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Treatments for COPD

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Summary The multicomponent nature of chronic obstructive pulmonary disease (COPD) has provided a challenging environment in which to develop successful treatments. A combination of pharmacological and non-pharmacological approaches is used to combat this problem, and an overview of these approaches and their possible future direction is given.

Bronchodilators are the mainstay of COPD treatment and can be combined with inhaled corticosteroids for greater efficacy and fewer side effects. A new generation of pharmacotherapeutic agents, most notably phosphodiesterase-4 inhibitors, which are already in the advanced stages of clinical development, and leukotriene B_4 inhibitors (in early clinical development), may shape future treatment as further insight is gained into the pathological mechanisms underlying COPD.

Non-pharmacologic treatments for COPD include long-term oxygen therapy (LTOT), nasal positive pressure ventilation (nPPV), pulmonary rehabilitation and lung-volume-reduction surgery (LVRS). Apart from smoking cessation, LTOT is the

Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; CXCR1/CXCR2, chemokine receptors 1 and 2; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; IL-8, interleukin-8; INPV, intermittent negative pressure ventilation; LABA, long-acting β_2-agonist; LTB_4, leukotriene B_4; LTOT, long-term oxygen therapy; LVRS, lung-volume-reduction surgery; NAC, *N*-acetylcysteine; NETT, National Emphysema Treatment Trial; NF-κB, nuclear factor-kappa B; nPPV, nasal positive pressure ventilation; PDE_4, phosphodiesterase-4; QoL, quality of life; SFC, salmeterol/fluticasone propionate combination; SGRQ, St. George's Respiratory Questionnaire; TNF-α, tumour necrosis factor-alpha; V'/Q', ventilation/perfusion ratio

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only treatment to date which has been shown to modify survival rates in severe cases; thus its role in COPD is well defined. The roles of nPPV and LVRS are less clear, though recent progress is reported here.

In the future, it will be important to establish the precise value of the different treatments available for COPD—evaluating both clinical and physiological endpoints and using the data to more accurately define candidate patients accordingly. The challenge will be to develop this base of knowledge in order to shape future research and allow clinicians to deliver tailored COPD management programmes for the growing number of patients afflicted with this disease.
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Introduction

Chronic obstructive pulmonary disease (COPD) is a multicomponent disease with inflammation at its core, in which patients experience progressively worsening lung function, disease symptoms and quality of life (QoL), as well as increasing exacerbations.[1] The therapeutic difficulty presented by COPD arises from the need to target all components of the disease. To this end, a clinician's paradigm for COPD management has been introduced—Global Initiative for Chronic Obstructive Lung Disease 2003 (GOLD 2003).[1,2] Current management options can be divided into pharmacologic and non-pharmacologic categories. Pharmacologic treatments include bronchodilators, inhaled corticosteroids (ICS), combination therapies and long-term oxygen therapy (LTOT). Non-pharmacologic interventions include smoking cessation, optimising nutrition, pulmonary rehabilitation, mechanical ventilation and lung-volume-reduction surgery (LVRS). Novel medications such as selective phosphodiesterase-4 (PDE_4) inhibitors are already in the advanced stages of clinical development; leukotriene B_4 (LTB_4) inhibitors also show potential for shaping future therapy, although they are only in the early stages of clinical development. Apart from smoking cessation, LTOT is the only treatment to date that has been shown to modify survival rates in severe COPD; thus it has a clear role to play in patients with COPD and chronic respiratory failure. The aim of this article is to provide an overview of the current and future treatment options available in COPD management.

Pharmacotherapeutic agents in COPD

Bronchodilators

Optimising treatment response

Bronchodilators are central to the symptomatic management of COPD and come in several forms—short-acting bronchodilators, including the β_2-agonist salbutamol and the anticholinergic ipratropium bromide, and long-acting bronchodilators, including the β_2-agonists salmeterol and formoterol, the anticholinergic tiotropium and theophylline. A fixed-dose combination of salbutamol/ipratropium (Combivent®) is also available.

Current guidelines recommend the inhaled delivery of long-acting bronchodilators as the preferred method of therapy. Several facts should be considered when choosing a bronchodilator for treatment of COPD. First, the lack of acute response to one class of bronchodilator does not necessarily imply non-responsiveness to another. Donohue[3] reported that 73% of 813 COPD patients increased their forced expiratory volume in 1 s (FEV_1) by $>12\%$ or 200 mL following long-term salmeterol treatment. However, 11% of patients showed a similar increase in FEV_1 following acute administration of ipratropium, 27% following salbutamol and 35% with both drugs combined. A second consideration is that a patient's FEV_1 response to acute bronchodilator therapy does not predict long-term response to bronchodilator therapy and may vary from day to day. Calverley et al.[4] performed acute bronchodilator testing using salbutamol, ipratropium bromide or a combination of the two on 660 COPD patients who had been classified according to both European Respiratory Society (ERS) and American Thoracic Society (ATS) spirometric criteria.[5,6] Over the 2-month study period, 55% of patients classified as irreversible under ATS criteria changed to reversible status on at least one of the visits.

In summary, the acute response to short-acting bronchodilators is of limited value in deciding future response to long-acting agents. Furthermore, while improvement in FEV_1 is important in assessing response to bronchodilator therapy, other outcome measures such as improvements in lung volumes, symptoms, exercise capacity, QoL and exacerbations may be of greater value in assessing the long-term response. The effects of commonly used bronchodilators on clinical outcomes in COPD are listed in Table 1.

Table 1 Summary of the effects of commonly used bronchodilators on clinical outcomes in COPD.

Bronchodilator	FEV_1	Lung volume	Dyspnoea	HRQoL	Exercise endurance
Short-acting β-agonist	Yes*	Yes†	Yes*	—	Yes†
Ipratropium bromide	Yes*	Yes†	Yes*	No†	Yes†
Long-acting β-agonist	Yes*	Yes*	Yes*	Yes*	Yes†
Tiotropium	Yes*	Yes*	Yes*	Yes*	Yes†
Theophylline	Yes*	Yes†	Yes*	Yes†	Yes†

FEV_1 = forced expiratory volume in 1 s.
*Randomised clinical trial, substantial numbers of studies with large study populations.
†Randomised clinical trial, few studies or studies with small study populations.

Combination bronchodilator therapy

Current guidelines highlight the fact that a combination of more than one class of bronchodilator may be more effective than the use of single agents with respect to improvements in lung function, symptoms, and reducing the risk of adverse events.[1] This has been supported by several clinical trials. For example, in a 12-week trial, ZuWallack et al.[7] showed that salmeterol plus theophylline caused significantly greater improvements in pulmonary function and symptoms, compared with either single agent ($N = 943$). Additionally, the combination of salmeterol and the short-acting anticholinergic ipratropium provided greater bronchodilation than either agent alone.[8] These additive effects are not surprising since these agents may have complementary mechanisms of action.[9]

Assessing bronchodilator efficacy

FEV_1 is not the only useful physiological endpoint in evaluating bronchodilator efficacy—changes in symptoms and QoL often occur independently of changes in lung function. Other important physiological effects of bronchodilators include the reduction of air trapping and dynamic hyperinflation. Assessments of bronchodilator efficacy should take these factors into consideration. For example, the degree of lung hyperinflation, determined using lung volume measurements of inspiratory capacity, may provide a better correlation than FEV_1, with improved exercise performance following bronchodilator therapy.[10] Clinical endpoints, such as the frequency of exacerbations, mortality, degree of breathlessness, exercise tolerance and health status should equally be incorporated.[11,12]

It should also be noted that some bronchodilators exhibit beneficial non-bronchodilator behaviour, such as the potential anti-inflammatory effects of theophylline[13] and other non-bronchodilatory effects of long-acting β_2-agonists (LABA).[14]

Safety of bronchodilators

It has been reported that the continued use of β_2-agonists may be associated with an increase in cardiovascular risk compared with placebo.[15] However, a recent meta-analysis ($N = 2853$) showed no clinically significant difference in the incidence of cardiovascular events between salmeterol and placebo.[16] Furthermore, a study in patients with cardiovascular disease showed no increased risk with the use of salmeterol, compared with placebo.[17] It has also been suggested that tolerance to the bronchodilator effects of LABAs may occur with their prolonged use. A recent study examining the bronchodilator effect of long-term use of salmeterol failed to demonstrate such an effect.[18]

The use of anticholinergics may be associated with class side effects, such as dry mouth, an increased risk of glaucoma and urinary retention. Long-term effects of ipratropium bromide may include an increased risk of cardiac events, as shown in the Lung Health Study, although these findings need further evaluation.[19] Theophylline is associated with tremors and nausea and less frequently, with cardiac arrhythmias and seizures.[20] The risk of such adverse events can be reduced, however, by monitoring drug plasma levels and reducing the dose accordingly.

Future challenges in bronchodilator therapy

Several new bronchodilators, currently in ongoing clinical trials, may improve the future treatment of COPD. These include β_2-agonists, which can be administered once a day or through nebulisation, PDE_4 inhibitors and combination therapies. Specific research targets include determining the long-term efficacy of ICS/LABA combinations and tiotropium, their effects on the natural history of COPD when used early in disease progression, and their long-term safety. The exploration of more reliable and sensitive markers for response to bronchodilator therapy is also a key objective.

Inhaled corticosteroids

The role of ICS in COPD was once controversial, but is now better established as a result of large clinical trials. Regular treatment with ICS is recommended (GOLD) for symptomatic patients who suffer frequent exacerbations, and whose FEV_1 is $<50\%$ of predicted.[1] The rationale for the use of ICS in COPD will be examined below.

Attempts to elucidate the ICS mechanism of action have been inconclusive. Although these agents appear to have minimal significant effects on key inflammatory chemoattractants, such as interleukin-8 (IL-8), tumour necrosis factor-alpha (TNF-α) and matrix metalloproteinases,[21] there are data to suggest an association with reduced neutrophil chemotaxis.[22]

ICS in COPD: physiological versus clinical endpoints

Four large, 3-year, randomised trials have failed to show a significant effect of ICS on the rate of decline of FEV_1, compared with placebo.[23] However, a meta-analysis by Sutherland et al.[24] showed that high-dose ICS reduced the rate of decline in FEV_1 by 9.9 mL per year compared with placebo ($P = 0.01$). Whether this effect is clinically important remains unresolved. Less contentious data showed that post-bronchodilator FEV_1 was significantly higher during ICS treatment compared with placebo in two long-term studies,[25,26] with particularly strong data in one study of fluticasone propionate.[25]

Despite the controversy regarding the effects of ICS on physiological endpoints, it is generally agreed that ICS have a positive influence on clinical endpoints in patients with COPD. For example, in the Inhaled Steroids in Obstructive Lung Disease in Europe trial, the median exacerbation rate was reduced by 25% with fluticasone propionate compared with placebo, with a concomitant significant reduction in health status deterioration.[25,27] Furthermore, these effects may be more pronounced in patients with severe airflow limitation—although the recent ATS/ERS statement put as much emphasis on symptoms to guide management decisions as lung function.[2] It is important to note that the COPE study also showed that withdrawal from treatment with ICS was associated with a more rapid onset and increased recurrence of exacerbations, and also with a significant deterioration in health-related quality of life (HRQoL).[28] Despite the contention surrounding the physiological effects of ICS, their effect on clinical endpoints supports their use in COPD.

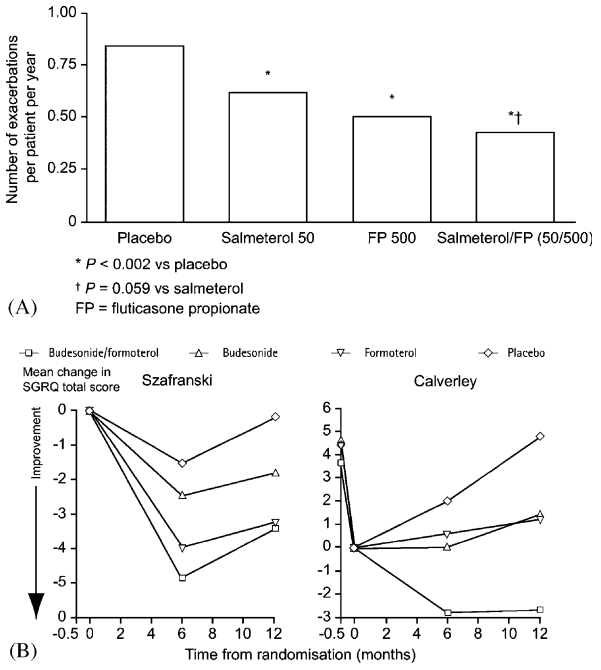

Figure 1 The effects of ICS/LABA combination therapy on (A) the number of exacerbations requiring oral steroid courses ($FEV_1 < 50\%$ predicted),[36] and (B) QoL in patients with COPD, as measured with the St. George's Respiratory Questionnaire (SGRQ).[32,33]

Combining ICS and LABA for greater effectiveness

Physiological and clinical data concur that combining ICS and LABA is more effective than either treatment alone.[29–33] More recently, it has been shown that short-term treatment with combined fluticasone propionate/salmeterol improves lung function and symptoms more effectively than the combination of salbutamol and ipratropium bromide.[34,35] In a pivotal study, Calverley et al.[29] ($N = 1465$) reported that treatment for 12 months with salmeterol/fluticasone propionate combination (SFC) significantly improved pre-treatment FEV_1 compared with placebo or either single agent alone. A clinically significant improvement in health status and a reduction in daily symptoms were also observed with combination treatment, together with a significant reduction in exacerbations (Fig. 1).[36] Other studies by Szafranski [32] and Calverley[33] showed that patients treated with a budesonide/formoterol combination have an improved QoL, as measured by the St George's Respiratory Questionnaire (SGRQ) score (Fig. 1).[32,33,37] Furthermore, a database study by Soriano et al.[38] indicated that there may be a survival advantage in using SFC combination treatment or fluticasone propionate alone—the 3-year TOwards a Revolution in COPD Health survival study

including over 6000 patients aims to evaluate this hypothesis further.[39]

In summary, ICS may have limitations as monotherapy in COPD. However, they have been shown to significantly improve important clinical outcomes in combination with LABAs, thus maintaining the rationale for their use among these patients.

The next generation of pharmacotherapeutic agents

Further insight into the pathogenesis of the chronic airway inflammation which underlies COPD has established new therapeutic targets, most of which are based on components of inflammatory pathways (Fig. 2).[40,41]

PDE_4 inhibitors

PDE_4 is commonly expressed in neutrophils, CD8+ cells and macrophages. The inhibition of PDE_4 causes an increase in cyclic adenosine monophosphate in immunomodulatory and inflammatory cells, with subsequent suppression of inflammatory cell function. A number of PDE_4 inhibitors are undergoing investigation (Fig. 3). Selective PDE_4 inhibitors,[42] such as cilomilast and roflumilast, are effective in COPD patients (Fig. 3). In particular, cilomilast treatment is associated with reductions in the numbers of CD8+ and CD68+ cells, indicating anti-inflammatory action.[43] The development of PDE_4 inhibitors is restricted by gastrointestinal side effects, although this problem could be overcome by the use of PDE_{4B}-selective inhibitors, which may be more specific and exert fewer side effects.[44]

LTB_4 inhibitors

Another inflammatory mediator, LTB_4, is a key chemoattractant of neutrophils, thereby making it an attractive target for therapeutic intervention in COPD. Antagonists of the two subtypes of LTB_4 receptor (e.g. LY29311[44] and SB201146[45]) are at the early stages of clinical development and have been shown to inhibit sputum-induced neutrophil chemotaxis (Fig. 4). Alternatively, inhibitors of LTB_4 synthesis (e.g. BAYx1005) produce a modest reduction in sputum LTB_4 concentrations,[46] although the clinical relevance of this result is still to be established.

Inhibiting cytokines and chemokines

There are a number of chemokines and cytokines that play important roles in mediating inflammation in COPD, and are therefore potential therapeutic targets. For example, IL-8 recruits and activates neutrophils via the chemokine receptors CXCR1 and CXCR2, and it can be inhibited by the small-molecule CXCR1/CXCR2 antagonist, reparaxin.[47] In addition, CXCR2-specific antagonists, such as SB 225002, block the CXCR2 receptor which is required for the recruitment of neutrophils.[44]

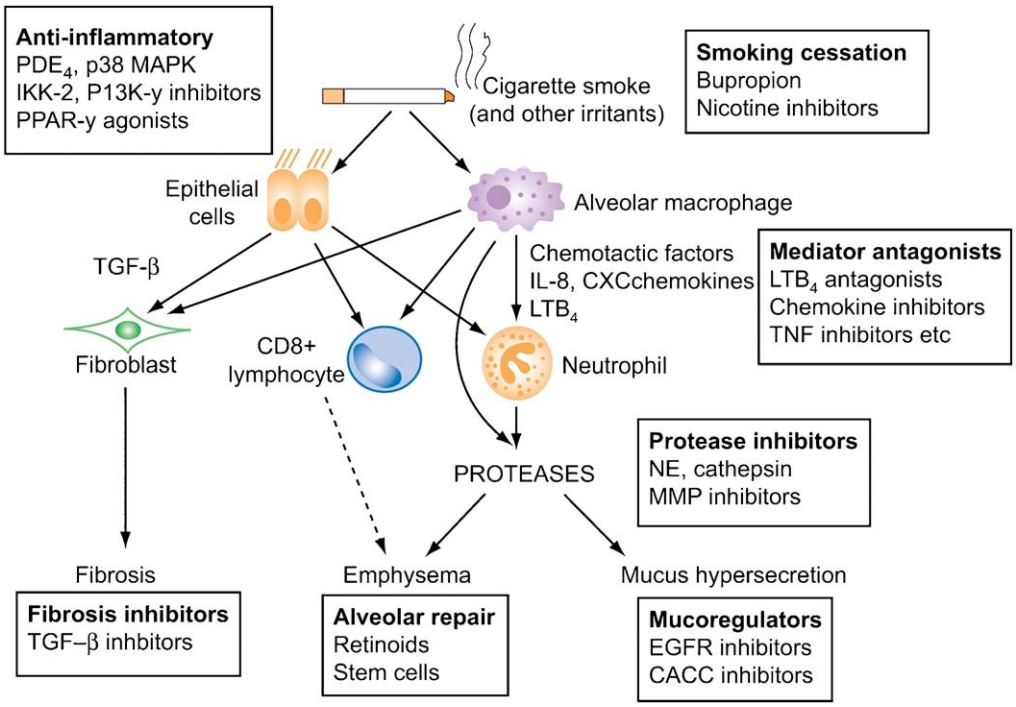

Figure 2 Components of inflammatory pathways with potential as therapeutic targets in COPD.[40,41]

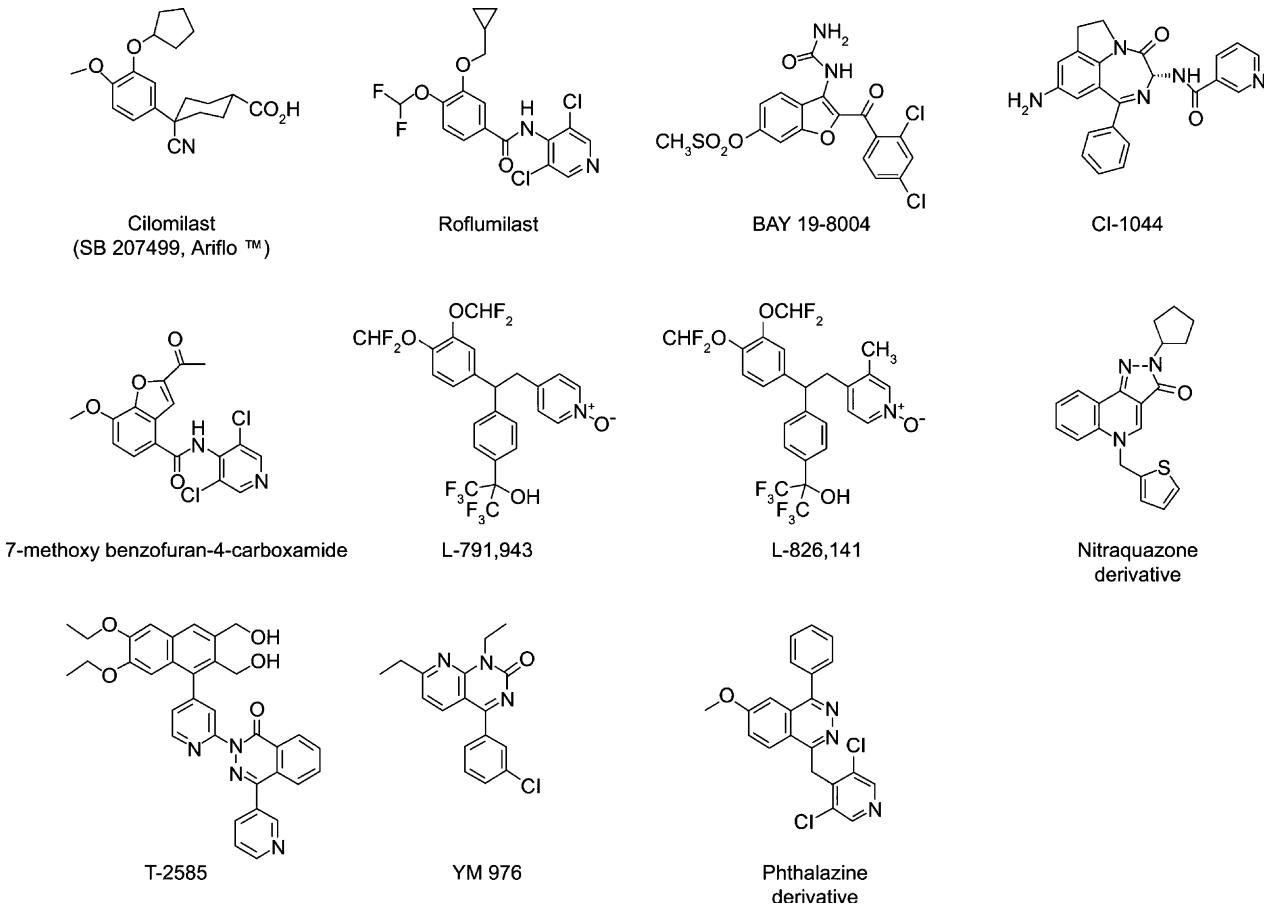

Figure 3 The next generation of phosphodiesterase-4 inhibitors.[42]

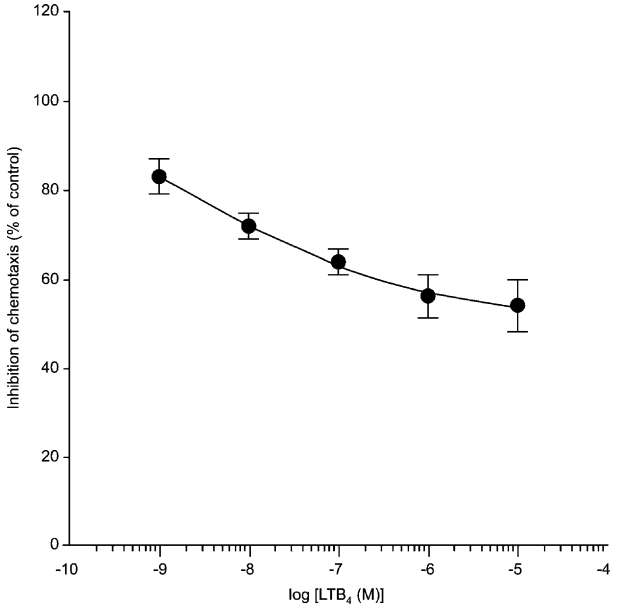

Figure 4 Effect of a leukotriene B_4 (LTB_4) receptor antagonist, SB 201146, on sputum-induced neutrophil chemotaxis.[46]

An alternative means of intercepting the IL-8 pathway is to use a human anti-IL-8 monoclonal antibody. However, chemokine pathways exhibit a degree of redundancy, so inhibiting any one element may not be effective. Thus Beeh et al.[45] investigated the effect of combining an anti-IL-8 antibody with an LTB_4 antagonist, and found that the combined effect was not significantly greater than the effect of either single agent alone.

A further addition to the list of therapeutic targets is TNF-α, which induces IL-8 via nuclear factor-kappa B (NF-κB). The use of humanised monoclonal antibodies (infliximab) and soluble TNF-α receptors (etanercept) is currently being investigated.[44] In addition, the direct inhibition of NF-κB is another means of intercepting the cytokines and chemokines involved in COPD. The p38 mitogen-associated protein kinase pathway, which also regulates the expression of inflammatory cytokines, is a further potential target for the development of small-molecular inhibitors, such as SB 239063, which has demonstrated anti-inflammatory activity in animal models.[48]

COPD: new treatment perspectives

Central to the pathogenesis of COPD, and in addition to inflammation, is the imbalance in the lung between endogenous proteinases and antiproteinases, and the production of oxidative stress. The use of *N*-acetylcysteine (NAC), to provide intracellular cysteine for the production of the endogenous antioxidant, glutathione, is one of several treatment options under investigation. Initial research suggests that oral NAC reduces the number of exacerbations in COPD[49,50] but a more recent randomised controlled trial failed to show that the addition of NAC, to treatment with corticosteroids and bronchodilators, can modify the outcome in acute exacerbations of COPD.[51]

In terms of restoring the balance between proteases and protease inhibitors in COPD, the development of small-molecular inhibitors of proteinases, especially those which show elastolytic activity, is a promising area.

Long-term oxygen therapy (LTOT)

Rationale

Supplemental oxygen therapy is the only existing approach shown to modify the long-term decline in lung function that is associated with COPD—no pharmacological treatment has so far demonstrated this ability. LTOT has also been associated with a variety of other benefits in patients with severe COPD, including increased survival,[52] reduced secondary polycythaemia, improved cardiac function during rest and exercise,[53] reduction in the oxygen cost of ventilation[54] and improved exercise tolerance.[55] Of particular note are the results of a longitudinal study showing that LTOT significantly improved HRQoL at 2 and 6 months, compared with a progressive decline in HRQoL in the non-LTOT group. In the LTOT group, 67% and 68% of patients (at 2 and 6 months, respectively) showed a clinically significant improvement in their chronic respiratory questionnaire scores.[49] Hence there is a convincing rationale for including LTOT in the treatment paradigm for patients with severe COPD.

Candidate patients for LTOT

Patients with $PaO_2 < 7.3$ kPa (55 mmHg; corresponding to $SaO_2 < 88\%$) whose disease is stable despite receiving otherwise comprehensive medical treatment, should receive LTOT. A patient whose PaO_2 is 7.3–7.8 kPa (55–59 mmHg; SaO_2 89%) should receive LTOT if they show signs of pulmonary hypertension, *cor pulmonale*, erythrocytosis, oedema from right heart failure or impaired mental state. If oxygen desaturation only occurs during exercise or sleep, then oxygen therapy should be considered specifically under those conditions. An optimal medical regimen can be established incorporating these guidelines (Fig. 5),[2] with the chief aim of achieving optimised ventilation:perfusion ratio matching (V'/Q) as a means of correcting hypoxaemia.

Oxygen therapy during sleep

COPD patients undergo episodes of O_2 desaturation of arterial blood during rapid eye movement sleep. Fletcher et al.[56] revealed that these desaturations occur both in non-hypoxaemic patients, and in patients who are hypoxaemic during the day. Further research by Plywaczewski et al.[57] showed that 47.6% of COPD patients treated with LTOT spent $>30\%$ of the night with an SaO_2 of $<90\%$, and thus required increased oxygen flow during sleep. The administration of oxygen at a flow rate higher than the daytime setting usually corrects nocturnal hypoxaemia.

Conflicting evidence surrounds the contention that patients who only desaturate during sleep will benefit from nocturnal oxygen treatment. Kimura et al. reported increased mortality among patients with nocturnal desaturation and daytime $PaO_2 \geqslant 8$ kPa (60 mmHg).[58] But while Fletcher et al.[56] found a beneficial effect of supplemental oxygen treatment in this patient group, other well-controlled studies have not shown that the use of nocturnal supplemental oxygen alters mortality or clinical course, other than slightly lowering pulmonary artery pressure.[59]

Oxygen therapy during exercise

Oxygen therapy during exercise decreases dyspnoea and improves exercise tolerance at submaximal exertion. The mechanical rationale underlying this observation is a decrease in dynamic hyperinflation, and reduced ventilatory drive.[55] LTOT is prescribed for patients who become more hypoxaemic during exercise, or who only become hypoxaemic during exercise, with oxygen settings determined while the patient is undergoing a typical level of exertion. Studies evaluating the long-term benefit of oxygen treatment solely for exercise have yet to be conducted.

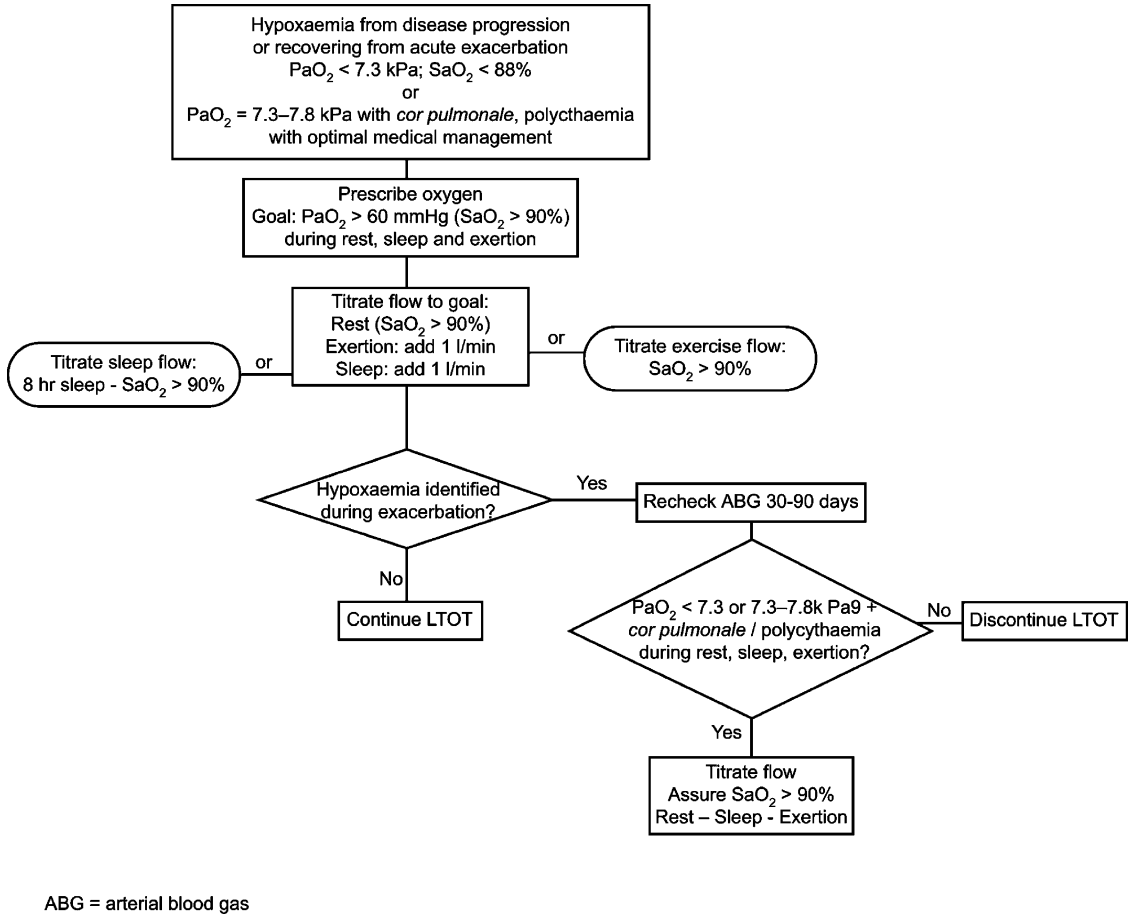

Figure 5 Algorithm for long-term oxygen therapy (LTOT).[2]

LTOT: cause for concern?

Carbon dioxide retention

Although LTOT may lead to hypercapnia with resulting respiratory acidosis,[60] this can usually be minimised by titrating the oxygen flow to maintain the PaO_2 at 8.0–8.6 kPa (60–65 mmHg). In fact, many patients with COPD have chronic CO_2 retention but because they have intact renal systems, they are able to maintain their pH within the normal range.

Patient education and compliance

A more immediate obstacle for successful LTOT administration is patient compliance. The mean number of oxygen breathing hours actually completed by patients may be fewer than prescribed, perhaps due to deficiencies in the practical implementation or understanding of the condition. Social barriers and psychological fears also play an important role. Increasing patient education is therefore a key challenge for the future. International agreement on the prescription of LTOT, selecting appropriate candidates and individualising oxygen prescriptions should establish clear understanding of treatment by both patients and clinicians.

Noninvasive ventilation

Introducing nasal positive pressure ventilation (nPPV)

Mechanical ventilation increases or substitutes for an individual's spontaneous respiration, as in the case of acute respiratory or ventilatory pump failure. Non-invasive ventilation, for example, intermittent negative pressure ventilation (INPV) or nPPV, have recently re-emerged as popular options that avoid the risks associated with invasive ventilation. nPPV is thought to assist ventilation, by improving inspiratory flow rate and correcting hypoventilation. Other possible mechanisms of action include resting respiratory muscles and resetting the central respiratory drive. In the

following section, the use of non-invasive ventilation in stable, chronically hypercapnic COPD patients will be examined.

Physiological endpoints revisited

In contrast to the evidence supporting the use of nPPV to tackle other causes of chronic respiratory failure, there is conflicting evidence regarding the benefits of nPPV in COPD.[61] Ambrosino et al.[62] presented evidence that nPPV corrects hypoventilation in patients with severe stable COPD and chronic hypercapnia ($n = 8$). In a study by Meecham-Jones et al.,[63] nocturnal and daytime gas exchange, total sleep time and QoL significantly improved with oxygen plus nPPV, compared with oxygen alone. Indeed, the level of improvement in daytime $PaCO_2$ correlated with the level of improvement in mean overnight $PaCO_2$ ($R = 0.69$, $P = 0.01$). Taken together, these studies provide support for the idea that non-invasive ventilation, and nPPV in particular, may be a useful addition to the treatment armoury for chronic hypercapnic COPD.

Randomised trials: conflicting results

Do randomised clinical trials of non-invasive ventilation support the use of this treatment modality? Results for INPV are unconvincing. In a 12-week double-blind study of 184 patients with severe COPD, no significant difference was observed in 6-min walk test results, cycle endurance time, severity of dyspnoea, HRQoL, respiratory muscle strength or arterial blood gas compared with sham treatment.[64] This suggests that inspiratory muscle rest has no benefits for patients with severe stable COPD, although poor patient compliance may have contributed to the results.

Regarding the administration of nPPV in patients with severe COPD, two 3-month crossover trials of similar design came to different conclusions. Strumpf et al.[65] found no improvement in physiological outcomes ($N = 19$). In contrast to this result is the study by Meecham-Jones et al.[63] mentioned in the previous section, in which nocturnal and daytime gas exchange, total sleep time and QoL significantly improved with oxygen plus nPPV ($N = 18$). The discrepancy between these results may be explained by the difference between patient sets at baseline: patients with greater CO_2 retention and more frequent nocturnal oxygen desaturations may benefit more from nPPV administration.

Unfortunately, this neat solution is not supported by subsequent trials. Despite efforts to recruit hypercapnic patients with severe COPD, Gay et al.[66] found no significant improvements in gas exchange, lung function or sleep quality compared with the sham group. A recent 1-year study was unable to demonstrate a beneficial effect of nocturnal nPPV in addition to LTOT in a similar patient group.[67]

In addition to these conflicting data on physiological endpoints is a lack of data showing whether nPPV treatment actually improves survival rates. Therefore, it appears that larger studies with greater statistical power are required, along with follow-up data on morbidity and mortality.

nPPV in COPD—bigger trials, better results?

Two large, multicentre trials have focused on nPPV in patients with severe hypercapnic COPD. One trial published as an abstract by Muir et al., which compared home nPPV plus LTOT with LTOT alone, indicates that there is no overall survival benefit in patients receiving nPPV plus LTOT, although there may be a slight improvement in survival for patients over 65.[68] A 2-year Italian multicentre study also examined the effects of nPPV plus LTOT compared with LTOT alone ($N = 122$). In this trial, nPPV plus LTOT improved $PaCO_2$ during breathing of the usual oxygen inspiratory fraction. Long-term improvements were also noted in dyspnoea and HRQoL in the nPPV plus LTOT group, but survival was similar between treatment groups.[69]

Currently, there is little evidence for the use of mechanical ventilatory support in the routine management of COPD. However, further large studies may be able to identify subsets of patients for whom nPPV would be beneficial.

LVRS for emphysema

Current understanding of LVRS

LVRS was originally proposed as a palliative treatment for patients with severe emphysema. The rationale for LVRS is based on the premise that these patients have severe hyperinflation and the goal of surgery is to remove functionally useless emphysematous lung. Generally, this involves the removal of 25–30% of lung tissue from both the left and the right sides. Benefits associated with LVRS are improved lung function (reduced lung volume and increased FEV_1) and exercise (including the distance walked in 6 min).[70] Although carefully

selected patients benefit from LVRS, questions remain concerning the magnitude and duration of positive outcome.

The National Emphysema Treatment Trial (NETT)

The NETT was a multicentre, randomised, large-scale clinical trial ($N = 1218$) to evaluate the effects of LVRS.[71] Eligible patients ($FEV_1 < 45\%$ predicted and bilateral emphysema) underwent a period of medical therapy plus pulmonary rehabilitation. After this period, patients were randomised to receive either LVRS ($n = 608$) or continue medical therapy ($n = 610$), with a mean follow-up time of 29 months. The two primary outcomes measured were survival and maximum exercise capacity 2 years after randomisation. Of note was the early identification of a subgroup of patients who suffered a high 30-day mortality rate and showed little benefit after LVRS. These patients exhibited an $FEV_1 \leqslant 20\%$ of predicted and either a homogenous distribution of emphysema or a carbon monoxide diffusion capacity $< 20\%$ of predicted.[72]

NETT results

Overall results from the NETT at 2-years post-randomisation indicate that LVRS improves exercise capacity, but does not improve survival compared with medical therapy. Patients in the LVRS group also reported improved health status and less dyspnoea compared with the medical group. Subgroup analyses showed that patients with upper-lobe predominant emphysema and low exercise capacity had improved survival with LVRS, compared with medical therapy; those patients with mainly non-upper-lobe emphysema and high exercise capacity showed reduced survival.[71] From these results, two key outcome predictors can be identified: distribution of emphysema and exercise capacity following pulmonary rehabilitation. Combined with the factors placing patients at high risk for LVRS, these predictors allow more targeted patient selection than was previously possible (Fig. 6).[71]

Future directions for LVRS research

Key questions remaining concern the role of pre-operative pulmonary rehabilitation, the mechanisms by which LVRS improves lung function and survival, and the impact of different surgical techniques on LVRS outcomes. The identification of long-term predictors of LVRS outcomes would be a welcome development, while investigating unilateral or repeated LVRS, as well as non-invasive

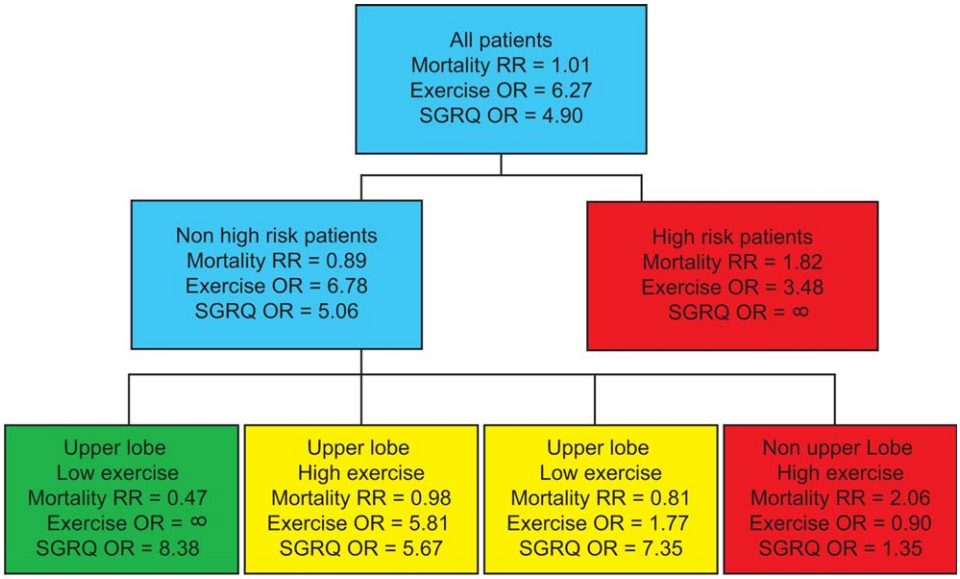

Figure 6 Algorithm for lung-volume-reduction surgery (LVRS) patient selection based on the National Emphysema Treatment Trial results and independent outcome predictors.[71] Patients with predominately upper lobe emphysema and lower exercise performance had substantially improved outcomes from LVRS, while those with predominately non-upper lobe emphysema and higher levels of exercise performance had poorer outcomes from this procedure.

techniques to reduce lung volume, may prove successful in the future.

Conclusions

Much recent progress has been made in the management of COPD, but there are still many outstanding questions to be resolved. There is an impetus to evaluate combination therapies, novel drugs such as PDE_4 and LTB_4 inhibitors, LTOT and LVRS and learn whether they will have a role in shaping future developments in patient-specific therapy. It is hoped that this momentum will be maintained and that, in years to come, COPD management will combine pharmacological and non-pharmacological therapies to drive and refine treatment algorithms for the individual patient with COPD.

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