Newer Therapies for Chronic Obstructive Pulmonary Disease

Rahul Kodgule*, Abhijit Vaidya**, Sundeep Salvi***

Introduction

The thick cloud cover over the understanding of pathophysiology of Chronic Obstructive Pulmonary Disease (COPD) is unveiling rapidly and this has contributed significantly to recent drug development and is likely to do so even in the future. Persistent exposure to an inhaled irritant like cigarette smoke, biomass smoke or industrial smoke leads to activation of several inflammatory pathways which contribute to the pathology of COPD in multiple ways. These irritants activate macrophages in the respiratory tract which then release multiple chemotactic factors to attract neutrophils, monocytes and T lymphocytes. These cells release a battery of proteins called as chemokines and cytokines which get involved in the various complex inflammatory and destructive pathways leading to chronic bronchitis and emphysema. Moreover, the steroids which arrest asthmatic inflammation quite effectively are found to be disappointingly less potent in COPD. As a ray of hope, the inflammatory process in COPD, has the potential to be inhibited at different stages of its pathway. Hence, recent drug discovery has focused on intervention of these pathways by inhibiting one of the steps. However, real challenge lies in developing such drugs that are not only effective, but also safe.

Another important mechanism implicated in the pathogenesis of COPD is oxidative stress. Physiologically, the load of oxidants is balanced by the levels of anti-oxidants in the lung. When the oxidant load exceeds the anti-oxidant response, it is known as oxidative stress. This oxidative stress fuels the inflammation in COPD and also contributes to airway remodeling and emphysema. Oxidative stress is also accused of contributing to steroid resistance in COPD. This knowledge has stimulated wide interest in the development of potent anti-oxidants.

Emerging Therapy

In this review article, we discuss the recent advances taken place in the development of newer drugs for managing Chronic Obstructive Pulmonary Disease.

Smoking Cessation

Smoking cessation is the only intervention that has been shown to attenuate the progression of disease (FEV1 decline) in COPD. However, attempts by smokers to quit smoking end up more commonly in failures than success. To assist smokers in smoking cessation, several drugs have recently been developed successfully. Drugs like Bupropion and Varenicline have been used as Nicotine replacement therapy (NRT) which has been shown to double the chances of smoking cessation in those who attempt it.

Currently, research is focusing on development of antibodies against the free nicotine circulating in the blood, in order to form antigen-antibody complexes. These antigen-antibody complexes being unable to cross the blood-brain barrier would not be able to stimulate the nicotine receptors and will thus make smoking non-enjoyable (Figure 1). Preliminary results of early clinical trials support a beneficial effect of this approach (Figure 2). Nicotine-Qbeta, CYT002-NicQb and NicVAX are currently three such vaccines under development. The combination of active and passive immunization may also be a good strategy.

Newer Bronchodilators

Bronchodilators are the mainstay of COPD management as they improve symptoms and quality of life significantly mainly by emptying the trapped air through dilatation of the distal airways. Thus bronchodilators provide symptomatic relief only and do not necessarily modify the disease process. Short
Ultra Long Acting Muscarinic Antagonists (ultra-LAMA)

Ultra-LAMAs are presently the best treatment available for COPD. The action of ultra-LAMAs like Tiotropium is mediated by good selectivity (for blocking) for and slow dissociation from M1 receptors in the lungs. They not only have better and sustained bronchodilatory effect but recently they also have been shown to have anti-inflammatory properties. It appears that LAMAs reduce the rate of exacerbation in COPD patients and hence, have the potential to partially halt progress of the disease and improve mortality.10,17

Aclidinium, glycopyrronium, darotropium, TD-4208, CHF5407, QAT-370, GSX-573719, Dexpirronium and RBx 343E48F0 are some of the ultra-LAMAs under development. Aclidinium is faster acting. Recent clinical trials have casted doubt on once-daily dosing of aclidinium and trials to investigate efficacy and safety of twice-daily dosing are underway. The other bronchodilators are being evaluated in clinical trials.9-16

Ultra long acting β2 agonists (ultra-LABA)

Ultra-LABAs have duration of action that lasts for at least 24 hours. Carmoterol, indacaterol, milveterol, vilanterol, olodaterol, LAS100977, PF610355, JNJ39758979, Saligenin- or indole-containing β2-agonists, UK-503590 and Compound X are some of the ultra-LABAs currently under development. Carmoterol, indacaterol, vilanterol, LAS100977 are faster acting compared to salmeterol. Indacaterol, a promising ultra-LABA has been approved in Europe and USA for bronchodilator treatment. Large clinical trials have shown that indacaterol may be better than salmeterol, formotherol and tiotropium in increasing trough FEV1 in COPD patients at doses of 150 and 300 mg and there was no evidence of tachyphylaxis. In asthma milveterol has been found to be safe and well-tolerated, with efficacy comparable to salmeterol. Its role in COPD is yet unexplored. Vilanterol is another ultra-LABA in clinical trials, and has been found to be safe and effective in both asthma and COPD patients.9,16

The deposition of inhaled drug into the lungs is usually less than 30%. However, using a formulation process like Modulite technology, the drug deposition of carmoterol has been shown to be improved up to 41%.9

Novel Combinations

Some COPD patients respond well to LAMAs and some to LABAs depending on various factors including variable predominance of beta-adrenergic or muscarinic receptors in these patients. Using a combination of the two may solve the problem of such variation in response to bronchodilators. Furthermore, LAMAs and LABAs have been shown to have synergistic effects.12,16 Since, these combinations are more likely to be used in severe or very severe COPD cases, addition of a steroid or anti-inflammatory drug would make sense, as steroids are likely to reduce the exacerbations in these patients.19 Various such triple drug combinations are presently available or would be available soon in the market.

India leads competition in this respect by launching the first triple inhaler containing tiotropium, formoterol and ciclesonide which is already available in India while such combinations are presently not there in most of the other countries including Europe and US.20 Some of the combinations in development are: aclidinium+formoterol+fluticasone/budesonide, tiotropium + formoterol ± Fluticasone/Budesonide, glycopyronium+formoterol+mometasone, indacaterol+glycopyronium (QVA-169), olodaterol + tiotropium, milveterol/vilanterol + darotropium, carmoterol + tiotropium and formoterol + dexpirronium.9,16

One of the limitations of such approach is delivery of LAMA and LABA at different locations in the lung which reduces their synergistic potential. A novel approach of combining these drugs in a single dimer molecule holds promise to deliver both the drugs at same locations in order to have maximum synergistic effect. Such molecules are known as dual-acting muscarinic antagonist- β2-agonist (MABA) bronchodilators. GSK-961081, Bicycloceth7-ylamine derivatives, TRXR-200495, TRXR-198321, LAS190792 and TD-5959 are some of the promising MABAs currently under development.9,13

Anti-Inflammatory Drugs

Drugs that can reduce the lung inflammation in COPD, safely and effectively, will undoubtedly be the drugs of choice for managing COPD. Years of research to discover such wonder drug has given birth to some anti-inflammatory agents or ideas, which may not be as effective as desired but can be of pragmatic use in clinical practice. Toiling research to understand the molecular reasons behind the unresponsiveness of COPD inflammation to corticosteroids, has led to the understanding that oxidative stress-mediated reduction in an enzyme known as Histone Deacetylase (HDAC) might be the culprit. Interestingly, theophylline has been shown to increase the cellular levels of HDAC. Hence, it is thought that oral theophylline given in low doses may augment the anti-inflammatory effect of inhaled steroids. A study on theophylline with budesonide (ADC4022) has already been successfully completed.21-23

PDE4 Inhibitors

Phosphodiesterase-4 (PDE4), an isoenzyme of phosphodiesterase, is specifically expressed in many pro-inflammatory cells such as neutrophils, macrophages, eosinophils, mast cells and lymphocytes. As a consequence, selective PDE4 inhibition may have inhibitory effects upon various inflammatory and immunomodulatory cells. Considering the problem of compliance with inhaled drugs and lack of availability of an effective anti-inflammatory drug, oral PDE4 inhibitors hold great promise. Roflumilast, a selective PDE4 inhibitor, has been developed and approved as an anti-
inflammatory agent for COPD. In a multi-centric clinical trial Roflumilast also improved FEV1 marginally, but significantly in COPD patients over and above tiotropium (Figure 3).24-27 Recently it has been suggested that PDe4 inhibitors are the best add-on therapy over LAMAs and LABAs for COPD. A combination of the inhaled PDE4 inhibitor GSK256066 (phase II) with a LAMA (potentially darotropium) in addition to, a LABA (either milveterol or Vilanterol) is also being explored. However, intolerable gastrointestinal side effects of present PDE4 inhibitors have prompted development of specific PDE4B and PDe7 inhibitors (Table 1).13

Antiproteases

Proteases like matrix metalloproteinas (MMP), which are released from macrophages, neutrophils and epithelial cells, digest elastin to cause emphysema. Selective MMP inhibitors like AZ11557272, have been shown to prevent emphysema and airway thickening in guinea pigs. MMP-9 and MMP-12 inhibitors are being currently investigated in Phase II and Phase III clinical trials and the results are awaited with interest. Midesteine and BAY-71-9678 are few other elastase inhibitors that have completed phase I studies.9-16

Cytokine Inhibitors

TNF-α (Tumour Necrosis Factor-α) is a key mediator of inflammation including systemic inflammation in COPD. Infliximab, an inhibitor of TNF-α, has been clinically tested and was however, not been found to be of any clinical benefit in COPD. Other cytokines that are being targeted presently for inhibition include interleukin (IL)-1β, IL-6 and IL-7. Tocilizumab, a potent inhibitor of IL-6, is yet to be tested in COPD patients. These drugs are still in the development phase.9-16

Chemokine antagonists

The chemotactic effects of chemokines CXCL8, CXCL1 and CXCL5 on neutrophils and monocytes are mediated by a common receptor, CXCR receptor (CXCR)2. ADZ8309, an oral CXCR1/2 antagonist has shown to inhibit neutrophil inflammation in humans. Antagonists have also been developed for other important chemokine receptors like CXCR3 and CXCR5. SCH-527123 and GSK656933 have already completed phase I studies.9-16

Fig. 4 : Oxidant-Antioxidant Imbalance

TGF-β Inhibitors

Transforming growth factor (TGF)-β plays a key role in fibrosis of small airways, which is a major cause of progressive FEV1 decline and reduced exercise capacity in COPD patients. SD-280, a TGF-β inhibitor has been developed. However, there are long-term concerns about inhibition of TGF-β.9-16

Nuclear factor-kB inhibitors

Nuclear factor-kB is a transcription factor that plays a key role in COPD inflammation by regulating the expression of CXCL8 and other chemokines, TNF-α and other inflammatory cytokines, as well as MMP9. Therefore, inhibition of NF-kB by inhibition of the inhibitor of NF-kB kinase (IKK)-2 seems to be a promising therapeutic option. Several (IKK)-2 inhibitors are currently under development.9-16

p38 MAP Kinase inhibitors:
p38 mitogen-activated protein kinase (p38 MAP kinase) is activated by cellular stress and regulates the expression of IL-8, TNF-α and MMPs, proteins involved in driving COPD airway inflammation. Inhaled formulations of p38 MAP kinase inhibitors, currently in the development phase, are GSK681323 and GSK856553.9-16

PI3K Inhibitors

Phosphoinositol 3-kinases (PI3Ks) are involved in the inflammatory process, specifically in neutrophil recruitment and activation. PI3K-γ and PI3K-β have been targeted for inhibition and several such inhibitors are currently in early drug development phase.9-16

PPAR Agonists

Peroxisome Proliferator-activated Receptors (PPARs) are a family of ligand-activated nuclear hormone receptors belonging to the steroid receptor super-family. Recently, PPAR-α and PPAR-γ have demonstrated immunomodulatory properties. PPAR-γ agonists also inhibit TGF-β and hence may be helpful in preventing fibrosis. The PPAR agonists currently being studied for therapeutic use in COPD are rosiglitazone and SB 219994.9-16

Table 1 : Common adverse events recorded in roflumilast trial

<table>
<thead>
<tr>
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<th>Placebo n=280</th>
<th>Roflumilast</th>
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<tr>
<td></td>
<td></td>
<td>250 mcg n=576</td>
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<tr>
<td>Patients experiencing ≥ 1 adverse event</td>
<td>174 (62%)</td>
<td>382 (66%)</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>65 (23%)</td>
<td>135 (23%)</td>
</tr>
<tr>
<td>Nasopharyngits</td>
<td>19 (7%)</td>
<td>42 (7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (2%)</td>
<td>28 (5%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14 (5%)</td>
<td>27 (4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1%)</td>
<td>16 (3%)</td>
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Antioxidants

Oxidative stress arising out of oxidant-antioxidant imbalance, contributes quite significantly to the pathophysiology of COPD in multiple ways (Figures 4 and 5). N-Acetyl-Cysteine (NAC) is one of the most widely used and tested anti-oxidants. NAC has been shown to reduce both local as well as systemic oxidative stress. Some studies have demonstrated that NAC reduces bronchial hypersecretion, prevents the decline in FEV1 and helps reduce the numbers of COPD exacerbations.\(^5,28\)

In our own study (unpublished data) comparing high dose NAC (1200 mg OD) with inhaled fluticasone in a randomized, double blind study in 23 subjects with moderate-to-severe COPD, we found a significant reduction of exhaled carbon monoxide (which is a biomarker for oxidative stress) by 1.09 ppm in NAC group against 0.43 ppm decrease in the fluticasone group after a 4 weeks treatment. Intriguingly, this was accompanied by an increase in FEV1 by 112ml in NAC group against a 30ml reduction in the fluticasone group (Figure 6). This suggests that in higher doses NAC reduces oxidative stress and may lead to mild bronchodilation, an added advantage over corticosteroids. However, the results are needed to be confirmed by large scale multi-centric clinical trial.\(^5,28\)

Several anti-oxidants like N-acestelyn (NAL), N-isobutyrylcysteine (NIC), erdosteine, procysteine and carbocysteine are currently under development. As against NAC, effective inhaled preparation of these anti-oxidants can be developed making it possible to deliver them in higher doses locally. NAL has been tested in clinical trials and was well tolerated. Erdosteine has additional property of reducing bacterial adhesiveness suggesting potential use to prevent bacterial exacerbations. NIC is less effective and procysteine more toxic.\(^5,28\)

NRF-2 Activators

Nuclear factor erythroid-2 related factor 2 (NRF2), a transcription factor, induces antioxidant expression, thus inhibiting oxidative stress. Plant products 6-methylsulfinilyhexyl isothiocyanate (6-HITC) found in Japanese horseradish, sulforaphane isolated from broccoli and wasabi are the NRF-2 activators currently being studied.\(^5,28\)

**Fig. 6: Outcomes of clinical trial using higher dose NAC**

**Statsin**

Statins or 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) are used widely as lipid lowering agents. However, recently statins have been found to have anti-inflammatory, antioxidant, anti-thrombogenic and vascular function-restoring actions. Retrospective studies indicate that statins might improve all-cause mortality, deaths from COPD, respiratory-related urgent care, COPD exacerbations, intubations for exacerbations of COPD, exercise capacity and lung function decline in COPD patients. Lipophilic statins such as atorvastatin and simvastatin are thought to be more effective than the hydrophilic pravastatin. However, statins have been inadequately studied and need further evaluation in objective clinical trials before they can be used in the management of COPD.\(^32-34\)

**Regenerative Therapies**

Presently COPD is managed only symptomatically and is a progressive disease. Any drug/therapy that restores the destroyed alveolar tissue may actually reverse the disease.

**Stem Cells**

Infusion with allogenic mesenchymal stem cells offer hope, as they have the potential to regenerate alveolar tissue by themselves or by secreting growth hormones, specifically, vasculo-endothelial growth factor (VEGF). However, lodging of the pulmonary blood vessels with the infused stem cells (arborization) leading to fatal outcome is an undeniable possibility. Trials investigating the efficacy and safety of stem cells in COPD patients are underway.

**Retinoic Acid**

Retinoic acid is known to increase alveolar septation during lung development. All-trans-retinoic acid has been shown to induce regeneration of the terminal respiratory tract and reverse elastase induced emphysema. However, this was not substantiated by a clinical trial evaluating health status on CT density.\(^9,16\)

**Anti-ageing Therapy**

Accumulating DNA damage caused by oxidative stress is a hallmark of accelerated ageing. Accelerated aging has been implicated in the pathogenesis of COPD and is mediated by inactivation of Silent Information Regulator Two (SIR2) protein-1 or sirtuin1 (SIRT1). Resveratrol, found in grape skin, seeds and nuts, activates SIRT1, and is being studied as a possible therapeutic agent for COPD. New SIRT1 activators under development are SRT1720, SRT501 and SRT2104. These molecules are many times more potent than resveratrol.\(^5,28,35\)

Apart from new drug discoveries, a lot of research is taking place to discover new devices, formulation strategies and drug
Table 2: Summary of newer therapies for COPD

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<thead>
<tr>
<th>Category</th>
<th>Substances</th>
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<tr>
<td></td>
<td>2. LABA and ICS: a. Carmoterol and budesonide c. Formoterol and mometasone (MF258) c. Formoterol and ciclesonide d. Indacaterol and mometasone (QMF-149) e. Indacaterol and QAE-397 (a novel corticosteroid) f. Fluticasone furoate and GSK-642444</td>
</tr>
<tr>
<td>d. PDE4 Inhibitors</td>
<td>1. Roflumilast 2. Cilomilast</td>
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<td></td>
<td>3. TGF-β Inhibitors: a. SD-280</td>
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<td></td>
<td>6. Nuclear factor-kb inhibitors</td>
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<td></td>
<td>7. p38 MAP Kinase inhibitors</td>
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<td></td>
<td>8. PI3K Inhibitors</td>
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<td></td>
<td>9. PPAR Agonists: a. Rosiglitazone b. SB 219994</td>
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Although the exciting novel therapies may take some time to reach practicing physicians, it is encouraging to realize that our COPD patients will be receiving more effective and safe treatment in near future (Table 2). We may soon make the inflammation in COPD respond to therapy. By then, smoking cessation remains the most important intervention and long acting-bronchodilators the most effective symptom-relievers.

References


34. B. John Mancini et al. Reduction of Morbidity and Mortality by Statins, Angiotensin-Converting Enzyme Inhibitors, and Angiotensin Receptor Blockers in Patients With Chronic Obstructive Pulmonary Disease. *Journal of the American College of Cardiology* 2006;47:12,