Effects of inhaled corticosteroids in patients with COPD

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Abstract
Chronic obstructive pulmonary disease (COPD) is one of the major respiratory Non-Communicable Diseases (NCDs) in the current decade and probably, the prevalence will further increase. According to the risk factors of COPD, it seems that this disease is preventable. Nevertheless, a great amount of money is spent on developing drug therapies for patients with COPD. One of these treatments are inhaled corticosteroids (ICS). ICS are known to beneficial for patients with asthma. Despite the differences between asthma and COPD in the pathogenesis, ICS have commonly been used to treat COPD patients. Therefore, this narrative review aims to collect and assess the available evidence of the effects of ICS in COPD. The special focus is on the comparison between placebo groups and groups that get ICS alone. Different randomized controlled trials with different study designs will be discussed. The effects of ICS alone depend mainly on the outcome measures. For further research, the comparison between ICS alone and placebo groups is not recommended.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the major respiratory Non-Communicable Diseases (NCDs) in the current decade (1). It affects around ten percent of the adult population and causes substantial morbidity and costs (2). Thereby, the prevalence, morbidity and mortality of COPD vary across different countries. In 2015, approximately 600,000 people had COPD in the Netherlands. Most of these patients were 55 years and older (3). The COPD prevalence will probably increase in the next decades because of the aging of the world’s population and the continued exposure to the main risk factors of COPD (3). In general, COPD is a chronic disease that is characterized by persistent respiratory symptoms and chronic limitations of expiratory airflow. These airflow limitations are caused by small Airways diseases and parenchymal destruction, called emphysema (1) and can finally lead to a decreased ability of the airways to remain open during expiration. Health affects like these are caused by an interaction of host factors, such as genetics, poor long growth during childhood and airway hyper-responsiveness and an exposure to environmental gases and particles (1). Moreover, cigarette smoking is being recognized as one of the
main causal factors for COPD (2). According to the risk factors of COPD, it seems that this disease is preventable. Therefore, the prevention of smoking and treatments that support nicotine addicted mankind to stop smoking is an important measure. Nevertheless, a great amount of money is spent on developing drug therapies for patients with COPD (3). In general, these treatments may reduce COPD symptoms, frequency and severity of exacerbations and may improve the health status of the patients (1). One of these treatments is the inhaled corticosteroids (ICS). ICS are glucocorticoids that may cause a reduction in lung inflammation. The ICS therapy can be used as monotherapy or in combination with long-acting β2-agonists. In general, ICS are known to be beneficial for patients with asthma. Despite the differences between asthma and COPD in the pathogenesis, ICS has also commonly been used to treat COPD patients. However, their role in treating patients with stable COPD remains controversial. Spite of evidence from randomized controlled trials (RCTs) (4). Also, it is known that ICS treatment in COPD is associated with several adverse effects. These include a higher prevalence of oral candidiasis, skin bruising and pneumonia (1).

This narrative review aims to collect and assess the available evidence of the effects of ICS in COPD. The special focus is on the comparison between placebo groups and groups that get ICS alone. The effect of ICS has been examined in previous years by many RCTs with different study designs, but so far, these studies show different results. The hypothesis is that beneficial effects of ICS in COPD are greater in studies that compare ICS alone with placebo groups than in studies who compare ICS with groups that get also other drugs.

**Analysis**

To assess the available evidence of the effects of ICS in COPD, several studies were included and reviewed. To select those studies databases were used. The databases that were used for this review are PubMed and Google Scholar. All studies that are included compare ICS alone with placebo groups. Some studies were excluded because of a too small study population or a too old publication date. Yet, in this review, several old studies were included because they are of high relevance for this discussion. The oldest study that is included in this review is from 1999. In the following, the selected studies are described and compared with each other. To give an overview of the different studies and their designs, table 1 summarizes additionally the most important characteristics of the studies.

**Randomized Controlled Trials of ICS alone**

In the past years, the effectiveness and safety of different pharmacologic therapies has been well investigated by many randomized controlled trials. Many of the early randomized controlled trials (RCTs) have been used to compare groups that get ICS alone with placebo groups. Two of these early studies are the studies by Pauwels et al. (1999) and by Vestbo et al. (2000). The trial by Pauwels et al.(5) was a double-blind, randomized, placebo-controlled study that aimed to evaluate the effect of the inhaled glucocorticoid budesonide on patients with COPD. Therefore, the primary outcome measurement was the rate of FEV₁ decline after the administration of budesonide. The study was carried out in patients between 30 and 65 years old who were all current smokers, who have failed to quit smoking in a three-month period during the run in. Only patients with mild to moderate COPD were included, with a baseline forced expiratory volume in 1 second (FEV₁) of 77% predicted. Subjects with a history of asthma or any other atopic diseases or with airflow limitations were excluded. The study included 1277 subjects who were randomly assigned to a twice-daily treatment with 400 µg of budesonide or placebo, inhaled from a dry-powder inhaler, for three years. The study group hypothesized a reduction in the decline of lung function in those patients. Nevertheless, Pauwels et al. were not able to report a long-term beneficial effect on lung function. A median decline in the FEV₁ after the three years of 140 ml in the budesonide group and of 180 ml in the placebo group was reported. Moreover, the FEV₁ was improved at the rate of 17 milliliters per year in the budesonide group in comparison with a decline of 81 milliliters per year in the placebo group. However, this effect was only during the first six months. From nine months to the end of the intervention period, the rate of decline in FEV₁ was similar in both groups. Thus, Pauwels et al. showed only a small one-time improvement (5). The study by Vesbo et al. (6) was published one year later and was just as the trial by Pauwels et al. a double blind, randomized, placebo-controlled study with the purpose to evaluate the effect budesonide. This study was also carried out...
in patients with mild to moderate COPD. Indeed, the patients had a baseline FEV$_1$ of 86% of predicted and was therefore higher than in the study population of Pauwels et al. The primary outcome measurement in this study was also the rate of FEV$_1$ decline after the administration of the budesonide and a reduction in the decline of lung function in patients with mild to moderate COPD was hypothesized. Beside the primary outcome measure, Vestbo et al. formulated secondary outcome measures, which are respiratory symptoms and frequency of exacerbations. However, there were some differences in the study population and the intervention between the two studies. Vestbo et al. also included only patients without asthma with a mean age of 59 years and excluded patients who have had long-term treatment with oral inhaled steroids within six months of study entry. However, this trial used only 290 patients, who were randomly assigned to budesonide or to placebo for 36 months. Those subjects in the budesonide group, were assigned to 800 µg plus 400 µg daily for six months, followed by a 30 months’ period of 400 µg twice daily. However, Vestbo et al. was not able to report a long-term beneficial effect in lung function as well. Similar as in the trial by Pauwels et al., Vestbo et al. were neither able to show a statistically significant effect of budesonide on the rate of decline in lung function. There was also no effect on respiratory symptoms and the exacerbation rate was also similar in both groups.

Another early study is the Lung Health study, which is a placebo-controlled, randomized trial. The Lung Health study investigated also the effect of ICS on COPD, but used triamcinolone acetonide instead of budesonide (7). In this study, patients with a lower FEV$_1$ were included. The mean FEV$_1$ was 56% of the predicted value. Just like the study by Pauwels et al., the Lung Health study included study subjects who were all current smokers or had quit smoking within the previous two years. The 1116 study subjects were randomly assigned to the placebo group or to a twice-daily treatment with 600 µg of triamcinolone for 40 months. Such as the previous discussed trials, the primary outcome measure in the Lung Health study was the rate of decline in FEV$_1$ after the use of the bronchodilator. Beside the primary outcome measure, the Lung Health study group defined respiratory symptoms, use of health care services, and airway reactivity as secondary outcome measures. Nevertheless, despite another dose of bronchodilator, the rate of decline in FEV$_1$ did not differ significantly between the two groups. Indeed, the study reported less respiratory symptoms during the follow-up period, which suggests a decreased airway inflammation, and less visits to a physician because of respiratory illness in the triamcinolone group. In addition to that, the intake of triamcinolone improved airway reactivity. In contrast to these trials, the following studies investigated the effect of ICS in COPD in patients with moderate-to-severe COPD who have a lower FEV$_1$. The ISOLDE trial is also a three year, double-blind, placebo-controlled study, who includes study subjects with a FEV$_1$ of 50% of predicted normal (8). Other inclusion criteria were consistent with the other trials. The 751 study subjects were current or former smokers with non-asthmatic COPD who received either 500 µg inhaled fluticasone propionate twice daily or a placebo. The main efficacy measures were also the rate of decline in FEV$_1$ after the intervention, but beside this, also the health status, frequency of exacerbations and respiratory withdrawals. However, similar to the other trials, the ISOLDE trial was not able to show a significant difference in the rate of decline in FEV$_1$, but was able to report a small increase in FEV$_1$. Indeed, the trial showed that fluticasone propionate caused a decrease in exacerbations of 25% from 1.32 a year on placebo to 0.99 a year on fluticasone propionate and a slower decline in health status as determined by the St. George’s Respiratory Questionnaire (SCRO). Another trial, with results that are in line with the ISOLDE trial, is the study by Szafranski et al., that examined the efficacy and safety of inhaled corticosteroids, budesonide and formoterol, in the treatment of COPD (9). Therefore, a randomized, double-blind, placebo-controlled, parallel-group study was designed and carried out in a twelve-month period. This study group included 812 patients, who also have moderate-to-severe COPD with a mean FEV$_1$ of 36% of predicted. The mean age of the study population was 64 years. To investigate the effect of the different drugs, the patients were assigned to two inhalations twice daily of either 160/4,5 µg of budesonide/formoterol, 200 µg budesonides or 4 µg of formoterol or placebo. Like the ISOLDE trial, this trial also studied the number of severe exacerbations and FEV$_1$. According to the results, budesonide/formoterol was able to cause a reduction in the number of severe exacerbations per patient per year by 24 % compared to the placebo group and by 23% compared to the
formoterol group. In addition to the reduction in the number of exacerbations, the FEV₁ also increased with all active treatments in comparison to the placebo group. Thus, based on their results, this study group suggested ICS in long-term management of moderate-to-severe COPD.

Table 1: Overview of the studies and their designs

<table>
<thead>
<tr>
<th>Author &amp; Publication date</th>
<th>Study design</th>
<th>Study population</th>
<th>Study duration</th>
<th>Intervention</th>
<th>Primary outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pauwels et al. (1999)</td>
<td>Double-blind, placebo-controlled study</td>
<td>1277 subjects, current or former smokers, FEV₁ 77% of predicted</td>
<td>3 years</td>
<td>400 µg of budesonide twice daily</td>
<td>Change over time in FEV₁</td>
<td>Small one-time improvement in lung function, no long-term effects</td>
</tr>
<tr>
<td>Vestbo et al. (2000)</td>
<td>Parallel-group, double-blind, placebo controlled study</td>
<td>290 subjects, FEV₁ 86% of predicted</td>
<td>3 years</td>
<td>800 µg plus 400 µg of budesonide daily</td>
<td>Rate of FEV₁ decline</td>
<td>No significant effect on FEV₁ decline</td>
</tr>
<tr>
<td>Lung Health study (2000)</td>
<td>Placebo-controlled, randomized trial</td>
<td>1116 subjects, Former or current smokers, FEV₁ 56% of predicted</td>
<td>40 months</td>
<td>600 µg of triamcinolone acetonide twice daily</td>
<td>Rate of decline in FEV₁</td>
<td>No effect on FEV₁ decline</td>
</tr>
<tr>
<td>ISOLDE trial (2000)</td>
<td>Double-blind, Placebo-controlled study</td>
<td>751 subjects, Current or former smokers, FEV₁ 50% of predicted</td>
<td>3 years</td>
<td>500 µg of fluticasone propionate twice daily</td>
<td>Rate of decline in FEV₁, health status, frequency of exacerbations</td>
<td>No effect on rate of decline in FEV₁, but small increase in FEV₁, fewer exacerbations, slower decline in health status</td>
</tr>
<tr>
<td>Szafranski et al. (2003)</td>
<td>Parallel-group, Double-blind, placebo-controlled study</td>
<td>812 subjects, FEV₁ 36% of predicted</td>
<td>1 year</td>
<td>160/4.5 µg of budesonide/formoterol of twice daily, or 200 µg of budesonide twice daily, or 4 µg of formoterol twice daily</td>
<td>Number of severe exacerbations, FEV₁</td>
<td>Budesonide/formoterol greater effects on severe exacerbations and FEV₁ than budesonide or formoterol alone.</td>
</tr>
</tbody>
</table>

Randomized controlled trials of LABA/ICS combinations

Because most of the RCTs that investigated the effect of ICS alone in patients with COPD did not find a statistically significant effect on the long-term decline of FEV₁, more recent RCTs investigated the effect of a LABA/ICS combination. One of these trials is the GLUCOLD study (10). The GLUCOLD study group aimed to compare the effects of a long-term ICS therapy, with and without LABA, on pulmonary function and on the reduction of inflammation. Therefore, this study is a four group, placebo-controlled, randomized, double blind study. Similar as the previous discussed trials, this study included current of former smokers and excluded patients with asthma and receipt of ICS within six months before the random assignment. In contrast to the previous discussed studies, this study randomly assigned the study subjects to four different groups. The 114 study subjects were either allocated to 500 µg of fluticasone propionate twice daily for six or thirty months, or to fluticasone 500 µg twice daily and salmeterol 50 µg twice daily for thirty months, or to placebo twice daily. The primary outcome of this study was cell counts in bronchial biopsies and induced sputum. This study group was able to report attenuation of the decline in lung function and a decrease in inflammation. However, adding LABA to the ICS therapy provided benefit for lung function but did
not alter the course of FEV\textsubscript{1} decline. In contrast to this study, other studies such as the TORCH trial, reported different results. According to the TORCH trial, there was a trend toward higher mortality in patients who received fluticasone propionate alone compared to the placebo group or those patients who were assigned to salmeterol in combination with fluticasone propionate (11).

**Safety of ICS in patients with COPD**

Beside the positive effects on lung function and quality of life, ICS may have several negative effects on patients with COPD which has to be taken into account. Different RCTs showed that ICS treatment is associated with a higher prevalence of oral candidiasis, skin bruising and pneumonia (1). Moreover, different reviews analyzed und summarized RCTs regarding to the side effects of ICS treatment. According to the review by Yang et al. (12) and the review by Kew et al. (1) different corticosteroids may lead to an increased risk of pneumonia. Kew et al. reported that budesonide as well as fluticasone propionate are associated with an increased risk of non-fatal adverse pneumonia events. Especially fluticasone propionate may cause a higher risk of pneumonia, whereas the effect of budesonide is less precise and based on shorter RCTs. Thus, according to Kew et al. the risk of adverse pneumonia events is higher in patients with fluticasone propionate treatment than in patients with budesonide treatment. In addition to that, there is no evidence that the risk of pneumonia is different in groups that receive fluticasone alone compared to a placebo group and groups that receive a fluticasone/LABA combination compared to LABA alone. Furthermore, this outcome is neither affected by different doses and trial duration. However, neither fluticasone propionate nor budesonide have an impact on mortality in comparison with controls.

**Discussion**

Using the rate of decline in FEV\textsubscript{1} as primary outcome measure didn't lead to a statistically significant result in the rate of decline in any of these early studies. Especially, the early trials by Pauwels et al. and Vestbo et al. (5, 6) who investigated the effect of budesonide could not report a positive outcome of their studies, because their main outcome measure was the rate of decline in FEV\textsubscript{1}. Pauwels et al. could at least report a small one-time improvement in lung function. In contrast, Vestbo et al. was not able to show any positive effect of ICS in patients with COPD, despite a higher dose. The Lung Health study formulated also secondary outcome measures in addition to the primary outcome measure (7). Using these secondary outcome measures, lead to the conclusion that triamcinolone acetonide has at least any positive effect on patients with COPD. Thus, based on the Lung Health study we may assume that ICS have a positive effect on respiratory symptoms, the use of health care services due to respiratory problems and airway reactivity. The ISOLDE trial also made use of secondary outcome measures, which leads to the assumption that ICS has a positive effect on patients with COPD (8). In this study, the health status and frequency of exacerbations was also investigated. Therefore, The ISOLDE study group made use of the bronchodilator fluticasone propionate. Another difference to the former studies is that in this study the patients had moderate to severe COPD. Although, the study group was neither able to show a positive effect on the rate of decline in the FEV\textsubscript{1}, they could report positive effects on the health status and the frequency of exacerbations. In the study by Szafranski et al one part is also the comparison of budesonide with placebo (9). Such as the ISOLDE trial, Szafranski et al. included only patients with moderate to severe COPD, but in this study the FEV\textsubscript{1} was even lower. Although the dose was lower than in the other studies, this trial could report positive effects of budesonide on the frequency of exacerbations and on the FEV\textsubscript{1}. However, the analysis of exacerbations in these early trials that lead to such results, is criticized by Ernst et al. According to Ernst et al. some of these studies did not weight the rate of exacerbations according to differences in duration of follow-up between patients and may lead to an exaggeration of the influence of subjects dropping out early (4). This problem is especially important in RCTs with a long follow-up period. As already discussed, these early studies have all a long duration of follow-up. Thus, they are susceptible for the problem that is addressed in the review by Ernst et al. and may overestimate the beneficial effects of ICS in reducing exacerbations in patients with moderate-to-severe COPD. In contrast, the more recent studies who investigate the effects of ICS in combination with LABA have according to Ernst et al. used weighting of exacerbations according to person-time of follow up. Even if ICS may reduce the frequency of exacerbations,
they increase are the risk of pneumonia. While the studied trials do not report a higher risk of pneumonia in the ICS group in comparison to the placebo group, some reviews investigated the safety of ICS in patients with COPD and conclude that mainly fluticasone propionate is less safe and may cause pneumonia.

**Conclusion**

Based on this analysis, we can conclude that it depends on the outcome measures whether ICS may lead to beneficial effects in patients with COPD. The first large trials used mainly the rate of decline in FEV\(_1\), whereas the younger studies also include exacerbation rate and health status. Because COPD is an irreversible disease, the decline in FEV\(_1\) may not be the best outcome measure. In addition to this, nowadays, it is unusual to compare ICS with placebo groups. In recent years, such studies are not carried out, because of ethical issues. Thus, it is not ethical to give placebo to patients with COPD, while the patients in the ICS group receive a treatment and have a chance to become better. Therefore, the recent studies do not compare ICS alone versus placebo, rather the study subjects receive always a co-treatment. Based on the trials that also include the combination of ICS and LABA, it seems that ICS alone is not superior to LABA. This causes why the treatment nowadays includes the combination of ICS and LABA. Finally, it is also important to take the safety of ICS into consideration. As seen in the analysis, the ICS therapy increases the risk of pneumonia. Therefore, it is important to weigh the benefits of reduced exacerbations against the risk of pneumonia.

**Recommendation**

Nowadays, based on the discussed issues, it is not recommendable to carry out RCTs who compare ICS alone and placebo groups. A good alternative would be to give first bronchodilators in maximal doses to the whole study population and then to divide the study population into two groups. One group would receive ICS and the other one a placebo. Moreover, it is important to not restrict the outcome measurement to the rate of decline in FEV\(_1\) but also to measure symptoms, exacerbation frequency and quality of life.

**Literature**


