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PRO AND CON EDITORIALS

Inhaled corticosteroids in COPD: the case against

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Chronic obstructive pulmonary disease (COPD), a disease that encompasses emphysema, chronic obstructive bronchitis and small airway obstruction and that is characterised by largely irreversible airflow obstruction, now affects around 10% of the population over the age of 40 yrs [1]. The sixth commonest global cause of death in 1990, currently fourth in developed countries, it is expected rise to third place globally by 2020 [2]. This increase is linked to the trends of its foremost risk factor, tobacco consumption during the twentieth century, and will track the worldwide smoking trends of this century. Besides smoking cessation and pulmonary rehabilitation, the treatment of COPD has previously consisted of bronchodilators early in the disease and oxygen in the late stages. However, because of the presence of inflammation in COPD, short courses of systemic corticosteroids have been used for decades in the treatment of exacerbations, often along with antibiotics. Their side-effects, however, made them unsuitable for the long-term treatment of stable COPD.

In the early 1980s, inhaled formulations of corticosteroids were shown to be highly effective for the treatment of asthma and were readily adopted in COPD with no scientific evidence of their benefit in this indication. This transition from asthma to COPD was so natural to prescribers that a Canadian survey conducted in 1994 found that one-third of patients admitted to hospital for COPD were already using inhaled corticosteroids (ICS) [3], despite the fact that no randomised controlled trials had evaluated their effectiveness in COPD. Today, market research studies estimate that the use of these drugs has increased to the point that they are used by >70% of patients with COPD in the USA and Europe, and are currently given as initial therapy to >50% of patients newly diagnosed with COPD, mostly in combination with a long-acting β-agonist (LABA) [4].

There is now increasing evidence that the use of ICS to treat COPD may have been aggressively promoted around a cascade of scientific inaccuracies regarding their effectiveness. Their current widespread use provides little or no benefit. Indeed, the cost of high doses of ICS in terms of drug costs and the costs of complications is now becoming detrimental. A re-examination of these data, which form the basis for all treatment guidelines, and of emerging evidence is clearly warranted.

THE STUDIES

The earliest randomised controlled trials to evaluate the effectiveness of ICS in the treatment of COPD were published only in the late 1990s. The first five trials found no improvement in the decline of lung function over time and no reduction in the rate of exacerbation with various ICS compared with placebo, over periods ranging from 6 months to 3 yrs [5–9]. Two subsequent randomised trials published in 2000 also found no change in lung function decline over time with ICS, but reported reductions in healthcare utilisation or exacerbation rates [10, 11].

The next wave of randomised controlled trials published from 2002 onwards all involved the evaluation of ICS combined with a LABA, either fluticasone propionate/salmeterol or budesonide/formoterol [12–19]. Most of these trials reported significant effects on lung function and reductions in exacerbation rates with the combination therapy, whereas the effects of ICS alone were equivocal. Figure 1 shows the time trends in the use of ICS in COPD, along with the publication timing of the randomised controlled trials that evaluated their effectiveness [4].

During this same period, the enthusiasm for ICS in COPD was heightened with a meta-analysis of the early randomised trials, which reported a significant 30% overall reduction in the rate of exacerbation with ICS [20]. In addition, a pooled analysis of data from seven trials found a significant 27% reduction in all-cause mortality with ICS compared with placebo [21]. Finally, observational studies of large population-based cohorts, formed using healthcare databases, reported highly significant reductions in all-cause mortality of 30–40% with ICS use, alone or in combination with a LABA [22–25].

Thus, clinicians then had available to them what appeared to be a class of drugs that, according to randomised controlled trials and meta-analyses, had only minor effects on lung function but resulted in fewer COPD exacerbations, particularly in combination with a long-acting bronchodilator. In addition, population-based observational studies were indicating that such benefits could be translated to mortality. Moreover, clinical guidelines for the management of COPD were using these trials to recommend the regular use of ICS in more advanced disease. As a result of this popularity, the use of these drugs given as initial therapy to patients with newly diagnosed COPD has been high and has increased substantially in combination with a long-acting bronchodilator (fig. 1). These market research data indicating high utilisation rates of ICS are corroborated by the treatment profiles of patients

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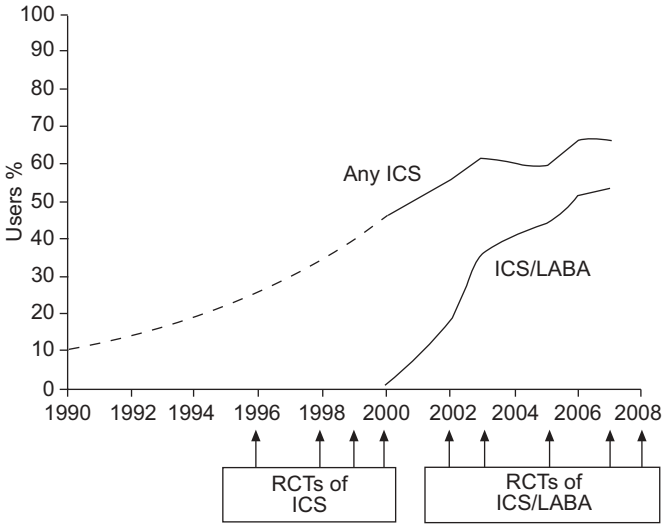

FIGURE 1. Proportion of patients with chronic obstructive pulmonary disease (COPD) who use any form of inhaled corticosteroids (ICS) and in combination with a long-acting bronchodilator (LABA), estimated from surveys in the USA and Europe between 2000 and 2007 (—) and extrapolated back to 1990 (---). Below the horizontal axis are the publication dates of randomised controlled trials (RCTs) of the effectiveness of ICS alone or in combination with a LABA in COPD. Data from [4].

entering recent randomised trials such as TORCH (Towards a Revolution in COPD Health; 48% ICS use at recruitment in 2000–2002), Optimal (77% in 2003–2005), INSPIRE (Investigating New Standards for Prophylaxis in Reducing Exacerbations; 50% in 2003–2004) and Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT; 61% in 2003–2004), as well as less recent trials such as Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE; 54% in 1992–1995) and the Trial of Inhaled Steroids and long-acting β_2-agonists (TRISTAN; 51% in 2000) [10, 14, 17–19, 26]. These rates are at odds with treatment guidelines that recommend their use only at the latter stages of the disease (which should include at most around 20% of patients) [2, 4].

SHORTCOMINGS OF THE STUDIES

The randomised trials that form the basis for the use of ICS in COPD have several important shortcomings. The first limitation of these trials was the requirement that patients abruptly discontinue their existing ICS use at the time of randomisation. As a result, all trials were actually estimating a mixture of the effect of introducing ICS and of discontinuing ICS. A recent reanalysis of one such trial showed that the effect of ICS on the likelihood of the first exacerbation was significantly protective only among patients who were users of ICS before randomisation but had to discontinue (hazard ratio 0.7; $p=0.03$) [27]. In contrast, it also showed that there was no effect of ICS in patients who did not use ICS before randomisation (hazard ratio 1.1; $p=0.68$) [27]. Thus, all trials that have reported a benefit for ICS may have simply shown an effect of abruptly discontinuing high-dose ICS use, which probably leads to side-effects such as relative adrenal insufficiency and other rebound steroid effects.

The second flaw was the incomplete follow-up of patients, who were observed only until discontinuation of the study drug, not the end of planned follow-up. This violates the fundamental intention-to-treat principle of clinical trials. This violation is particularly important because of the very high and early rates of discontinuation in COPD trials. The resulting bias was demonstrated with studies that had incomplete follow-up and that found a significant 27% ($p=0.04$) reduction in all-cause mortality with ICS [21] compared with the recent TORCH trial, which followed-up all patients for 3 yrs to identify all deaths for a proper intent-to-treat analysis, that found a non-significant 6% ($p=0.53$) increase in mortality with fluticasone propionate [17]. The OPTIMAL trial also avoided this bias by identifying exacerbations, the primary outcome, for the entire 1-yr follow-up period and found no benefit of ICS [18]. Thus, both studies designed for valid intent-to-treat analyses found no benefit of ICS on their primary outcome measure.

The effect of the absence of intent-to-treat analyses was also noticeable in the analysis of forced expiratory volume in 1 s (FEV_1) decline in all trials including TORCH. In the TORCH trial [17], nearly 18% of patients on placebo did not contribute a single FEV_1 value to the analysis of FEV_1 decline, compared with only 9% of patients allocated to combination therapy [28]. Because these excluded patients probably would have had worse FEV_1 values at their initial visit, the slope of decline in the remaining subjects with better FEV_1 values at the first visit may have been affected by regression to the mean [29]. Such differential exclusion rates can introduce selection bias and may have created the impression of an ICS effect on FEV_1 decline.

Another issue with the combination therapy in COPD relates to the effect of each component. A more inclusive data analysis of the TORCH trial data, which used the complete data from the 2×2 factorial study design, evaluated the independent contribution of each component of the combination of salmeterol and fluticasone on mortality and found a reduction in mortality that was entirely due to the salmeterol component (17% reduction in mortality), and none whatsoever attributable to the ICS component (0% reduction) [27, 30].

The meta-analysis of the early randomised trials, which reported a highly significant 30% reduction in exacerbations with ICS, used faulty statistical techniques [31]. These produced biased estimates and exaggerated statistical significance, such that the $p=0.07$ reported by one study transformed to $p=0.005$ by the meta-analysis [20]. Although the falsely significant results of this meta-analysis were used as the source of level 1A evidence in recommending the use of ICS in previous COPD treatment guidelines, the latest versions do not [2].

Finally, the observational studies suggesting a reduction in mortality with ICS use were all shown to be flawed with immortal time bias. Through their design, the studies introduced a survival advantage to the ICS users by defining exposure in such a way that they had to be alive to receive their ICS prescription, thus creating immortal time bias: a proper analysis eliminated any apparent protective effect of ICS [32–35].

SAFETY CONCERNS

ICS have been shown to somewhat increase the risk of glaucoma, whereas the risk of osteoporotic fractures is equivocal [36–38]. The risk of cataracts and of their extraction was consistently found to be elevated and shown to increase with the dose and duration of ICS use [39–41]. Recently, the TORCH study and another large study of ICS identified an elevated risk of pneumonia reported in the trial as a serious adverse event [16, 17]. This risk was confirmed and a dose–response effect was demonstrated in a population-based cohort of over 175,000 patients with COPD [42].

WHY DO ICS NOT WORK IN COPD?

Although ICS are very effective in suppressing airway inflammation in patients with asthma, even high doses are ineffective, poorly effective or inconsistent in suppressing inflammatory cells or mediators in patients with COPD, either in induced sputum or in bronchial biopsies [43–48]. This cannot be explained by poor access of ICS to the peripheral sites of inflammation because high doses or oral corticosteroids are also ineffective [43]. One reason for the corticosteroid resistance in COPD may be the reduced expression and activity of the critical nuclear enzyme histone deacetylase-2 (HDAC2), which is required by corticosteroids to switch off activated inflammatory genes [49, 50]. This appears to be the downstream consequence of oxidative and nitrative stress in the lungs of patients with COPD.

Of course COPD is a heterogeneous disease with several different pathological mechanisms, including emphysema, small airway disease and mucous hypersecretion, so it is possible that corticosteroids might work more effectively on some components of disease than on others, but this has so far not been investigated in clinical trials. Patients with COPD who have clinical features of asthma, with greater reversibility of airways obstruction, may show a response to corticosteroids exemplified by a reduction in sputum eosinophils and this probably represents coexistent asthma [51].

CONCLUSION

The introduction of ICS in the treatment of COPD has been rather unorthodox. These drugs, demonstrated as effective for the treatment of asthma, were widely adopted in COPD, a disease for which few treatments were available. Yet this adoption was made in the absence of any scientific evidence of their effectiveness in COPD and with the conviction that their lung-localised delivery made them harmless. The randomised trials conducted to substantiate this adoption were first negative, then ambiguous, and eventually reported beneficial effects but only after a long-acting bronchodilator was added to the ICS. More importantly, these trials had two important flaws that biased their findings, resulting from the discontinuation of existing treatment and the absence of the fundamental intent-to-treat analysis. Two recent trials designed for a proper intent-to-treat analysis of the primary outcomes both found no benefit of ICS in COPD.

Taken together, all trials to date suggest instead that the bronchodilator component of the combination therapy widely used today, and not the ICS component, is effective in COPD. This effect of bronchodilation may in fact explain, notwithstanding the two limitations previously described, why the earliest randomised trials of ICS alone found no benefit, whereas only the subsequent ones evaluating ICS combined with LABAs did start to report important beneficial effects.

The randomised controlled trial is the fundamental scientific pillar in the assessment of the benefit of drugs. The practising clinician justly assumes that results from randomised trials are valid and reliable, particularly when they form the basis for evidence in treatment guideline recommendations. After several inadequately designed or analysed trials, it is now evident that the only two trials that have been correctly performed found no benefit for the ICS component of COPD treatment. It is therefore objectionable that, today, the majority of patients with COPD are subjected to ICS, largely obscured in a single device of combination therapy with a bronchodilator, despite the initial absence of proof of effectiveness and now in the face of proof of absence of effectiveness. With the significant risks that these drugs carry for the estimated 20 million, mostly older, Americans and Europeans with COPD who are using them, as well as millions of others worldwide, it is time to reassess the studies and clinical guidelines that recommend this treatment practice, and urgently so, to prevent serious harm to these patients [52]. Moreover, to provide data reliable for clinical practice, future randomised trials in COPD will have to be designed to address the relevant clinical question in the appropriate study population, recognising the different COPD subtypes, with sufficiently extensive and complete follow-up, particularly if the drugs under study seek to modify the course of a disease that takes decades to develop.

STATEMENT OF INTEREST

Statements of interest for S. Suissa and P.J. Barnes can be found at www.erj.ersjournals.com/misc/statements.dtl

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