Tidsskriftet Tidsskrift for Den norske legeforening

COPD – can we reduce mortality with drugs?

PERSPECTIVES

PER SIGVALD BAKKE

per.bakke@uib.no
Per Sigvald Bakke, specialist in respiratory medicine and internal medicine, and professor and dean of the Faculty of Medicine at the University of Bergen. He has conducted clinical and epidemiological studies into COPD.
The author has completed the ICMJE form and declares the following conflicts of interest: He has received lecture fees from AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline, and he has received consultancy fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols and Sanofi.

KRISTIAN JONG HØINES

Kristian Jong Høines, specialist in general practice medicine and general practitioner at Tananger Medical Centre. He is the head of the general practitioner network Respiratory Medicine in Practice.
The author has completed the ICMJE form and declares the following conflicts of interest: He has received lecture fees from AstraZeneca, Chiesi and GlaxoSmithKline, and he has held positions at AstraZeneca and GlaxoSmithKline.

FRODE GALLEFOSS

Frode Gallefoss, specialist in respiratory medicine and internal medicine. He has been the research director at Sørlandet Hospital and professor of respiratory medicine at the University of Bergen. He has conducted clinical studies into asthma and COPD.
The author has completed the ICMJE form and declares the following conflicts of interest: He has received payment for lectures at meetings arranged by AstraZeneca in the past 36 months, and he is a member of the DSMB in the Colonize study.

New studies of patients with chronic obstructive pulmonary disease (COPD) indicate that, for the first time, we can now influence the mortality of the disease with drugs. We present these studies and place them in context.

The main regular pharmacological treatment of chronic obstructive pulmonary disease (COPD) has for many years been inhalation therapy with long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA) and inhaled corticosteroids (ICS). The pharmacological treatment of COPD was previously determined by the degree of obstruction on spirometry (1), but now the severity of symptoms and frequency of moderate or severe exacerbations determine the recommended composition of this pharmacological treatment (2).

For several decades, the thinking has been that the pharmacological treatment of COPD could relieve patients' symptoms but not influence disease mortality. However, in recent years, results have been published indicating that it is now also possible to improve COPD survival rates with pharmacological treatment. The aim of this article is to present these new studies and to discuss the mechanisms that mark the dawn of a new era in COPD treatment. Finally, we will comment on whether the guidelines on the treatment and follow-up of this patient group should be revised.

COPD mortality

Approximately 2,300 people die of COPD in Norway each year (3). Increasing respiratory symptoms, cough, mucus and decreasing lung function measured using forced expiratory volume in one second (FEV1) as a percentage of the predicted value, increase the mortality of COPD. Severe exacerbations with hospitalisation are associated with a mortality rate of 20–25 % within one year. (3). The corresponding figure following myocardial infarction is approximately 3 % (4). Moderate COPD exacerbations are also associated with increased mortality (5).

The effect of LAMA and ICS monotherapy on mortality has been investigated in several studies, but objections can be raised to several of these studies in that they either did not have mortality as the primary endpoint (6, 7) or that the studies had a retrospective design (4). As far as we know, a mortality-reducing effect of LABA alone has not been studied in subjects with COPD. The combination of two of the aforementioned drugs has been studied, with no significant effect on mortality being found (5).

Recent studies

In recent years, there have been studies into the combination of all three types of drugs, which is referred to as triple therapy (ICS/LABA/LAMA). Two studies have randomised 10,400 and 8,500 subjects, respectively, with COPD and a medical history of exacerbations in the past 12 months to triple therapy, ICS/LABA or LABA/LAMA (8, 9) (Table 1). The patients were followed up for 52 weeks. In both studies, patients who received triple therapy had significantly lower all-cause mortality than those who received LABA/LAMA therapy. The annual relative/absolute risk reduction in mortality was 28 %/0.83 % and 49 %/1.24 % for the triple therapy group compared to the LABA/LAMA group in the IMPACT (8) and ETHOS studies respectively (9). The triple therapy group also had lower all-cause mortality than the group that received LABA/ICS, but the differences were not statistically significant in either study. One of the studies included two groups receiving triple therapy with differing strengths of the ICS component (9). The group with the highest ICS dose had the lowest mortality, with the difference being statistically significant.

Table 1

Key features of two studies (IMPACT and ETHOS) that investigated the effect of pharmacological treatment on COPD mortality.

	IMPACT	ETHOS
Study design	Prospective randomised	Prospective randomised
Number of participants	10,355	8,588
Inclusion criteria		
Age (years)	≥ 40	≥ 40
CAT score	≥ 10	≥ 10
FEV1 and exacerbations	FEV1 <50 % and ≥ 1 moderate to severe exacerbation	FEV1 <50 % and ≥ 1 moderate to severe exacerbation
	or	*or*
	50 % < FEV1 < 80 % and ≥ 1 severe exacerbation	50 % < FEV1 <65 % and ≥ 1 severe exacerbation
	or ≥ 2 moderate exacerbations	or ≥ 2 moderate exacerbations
Treatment arms	1. ICS (FF) + LAMA (UMEC) + LABA (VI)	1. ICS (BUD320µg) + LAMA (GLY) + LABA (FOR)
	2. ICS (FF) + LABA (VI)	2. ICS (BUD160µg) + LAMA (GLY) + LABA (FOR)
	3. LAMA (UMEC) + LABA (VI)	3. ICS (BUD320µg) + LABA (FOR)

	IMPACT	ETHOS
		4. LAMA (GLY) + LABA (FOR)
Patient characteristics on inclusion		
Mean age, SD, (years)	65 (8)	65 (8)
FEV1, % predicted, SD	46 (15)	43 (10)
Follow-up period (weeks)	52	52

CAT: COPD Assessment Test; FEV1: forced expiratory volume in one second; ICS: inhaled corticosteroids; FF: fluticasone furoate; LAMA: long-acting muscarinic antagonist; UMEC: umeclidinium; LABA: long-acting beta-2 agonist; VI: vilanterol; BUD: budesonide; GLY: glycopyrrolate; FOR: formoterol

Both studies were designed with mortality as a secondary endpoint. The reduced mortality in both studies was attributed to a reduction in mortality caused by cardiovascular and respiratory death.

> ***«For the first time we now have two large prospective studies which have demonstrated, independently of each other, that triple therapy significantly reduces the mortality of the disease»***

Discussion

Even though several previous studies have indicated that disease course and mortality of COPD can be improved with pharmacological treatment, for the first time we now have two large prospective studies which have demonstrated, independently of each other, that triple therapy significantly reduces the mortality of the disease. Some people have been critical of these findings and pointed out that mortality was not the primary endpoint. Another criticism has been that the ETHOS study was designed to demonstrate an effect of triple therapy on COPD mortality since 70–80 % of patients who were randomised to the LABA/LAMA arms had ICS discontinued on inclusion, which could increase the risk of exacerbations and death (10). However, other people have pointed out that the reduced mortality in the group receiving triple therapy compared to the group receiving LABA/LAMA was maintained throughout the study, and thus could not be attributed to discontinuation of ICS in the LABA/LAMA arm (11, 12). New long-term studies (at least three years) with mortality as the primary endpoint are required to get a definitive answer as to whether triple therapy improves COPD mortality.

«New long-term studies with mortality as the primary endpoint are required to get a definitive answer as to whether triple therapy improves COPD mortality»

What might be the mechanism resulting in the reduced mortality? The fact that mortality in the group receiving triple therapy is almost the same as that in the group receiving ICS/LABA may indicate that the reduced mortality is related to ICS. Such an association is supported by a dose-response relationship between increased ICS dose and reduced mortality in one of these two studies. Chronic inflammation plays a key role in both stable COPD and COPD exacerbations, and it is also a contributory factor in several of the typical COPD-related comorbidities (13). It is likely that treatment with ICS acts via various mechanisms. It has been demonstrated that ICS treatment lowers serum CRP levels, indicating decreased systemic inflammation, which may in turn contribute to reduced mortality. ICS may also lead to decreased cardiovascular inflammation. This is consistent with the reduction in death from cardiovascular disease in particular, which resulted in improved survival in the group receiving triple therapy in the IMPACT and ETHOS studies (8, 9). It is also likely that ICS treatment may contribute to a reduction in the frequency of exacerbations. The primary endpoint in both these studies (8, 9) was the incidence of COPD exacerbations, and the groups receiving triple therapy had the lowest rate of exacerbations, with the difference being significant.

«Does this mean that all COPD patients should receive triple therapy?»

It can also be argued that the reduced mortality in the triple therapy group may be due to an interaction between the ICS treatment and the two bronchodilators (LABA and LAMA). The synergistic effect of ICS and LABA in the same inhaler is well-known. Increased bronchodilation can contribute to a reduction in hyperinflation and the tendency to pulmonary hypertension, which in turn can contribute to reduced right ventricular load. In addition, it has been pointed out that LABA and LAMA also have an anti-inflammatory effect (14).

Does this mean that all COPD patients should receive triple therapy? No, it does not. The latest guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2) recommend that triple therapy should be reserved for patients with two or more moderate exacerbations or one or more severe exacerbations in the last 12 months as well as a blood eosinophil count above 300 U/L, irrespective of symptom score and lung function. Patients with the aforementioned exacerbations but a blood eosinophil count below 300 U/L should receive a LABA/LAMA combination first of all, and if the patient does not improve with this treatment, triple therapy can then be tried. Patients with a history of asthma should always receive triple therapy.

These recommendations are less restrictive as regards the use of triple therapy than those of the Norwegian Directorate of Health (15), which states that the indication for inhaled steroids has been tightened to reduce overuse (15).

Several studies have demonstrated that ICS increases the risk of pneumonia caused by streptococci and *Haemophilus influenzae* in COPD patients (16, 17). However, ICS also protects against exacerbations, and this protection outweighs the risk of pneumonia. Compared with LABA/LAMA, three COPD patients must receive triple therapy for 12 months to prevent a moderate or severe exacerbation (number needed to treat (NNT) = 3). For one person to experience treatment-related pneumonia, 58 patients must receive triple therapy instead of LABA/LAMA for 12 months (number needed to harm (NNH) = 58) (18). Whilst we agree with the Norwegian Directorate of Health that there is overuse of ICS among COPD patients, we nevertheless support the GOLD recommendations regarding ICS described above, rather than those of the Norwegian Directorate of Health.

For many years, there has been a stigma attached to COPD, with it being said that patients are to blame for their disease since it has been self-inflicted by smoking (19). Other than asking the patient to stop smoking, there was little that could influence survival. Pharmacological treatment has been symptomatic up to now and had little effect on the course of the disease. This perception of the disease is undeserved. As the prevalence of smoking decreases, the relative significance of other risk factors will increase, for example occupational exposure, air pollution, poor indoor environment and hereditary factors. We hope that this will help to improve the current image of the disease.

A recent article in the Journal of the Swedish Medical Association (20) points out that the potential impact on COPD mortality that can be achieved by pharmacological treatment is now actually of the same order of magnitude as that which can be achieved in cardiovascular disease by means of statins and antihypertensive drugs.

Conclusion

There are now two prospective randomised studies indicating that the survival of COPD patients can be improved with combination products containing inhaled corticosteroids. The mechanism may involve reduced systemic inflammation, reduced cardiovascular inflammation and/or a reduced risk of exacerbations. This does not mean that all COPD patients should receive triple therapy. It should be reserved for COPD patients with a history of asthma, frequent exacerbations and patients with a blood eosinophil count > 300 U/L. It is to be hoped that the image of COPD will improve in the future with the reduced relative significance of smoking in the incidence of COPD, as well as the increased options to potentially influence the course of the disease and its mortality.

REFERENCES

1. Bakke PS, Høines KJ. Legemidler mot kols. Tidsskr Nor Legeforen 2019; 139. doi: 10.4045/tidsskr.19.0181. [PubMed][CrossRef]

2. Global Initiative for Chronic Obstructive Lung Disease. 2024 GOLD Report. https://goldcopd.org/2024-gold-report/ Accessed 21.10.2024.

3. Strøm MS, Sveen KA, Raknes G et al. Dødsårsaksregisteret. Dødsårsaker i Norge 2022. https://www.fhi.no/contentassets/63e48530e2094601b0e4dab313001f60/dodsarsaker-i-norge-rev-2.pdf Accessed 21.10.2024.

4. Manoharan A, Short PM, Anderson WJ et al. Impact of long-acting bronchodilators and exposure to inhaled corticosteroids on mortality in COPD: a real-life retrospective cohort study. Lung 2014; 192: 649–52. [PubMed][CrossRef]

5. TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007; 356: 775–89. [PubMed][CrossRef]

6. Burge PS, Calverley PM, Jones PW et al. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000; 320: 1297–303. [PubMed][CrossRef]

7. UPLIFT Study Investigators. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009; 180: 948–55. [PubMed][CrossRef]

8. Lipson DA, Crim C, Criner GJ et al. Reduction in all-cause mortality with fluticasone furoate/ umeclidinium/ vilanterol in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2020; 201: 1508–16. [PubMed][CrossRef]

9. Martinez FJ, Rabe KF, Ferguson GT et al. Reduced all-cause mortality in the ETHOS trial of budesonide/glycopyrrolate/ formoterol for chronic obstructive pulmonary disease. A randomized, double blind, multicenter, parallel-group study. Am J Respir Crit Care Med 2021; 203: 553–64. [PubMed][CrossRef]

10. Soumagne T, Zysman M, Karadogan D et al. Impact of triple therapy on mortality in COPD. Breathe (Sheff) 2023; 19. doi: 10.1183/20734735.0260-2022. [PubMed][CrossRef]

11. Calverley P. Reigniting the TORCH: Chronic Obstructive Pulmonary Disease Mortality and Inhaled Corticosteroids Revisited. Am J Respir Crit Care Med 2021; 203: 531–2. [PubMed][CrossRef]

12. Han MK, Lipson DA, Singh D et al. One More Time: The Impact of Inhaled Corticosteroid Withdrawal on IMPACT. Am J Respir Crit Care Med 2020; 202: 1205–6. [PubMed][CrossRef]

13. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009; 33: 1165–85. [PubMed][CrossRef]

14. Beeh KM, Burgel PR, Franssen FME et al. How do dual long-acting bronchodilators prevent exacerbations of chronic obstructive pulmonary disease? Am J Respir Crit Care Med 2017; 196: 139–49. [PubMed][CrossRef]

15. Helsedirektoratet. Oppdatert nasjonal retningslinje for kols (2019), siste faglige endring 4.5.2022. Innholdet er arkivert. https://www.helsedirektoratet.no/om-oss/om-nettstedet/innholdet-er-arkivert Accessed 16.11.2024.

16. Heerfordt CK, Eklöf J, Sivapalan P et al. Inhaled corticosteroids in patients with chronic obstructive pulmonary disease and risk of acquiring streptococcus pneumoniae infection. A multiregional epidemiological study. Int J Chron Obstruct Pulmon Dis 2023; 18: 373–84. [PubMed][CrossRef]

17. Johnsen RH, Heerfordt CK, Boel JB et al. Inhaled corticosteroids and risk of lower respiratory tract infection with Moraxella catarrhalis in patients with chronic obstructive pulmonary disease. BMJ Open Respir Res 2023; 10. doi: 10.1136/bmjresp-2023-001726. [PubMed][CrossRef]

18. Rabe K, Martinez F, Ferguson G. COPD exacerbation benefits relative to pneumonia risk with budesonide/glycopyrronium/ formoterol metered dose inhaler: analyses from ETHOS. Eur Respir J 2020; 56 (Suppl 64): 5230.

19. Madawala S, Osadnik CR, Warren N et al. Healthcare experiences of adults with COPD across community care settings: a meta-ethnography. ERJ Open Res 2023; 9: 00581–02022. [PubMed][CrossRef]

20. Larsson K, Lindberg A, Sandelowsky H et al. Behandling med läkemedel kan reducera mortaliteten vid KOL. Lakartidningen 2022; 119: 21155. [PubMed]

Publisert: 2 December 2024. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.24.0370
Received 30.6.2024, first revision submitted 2.9.2024, accepted 21.10.2024.