Therapeutics in Respiratory Pathology

Subjects: Pathology

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As aerobic organisms, we are continuously and throughout our lifetime subjected to an oxidizing atmosphere and, most often, to environmental threats. The lung is the internal organ most highly exposed to this milieu. Therefore, it has evolved to confront both oxidative stress induced by reactive oxygen species (ROS) and a variety of pollutants, pathogens, and allergens that promote inflammation and can harm the airways to different degrees. Indeed, an excess of ROS, generated intrinsically or from external sources, can imprint direct damage to key structural cell components (nucleic acids, sugars, lipids, and proteins) and indirectly perturb ROS-mediated signaling in lung epithelia, impairing its homeostasis. These early events complemented with efficient recognition of pathogen- or damage-associated recognition patterns by the airway resident cells alert the immune system, which mounts an inflammatory response to remove the hazards, including collateral dead cells and cellular debris, in an attempt to return to homeostatic conditions.

Keywords: oxidative stress ; inflammation ; respiratory diseases ; therapeutic strategies

1. Introduction

Due to its continuously exposed surface to the external environment, the lung exhibits a formidable defense system constituted by a high number of interacting mechanisms [1][2]. First, anatomical retention features such as the nasopharyngeal barrier filter particles or microorganisms higher than 2–3 μm [3][4][5]. Secondly, there are systems to expel the external elements, i.e., the cough [6], and the mucociliary system [7]. Whether or not the external and potentially harmful particles overcome these mechanisms, the humoral factors come into play, including bactericidal and antiviral secretions (mucins, defensins, lactoferrin, complement factors, etc.) [8][9], and cellular factors of the innate [10] and adaptive immune system. These include the airway epithelial cells [11]; the phagocytic cells that, in turn, comprise polymorphonuclear (PMN) cells such as neutrophils (the most abundant immune cell type) [12] or eosinophils [13]; monocytes and macrophages [14][15]; natural killer cells (NKC) [16]; mastocytes [17]; and dendritic cells [18]. All these cells recognize pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) through pattern recognition receptors (PRRs) [19], and Toll-like receptors (TLR) are the most studied [20]. Their stimulation triggers the activation of antimicrobial genes and inflammatory cytokines and chemokines, as well as the direct response against antigens [21], activating the adaptive immune system, namely B and T lymphocytes [22][23].

2. Reactive Oxygen Species Production in the Airways

Environmental pollutants such as ozone (O_3) and nitrogen dioxide (NO_2) react with several molecules at the respiratory surface and generate secondary reactive oxygen species (ROS) such as superoxide radicals ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^{\bullet}$) [24][25]. Additionally, lung cells generate ROS as by-products of aerobic metabolism involving enzymatic reactions in the mitochondrial electron transport chain (e.g., through activity of amine oxidases, α-ketoglutarate dehydrogenase (α-KGDH), and pyruvate dehydrogenase (PDH), and activation of the p66shc adaptor protein) [26][27][28]. Furthermore, ROS can be produced in peroxisomes [29], or by cytochrome P450 enzymes, cyclooxygenases, and lipoxygenases [30]. Nitric oxidase synthases (NOS) expand the spectrum of ROS producing reactive nitrogen species (NO_2 or $ONOO^-$) [31]. ROS are also produced as mediators of biological functions, with a role in inflammatory processes involving epithelial and endothelial cells, alveolar macrophages, and granulocytes [32][33]. NADPH oxidases (NOX) enzymes are involved in both bacterial killing and regulation of inflammatory mediators [34]. Indeed, dual oxidases, DUOX1 and DUOX2, the major isoform of NOX, are expressed preferentially in the respiratory epithelium [35][36][37].

3. Respiratory Surface: Antioxidant Defenses

The air–liquid interface covering the developed airways is an environment subjected to continuous oxidative stress. Accordingly, the respiratory epithelium is exposed to endogenous and also to environmental ROS. Therefore, it expresses a variety of antioxidant enzymes. Superoxide dismutases such as SOD3 (an extracellular SOD, EC-SOD) [38][39][40], highly-expressed in the lung at the extracellular matrix and at the cell surfaces [41], generate H_2O_2 which is detoxified by other enzymes. Catalase, decomposes H_2O_2 into H_2O and O_2, predominantly within alveolar macrophages and type II epithelial cells [42][43]. Glutathione (GSH) peroxidase (GPX) catalyzes the reduction of H_2O_2 or other peroxides to glutathione disulfide (GSSG) and H_2O, of which GPX1 is thought to be responsible for 95% of overall lung tissue GPX activity [44]. Peroxiredoxins (PRX), with all six mammalian family members expressed in different compartments within the lung [45], particularly PRX I, III, V, and VI in the bronchial epithelium, PRX V and VI in the alveolar epithelium, and PRX I and III in alveolar macrophages, decompose H_2O_2 and protect against oxidative stress [46][47][48]. Thioredoxin (TRX), whose main antioxidant role is related to its ability to regenerate oxidized forms of PRX [49][50], catalyzes the reduction of disulfide bonds, modulates signal transduction pathways, and has anti-inflammatory properties [51][52]. Finally, glutaredoxins (GRX) participate in the reduction of oxidative modifications involving GSH [53][54].

The following small non-enzymatic low-molecular-weight antioxidant molecules are highly relevant: ascorbic acid (vitamin C) [55], uric acid [56], GSH [57][58], and α-tocopherol (vitamin E) [59]. These non-enzymatic molecules are the most prominent antioxidants reacting with reactive oxidant gases such as O_3 and NO_2 [60][61][62][63] and with the secondary oxidants generated by them, which can increase the oxidative injury [64]. Furthermore, the enzymatic antioxidants complement the function of these small molecules. Nuclear factor erythroid 2-related factor (Nrf2) regulates the transcription of both antioxidant genes coding for many of the above-highlighted enzymes and phase II detoxification genes [65][66][67][68].

4. Inflammation and Oxidative Stress in Pulmonary Diseases

A variety of immune and non-immune cells are activated during an inflammatory process. Each cell type releases cytokines and mediators that modify the activities of other cells, inducing an inflammatory network that progresses and resolves towards healthy homeostatic, or pathological outcomes. The lung is a vital organ for gas exchange and is constantly exposed to harmful airborne pathogens. Therefore, an immediate and intense protective/defensive inflammatory action is required to eliminate the invaders as early as possible. Nevertheless, excessive inflammation can be life threatening [1]. Consequently, a delicate balance between inflammation and anti-inflammation is essential for lung homeostasis and for the prevention of chronic inflammation [69]. Among the main inflammatory mediators involved in the pathogenesis of respiratory diseases are biochemical mediators such as histamine, thrombin, complement anaphylatoxins, prostaglandins, nitric oxide (NO), and molecules induced by oxidative stress [70]. These compounds mediate cell signaling and enhance cytokine production, among other activities.

Thus, airborne toxicants stimulate local ROS production inducing protein oxidation, lipoxidation, glycation end products, and DNA damage, and leading to mitochondrial dysfunction, cell death, the recruitment of inflammatory cells (mainly macrophages and neutrophils), profibrotic changes or mucus hypersecretion. These oxidative stress-mediated cellular processes drive the development of key environmental respiratory diseases such as acute lung injury/respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, and pulmonary fibrosis, and affect the progression of the most common hereditary disease affecting the lung, i.e., cystic fibrosis.

5. Prospective Therapeutic Strategies

5.1. ALI/ARDS

The scientific rationale for emerging therapies in ARDS is to pursue fundamental processes and mediators of its complex pathophysiology [71]. There are emerging therapies in Phase 3 trials assessing the potential benefits of corticosteroids such as dexamethasone [72][73] or budesonide/formoterol [74][75]. Moreover, supplementation with vitamin D [76] in a Phase 2 trial has shown a reduction in markers of vascular permeability from lung injury patients following esophagectomy in the post-operative period [77], although another trial using vitamin D to prevent acute respiratory tract infections has been less conclusive [78]. Other emerging therapies in Phase 2 trials include aspirin, which has attracted interest as a repurposed drug for ARDS [79][80], with some clinical studies [81] that show significant reduction in neutrophil infiltration into the alveolar space. Alternatively, different studies using mesenchymal stem cells (MSCs) and multipotent adult progenitor cells (MAPCs) have shown a biological decline in angiopoietin and a concomitantly reduced 28-day mortality, higher ventilator-free days, and higher ICU-free days [82]. Vitamin C acts as ROS scavenger, modulator of inflammatory mediators, and

cofactor. In mouse models, ALI prevents the activation of NF-κB, and therefore attenuates the production of proinflammatory cytokines and boosts ion channel and pump expression, enhancing fluid clearance in the alveolar epithelium [83]. The phase 2 CITRIS-ALI trial is presently investigating the usefulness of vitamin C in sepsis-induced ALI [84] but no positive results have been reported as yet [85]. It was found that nebulized liquid heparin increased the number of ventilator-free days [86], and a Phase 2 trial to confirm the findings is awaited [87]. Anti-tissue factor antibodies such as ALT-836, which blocks binding to coagulation factor VIIa, have demonstrated attenuation of sepsis-induced ALI in animal models, and was successfully tested in a Phase 1 trial for ARDS [88]. A Phase 2 trial has been recently completed and disclosure of the results is pending [89]. Dilmapimod, a p38 MAPK inhibitor, has proven useful for reducing the severity of ALI in animal studies, although in human trials it has been unreliable [90][91]. Neutrophil elastase inhibitors such as sivelestat, have been shown to increase the ventilator-free days in ARDS patients with a high extravascular lung water content (>10 mL/kg) as compared with those with low pulmonary edema [92], although contradictory results have also been obtained [93][94]. Ulinastatin (or urinary trypsin inhibitor) is another physiological inhibitor of human neutrophil elastase with positive results in preclinical studies [95]. A meta-analysis of 29 Chinese randomized controlled trials (RCTs) indicated that ulinastatin was effective ameliorating ARDS [96]. Another multi-center Phase 2 RCT is ongoing to assess its safety and efficacy in ARDS [97]. Regarding granulocyte-macrophage colony stimulating factor (GM-CSF), preclinical models have demonstrated that it can limit alveolar epithelial cell injury and promote alveolar macrophage maturation. Nevertheless, a Phase 2 RCT enrolled only two-thirds of its intended number of participants and, although GM-CSF treatment appeared to be safe, it did not decrease ventilator free days or mortality of the ALI/ARDS patients [98]. Anti-CD14 antibodies protected against septic hypotension in animal models of pneumonia [99]. Two Phase 2 trials have been initiated in this regard, the former, in 2007, failed in recruiting people; and the latter is still recruiting [100]. Inhaled prostaglandins, such as epoprostenol and alprostadil, have been suggested to regionally dilate the pulmonary vasculature increasing arterial oxygenation in ARDS. However, a meta-analysis of 25 studies concluded that, although indeed inhaled prostaglandins improved oxygenation in ARDS, they did not improve pulmonary physiology or mortality [101].

5.2. Asthma

Over the last few years, multiple biologics (typically mAbs) have been developed targeting various participants in allergies and asthma, but mainly directed toward the complex type 2 endotype [102][103]. In general, they are anti-inflammatory treatments [104]. The most prevalent biologics are omalizumab (anti-IgE) and mepolizumab (anti-IL-5). IL-5 has become a major target for both asthma and COPD due to the high proportion of patients with airway eosinophilia associated with disease severity [105]. Currently, three biologics, targeting IL-5 or its receptor, have been cleared by the Food and Drug Administration (FDA). Omalizumab was initially approved by the FDA in 2003 and binds to both the high-affinity and low-affinity IgE receptors, preventing free IgE from occupying the surface of mast cells and basophils [106]. It has several disadvantages, i.e., it must be administered by subcutaneous injection [107], it is expensive [108] and, moreover, an unusual form of anaphylaxis [109] and a possible higher rate of cardiac and cerebrovascular events can be ensued by this treatment. Anti-IL-5 (mepolizumab) was approved in late 2014 and receiving patients had decreased eosinophilic inflammation, reduced asthma exacerbations, improved asthma control markers, better quality of life [110][111], and reduced levels of some of the proteins that drive airway remodeling [112]. In another study on moderate persistent asthma, despite high-dose ICS, patients also showed decreased blood and sputum eosinophils but no change in FEV1, symptom scores, or need for rescue inhaler. After stopping anti-IL-5 treatment, eosinophils and asthma symptoms again increased [113]. Reslizumab, another mAb targeting IL- 5, approved in 2016 for patients with eosinophilic asthma, has proven beneficial on moderate-to-severe asthma symptoms, improving lung function and reducing exacerbations as compared with a placebo [114]. Reslizumab also decreased blood, sputum, and airway eosinophils and, more recently, reduced systemic corticosteroid dosing nearly 75% [115][116][117]. Benralizumab, a mAb targeting the IL-5Rα, was approved recently by the FDA [118] with positive results in asthma [119][120][121]. Finally, dupilumab, a mAb approved in 2017 that inhibits the IL- 4R subunit [122], has also shown encouraging results in asthma [123][124]. Regarding relevant future targets pending approval, lebrikizumab and tralokinumab, mAbs that target IL-13 [125][126], have not shown positive effects [127][128]. Tezepelumab (AMG157), a humanized mAb currently in Phase 3 [129] binds thymic stromal lymphopoietin, an epithelial cell-derived cytokine that drives allergic inflammatory responses [130]. Additionally, anti-IL-33 therapies are currently under development [131]. Conversely, non-Th2 inflammation targets are also being studied. IL-6 and IL-17 may promote both Th2 and non-Th2 inflammatory cascades. Brodalumab is a human mAb binding IL-17RA, which inhibits signaling of IL-17 and IL-25, with disappointing results in clinical trials [132]. Thus, this therapy has not been further pursued for asthma or COPD. C-X-C motif chemokine receptor 2 (CXCR2) antagonists such as navarixin (which decrease IL-8 levels) have reduced sputum and blood neutrophils, with no significant change in FEV1 [133], but has progressed to a Phase 2 trial [134]. An antisense oligonucleotide against C-C chemokine receptor 3 (CCR3) (co-administered with an antisense oligonucleotide that targets the c subunit of the IL-3, IL-5, and GM-CSF receptors), named TPI ASM8, has shown some efficacy in phase 2 trials [135]. Imatinib is a tyrosine kinases inhibitor that has shown promising results in a clinical study, reducing airway hyper-responsiveness as compared with a placebo [136]. Among drugs targeting TNF-α, etanercept stands out as a

repositioning drug for asthma. A few studies employing etanercept have reported satisfactory results reducing bronchial hyperreactivity [137][138], whereas other studies have informed poor clinical efficacy in terms of lung function improvement and quality of life [139]. Others have shown a small but significant increase in the quality of life without changes on lung function [140].

Among anti-inflammatory treatments, antioxidant treatments stand out [141][142]. Vitamins (E, C, D, and A), carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene), and food supplements (selenium and zinc) seem to improve the prognosis of the disease [143][144][145]. Asthmatic adults with antioxidant-poor diets have lower forced expiratory volume in the first one second to the forced vital capacity (FEV1/FVC) ratio scores, increased plasma C-reactive protein, and were more likely to exacerbate than those on an antioxidant-rich diet [146]. Indeed, dietary antioxidant supplementation notably improved both symptoms and lung function in exercise induced asthma [147].

5.3. COPD

Thus far, no anti-IL-5 therapies have been approved for use in COPD. However, two Phase 3 studies using mepolizumab showed improvements in exacerbation frequency from subjects who had an eosinophilic phenotype and a history of COPD exacerbations, despite triple therapy [148]. Nevertheless, other studies have indicated no positive effects [149]. Reslizumab has yet to be formally evaluated in clinical trials for COPD. Conversely, in a Phase 2 trial including COPD patients with eosinophilia, benralizumab treatment did not significantly reduce the annual rate of moderate or severe exacerbations [150][151]. However, significant improvements in FEV1 were observed in the overall study population, and the results of pre-specified subgroup analyses by baseline blood eosinophil count in individuals with benralizumab versus placebo have led to an ongoing Phase 3 trial to evaluate this biologic in COPD [152]. As in asthma, non-Th2 inflammation targets include CXCR2 and CCR3. Regarding corticosteroids, in contrast to asthma, glucocorticoid treatment of established COPD is rather ineffective in reducing chronic airway inflammation and progressive airway obstruction [153]. Current national and international guidelines endorse the use of inhaled long acting bronchodilators, ICSs, and their combination for maintenance treatment of moderate-to-severe stable COPD [154], although adverse effects may arise [155]. In fact, large clinical trials assessing the combination therapy (ICSs + LABAs) in a single inhaler for stable COPD patients have shown a good safety profile, a discreet but statistically significant reduction of severe exacerbations, and improvements of FEV1, quality of life, and respiratory symptoms in these patients [156][157]. Overexpression of histone deacetylase 2 restores glucocorticoid sensitivity in BAL macrophages from COPD patients [158]. Anti-cytokine and anti-chemokine treatments are being exploited in COPD but scarce trials using blocking antibodies against cytokines and chemokines or their receptors have proven successful [153]. Among those showing positive effects, the CXCR2 inhibitor MK-7123 (also known as SCH527123 or navarixin, already described in asthma) could reduce the chemotaxis of neutrophils [153]. MK-7123 treatment resulted in a significant reduction of sputum neutrophils and of sputum and plasma MMP9 and myeloperoxidase levels [159]. Numerous other drugs, including antibodies directed against specific inflammatory mediators such as cytokines (IL-18, IL-22, IL-23, IL-33, TSLP) and growth factors (GM-CSF) are under investigation for COPD.

5.4. Idiopathic Pulmonary Fibrosis (IPF)

After several disappointing years of promising therapies that moved into clinical trials but failed to demonstrate efficacy in IPF [160], the anti-fibrotic drugs pirfenidone and nintedanib have been associated with significantly slower respiratory deterioration and perhaps prolonged survival [161][162][163], although with heterogenous responses and side effects. The understanding of the complex pathogenesis of IPF continues to increase [164][165]. Sustained alveolar epithelial cell injury and abnormal repair are increasingly recognized as the core mediators of the fibrotic process, with a relevant involvement of environmental triggers. The activation of multiple pathways related to maladaptive repair, involving fibroblast migration, proliferation, and extracellular matrix deposition has revealed a variety of prospective molecular targets of novel therapeutic agents currently being tested in early phase clinical trials. Pentraxin-2 (PTX-2) is a circulating protein that binds to monocytes, promoting epithelial healing and resolution of fibrosis. Thus, a recombinant human PTX-2 (serum amyloid P) analogue (PRM-151) has been shown to inhibit monocyte to fibrocyte differentiation and ameliorate fibrosis in a bleomycin-induced animal model of fibrosis [166][167]. A Phase 1 trial showed a non-significant but improving effect of PRM-151 on FVC and six-min walking distance (6MWD) during the treatment [168]. Further Phase 2 studies have demonstrated a significant reduction in pulmonary function deterioration and stability in 6MWD over 24 weeks as compared with a placebo, although with relevant adverse events [169][170]. The launch of a Phase 3 trial for PRM-151 in IPF has been announced, using FVC as a primary end point and 6MWD as a key secondary end point. Among the anti-connective tissue growth factor antibodies, the antagonist pamrevlumab (FG-3019) in the PRAISE study [171] was established to have a significant effect preventing lung function decline of 160 IPF patients, yet full peer-reviewed data are still awaited [172]. The re-initiation of Phase 3 trials has just been announced. PBI-4050 is a synthetic analogue of a

medium-chain fatty acid acting through G protein-coupled receptors and showing anti-fibrotic activities such as inhibition of epithelial–mesenchymal transition and fibrocyte/fibroblast recruitment, migration, proliferation and differentiation, among others [173]. A Phase 2 trial has shown no safety concerns [174]. While there was slowing or stability in FVC, a statistically significant decrease was observed only combining PBI-4050 and pirfenidone but not PBI-4050 and nintedanib, implying a possible drug–drug interaction. Additional studies of PBI-4050, either alone or in combination with nintedanib, are currently being considered. In a Phase 2a study [175], GLPG1690, an oral selective inhibitor of autotaxin (an enzyme increased in IPF and involved in cell apoptosis and endothelial cell damage) was analyzed and was well tolerated by IPF patients, with a good safety profile. Moreover, as secondary end points, preliminary efficacy analyses demonstrated target engagement and encouraging results towards halting FVC decline [176]. International Phase 3 trials to assess the efficacy of GLPG1690 in IPF are ongoing [177]. Leukotrienes are also increased in IPF [178][179]. Thus, additional ongoing trials include leukotriene antagonists such as tipelukast, currently explored in a Phase 2 trial [180]. Among protein kinase inhibitors, a recent Phase 1 study showed proper safety and tolerability of a selective protein kinase inhibitor of the Rho-associated coiled-coil containing protein kinase 2 (ROCK2). The trial is currently in Phase 2 [181][182]. Moreover, a current Phase 2 [183] trial is evaluating CC-90001, a second-generation Jun N-terminal kinase (JNK) inhibitor after a first-generation JNK inhibitor (CC-930) showed a dose-dependent trend of reduction in MMP7 and surfactant protein D (SP-D) biomarker plasma levels [184]. Regarding anti-integrin antibodies, a partial inhibition of integrin αvβ6 in rodents blocked the development of pulmonary fibrosis processes without aggravating the inflammatory response [185]. The safety and tolerability of a humanized monoclonal antibody (BG00011) against this integrin has been analyzed in a Phase 2 trial [186]. The study has been completed recently, although its outcome is still pending. Phosphatidylinositol 3-kinase/Protein kinase B (PI3K/Akt) pathway inhibitors may be associated with halting fibrosing processes [187], as suggested in a Phase 1 trial [188][189] and evidenced in another recent study using omipalisib [190]. Sirolimus is currently under examination in a Phase 2 trial [191]. The B lymphocyte antigen CD20 is targeted by rituximab, which is currently being assessed in an IPF Phase 2 study [192]. Furthermore, a Phase 2 trial examined combined plasma exchange, rituximab, and steroids [193]. While peer-reviewed results are pending, a pilot trial stated good outcomes regarding autoantibody reduction for acute IPF exacerbations [194]. A Phase 3 trial testing the antibiotic combination co-trimoxazole (trimethoprim and sulfamethoxazole) is currently operating [195]. Finally, other anti-inflammatory drugs are likewise in clinical research for IPF, i.e., lebrikizumab [196], tralokinumab [197], and azithromycin [198].

5.5. Cystic Fibrosis (CF)

To address the most prevalent causal defects in the CFTR Cl– channel leading to CF, two biomolecular modulators are needed, i.e., CFTR correctors, to increase the amount of properly folded mutant CFTR protein at the plasma membrane, and CFTR potentiators, to allow effective gating (channel opening and closing) of the abnormal CFTR [199][200][201]. Nevertheless, a more thorough division might also include stabilizers, read-through agents, and amplifiers [202]. Either alone or combined, these modulators tend to restore transepithelial Cl^- transport to CF airway epithelia expressing CFTR mutations such as the most prevalent F508del, improving hydration and restoring mucociliary clearance [203][204]. Four drugs have been recently approved by the FDA for that purpose [201], the potentiator Ivacaftor (VX-770) for individuals with CF holding a G551D CFTR mutation, and the following three correctors: Lumacaftor (VX-809), developed to increase the amount of F508del CFTR that reaches the cell surface [205][206], Tezacaftor (VX-661), and Elexacaftor (VX-445). Furthermore, their combinations are also being assayed, i.e., Orkambi (lumacaftor/ivacaftor) for patients homozygous for F508del CFTR [207], Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor). Most recently, there has been an explosion of novel modulators [208] and others are under investigation including ELX-02, Posenacaftor (PTI-801), Galicaftor (ABBV-2222), ABBV-3221, FDL169, Deutivacaftor (VX-561), ABBC-974 (GLPG-1837), and Nesolicaftor (PTI-428) [209][210][211][212][213][214][215][216][217][218], among others.

Despite a thorough knowledge of the undergoing inflammatory process in CF, there are relatively few anti-inflammatory drugs in clinical use [219]. Corticosteroids were shown to confer some benefit but their long-term use is associated with unacceptable side effects [220][221][222]. The non-steroidal anti-inflammatory agent ibuprofen has also demonstrated benefits [223][224]. Particularly in younger patients, it has been associated with an increased survival rate [225][226], but it requires a strict dose control and has associated renal and gastrointestinal side effects [223]. A large Phase 2 RCT of the leukotriene B4 (LTB4) receptor antagonist, BIIL 284 BS (amelubant), surprisingly demonstrated an excess of pulmonary exacerbations as compared with a placebo [227]. Conversely, CTX-4430 decreases the production of LTB4, an inflammatory mediator elevated in CF [228] and is presently undergoing a Phase 2 trial [229]. Andecaliximab, an antibody against MMP9, is undergoing a Phase 2b trial [230] but the baseline FEV1 required for this drug limits its use in very severe CF and this trial has been discontinued. Another compound in Phase 1 is POL6014, a synthetic neutrophil elastase blocker [231]. Other anti-inflammatory compounds under clinical development are α-1 anti-trypsin [232], the elastase inhibitor AZD9668 [233], and JBT-101 (ajulemic acid, or Lenabasum), an oral selective cannabinoid receptor type 2 (CB2) agonist that decreases neutrophilic inflammation inhibiting LTB4 and promotes resolution of inflammation through

modulation of arachidonic acid metabolism [234]. A Phase 2, double-blind, placebo-controlled study, in adult CF patients, demonstrated decreased levels of several sputum inflammatory markers and reduced exacerbations in response to JBT-101, with no serious adverse effects reported [235][236]. A Phase 2b study is underway. Indeed, CB2 activation has shown anti-inflammatory effects including stimulating lipoxin A4 (LXA4) synthesis, decreasing proinflammatory cytokine secretion, and neutrophil trafficking to the lung [237][238].

Anti-proteases have been under investigation in CF since 1990. For example, the already described α1-antitrypsin suppressed inflammatory markers including free neutrophil elastase, proinflammatory cytokines, and neutrophils [239][240]. Other neutrophil elastase inhibitors include recombinant secretory leukocyte protease inhibitor (rSLPI) and the small-molecule drug EPI-hNE4 (depelstat) [241]. Among other inflammatory therapies, hydroxychloroquine, a dihydrofolate reductase inhibitor that increases intracellular pH, was negatively evaluated in a small 28-day study in CF [242]. A CF clinical trial regarding SB-656933, a CXCR2 antagonist, concluded that this molecule might modulate airway inflammation [243]. Conversely to refractory asthma, few CF studies have considered the use of chemotherapeutics. Low dose of the immunosuppressant cyclosporin A diminished the need for systemic corticosteroids in one small case series. In a pilot study, methotrexate increased FEV1 and decreased total serum immunoglobulins in five CF patients after one year of treatment [244], showing tolerable adverse effects. IL-8 decoys are used as an anti-inflammatory anti-neutrophil elastase strategy [245][246]. Other novel anti-inflammatory compounds under review include the already mentioned lipoxins and resolvins. Arachidonic acid-derived lipoxins such as LXA4 attenuate neutrophil chemotaxis, respiratory burst, IL-8 production, and accelerate apoptosis [247][248][249]. Because of low LXA4 levels in CF airways, stable LXA4 agonists have been developed as prospective therapeutics. Decosahexanoic acid- and omega-3 eicosapentanoic acid-derived resolvins D1 and E1 also mitigate inflammation, preventing chemotaxis and promoting clearance of apoptotic neutrophils [250][251][252][253]. Analogously to LXA4, resolvins stimulate a cytoprotective effect on airway epithelial cells [254][255]. Retinoids foster extracellular matrix homeostasis. Recent Phase 1b studies involving LAU-7b, an oral solid-dosage form of the retinoid fenretinide, showed safety and tolerability in adult CF patients, encouraging progression to Phase 2 trials [256].

Antioxidant therapies have not been yet settled in clinical practice [257]. In fact, despite the commercial development of many natural antioxidants as dietary supplements, there is no sound clinical trial evidence of their effectiveness in any clinical condition [258] with the exception of GSH (administered either orally or by inhalation) [259][260][261] with some drawbacks [262]. Though not quite clear [263], high doses of β-carotene appear to improve lung function and decrease oxidative stress in some cases [264]. The application of deferiprone (L1) as an iron chelating drug/pharmaceutical antioxidant is under way. Its use is being considered as a main, alternative, or adjuvant therapy in many diseases involving oxidative damage [265][266]. N-acetyl cysteine, initially developed as a mucolytic, is being repurposed as an antioxidant [267], inhibiting H_2O_2 and increasing GSH [260]. Of significance is the malabsorption of fat-soluble antioxidants in CF patients such as tocopherols, carotenoids, and coenzyme Q10 (Co-Q10), and that of essential fatty acids. Vitamin E might become a good supplementation to overcome this deficiency [268][269][270][271][272], along with carotenoids [273] and ascorbic acid (vitamin C) as nutritional supplements. Multivitamin supplements with high bioavailability containing Co-Q10 would also be a good alternative [274][275]. One recent study regarding multivitamin supplements showed a decrease in circulating inflammatory markers and a decrease in pulmonary exacerbations [276]. Alternatively, several hydro soluble antioxidants, oligoelements, and enzymatic antioxidants such as Vitamin C, selenium and selenium-dependent peroxidases [277][278][279], zinc, and copper [280] have yielded promising results awaiting further clinical trials. A randomized double-blind placebo-controlled trial has examined the outcome of short-term melatonin administration (3 mg for three weeks) on sleep and oxidative stress markers in CF [281]. Accordingly, with the expected activity synchronizing the sleep-wake cycle and its antioxidant properties, treatment with this hormonal substance reduced nitrite levels in exhaled breath condensate and improved sleep indices.

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