Anti-inflammatory therapy

Non-steroidal anti-inflammatory therapy

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Background

Prevention of lung deterioration is one of the most important goals in CF therapy. Persistent pulmonary infection causes a hyperactive inflammatory response and inflammation mediators give an important contribution to airway damage. The inflammation of the CF lung is dominated by neutrophils that release oxidants and proteases, particularly elastase, in the CF airway secretions. As previously detected (Cantin AM, 2015), several defective inflammatory responses have been linked to CFTR dysfunction, including innate and acquired immunity dysregulation, cell membrane lipid abnormalities, various transcription factor signalling defects, as well as altered kinase and toll-like receptor responses. Recently (Patergnani S, 2020) it has been suggested that a decline in mitochondrial function endorses the development of hyperinflammation in CF and that new therapeutic avenues, that aim to target the mitochondrial inflammation, can improve CF patient's inflammatory state.

Up to date, in addition to systemic corticosteroids and azithromycin, between non-steroidal anti-inflammatory drugs (NSAIDs) only high doses ibuprofen (serum concentration higher than 50 micrograms per millilitre), has been recommended to prevent the loss of lung function.

International Guidelines (Flume PA, 2007) suggested that ibuprofen had to be prescribed in individuals with FEV1 greater than 60% predicted, even if a previous international committee (Mogayzel PJ, 2013) has narrowed the previous recommendation to include only children 6–17 years of age, because of the insufficient information about adult population and has stressed the necessity to maintain the ibuprofen serum concentration of 50–100 mcg/ml, because neutrophil migration increases, rather than decreases, at lower serum levels.

The necessity to study efficacy and safety of antinflammatory new drugs has been, far back, discussed (Banner KH, 2009), revised three years later (Rowe SM, 2012) and in 2015 (Cantin A, 2015), (Sagel SD, 2015). In particular, on the basis of the results about the LTB4 receptor antagonist use in CF (Konstan MW, 2014), it has been speculated that the administration of potent anti-inflammatory compounds to individuals with chronic infections may increase the risk of infection-related adverse events, because of the potential to significantly suppress the inflammatory response.

Recently (Consalvi S, 2021) a review has discussed the rational for further studies of COX-2 inhibitors -NO releaser hybrids (NO-Coxibus), compounds already studied for the treatment of arthritis in case of airway inflammation in CF.

The Cystic Fibrosis Foundation, in early 2014, established a working group to address anti-inflammatory drug development in CF. It has been suggested that, before bringing new anti-inflammatory drugs to clinical trial, preclinical safety studies must be conducted in disease-relevant models, to assuage safety concerns, and that pharmacokinetic-pharmacodynamic studies and early-phase safety studies have to be performed before proceeding to larger studies of longer duration (Torphy TJ, 2015).

Issues

- NSAIDs efficacy in preventing pulmonary deterioration, evaluated in terms of lung function evolution, lung infection exacerbation frequency, quality of life and survival.
- Short-term and long-term NSAIDs therapy-associated adverse events (above all increase of pulmonary infective exacerbations, haemorrhagic episodes, gastrointestinal symptoms, allergic reactions, fluid retention, kidney and liver problems).
- Useful markers of inflammatory status.

What is known

One CDSR (Lands L C, 2019) identified 17 trials; four have been included in the review (287 participants aged five to 39 years; maximum follow up of four years), one was awaiting full trial report and two were ongoing. Three trials compared ibuprofen to placebo and one trial assessed piroxicam versus placebo. The three trials about ibuprofen were deemed to have good quality, but used various outcomes and summery measures. High dose ibuprofen demonstrated to be able to slow lung disease progression, especially in children.

One RCT published in 2007 (Brennan S, 2007) showed a clear reduction of airway inflammation after alpha1-antitrypsin treatment, although no effect on lung function was observed.

One RCT published in 2012 (Elborn JS, 2012) evaluated the safety and the efficacy of the neutrophil elastase inhibitor AZD9668 on clinical outcomes, inflammation biomarkers and tissue damage. In the AZD9668 group, there was a trend towards reduction in sputum inflammatory biomarkers (interleukin-6, RANTES, and urinary desmosine).

One phase II RCT published in 2013 (Nahrlich L, 2013) studied the sphingomyelinase inhibitor acid Amitriptyline, which showed, in

mices, to be able to normalize mucociliary clearance, chronic inflammation and infection susceptibility to pulmonary P. aeruginosa by reducing ceramide levels. In this study Amitriptilyne showed to reduce ceramide levels in nasal epithelial cells, to be safe and to increase FEV1 values in the 44 CF enrolled patients.

In 2015 (Chmiel J F, 2015) it has been published an open-label, controlled trial to assess IL-6, IL-8, TNF-?, IL-1-?, free neutrophil elastase, and white cell counts, in patients randomized to high dose of ibuprofen or to routine care. IL-6 was the only biomarker with significant within-group change among ibuprofen-treated subjects and no change in the control group.

In 2018 (Konstan MW,2018) an association was observed between high-dose ibuprofen use and both slower lung function decline and improved long-term survival, in a study including 775 high-dose ibuprofen users and 3,665 non-users CF children. In the same year (Shah PN, 2018) it has been demonstrated that in vitro ibuprofen is effective in reducing the growth rate and bacterial burden of PA and B. cepacia.

In 2016 an RCT (Adams C, 2016) showed that Amitriptyline significantly increases FEV1, reduces ceramide in lung cells and increases weight in patients treated with 25 mg amitriptyline twice daily observed after one, two and three years after continuous use of the drug.

In 2016 (Gaggar A, 2016) a RCT has studied the safety of therapy with Inhaled alpha1-proteinase inhibitor prescribed once daily for 3 weeks in 30 CF adults and has showed that it is safe and well tolerated.

One RCT published in 2018 (Jain R, 2018) showed that KB001-A, an anti-PcrV PEGylated monoclonal antibody fragment to the Type III secretion system of P.aeruginosa, is safe, well-tolerated and associated with a modest FEV_1 benefit and reduction in select sputum inflammatory markers.

In the 2022 CFF drug development Pipeline , besides Ibuprofene, three compounds are taken into consideration regarding anti-inflammatory therapy:

- efficacy and safety of retinoid fenretinide (LAU-7b)A evaluated in a phase 2 RCT Study in the Treatment of Cystic Fibrosis (NCT03265288);
- 2 in phase one: a compound designed to block the function of neutrophil elastase (POL 6014) and CB-280, an oral drug designed to increase in the lung the amount of arginine for the production of nitric oxide (NO), that is an important factor to reduce inflammation.

One double-blind, randomized, placebo-controlled Phase 2 study (Konstan MW, 2024) investigated the efficacy and safety of LAU-7b in a Phase 2 trial in adults with CF. LAU-7b or placebo was administered over 24 weeks as six 21-day treatment cycles each separated by 7 days. A total of 166 subjects received at least one dose of study drug (Intent-To-Treat population, ITT), of which 122 received ?5 treatment cycles (Per-Protocol population, PP). Both treatment arms showed a mean lung function loss at 24 weeks of 1.18 ppFEV(1) points with LAU-7b and 1.95 ppFEV(1) with placebo, a 0.77 ppFEV(1) (40 s) difference, p=0.345, and a 0.95 ppFEV(1) (49 %) difference in the same direction in PP population, p=0.263. Primary analysis of mean ppFEV(1) through 24 weeks showed differences of 1.01 and 1.23 ppFEV(1), in the ITT (65 % less loss, p=0.067) and PP populations (78 % less loss, reaching statistical significance p=0.049), respectively. LAU-7b had an acceptable safety profile. Although the study did not meet its primary efficacy endpoint in the ITT population, LAU-7b was generally well tolerated and showed evidence of preservation of lung function to support further development.

A randomized, double-blind, placebo-controlled Phase 2b trial (West NE, 2025) investigated the safety and efficacy of cannabinoid receptor 2 agonist, lenabasum, for the treatment of pulmonary exacerbations in CF. PwCF were ?12 years old with 2-3 pulmonary exacerbations (PEx) treated with intravenous (IV) antibiotics (or 1 PEx treated with IV and ?1 PEx treated with oral antibiotics) in the past year. 447 subjects from 21 countries, mean age was 26.9 (10.3 SD) years, 53.6% were female, 45.2% homozygous for F508del, and 24.9% received CFTR modulators. Subjects were randomized 2:1:2 to lenabasum 20 mg BID, lenabasum 5 mg BID, or placebo BID. PEx incidence over 28 weeks was 0.84 for placebo, 0.75 for lenabasum 5 mg BID, and 0.91 for lenabasum 20 mg BID; rates were not lower relative to placebo in the 5 mg (incidence rate ratio (IRR)=0.89, 95% CI 0.66 to 1.19, p = 0.44) or the 20 mg group (IRR 1.08, 95% CI 0.86 to 1.37, p = 0.51). PEx occurred less frequently in participants from Eastern Europe, but there was no evidence of regional variation in treatment efficacy. Lenabasum was well tolerated, without safety signals. Lenabasum did not improve key clinical outcomes in this Phase 2b study in pwCF.

Unresolved questions

No conclusions are available either on efficacy and safety of the new antinfiammatory drugs and efficacy and safety of ibuprofen therapy for a prolonged period, mainly in children, also in pre-symptomatic ones.

The following RCTs are ongoing :

- A Phase IIa, RCT will evaluate safety and efficacy of subcutaneous administration of Anakinra in Patients With Cystic Fibrosis who are ? 12 years of age (NCT03925194) on LCI.

- An open label study updated in October will examine the effects of losartan on mucociliary clearance (MCC) in patients >18 years of age not eligible for CFTR rescue therapies (NCT03435939). The study is active but patients are not still recruiting.

Keywords

Anti-Inflammatory Agents; Leukotriene antagonists;