Role of corticosteroids in cystic fibrosis lung disease

Ian M Balfour-Lynn BSc MD MRCP FRCS(Ed)   Robert Dinwiddie DCH FRCP

INTRODUCTION

Most patients with cystic fibrosis (CF) die from advanced lung disease and cor pulmonale. The predominant problem in the lungs is chronic infection which is exacerbated by airway obstruction and impaired mucociliary transport. The continued presence of bacteria, particularly *Pseudomonas aeruginosa*, on the airway mucosa provokes a vigorous inflammatory response. Although this contains the infection within the lungs, it usually fails to eradicate the organisms. The continuous cycle of infection and inflammation means that the host defence mechanism is responsible for much of the lung injury which contributes so much to the morbidity and mortality of CF (Figure 1).

Emphasis has recently turned to developing anti-inflammatory strategies for the management of CF. This has involved long-term trials of both non-steroidal[1] and steroidal anti-inflammatory drugs[2,3]. This review will consider the role of corticosteroids given to control lung inflammation in CF. It will not discuss the other well-established uses of corticosteroids in CF, namely treatment of allergic bronchopulmonary aspergillosis[4], concomitant asthma or CF-related wheezing that is difficult to control with β-agonists alone.

CF LUNG INFLAMMATION

Neutrophil-dominated and significant

CF lung inflammation is characterized by the predominance of neutrophils in the airways. This contrasts with the usual situation in which the alveolar macrophage is the predominant phagocyte in the lungs[5]. The abundant neutrophils are responsible for some of the purulent sputum, whilst degraded neutrophil DNA makes a significant contribution to sputum viscosity (about 10%). Although relatively quiescent, the alveolar macrophages are a source of interleukin-8 (IL-8) in CF[6]. IL-8 is the principal neutrophil chemoattractant and elevated levels of IL-8 in sputum and bronchoalveolar lavage fluid correlate significantly with disease severity in CF[7]. Other neutrophil chemoattractants found to be elevated in CF include the complement component C5a[8] and the lipoxygenase product

leukotriene B_4 (LTB$_4$) (Figure 2)[9]. Other cytokines, including interleukins-1 and -6, and tumour necrosis factor-alpha (TNFα), all of which contribute to the inflammatory process, are known to be producd in the infected CF lung in increased amounts[5].

Apart from the bacteria, it is the neutrophil products that are probably responsible for most of the lung damage in CF. Neutrophils can injure tissue directly by releasing large amounts of reactive oxygen metabolites as well as digestive enzymes and proteases[10]. Neutrophils also release LTB$_4$ and several cytokines, including IL-8, hence the inflammatory process is amplified as these substances recruit further neutrophils (Figure 3). Principal among the proteases is neutrophil elastase: the epithelial surface of the lung is normally protected from neutrophil elastase by two antiproteases, α_1-antitrypsin and secretory leukoprotease inhibitor. However, the enormous quantities of neutrophil elastase released in the CF lung overwhelm the antiproteases, allowing active neutrophil elastase to remain unbound and chronically injure the epithelium[11]. This includes damage to structural proteins leading to bronchiectasis, compromised mucociliary function and induction of secretory cell metaplasia[5]. Neutrophil elastase also interferes with local host defence by adversely affecting opsono-phagocytosis[5]. Enzyme release into the tissues is also enhanced by incomplete phagocytosis of pseudomonas colonies protected by their mucoid layer. Despite this impressive inflammatory response, it should be stressed that, in the CF lung, the host defence still fails to eradicate the organisms.

Occurring early in life

A significant inflammatory response has been shown to occur in the CF lung at a much younger age than previously
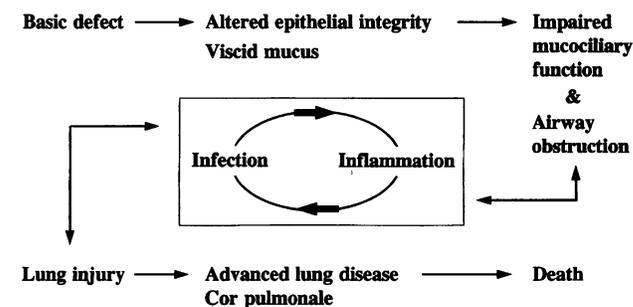

Figure 1 Pathogenesis of lung inflammation in cystic fibrosis

Respiratory Unit, Great Ormond Street Hospital for Children NHS Trust, Great Ormond Street, London WC1N 3JH, England
Correspondence to: Dr Balfour-Lynn

Chemoattractants

Bacterial products eg FMLP
Complement fragments eg C5a
Cytokines eg Il-8
Lipid mediators eg leukotriene B$_4$

Activators

Bacterial products eg lipopolysaccharides
Cytokines eg Il-1, TNFα

Products

Cytokines eg Il-1, Il-6, Il-8, TNFα
Oxygen metabolites eg hydrogen peroxide, superoxide
Enzymes eg elastase, cathepsin G, collagenase, myeloperoxidase
Lipid mediators eg leukotriene B$_4$, platelet-activating factor
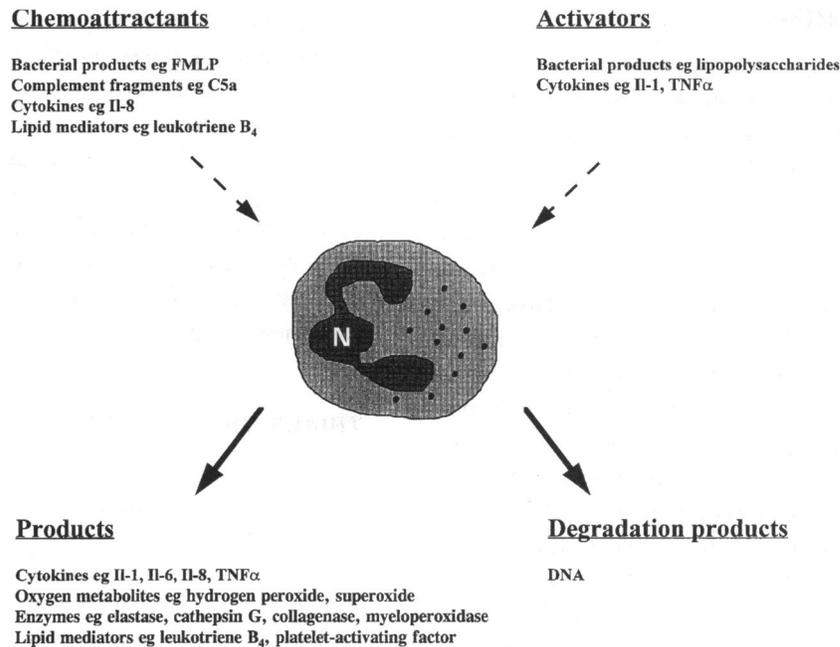
Degradation products

DNA

Figure 2 Principal chemoattractants and activators of the neutrophil (N) along with its main products

suspected. Included in a study of 27 children with CF were four children aged 1 year. All four had bacteria cultured from their bronchoalveolar lavage (BAL) fluid and two of them had active free neutrophil elastase in the epithelial lining fluid[11]. This was the first BAL evidence that the cycle of infection and inflammation started within the first year of life. In a recent and important study, 16 infants aged 4 weeks to 1 year (mean 6 months) underwent BAL[6]. Compared to 11 controls (pulmonary illness excluding CF), the CF infants had significantly greater neutrophil counts, free and α_1 antiprotease-bound neutrophil elastase activity and IL-8 in the BAL fluid. This confirmed the presence of

significant lung inflammation in CF infants as young as 4 weeks. Finally, another study has shown infection to be present in 17/45 infants under 3 months who had BAL performed; over a third of the infants with infection were asymptomatic at the time of lavage[12]. Compared to the non-infected infants and controls, the infected infants also showed significantly increased markers of inflammation (macrophage and neutrophil counts, IL-8 levels).

Not restricted to severe disease and exacerbations

A study has been carried out in which BAL was performed on 18 patients considered to have clinically mild CF lung disease and 23 normal subjects[13]. The patients were all over 12 years of age, did not produce sputum and had forced expiratory volume in 1 s (FEV$_1$) > 60% predicted. Furthermore, they had all been free of exacerbations for at least 2 months, and half had never been hospitalized or received intravenous antibiotics. However, pathogenic bacteria were cultured from all BAL samples and increased neutrophil counts with clearly detectable free elastase activity were found. Although these patients would be considered to be colonized only, this term is clearly inappropriate when the bacteria are causing active and potentially harmful inflammation. Airway damage from infection and inflammation is therefore a continuous process, and not restricted to acute exacerbations. In the light of this study, it has even been suggested that the concept of the colonized CF lung should now be abandoned[14].
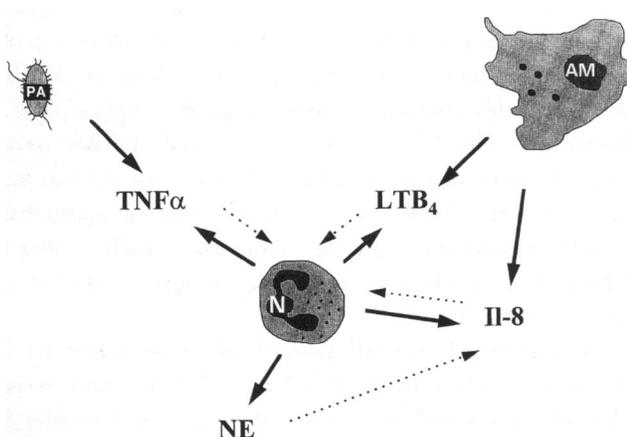
Figure 3 Amplification process by which activated neutrophils produce substances which recruit further neutrophils into the cystic fibrosis lung. PA=*Pseudomonas aeruginosa*; AM= alveolar macrophage; N=neutrophil; NE=neutrophil elastase;
— =production; - - - =chemoattractant/activator

Preceding infection

In Khan's study of 16 infants discussed above[6], another important finding was that in seven of the infants with significant lung inflammation there was no evidence of current bacterial, viral or fungal infection. The implication here is that lung inflammation may precede infection and hence may be inherent to CF: it is further suggested that perhaps the fundamental defect in CF contributes directly to the exaggerated inflammatory response[14]. However, an alternative explanation for this finding is that the microbial cultures were falsely negative, although this is unlikely considering the stringent criteria used to define infection in the study. It was also possible the infants had a previous infection that had been cleared by the time of lavage, but this is also unlikely as once bacteria are present in the CF lung, it is unusual for them to be totally eradicated. Khan's findings were not confirmed by the Australian study in which increased inflammation was not observed in the 20 infants who were free of infection, compared to controls[12]. However there has been another study on BAL in 14 children with CF aged 4 months to 7 years in which inflammation was present (increased neutrophils, IL-1β, IL-8, TNFα and neutrophil elastase) in the absence of pathogenic bacteria[15]. In some of the samples with significant inflammation there were no microbes at all, whilst in others there were normal oral commensals only. Interestingly, it has been recently shown that production of IL-10 in the airways is reduced in cystic fibrosis: the importance of this is that IL-10 is a regulatory cytokine that decreases the inflammatory response and T-cell stimulation[16]. It is not yet known what causes the defect in IL-10 production in CF, but this may explain how normal oral commensals might cause inflammation in the CF lung.

ANTI-INFLAMMATORY ROLE OF CORTICOSTEROIDS

It is clear, therefore, that anti-inflammatory therapy should benefit patients with CF, and corticosteroids were an obvious place to start when choosing such therapy. Corticosteroids block the production and sometimes the action of several inflammatory cytokines and this forms the basis of many of their immunosuppressive and anti-inflammatory effects[17]. Affected cytokines include interferon-γ, interleukins-1, -2 and -5, and TNFα[17,18]. Indeed, modulation of cytokine gene expression forms part of the rationale for corticosteroid therapy in bronchial asthma[18]. In addition, production of eicosanoids (e.g. leukotriene B$_4$) is inhibited by corticosteroids in vitro, although this effect has not yet been proven to occur in vivo[17].

Corticosteroids have several effects on neutrophils which are most relevant for cystic fibrosis. Although the number of circulating neutrophils increases after just a single dose of glucocorticoid, steroids can inhibit priming of the neutrophils into an active state[19]. Corticosteroids also inhibit migration of neutrophils into tissues by blocking release of recruitment factors such as lipid metabolites and cytokines, including interleukin-8[20]: they may also block this migration via an effect on the endothelium of the blood vessels[19]. Furthermore, corticosteroids inhibit neutrophil extracellular proteolytic activity although superoxide generation is not affected[21]. The exact mechanisms by which corticosteroids have these effects on neutrophils is not clearly understood.

TRIALS OF ORAL CORTICOSTEROIDS

One of the earliest reports of the use of oral corticosteroids appeared only in abstract form[22]. Sixteen patients were given prednisone 2 mg/kg/day during acute illness which was then continued as alternate day or daily low dose therapy. There was a significant improvement in forced vital capacity (FVC) and Schwachmann scores accompanied by a significant fall in circulating immune complex levels. One boy did, however, suffer from lumbar vertebral compression, thought to be as a result of the steroids.

In 1985, Auerbach et al.[2] reported results of a 4 year double blind, placebo controlled study using 2 mg/kg oral prednisone on alternate days. There were 45 patients enrolled aged 1–12 years, all with mild to moderate lung disease. The steroid-treated group showed significant advantage compared to controls in terms of growth (height and weight), lung function (vital capacity, FEV$_1$, and peak flow rate), and inflammatory parameters (erythrocyte sedimentation rate and serum IgG). The treatment group also had fewer hospital admissions for pulmonary exacerbations. It is worth noting, however, that almost 25% withdrew from the study for a variety of reasons and, surprisingly, there were said to have been no steroid-induced side effects at all. Five years later, however, a report appeared in abstract form describing long-term follow-up of the original patients in Auerbach's study[23]. None of the six authors on this abstract were authors on the original paper. Fourteen of the 17 patients who received steroids were included, some of whom had continued to take steroids for over 10 years. Reported side effects included substantial growth impairment, glucose intolerance, early cataract formation, multiple bone fractures, cushingoid appearance and anorexia nervosa.

A small trial in the UK assessed oral prednisolone for 3 weeks in 20 clinically stable adults[24]. Patients only were blinded and received either 20 or 30 mg prednisolone after 3 weeks of placebo. There was no benefit seen in terms of lung function, symptoms or sputum production. Two patients developed pneumothoraces whilst on steroid but this may have been coincidental: other side effects seen were glycosuria and mild fluid retention. It was suggested by the authors that the

negative result may have been due to the fact that all the patients had severe airflow obstruction (median FEV_1 was 27% predicted) and possibly the disease had progressed to a stage where the obstruction was now irreversible.

Following the encouraging results from Auerbach[2]—and before the side effects were reported—a large multicentre trial was initiated across North America. In 15 CF centres, 285 patients were enrolled from 1986 to 1987 by the Cystic Fibrosis Foundation Prednisone Trial Group into a 4 year double-blind placebo-controlled study. Patients were aged 6–14 years with mild to moderate disease ($FEV_1 > 60\%$ predicted). Treatment groups received alternate day prednisone at either 1 mg/kg (low dose) or 2 mg/kg (high dose). In 1990 the unblinded study ombudsman and special advisory panel recommended that the high dose group discontinue the study due to the high incidence of adverse effects[25]. These included glucose intolerance, growth retardation and cataract formation. At the time, no significant increase in complications had been noted in the low dose group so the rest of the trial continued. However, in 1991 the data safety monitoring committee recommended the low dose group also discontinue due to an excess of adverse events and the trial was terminated: final results were published in 1995[3].

The main findings were that a dose of 1 mg/kg prednisone led to a significant improvement in FVC, first evident at 6 months, which persisted for the 4 years of the trial. However, there was no additional advantage in taking the higher dose. Importantly, benefit was only seen with either dose in patients who were colonized with Pseudomonas aeruginosa. Improvement in FEV_1 was only seen in the low dose group, with the high dose group having a similar decline to the placebo—but it is not clear why this was the case. Hospitalization rates were the same for all groups, in contrast to Auerbach's study. Both prednisone-treated groups had a significantly greater reduction in serum IgG levels compared to placebo. As mentioned, adverse events were so significant that the whole trial was halted prematurely. However, effects on growth were only seen after 24 months' treatment in the low dose group compared to 6 months in the high dose. Glucose abnormalities were only seen with the high dose and cataracts were seen in both groups. The conclusion of the trial group was that there is a role for alternate-day prednisone therapy at a dose of 1 mg/kg for patients with mild to moderate disease and Pseudomonas colonization. Treatment should be discontinued if there is no improvement by 6 months and should be limited to 24 months. Obviously, the children must be carefully monitored for side effects.

Most of the trials described have concentrated on clinical aspects, although serum IgG has been used as a marker of inflammation in some of them[2,3]. This is because raised serum IgG is frequently associated with chronic pulmonary infections in CF and, furthermore, is associated with a poorer overall prognosis[26]. One study has looked at the effects of oral prednisolone on inflammatory cytokines in the serum[27]. Twenty-four children were given 2 mg/kg for 14 days then 1 mg/kg alternate days for 10 weeks in a placebo-controlled double-blind trial. Improved lung function was seen at 14 days, which was less marked by the end of the period on the lower dose. This was accompanied by a decrease in serum interleukin-1α (IL-1α) and soluble interleukin-2 receptor (S/L-2R) as well as serum IgG. This is important since IL-1α is one of the earliest cytokines produced in response to antigen and may initiate release of a cascade of other inflammatory cytokines. Furthermore, S/L-2R is a marker of T lymphocyte activation and T cells have a central role in control of the immune response. Both IL-1α and S/L-2R had previously been shown to be significantly raised in children with CF[28,29]. This evidence further supports the rationale for anti-inflammatory therapy in CF.

Although the administration of oral corticosteroids would seem to be beneficial to patients with cystic fibrosis in terms of lung function and reduction of inflammation, the occurrence of serious side effects outlined above limits their use. Unfortunately, it can not be predicted which patients will be adversely affected. The occurrence of steroid-induced cataracts in CF does not seem to be related to length of treatment or dose of steroid[30]. The prevalence of glucose intolerance increases with age in CF[31], and corticosteroids can easily convert simple glucose intolerance into frank diabetes. It would, therefore, seem prudent to avoid giving steroids to any patient who has been shown to have borderline glucose tolerance, for example intermittent glycosuria. The problem of adverse systemic effects is further exacerbated in patients with CF due to their altered prednisolone pharmacokinetics. In CF there is a marked increase in prednisolone clearance which means more frequent or higher doses of steroids would be required, leading to an even worse risk–benefit ratio[32].

TRIALS OF INHALED CORTICOSTEROIDS

Given the drawbacks of systemic corticosteroids, the obvious choice for an anti-inflammatory agent would be atopical inhaled steroids; adverse systemic effects are minimal, particularly if high doses are avoided and spacer devices are used to administer the drug[33]. There have been surprisingly few studies published of their use in CF however. This is even more surprising when put in the context that, in the Cystic Fibrosis Clinic at Great Ormond Street Hospital for Children, approximately 20% of patients are on inhaled steroids, although some of these are given to control troublesome wheezing.

The first study was double-blind placebo-controlled and involved 26 patients (aged 4–29 years) who were given

beclomethasone dipropionate (400 μg/day) or placebo for 16 weeks[34]. The patients were all chronically colonized with *Pseudomonas aeruginosa* and the study did not demonstrate any beneficial effect on lung function (peak expiratory flow rate, FVC) or local production of inflammatory mediators (proteolytic activity, albumin concentration and immune complex activity in sputum). The authors suggested the lack of effect may have been due to the low dose or lack of penetration of the drug to the principal sites of inflammation due to the viscid mucus secretions.

It was over 10 years before another study was reported. Twelve adult patients were given 1600 μg budesonide per day in a double-blind cross-over study for 6 weeks[35]. There was no increase in lung function although there was a significant improvement in bronchial responsiveness to histamine. The patients also had a small clinical improvement in cough and dyspnoea scores. Another study has been performed in 49 patients with moderate to severe lung disease ($FEV_1 < 55\%$ predicted) who were all hospital in-patients for about 1 month[36]. They were given high-dose (1500 μg/day) beclomethasone dipropionate via a spacer device or placebo. Significant improvement of lung function was noted in the steroid group but this must be put in the context of 1 month of in-patient therapy. The only other study reported was a double-blind placebo-controlled study of 15 children given 1500 μg/day beclomethasone dipropionate for 22 weeks[37]. A signficant decrease in inflammatory markers (serum eosinophilic cationic protein and myeloperoxidase) was seen in the steroid-treated group. Unfortunately, the poor design of the study led to a high drop-out rate (almost 50%) so any results must be treated with caution.

Most of these studies have involved older patients in whom destructive changes to the lungs have already resulted in irreversible damage, so the largely negative effects on lung function are not that surprising. It would be more productive to study the effects of inhaled corticosteroids on inflammatory markers, because a significant decrease in them, even if lung function was unaffected, would justify the use of inhaled steroids in CF. For this reason, we have conducted a double-blind placebo-controlled cross-over study using moderately high doses of inhaled fluticasone propionate (400 μg/day) for 6 weeks. The primary parameters were inflammatory markers in the sputum and results of this study should be available by early 1996.

CONCLUSION

One key to improving morbidity and mortality in CF may be to control the relentless lung inflammation that starts at such an early age. The concept of anti-inflammatory therapy for CF is well established, and it is now time to find the right agent. This agent must have a high safety profile since treatment will need to continue for a number of years. Oral corticosteroids are associated with too many serious side effects to make them a practical option. Inhaled corticosteroids on the other hand may well be the answer, and although this is speculation, perhaps they should be started at the time cystic fibrosis is first diagnosed or very early in the course of the illness.

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