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Treatment of Severe Small Airways Disease in Children with Cystic Fibrosis

Alternatives to Corticosteroids

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Contents

Abstract

A group of patients with cystic fibrosis (CF) have severe small airways disease characterized by wheeze, chest tightness and limited sputum production, often with deteriorating lung function. Suggested mechanisms include mucosal edema secondary to infection and inflammation, smooth muscle contraction caused by inflammatory mediators, and collapse of bronchiectatic airways.

While treatment with long-term oral corticosteroids may result in symptomatic improvement, adverse effects often make them intolerable. Inhaled corticosteroids are used in many centers despite the lack of conclusive evidence of their efficacy. Therapeutic alternatives to corticosteroids are aimed at reversing bronchoconstriction and reducing inflammation.

Many patients with CF are treated with short- and long-term inhaled bronchodilators, but data to support their use are inconclusive. Other attempted routes of administration for short-acting bronchodilators include the subcutaneous and intravenous routes, but clinical data are again lacking. Sodium cromoglycate (cromolyn sodium) has been studied, with little evidence of benefit. Theophyllines have also been studied, both intravenously and orally, with some effect, but are not often used in clinical practice. Nonsteroidal anti-inflammatory therapies include ibuprofen, macrolide antibiotics, intravenous immunoglobulin, cyclosporine, and leukotriene antagonists. Ibuprofen has been shown to be useful in patients with mild CF disease, but concerns about potential adverse effects have limited its use. The results of various macrolide studies are awaited, but to date there are no long-term studies published. While there is great interest in the potential of intravenous immunoglobulin,

cyclosporine and leukotriene antagonists, the evidence for their effectiveness comes from anecdotal reports, thus there is currently insufficient data to support their use. Since this is a small group of patients, it is unlikely that sufficient numbers will ever be recruited for these studies; thus it is probable that drugs will be tried on an individual patient basis. The order in which they are attempted is unclear, but it would be sensible to try the least invasive medication with the least adverse effects first, moving on to more potent, but more toxic drugs if that treatment fails.

Lung disease accounts for much of the morbidity, and most of the mortality, in patients with cystic fibrosis (CF). Young children may have few respiratory symptoms or signs, but with advancing age, lung disease becomes increasingly evident and is usually characterized by recurrent cough, sputum production, and exercise limitation.[1] In many patients, wheeze may be an additional feature, particularly during an infective exacerbation. However, there is a group of patients with CF and deteriorating lung function who have persistent wheeze and do not produce sputum, despite the fact that their airways are full of secretions and they are on maximal antibacterial therapy. Imaging often reveals air trapping with minimal bronchiectasis. High-resolution computerized tomography (HRCT) often reveals hyperlucency and attenuated vessels similar to that seen in obliterative bronchiolitis.[2] However, patients with obliterative bronchiolitis have severe small airways involvement which differs from that commonly seen in patients with CF. While this group comprises a small percentage of the total CF population (approximately 5% in our practice), they present a difficult management challenge and require a disproportionate amount of consultation time, with inevitable cost implications. They may present at any age and have a variety of bacterial flora in their sputum. Some may be chronically infected with *Aspergillus* but do not have allergic bronchopulmonary aspergillosis. Although these children sometimes respond to oral corticosteroids,[3] adverse effects may make their long-term use intolerable.[4]

1. Pathogenesis of Small Airways Disease

Most, but not all, studies suggest that a newborn baby with CF has healthy lungs at birth. However, within a few days of life there is evidence of submucosal gland hypertrophy, duct obstruction, and mucous cell hyperplasia of the large airways, despite the apparent absence of detectable clinical infection in babies with CF.[5] Using bronchoalveolar lavage, Khan et al.[6] demonstrated an increase in neutrophils and interleukin-8 (IL-8) in babies as young as 4 weeks of age, without evidence of infection. Other studies suggest that it is the infection which precedes inflammation.[7] At present it is unclear which is the initiating factor in the inflammatory cascade, but it is likely that CF cells exist in a pro-inflammatory state. The most characteristic feature of inflammation in the CF lung is the presence of a large number of neutrophils in the airways. The clinical importance of this is that the excessive neutrophil influx results in an inflammatory cascade, with subsequent lung damage. The DNA from this huge number of neutrophils is partly responsible for the tenacious sputum in CF. Neutrophils are also responsible for the production of elastase, oxidants and proteases. The elastase digests elastin in the airway wall, resulting in bronchiectasis,[8] and directly causes an increase in mucus secretion, thus worsening airway obstruction. Elastase also promotes the generation of IL-8 and leukotriene B_4 (LTB_4), which are potent neutrophil chemoattractants, thus recruiting more of these cells and perpetuating the cycle of inflammation and lung destruction. The earliest macroscopic finding is plugging of the small airways with mucus. This in turn may progress to lobar collapse and/or consolidation. Before the introduction of appropriate therapy, the bronchioles became full of pus with consolidation of the surrounding lung parenchyma.[9] The lower airway in CF is characterized by mucus hypersecretion, bronchiectasis, endobronchial abscesses and bronchopneumonia. Bronchiectasis increases with age, primarily affecting proximal airways, and is more marked in the upper lobes.

Small airways have been defined as those conducting airways which are <2mm in diameter,[10] and contribute to approximately 10% of total airway resistance.[11] The term 'small airways disease' has been coined because abnormal airway function, together with airway inflammation, is thought to be a precursor to chronic airway obstruction in lung disease. Measurements of small airway function include determination of airway flows at low lung volume and vital capacity [$FEF_{25-75\%}$ (forced expiratory flow at 25 to 75% of forced vital capacity or FVC)]; however, it is recognized that there is great variability in these measurements, particularly in the CF population.[12] Small airways disease is characterized by worsening of airflow obstruction, with an increase in residual volume to FVC ratio. With worsening of lung disease, all spirometric indices ultimately become abnormal. The development of more sophisticated tests, such as the multiple-breath washout, will lead to further understanding of the small airway involvement in CF.[13]

Airway obstruction and hyper-responsiveness are common in patients with CF.[14] It is thought that the mechanism of hyper-

responsiveness in patients with CF is different from that seen in patients with asthma because patients with CF bronchodilate in response to exercise and challenge with hypertonic saline, in contrast to the bronchoconstriction seen in asthma.[15,16] In addition to causing lung damage, it has been suggested that neutrophils are also responsible for small airways disease in CF. Neutrophil recruitment causes inflammation, which in the presence of an irritant, may lead to airway hyper-responsiveness. Additional suggested mechanisms include mucosal edema secondary to infection and inflammation, smooth muscle contraction caused by mediators of airway inflammation and infection and autonomic nerve stimulation, and the collapse of bronchiectatic airways. The cycle of inflammation and infection causes increased mucus secretion, localized tissue edema, bronchospasm, and ultimately fibrosis. It is hoped that modulation of the inflammatory pathway might lead to a reduction in sputum production, decreased hyperreactivity, and improvement in small airway function, which ultimately should decrease mortality.

2. Management of Small Airways Disease

Small airways disease should be considered in patients who, despite maximizing anti-infective measures and physiotherapy, still have dyspnea, wheeze, and are minimally productive of sputum. Importantly, chest x-rays and HRCT images often reveal minimal bronchiectasis with air trapping and features of small airways disease.

2.1 Exclusion of Other Diagnoses

Prior to considering alternative therapeutic options, certain treatable conditions need to be considered.

2.1.1 Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) presents with wheeze, dry cough, and shortness of breath. There may be focal shadowing on the chest x-ray, and the presence of a high immunoglobulin E (IgE). *Aspergillus*-specific radioallergosorbent test (RAST), together with positive *Aspergillus* precipitins, *Aspergillus* in sputum, and a positive skin prick test are also suggestive of the diagnosis. A 4-fold rise in IgE has been reported to be the most sensitive marker.[17] Treatment of this condition is with oral corticosteroids. Oral antifungals may be of additional benefit, although the evidence for this is inconclusive.[18,19]

2.1.2 Gastroesophageal Reflux

Another disease that may cause intractable wheeze is gastroesophageal reflux. This is common in CF, and causation is multifactorial and contributes to the progression of lung disease.[20] Generally, wheeze may result from micro-aspiration of stomach contents, or from acid in the lower esophagus.[21] There is some evidence that this may be related to physiotherapy,[22] but this has not been verified in all studies.[23] All children with wheezy symptoms in whom this condition is suspected should undergo a 24-hour pH study as medical anti-reflux therapy may improve symptoms.

2.1.3 Asthma

It is known that 40 to 60% of children with CF have a bronchial hyper-reactive response to smooth muscle constrictors such as histamine and methacholine.[14,16] It has been suggested that the mechanism of bronchial hyper-reactivity in CF is different from asthma; however, it is not unusual for CF and asthma to coexist. Epidemiological data from North America suggest that approximately 19% of patients with CF also have asthma,[24] while in Europe this figure is 17%.[25] This has been recently reviewed.[26] The diagnosis of asthma is suggested by a family or personal history of atopy manifest by hayfever or eczema. In addition, the diagnosis may be supported by a therapeutic response to both short- and long-acting bronchodilators. Therefore, in wheezy patients with CF, a trial of inhaled bronchodilators, together with inhaled corticosteroids, should be undertaken before considering alternative therapeutic measures. However, there is no good evidence suggesting that continued use of inhaled corticosteroids in patients with CF is beneficial in those who do not have symptomatic relief.[27]

3. Nonsteroidal Drug Therapy

In an attempt to modulate the inflammatory process in CF, the effect of alternate day oral corticosteroids has been previously studied.[28] Although the results were encouraging, a more recent 4-year study found that adverse effects such as growth retardation outweighed the gains in pulmonary function.[4] A recent review of the use of oral corticosteroids in CF suggests that the risks of adverse effects outweigh the benefits.[29] The results have highlighted the need for alternative nonsteroidal therapies to treat patients with CF.

3.1 Bronchodilator Therapies

Because airway hyper-responsiveness is also present in some patients with CF[16] it is likely that the use of β_2-agonists would overcome some of this obstruction by reversing bronchospasm. Another possible beneficial mechanism is by increasing mucociliary transport in CF, which may aid airway clearance,[30] although this is controversial. It is known that patients with CF have a variable response to bronchodilators. Most studies[14] have

shown that while bronchodilators improve lung function in approximately one-half of patients with CF, 10 to 20% of patients with CF have a deterioration, and one-third show no response. Furthermore, there is great individual variability from day to day. A recent review identified 14 trials of short- and long-acting β_2-agonists, only two of which were conducted for >2 weeks.[14]

3.1.1 Short-acting β_2-agonists

Inhaled

Bronchodilators are often prescribed in patients with CF for symptomatic relief and for routine administration prior to physiotherapy to aid mobilization and expectoration of sputum. It has been estimated that >80% of patients with CF use bronchodilators daily;[31] however, data to support their use are distinctly lacking. Studies have demonstrated an increase in lung function when used both short term[32] and over the course of a year.[33] Importantly, some studies[34] demonstrated a large patient intervariability, suggesting that it is difficult to predict which patients will respond, although those with a baseline bronchodilator response tend to have responsiveness throughout the study. In practice, despite the lack of definite evidence of improvement, it is likely that patients will continue to be prescribed short-acting β_2-agonists, particularly if there is subjective improvement.

Intravenous

Only one study has investigated the effects of an intravenous β_2-agonist in CF. In a double-blind study, Finnegan et al.[35] compared nebulized with intravenous terbutaline in 23 patients with CF during the first 4 days of infective pulmonary exacerbations. The group receiving intravenous terbutaline demonstrated a significantly more rapid rate of improvement in peak flow when measured at day 10 compared with the group receiving nebulized terbutaline; however, there was no difference in other spirometric values. The authors suggested that an initial 4-day treatment with intravenous terbutaline resulted in a complete and more rapid reversal of airways obstruction than nebulized treatment. However, the lack of effect on small airways and other lung function values, particularly forced expiratory volume in 1 second (FEV_1), remains a weakness of the study. To date, no one has studied the long-term effect of intravenous β_2-agonists in CF.

Subcutaneous

Because of the long-term difficulty of administering bronchodilators via the intravenous route, subcutaneous delivery may have a role. There is evidence for clinical effectiveness using long-term subcutaneous salbutamol (albuterol) in adults with brittle asthma,[36] and from our own experience, of subcutaneous terbutaline in children with difficult((**Author: please explain meaning of 'difficult', i.e. do you mean difficult to treat?**)) asthma.[37,38] To date, there are no long-term studies of subcutaneous terbutaline in patients with CF. We have anecdotal experience in five children with CF and severe small airways disease. The intravenous preparation (0.5 mg/ml) is delivered via a pump (Graseby Medical Ltd, Watford, UK) at a starting dosage of 2.5 to 10 mg/day. We have recently used it in a 13-year-old girl with CF and severe small airways disease in whom long-term corticosteroids had been given on many occasions, but because of severe effects on growth velocity, other therapeutic treatments were explored. Following 1 week of subcutaneous treatment at 5 mg/24 hours, her FEV_1 rose by 7%, and $FEF_{25-75\%}$, a measure of small airways disease, doubled. While it is recognized that the repeatability of this measure is poor in patients with CF((**Author: please explain what you mean by 'the repeatability of this measure is poor', your meaning is unclear.**)),[12] the child felt much improved and was able to climb two flights of stairs without feeling 'tight'. There is a need for a proper controlled study using subcutaneous terbutaline in CF, but it is unlikely that sufficient numbers of patients will ever be recruited for a study of sufficient statistical power. Therefore, a therapeutic trial, which would ideally include a placebo limb to exclude a potential placebo effect, should be considered in certain patients.

3.1.2 Long-acting β_2-agonist

There have been two studies which have assessed the efficacy of salmeterol, a long-acting bronchodilator in patients with CF. In a nonblind crossover study, Bargon et al.[39] studied the effects of salmeterol in 26 patients with CF over 4 weeks. Following treatment, there was a significant rise in peak flow, and patients reported symptomatic improvement. Hordvig et al.[40] compared salmeterol with salbutamol in a placebo-controlled, double-blind study in hospitalized patients with CF. Lung function measurements demonstrated that salmeterol compared favorably with the short-acting β_2-agonist and, importantly, this effect lasted longer over the day. The effect of maintenance therapy with long-term β_2-agonists has not been assessed in CF, but in practice they are often added to inhaled corticosteroids in a similar manner to asthma management.

3.1.3 Ipratropium Bromide

It has been suggested that an increased vagal tone in CF leads to increased bronchial tone which may be reduced by ipratropium bromide, an anticholinergic bronchodilator.[15] Various studies have demonstrated an increase in lung function in patients with CF treated with ipratropium bromide.[41-43] However, the results are conflicting. Some studies have demonstrated that ipratropium bromide in combination with β_2-agonists was not better than ipratropium bromide alone.[41] Conversely, Sanchez et al.[42] demon-

strated that in patients who responded, a combination of ipratropium bromide and a β_2-agonist was superior to ipratropium alone. In a recent randomized, double-blind, placebo-controlled study, Ziebach et al.[44] compared salbutamol with ipratropium bromide alone and in combination over a 4-day period. They found that combination therapy and salbutamol alone were superior to ipratropium bromide alone; however, there was no significant difference between the drugs in combination and salbutamol alone((**Author: preceeding sentence needs to be reworded as it does not make sense. Do you mean 'the difference was not statiscally significant?**)). The contradictory findings of the above trials have resulted from different trial protocols, doses and outcome measures. The case for short-term ipratropium bromide remains inconclusive and no-one has yet studied the long-term effects of maintenance therapy with ipratropium bromide.

3.1.4 Sodium Cromoglycate (Cromolyn Sodium)

Following the report that sodium cromoglycate (cromolyn sodium) protected against bronchoconstriction in 4 of 15 patients with CF,[45] Sivan et al.[46] studied 14 patients with CF who had bronchial hyper-reactivity in a long-term, double-blind, placebo-controlled trial. They did not demonstrate any benefit from sodium cromoglycate. In contrast, Chua et al.[47] demonstrated that pre-treatment with sodium cromoglycate prevented ticarcillin-induced bronchoconstriction in a group of children with CF; however, it was not as effective as salbutamol. Because of the lack of data for clinical effectiveness in children with CF, sodium cromoglycate is not recommended.

3.1.5 Theophylline

Because the xanthines have been used with some success in patients with asthma, various groups have assessed their efficacy in patients with CF.[48-51] Xanthines primarily act as bronchodilators, but they may also have a direct effect on mucociliary clearance.[52] Larsen et al.[48] measured lung function following a 5-hour intravenous administration of aminophylline in 10 adolescents with CF. They demonstrated significant improvement in thoracic gas volume, airway conductance and maximal expiratory flow at 60% total lung capacity. Similar smaller changes were observed by Pan et al.,[50] who administered one dose of either theophylline or saline over 30 minutes on consecutive days. Because of the difficulties with intravenous administration, some groups have assessed the effect of oral theophylline in CF. Work by Eber et al.[49] showed little effect of oral theophylline on lung function; however, Avital et al.[51] demonstrated an increase in FEV_1 of 11% in 5 of 12 patients treated for 12 days. Interestingly, the treated group experienced less lung desaturation during sleep((**Author: rewording okay?**)).

The role of long-term theophylline therapy in the treatment of small airways disease in children with CF remains to be elucidated. Importantly, many children exhibit adverse behavioral effects when treated with theophyllines. In addition, there is a need for repeated venepuncture to monitor drug concentrations which makes this treatment less suitable for use in children.

3.2 Anti-inflammatory Therapies

3.2.1 Ibuprofen

Ibuprofen has been shown to inhibit neutrophil migration, adherence and aggregation.[53] Konstan et al.[54] studied 85 patients with mild CF disease using high-dose ibuprofen twice daily for over 4 years in a double-blind, placebo-controlled trial. They demonstrated significantly less deterioration in annual lung function over 4 years. Although the authors did not attribute adverse effects to the drug during the trial, there are concerns about the potential gastrointestinal and renal adverse effects, which may outweigh the benefits. In particular, the combination with other nephrotoxic drugs, such as aminoglycosides, may be associated with renal failure.[55] In addition, because of the wide variability in ibuprofen metabolism in patients with CF,[56] blood concentrations need to be monitored, which requires venepuncture at least every 2 years after steady state concentrations are reached. To compound this problem, there is a wide interpatient variability in the dosage required to achieve optimal serum concentrations. Use of ibuprofen is very dependent on the beliefs of the CF center, and as such has not taken off in the UK[57] or in some centers in the US.[58] A recent Cochrane review has concluded that currently the routine use of nonsteroidal anti-inflammatory drugs cannot be recommended, and larger studies are needed to further assess tolerability and efficacy.[59]

3.2.2 Macrolides

There are striking similarities between CF and diffuse panbronchiolitis, a disease common in Japan.[60] Macrolides such as erythromycin and azithromycin have been used long term with great success in diffuse panbronchiolitis, with a reported significant reduction in symptoms and increase in 10-year survival from 12% to over 90% in patients colonized with *Pseudomonas aeruginosa*.[60-64] There is good *in vivo* and *in vitro* evidence that macrolides exert an anti-inflammatory effect at doses lower than their minimum inhibitory concentration.[62,63] To date there are two published clinical studies in patients with CF.[65,66] A non-blind study in seven children given daily azithromycin for >6 months demonstrated a significant increase in lung function.[65] A recent short-term study demonstrated no difference following 6 weeks of clarithromycin in 10 adults with CF, which is not

surprising given the treatment duration and the small number of patients.[66] There have been other preliminary studies published in abstract form only which have been recently reviewed.[67]

Various anti-inflammatory mechanisms of macrolides have been postulated, including an effect on neutrophil chemotaxis and apoptosis, modulation of the inflammatory pathways, and bacterial adherence.[67] With relevance to small airways disease, there are various reports of a direct effect of macrolides on bronchoconstriction. Recently Takizawa et al.[68] demonstrated a reduction in endothelin-1 messenger RNA levels, as well as endothelin-1 release in normal and transformed human bronchial cells treated with erythromycin and clarithromycin, similar to that seen with dexamethasone. Endothelin-1 is a very potent vasoconstrictor produced by endothelial cells which is known to induce bronchoconstriction.[69] Further evidence for a reduction in bronchoconstriction by macrolides comes from Tamaoki et al.[70] who studied the contractile response of isolated human bronchial strips to electrical stimulation and acetylcholine. Erythromycin attenuated the responses to electrical stimulation. The authors suggested that macrolides reduce bronchoconstriction via inhibition of cholinergic responses in the human airway smooth muscle. Further support for an effect of macrolides on bronchoconstriction comes from many reports of successful use in children with asthma.[71-75] The potential role and mechanism of macrolides in CF remains to be elucidated, and the results of various worldwide controlled trials are eagerly awaited.[76]

3.2.3 Intravenous Immunoglobulin

Use of intravenous immunoglobulin (IVIg) as an anti-inflammatory agent in CF has arisen from reports of success in patients with asthma who are corticosteroid-dependent. While some studies have demonstrated a reduction in corticosteroid use in this group,[77-80] to date trials have failed to conclusively demonstrate benefit to support the use of IVIg in asthma. The mechanism of action of IVIg in asthma remains unclear. *In vitro* evidence supports synergy with dexamethasone, suppression of lymphocyte proliferation, and inhibition of IgE production.[79,81]

There are only a handful of trials to support the use of IVIg in CF. In a double-blind, placebo-controlled study, Winnie et al.[82] examined the effect of IVIg 0.1 mg/kg infused on 3 successive days in patients with mild to moderate CF disease undergoing intravenous antibiotic treatment for an infective exacerbation. They demonstrated an increase in lung function in the treated group but this was not sustained at 6 weeks following treatment. The exact mechanism of action of IVIg in these patients is unknown but it is possible that it reduces the number of viral upper respiratory tract infections or acts against *Pseudomonas aeruginosa*. *In vitro* evidence to support this comes from Fick et al.[83] who demonstrated increased phagocytosis by alveolar macrophages with the addition of IVIg which contains intact anti-*Pseudomonas* IgG2. Furthermore, it has been suggested that IVIg contains antibodies to *Pseudomonas* lipopolysaccharides and endotoxin, which may enhance the killing of this organism.[82] In theory, these anti-*Pseudomonas* antibodies may decrease immune complex formation, which have been implicated in lung destruction.

Van Wye et al.[84] examined the effect of passive immunotherapy by using *Pseudomonas*-specific hyperimmune globin in an uncontrolled, nonblind study. They studied its effect in 10 adult patients with CF chronically infected with *Pseudomonas aeruginosa* who were admitted during infective exacerbation episodes. In addition to demonstrating an improvement in lung function, there was an increase in anti–*Pseudomonas aeruginosa* lipopolysaccharide IgG for eight immunotypes, an increase in serum anti–*Pseudomonas aeruginosa* opsonic activity, and a decrease in sputum *Pseudomonas aeruginosa* density. The authors concluded that *Pseudomonas* IVIg is a 'safe' adjunct to conventional therapy that may be associated with greater improvement in lung function than standard therapy.

There has been one case report of successful corticosteroid dosage reduction in a 12-year-old child with CF who developed severe small airways disease unresponsive to corticosteroids, methotrexate and cyclosporine, following high-dose monthly IVIg.[3] Therapy resulted in an increase in FVC and FEV_1. However, there are no published trials assessing efficacy of IVIg in children with CF with severe small airway involvement. We have assessed the efficacy of IVIg in 17 children who received therapy for between 1 and 66 months.[85] Of the 13 children on regular oral corticosteroids prior to treatment, eight stopped corticosteroids completely and three had their dose halved. All patients were on inhaled high-dose corticosteroids (800 to 6000 μg/day budesonide equivalent) prior to IVIg. Following treatment, six were able to reduce their dosage. It was felt that treatment had been successful in 11 of the 17 patients. Adverse effects included fever (n = 1), headache (2), chest tightness (1), hypotension (1) and aseptic meningitis (1). It is an expensive, time-consuming treatment with a theoretical but negligible risk of blood-borne organisms, but it may merit a therapeutic trial in patients who have severe adverse effects from oral corticosteroids.

3.2.4 Cyclosporine

Cyclosporine is a potent anti-inflammatory drug which has been used successfully as an alternative to oral corticosteroids in some children with asthma.[86] To date, there have been no trials to assess efficacy in patients with CF. However, recently Bhal et al.[87] reported its use in six children with CF who exhibited sig-

nificant adverse effects from treatment with oral corticosteroids. Following treatment with cyclosporine, four patients were successfully weaned off oral corticosteroids after 18 months. In two patients, treatment was unsuccessful. In the four successful patients, improvement was seen in lung function, radiography scores, and growth velocity. Three patients developed renal impairment, which was severe enough to stop treatment in one patient. Other adverse effects included gingival hyperplasia and hirsutism. Importantly, there is a need for regular cyclosporine concentration and renal function monitoring. Thus, cyclosporine may provide a possible alternative to oral corticosteroids in patients with CF but needs to be evaluated in a long-term trial; however, given the low numbers of children with severe small airways disease this is likely to be impossible.

3.2.5 Leukotriene Antagonists

Cysteinyl leukotrienes have been implicated in a wide range of inflammatory lung diseases such as asthma and CF. They are products of arachidonic acid metabolism, and the cysteinyl leukotrienes (LTC_4, D_4 and E_4) are thought to have an effect on vascular permeability, mucus production, and bronchial smooth muscle. LTB_4, a noncysteinyl leukotriene, is a major neutrophil chemoattractant with no effect on bronchoconstriction. New therapies aimed at blocking the cysteinyl leukotriene receptor or inhibiting leukotriene synthesis have been shown to be beneficial in some patients with asthma. There is evidence of elevated levels of cysteinyl leukotrienes and LTB_4 in the lungs of patients with CF, and both classes of leukotrienes have been implicated in the pathophysiology of lung disease in CF.[88-90] To date, anti-LTB_4 drugs or 5-lipo-oxygenase inhibitors such as zileuton have not been assessed in CF but there is anecdotal evidence that anti-cysteinyl drugs such as montelukast and zafirlukast may have a role in treating patients with CF. Morice et al.[91] have recently reported a nonblind study in 11 adult patients with CF treated with montelukast 10mg nightly for 2 weeks. They reported a significant improvement in morning peak flow and peak flow variability. Peak flow measures large airways function and is of limited value in CF; there was no change in FEV_1. Subjective symptom scores improved; however, it must be noted that the trial was uncontrolled. Interestingly the patients who benefited the most had positive *Aspergillus* serology. The authors speculate that *Aspergillus* stimulated T helper 2 cells, and thus leukotriene synthesis. The future role of anti-cysteinyl drugs in the treatment of patients with CF and small airways disease remains to be elucidated.

4. Conclusions

Severe small airways disease in patients with CF remains a difficult management challenge. Although they represent a small number of patients, they require a disproportionate amount of consultation time, with inevitable cost implications. While corticosteroids are often the drug of choice, adverse effects mean that they are often not tolerated long term. There have been many attempts to use alternative treatments, often taken from experience in treating patients with asthma and applying this to patients with CF. Despite the lack of conclusive evidence, many patients are treated with short- and long-term inhaled β_2-agonists. The roles of ipratropium bromide and theophylline are less clear and these agents are rarely used in clinical practice.

From the above discussion, it is obvious that evidence for the other alternative anti-inflammatory therapies, such as IVIg and cyclosporine, is hampered by the lack of controlled trials. This is more problematic because of the difficulty in defining the condition. If these treatments are to be assessed properly for future use, then multicenter studies will need to be set up in order to recruit enough patients to obtain statistically powerful results. However, in reality, because only a small number of patients with CF have such severe small airways involvement, it is unlikely that sufficient numbers will ever be recruited for these studies. Thus, it is probable that individual drugs will be tried on an individual patient basis. The order in which they are administered is unclear but it would be sensible to try the least invasive medication with the least adverse effects first, moving on to more potent, but more toxic drugs if that treatment fails.

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