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EDITORIAL

Why don't anti-inflammatories work in cystic fibrosis?

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Targeting inflammation is a key research priority in cystic fibrosis (CF) therapeutics due to the central role it plays in lung disease onset and progression. It will also remain so, despite the transformative impact new cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies have had on the lives of those who have access to and are eligible for them. Increasing evidence suggests that inflammation persists despite the impact of CFTR modulators, and so additive, complimentary, and therapeutic strategies are likely required to prevent lung disease progression. The development of anti-inflammatory therapies, however, has been fraught with challenges, with very few recommended for clinical use in CF. We review some of the lessons learned from previous clinical trials and how this can potentially pave the way for future success, particularly in a new era of CF medicines and post modulator therapies. This will be helped by an increased drive to identifying novel trial design methods, noninvasive biomarkers, and appropriate patient stratification to the therapy under investigation.

Inflammation plays a key role in CF lung disease pathogenesis, with neutrophilic inflammatory mediators, such as neutrophil elastase (NE), detected early in life, shown to be predictive of future exacerbations and bronchiectasis progression [1]. Inflammation is detected in CF airways even in the absence of infection; thus, the hyperinflammatory phenotype seen in CF is likely the result of a complex interplay of the basic protein defect (CFTR) and repeated cycles of infection. It represents a combination of an exaggerated hyperinflammatory response driven by neutrophil dominant immune cell recruitment and an impaired resolution process, providing multiple targets for therapeutic intervention [2]. New therapies which target CFTR function, termed CFTR modulators, have had a transformative impact on the landscape of CF care. However, evidence from recent studies assessing the triple combination modulator – Elexacaftor/Tezacaftor/Ivacaftor (ETI) – suggest inflammation persists, albeit at a reduced level to that prior to treatment initiation [3,4]. Thus, the development of effective anti-inflammatory therapy remains a research priority. Drug trials assessing multiple anti-inflammatory strategies in CF have been conducted for over 40 years (Table 1), with very few recommended for routine clinical use, including the first randomized control trial of prednisolone, which was conducted in the 1980s [5]. These early studies have however helped inform key principles in anti-inflammatory drug development and important considerations in designing clinical trials to evaluate anti-inflammatory therapies.

Firstly, the choice of anti-inflammatory target. The aim of anti-inflammatory therapy in CF is to achieve a balance between attenuating an inappropriate exaggerated inflammatory response and not completely inhibiting appropriate immune defenses to infection. This valuable lesson was learned from a large phase two clinical trial of a potent neutrophil chemoattractant leukotriene B4 (LTB4) receptor antagonist; BIIL 284 BS. The study was terminated early due to the interim safety analysis demonstrating an increased frequency of adverse events [6]. In a subsequent study in *Pseudomonas aeruginosa* infected mice treated with BIIL 284 BS, the deleterious effects of the drug were demonstrated, with increased rates of bacteremia and elevated concentrations of pulmonary cytokines. Interestingly, at lower doses, the intended anti-inflammatory effect was achieved with less bacterial suppression and subsequent adverse impact, than that found at higher doses such as those used in the clinical trial [7].

In addition to the importance of choosing an appropriate drug target and establishing safety, this early study also highlighted the need to consider what impact study population characteristics may have on drug efficacy, tolerance, and clinical outcomes. The increased exacerbation frequency in the BII 284 BS study was observed in adults only, indicating age may affect response to and tolerance of an anti-inflammatory therapy [6]. Indeed, a combined analysis of the two largest studies assessing high-dose ibuprofen, the only current recommended anti-inflammatory in CF, the benefit on slowed lung function decline was mainly attributed to children, particularly with mild lung disease [8,9]. Given the presence of inflammation as early as three months of age and its association with future disease severity and bronchiectasis development, anti-inflammatory therapy introduced in childhood may have a role in preventing end-organ damage [1]. This is obviously a very different patient subgroup to an adult cohort, with chronically infected airways and established bronchiectasis, in whom the inflammatory burden is significant and most

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Table 1. Summary of discussed anti-inflammatory therapies investigated in CF.

Drug class or therapeutic target	Drug evaluated	Clinical outcome	Impact on inflammatory mediators	Clinical studies (references)
Corticosteroids	Prednisolone	Slowed FEV_1 decline in children	Reduced systemic inflammatory mediators	[5]
		No significant improvement in clinical outcomes assessed in adult patients treated during pulmonary exacerbation versus those treated with antibiotics alone	No difference in C-reactive protein measured between groups	[15]
Antibiotic	Azithromycin	Reduced pulmonary exacerbation frequency Improved FEV_1 in *P.aeruginosa* infected patients	No significant impact on airway inflammatory mediators measured	[10,11]
Non-steroidal anti-inflammatory drugs	Ibuprofen	Slowed FEV_1 decline	Not reported	[8,9]
Leukotriene pathway inhibition	BIIL 284 BS (LTB4 receptor antagonist)	Terminated early due to adverse events	Not reported	[6]
	Acebilustat (LTA4 hydrolase inhibitor)	No significant improvement in clinical outcomes at week 48	No significant impact on inflammatory mediators measured	[14]
Cannabinoid receptor type 2 agonist	Lenabasum	No significant improvement in clinical outcomes at week 12	Reduction in airway inflammatory mediators	[12]
CFTR modulator drugs	Elexacaftor/ Tezacaftor/ Ivacaftor	Improved FEV_1 Reduced pulmonary exacerbation frequency Increased weight	Reduced systemic and airway inflammatory mediators	[3,4]

likely more difficult to treat. The airway microbiology can also impact on anti-inflammatory efficacy and therefore agent choice. If we consider azithromycin, a macrolide antibiotic with broad spectrum antimicrobial coverage with extended benefits thought to be mediated via immunomodulatory/anti-inflammatory pathways – however, these benefits have only been consistently demonstrated in patients chronically infected with *P.aeruginosa* [10]. A subsequent large observational study using the US CF Foundation Registry corroborated this showing a slower decline in lung function in patients treated with azithromycin if also infected with *P.aeruginosa* [11]. A further important consideration in patient stratification relates to the use of CFTR modulators, with a wide variation and spectrum of disease severity among different patients with CF, particularly between those on CFTR modulators and those who are not, and the unknown impact early introduction of these therapies may have on airway microbiota and inflammation.

An additional challenge in CF anti-inflammatory clinical trial design is that short-term impact on standard clinical trial endpoints (e.g. lung function) are not usually demonstrated. Importantly, this does not necessarily predict long-term benefit, as highlighted by studies of high-dose ibuprofen which did not show acute change in lung function, but instead, over a 4-year period, demonstrated slowed lung function decline with associated improved survival [8,9]. To achieve meaningful impact on lung function trends, clinical trials of anti-inflammatories need to be of long duration and require large study participant numbers, which is a limiting factor in attracting drug development programs. This becomes even more challenging in the era of CFTR modulators where patients enrolled on clinical trials may have mild disease and even normal lung function, with reduced frequency of pulmonary exacerbations. In certain CF anti-inflammatory trials impact on inflammatory biomarkers is demonstrated early in the study course without any acute change in clinical parameters. In a phase 2b study of the anti-inflammatory agent lenabasum, an oral selective cannabinoid receptor type 2 (CBD2) agonist, no significant change in lung function was demonstrated at study end (week 12). However, a reduction in sputum neutrophils and key neutrophil inflammatory mediators, such as NE and interleukin-8, was seen from baseline to week 12, highlighting the anti-inflammatory effect of the drug and potential to reduce exacerbations and stabilize lung function, if studied over a longer duration [12]. The CF community, recognizing the critical need to develop novel study designs to adequately assess efficacy and safety of anti-inflammatory therapies in a realistic timeframe, has made an international collective effort to address these challenges. The aims of which are to identify and standardize novel study design and sensitive biomarkers for use in clinical trials [13].

It remains unclear how treatment with CFTR modulators may impact inflammation in the long-term or how it may affect clinical trial design for anti-inflammatory therapeutics. The aforementioned publications of ETI both demonstrated a significant sustained reduction in airway and systemic inflammatory mediators 12-months post-ETI initiation. Importantly, airway inflammatory markers and protease levels did not resolve to levels of that found in healthy controls [3], and in fact, in the second study were demonstrated to reach those found in patients with non-CF bronchiectasis, a chronic inflammatory lung disease control [4]. This indicates not only are additive anti-inflammatory strategies still required in certain patient cohorts post-ETI therapy, but also emphasizes the importance and potential disease modifying properties of ETI introduced in early lung disease. The potential additive benefit of an anti-inflammatory was demonstrated in the phase 2b trial of acebilustat, an inhibitor of LTA4 hydroxylase. This

study, despite not meeting its primary endpoint of improvement in lung function or reduced exacerbations at 48-weeks in the overall study population, did demonstrate a trend toward a reduction in exacerbation frequency in patients taking CFTR modulators [14]. Thus, future clinical trial design of anti-inflammatories should consider stratification by CFTR modulator usage. A tailored approach, such as restricting treatment to a period of heightened inflammation (e.g. during an exacerbation), also requires consideration. A recent exacerbation study incorporating a secondary analysis investigating the potential added benefit of empiric corticosteroid treatment to standard intravenous antibiotic treatment failed to show a difference [15]. However, a recently completed large multicenter, randomized, placebo-controlled trial of corticosteroid treatment during exacerbations may provide more definitive answers, as well as insights into subgroups of patients who are more likely to respond – the results of this study are eagerly awaited (NCT03070522).

Further stratification may involve separating patients based on their predominant or 'residual' inflammatory phenotype such as focusing on the potential added benefit of antiprotease therapy or NE inhibition in those patients with persistent elevated NE levels. This approach to categorizing patients based on inflammatory biomarkers was proposed by Keir et al. in patients with both CF and non-CF bronchiectasis, whereby patients were grouped as 'low' or 'high' NE, with the purpose of stratifying those felt more likely to gain benefit from protease inhibition [16]. This may be important when interpreting results of an ongoing phase 2 study of an oral reversible inhibitor of dipeptidyl peptidase-1 (DPP-1) Brensocatib for patients with CF, an enzyme responsible for neutrophil serine protease activation, NCT05090904.

In an era where we have advanced CF therapeutics to treat the underlying protein defect revolutionizing care for many patients, the CF community has demonstrated how precision medicine is possible but also how more can always be achieved. In the CFTR modulator era, inflammation remains an important treatable trait with increasingly definable subgroups of patients that may require a tailored approach. We are now armed with the lessons learned from previous successful and unsuccessful anti-inflammatory strategies and trial designs. This, coupled with increasing expertise in novel inflammatory and outcome biomarkers, means we are now more than ever in a position to drive anti-inflammatory research forward in the next chapter of CF therapeutics.

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