Anti-inflammatory therapy

Oral steroids in cystic fibrosis

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Background

In CF, airway obstruction and recurrent respiratory infections lead to inflammation, long-term lung damage, respiratory failure and death. Current evidence suggests that inflammation occurs early in life and may contribute to progression of lung damage. This is the rationale for the use of anti-inflammatory therapy in CF. Anti-inflammatory drugs for CF lung disease appear to have beneficial effects on disease progression. These agents include oral corticosteroids and ibuprofen, as well as azithromycin, the latter in addition to its antimicrobial effects, also possesses anti-inflammatory properties. Adverse effects limit therapy with oral corticosteroids and ibuprofen (Pressler T et al, 2011). Oral corticosteroids are indicated for an acute pulmonary exacerbation (APE) in CF characterized by increased pulmonary symptoms attributed to bacterial colonization, neutrophil recruitment, and inflammation. A retrospective study examined the use of oral steroids dosed at 2 mg/Kg/die up to 60 mg/die in a children's hospital from 2013 to 2017 during CF APE treatment following at least 1 week of inpatient therapy without expected clinical improvement. Main results suggested that during APE corticosteroids do not impact important outcome measures as FEV1 (Muirhead C et al, 2021).

Recently novel therapeutic approaches have been reviewed, including new modulators, that may exert beneficial effects in CF patients (Ghigo A et al, 2021) beyond oral corticosteroids.

Oral corticosteroids are the cornerstone of ABPA secondary to CF, however side effects can be significant limitations in an already high-risk patient population.

Issues

1. To assess the effectiveness of long-term use of oral corticosteroids (OC) in:

   - reducing the number of days of intravenous antibiotics for respiratory exacerbations;
   - reducing the need for hospital admission for respiratory exacerbations;
   - improving or preventing the decline of lung function;
   - improving exercise tolerance;
   - improving nutritional status;
   - improving quality of life;
   - improving survival.

1. To identify any adverse event associated with the use of OC including changes in cushingoid appearance, growth suppression, diabetes mellitus, cataracts, osteoporosis and the onset of opportunistic infection.

What is known

1 CDSR (Cheng K et al, 2015) was performed with the aim to assess the effectiveness of OC on lung function in CF for a long-term use.

Among eleven identified studies, three studies included 354 participants, two with a four-year follow up and one with 12-weeks follow up. No predefined outcomes were found; common outcomes were examined at different time-points. Meta-analyses were not possible.

Four further trials not included in the CDSR were assessed.

1. Regarding to the first issue a few data are available on the effect of OC on the decline of lung function in CF. On the basis of four reviewed trials with a total of 378 participants followed from 1 year to 19.5 years at all stages of lung disease, one for six weeks, one for 12 weeks and two with a four-year follow up, OC from 1mg/kg to 2 mg/kg (prednisolone equivalent) given every day seemed to slow the advance of lung disease. In only one RCT study, oral corticosteroids at prednisolone-equivalent dose of 1 mg/kg alternate days slowed progression of lung disease; at two and four years, % predicted FEV1 in the 1 mg/kg group changed significantly more than in the placebo group (p<0.02). These data were not confirmed when the 2 mg/kg treated group was evaluated during the first two years, compared to placebo group. Linear growth retardation was observed from six months in the 2 mg/kg alternate days prednisolone group and from 24 months in the 1 mg/kg alternate days prednisolone group. No data are reported that may define the impact of OC exercise tolerance or, nutritional status, neither on quality of life and survival.

2. Regarding to issue 2 serious adverse effects were reported such as cataracts and the slowing of growth at higher doses, but not all the same adverse events were reported in the four studies. Follow-up data show that catch-up growth started two years after the treatment was stopped. Alternate-day treatment with oral corticosteroids may have impaired growth until adulthood in boys.

Current evidence suggests that oral corticosteroids at a prednisolone equivalent dose of 2 mg/kg on alternate days is effective, but it
should not be used due to the high risk of occurrence of important side effects. A dose of 1 mg/kg on alternate days might be considered for up to 24 months, but close attention to the occurrence of adverse effects is warranted.

Unresolved questions

OC at prednisolone-equivalent dose of 1 to 2 mg/kg alternate days appear to slow progression of lung disease in CF; benefit should be weighed against occurrence of adverse events. Risk-benefit analysis of low-dose alternate days corticosteroids is important and the short-term use of oral corticosteroids should be better evaluated.

The two outcomes selected in CDSR in 2015 were lung function and adverse events. Other issues as exercise tolerance, number of days of intravenous antibiotics for respiratory exacerbations, quality of life, nutritional status and survival were not entirely explored by RCTs during OC therapy.

Further trials should consider OC in conjunction with other conventional therapies by targeting individuals who could benefit from OC. Multicenter clinical trials are needed to follow-up several adverse effects related to early treatment by OC, such as osteoporosis and diabetes in the long term therapy.

New therapies may impact on chronic inflammation, reducing the need of oral corticosteroids in selected patients.

Keywords

Anti-Inflammatory Agents; Steroids;