Abstract

COPD has a high mortality rate and it leads to an economic and social burden. The prevalence of COPD is increasing and will probably increase even more over the coming years, because there will be more exposure of the risk factors. There are many different types of medicine available, like inhaled corticosteroids (ICS). These are anti-inflammatory and often used for asthma patients, the effectiveness for COPD patients is not clear. Studies show that ICS have a positive effect on different domains, like mortality, exacerbation frequency and health status. However, the magnitude of these effects are questionable.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation and persistent respiratory symptoms. COPD has a high morbidity and mortality rate; it is one of the leading causes of death worldwide. COPD leads to an economic burden, because of the high direct and indirect costs. In the European Union (EU), COPD accounts for 56% of the costs of respiratory diseases (American Thoracic Society Foundation, 2014). The social burden is also important to mention, because of the high rates of mortality and disability it entails. A main risk factor is tobacco smoking. Studies have shown that the prevalence of COPD is substantially higher for people who are current smokers or have smoked in the past, than for people who have never smoked (Halbert et al., 2006). The same study has shown that the prevalence is also increased in the older age groups. For people of 40 years and older, the prevalence is higher than for people younger than 40 years old. It usually takes at least 10 to 15 years of smoking before COPD occurs. This can also be because as people become older, the exposure to risk factors will be continued over more years and that will increase the prevalence. Air pollution is also an important risk factor, the prevalence increases if there is a lot combustion, for example wood. With increasing age, lung elastic recoil also decreases, which also results in a reduced expiratory flow. The prevalence of COPD is increasing and will probably increase even more over the coming years, because of ageing of the population and because there will be more exposure to the risk factors. Patients suffering from COPD mostly have cough with sputum and other symptoms like dyspnea, wheezing and chest-tightness (GOLD, 2017). For obstructive lung diseases, there are many different types of medicines available, like short-acting and long-acting bronchodilators, inhaled corticosteroids (ICS) and
combination drugs. ICS are anti-inflammatory drugs which are often used by asthma and COPD patients. ICS are very effective for asthma patients, but the effectiveness for COPD patients is not clear. The outcomes of ICS treatment for COPD patients are based on many studies, mostly randomized controlled trials, which can be described in different terms of benefit. Exacerbation frequency, lung function, mortality, health status or composite outcomes of combination measures, are some of the domains which recur often as outcome measurements. Because of these different domains, the beneficial effects may seem to be described controversial. The effects may be bigger in one domain than another. Also, effects can be described bigger than they actually are because of unjustified generalization. Most studies have a comparison between an ICS combination and another type of treatment, like bronchodilators. When studying the effects of ICS in COPD, it is more feasible to look at endpoints like exacerbation frequency than lung function when bronchodilators are used in the study too. ICS are anti-inflammatory, so when looking for the effects of ICS it is better to take a look at exacerbation frequency since exacerbations are usually associated with an increase in airway inflammation. Bronchodilators are drugs which cause airway smooth muscle relaxation, resulting in an increase of the airflow in and out of the lungs. Therefore, an increase in lung function will be probably an effect caused by the bronchodilator and not by ICS. Effects on lung function are relatively small, in the recent years exacerbation frequency is used as more relevant outcome. This narrative review aims to collect and assess the available evidence of the outcomes of ICS in COPD, with special focus on the different beneficial effects. In this narrative review, the beneficial outcomes of the different domains, like exacerbation frequency, mortality and health status, will be discussed. We take a closer look at the magnitude and relevance of those effects.

The effects of ICS on mortality

COPD causes high rates of mortality, as it is a progressive lung disease. How much the reduction in life span of COPD patients will be, depends on the stage of the disease and symptoms like exacerbation frequency or dyspnea. Because of COPD, the life expectancy of the patients will be reduced. Patients in stage one or two of the disease will lose a few years in their life expectancy. Those who smoke and are in stage three or four can lose about six years of life expectancy. Smoking itself can cause a reduction of almost four years (Shavelle et al., 2009). So, COPD can have quite a big effect on the life expectancy of the patients. It is also important to keep in mind that not all patients die from COPD or its complications, but they all do die with this disease. Studies have shown that COPD patients, who receive ICS, have an increased risk of pneumonia (Singh et al., 2009). This could indicate that these patients have a higher risk of hospitalization and mortality. It is not clear if this really is the case, because this can also be influenced by the way that people are diagnosed and how the cause of mortality is registered. The diagnostic accuracy can be of influence as well. Some COPD treatments, like ICS, are thought to have positive effects on the mortality, so it will lengthen the life expectancy of the patients. Mortality is often used as measurement because it is clinically meaningful; it is a direct endpoint as it directly measures the survival of patients (Sullivan, 2012). The ‘Observational study of inhaled corticosteroids on outcomes for COPD patients with pneumonia’ showed that the use of ICS indeed would have benefits on mortality (Chen et al., 2011). In this retrospective cohort study, the 30- and 90- day mortality of COPD patients, admitted to the hospital for pneumonia, have been investigated. 8271 patients with prior use of ICS and 7497 patients with no prior use of ICS were included, in the period from 2002 until 2007. As a second endpoint, the use of mechanical ventilation and vasopressor support were studied during the hospitalization. This study showed that both the 30- and 90- day mortality was decreased in patients with prior use of ICS. For the 90-day mortality, ICS-users had a rate of 17.3% and the non ICS-users had a rate of 22.8%. It can be concluded that the prior use of ICS reduces the mortality rate with 5.5%, compared to no prior use of ICS. Also, the rates of mechanical ventilation use were lower for the ICS-users than for the non ICS-users in this study. However, this is a meta-analysis which is uncontrolled, the researchers were not able to determine which of the patients received which treatment. If a study is not controlled, confounding variables can occur. As most of the patients in the database of this study were males, gender could be seen as a possible confounding variable. When due to a possible confounding variable, a suggestion is made about a correlation between mortality and use of ICS, this can lead to bias.
Another study also showed a reduction of around 5% in mortality because of the use of ICS (Yamauchi et al., 2016). This study compared 3331 COPD patients receiving long-acting inhaled bronchodilators (IBD) with 3702 patients receiving a combination of IBD and ICS, in the period between 2010 and 2013. The first endpoint is all-cause mortality of patients hospitalized with pneumonia. Also other endpoints like length of stay and requirement for ventilation were investigated. The outcome showed there was a lower in-hospital mortality associated with pneumonia for the IBD/ICS combination users (8.1%) than for the IBD alone users (13.2%). Also length of stay was reduced for the IBD/ICS group compared to the IBD group. However, it is not completely clear that the mortality is caused by COPD, as the all-cause mortality was taken as endpoint. COPD patients often have co-morbidities. Of all patients in this study 17.4% had congestive heart failure. The IBD alone group had more patients with this other disease, so it is likely that this can have slightly an influence on the mortality rates. All-cause mortality as an endpoint can give a false impression in this case, as the study actually wants to investigate the effects of ICS on COPD patients (Laessig, 2010). These two studies both showed a difference in mortality, so as an overall conclusion we might be able to conclude that ICS does have a positive influence on the mortality rate in COPD patients who are hospitalized for pneumonia. However, in the meta-analysis of Chen et al. (2011), might be bias due to confounding variables. In the study of Yamauchi et al. (2016) might be bias due to the choice of the primary endpoint. All-cause mortality was used for this, so this rates can be influenced by co-morbidities.

**The effects of ICS on exacerbation frequency**

Exacerbations are common events for patients suffering from COPD, it is a flare-up and the ability to breathe is worse than usual. ICS are anti-inflammatory drugs, so exacerbation frequency is often used as an endpoint for studies, as this is a relevant and subjective measurement (Sullivan, 2012). Exacerbations can also have an effect on health status and lung function. In the TORCH study (Calverley et al., 2007), different treatment groups were investigated from 6112 patients in total. There was a salmeterol/fluticasone propionate combination group, a placebo group, a salmeterol alone and a fluticasone propionate alone group. The patients had to take their medicine twice a day with a single inhaler and they were followed for three years. During the study, 2342 patients were withdrawn, so only 3769 patients genuinely completed the study. This study used an intention-to-treat analysis. This is preferable over the per-protocol analysis, because the per-protocol analysis can lead to bias. Intention-to-treat analysis maintains the originate randomization and is a better reflexion of the reality (Shah, P.B., 2011). The first endpoint of this study was to investigate deaths from any cause, but there was no significant evidence of benefit. However, this study showed an effect of these treatments in exacerbation frequency and health status, which were secondary endpoints of the study. The combination treatment of 50 μg salmeterol and 500 μg fluticasone propionate led to a decreased frequency of exacerbations compared to placebo. The placebo group had an exacerbation rate of 1.13 in a moderate/severe annual rate, while the combination group had a rate of 0.85. The salmeterol and fluticasone alone groups had rates of around 0.9, which show that these medicine alone already have a small positive effect on the exacerbation rates. The effect is bigger when combination treatment is used. However, the magnitude of this effect is not really clear. If the rate goes from 1.13 to 0.85, patients may not experience much improvement. But the number needed to treat to prevent an exacerbation is 4, which is quite low. This means that only four people need to have the combination treatment for one person to have a benefit. Another study investigating the effects of ICS on exacerbations is the ISOLDE trial (Burge et al., 2000). 751 men and woman aged between 40 and 75 years, from 18 participating hospitals in the United Kingdom, were divided into two groups. One group inhaled 500 μg fluticasone propionate twice a day with an inhaler, the other group used placebo. The patients were current or former smokers with non-asthmatic COPD. The exacerbation rate was also in this study a secondary endpoint and this reduced to 0.99 a year with the fluticasone treatment compared to 1.32 in the placebo group. However, the exacerbation rates were a secondary endpoint of this study, so these results are analyzed later on. This means the study is not randomized and/or powered for these outcomes.
The change in score must be at least four units to be rewarded as clinically relevant (Jones et al., 1992). From this we can conclude that there is an effect in health status, but as the improvement is approximately four units, the magnitude of the effect is not very big. The TORCH study (Calverley et al., 2007), as discussed before, used health status as secondary endpoint. The questionnaire for this measurement was again the SGRQ. The time between the first measurement of scores and the second time was longer than the measurements of the meta-analysis (Kew et al., 2014), it was over a period of three years. The time period in this study was longer, but the improvement in health status was less. Combination treatment of salmeterol and fluticasone showed a decrease of 3 units. However, this decrease is not big enough to be a significant effect. The ISOLDE trial (Burge et al., 2000), investigated changes in health status too as a secondary endpoint. Again, the SGRQ was used as measurement method. Results of this study show that the decline in health status for the placebo group was 3,2 units in a year. The fluticasone propionate group had a decline of 2 units a year, this means there is a slower decline in health status for patients using ICS. However, this difference between the placebo and ICS group is only 1,2 units. This result cannot be assessed as a significant effect, as the change is less than four units. All the studies used the St. George's Respiratory Questionnaire to measure health status. These studies show that ICS indeed have an effect on health status, they all show an improvement in units. However, these improvements may seem to be bigger than they actually are. If the change in units is at least four units, this can be assessed as a clinically relevant effect (Jones et al., 1992). Most of the studies showed a change less than four units, which means the effect is not significant. The study from Kew et al. (2014), showed a change of 4,04 and 4,05 units, which is relevant. But the magnitude of this effect is probably not very big, because the changes are only 0,05 units higher than the minimal improvement to be significant. If we take a look on the exacerbation frequency for users of ICS, we saw a small reduction. Exacerbations do have an effect on the health status of the patient, this will also be made clear from the results of the questionnaires. The SGRQ has questions about the symptoms of COPD, including questions about the frequency of exacerbations. It is logical that the health status of a patient will improve if the frequency of exacerbations decreases. We can conclude that ICS do show an effect on health status in COPD patients,

The effects of ICS on health status

As said before, COPD leads to social burden, as patients suffer from dyspnea, chest-tightness and exacerbations. Health status can say something about the quality of life of a person, which means this is an important parameter for an individual suffering from COPD. Sometimes health status is used as a primary endpoint, but mostly as secondary. To measure this, questionnaires are used because this endpoint is objective. In the meta-analysis from Kew et al. (2014) is shown that ICS do have a positive effect for patients with COPD. In this study, 71 randomized control trials were investigated. The St. George's Respiratory Questionnaire (SGRQ) was used to measure the health status of the 73062 COPD patients participating in this study. In this questionnaire, three main components are calculated and after this the total score is calculated. The main components are symptoms, activity and impacts. The SGRQ consists out of 50 units. The changes in health status were investigated at two time points; after six months and after twelve months. The SGRQ is a valid questionnaire with a score range from zero to hundred. Different groups were investigated; LABA-users, LAMA-users, ICS-users, LABA/ICS combination users and placebo. For the only ICS-users, there was a mean increase shown of 2 health status units. The most improvement was shown for the LABA/ICS combination group, after a period of six months. The mean improvement of this group was 3,89 units, with the most effect for the salmeterol/fluticasone and formoterol/budesonide combinations. The salmeterol (50 mcg) and fluticasone (500 mcg) combinations showed a decrease of 4,05 units. The formoterol (12 mcg) and budesonide (160 mcg) combination showed a decrease of 4,04 units. The ICS-users alone were ranked fourth in this study, so this study shows that the effect of ICS itself is not big on health status. The combination of ICS and LABA is necessary to have an improvement. The change in score must be at least four units to be
especially for patients who have less exacerbations using ICS. However, the magnitude of these positive effects on health status may seem bigger than they actually are because the improvements is only in a few units of the SGRQ.

**Effects on other domains**

As said before, ICS are anti-inflammatory and it is better to look at the domains of outcomes as discussed above than for example lung function. However, some studies have shown that ICS causes positive effects in lung function. The study of Hanania et al. (2003), showed that ICS does have an effect on the FEV1 of the COPD patients. FEV1 is the forced expiratory volume in one second, this is an often used measurement for the lung function. In this study, 723 COPD patients above the 40 years old and a predicted mean FEV1 baseline of 42%. The comparison was made between fluticasone propionate (250 µg), salmeterol (50 µg), a combination of these two and a placebo group. The patients had to take their medication twice a day for 24 weeks. In the results was shown that combination treatment leads to an increased 2-hours postdose compared with fluticasone propionate alone and placebo. And it would lead to an increased morning predose compared to the salmeterol group alone and placebo. From this can be concluded that fluticasone indeed has a positive extra effect on the FEV1. However, this improvement in lung function is only shown in combination treatment with LABA.

**Discussion**

The studies as discussed above, all show that ICS do have a positive effect on COPD patients. These effects can be divided in several domains, like mortality, exacerbation frequency and health status. The studies of Chen et al. (2011) and Yamauchi et al. (2016) both showed that ICS would have a positive influence on the mortality rates, these would decrease with approximately 5%. However, the meta-analysis of Chen et al. is a non-experimental study, so this might have bias due to confounding variables. The study of Yamauchi et al. might give a false assumption because all-cause mortality is used as endpoint and co morbidities occur often in COPD patients. The TORCH study (Calverley et al., 2007) and the ISOLDE trial (Burge et al., 2000) both showed that ICS would have a positive influence on the exacerbation rate. In the TORCH study the rate was decreased from 1.13 to 0.85 exacerbations. In the ISOLDE trial, the rate was decreased from 1.32 to 0.99 exacerbations. It is questionable if this decrease is really an improvement for the patients. The magnitude of this effect may not be as big as expected, but the number needed to treat is quite low. The exacerbation frequencies were for both studies secondary endpoints. This can possibly lead to bias, as the studies are not randomized or powered for this outcome. The studies which investigated the effect of ICS on health status all used the St. George’s Respiratory Questionnaire to measure this and all showed an improvement in units. However, the magnitude of this effect may seem bigger than it actually is. The TORCH study and the ISOLDE trial showed an improvement of less than four units, which cannot be assessed as a relevant effect (Jones et al.,1992). The study of Kew et al. (2014), showed an improvement of 4.04 and 4.05 units, this can be assessed as a significant effect. The magnitude of this effect may be probably not very big, because the changes are only 0.05 higher than the minimal improvement to be relevant. If there is an effect of ICS on the exacerbation frequency of COPD patients, it is logical that the health status will be effected too. The SGRQ has questions about the symptoms, so if the patient will have less exacerbations, this will be shown in the results of the questionnaire too. The TORCH study and ISOLDE trial showed less improvement than the study of Kew et al., this can be caused due to the fact that these two studies used health status as secondary endpoint. There are also studies showing effects of ICS on less often occurring domains, like lung function. The study of Hanania et al. (2003) for example, showed an improvement of the FEV1. However, for other domains there are less studies available and these mostly do not show much effect. From the mentioned studies, there are some findings summarized (table 1). Because many studies use combination treatment, it is hard to state that the positive effects are really caused by ICS. For example the study of Yamauchi et al., which investigated a comparison between long-acting inhaled bronchodilators (IBD) and a IBD/ICS combination. However, in some studies was shown that combination treatment was the most effective, but ICS treatment alone was also effective. For example the TORCH study and the study of Kew et al. The different types of ICS used and the different dosages make it also hard to
consider whether ICS is effective. Dosages, concentrations and type of medicine can have a huge influence, but this information is not very clear in every study and differs a lot between the studies. For further research, it would be useful to investigate the domains as primary endpoints, so the study will be randomized and powered for that specific endpoint. For the mortality endpoint, it would be better only to investigate the mortality from COPD and not all-cause mortality. Using all-cause mortality can give false assumptions, as COPD patients often have co morbidities. At last, it could be useful to compare more treatment groups. As seen in the studies above, combination treatments are more effective, but it is good to have groups of for example ICS-users alone too. In this way, you are more able to say something about the effect of one drug alone too. As an overall conclusion we may be able to state that ICS do have effect on patients with COPD. This effect may be bigger in the one domain than the other, because the magnitude of the effects is not always as big as expected. In addition, the studies can also contain bias due to confounding variables. The use of endpoints is important too, sometimes the outcomes were used as secondary endpoints, which may influence the results. Using all-cause mortality as an outcome measure can give false assumptions.

**Literature**


