PHARMACOTHERAPY IN COPD- RECENT INNOVATIONS AND RESEARCH

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ABSTRACT

BACKGROUND
COPD remains to be one of the major and increasing health problems worldwide. The treatment approach needs to be multidimensional, but pharmacotherapy claims the superiority though demands more rationalisation in terms of patient selections, dosing, authentication of new innovative molecules and drug delivery systems. Here, we present a review of various recent studies on pharmacotherapy of COPD done by searching through the PubMed, Google Scholar, Cochrane, along with the FDA website for the newer drug approvals. We selected the highly relevant articles on the newly-approved drugs and pivotal and post hoc studies and reviews related to them. In newer innovations, both tiotropium and indacaterol were compared and there was favourable difference in case of tiotropium in preventing exacerbations. In the search of newer therapeutic targets phosphodiesterase inhibition, two studies showed increase in the prebronchodilator FEV1 by 48 mL. REACT trial showed that the exacerbation was lowered by 13.2% by roflumilast. In infectious exacerbations, two trials MACRO and COLUMBUS study showed beneficial effect of azithromycin in the frequency of exacerbations. Calculating the pharmacotherapeutic risks, TORCH study showed that those who are receiving ICS, the development of pneumonias was more common with elderly fellows. Azithromycin is associated with cardiac-related deaths and hearing loss. On individualised treatment approach, WISDOM study showed that there was no significant difference in exacerbation rates once the ICS is withdrawn in the two groups, i.e. LABA/ICS combination and a LAMA for six weeks.

In conclusion, devising rational treatment for COPD is of paramount importance. Treatment strategy will depend on severity of the obstruction and acute exacerbations. More severe disease needs more extensive approach possibly the inclusion of anti-inflammatory drugs, which can be gradually withdrawn. ICS benefits the patients in terms of exacerbations without any significant changes in the lung functions. They do so more in patients with more asthma like history, but again there is risk of pneumonia especially with fluticasone preparations. LAMAs do better than LABAs in COPD. Newer innovations like long-term antibiotics and PDE IV inhibitors maybe add on choice for not responding patients.

KEYWORDS
COPD, Pharmacotherapy, Clinical Trials in COPD.

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BACKGROUND
Unlike asthma, COPD is thought to be a systemic, not fully reversible disease. Accordingly, the treatment approach becomes multidimensional including smoking cessation, pharmacotherapy, domiciliary oxygen therapy, rehabilitation, surgical management, immunisation, etc. Despite the availability of the various therapeutic options, pharmacotherapy still claims the superiority though demands more rationalisation in terms of patient selections, dosing, authentication of new innovative molecules and drug delivery systems.

Exacerbation is an important component in the natural history of disease, which has detrimental consequences on the survival, economic burden and productivity of the patient. Similarly, we cannot ignore the symptomatic assessment of the disease. Global initiative for chronic obstructive lung diseases (GOLD) has considered the limitations of grouping the patients solely on the basis of spirometric (forced expiratory volume in first second, FEV1) values. Their recent guidelines have now incorporated the symptomatic assessment, frequency of exacerbations and spirometric variables to categorise the patients based on their risk and symptom-based behaviour. This appears to be a more scientific approach as mere spirometric variables may not depict the full disease condition of the patient. Though, this may have limitations in the form of spontaneous variations in the exacerbation status of the patient, it’s definitely a good initial approach.

Recent changes in the established management of exacerbations include reducing the duration of oral corticosteroid to just 5 days.1 This strategy has proved to be as good as giving it for longer duration. Giving antibiotic therapy during acute exacerbation has also proved to improve the outcome and lessen the chances to develop subsequent pneumonias.2
REVIEWS OF LITERATURE

Newer Innovations in Pharmacotherapy- Tiotropium

was the first molecule to have the 24-hour dosing interval and was in concordance with the persistence of symptoms in COPD patients, i.e. it provided better mean trough FEV1 values than the LABAs of the time with twice daily dosing. One large trial based on Cost Effective Analysis (CEA) study, Prevention of Exacerbations with Tiotropium (POET)-COPD randomised the patients to receive either the tiotropium or twice daily salmeterol was fair enough to show clinically significant difference in the favour of former as there was an increased time interval for first exacerbation, total number of exacerbations and exacerbation-related cost. Tiotropium had then to compete with the availability of first ultra LABAs with 24-hour dosing interval, i.e. indacaterol. This molecule also showed higher trough values as compared to placebo or the famous salmeterol/fluticasone combination. Donohue et al in their 26 weeks follow-up established the equivalent efficacy of indacaterol and tiotropium in terms of reduction in dyspnoea and improvements in the lung function. But, then came the report of invigorate trial, which randomised 3,444 patients to receive either indacaterol 150 µg or tiotropium 18 µg and followed them for a year. Spirometric values were not different in the two arms, but there was favourable difference in case of tiotropium in preventing exacerbations. So, it was clear that the inhaled long-acting antimuscarinic therapy is better in COPD as compared to the beta agonists especially in preventing exacerbations.

Moreover, though having its maximal effect at the dose of 300 µg, the US regulatory agencies have approved its marketing at 150 µg, which can be due to the concern of cardiotoxicity as is in cases of LABA drugs gained through the TORCH study.

Two new ultra LABAs, olodaterol and vilanterol, which are suitable for once daily dosing are available and approved for their use in COPD patients. Olodaterol approval was based on two randomised placebo controlled replicate studies of 48 weeks, which showed significant improvement in FEV1 area under curve from 0-3 hours (AUC0-3) and its trough level at 12 weeks. Again in one more phase III randomised active-controlled replicate studies comparing combined olodaterol and tiotropium in Fixed Dose Combinations (FDCs) with individual drugs designed in five arms, it was concluded that the FDCs were better in terms of FEV1 AUC0-3 and trough FEV1, though the St. George Respiratory Questionnaire Score was significantly better only with 5/5 µg FDC.

Tiotropium was further succeeded by development of two new LAMAs, umeclidinium and glycopyrronium. In the pooled post hoc analysis of two phase III studies, glycopyrronium bromide in COPD airways clinical study 1 and 2 (GLOW 1 and 2), Least Squares Mean (LSM) trough FEV1 was significantly higher with this molecule versus placebo on several occasion. Most patients attained trough values more than 100 mL as compared to placebo. Improvement in FEV1 was significant even on first day as compared to placebo as well as tiotropium. Even time to first moderate or severe exacerbation was prolonged. Notable is fixed dose dry inhalational powder of glycopyrronium and indacaterol first approved in Japan and Europe in 2013 and as of now in over 40 countries. One of the large scale study enrolling 2144 patients in five arms compared this FDC with its monocomponents and open label tiotropium. The trough FEV1 at 26 weeks was significantly better than that of individual components as well as the tiotropium. Umeclidinium has been approved by regulatory agencies to be used with vilanterol as inhalational powder.

A new formulation of fluticasone furoate also now finds its use as once daily dosing in asthma and COPD. In COPD, it has shown to improve the 24-hour FEV1 level, though modest without improvement in dyspnoea. As of now, it has not been approved to be used as single drug monotherapy in COPD, but finds its use in combination with the once daily dosing of vilanterol. Dransfield et al showed that the fluticasone in higher dose was associated with greater reduction in exacerbation, although the changes in FEV1 were not convincing. Acilidinium bromide earlier developed to be used in once daily dose of 400 µg has now been registered for twice daily dosing as 200 µg also. This new dosing schedule finds its use in combination with forometerol. The pooled data of two studies ACLIFORM and AUGMENT with this combination showed it to be superior to placebo and individual components in 24-hours symptom control. Moreover, it also reduced the frequency of exacerbations as compared to placebo.

N-acetyl cysteine, once thought to be a convincing drug for COPD due to its antioxidant effect was set aback by the findings of Bronchitis Randomised on NAC Cost-Utility Study (BRONCUS) that its effect on exacerbation was only when patients were not on the backup treatment of inhaled corticosteroid. Similarly, another derivative carbocysteine was also found to reduce the number of exacerbation, but was limited to those who were not on the backup treatment. Contrary to these findings, a study from china gives a new hope as N-acetylcysteine in double dose reduced the number of exacerbations when given along with backup inhaled treatment, but head-to-head comparison is still needed.

There were some concerns regarding the drug delivery in COPD especially with tiotropium given by Respimat device. Studies showed more number of deaths in the treatment arm as compared to placebo. But, subsequently a larger randomised-controlled trial comparing this effect in patients receiving tiotropium by Respimat or HandiHaler (which was deemed to be safe by the time), found no difference as far as mortality due to device was concerned.

Searching Newer Therapeutic Targets- COPD is a systemic disease and has different arms of pathogenesis. In due consideration, the treatment demands the search of such therapeutic targets other than the conventional bronchodilators namely LABAs and LAMAs.
Phosphodiesterase inhibition is a relatively new target on which a good amount of work has been done recently and roflumilast got the approval and is being marketed for COPD patients. In the pooled analysis of its two pivotal studies, the drug led to increase in the pre-bronchodilator FEV1 by 48 mL as compared to placebo. Similarly, there were reductions in exacerbations by 17%, which was statistically significant in comparison to placebo.23 The overall improvements in lung function and exacerbation frequency were present in all patients receiving roflumilast irrespective of bronchodilators they were receiving, i.e. LABA and SAMA.24 In its add on studies, comparing the role of roflumilast when given along with two bronchodilators salmeterol and tiotropium respectively, the pooled analysis revealed improvements in pre-bronchodilator FEV1 of 49 mL and 80 mL as compared to placebo. The post-bronchodilator values also improved in these two studies.25 Later on combining the data of the two pivotal studies and post hoc, the pooled analysis suggested that the roflumilast decreased exacerbation by 14.3% as compared to placebo and this finding was significant with special subsets of patients who were having chronic bronchitis, cough, sputum production and concurrent ICS use.26 The data from recent ‘Roflumilast and Exacerbations in patients receiving Appropriate Combination Therapy (REACT)’ trial, which was to assess the efficacy of roflumilast on preventing exacerbations in patients who were frequent exacerbators and who were being treated adequately with LABA/ICS combinations (even those who were using tiotropium previously were allowed) showed that the exacerbation was lowered by 13.2% in roflumilast group as compared to the placebo. Still the most frequent serious adverse events reported were the exacerbations and pneumonia.27 GOLD has included the roflumilast in its recent guideline to be used in group C and D.28

There is emerging evidence in the favour of hypothesis of infectious exacerbations due to increased microbial load by the process of colonisation of the airways. Two large trials have further potentiated this fact. National Heart Lung Blood Institute (NHLBI) sponsored MACRO trial was designed to give azithromycin 250 mg versus placebo to 1142 COPD patients randomised to ratio of 1:1 for one year. There was improvement in median time to first exacerbation (266 versus 174), frequency of exacerbations (1.48 versus 1.83 per person year) especially in patients who were ex-smokers with grade 2 disease and on minimal background treatment. There was also decrease in incidence of colonisation and improvement in the quality of life.29,30 Another relatively smaller, COLUMBUS study recruited 92 patients with history of more than three exacerbations a year and inferred to have beneficial effect of azithromycin in the frequency of exacerbations (1.94 versus 3.2 per person year) even in those who were on regular background treatment.31

Statins are supposed to have anti-inflammatory effect. Experimental studies and database reviews were favouring its role in reducing the risk of exacerbation and hospitalisation.32 STATCOPE study was a randomised placebo-controlled prospective study to give COPD patients with no indications for lipid-lowering agents as per Adult Treatment Panel III (ATP III) criteria and who were free from diabetes and cardiovascular disease and who were smoker (more than 10 pack years) and were on glucocorticosteroid, supplemental oxygen, antibiotics or had exacerbations in the previous year, either simvastatin 40 mg or placebo. The results did not favour the use as there was no significant difference in number of exacerbations, time to first exacerbations or in the number of nonfatal serious events per person year in those who took the drugs versus those who were on placebo.33

P38 MAP kinase inflammation pathways may have a role in the pathogenesis of COPD. Blocking this pathway with an oral antagonist did not seem promising. Although, study by MacNee et al showed it to increase the FEV1 and reduce dyspnoea, but a relatively larger trial, which compared oral doses of losmapimod to placebo did not translated into improvement in 6-minute walk test as primary endpoint.34,35 Though, further study is the worth requirement of time.

Benralizumab is a newer biological agent to be studied in COPD population, but again the result was not at par as far as exacerbation is concerned. Further studies are needed in this area before coming to conclusion.36

Calculating the Pharmacotherapeutic Risks-Pneumonia was a concern in patients receiving inhaled corticosteroid in the landmark TORCH trial of COPD.37 Similar findings were confirmed in other studies and reviews later.38,39,40 Though it seems usual side effect of ICS, but findings of TORCH study also showed that the incidence was more common with elderly fellows having lower lung function and those having higher degree of breathlessness.37 Fluticasone was then identified as the chief culprit drug and budesonide to be the safer alternative.40,41

Roflumilast has lesser group (PDE IV) related adverse effects like diarrhoea, nausea, headache and cardiac effects, but the drug has been found to cause significant weight loss, which averages 2.17 kilograms especially in obese individual, but is reversible on discontinuation.24,27,42

Azithromycin though safe has a concern of increased cardiac-related deaths, especially in elderly individuals. Moreover, hearing loss in excess of 5% as compared to placebo was seen in MACRO study.29 The study also observed increased incidence of colonisation by drug-resistant organism. COLUMBUS study reported diarrhoea more in study group as compared to placebo (19% versus 2%).31 Apart from these, increased prescription may lead to emergence of antibiotic resistance in the community.43

Other group-related side effects are known and predictable for most of the available drugs.

Individualised Treatment Approach- COPD as a disease has various phenotypic characteristics. So, it is the need of the time to identify the right drug for the right patient for the right duration. ‘Withdrawal of inhaled glucocorticoids and exacerbations of COPD (WISDOM) study’ by Magnussen H, et al was intended to know whether the patients had increased exacerbations once the ICS is withdrawn. It recruited over 2000 patients of COPD having moderate-to-
severe disease. Included patients were given LABA/ICS combination and a LAMA for six weeks and were then randomised to the groups for continuation or gradual withdrawal of ICS. There was no significant difference in exacerbation rates in the two groups, but statistically significant differences do exist in lung function and health status. The study had the clear-cut message that the patient once stabilised on extensive regimen can be tapered off without compromising of the risk of exacerbation. This is something like 'step up' and 'step down' therapy of asthma, but a similar extensive and rationalised approach with COPD is still due.

There is increasing ideology whether COPD shares asthma like features or in other words can it be a more oesinophilic type COPD. Study by Bafadhel M et al supported the notion and it was advocated that more inflammatory type COPD can be benefitted by anti-inflammatory treatment as compared to pauci-inflammatory subset where bronchodilator therapy will be of greater value. Similarly, a Canadian Database Study in elderly COPD patients concluded that in general patients were benefitted more with LABA/ICS combinations as compared to LABA alone, but the benefit was more pronounced if they have asthma-like history in the past.

CONCLUSION

Though COPD in itself is a disease of phenotypic variations, recent studies have paved and smoothened the way for devising rational treatment. More severe disease needs more extensive approach possibly the inclusion of anti-inflammatory drugs, which can be gradually withdrawn. ICS benefits the patients in term of exacerbations without any significant changes in the lung functions. They do so more in patients with more asthma like history, but again there is risk of pneumonia especially with fluticasone preparations. LAMAs do better than LABAs in COPD. Newer innovations like long-term antibiotics and PDE IV inhibitors maybe add on choice for not responding patients.

Search Strategy and Selection Criteria- We searched the PubMed, Google Scholar, Cochrane, for the keywords ‘COPD’, ‘Pharmacotherapy’ and ‘recent clinical trials in COPD’ in combinations. We also searched the FDA website for the newer drug approvals. We selected the highly relevant articles on the newly-approved drugs and pivotal and post hoc studies and reviews related to them.

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