Indacaterol/Glycopyrronium in the Treatment of Severe Respiratory Failure: Marked Improvement of Respiratory Failure in a Few Weeks – A Case Report

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Keywords

Indacaterol/glycopyrronium · Chronic obstructive pulmonary disease · Severe respiratory failure

Abstract

Chronic obstructive pulmonary disease is a highly prevalent disease, especially in the aging population, associated with several functional disabilities and a high economic burden. Dual bronchodilation with prefixed associations of long-acting β_2 -agonists and long-acting muscarinic antagonist have a significant role in the management of this condition. The newer combination, indacaterol/glycopyrronium, is useful as a once-a-day therapy and has proven superior to other treatment strategies including inhaled corticosteroids for improving symptoms and clinical condition with a very rapid effect. We report our experience with a patient suffering from severe respiratory failure who improved significantly when the indacaterol/glycopyrronium combination was added to his therapy.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a very common disease with high rates of morbidity and mortality worldwide and a prevalence increasing with age [1]. However, it is both preventable and treatable as it regards the progressive decline in lung function [2]. Pharmacological treatment can control symptoms and reduce the number and frequency of acute exacerbations requiring hospital admission [3, 4]. The new Global Strategy for Diagnosis, Management and Prevention of COPD (GOLD 2017) guidelines suggest that prolonged bronchodilation with long-acting muscarinic antagonists (LAMA) and/or long-acting β_2 -agonists (LABA), with or without inhaled corticosteroids (ICS), should be the strategy of choice in COPD patients [2, 3, 5]. Of note, ICS should be reserved only for symptomatic and frequently exacerbating COPD patients [5].

LABA and LAMA can be used alone or in prefixed combinations, the latter maximizing their bronchodilation through a synergic effect [6]. Newer agents, such as indacaterol and glycopyrronium, which have a prolonged duration of effects up to 24 h, are the main molecules used in fixed combinations. The coadministration of these two

bronchodilators leads to a synergistic improvement of bronchodilation, by leveraging different receptor types at submaximal doses with enhanced therapeutic benefits and reduced dose-dependent side effects [7, 8], and thus making these drugs stand out in the pharmacological armamentarium.

We present the case of a patient with severe respiratory failure whose lung function remained severely compromised with conventional therapy, but showed an immediate and marked improvement after introducing the indacaterol/glycopyrronium combination to his therapy.

Case Description

A 72-year-old man with a previous history of heavy smoking with chronic cough and mucus presented to the outpatient clinic for severe dyspnea with a modified Medical Research Council (mMRC) score of 3. His shortness of breath had been progressively worsening over the last 2 years, following a car accident with multiple rib fractures, lung contusion, and hemothorax. On admission, chest radiography showed multiple areas of lung and pleural fibrosis coupled with a raised hemidiaphragm on the left side, whereas only a slight increase of lung transparency was noted on the right side. The respiratory rate was mildly increased, with the patient maintaining an upright thorax position while sitting and his lips showing evident cyanosis. Diffuse reduction of lung sounds was perceived on the left hemithorax, with some wheeze and crackles audible on the right side.

Spirometry revealed a reduction of total lung capacity to 72% of the predicted value, with a marked reduction of forced vital capacity (FVC, 65%) and forced expiratory volume in the first second (FEV₁, 45%). The FEV₁/FVC ratio was 55% (normal value >70%). The arterial blood gas analysis revealed a PaO₂ pressure of 35 mm Hg and a PaCO₂ pressure of 52 mm Hg, with a pH of 7.41. Given the diagnosis of acute severe respiratory failure, immediate hospital admission was deemed necessary for the patient, but he refused hospitalization. The following therapy was then prescribed for 2 weeks: prednisone 50 mg once daily, cefditoren/pivoxil 400 mg twice per day, ipratropium bromide 80 mg and salbutamol 400 µg 4 times a day by aerosol, and low-flow oxygen through a Venturi mask with a FiO₂ of 0.28; a follow-up visit was scheduled at the end of this treatment.

When the patient presented to the clinic for follow-up, arterial blood gases showed only little improvements (PaO₂ 41 mm Hg and PaCO₂ unchanged), but dyspnea and general discomfort were still present. Thus, the therapy was modified as follows: prednisone 25 mg once daily for 2 weeks and then 12.5 mg once daily until the follow-up visit, oxygen as before, and the prefixed inhaled combination indacaterol/glycopyrronium once daily. A control visit was scheduled 4 weeks later.

At that time, the clinical situation of the patient was substantially improved: dyspnea decreased (mMRC score 2) and PaCO₂ was normalized, whereas PaO₂ had reached 51 mm Hg. Oral steroids were switched to ICS (fluticasone propionate 500 µg twice per day), oxygen FiO₂ was reduced to 0.24, indacaterol/glycopyrronium was maintained. After 3 months, the patient is slowly pro-

gressing (PaO₂ up to 58 mm Hg), and the clinical question of whether to interrupt ICS with the patient under strict supervision is burning.

Discussion

The progressive decline in lung function, typical for COPD, is responsible for high morbidity and mortality rates [2], with estimates of COPD as the fourth leading cause of death worldwide, going for third place. Of note, acute COPD exacerbations requiring hospitalization carry a 3-fold higher mortality rate in the aging population [9], the subgroup of patients in whom COPD prevalence is the highest [1]. COPD accounts for about 6% of all deaths globally [10].

Importantly, COPD impairs the functional capacities of the individuals, and thus their working skills are also affected [11]. All these features imply that COPD carries a high economic burden [1].

The pharmacological strategies currently available for COPD patients mainly focus on prolonged bronchodilation, as suggested by the GOLD 2017 guidelines, as a way to improve symptoms and reduce exacerbations. LAMA and LABA, either alone or in combination, are the most important drugs in this field, together with ICS [2, 5]. The fixed combinations show a synergic effect of maximized bronchodilation which allows for a lower rate of dose-dependent side effects [6].

Moreover, the recent CRYSTAL study, focused on the combination of indacaterol and glycopyrronium, showed the superiority of the assessed combination over the association of LABA/ICS or LAMA in reducing symptoms and rapidly improving lung function [12–14]. Of note, the improvement of dyspnea is evident immediately after the switch from the previous treatments [13]. This evidence further supports the positive effects shown with indacaterol/glycopyrronium on exacerbation prevention versus salmeterol/fluticasone in the FLAME study.

This combination shows a synergistic action for improved bronchodilation [6], secondary to reciprocal potentiation of the two molecules [15]. Several possible mechanisms are advocated for this synergy: the high density of β₂-adrenergic receptors and the pathogenic role of neurogenic cholinergic mechanisms result in the leveraging of different receptor types at submaximal doses, increasing the therapeutic benefits and minimizing the dose-dependent side effects [7, 8]. Laboratory studies have shown that β₂-adrenoceptor agonists activate pre-junctional β₂-adrenoceptors to reduce acetylcholine re-

lease, and that an inhibitory crosstalk may exist between M3 receptors and β_2 -adrenoceptors in airway smooth muscle cells [15, 16].

All these speculations may explain the clinical improvement of our patient when the indacaterol/glycopyrronium combination was started. Notably, the patient markedly improved after just a few weeks of indacaterol/glycopyrronium, whereas the previous treatment did not prove efficacious in improving his clinical condition.

Acknowledgement

The authors thank Luca Giacomelli, PhD, for providing medical writing on behalf of Content Ed Net; this assistance was funded by Novartis Farma SpA.

Financial Disclosure and Conflicts of Interest

The authors have no conflicts of interest directly relevant to this paper.

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