through which these agents control inflammation and affect cystic fibrosis pulmonary disease has not been elucidated. Investigators have proposed that the antiinflammatory actions of corticosteroids in cystic fibrosis are mediated through inhibition of interleukin (IL)-1α and IL-2 receptor expression.[25] Serum immunoglobulin G (IgG) concentrations are also significantly decreased with systemic corticosteroid therapy. This effect may reduce immune complex formation and complement activation, thereby diminishing lung damage.

Oral

Prednisone and prednisolone are oral glucocorticoids with potent antiinflammatory effects. Prednisone has effectively controlled the inflammation of cystic fibrosis pulmonary disease; however, safety concerns limit its use for long-term treatment in children with the disease.[25–28]

The benefits of oral prednisone on morbidity and progression of lung disease in children with cystic fibrosis was first reported in a 4-year prospective, randomized, double-blind, placebo-controlled trial of 45 patients aged 1–12 years with mild-to-moderate cystic fibrosis lung disease.[26] Of these patients, 24 (mean age 6.3 yrs) were randomly allocated to placebo, and 21 (mean age 6.7 yrs) to treatment with prednisone 2 mg/kg, maximum 60 mg, every other day.

After 4 years, the prednisone-treated group exhibited significantly higher values than the placebo group with respect to vital capacity ($p<0.01$), peak expiratory flow rate ($p<0.005$), and forced expiratory volume in 1 second (FEV_1) ($p<0.005$). In the prednisone group, five (24%) patients required nine hospital admissions for cystic fibrosis–related pulmonary disease; in the placebo group, 10 (42%) patients required 35 admissions ($p<0.001$). Gains in height ($p<0.025$) and weight ($p<0.005$) were significantly better in the treatment versus placebo group at the conclusion of the study.

To confirm the outcomes reported in the first trial, a second, larger, prospective, double-blind, placebo-controlled study was conducted.[27] A total of 285 patients aged 6–14 years (mean 9.5 yrs) with clinically stable cystic fibrosis and a ratio of FEV_1:forced vital capacity (FVC) greater than 60% were equally stratified in a randomized manner to either placebo or alternate-day prednisone 1 mg/kg (low dose) or 2 mg/kg (high dose, maximum 60 mg). The study was discontinued prematurely in the high- and low-dose groups after 2 and 3 years, respectively, secondary to unacceptable adverse effects.

Predicted FVC was greater in patients receiving prednisone 1 mg/kg ($p<0.0001$) or 2 mg/kg ($p<0.01$) than in those receiving placebo. No significant difference in effect was observed between the two prednisone-treated groups ($p>0.21$). In the 1-mg/kg group, improvement in FVC was first noted at 6 months, plateaued thereafter, and was sustained for the rest of the study period ($p<0.0025$). Mean predicted FEV_1 declined to a significantly lesser extent in the 1-mg/kg group than in the placebo group ($p<0.02$). Hospitalization rates and length of stay, Shwachman score, Brasfield score, and peak expiratory flow rate were not significantly different between the prednisone and placebo groups.

In a follow-up study assessing the long-term effects of prednisone, the improvement in pulmonary function observed in patients treated with alternate-day prednisone 1 mg/kg was no longer present 6–7 years after therapy was discontinued.[29] In fact, the 13.5% decline in FEV_1 in the low-dose prednisone group during the follow-up period was 3 times greater than the 4.5% decline in the placebo patients. The weight of the prednisone-treated children declined to baseline weight within 1–2 years after treatment discontinuation.

Although effective, the utility of corticosteroids in the treatment of cystic fibrosis pulmonary disease is limited by long-term safety concerns.[27, 28] An early study suggested that therapy with oral prednisone in children with cystic fibrosis would not produce significant adverse effects.[26] However, better-powered studies concluded that long-term treatment with corticosteroids was associated with significant risks.[27, 28] Glucose intolerance, cataract formation, multiple bone fractures secondary to osteoporosis or osteopenia, cushingoid effects, and anorexia nervosa occurred in a dose-dependent fashion.[27, 28, 30] The percentage of patients colonized with *Pseudomonas aeruginosa* increased from baseline when prednisone 1 mg/kg ($p<0.01$) and 2 mg/kg ($p<0.05$) every other day were given.[27] Prednisone 2 mg/kg every other day for more than 6 months or 1 mg/kg every other day for more than 24 months was associated with substantial negative effects on growth.[27–29]

Catch-up growth occurs in most children, both boys and girls, 2–3 years after discontinuation of prednisone therapy.[29] However, growth impairment among prepubertal boys, most prominently those aged 6–8 years, persists for 10 years after

Table 1. Studies of Inhaled Corticosteroid Therapy in Patients with Cystic Fibrosis

Study Design	No. of Patients	Age Range, Mean, Median (yrs)	Drug and Dosage (µg/day)	Treatment Duration (wks)	Sputum Inflammatory Marker Improvement from Baseline	Change in FEV_1 and FVC vs Placebo
R, DB, PC[34]	13	4–29, NR, 14	Beclomethasone 400	16	NS[a]	FVC: NS[a]
R, DB, CO, PC[35]	12	16–45, 27, NR	Budesonide 1600	6	NA	FEV_1: NS[a] FVC: NS[a]
R, PC[36]	25	6–28, 20, NR	Beclomethasone 1500	4	NA	FEV_1: NS[a] FVC: NS[a]
R, DB, PC[37]	30	NR, 20, NR	Budesonide 1600	9–20	NS[a]	FEV_1: NS[a] FVC: NS[a]
R, DB, CO, PC[38]	23	7–17, 10, NR	Fluticasone 400	6	NS[a]	FEV_1: NS[a] FVC: NS[a]
R, OL, PC[39]	12	16–38, NR, 26	Fluticasone 1000	3	NS[c]	FEV_1: NS[b] FVC: NS[c]

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; R = randomized; DB = double-blind; PC = placebo-controlled; CO = crossover; OL = open-label; NR = not reported; NA = safety data not assessed; NS = not significant.
No significant differences were observed in adverse drug reactions for study drug compared with placebo in all studies except reference 36, in which adverse events were not assessed.
[a]$p>0.05$.
[b]$p>0.1$.
[c]$p>0.2$.

treatment with prolonged alternate-day prednisone. The final predicted height in this patient subgroup is significantly reduced ($p=0.02$). The risk of corticosteroid-induced adverse effects is greater during concomitant therapy with itraconazole and corticosteroids since itraconazole is a potent inhibitor of corticosteroid metabolism.[31, 32] When corticosteroids and itraconazole are administered concomitantly to treat allergic bronchopulmonary aspergillosis, monitoring patients for symptoms suggestive of drug-related adverse events is indicated.

In children with cystic fibrosis, treatment with prednisone improves pulmonary function.[26, 27] However, given the short-lived benefits and serious adverse effects, prolonged prednisone therapy for suppression of inflammation cannot be recommended for children with cystic fibrosis.[27–32] When indicated, prednisone should be administered in the lowest effective dose for a limited time.

Inhaled

Inhaled corticosteroids are better tolerated and produce fewer adverse effects than systemically administered dosage forms.[33] Of the five available inhalation corticosteroids, beclomethasone, budesonide, and fluticasone have been evaluated in children with cystic fibrosis.[34–39]

Although one uncontrolled study suggested that inhaled corticosteroids might modulate neutrophil influx into the cystic fibrosis airway, mitigation of pulmonary inflammation has not been observed in placebo-controlled trials.[34, 37–40] Inhaled corticosteroids may attenuate bronchial hyperresponsiveness in patients with cystic fibrosis and may improve cough and dyspnea.[35, 37] However, in six controlled studies involving a total of 191 patients aged 4 years or older, no clinically or statistically significant benefit in FEV_1 or FVC was observed (Table 1).[34–39]

In clinical trials involving children and adults with cystic fibrosis, treatment with inhaled corticosteroids was well tolerated for up to 20 weeks.[34, 35, 37–39] Whereas an apparent increase in *P. aeruginosa* colonization in patients with cystic fibrosis was observed incidentally in one small study,[35] no significant difference was reported in two separate controlled trials.[40, 41] Whereas long-term studies assessing the effect of inhaled corticosteroids on growth are lacking for children with cystic fibrosis, final predicted height and bone mineral density are generally attained in this pediatric population.[33, 42]

Adrenocorticotropic hormone suppression tests in patients with cystic fibrosis have indicated little or no systemic effect of inhaled corticosteroids on the adrenal axis.[37, 40] However, Cushing's syndrome and complete suppression of endogenous glucocorticoid secretion have occurred with administration of inhaled

budesonide combined with itraconazole.[43, 44] This effect is attributed to inhibition of budesonide metabolism by itraconazole by the cytochrome P450 3A enzyme system. Routine monitoring for adrenal insufficiency is indicated when inhaled corticosteroids and itraconazole are concomitantly administered.

Delivery of aerosolized agents to the lungs, which averages 10–40% of total drug delivered, is dependent on the severity of lung disease and the specific delivery device and technique used.[33, 42] In patients with cystic fibrosis, the fraction of the dose ultimately reaching the site of the most severe inflammation may be poor given the viscous, mucus-lined epithelium through which it must pass. In children, the drug may never reach its primary site of action, which may account for the lack of efficacy demonstrated by inhaled corticosteroids in controlled clinical trials.

In theory, inhaled corticosteroids are a novel approach—administering a potent antiinflammatory agent directly to the disease site—to treating pulmonary inflammation in patients with cystic fibrosis. Although potentially safe, studies have failed to demonstrate any benefit after treatment with these drugs in children with cystic fibrosis. Thus, evidence-based medicine suggests that further studies are necessary before routine treatment with inhaled corticosteroids can be recommended.

Ibuprofen

Ibuprofen is an oral nonsteroidal antiinflammatory drug commonly used in children to treat acute pain and fever.[45] The recommended antipyretic and analgesic dosage is 5–10 mg/kg 3–4 times/day. In one study, ibuprofen 20–30 mg/kg twice/day had beneficial effects on both pulmonary function and nutrition in children with cystic fibrosis.[46] Based on these results, the Cystic Fibrosis Foundation has advocated ibuprofen as an antiinflammatory agent for treating patients aged 5 years or older with cystic fibrosis whose predicted FEV_1 is 60% or greater.[47] Despite reported benefits in children aged 5–13 years, less than 10% of patients with cystic fibrosis in the United States are treated with high-dose ibuprofen.[13] The percentage of children receiving ibuprofen may be low due to the need for therapeutic drug monitoring and concerns regarding the clinical safety and tolerability of this agent.

Ibuprofen is an inhibitor of cyclooxygenase and, at high doses, lipoxygenase. Through inhibition of the lipoxygenase pathway, leukotriene B_4 production is mitigated, and neutrophil migration and function are impaired.[48–59] The antiinflammatory effects of ibuprofen in patients with cystic fibrosis occur when peak plasma concentration exceeds 50 µg/ml.[59] Concentrations below this threshold result in a paradoxical increase in inflammation.[56–60] This proinflammatory effect is believed to occur as a result of substrate shunting from the cyclooxygenase to the lipoxygenase pathway.[59] Therefore, with plasma concentrations less than 50 µg/ml, ibuprofen may hasten cystic fibrosis lung deterioration.

In children with cystic fibrosis, ibuprofen peak plasma concentration and area under the concentration-time curve are decreased; however, the apparent volume of distribution and clearance are significantly increased.[61] As the pharmacokinetics of ibuprofen are dependent on the dose and dosage form used and on the patient's body weight and fasted or fed state, significant variability occurs among individual patients with cystic fibrosis.[61–63] In view of ibuprofen's narrow therapeutic window, and the significant interpatient pharmacokinetic variability, therapeutic drug concentration monitoring is necessary.[46]

Ibuprofen is most commonly given in tablet form. Children often cannot swallow tablets; thus, suspension and chewable tablet formulations are attractive alternatives. The suspension form is absorbed most rapidly.[64–66] Plasma concentrations should be obtained at 30, 45, and 60 minutes after administration of a dose.[65, 66] Time to the peak plasma concentration is longer with ibuprofen tablets than with the liquid formulation. Thus, plasma concentrations should be checked at 1, 2, and 3 hours after administration with the tablet form.[61, 64–66] Given the limited available data, no definitive dosing recommendations or blood sampling guidelines can be provided for ibuprofen chewable tablets.[65] To optimize therapy regardless of the form of ibuprofen administered, peak plasma concentration must be accurately determined to prevent misguided dosage adjustments.

In a randomized, double-blind, placebo-controlled trial, high-dose ibuprofen had clinically beneficial effects on FEV_1 and ideal body weight (IBW).[46] The study involved 85 patients, aged 5–39 years, with cystic fibrosis. Patients were excluded if they had received systemic corticosteroids, inhaled corticosteroids, or nonsteroidal antiinflammatory drugs for more than 2 weeks within 2 years of recruitment or

inhaled cromolyn in the 6 months preceding the study. Of the 85 patients, 43 were randomly assigned to placebo, 42 to ibuprofen tablets. Food and pancreatic enzymes were withheld for 2 hours after each dose. Ibuprofen 20–30 mg/kg twice/day was the starting dosage. This was adjusted using pharmacokinetic analysis, with a goal peak plasma concentration of 50–100 µg/ml.

Ibuprofen 20–30 mg/kg produced a peak plasma ibuprofen concentration of 50–100 µg/ml in most patients. The dose range at which all patients attained therapeutic concentrations was 16–32 mg/kg. The dose was adjusted based on pharmacokinetic analysis every 3 years, or sooner if body weight increased 25%. The primary outcome measure, FEV_1, declined 59% more slowly in patients treated with ibuprofen than in those assigned to placebo in the completed-treatment analysis (p=0.03). This benefit was observed only in patients who were younger than 13 years at the start of treatment. In this subgroup, the rate of decline in FEV_1 was reduced by 65% (p=0.01) and 88% (p=0.005) in the intent-to-treat and completed-treatment analysis, respectively. The FVC and forced expiratory flow at 25–75% of FVC ($FEF_{25–75}$) also deteriorated, to a lesser extent, in ibuprofen-treated patients at study completion (p<0.05).

Patients in the ibuprofen group maintained their percent IBW throughout the 4-year study period (p=0.01). Compliance as assessed by tablet count and blood monitoring was approximately 70% in each group. Although ibuprofen effectively improved FEV_1 and percent IBW, the results of this study must be interpreted with caution. The effect of ibuprofen on IBW was most pronounced in the younger patients (5–13 yrs), and the improved FEV_1 was observed only in this group. Since the information representing these younger patients was a post hoc analysis involving only 36 patients, further studies are needed to determine the clinical importance of these findings in this age group.

In healthy children, intermittent ibuprofen in recommended dosages is associated with minimal risk for gastrointestinal bleeding and nephrotoxicity.[67] Since higher ibuprofen dosages have increased the risk for gastrointestinal adverse effects, one might expect high-dose ibuprofen to be poorly tolerated by patients with cystic fibrosis.[68] Neither a randomized, double-blind, placebo-controlled trial of 85 patients nor a retrospective review of 1354 patients prescribed an initial dosage of ibuprofen 20–30 mg/kg twice/day reported a significant increase in the risk of gastrointestinal toxicity in children with cystic fibrosis.[46, 69] However, safety data from the randomized trial were derived from a small patient pool, with only 17 patients aged 5–13 years, the age group in which ibuprofen has had the most pronounced benefit.[46] Indeed, anecdotal evidence and clinical experience with high-dose ibuprofen suggest that this regimen is not without gastrointestinal adverse effects.[70]

Risk of renal toxicity is a second concern associated with ibuprofen therapy. Studies have not evaluated the effects of high-dose ibuprofen on renal function in patients with cystic fibrosis. However, an increased risk for renal toxicity has been reported when this agent is used with intravenous aminoglycosides.[71, 72] Ibuprofen administration can be interrupted during aminoglycoside therapy without producing a rebound increase in pulmonary inflammation, and this practice is recommended.[60] Data concerning safety and efficacy after long-term therapy with high-dose ibuprofen are lacking.

Based on the studies described, ibuprofen therapy improves maintenance of percent IBW and slows the decline of lung function when treatment is begun in children with cystic fibrosis, aged 5–13 years, who have a predicted FEV_1 of 60% or greater.[46] Although data directly assessing the effect of ibuprofen on long-term survival in patients with cystic fibrosis are lacking, FEV_1 and percent IBW are predictors of mortality.[73] The recommended initial dosage is ibuprofen 20–30 mg/kg twice/day, titrated as needed to a dosage that produces a peak plasma concentration of 50–100 µg/ml based on pharmacokinetic monitoring.

Patients or caregivers should be instructed to separate the administration time of ibuprofen and pancreatic enzymes by at least 2 hours and to administer the ibuprofen on an empty stomach, if tolerated, to allow optimal absorption.[46] To ensure that therapeutic concentrations are maintained with prolonged treatment, pharmacokinetic analysis should be performed every 3 years or with body weight increases of 25% or more. The need for periodic pharmacotherapeutic monitoring and the lack of adequate safety data in patients aged 5–13 years when treated with high-dose ibuprofen have limited the routine therapeutic use of this agent in children with cystic fibrosis.

Cyclooxygenase-2 inhibitors, such as celecoxib, rofecoxib, and valdecoxib, are often better tolerated than ibuprofen.[74–76] However, the antiinflammatory mechanism of ibuprofen in

cystic fibrosis differs from cyclooxygenase inhibition.[48–59] Treatment with cyclooxygenase-2 inhibitors in healthy children or in children with cystic fibrosis has not been evaluated.

Azithromycin

Azithromycin is a macrolide commonly used for its antibacterial activity in both children and adults. It is approved for treatment of acute otitis media and community-acquired pneumonia in patients older than 6 months and for treatment of pharyngitis or tonsillitis in those aged 2 years or older.[77] Azithromycin has a long tissue half-life and accumulates in the sputum and lungs of treated patients.[78] The potential role of azithromycin in cystic fibrosis is extrapolated from experience with diffuse panbronchiolitis, a respiratory disease similar to cystic fibrosis. In patients with diffuse panbronchiolitis, long-term erythromycin therapy improved both symptoms and survival.[79, 80]

Azithromycin has been evaluated as a treatment option for patients with cystic fibrosis for its antiinflammatory properties.[81] The precise mechanism through which azithromycin exerts these effects has not been elucidated (Figure 2).[82–99] Antimicrobial classes typically used in the treatment of acute cystic fibrosis exacerbations, such as third-generation cephalosporins, aminoglycosides, and fluoroquinolones, do not appear to exert any significant direct antiinflammatory action and have not been included in this review.[100]

Treatment with either erythromycin or clarithromycin has not been beneficial in cystic fibrosis.[101] Six trials have evaluated the effects of azithromycin in children and adults with cystic fibrosis (Table 2).[102–107] Of the three randomized, placebo-controlled trials conducted, two involved patients younger than 18 years.[106, 107] Although a benefit with azithromycin was observed in both of these studies, the more recent one provides the most compelling evidence of therapeutic improvement.[107]

In a randomized, double-blind, placebo-

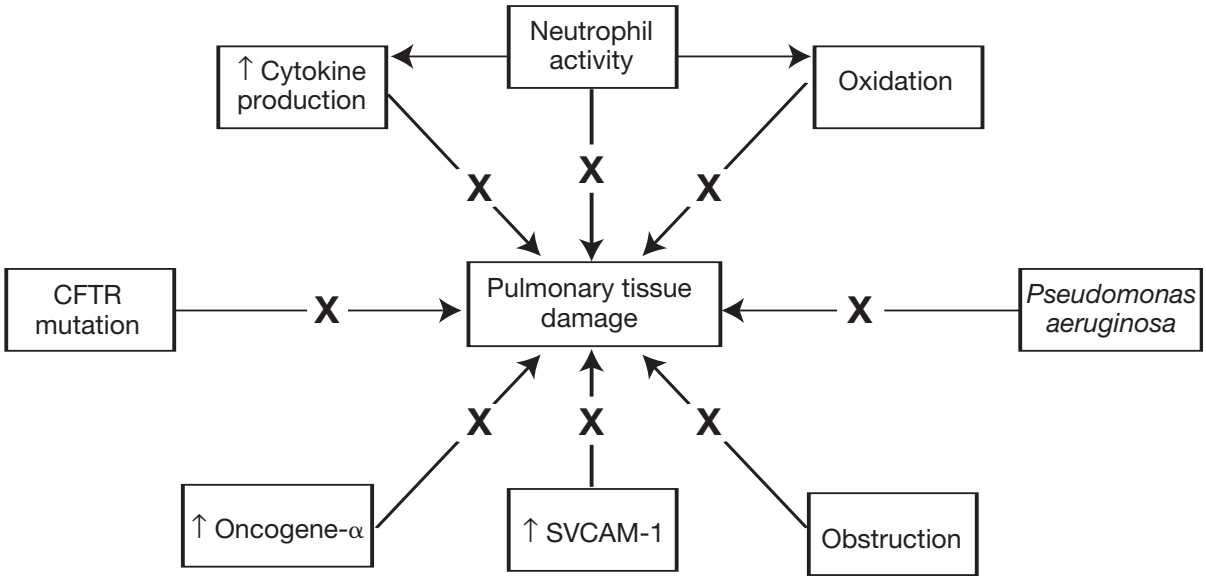

Figure 2. Proposed antiinflammatory mechanisms of macrolide antibiotics. The precise mechanism by which azithromycin mitigates inflammation is unknown, but it affects neutrophils through mediation of apoptosis, migration, chemotactic activity, and phagocytic function. Azithromycin is an indirect antioxidant and may prevent lung damage through this function. Therapy with this agent has inhibited production of nitric oxide, prostaglandin E_2, and proinflammatory cytokines interleukin (IL)-8, IL-1α, and tumor necrosis factor (TNF)-α. Azithromycin may also downregulate growth-related oncogene-α as well as soluble vascular cell adhesion molecule (SVCAM)-1. Reduced sputum viscoelasticity and improved mucociliary and cough transportability of airway secretions has been noted. Antagonism of the virulence of *Pseudomonas aeruginosa* has been proposed as a mechanism, an effect mediated through a decrease in airway adherence, inhibition of production of various exoproducts, and interference with *Pseudomonas* mucoid-alginate biofilm formation. In addition, it may affect *Pseudomonas aeruginosa*'s viability directly despite subinhibitory minimum inhibitory concentrations. Restoration of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel is an additional possible mechanism. X = mitigation of adverse effect. (From references 82–99.)

Table 2. Studies of Azithromycin Therapy in Patients with Cystic Fibrosis

Study Design	No. of Patients	Age Range, Mean, Median (yrs)	Azithromycin Dosage	Treatment Duration (mo)	Change in FEV_1, FVC, $FEF_{25–75}$ (% increase)	Adverse Drug Reactions
OL[102]	7	6–17, 12, NR	NR	Median 7.2	FEV_1: 11.0[a] FVC: 11.3[a]	NS
M, PC[103]	36	NR, NR, NR	250 mg q.d.	Mean 9.4	FEV_1: 2.2[b] FVC: 5.7[c]	NS
Observational[104]	14	NR, 24, NR	250 mg q.o.d.[d]	Mean 22.3	FEV_1: 5.8[b] FVC: 4.8[e] $FEF_{25–75}$: 6.5[a]	NS
R, DB, PC[105]	60	18–44, 28, NR	250 mg q.d.	3	FEV_1: 3.0[a] FVC: 3.8[a]	
R, DB, PC, CO[106]	41	8–18, NR, 14	250 mg q.d. (ABW ≤ 40 kg) 500 mg q.d. (ABW > 40 kg)	6	FEV_1: 5.4[e] FVC: 3.9[e] $FEF_{25–75}$: 11.4[e]	NS
R, DB, PC[107]	185	6–Adult, 20, NR	250 mg MWF (ABW < 40 kg) 500 mg MWF (ABW ≥ 40 kg)	6	FEV_1: 4.4[c] FVC: 3.7[c]	Nausea, diarrhea, wheezing[f]

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; $FEF_{25–75}$ = forced expiratory flow at 25–75% of FVC; OL = open-label; M = matched; PC = placebo controlled; CO = crossover; NR = not reported; NS = no significant difference compared with placebo; ABW = actual body weight; MWF = Monday, Wednesday, and Friday.
[a]$p<0.05$ vs baseline.
[b]$p=0.05$ vs placebo.
[c]$p<0.01$ vs placebo.
[d]Adjusted to 250 mg/day in 8 of 14 patients.
[e]$p>0.05$.
[f]$p<0.05$ vs placebo.

controlled study involving 60 adults with cystic fibrosis, treatment with azithromycin led to an improvement in total quality of life ($p=0.035$), a reduction in antibiotic therapy associated with acute respiratory exacerbations ($p<0.037$), and a slowed rate of decline in predicted FEV_1 ($p=0.047$) and FVC ($p=0.001$).[105] This benefit was observed despite baseline patient characteristics indicating the treatment group had less lung function than the placebo group (mean FEV_1 50.9% vs 62.3%, mean FVC 67.3% vs 77.5%). The treatment group also was shorter, on average, and weighed less than the placebo group. However, outcome changes in lung function were small, indicating maintenance rather than improvement.

In the first trial involving patients younger than 18 years with cystic fibrosis, pulmonary function was only modestly affected after a 6-month course of azithromycin.[106] This study—a 15-month, prospective, randomized, double-blind, placebo-controlled, crossover trial—included 41 children (18 boys, 23 girls) aged 8–18 years, with a median FEV_1 of 61% (range 33–80%). A history of chronic *P. aeruginosa* colonization was not a specific entry criterion. Exclusion criteria were liver disease, hearing impairment, *Burkholderia cepacia* colonization, previous organ transplantation, treatment with macrolide antibiotics or oral corticosteroids for more than 14 days, or treatment with dornase alfa begun within 2 months of enrollment.

Azithromycin dosage was based on weight; patients weighing 40 kg or less received 250 mg once/day; those weighing more than 40 kg received 500 mg once/day. A clinically significant change in the primary outcome measure, FEV_1, and the secondary outcome measures, FVC and $FEF_{25–75}$, was defined as a change of more or less than 13%, 13%, and 20%, respectively. At every time point during treatment, mean FEV_1, mean FVC, and mean $FEF_{25–75}$ were higher in the azithromycin-treated patients than in the placebo patients. However, the median relative difference in predicted FEV_1 between azithromycin and placebo was only 5.4% ($p>0.05$). Improvement in FEV_1 greater than 13% was noted in 13 of 41 patients, whereas deterioration of more than 13% was observed in five ($p=0.059$). The median relative difference in predicted FVC and $FEF_{25–75}$ between the two groups was 3.9% and 11.4%, respectively ($p>0.05$). The results of this study

suggest that azithromycin treatment in children and adolescents may exert clinically important beneficial effects on pulmonary function in approximately 33% of patients but may result in worsening lung function in approximately 10–20% of patients.

The second study involving patients younger than 18 years was a randomized, controlled study in 185 patients aged 6 years or older with a history of chronic *P. aeruginosa* colonization and a predicted FEV_1 of 30% or more.[107] Of the 185 patients, 15 (average body weight < 40 kg) received azithromycin 250 mg 3 times/week, 72 (average body weight ≥ 40 kg) azithromycin 500 mg 3 times/week, and 98 placebo. Study exclusion criteria were a history of *B. cepacia* or nontuberculosis mycobacteria within 2 years of screening, active liver disease, therapy with intravenous or oral antibiotics within 14 days of screening, therapy with a corticosteroid 20 mg or more within 30 days of screening, and therapy with inhaled tobramycin, dornase alfa, or high-dose ibuprofen begun within 60 days of screening.

Use of dornase alfa and inhaled tobramycin were similar in the treatment and placebo groups. In the azithromycin group (both dosage groups) nine patients were 6–12 years of age, 35 were 13–18 years, and 43 were older than 18 years. The primary end point, relative change in FEV_1, was 6.2% in favor of azithromycin. This was depicted through a 4.4% improvement in the azithromycin group and a decline of 1.8% in the placebo group (p=0.001). The response was observed at day 28 and persisted until the end of treatment.

Four weeks after azithromycin discontinuation, FEV_1 returned to nearly baseline percentages, indicating the need for prolonged therapy to maintain beneficial effects. Predicted FVC improved 3.7% in the azithromycin group but declined 1.3% in the placebo group (p=0.002). The rate of weight gain was higher in the azithromycin-treated patients, who gained an average of 0.7 kg more than those treated with placebo (p=0.02). Azithromycin treatment resulted in significantly fewer respiratory exacerbations (p=0.03) and was associated with fewer hospitalizations (p=0.05). Based on the cystic fibrosis quality-of-life questionnaire, physical functioning improved (p=0.05) but not total quality of life (p=0.35). This study reported improvement in two predictors of mortality in patients with cystic fibrosis—pulmonary function and nutritional status—which suggests that azithromycin may be of benefit in children with this disease.

Clinical experience suggests that azithromycin is better tolerated than other macrolide antibiotics. Two placebo-controlled studies reported that azithromycin treatment produced no adverse effects in children or adults with cystic fibrosis.[105, 106] In a third study with safety as a primary end point, most adverse events were of mild-to-moderate intensity.[107] In azithromycin and placebo groups, nausea (33% vs 16%), diarrhea (23% vs 8%) and wheezing (17% vs 4%) occurred more frequently in azithromycin-treated patients (p≤0.01). Increased mobilization of respiratory tract secretions was believed to have caused the increased wheezing.

Staphylococcus aureus colonization often occurs at an early age in children with cystic fibrosis.[108] An increased risk of selecting macrolide-resistant staphylococcal species after azithromycin therapy has been observed in patients with cystic fibrosis.[109, 110] Since *S. aureus* is rarely a significant cystic fibrosis pathogen in adolescents or adults, the clinical implications of this finding are debatable.

Nontuberculosis mycobacteria is a second potential respiratory pathogen in cystic fibrosis. Colonization occurs in approximately 13% of patients with cystic fibrosis, and prevalence increases with age.[111, 112] Although nontuberculosis mycobacteria does not appear to have short-term adverse effects on lung function in patients with cystic fibrosis, effects on long-term outcome cannot be ruled out.[112] To minimize the risk for selection of macrolide-resistant strains, physicians are advised to screen for nontuberculosis mycobacteria in patients with cystic fibrosis before the start of azithromycin treatment and then every 6 months.[113] Azithromycin has not increased the risk of bacterial resistance in controlled studies involving patients with cystic fibrosis treated for up to 6 months.[105–107]

Azithromycin has been implicated in fewer drug-drug interactions than other macrolide antibiotics[114] but has had a strong inhibitory effect on the actions of dornase alfa in vitro, possibly by binding to human DNA and/or to dornase alfa itself.[115] The suggested interaction between azithromycin and dornase alfa was observed clinically in one randomized controlled study.[106] However, a subsequent study reported a benefit in lung function associated with azithromycin therapy even though 75% of patients in the active treatment group were concomitantly treated with dornase alfa.[107]

Azithromycin appears to be a well-tolerated and clinically efficacious antiinflammatory

treatment modality for maintenance of lung function in children and adults with cystic fibrosis.[105–107] Most experience with azithromycin has been with patients older than 13 years with a history of chronic *P. aeruginosa* colonization; it has not been studied in children younger than 6 years. Azithromycin 250 mg 3 times/week in patients weighing less than 40 kg and 500 mg 3 times/week in those weighing 40 kg or more may be recommended in patients aged 6 years or older with chronic *P. aeruginosa* colonization. Azithromycin may benefit patients without a documented history of *P. aeruginosa* with suspected infection, although supporting literature is lacking.

The beneficial effects of azithromycin in patients with cystic fibrosis are generally observed as early as 1 month after the start of treatment but may be delayed for 4–6 months in some patients.[106, 107] Both caregivers and patients should be informed of this variability in response time. Azithromycin therapy for up to 6 months appears to be safe; nausea, diarrhea, and wheezing are the predominant adverse effects.[107] Continuing therapy seems necessary to maintain the benefits associated with azithromycin therapy. An evaluation of the safety and efficacy of this agent for treatment periods longer than 6 months is in progress.

Additional Therapies with Possible Antiinflammatory Effects

Colchicine

Colchicine is an antiinflammatory agent commonly prescribed for treatment of acute attacks of gout. A single open-label study evaluated the potential benefits of colchicine in patients with cystic fibrosis lung disease.[116] The study involved eight patients aged 5–28 years (median 13.5 yrs) with end-stage cystic fibrosis lung disease unresponsive to conventional therapy. Treatment with colchicine 1 mg/day for 6–12 months (median 7 mo) was associated with a subjective improvement in clinical status, a significant decrease in antibiotic requirement, and a potential improvement in pulmonary function.

Among the eight patients studied, baseline median predicted FEV_1 and FVC, respectively, were 62% (range 32–68%) and 54% (range 21–63%). Colchicine treatment was associated with a statistically significant decrease in median days of antibiotic therapy, from 5 days/month to 1.2 days/month ($p<0.05$). A significant improvement in FEV_1 and FVC was not observed; however, the predicted FEV_1 increased in six of the eight patients treated. Mild diarrhea was reported in two patients, but colchicine treatment was generally well tolerated.

The results of this study are compelling enough to justify a large, randomized trial to further evaluate the role of colchicine in patients with cystic fibrosis lung disease.

Dornase alfa

Dornase alfa (recombinant human deoxyribonucleic acid I) is a mucolytic agent that improves mucociliary clearance through the hydrolysis of extracellular deoxyribonucleic acid in mucus of the cystic fibrosis airway.[117] In randomized trials, dornase alfa 2.5 mg/day improved pulmonary function (increase in FEV_1 3–16%) and decreased the risk of pulmonary exacerbations.[118–121] The response is variable, and younger patients appear to respond better than older patients.[118, 121, 122] Treatment with dornase alfa has been well tolerated for up to 2 years.[118–121, 123] Although experience is limited regarding administration of this agent to patients younger than 5 years, it may be given to certain patients deemed to be at significant risk of pulmonary function deterioration and/or respiratory tract infection.[117] Upper airway irritation, characterized by voice alteration and laryngitis, are the only adverse effects reported more frequently with dornase alfa than placebo.[118]

Airway inflammation may transiently increase after the start of treatment with dornase alfa.[124, 125] However, long-term therapy (3 yrs) appears to mitigate inflammation by preventing the progressive increase in total IL-8 sputum concentrations and free elastase activity that accompanies cystic fibrosis lung disease.[126] The antiinflammatory mechanism of dornase alfa is unclear. It may modulate inflammation by increasing the clearance of neutrophil and neutrophil-degradation product-rich secretions, or by decreasing the frequency of pulmonary exacerbations, thus limiting neutrophil infiltra-tion and the release of neutrophil-degradation products.

Methotrexate

Methotrexate is a folic acid antagonist with well-known antiinflammatory properties. Although the antiinflammatory mechanism of methotrexate in the cystic fibrosis lung is unknown, the promotion of adenosine release and/or the inhibition of transmethylation

reactions may play a role.[127] In a retrospective study, clinical data were analyzed for five patients with *P. aeruginosa* colonization and advanced cystic fibrosis lung disease (predicted FEV_1 25–65% at the start of treatment) unresponsive to conventional therapy.[128] The patients, aged 8.2–19.2 years, received oral methotrexate 10–20 mg/m^2 once/week. In the year preceding the start of treatment, a median 10.5% decrease in FEV_1 was observed ($p<0.005$). After 1 year of treatment, FEV_1 increased by a median of 9% (range 2–15%, $p<0.05$). In four of the five patients, IgG levels decreased after initiation of methotrexate. No severe adverse effects were observed.

These data suggest a potential benefit of methotrexate in patients with advanced cystic fibrosis lung disease. However, the retrospective study design and the small number of patients involved precludes firm conclusions regarding the safety or efficacy of methotrexate. Controlled, prospective studies are needed.

Montelukast

The selective cysteinyl leukotriene receptor antagonist montelukast is indicated for treatment of asthma and for relief of symptoms associated with seasonal allergic rhinitis.[129] Most patients with cystic fibrosis have insufficient bronchial lability to meet the diagnostic criteria for asthma.[130] As with asthma, however, patients with cystic fibrosis have increased airway cysteinyl leukotriene levels, which may contribute to airway inflammation.[131] Montelukast has been studied as a treatment for patients with cystic fibrosis.[130, 132] The pharmacokinetic profile of montelukast does not appear to be different in patients with cystic fibrosis compared with the general population.[133] The dose and dosing interval used to treat asthma may be extrapolated to cystic fibrosis if similar target concentrations are desired.

Two studies have evaluated the safety and efficacy of montelukast in children and adults with cystic fibrosis.[130, 132] In an open-label, observational study, 11 patients aged 16–44 years (mean 25.9 yrs) with stable cystic fibrosis (predicted $FEV_1 < 65\%$) were treated with montelukast 10 mg at bedtime for 2 weeks.[130] At study conclusion, improvement was observed in exercise tolerance ($p=0.008$) and morning peak expiratory flow rate ($p=0.003$), but FEV_1 remained unchanged. Of interest, the patients who improved the most were those who also had positive *Aspergillus* serology results.

The second study was a randomized, double-blind, placebo-controlled crossover trial involving 16 patients (10 boys, 6 girls), aged 6–18 years (median 9.5 yrs), with mild cystic fibrosis lung disease (predicted FEV_1 70–125%).[132] Patients were treated with montelukast 5 mg (those aged 6–14 yrs) or 10 mg (those aged > 14 yrs) once/day for 21 days in a crossover design with a 4-week washout period. Treatment with montelukast was associated with reduced eosinophilic inflammation, which was noted by a decrease in serum eosinophil cationic protein ($p\leq0.02$) and eosinophil count ($p\leq0.027$). However, no significant change was noted in clinical symptom score or lung function parameters (FEV_1, FVC).

Montelukast was well tolerated in both studies.[130, 132] Large, multicenter trials with longer observation periods are needed to further evaluate the safety and efficacy of montelukast as an antiinflammatory agent in patients with cystic fibrosis. Montelukast 4 mg for patients aged 5 years or younger, 5 mg for those aged 6–14 years, and 10 mg for those aged 15 years or older may benefit patients with cystic fibrosis who also have an asthmatic or allergic rhinitis component.

Pentoxifylline

Pentoxifylline, a nonspecific inhibitor of phosphodiesterase, is believed to moderate inflammation by increasing intracellular cyclic adenosine 3′,5′-monophosphate.[134] Pentoxifylline blocks the inflammatory actions of tumor necrosis factor (TNF)-α and affects cytokine expression in a concentration-dependent manner.[135–146] Neutrophil function may be mitigated through antagonism of these mediators.[135, 147–150] Ex vivo, pentoxifylline has blocked the destructive action of stimulated neutrophils in isolated perfused lungs.[147] Studies have demonstrated the ability of pentoxifylline to suppress neutrophil influx and ameliorate pulmonary damage of primates infected with *P. aeruginosa*[148] and improve airway patency and responsiveness in healthy volunteers treated with an inhaled endotoxin.[151] These findings led to the investigation of pentoxifylline in patients with cystic fibrosis.

In a randomized, double-blind, placebo-controlled study, 16 patients with *P. aeruginosa* colonization were treated with pentoxifylline or placebo for 6 months.[152] Nine patients aged 12–33 years (mean ± SD 8.2 ± 8.0 yrs) received sustained-release pentoxifylline 400 mg 4

times/day, mean dose 42.6 ± 4.2 mg/kg/day; seven patients aged 12–32 years (mean ± SD 20.7 ± 7.0 yrs) received placebo.

At study conclusion, mean sputum elastase concentration was significantly higher than at baseline in the placebo group ($p<0.05$). Concentrations were decreased in two of the nine patients in the treatment group, but were similar to those at baseline in the remaining seven patients. The FVC was improved in four patients receiving pentoxifylline versus none in the placebo group. Mean FVC declined 7.2% and 0.8% in the placebo and treatment groups, respectively ($p=0.33$). Values for FEV_1 and $FEF_{25–75}$ also were not significantly different between the two groups. Of the seven placebo patients, four had a pulmonary exacerbation requiring hospitalization for antibiotic treatment, whereas only one of the nine pentoxifylline-treated patients was hospitalized for treatment ($p=0.077$).

This study suggests a potential role for pentoxifylline in patients with cystic fibrosis. Larger, randomized trials need be conducted in both children and adults with cystic fibrosis before treatment with this agent can be recommended. However, even if further studies suggest a benefit, compliance with a 4-times/day regimen would likely be difficult.

Nutritional Supplements

In patients with cystic fibrosis, the lungs are exposed to extensive oxidative stress, an effect that may result from a decrease in antioxidant defenses.[14, 15] The low plasma levels of antioxidants may result from an increase in turnover or metabolism of these substances.[16] Supplementation could correct this imbalance and thus possibly attenuate lung inflammation.

β-Carotene

Plasma levels of β-carotene are significantly lower in patients with cystic fibrosis than in healthy controls, and the plasma level of β-carotene is inversely correlated with IgG levels.[16, 153–161] Together, this suggests a possible relationship between β-carotene deficiency and pulmonary inflammation.[16] Improving plasma β-carotene concentrations with supplementation has been associated with improved pulmonary function and a reduced rate of exacerbations.[159, 160, 162]

Supplementation with β-carotene 0.5–1.0 mg/kg can correct the deficiency commonly observed in patients with cystic fibrosis.[154, 155, 157–161] Studies have indicated that nearly normal concentrations of β-carotene were reached 3–4 weeks after the start of therapy and plateaued thereafter.[155, 157–159] Treatment with β-carotene also has reduced malondialdehyde concentrations, a mediator of pulmonary dysfunction.[155–161, 163]

Two controlled studies[159, 160] evaluating the clinical efficacy of β-carotene supplementation in cystic fibrosis were conducted in a total of 48 patients (mean age 11.7 yrs[160] and 12.8 yrs[159]). In both studies, patients were treated for 12 weeks with β-carotene 1 mg/kg, to a maximum dosage of 50 mg/day. Pulmonary exacerbations, depicted as the number of days patients were treated with antibiotics, were significantly reduced in both studies ($p<0.05$). In addition, predicted FEV_1—but not predicted FVC—was improved in the first study's younger patients.[159] This benefit was not statistically significant, but the improvement in pulmonary function was correlated with β-carotene concentrations. The second study demonstrated no improvement in pulmonary function.[160] Data assessing the effect of β-carotene on pulmonary function are conflicting.

Further studies are needed to determine definitively the effect of this supplement on pulmonary function because these two studies were inadequately powered to detect a difference if one existed. Therapy with β-carotene 0.5–1 mg/kg/day, to a maximum dosage of 50 mg/day, appears to be well tolerated.[155, 159, 160]

Essential Fatty Acids

Patients with cystic fibrosis are often deficient in essential fatty acids. This deficiency may result from innate abnormalities in fatty acid metabolism.[164–167] Plasma omega-3 fatty acid concentrations have correlated with pulmonary function in cystic fibrosis.[168] These fatty acids inhibit generation of leukotriene B_4 by neutrophils and may suppress the production of IL-1 and TNF-α.[24]

A short-term benefit has been observed after intense supplementation with intravenous fatty acids.[169] However, parenteral therapy does not seem to offer substantial clinical benefit, and addition of routine intravenous therapy may add undue psychological stress to treated patients.[169, 170] Orally administered omega-3 fatty acids in the form of fish oil may mitigate lung damage in patients with cystic fibrosis. Fish oil contains the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid; both possess antiinflammatory properties. Several studies have demon-

strated the feasibility of correcting fatty acid deficiency and pancreatic insufficiency through dietary fish oil supplementation in patients with cystic fibrosis.[171–174] Decreased production of leukotriene B_4 in the airways, with a subsequent decrease in exposure of leukotriene B_4 to circulating neutrophils, has been suggested by several studies as the mechanism for this potential clinical benefit of fish oil in patients with cystic fibrosis.[167, 173, 175, 176]

Two studies observed that treatment with fish oil was associated with beneficial effects on pulmonary function.[167, 175] The first study, a randomized, double-blind, placebo-controlled trial, involved 16 patients with cystic fibrosis and colonized with *P. aeruginosa*.[175] The patients, aged 12–26 years (median 17 yrs), were treated with a 6-week course of fish oil capsules providing 2.7 g/day of eicosapentaenoic acid. Treatment resulted in a significant reduction in sputum volume ($p=0.015$) and an improved Shwachman score ($p=0.034$), FEV_1 ($p=0.006$), and vital capacity ($p=0.011$) compared with placebo.

The second study involved 30 patients with cystic fibrosis, aged 0.8–24.0 years (mean 12.4 yrs), with *P. aeruginosa* colonization and pancreatic insufficiency.[167] These patients were treated with omega-3 fatty acids in the form of fish oil in a mean daily dose containing 1.28 g of eicosapentaenoic acid and 0.93 g of docosahexaenoic acid. After 8 months of supplementation, a small improvement was observed in FEV_1 ($p<0.05$) and in number of days of antibiotic treatment ($p<0.05$).

Fish oil is a relatively benign therapy when administered to patients with cystic fibrosis. Gastrointestinal symptoms are the most commonly reported adverse effects; eructation, diarrhea, and steatorrhea often necessitate an increased dosage of pancreatic enzymes.[172, 173, 175] Persistence of these gastrointestinal symptoms, or the need for higher dosages of enzymes than recommended, may limit the utility of fish oil therapy in certain patients. Elevations of alanine aminotransferase may also occur with supple-mentation with omega-3 fatty acids.[177] Liver function tests should be monitored before treatment with fish oil and as indicated during treatment.

Future Directions

In healthy individuals, the epithelial surface of the lung is protected from the destructive action of neutrophil elastase by two antiproteases: α_1-antitrypsin and secretory leukoprotease inhibitor (SLPI).[9, 18, 19] The lower respiratory tract is protected predominantly by α_1-antitrypsin, whereas SLPI provides the major anti–neutrophil elastase protective screen at the epithelial surface of the upper airways.[19, 178] Although present in normal concentrations, α_1-antitrypsin and SLPI are overwhelmed by neutrophil elastase in the cystic fibrosis lung at an early age.[9, 17–19] Active neutrophil elastase is thus allowed to injure the lung continuously, increasing secretion of mucus; enhancing chemoattraction; stimulating production of chemoattractants, such as IL-8, IL-6, and leukotriene B_4; and impairing opsonization and the ability of the host to eliminate bacterial pathogens, such as *P. aeruginosa*.[18]

Pharmacologic replacement of active antiproteases may be a novel therapeutic approach to reduce the neutrophil elastase burden on the respiratory epithelial surface in patients with cystic fibrosis, thus ameliorating inherent inflammatory actions. The potential utility of both SLPI and α_1-antitrypsin in patients with cystic fibrosis lung disease have been investigated.[17, 178–186]

In patients with cystic fibrosis, inhalation of recombinant (r) SLPI 100 mg every 12 hours effectively increases epithelial lining fluid SLPI and decreases epithelial lining fluid neutrophil elastase and IL-8 concentrations.[180, 181] The increase in anti–neutrophil elastase capacity is immediate and coincides with the rise in epithelial lining fluid SLPI concentrations, whereas the decrease in epithelial lining fluid neutrophil elastase concentrations correlates with the reduction in IL-8.[180] Hence, suppressing neutrophil elastase, a stimulus for IL-8 production, which decreases neutrophil chemoattraction to the lung and further lessens neutrophil elastase concentrations, may mitigate lung damage. In addition to its effects on neutrophil elastase, rSLPI also raises epithelial lining fluid concentrations of the antioxidant glutathione, which are often lower than normal in patients with cystic fibrosis.[182, 187] The subsequent increase in antioxidant capacity of the epithelial lining fluid is delayed for 24 hours after inhalation.[182]

Treatment with rSLPI 100 mg every 12 hours was administered to 45 adults (mean ± SD age 27 ± 2 yrs) with cystic fibrosis for 7 days without adverse effects.[180, 181] Tissue concentrations of rSLPI did not accumulate.[181] Because the imbalance of protease and oxidant constitutes a major component of inflammation in cystic

fibrosis lung disease, rSLPI may provide a dual benefit. However, rSLPI does not distribute well to poorly ventilated and highly inflamed areas of the lung.[188] Therefore, although functional lung tissue may be protected, inhaled rSLPI may be of minimal benefit in patients with severe lung disease. Controlled studies are needed to assess the safety and efficacy of rSLPI for pulmonary function in patients with mild-to-moderate cystic fibrosis lung disease.

The antiprotease α_1-antitrypsin increases epithelial lining fluid α_1-antitrypsin concentrations; suppresses active neutrophil elastase, increasing the anti–neutrophil elastase capacity; reduces proteolysis; and reverses the ability of respiratory epithelial lining fluid to interfere with neutrophil killing of *P. aeruginosa*.[184, 185] In contrast to rSLPI, α_1-antitrypsin does not increase epithelial lining fluid glutathione levels and thus has no direct antioxidant activity.

Inhaled α_1-antitrypsin distributes to the distal air spaces of the lung.[189, 190] In a study of 26 patients with cystic fibrosis, α_1-antitrypsin 100, 250, and 350 mg twice/day significantly decreased neutrophil elastase activity.[186] A trend toward greater elastase inhibition was noted with higher dosages. Treatment has also been associated with reduced proteolysis, but no benefit in lung function has been observed.[185] Inhaled α_1-antitrypsin has been well tolerated.[186] The effect of α_1-antitrypsin on lung function and progression of lung damage in patients with cystic fibrosis is unknown.

The utility of inhaled recombinant human monocyte and neutrophil elastase inhibitor, the oral antiproteases L-658,758, DMP 777, ICI 200,355, and chemically modified tetracyclines is under investigation.[1, 191–196] Initial in vitro and animal data are intriguing, and further studies investigating the role of these anti–neutrophil elastase agents are warranted. The host defense of a patient with cystic fibrosis lung disease may be augmented through administration of IL-10.[197] The use of a recombinant IL-10 preparation is under investigation.

Conclusion

Inflammation is a major component of the vicious cycle characterizing cystic fibrosis pulmonary disease. If untreated, this inflam-matory process irreversibly damages the airways, leading to bronchiectasis and ultimately respiratory failure. Most morbidity and nearly all mortality in patients with cystic fibrosis are associated with pulmonary disease. Thus, interrupting the cycle of obstruction, infection, and inflammation with antiinflammatory agents may have a positive impact on disease progression.

Investigators have observed that pulmonary inflammation can be mitigated pharmacologically by drugs and supplements that affect the function or migration of neutrophils, modify the activity of proinflammatory and antiinflammatory cytokines and chemokines, antagonize the virulence of bacteria such as *P. aeruginosa*, improve the oxidant-antioxidant and protease-antiprotease imbalance, or possibly directly affect the cystic fibrosis transmembrane conductance regulator gene.

Treatment with oral corticosteroids and ibuprofen is associated with beneficial effects on several disease parameters; however, oral corticosteroid therapy is limited by adverse effects. Children with cystic fibrosis can be treated with ibuprofen, assuming treatment is begun when they are aged 5–13 years and the clinician commits to evaluating patient tolerability and to monitoring plasma concentrations routinely to ensure efficacy and minimize toxicity. Inhaled corticosteroids, though well tolerated, do not appear to affect inflammation of the cystic fibrosis airway to a great extent. The decision to administer inhaled corticosteroids in children with cystic fibrosis should be made on a patient-to-patient basis.

Azithromycin, which has been effective and well tolerated, is the most promising anti-inflammatory therapeutic agent for treatment of cystic fibrosis pulmonary disease. Therapy with this agent can be recommended for children aged 6 years or older with *P. aeruginosa* colonization or a suspected history of *P. aeruginosa* colonization.

The most appropriate patient age at which antiinflammatory treatment should be started is a topic of debate. However, because the antiinflammatory therapies are preventive, younger patients would be expected to benefit to a greater extent than those in whom substantial lung damage has already occurred. Therefore, early initiation of antiinflammatory therapy should be recommended. Future studies should be directed toward establishing the safety and efficacy of these therapies in children younger than 5 years.

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