Corticosteroid treatment in cystic fibrosis

Lung damage in cystic fibrosis originates in airway mucosal cells where failure of chloride secretion and enhanced sodium absorption lead to excessive absorption of water. There is loss of the sol phase lining the epithelium and viscid mucous, which interferes with ciliary transport and provides a breeding ground for bacteria, accumulates on the airway wall. In these circumstances the protective and self limiting inflammatory response initiated by pulmonary macrophages is not sufficient to eliminate infection. The continuing presence of bacteria provokes a vigorous systemic inflammatory response that prevents dissemination of infection beyond the lung, but in doing so may contribute to lung injury. Corticosteroid treatment could be beneficial by suppressing those components of the immune response that are damaging the lung.

Unrestrained inflammation in the cystic fibrosis lung

Polymorphonuclear neutrophil leucocytes (PMN) are the principal effector cells of potentially damaging inflammation in the cystic fibrosis lung. They produce free radicals, proteolytic enzymes, and leukotriene B4 (LTB4), which are capable of causing lung destruction and potentiating the inflammatory process. Much of PMN behaviour is governed by immunological signals derived from T cells, B cells, and mononuclear phagocytes in a series of complex interactions.

The main antigen presenting cells are pulmonary macrophages which produce polypeptide signals (cytokines) in response to infectious stimuli. Interleukin (IL)-1 is one of the earliest cytokines generated in the presence of antigen. It is itself a potent chemoattractant and activator of PMNs, but can also initiate the release of a cascade of other proinflammatory cytokines, including IL-8 and tumour necrosis factor-α (TNF-α). These cytokines have potent chemotactic effects on PMNs and can induce their degranulation. They promote neutrophil margination and their transendothelial passage to sites of active inflammation. IL-1 also upregulates the expression of high affinity receptors for IL-2 on T cells and activates them by stimulating the release of IL-2.

Clinical studies in cystic fibrosis suggest that these cytokines are participating in the inflammatory response. Neutrophils are the predominant cell recovered from lavage fluid in patients with cystic fibrosis. They are present in quantities that correspond with concentrations of IL-1β and IL-8. Plasma IL-1α and TNF-α are also increased; concentrations of the latter correlate with those of neutrophil elastase antiprotease complexes. Evidence for T cell activation is provided by the observation that soluble IL-2 receptors are raised in sera from patients with cystic fibrosis.

Histological studies have demonstrated that significant numbers of T and B lymphocytes are also present in the airway in cystic fibrosis. IL-1 and IL-2 may have a synergistic effect on B cells, attracting them to sites of inflammation and promoting their differentiation into mature plasma cells capable of producing immunoglobulin.

Hypergammaglobulinaemia G frequently accompanies chronic pseudomonas infection in children with cystic fibrosis and is associated with a poorer prognosis. Immuno-globulin G is the important isotype for bacterial opsonisation; however, in cystic fibrosis there may be a mismatch between the subclass produced and its Fc receptors on macrophage/monocytes. Although the opsonic capability of certain cystic fibrosis sera depends on the ability to form immune complexes with bacterial antigens is preserved. Immune complexes are present in sputum and the circulation of patients with cystic fibrosis and are capable of local complement activation. Fick et al found increased concentrations of the powerful neutrophil chemoattractant (C5a) in cystic fibrosis lavage fluid that correlated with its elastolytic activity. In addition, immune complexes and C5a can further stimulate macrophages to produce other potent PMN chemoattractants, including LTB4, IL-8, and TNF-α.

Neutrophil elastase may be an important regulatory enzyme of the inflammatory response; it is produced in quantities sufficient to overwhelm local antiprotease systems. Sputum elastolytic activity increases during infective exacerbations and correlates significantly with pulmonary disease severity. Neutrophil elastase may synergise with exoproteases derived from mucoid strains of Pseudomonas aeruginosa to degrade elastin and other components of lung connective tissue. Evidence for lung proteolysis is suggested by studies that demonstrate raised urinary desmosine concentrations (cross linking amino acids in elastin) in those with cystic fibrosis. Neutrophil elastase may also have an immunomodulatory role. Free neutrophil elastase may render bacterial opsonophagocytosis defective by degrading interactive sites on complement components (C3 and C5), destroying complement receptors on phagocytes, and cleaving the Fc portion of immunoglobulin and immune complexes. These molecules retain their respective abilities to attract neutrophils, activate complement, and induce cytokine expression.

When colonisation with mucoid strains of P aeruginosa occurs, it presents additional problems for host defence mechanisms, which render it virtually impossible to eradicate. Its mucoid layer protects it from opsonisation and phagocytosis by host macrophages. Exoproteases derived from mucoid strains of P aeruginosa can cleave CD4 receptors on T lymphocytes, inhibit human neutrophil chemiluminescence, and inactivate cytokines (IL-1 and IL-2). Thus, the inflammatory cycle is perpetuated without clearance of the offending organism. Respiratory allergy and specific hypersensitivity to Aspergillus fumigatus may place additional inflammatory burden on the already compromised cystic fibrosis lung. Although they are potentially amenable to corticosteroid treatment, their inflammatory mechanisms are too detailed to be discussed in the present annotation.

High concentrations of cyclo-oxygenase products (thromboxanes and prostaglandins) and lipoxygenase...
products (the leukotrienes) have been documented in cystic fibrosis. LTB4 and the cysteinyl leukotrienes are present in cystic fibrosis sputum at concentrations sufficient to cause airway inflammation, mucous hypersecretion, and bronchial lability.\(^7\) Taken together, these observations suggest that arachidonic acid metabolism is disturbed; in fact, this was originally proposed as a component of the basic defect in cystic fibrosis.\(^8\) However, it is now known TNF-\(\alpha\) can upregulate human neutrophil phospholipase A\(\_2\) and 5-lipoxgenase to produce more lipid mediators ex vivo.\(^9\)\(^,\)\(^10\) Significant quantities of TNF-\(\alpha\) are present in sputum from patients with cystic fibrosis, which not only correlate with pulmonary disease severity but also with sputum leukotriene concentration, suggesting that 5-lipoxgenase priming is occurring in vivo.\(^11\) IL-8 may have a similar effect,\(^12\) therefore it is probable that the observed abnormalities of arachidonic acid metabolism represent a cytokine mediated response to chronic infection.

**Corticosteroid treatment: mechanisms of action**

Corticosteroids are potent anti-inflammatory drugs but their precise mechanism of action remains unknown. Earlier work suggested that their effect was attributable to the inhibition of eicosanoid release by inflammatory leucocytes\(^13\) through the induction of lipocortin, which antagonises the activity of phospholipase A\(\_2\), and reduces the availability of arachidonic acid, derived from membrane phospholipids, for both the 5-lipoxgenase and cyclo-oxygenase pathways. This effect may be important in cystic fibrosis patients where there is evidence of excessive phospholipase A\(\_2\) activity. However, in vivo studies addressing the corticosteroid effect on eicosanoid production in man have failed to demonstrate a convincing suppressant effect on arachidonic acid metabolism.\(^14\)\(^,\)\(^15\) While their effect on phospholipase A\(\_2\) in vitro is well documented, corticosteroids operate at many other levels of the inflammatory response. They have important inhibitory effects on neutrophil chemotaxis, adhesion, and tissue infiltration in vivo.\(^16\) Corticosteroids do not appear to influence directly the expression of vascular adhesion molecules, but may do so indirectly suppressing IL-1 and TNF-\(\alpha\) production by monocytes.\(^17\) In addition, corticosteroids are potent inhibitors of in vitro T lymphocyte proliferation.\(^18\) They suppress the production of IL-2 and the expression of its receptor on lymphocytes.\(^19\) The inhibitory effects of corticosteroids on cytokine expression may block communication between cells of the immune system and presumably underly many of their immunosuppressive and anti-inflammatory properties. They may have particular relevance to cystic fibrosis where cytokine networks are being increasingly implicated in the regulation of the inflammatory process.

**Indications, efficacy, and safety in cystic fibrosis**

Despite the emerging evidence that indicates that the inflammatory response is harmful, the only firm indication for systemic corticosteroid treatment in patients with cystic fibrosis is allergic bronchopulmonary aspergillosis. Previous studies in subjects with asthma and cystic fibrosis suggest that this complication is eminently treatable with systemic corticosteroids.\(^20\) Few studies have addressed the mechanisms of action, efficacy, or safety of systemic steroids in patients with stable cystic fibrosis lung disease. In an early uncontrolled study, prednisolone caused a reduction in circulating immune complexes that correlated with improvements in lung function.\(^21\) Later, prednisolone, 20–30 mg daily for three weeks, failed to relieve airflow obstruction in a group of severely affected adults (median forced expiratory volume in one second, 27% predicted).\(^22\) However, a larger North American double blind, placebo controlled study (2 mg/kg on alternate days for four years) showed that the actively treated group had better nutrition, lower IgG concentrations, fewer hospitalisations, and a slower decline in lung function.\(^23\) There were no problems with disseminated infection and surprisingly no steroid side effects were reported. Fourteen of the original 17 who received active treatment were followed up for a further six years. They had a high incidence of growth retardation and glucose intolerance. Osteoporosis (n=2) and cataract formation (n=2) were also reported.\(^24\) A definitive multicentre trial is presently being analysed. The long term administration of prednisolone 2 mg/kg on alternate days is being compared with 1 mg/kg on alternate days and placebo. In an interim report, the unblinded study ombudsman recommended that the high dose limb of the study be discontinued because of a much higher incidence of glucose abnormalities, cataracts, and growth retardation.\(^25\) These results might prompt one to examine the role of inhaled steroid treatment. So far only one double blind, placebo controlled study has evaluated the efficacy of inhaled steroids (beclomethasone 400 \(\mu\)g a day) in patients chronically colonised with mucoid strains of P aeruginosa. This failed to demonstrate an effect on lung function or on local production of inflammatory mediators.\(^26\)

It is becoming increasingly recognised that immune hyperstimulation often precedes the development of lung disease. Balough et al have shown increased concentrations of IL-8 and neutrophils in epithelial lining fluid from young patients with cystic fibrosis without established lung disease that did not correlate with bacterial infection.\(^27\) Increased serum concentrations of soluble IL-2 receptor are found in young children who have sterile sputum and normal pulmonary function, suggesting that T cell activation occurs before chronic bacterial colonisation and precedes the development of immunologically mediated lung injury.\(^28\) Therefore, the supplemental use of newer, potent, and more topically active corticosteroid compounds given by the inhaled route may provide the best hope of arresting the development of the inflammatory cycle without causing systemic side effects. If administered to patients without established lung disease, corticosteroids may maintain the cystic fibrosis lung in good condition until treatments, which redress the cystic fibrosis defect, become available for general use.

**Conclusion**

Systemic corticosteroids are the recognised treatment for confirmed allergic bronchopulmonary aspergillosis. Long term administration of high dose prednisolone (2 mg/kg on alternate days) may have beneficial effects in the lung in uncomplicated stable cystic fibrosis patients. However, this is associated with an unacceptably high incidence of systemic side effects. The effects of lower doses (1 mg/kg on alternate days) are not yet known. The supplemental use of corticosteroids during acute infective exacerbations merits further investigation. Multicentre trials are now required to evaluate the efficacy of long term inhaled corticosteroids in younger patients without lung disease.

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