REVIEW ARTICLE

The Pharmacological Treatment of Chronic Obstructive Pulmonary Disease

Adrian Gillissen, Peter Haidl, Martin Kohlhäufl, Klaus Kroegel, Thomas Voshaar, Christian Gessner

SUMMARY

Background: Inhaled corticosteroids (ICS) are markedly less effective against chronic obstructive pulmonary disease (COPD) than against asthma, and also have worse side effects. Whether ICS should be used to treat COPD is currently a matter of debate.

Methods: This review is based on pertinent articles retrieved by a selective search in PubMed and the Excerpta Medica Database (EMBASE) carried out in May 2015. We analyzed clinical trials of ICS for the treatment of COPD with a duration of at least one year, along with meta-analyses and COPD guidelines.

Results: ICS lower the frequency and severity of COPD exacerbations in comparison to monotherapy with a long-acting β_2-agonist, but have no effect on mortality. Compared to placebo, ICS monotherapy lessens the decline of forced expiratory volume in one second (FEV_1) over one year by merely 5.80 mL (statistically insignificant; 95% confidence interval: [–0.28; 11.88]) and only marginally improve quality of life. ICS use in patients with COPD increases the risk of pneumonia. A combination of ICS with a long-acting bronchodilator improves FEV_1 by 133 mL [105; 161] and lowers the frequency of severe exacerbations by 39%. The frequency of exacerbations is lowered mainly in patients who have many exacerbations; thus, ICS treatment is suitable only for patients with grade III or IV COPD.

Conclusion: ICS monotherapy has no clinically useful effect on pulmonary function in COPD. The main form of drug treatment for COPD is with bronchodilators, either alone or in combination with ICS. ICS can be given to patients with grade III or IV COPD to make exacerbations less frequent. Patients with an asthma–COPD overlap syndrome (ACOS) can benefit from ICS treatment.

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Department of Pulmonary Medicine, Kassel General Hospital: Prof. Dr. med. Gillissen M.Sc.

Fachkrankenhaus Kloster Grafschaft, Schmallenberg: Dr. med. Haidl

Klinik Schillerhöhe, Stuttgart: Prof. Dr. med. Kohlhäufl

Department of Internal Medicine I: Pneumology & Allergology/Immunology, Friedrich Schiller University Jena: Prof. Dr. med. Dr. rer. nat. Kroegel

Department of Pneumology and Allergy, Medical Clinic III, Bethanien Hospital Moers: Dr. med. Voshaar

Department of Pneumology, University of Leipzig: PD Dr. med. Gessner

Inhaled corticosteroids (ICS) are less clinically effective in chronic obstructive pulmonary disease (COPD) than in asthma. In asthma, they inhibit the underlying bronchial inflammation, thus optimizing both lung function and the prognosis. In COPD, the improvement they bring in terms of forced expiratory volume (FEV_1), quality of life, and prognosis is much lower. Then there is the additional dilemma that, although ICS reduce exacerbation frequency in COPD, they do not influence mortality. For this reason, the decision to use ICS in patients with COPD must be much more cautious and more carefully targeted, requiring very precise patient characterization, because their long-term use is associated with more unwanted effects than in asthma. The following drugs are licensed for treatment of COPD: beclomethasone dipropionate, budesonide, and fluticasone propionate/fluticasone furoate. In COPD—again in contrast to asthma—ICS are used only in combination with at least one long-acting bronchodilator, usually a long-acting β_2-agonist (LABA) (1). Unfortunately, in practice ICS are prescribed too often in COPD: 38.9% of all COPD patients (n = 334 out of a total of n = 859) with stage I–II disease in a London cohort received ICS as monotherapy or in combination therapy, against guideline recommendations (2). For the present review, PubMed and the Excerpta Medica Database (EMBASE) were selectively searched for randomized, controlled long-term studies evaluating the effect of ICS given to COPD patients for ≥ 1 year, alone or in combination. In addition, meta-analyses including Cochrane Reviews on particular topics were selectively included, as were review articles, 6-month studies, COPD guideline recommendations (Global Initiative for COPD [GOLD], and the recommendations of the German Respiratory Society/German Airway League (Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin/Deutsche Atemwegsliga). We provide an up-to-date overview of the efficacy of ICS and their limitations, and present a recommendation for their rational use in the treatment of COPD.

Features of the various therapeutic options

Monotherapy with inhaled corticosteroids

Large 6-month to 3-year studies of ICS as monotherapy in the 1990s produced variable results regarding the clinical efficacy of ICS (*eTable*).

TABLE

Characteristics of asthma and chronic obstructive pulmonary disease*

Characteristic	Probably asthma	Probably COPD
Patient age	Disease onset <20 years	Disease onset >40 years
Symptoms	Symptoms are very variable, occur at night or in the early morning, are worse on exertion or on exposure to specific and nonspecific triggers, and respond well to asthma medication	Symptoms persist without much variation; patient has good days and bad days, but always has symptoms, chronic productive cough, and dyspnea without an obvious trigger
Pulmonary function	Airway obstruction variable, responds well to asthma medication	Persistent airway obstruction
Pulmonary function between symptoms	Normal	Persistent airway obstruction and hyperinflation
Medical history	Personal or family history of asthma or allergies	Previous diagnosis of COPD or emphysema, long-term (years) inhalation exposure, usually to cigarette smoke
Chest X-ray	Normal	Signs of pulmonary hyperinflation

*Adapted from GOLD (1)
COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease

Apart from the TORCH study, carried out over 3 years, most of the large long-term COPD studies found that ICS monotherapy had little or no effect on lung function. Above all, whichever active ingredient was used, ICS monotherapy either failed to slow the accelerated annual decline in FEV_1 seen in this patient group or slowed it very little (3–6). The Cochrane Review, which included 55 studies involving over 16 000 patients, came to the sobering conclusion that, compared to placebo, and averaged over all the studies, an ICS-induced reduction in annual FEV_1 decline of only 5.80 mL/year (95% confidence interval: [–0.28; 11,88]) was achievable (e1). The main contributor to this effect was the TORCH study, which showed that FEV_1 declined by 42 mL/year with fluticasone (2 × 500 µg/day) versus 55 mL/year with placebo over a study period of 3 years. However, this study included a selected patient population that responded particularly well to ICS (7). In the ISOLDE study, at the end of 3 years, inhaled fluticasone reduced exacerbation frequency from 1.32 exacerbations/year to 0.99/year (p = 0.026) and improved health status compared to placebo as measured using the St. George Respiratory Questionnaire (SGRQ) (p = 0.0043) (5).

In conclusion, the clinical efficacy of ICS monotherapy on lung function is very small; clinically, it is insignificant.

Combination of inhaled corticosteroids with long-acting β_2-agonists

The *eTable* gives an overview of the most important ICS/LABA COPD studies that lasted for longer than 12 months and their results and limitations (*eTable*). TRISTAN was the first large study, investigating the effect of combined salmeterol (2 × 50 µg/day) and fluticasone (2 × 500 µg/day) in almost 1500 patients. In this study, at the end of 1 year FEV_1 had improved by 133 mL [105; 161] (p <0.0001) in comparison to placebo, by 73 mL [46; 101] (p <0.001) in comparison to salmeterol, and by 95 mL [67; 122] in comparison to fluticasone (p <0.0001). Severe exacerbations, treated with steroids, were reduced by 39% in the combination group (p <0.0001), 29% (p = 0.0003) in the salmeterol group, and 34% (p = 0.0001) in the fluticasone group. Health status (SGRQ) and symptom scores were also positively affected (8).

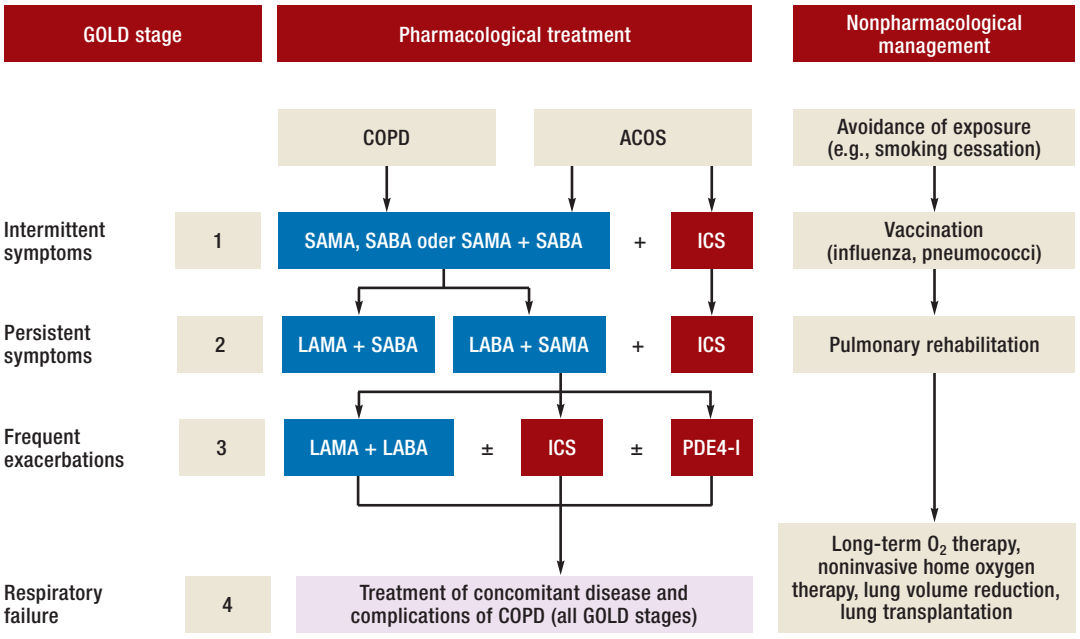
In the TORCH study, the fluticasone/salmeterol combination reduced the annual exacerbation frequency compared to placebo, from 1.13 to 0.85 exacerbations/year (p <0.001), but not compared to salmeterol monotherapy. This observation was exclusively a result of the salmeterol treatment, without any relevant additive effect from the ICS component. Mortality (primary outcome parameter) remained unaffected by the fluticasone/salmeterol combination (7). This is why the result of a similar study by Mahler et al. surprised no one, showing that fluticasone/salmeterol compared to placebo had no effect on time to first exacerbation (9).

Similar results came out of the long-term budesonide/formoterol studies. The combination of budesonide with formoterol reduced severe exacerbations by 23% [0.8; 40.1) compared to formoterol alone, by 11% [–15.9; 31.8] compared to budesonide alone, and by 24% [1.9; 41.4] compared to placebo. This study too included patients who responded particularly well to ICS. Accordingly, the pulmonary function values were better in the fixed combination arm than in either of the single-component arms (10). Comparison of combined meclometasone/formoterol versus formoterol alone produced a similar result (11). Combined fluticasone fuorate/vilanterol increased the time to next exacerbation in comparison to the single component arms, but the frequency of severe exacerbations did not change.

Compared to monotherapy with a long-acting β_2-agonist, additional administration of ICS resulted in a downward trend in the frequency of severe exacerbations, but not a significant reduction. However, the frequency of moderately severe exacerbations was reduced to 0.82/year [0.72; 0.92]. This allowed calculation of a number needed to treat (NNT) of 31 [20; 93] in order to prevent one exacerbation (12). Quality of life improved slightly (–1.88; 9% [–2.44; –1.33]), although without reaching the clinically relevant threshold of –4 points (13).

It may be concluded that, compared with the single components and with placebo, despite some differences in the study comparisons, and depending on the various components used, the ICS/LABA combination mainly

FIGURE



Pharmacological and nonpharmacological management of COPD

ACOS, asthma–COPD overlap syndrome; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LAMA, long-acting anticholinergic; LABA, long-acting ß$_2$-agonist; PDE4-I, phosphodiesterase-4 inhibitor; SAMA, short-acting muscarinic receptor antagonist; SABA, short-acting ß$_2$-agonist

reduced exacerbation frequency in patients with frequent exacerbations. This would suggest that ICS are only suitable for patients with grade III and IV COPD who have a higher frequency of exacerbations.

Combination of inhaled corticosteroid with long-acting ß$_2$-agonists and anticholinergics

The value of triple therapy with a combination of ICS, LABA, and a long-acting anticholinergic (LAMA, long-acting muscarinic receptor antagonist)—an important question for clinical practice—was investigated in a meta-analysis of seven studies by Kwak et al. (14). This showed that triple therapy is clinically more effective than monotherapy with tiotropium: FEV_1 improved, by 63.68 mL [45.29; 82.73], and so did quality of life (SGRQ), by –3.11 points [–6.0; –8.0]. In a 12-week study, Welte et al. showed that triple therapy consisting of tiotropium plus budesonide/formoterol in patients with severe COPD (FEV_1 38% of normal) compared with tiotropium plus placebo raised predose FEV_1 by 6% and postdose FEV_1 by 11%. In addition, the number of severe exacerbations dropped by 62%. However, in regard to this last, the study was too short and had too few patients (n = 660) for this to have statistical significance for clinical practice (15).

The SUMMIT study, which ended in June 2015 and was reported on in an oral presentation at the annual conference of the European Respiratory Society 2015 in Amsterdam and via a press release (www.gsk.com/en-gb/media/press-releases/2015/gsk-and-theravance-announce-results-from-the-summit-copd-cv-survival-study), investigated whether the combination of fluticasone furoate (100 µg) and vilanterol (25 µg), compared to the individual components or placebo, reduced all-cause mortality in 16 000 COPD patients with increased cardiovascular risk after a treatment duration of 15–44 months. Mortality in the combination group was 12.2% lower than in the placebo group (p = 0.317). Annual FEV_1 decline in the combination group was reduced by 8 mL (p = 0.019).

In a case–control study based on a US veterans database, triple therapy with an ICS and an inhaled LABA together with tiotropium, compared to ICS/LABA, reduced mortality (hazard ratio [HR]: 0.60 [0.45; 0.79]). At the same time, this treatment reduced both the exacerbation risk (HR: 0.84 [0.73; 0.97]) and the risk of COPD-related hospitalization (HR: 0.78 [0.62; 0.98]) (16).

To conclude, the effects on lung function and exacerbation reduction when ICS are added to existing

LABA/LAMA therapy are small, and are clinically relevant only in the subpopulation of COPD patients at high risk of exacerbations.

Combination of inhaled corticosteroids with roflumilast

In the REACT study, giving roflumilast in addition to LABA/ICS combination therapy reduced exacerbation frequency (0.823/year with roflumilast versus 0.995 with placebo; p = 0.0424); about two-thirds of all study patients were also treated with tiotropium (triple therapy). Thus, dual anti-inflammatory treatment of this kind is clinically more effective in the patient subtype with frequent exacerbations (≥ 2/year) and symptoms of chronic bronchitis than is LABA/ICS therapy alone (17). However, unwanted gastrointestinal effects are frequent with roflumilast.

Inhaled corticosteroids in COPD with eosinophil-dominated inflammation

In a disease otherwise dominated by neutrophils, sputum eosinophil percentages are above 2% or higher in about 10% to 40% (18) or even up to 60% of all patients with frequent exacerbations (19). Blood eosinophil counts of ≥ 340 cells/μL are associated with a 1.76 times higher exacerbation rate (20). In patients with a blood eosinophil percentage of ≥ 2% (or 200 cells/μL or higher), vilanterol/fluticasone furoate in comparison with vilanterol reduced the annual exacerbation frequency by 29% (0.79 versus 0.89; p<0.0001). If the eosinophil percentage was ≥ 2% to <4%, the reduction was 32%; if the eosinophil percentage was ≥ 4% up to <6%, the reduction was 42% (19).

Inhaled corticosteroids in mixed-type asthma and COPD

The asthma–COPD mixed-type is currently subsumed under the term ACOS (asthma–COPD overlap syndrome) (21). Between 5% and 20% of all patients with COPD also show features of asthma. If the overlap is characterized by sputum and/or blood eosinophilia, ICS improve FEV_1 significantly more than in patients in whom this type of inflammation is not dominant (19, 22). A single-center study carried out on ACOS patients in Korea did not find an ICS-related drop in exacerbation frequency, improvement of lung function, or quality of life (23). The small study size and lack of patient selection according to dominant phenotype could explain this finding. The absence of a definition of ACOS, the small number of studies carried out on this topic, and the comparative heterogeneity of the original studies make it hard to draw conclusions for clinical practice, and therefore we will not enter into this discussion here. Finally, all that remains is the recommendation to treat the primarily dominant disease in the mixed type.

To conclude, giving roflumilast to unstable COPD patients who have already received maximum inhalation treatment (ICS/LABA/tiotropium) reduces exacerbation frequency more than treatment with ICS/LABA alone. ICS treatment improves lung function more in patients with features of asthma (*Table*) than in those with COPD. ICS reduce exacerbation frequency in dependence on blood eosinophil count.

Side effects and differences in efficacy of various ICS

A Canadian cohort study found that ICS increased the risk of pneumonia in COPD patients to 69% in a dose-related and duration-related manner (relative risk [RR]: 1.69 [1.63; 1.75]). The risk was higher with fluticasone treatment (RR: 2.10 [1.93; 2.10]) than with budesonide (RR: 1.17 [1.09; 1.26]), thus confirming the results of prospective studies of ICS in COPD (24). Depending on the ICS product in use, the ICS dose, and the duration of the study, but not the drug combined with ICS, a number needed to harm (NNH) of 14 to 20 was calculated for a treatment duration of 24 weeks or more (25). Despite the risk of pneumonia, exacerbation frequency fell in the prospective studies, because the pneumonia cases seen were predominantly low-grade, so this risk should not be important in practice.

Cessation of ICS treatment

After abrupt cessation of 4 months' treatment with inhaled fluticasone (2 × 500 μg/day), the exacerbation risk at the end of the 6-month study period in the placebo group was increased by a factor of 1.5 [1.05; 2.1] compared to the group that received fluticasone (26). The findings for symptom score and quality of life reflected this. Withdrawal of fluticasone (2 × 500 μg/day) compared to continuation of the initial fluticasone/salmeterol combination therapy resulted after 1 year in an increase in the annual decline in FEV_1 to –4.4% versus –0.1%. In addition, the frequency of severe exacerbations increased (1.6 versus 1.3/year) (27). In the WISDOM study, however, it was demonstrated that in stable but severely ill COPD patients (FEV_1 34% of normal), gradual reduction of ICS over a 9-month observation period, during which the patients were treated only with inhaled bronchodilators, did not increase the exacerbation risk. However, lung function deteriorated significantly (40 mL) compared to the ICS group (28).

To conclude, ICS treatment slightly raises the incidence of pneumonia, but apparently only mild forms of pneumonia are involved. ICS can be gradually reduced in stable COPD patients without increasing the frequency of exacerbations.

Suggestions for the use of ICS in clinical practice

Unlike in asthma, in COPD ICS are in every respect inferior to long-term, long-acting bronchodilators for symptom control. The primary indication for their use is in patients who suffer frequent exacerbations. Regarding the correct use of ICS in COPD, we make the following recommendations (*Figure*):

- Only use ICS in combination with at least one inhaled bronchodilator.
- The primary indication for ICS is to reduce a higher exacerbation frequency in patients with grade III or IV COPD (COPD groups C and D)

KEY MESSAGES

- Inhaled corticosteroids (ICS) are much less effective in chronic obstructive pulmonary disease (COPD) than they are in asthma.
- The effect of ICS on reducing the annual decline in FEV_1 is clinically insignificant.
- ICS reduce the frequency of COPD exacerbations; their efficacy increases as blood eosinophil counts rise.
- ICS are used as a second-line treatment after bronchodilators.
- In stable patients, ICS can be gradually reduced.

with a FEV_1 <50% of normal and/or who have two or more exacerbations per year. Stage I and II COPD (groups A and B) should be treated in the first instance with one or two inhaled bronchodilators, in accordance with the German National Disease Management Guideline COPD (NVL-COPD) and the GOLD guideline (1).

- Because of the risk of pneumonia, patients with an increased incidence of pneumonia should be given ICS at the lowest possible dosage (29).
- In COPD patients with features of asthma (*Table*) and a raised blood eosinophil count (e.g., ≥ 2%), ICS treatment should be considered as a therapeutic option early on.
- Gradual reduction of ICS can be justified in stable patients (28).
- ICS should not be used with the aim of improving lung function.

It is essential to ensure that the prescribed inhalation systems are correctly used. Patients should be given repeated training in how to carry out their inhalation treatment properly.

Conflict of interest statement

Professor Gillissen has received consultancy fees from Chiesi, Teva, Elpen, and Berlin-Chemie. He has had conference fees reimbursed by Chiesi and Teva. He has had travel expenses reimbursed by Chiesi, Teva, Boehringer Ingelheim, Elpen, Almirall, and Berlin-Chemie. He has received lecture fees from AstraZeneca, Elpen, Chiesi, Boehringer Ingelheim, and Berlin-Chemie.

Dr. Haidl has received consultancy fees from Chiesi and Mundipharma. He has received lecture fees from GlaxoSmithKline (GSK), Chiesi, Mundipharma, AstraZeneca, Novartis, and Boehringer Ingelheim.

Professor Kroegel has received consultancy fees from Chiesi.

Dr. Voshaar has received consultancy fees from Chiesi, Boehringer Ingelheim, Novartis, Teva, and Berlin-Chemie. He has received lecture fees from Chiesi, Boehringer Ingelheim, Teva, and Berlin-Chemie.

Dr. Gessner has received consultancy fees from Novartis, Chiesi, Teva, Boehringer Ingelheim, and AstraZeneca. He has received lecture fees from Chiesi, Teva, Novartis, Boehringer Ingelheim, and AstraZeneca. He has received third-party research funding from Chiesi, Novartis, Boehringer Ingelheim, Teva, AstraZeneca, and GSK.

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Corresponding author:
Prof. Dr. Adrian Gillissen
Klinikum Kassel
Klinik für Lungen- und Bronchialmedizin
Mönchebergstr. 41–43
34125 Kassel, germany
adrian.gillissen@web.de

Supplementary material
For eReferences please refer to:
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eTABLE

Important placebo-controlled, double-blind, multicenter studies*

Study	Comparison groups and number of participants	Main patient inclusion criteria	Study effects and significant unwanted effects	Study duration
ICS monotherapy studies				
Vestbo 1999 (3)	• Bud 800 µg plus 400 µg daily for 6 months then 2 × 400 µg (n = 145) • Placebo (n = 145)	FEV_1/vital capacity ≤ 0.7	FEV_1 decline/year (primary outcome parameter): 41.8 mL (placebo) and 45.1 mL (Bud); 155 exacerbations in the Bud group and 161 in placebo group; no significant differences between groups	3 years
Pauwels 1999 (4)	• Bud 2 × 400 µg (n = 634) • Placebo (n = 643)	≥ 10 pack-years FEV_1 ≥ 50% of normal	FEV_1 decline at end of study (primary outcome parameter): 140 mL (Bud) vs. 180 mL (placebo); the difference was primarily in the first 6 months, during which FEV_1 rose in the Bud group but declined in the placebo group. 10% (Bud) vs. 4% (placebo) of patients suffered skin injuries.	3 years
Calverley 2008 (30)	• Mometasone 2 x 400 µg (n = 308) • Mometasone 1 x 800 µg (n = 308) • Placebo (n = 295)	≥ 10 pack-years FEV_1 30–70% of normal	FEV_1 change compared to start of study (primary study endpoint): 50 mL (mometasone 1 × 800 µg) vs. 53 mL (2 × 400 µg) vs. –19 mL (placebo); lower exacerbation frequency (p = 0.031), health status and quality of life in both mometasone groups vs. placebo	1 year
Burge 2000 ISOLDE (5)	• FP 2 × 500 µg (n = 376) • Placebo (n = 375)	FEV_1 ≥ 800 mL, but <85% of normal	No differences between groups in annual FEV_1 decline (primary outcome parameter); annual exacerbation frequency: 1.32 (FP) vs. 0.99 (placebo; p = 0.026); health status deteriorated by 2.0 (FP) vs. 3.2 points (placebo; p = 0.0043)	3 years
ICS/LABA studies				
Anzueto 2009 (31)	• Salm 2 × 50 µg (n = 403) • Salm/FP 2 × 50/250 µg (n = 394)	≥ 10 pack-years FEV_1 ≤ 50% of normal ≥ 1 severe exacerbation within the 12 months before study enrollment	Exacerbation frequency (primary outcome parameter) reduced with Salm/FP compared to Salm by 30.4% (1.10 vs. 1.59 exacerbations/year; p<0.001); more cases of pneumonia in Salm/FP group (7%) vs. Salm group (2%)	1 year

Study	Comparison groups and number of participants	Main patient inclusion criteria	Study effects and significant unwanted effects	Study duration
Calverley 2010 (11)	● Form 2 × 12 µg (n = 239) ● Form/Bud 2 × 12/400 µg (n = 242) ● Form/Bec 2 × 12/200 µg (n = 237)	≥ 20 pack-years FEV_1 50–30% of normal ≥ 1 severe exacerbation within the 2 to 12 months before study enrollment	FEV_1 change compared to start of study and exacerbation frequency (combined endpoint): FEV_1 improvement of 0.077 L (Form/Bec), 0.080 L (Form/Bud) vs. 0.026 L (Form; p = 0.046 vs. Form/Bec); exacerbations/year 0.414 vs. 0.423 vs. 0.431 = no significant differences between groups (including in relation to quality of life, symptoms, and use of emergency medication)	11 months
Szafranski 2003 (32)	● Form 2 × 12 µg (n = 201) ● Bud 2 × 320 µg (n = 198) ● Form/Bud 4 × 4.5/160 µg (n = 208) ● Placebo (n = 205)	≥ 10 pack-years FEV_1 ≤ 50% of normal	Reduction in severe exacerbations with Form/Bud vs. placebo 24%, vs. Form 23%; FEV_1 increase 15% vs. placebo and 9% vs. Bud (both primary outcome parameters)	1 year
Lapperre 2009 (33)	● FP 2 × 500 µg (n = 26) ● Salm/FP 2 × 50/500 µg (n = 28) ● FP followed by placebo (n = 31) ● Placebo (n = 29)	≥ 10 pack-years FEV_1 30–70% of normal 1 × COPD exacerbation/year in the previous 3 years	Reduced inflammatory cells in bronchial mucosal biopsy samples; reduced bronchial hyperreactivity	2.5 years
Calverley 2003 (TRISTAN) (34)	● Salm 2 × 50 µg (n = 372) ● FP 2 × 500 µg (n = 374) ● Salm/FP 2 × 50/500 µg (n = 358) ● Placebo (n = 361)	≥ 10 pack-years FEV_1 25–70% of normal 1 × COPD exacerbation/year in the 3 preceding years	FEV_1 improvement after 12 months of treatment (primary endpoint) with Salm/FP vs. placebo (133 mL, confidence interval: [105; 161]); in addition, improvement in health status and symptom reduction; Salm 73 mL; p<0.0001) and FP 95 mL vs. placebo (all comparisons p<0.0001)	1 year
Calverley 2003 (35)	● Form 2 × 9 µg (n = 255) ● Bud 2 × 400 µg (n = 257) ● Form/Bud 2 × 9/320 µg (n = 254) ● Placebo (n = 256)	≥ 10 pack-years FEV_1 <50% of normal 1 × COPD exacerbation/year 2 to 12 months before study enrollment	Reduction of time to first exacerbation (primary outcome parameter) with Form/Bud vs. Bud (22.7%), vs. Form (29.5%) and vs. placebo (28.5%, p = 0.006); reduction in exacerbation frequency with Form/Bud vs. placebo (23.6%; p = 0.029) and Form (25.5%); but not vs. Bud (13.6%)	1 year
Rennard 2009 (36)	● Form 2 × 9 µg (n = 495) ● Form/Bud 2 × 9/160 µg (n = 494) ● Form/Bud 2 × 9/320 µg (n = 494) ● Placebo (n = 481)	> 10 pack-years FEV_1 ≤ 50% of normal	Primary combined endpoint: trough FEV_1 was better in the Form/Bud 9/320 group than in the placebo group (p<0.001) or the Form group (p = 0.023); both Form/Bud groups were better vs. placebo for the 1-h post-dose FEV_1 parameter (p<0.001); both combinations extended the time to first exacerbation and the exacerbation frequency vs. placebo (p < 0.004/p<0.001) and Form (p = 0.026/p<0.004)	1 year
Calverley (TORCH) 2007 (7)	● Salm 2 × 50 µg (n = 1521) ● FP 2 × 500 µg (n = 1534) ● Salm/FP 2 × 50/500 µg (n = 1533) ● Placebo (n = 1524)	>10 pack-years FEV_1 <60% of normal	No difference between groups in terms of mortality (primary endpoint); FP/Salm reduced the exacerbation frequency from 1.13 to 0.85/year and improved health status and FEV_1 (p<0.001) vs. placebo; more cases of pneumonia in FP and Salm/FP groups vs. Salm and placebo groups (84 and 88 vs. 52 and 52/1000 treatment-years)	3 years
Ferguson 2008 (38)	● Salm 2 × 50 µg (n = 388) ● Salm/FP 2 × 50/250 µg (n = 394)	>10 pack-years FEV_1 ≤ 50% of normal ≥ 1 exacerbation within the 12 months before study enrollment	Exacerbations/year (primary outcome parameter): 1.06 (Salm/FP) vs. 1.53 (Salm; p<0.001); other effects of Salm/FP: time to first exacerbation extended by 25% (p = 0.003), severe steroid-dependent exacerbations reduced by 40% (p<0.001); pneumonia incidence: 7% (Salm/FP) vs. 7% (Salm)	1 year

Study	Comparison groups and number of participants	Main patient inclusion criteria	Study effects and significant unwanted effects	Study duration
ICS/LABA–tiotropium comparative studies				
Wedzicha (INSPIRE) 2008 (39)	● Tiotropium 1 × 18 µg (n = 665) ● Salm/FP 2 × 50/500 µg (n = 658)	≥ 10 pack-years FEV_1 ≤ 50% of normal	No difference between groups as to use of the healthcare system (primary outcome parameter: use of the healthcare system); annual exacerbation frequency: 1.28 (Salm/FP) vs. 1.32 (tiotropium), quality of life (SGRQ): 2.1 lower in Salm/FP group vs. tiotropium group; mortality: 3% (Salm/FP) vs. 6% (tiotropium; p = 0.032); high incidence of pneumonia in the Salm/FP group (p = 0.008).	2 years
Aaron 2007 (40)	● Tiotropium 1 × 18 µg ● Tiotropium 1 × 18 µg + Salm 2 × 50 µg ● Tiotropium 1 × 18 µg + Salm/FP (2 × 50/500 µg)	≥ 10 pack-years FEV_1 <65% of normal ≥ 1 exacerbation 12 months before study enrollment	No difference between the 3 groups in terms of exacerbation frequency (primary outcome parameter). Compared to tioitropium, tiotropium/Salm/FP improved FEV_1 (p = 0.049) and quality of life (p = 0.01).	1 year

* on treatment of COPD using ICS or ICS/LABA and with a study duration of ≥ 12 months

Bec, beclomethasone; Bud, budesonide; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second in pulmonary function testing; Form, formoterol; FP, fluticasone propionate; ICS, inhaled corticosteroids; INSPIRE, Investigating New Standards for Prophylaxis in Reduction of Exacerbations; ISOLDE, Inhaled Steroids in Obstructive Lung Disease in Europe; LABA, long-acting β_2-agonists; pack-years, average cigarettes consumption (1 pack-year = 1 pack of 20 cigarettes smoked every day for 1 year); Salm, salmeterol; SGRQ, St. George Respiratory Questionnaire; TORCH, Towards a Revolution in COPD Health; TRISTAN, Trial of Inhaled Steroids and Long-Acting β_2-Agonists