

## **EDITORIAL**

# **Is lung function really a good parameter in evaluating the long-term effects of inhaled corticosteroids in COPD?**

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Recently several large trials evaluating the effects of long-term medication in chronic obstructive pulmonary disease (COPD) have appeared and there are still several which will be published in the coming years. The primary outcome of these trials was the decline in lung function. The long-term medication investigated was mainly inhaled corticosteroids. In contrast to asthma, COPD is a progressive and, to a large extent, irreversible pulmonary disease. One of the consequences is that the effectiveness of (for instance) inhaled corticosteroids in COPD can probably be measured to a limited extent on the basis of the lung function. Which parameters should be used to evaluate whether or not long-term medication in COPD is justified?

### **Effects of inhaled corticosteroids on chronic obstructive pulmonary disease**

In one of the first prospective studies investigating the long-term use of inhaled corticosteroids, no distinction was made between asthma and COPD [1]. This study can therefore not provide the actual answer to the above-mentioned questions. Moreover, the selection criteria used in this study were such that more patients with asthma than with COPD were selected.

The study of DOMPELING *et al.* [2] showed that the administration of inhaled corticosteroids to COPD patients did lead to a clear improvement in lung function during the first 6 months (beclomethasone 800 µg daily), but also that there was no change in the subsequent annual decline of the lung function. In asthma, however, this change did clearly occur [2]. Asthma patients can gain much more from the treatment with inhaled corticosteroids than COPD patients. Not only is the initial peak effect (the effect of the inhaled corticosteroids during the first 3–6 months) in COPD less strong, but, because the subsequent annual decline of lung function (expressed in the decline of the forced expiratory volume in one second (FEV<sub>1</sub>) per year) does not show any change, the final long-term effect of inhaled corticosteroids on COPD with regard to this variable is also limited [3]. On the basis of extrapolation of these data, the gain in time because of the use of inhaled steroids until the patients reach the 0.5 L level (a lung function usually indicating severe dis-

ability or death) is <1.5 yrs in COPD, whereas in asthma it is almost 9 yrs [2].

These findings in COPD were confirmed by subsequent studies. In 58 COPD patients who were treated with 1,600 µg budesonide for 2 yrs, RENKEMA *et al.* [4] observed some decrease in symptoms. They found no clear improvement in the annual decline of the lung function [4]. The study of PAGGIARO *et al.* [5] involving 281 COPD patients also showed that fluticasone 500 µg twice a day during 6 months resulted in only a slight decrease in symptoms, a slight improvement of the peak flow and a small shift from severe to moderate exacerbations [5]. The most relevant finding in this study of COPD patients was the clear improvement in the outcome of the 6-min walking test, which probably means an improvement in the functioning of COPD patients [5].

As mentioned already, in the last few years, great international efforts have been made to find an adequate answer to the question of the long-term effectiveness of inhaled corticosteroids in COPD. Several of these studies were recently published [5–7]. In the Euroscop Study [6] 1,277 patients with COPD were treated daily with budesonide 800 µg *versus* placebo for 3 yrs. Again it turned out that there was only an effect on lung function during the first 6 months (~100 mL improvement of the FEV<sub>1</sub> compared with placebo). Subsequently, the decrease in lung function in the inhaled corticosteroid group was identical to that in the placebo group. Also, in other respects no clinically relevant differences were found between the two groups. The trial group consisted of patients with a relatively mild type of COPD who had smoked heavily (on average ~40 pack-years). It was striking that COPD patients who had smoked less heavily responded better to inhaled corticosteroids [6], a finding which had been observed previously [2].

The Copenhagen City Lung Study [7] showed no relevant clinical differences between patients with mild COPD who had been treated daily with budesonide 800 µg *versus* placebo. The Isolde Study [8], which has not been completely published, on the other hand, did show some effects. The difference between the two studies was probably primarily the result of the fact that the latter study focused on patients with a more severe type of COPD. The Isolde Study [8] involved some 750 patients who were treated with fluticasone 500 µg twice a day *versus* placebo for 3 yrs. Again, during the first months, an initial increase in the lung function (increase in FEV<sub>1</sub> of ~75 mL) was found in the treatment group. No difference was found between the inhaled corticosteroid group and the placebo group with regard to the subsequent

decrease in lung function. There remained a difference between the two groups therefore until the end of the study. However, the researchers did find a clear reduction in the number of exacerbations (~25%) and observed a clear improvement in the functional status. Remarkably enough, there are indications that this improvement in the functional status occurred during the whole trial period and was independent of the lung function.

It is clear that the effects of inhaled corticosteroids on the lung function in COPD are small, certainly when compared with the effects in asthma. Also a recent meta-analysis points to a positive effect on the lung function in COPD [9]. But most studies show that this positive effect is no more than an initial effect during the first months of use. As already stated, the clinical relevance of this initial peak effect is limited: there is a small gain in time with regard to reaching a low (disabling) lung function level.

#### **How relevant is the decline in forced expiratory volume in one second in chronic obstructive pulmonary disease?**

The question is therefore whether lung function is the parameter with which the effects of medication can best be evaluated. Probably of much more importance are the effects on the quality of life, functional status (*e.g.* the 6-min walking distance) and exacerbations. In this respect, the clearest results are, for the time being, those of the Isolde Study [8]. For the patients with severe COPD who were treated in this trial, there was a clear gain in quality of life and they also experienced a decrease in symptoms. This is more important than one might realize at first sight. For a COPD patient aged 70 with clearly reduced lung function, a slight improvement in lung function is probably not very relevant. For such patients, it is more relevant that fewer exacerbations occur and that their daily functioning improves. It can be very important that patients in the last 10 yrs of their lives can still climb the stairs in one go, can take a walk with other people of about their age or do not need to go as often to their general practitioner because of an exacerbation. Also studies with medication other than inhaled steroids as well as nondrug intervention (such as rehabilitation programmes) [10] show a limited effect on lung function, but sometimes a considerable effect on functional status. Effective new tools are urgently needed to enable the measurement of changes in functional status when evalu-

ating drug treatment. These instruments should be easy applicable in daily medical care.

#### **References**

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