Chronic obstructive pulmonary disease lost in translation: Why are the inhaled corticosteroids skeptics refusing to go?

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Abstract:
A survey of pulmonologists attending a clinical meeting of the Saudi Thoracic Society found that only 55% of responders considered that inhaled corticosteroids (ICS) had a positive effect on quality of life in Chronic Obstructive Pulmonary Disease (COPD). Why the divergence of opinion when all the guidelines have concluded that ICS improve quality of life and produce significant bronchodilation? ICS unequivocally reduce the rate of exacerbations by a modest 20%, but this does not extend to serious exacerbations requiring hospitalization. Bronchodilatation with ICS is now documented to be restricted to some phenotypes of COPD. Withdrawal of ICS trials reported a modest decline of FEV1 (<5%) in half the studies and no decline in the other half. In spite of the guidelines statements, there is no concurrence on whether ICS improve the quality of life and there is no conclusive evidence that the combination of long-acting ß2 agonists (LABA) with ICS is superior to LABA alone in that regard. The explanation for these inconclusive results may be related to the fact that COPD consists of three different phenotypes with divergent responses to LABA and ICS. Therapy tailored to phenotype is the future for COPD.

Key words: COPD, inhaled corticosteroids, phenotyping

We surveyed pulmonologists attending a scientific meeting of the Saudi Thoracic Society on whether the use of inhaled corticosteroids (ICS) results in improvement of quality of life in Chronic Obstructive Pulmonary Disease (COPD). Only 55% responded affirmatively while 45% thought ICS had no effect on quality of life. Why this divergence of opinion when all major guidelines concluded that ICS improve quality of life and produce significant spirometric improvement in COPD? The skepticism is not limited to Saudi pulmonologists: Studies and surveys document large differences in ICS use between various countries. Also, medical journals are still airing dissenting views that challenge the mainstream belief in ICS in COPD as enshrined in the guidelines. Why the confidence gap?

Inhaled corticosteroids and COPD
A Google search for COPD and corticosteroids yielded 685,000 results! A PubMed search yielded 2,307 results (including 768 reviews). Given this staggering amount of research and reviews, it is surprising that the role of ICS in COPD is still controversial. Table 1 summarizes the areas of controversy.

The position of various scientific bodies on the role of inhaled corticosteroids
The Global Initiative for Chronic Obstructive Lung Disease (GOLD) states that ICS improve symptoms, lung function, and quality of life, and reduce the frequency of exacerbations (Evidence A). Withdrawal from treatment with ICS—GOLD concluded—may lead to exacerbations in some patients and that regular treatment with ICS neither modify the long-term decline of FEV1 nor mortality (Evidence A). When it comes to the combination, ICS/long-acting ß-2 agonists (LABA) GOLD states that a large prospective clinical trial failed to demonstrate a significant effect on mortality, but a subsequent meta-analysis found that combination therapy may reduce mortality (Evidence B). The US Food and Drug Administration (FDA) approved the combination of ICS/LABA for the reduction of exacerbations and for improving the FEV1 above

Table 1: Controversy of the role of ICS in COPD

| Areas where ICS* is widely (but not universally) accepted | Areas where the effect of ICS is still debated |
|----------------------------------------------------------|-----------------------------------------------|
| Modest reduction of exacerbations                         | ICS produce a bronchodilator effect           |
| Withdrawal of ICS causes increased exacerbation rates     | Improvement in the quality of life            |
| Do not slow deterioration of FEV1                         | Abrupt withdrawal of ICS trigger spirometric deterioration |
| No reduction of mortality                                 |                                               |
| Small but significant increase of the risk of pneumonia without corresponding increase of mortality (ICS*) |

*ICS = Inhaled corticosteroids
what LABA could achieve. The FDA took the further step of approving a role for COPD not only “with chronic bronchitis but also emphysema or both conditions.”

The reduction of exacerbations by ICS is marginal compared with LABA and does not extend to exacerbations requiring hospitalization.

In the Torch study, one of the best designed and frequently quoted studies, the mean annual exacerbation rates (no./pt./yr) were as follows [Table 2]:[9]

As exacerbations requiring hospitalization are disproportionately responsible for financial cost and mortality, it is clear that the impact of therapy is not huge. Another large study used requiring oral corticosteroids as a marker of severity of exacerbation; the rates were 1.14 (placebo), 0.91 (formoterol), 0.87 (budesonide), and 0.63 (combination).[8] These findings— unlike those of the Torch Study—lend support to the theory that ICS and LABA are synergistic to each other’s effect, with the reduction of exacerbation with the combination greater than with either drug alone. However, that study used patients who smoked as little as 10 packs/year, where they are likely to be suffering from irreversible asthma and not COPD.[7] In the Tristan study, the exacerbation rate was 1.3 (P), 1.04 (LABA), 1.05 (ICS), and 0.97 (Comb).[8] Although a statistically significant difference exists between the LABA and combination arms, the difference was of little practical significance (0.07 exacerbations per year). Szafranski et al. reported rates of 1.87, 1.84, 1.59, and 1.42, respectively.[9] Calverley et al. recently reported no difference between LABA and the combination.[10]

In conclusion, the effect of combination is only marginally better than LABA (and absent in some studies) but does not extend to hospitalization. A recent meta-analysis found that the rate of exacerbations requiring oral corticosteroids was 17.5% with the combination and 20.1% with LABA.[11] The same meta-analysis found no significant difference in exacerbations requiring hospitalization.[11] This supports the findings of the TORCH study.

Withdrawal of ICS is associated with a small risk of increased exacerbations. Interestingly, a recent study found that the risk of exacerbations in COPD is associated with sputum eosinophilia, long duration of symptoms, and smoking ≤ 40 packs/year.[12] Other studies documented that these features are indicative of a steroid-responsive phenotype of COPD, or a diagnosis of irreversible asthma.[7,13,14] As discussed below, phenotyping can predict responsiveness to ICS.

The effect of ICS and LABA + ICS on quality of life is not consistent and usually below the level of clinical relevance.

We reviewed 11 studies which reported on changes in health-related quality of life of which 10 had a duration of 12 months or more.[5,6,8-10,15-20] LABA were associated with deterioration of quality of life in two studies and with improvement in six other studies. ICS were associated with deterioration in one study and improvement in five other studies (none of them above the four-point threshold of clinical relevance). The combination of LABA + ICS produced the same pattern: two studies showed deterioration of quality of life, and another six showed improvement. In only three of these, the improvement was above the 4-point threshold. In one of these, the LABA + ICS produced an impressive

| Table 2: The mean annual exacerbation rates of COPD in torch study |
|----------------------|-----------------|----------------|----------------|
|                     | Placebo         | Salmeterol     | Fluticasone    | Salm+Flut      |
| Rate ratio          | 1.13            | 0.97           | 0.93           | 0.85           |
| (95% CI)            | (0.78-0.93)     | (0.76-0.89)    | (0.69-0.81)    |
| Versus placebo      | 0.19            | 0.16           | 0.17           | 0.16           |
| Rate ratio          | 0.82            | 0.88           | 0.83           |
| (95% CI)            | (0.69-0.96)     | (0.74-1.03)    | (0.71-0.96)    |

| Table 3: Studies showed change in St. George’s Respiratory Questionnaire in COPD |
|--------------------------------|----------------|----------------|----------------|
| Study                           | Placebo | LABA | ICS | LABA + ICS |
| Torch 2007[9]                   | +0.2    | -0.8 | -1.8 | -3         |
| n = 6112                        |         |      |     |            |
| Tristan 2003[9]                 | -2.30   | -3.4 | -3.1 | -4.5       |
| n = 1465                        |         |      |     |            |
| Szafranski 2003 et al[8]        | -0.03   | -3.6 | -1.9 | -3.9       |
| n = 812                         |         |      |     |            |
| Rennard 2009[18]                | -1.50   | 2.90 |      | -3.90      |
| n = 1964                        |         |      |     |            |
| Anzueto 2009[20]                | +3.28   |      |      | +2.49      |
| n = 797                         |         |      |     |            |

SGRQ = St. george’s respiratory questionnaire

improvement of − 7.5.[8] However, the improvement was against placebo (and not baseline); the placebo itself had registered a deterioration of about 4.5 units.[8] The real change (from baseline) after 12 months of therapy with LABA + ICS was less than 3 points [Table 3].[9]

A large number of studies showed ICS (alone or in combination with LABA) to improve FEV1. Why should that be the case?

A large bulk of COPD studies deal with the effect of ICS on pulmonary function and have reported a significant positive effect on FEV1.[10,21-24] Some of these studies reported average rise of FEV1 of 29% in the “reversible” group of COPD patients following therapy with LABA + ICS.[21,22] Fluticasone and budesonide were the drugs of choice used in these studies but claims were made for other corticosteroids.[10] The explanation given for a “bronchodilator” effect of ICS is their anti-inflammatory effect. The claims for ICS contradict all published evidence for the following reasons:

1. About a dozen studies reported on the effect of ICS on inflammatory cells in sputum, bronchial biopsy, or bronchi alveolar lavage of COPD patients. With the exception of two studies (with marginal reduction in cells), all demonstrated no reduction of inflammatory cells, particularly neutrophils.[14,25-30] Also, ICS had no effect on inflammatory markers or protease—antiprotease balance.[36,37]
2. In both asthma and COPD, multiple inflammatory genes are activated as a result of acetylation of core histones around which DNA is wound. This facilitates gene transcription and synthesis of inflammatory mediators. Histone deacetylase 2 are recruited by corticosteroids to switch off this process.\cite{33,35} Barnes hypothesized that oxidative stress in COPD impair the function of HDAC 2 and render the condition unresponsive to corticosteroids even after cessation of smoking.\cite{33,34} The drugs proposed to reverse the steroids unresponsiveness—like antioxidants, theophylline, nortriptyline, or phosphoinositide – three – Kinase inhibitors although exciting are still experimental or unproven in large clinical trials.\cite{33-35}

We suggested in 2004 that one of the largest studies demonstrating a bronchodilator effect of ICS of COPD had inadvertently included patients with asthma.\cite{36} This was based on the fact that patients aged 40 to 49 years and patients with previous (but not current) history of asthma were included.\cite{36} Also, half the patients were “reversible” with 30% rise of FEV1 in response to inhaling 400 μcg of salbutamol.\cite{22} Although short-term response to Salbutamol is unreliable in differentiating asthma and COPD, patients with the latter condition have generally a much lower FEV1 response. Lastly, the improvement of FEV1 was manifest only after 24 hours of ICS therapy, a behavior not compatible with asthma not COPD outside exacerbations.\cite{22}

We had to wait a decade to build evidence that whenever a form of phenotyping was used, COPD was split into two entities: steroid-responsive and non-responsive. Table 4 summarizes some of these studies.

The old concept of “chronic bronchitis” form of COPD free of emphysema (and represented by blue bloaters) is not only challenged by CT scanning, but also postmortem studies.\cite{40,41} Although pink puffors and blue bloaters show clinical differences, they do not represent major difference in the degree of emphysema at death.\cite{42} The above studies and others show that the following phenotypes are not ICS or prednisolone responders: bronchial histology showing no thickening of basement membrane, lack of eosinophilia in sputum, short duration of smoking, reduced carbon monoxide diffusion capacity (DLCO), or predominant emphysema by CT scanning.\cite{13,14,37-39,42} The opposite is also true: eosinophilic COPD (20 - 40% of all cases), uniform thickening of basement membrane, or patients in the lowest percentile for CT scan-diagnosed emphysema (even if severely obstructed) have many features of asthma including significant responsiveness to β2-agonists and corticosteroids.\cite{7,12,13,37-39,43,44}

Whenever phenotyping was used (CT, bronchial biopsy, sputum eosinophilia, . . . etc), COPD splits into a steroid-responsive and steroid-unresponsive groups. Some workers have recently expressed the view that treatment should be targeted to the phenotype of COPD whether asthma, mixed COPD, or predominantly emphysema.\cite{43,46}

### Spirometric decline on withdrawal of inhaled corticosteroids

Four studies reported on the effect of withdrawal of corticosteroids on FEV1 and produced contradictory results. Two studies documented decline of FEV1 but another two found no decline.\cite{47-49} In one of the studies although the mean FEV1 significantly dropped, the decline occurred in some but not all patients, and some patients had normal DLCO.\cite{47}

| Paper | Method of phenotyping/ drug tested | Main results |
|-------|-----------------------------------|--------------|
| Chanez et al (1996)\cite{37} | Bronchial biopsy/oral prednisolone | 12/25 patients with > 12% reversibility of FEV1 after prednisolone had histology of asthma |
| Brightling et al (2000)\cite{12} [Figure 1] | Sputum eosinophilia/oral prednisolone versus placebo | Significant rise of FEV1, shuttle walk distance, and health status (CRQ) only with eosinophilia > 3% |
| Brightling et al (2005)\cite{14} [Figure 2] | Sputum eosinophilia/inhaled mometasone versus placebo | Significant rise of FEV1, only in the most eosinophilic tertiile. No significant change of health status (CRQ) in any tertile. |
| Fujimoto et al (1999)\cite{38} | Sputum eosiosphiila/ oral prednisolone | Rise of FEV1, correlated with eosinophils (not neutrophils) percentage in sputum. |
| Lee et al (2010)\cite{39} | CT scan (computerized score/Fluticasone + Salmeterol or Budesonide + formoterol for 3 months | Emphysema – dominant subtype showed no improvement of FEV1 (32 ml) or dyspnea scale (0.16). However, patients with severe obstruction without emphysema (mean FEV1 37% pred.) had normal mean DLCO (85.6% pred.) and improved FEV1 by 207 ml and dyspnea by – 0.68 |
| Al-Kassimi et al (2011)\cite{7} | CT scan (Qualitative visual), bronchial biopsy, and hypercapnic respiratory failure to classify into COPD and irreversible asthma/Budesonide + Formoterol for 12 months | COPD patients showed no significant rise of FEV1 while irreversible asthma group improved their mean FEV1 by 350 ml. |
| Al-Kassimi et al (2011)\cite{40} | CT scan, bronchial biopsy, ABG,KCO/Budesonide + Formoterol | Abrupt withdrawal of budesonide produced no significant drop of FEV1 in COPD after excluding irreversible asthma cases |
| Fujimoto et al (2006)\cite{41} | CT scan (visual semi-quantitative) to detect emphysema and bronchial wall thickening (BWT) | A Phenotype: 18% are never smokers/most patients had normal DLCO/ Salbutamol reversibility significant (13.1 %) |
| | • No or little emphysema (A phenotype) 22.7% |
| | • Emphysema without BWT (E phenotype) 51.7% |
| | • Emphysema with BWT (M phenotype) 25.6% |
| | M phenotype: practically all smokers DLCO (61.6%+2.8)/salbutamol reversibility significant (16.8%) |
| | E Phenotype: practically all smokers (DLCO 49.3% +2.1/mean reversibility Salbutamol not significant (10.7%) |
The discrepancy between patients may represent the effect of studying a mixed group of irreversible asthma and COPD. Al-Kassimi et al. reported no spirometric deterioration in a group selected for the following proper COPD phenotype: panlobular emphysema on CT scan, chronic hypercapnic respiratory failure (never described in stable asthma outside exacerbations), bronchial histology indicative of COPD, and low coefficient for carbon monoxide diffusion (KCO).

Overall view of inhaled corticosteroids in chronic obstructive pulmonary disease
We believe that the contradictory and inconclusive results obtained from ICS trials in COPD (outside reduction of exacerbations) reflects the heterogeneous nature of COPD and the relative weight of irreversible asthma cases in the COPD population under study. A large meta-analysis concluded that ICS did not slow down the rate of decline of FEV1. A similar meta-analysis reached a different conclusion and reported a slowdown of FEV1 by 7.7 ml/year. The second meta-analysis was tipped in favor of ICS by including one study which made only a small contribution to the meta-analysis and which was published as an abstract not a peer reviewed Journal article. In a large (47 primary studies) Cockrane Database review, use of ICS resulted in a small improvement of FEV1 in some but not all studies. This again highlights the heterogeneity of COPD. Barnes concluded that only some COPD patients with “concomitant asthma” may benefit from ICS. Regrettably, the atmosphere of confusion has resulted in many practitioners prescribing ICS outside the accepted GOLD recommendation of FEV1 < 50% and frequent exacerbations. Only a minority of COPD cases belong to that group. In the average patient, ICS would prevent 0.26 exacerbation per year (or one attack every four years), not extending to attacks requiring hospitalization. More importantly, the guidelines should spell the bitter truth: COPD is not one entity that can be managed in the same way! Phenotyping should influence therapy with ICS and must be incorporated in clinical practice. The recently expressed calls for targeting treatment to the phenotype of COPD should be heeded.

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