

Anti-inflammatory therapy in cystic fibrosis

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Abstract

Inflammation plays a major role in the pathophysiology of lung disease in CF. This response is probably triggered primarily as a reaction to the inability of the affected lung to resist the invasion of the most common bacterial pathogens seen in this disease, namely, *Staphylococcus aureus*, *Haemophilus influenzae* and *Pseudomonas aeruginosa*. Debate continues as to whether there may or may not be a pre-inflammation of the lungs as part of the basic functional defect of CFTR.

The anti-inflammatory treatment modalities most tested to date are: oral corticosteroids, effective but associated with significant long-term side effects, inhaled corticosteroids, so far not proven to be effective probably because of difficulty with absorption through the viscid surface secretions of the lung and ibuprofen, potentially effective but inhibited by the need to monitor drug levels invasively and potential gastrointestinal side effects. The most promising newcomer is macrolide antibiotics such as azithromycin acting as a long-term anti-inflammatory agent with an excellent safety profile.

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1. Introduction

Inflammation is a major pathophysiological feature of chest disease in cystic fibrosis. A number of hypotheses have been put forward as to its possible aetiology. The abnormal CFTR, particularly that which is found in homozygous delta F508 patients, is probably also involved in this pro-inflammatory process [1]. One of the most characteristic changes of inflammation in CF is a large infiltration by neutrophils into the lung parenchyme. These cells produce a number of local tissue damaging products, particularly elastase, which causes long-term structural airway damage. When the neutrophils degenerate DNase is released from the nuclei and this contributes to the increased viscosity of sputum which is characteristic of the illness. Armstrong et al. [2] have suggested that inflammation may even precede infection in this disease. This has also been suggested by the presence of increased neutrophils and cytokines such as IL-8 detected in young infants with cystic fibrosis with no overt evidence of

infection at the time [3]. It is therefore logical to assume that anti-inflammatory therapy could play an important role in the long-term management of the illness aimed at limiting the degree and severity of lung damage over a period of years.

Anti-inflammatory therapy can be provided in various forms. These include the use of oral corticosteroids which are potentially highly effective but which carry with them the risk of long-term systemic side effects. Inhaled corticosteroids also have considerable potential because of their local action within the lung. Their potential therapeutic disadvantage is the difficulty of penetrating the viscid mucus which lines the airway in CF patients particularly as the disease progresses. Potentially higher doses than those currently licensed for clinical use might be needed in order to produce a clinical response. Other anti-inflammatory agents such as ibuprofen have considerable potential and have been the subject of various studies over the years. More recently macrolides have come forward as potent anti-inflammatory agents and are beginning to have an established place in the therapeutic regimen for patients with long-term *Pseudomonas* infection. Other agents which have been used include immunoglobulins and dornase alpha

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(DNase) which may have an anti-inflammatory role as well as being mucolytic. Montelukast a cysteinyl-leukotriene receptor antagonist is also under study.

2. Oral corticosteroids

In 1985 Auerbach et al. [4] reported the results of a study in which patients were given 2 mg/kg of prednisone on alternate days during a 4-year period. This was a double blind placebo controlled trial including 45 children aged 1–12 years. The steroid group had better maintained lung function including FVC and FEV1, better growth velocity in terms of height and weight and less inflammation as assessed by ESR and serum IgG. They also had fewer admissions to hospital with acute exacerbations of the underlying disease. Adverse effects or non-compliance was however a significant problem and as many as 25% of patients failed to complete the study protocol. Later reported side effects included growth impairment, glucose intolerance, early cataract formation, bone fractures and cushingoid appearance [5].

A subsequent large multicentre North American Study was reported by Eigen et al. in 1995 [6]. Two hundred and eighty five patients aged 8–14 were randomised into a 4-year double blind placebo controlled study. Treatment consisted of either 1 or 2 mg/kg/day of prednisone. A significant incidence of side effects occurred in the 2-mg/kg alternate day group including glucose intolerance, cataract formation and impaired growth [7]. Similar side effects subsequently emerged later in the lower dose group as well. These studies [6] showed that at 1 mg/kg on alternate days, there was a significant improvement in FVC after 6 months in those who were chronically infected with *Pseudomonas aeruginosa*. Impaired growth only became evident after 2 years of treatment. In this study there was no reduction in the rate of hospitalisation between treatment groups. Recent studies have highlighted the prevalence of osteoporosis as a long-term complication in CF [8]. This would therefore be a further contraindication to the long-term use of oral corticosteroids to control the chronic lung disease in CF. At the present time therefore these agents cannot be recommended for the overall control of this aspect of the underlying disease process.

There are however other situations in CF where long-term oral steroids can be helpful in suppressing complications including chronic allergic bronchopulmonary aspergillosis (APBA) and concomitant moderate or severe asthma which does occur in a small but significant sub-group of patients [9].

Because of their powerful anti-inflammatory effects, oral corticosteroids can be very useful in the management of acute pulmonary exacerbations of CF lung disease. In this situation they are used in conjunction with intensive intravenous antibiotic therapy as well as bronchodilators, mucolytics such as DNase and appropriate modes of chest

clearance techniques depending on the patients age, severity of lung involvement and ability to cooperate with the relevant treatment modalities.

3. Inhaled corticosteroids

The evidence for the role of inhaled corticosteroids remains largely unproven in the long-term management of patients with CF. Theoretically they have considerable potential benefit as long-term anti-inflammatory agents. A small number of studies have been undertaken to assess the use of these agents with varying results [5,10]. A significant proportion of CF patients do however receive them on a regular basis as part of their therapeutic regimen.

Shiotz et al. [11] reported on 26 patients aged 4–29 given Beclomethasone dipropionate 400 mcg/day in a double blind placebo-controlled trial over 16 weeks. All patients were infected with *P. aeruginosa*. No significant effects of treatment were seen. The lack of therapeutic effect was thought to be due either to inadequate dosage of the drug or its inability to penetrate the highly viscid lung secretions of the CF patient. Van Haren et al. [12] reported on 12 adult patients given 1600 mcg of budesonide versus placebo over 6 weeks. This resulted in an improvement in bronchial hyperresponsiveness but not in basic spirometry. The patients also reported a decrease in cough during the treatment period.

Balfour-Lynn et al. [10] reported on a double blind placebo randomised crossover trial of fluticasone propionate (400 mcg/day) given for a 6-week period in 23 children with CF aged 7–17 years. No measurable therapeutic benefit was seen during the active treatment period. Neither atopic status, baseline FEV1 nor concomitant DNase therapy had any effect on treatment response.

Skov et al. [13] also reported that the combination of budesonide therapy with itraconazole to treat allergic bronchopulmonary aspergillosis resulted in adrenal insufficiency in 11 of 25 patients studied. This was reversible when itraconazole was discontinued. It is thought that itraconazole caused an increase in systemic budesonide concentration and an associated inhibition of adrenocorticoid hormone secretion.

Inhaled corticosteroids might be more effective in young children before significant hyperviscosity of lung secretions has developed. Wojtczak et al. [14] reported on a 2-month trial of Beclomethasone in infants. This resulted in a decrease in lower airway neutrophils but did not show any adverse effects on the adrenal glands.

The precise role of inhaled corticosteroids in the long-term management of CF lung at all ages thus remains to be elucidated.

Inhaled steroids are widely used for the treatment of patients with significant CF lung disease but as yet there are few convincing properly powered studies demonstrating long-term efficacy. They may however have a particular role

in those with either associated atopic asthma or where there is bronchial hyper-reactivity [15,16].

4. Ibuprofen

Ibuprofen is a substance known to have significant anti-inflammatory effects principally effected through a direct action on inhibiting the motility, adherence and localised aggregation of neutrophils within the lung tissue itself. Konstan et al. [17] reported on a double blind trial of high dose ibuprofen in 85 CF patients aged 5–39 years. The patients had relatively mild lung disease with FEV1 > 60% predicted. The trial lasted for 4 years. Those given active treatment had a slower annual rate of decline of FEV1 than those given placebo ($P=0.02$) and weight (as a percentage of ideal body weight) was better maintained over this time period in the actively treated group. There was no significant difference between the two groups in the frequency of hospitalisation. The beneficial effects were most evident in those aged 5–12 years.

This treatment regimen requires regular measurements of ibuprofen plasma levels. There was also concern about possible long-term side effects such as a small risk of gastrointestinal haemorrhage. Despite the results of this study ibuprofen is not used by many CF centres as standard treatment; less than 10% in the US [17] and less than 1% in the UK.

5. Macrolides

One of the most interesting new anti-inflammatory therapies introduced in recent years is the use of macrolides, particularly azithromycin. The agents are thought to act by suppressing pro-inflammatory cytokines and causing direct alterations in the function of neutrophils [18,19]. There have been three randomised controlled trials of azithromycin versus placebo in patients with CF [20–22]. A meta-analysis of these studies demonstrated a significant improvement or maintenance of FEV1 and FVC in treated patients versus controls after 6 months of therapy. There was no reduction in the need for intravenous antibiotic therapy or days of hospitalisation in any of these studies.

There is evidence to suggest that the use of azithromycin on a regular basis does produce a small but significant improvement in lung function over a period of time. Side effects such as mild disturbance of liver function tests are rare. Azithromycin probably does have a useful therapeutic role in patients with moderate to severe lung disease.

6. Immunoglobulins

A recent retrospective case note review of 16 children aged 3–16 years with advanced CF (Balfour-Lynn et al.,

2003) demonstrated a significant improvement in FVC with an average increase of 13% ($P<0.05$) when given monthly therapy for a median duration of 7.5 months. FEV1 was unchanged but the total daily dose of inhaled corticosteroid was reduced from a median of 2000 mcg/day by a median change of -400 mcg/day ($P<0.05$). This therapy was generally well tolerated although occasional side effects including headache, fever, hypertension, aseptic meningitis and chest tightness were reported. The total daily dose of oral Prednisolone was reduced from 0.6 mg/kg/day by a median amount of 0.6 mg/kg/day ($P<0.007$) thus in this series it was possible to discontinue oral steroid therapy completely in 16 of the children studied. This therapeutic regimen may therefore have a use in individual patients with advanced chest disease and may be effective in reducing the need for both oral and inhaled corticosteroids.

7. Other agents

A number of other possible anti-inflammatory agents are currently under investigation for this group of patients. These include recombinant human dornase alpha (DNase) [23] and Montelukast, a cysteinyl-leukotriene receptor antagonist [24].

8. Conclusions

Anti-inflammatory therapy has a logical basis as part of the overall treatment of CF lung disease. As well as reducing the effects of the neutrophil burden on the lungs by inhibition of locally active cytokines, these agents can have acute beneficial effects such as those seen in asthma. These can result in improved airway calibre by reduction of mucosal oedema and stabilisation of airway narrowing as a result of acute bronchospasm. Oral corticosteroids are also vital for the control of other lung related complications such as allergic bronchopulmonary aspergillosis (ABPA).

Inhaled corticosteroids delivered in sufficient amounts are known to be powerfully anti-inflammatory in asthma. Their role in the long-term management of CF lung disease has yet to be defined. A number of studies using conventionally approved dosage schedules have failed to show significant benefit in the long-term. It may be that much higher doses are required in order to penetrate the thick surface epithelial mucus layer seen in those with advanced CF lung disease before therapeutic efficacy is reached. Given the relatively good safety profile of these agents, further studies of their use are warranted.

The use of other anti-inflammatory agents such as ibuprofen has been elucidated by carefully controlled clinical studies. The varying bioavailability of the drug and the consequent need to monitor blood levels on a regular basis have inhibited its widespread use by CF clinicians. The potential for gastrointestinal side effects

is another reason why it has not entered widespread clinical use.

Intravenous immunoglobulin may have a place in selected patients especially those dependent on long-term oral corticosteroid therapy. Long-term macrolides especially azithromycin do appear to have a place in the treatment of patients with moderate to severe CF lung disease.

Macrolides such as azithromycin have recently come into use because of their anti-inflammatory role in patients with long-term *Pseudomonas* infection. Controlled clinical trials have increasingly shown benefit over significant periods of time in these patients. The once daily dosage regimen and their excellent safety profile will no doubt result in their increasing use with time.

A number of other promising anti-inflammatory agents which hold considerable potential for future use are currently under investigation.

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