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EDITORIAL

About the role of indacaterol in obstructive airways disorder: PRO☆

A propósito do papel do Indacaterol na patologia obstrutiva das vias aéreas: PRÓ

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of mortality and chronic morbidity throughout the world.[1]

COPD is nowadays the fourth leading cause of death[2] and its mortality is estimated to increase in the coming decades.[3]

Most studies have indicated that the existing pharmacologic treatment for COPD do not modify the long-term decline of pulmonary function,[4,5] so pharmacotherapy is mainly used to decrease symptoms and/or complications.[1]

Bronchodilator medications are central to the symptomatic management of COPD and β2 agonists are recommended in all stages of severity of COPD.[1]

As with all chronic diseases, non-adherence to treatment is common in patients with COPD.[6] More complex regimens generally result in suboptimal adherence, with dosing and the absence of immediate effect on symptoms regarded as the principal factors negatively influencing adherence.[7]

Indacaterol is an innovative, inhaled, ultra-long acting β2 agonist that has been approved in more than 50 countries worldwide, including throughout the European Union at the doses 150 μg and 300 μg once-daily for COPD treatment.[8]

This molecule is the result of bio-engineering, being highly lipophilic, a property that allows a longer and more stable association with membrane β2-receptors,[9] resulting in an ultra-long duration of action, similar to salmeterol and tiotropium.[10,11] Furthermore, this strong interaction results in a rapid citoplasmatic molecule activation leading to rapid onset bronchodilation. In preclinical studies, the onset of action of indacaterol was similar to that of salbutamol and formoterol,[12,13] a result confirmed by clinical trials.[14]

The efficacy of indacaterol in the maintenance treatment of COPD in adults has been assessed in four fully published, large (>400 patients), randomized, double-blind parallel-group, placebo-controlled, multicentre, phase III trials.[10,15–17] The primary endpoint in the four placebo-controlled trials was the 24-h post-dose FEV1 after 12 weeks.

In the INHANCE study[10] both doses of indacaterol achieved higher post-dose FEV1 values ($p \leq 0.01$) than tiotropium 18 μg once-daily, with absolute differences of 40–50 ml between the former and the latter. Furthermore, when dividing patients into subgroups such as age under/over 65; non/current smokers and non/inhaled corticosteroids users, indacaterol (both doses) was non-inferior to tiotropium in all subgroups.[10]

The INVOLVE[15] and INLIGHT[17] studies, suggested that indacaterol 300 μg once daily was significantly ($p \leq 0.001$) more effective than formoterol 12 μg twice daily,[15] and indacaterol 150 μg once daily was significantly ($p < 0.001$) more effective than salmeterol 50 μg twice daily,[17] as measured by 24-h post-dose FEV1 at 12 weeks.

Furthermore, it has been proven that indacaterol leads to a reduction in rescue medication when compared to formoterol[15] and tiotropium.[10] More recently, the INTENSITY study[18] revealed a great reduction in rescue medication use with indacaterol over tiotropium, with patients on indacaterol experiencing an additional 5% of days free from rescue medication use.

Regarding quality of life (QoL), three studies[10,15,17] were designed and performed to compare the QoL impact of indacaterol. This impact was assessed using St. George's Respiratory Questionnaire (SGRQ).

In the INHANCE study,[10] mean SGRQ total scores versus placebo were significantly greater for indacaterol 150 μg once daily, but not for 300 μg recipients than for tiotropium ones after 26 therapy weeks.

SGRQ score versus placebo was also significantly greater for indacaterol than for salmeterol recipients at 12-week assessment in INLIGHT study.[17]

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In INVOLVE study,[15] there were no significant differences between indacaterol and formoterol at 12 and 52 week assessments, in what concerns QoL.

Limitation in exercise capacity represents an important feature of COPD, and is one of the main factors which have a negative impact on patient quality of life. O'Donnell et al.[5] have already demonstrated that indacaterol achieved a significant improvement in end-exercise inspiratory capacity after 3 weeks of treatment with a difference from placebo of 280 ml. Improvement in exercise endurance time was also higher with indacaterol than with placebo. This observed exercise capacity amelioration with indacaterol could be explained by the improved health status observed in long-term studies[10,15] assessed using SGRQ.

In cases of use of short-term β2-agonist in patients undergoing long acting β2-agonists (LABA), none of the indacaterol doses caused a change in isoprenaline-induced relaxation. In contrast, even the lowest concentration of salmeterol significantly antagonized the effects of isoprenaline.[12]

It has been suggested that a partial agonist such as salmeterol has to occupy more receptors than a full agonist and thereby creates a situation in which functional receptor number becomes limiting in terms of obtaining a maximal response. As a consequence, a partial agonist behaves as an antagonist in the presence of an agonist with higher efficacy acting on the same receptor.[12]

Data regarding rates of exacerbations are limited, but INHANCE study[10] showed that they were similar between both doses of indacaterol and tiotropium, and lower than observed in placebo group.

In relation to adverse events, INHANCE study[10] showed that this events occurred in similar percentages of patients across all treatment groups (indacaterol 150 and 300 μg, placebo and tiotropium 18 μg) in the 26-week study period. Adverse events were typical of those expected in patients with moderate or severe COPD and were predominantly of mild or moderate severity. The most frequent adverse events were respiratory tract infections which occurred in similar numbers of patients in each treatment group.[10,18]

The INLIGHT study[16] provided further evidence of the favorable safety profile of indacaterol 150 μg once daily. During this study, adverse events occurred in similar numbers of patients in indacaterol ($n = 104$, 49.3%) and placebo groups ($n = 96$, 46.8%). The most frequent individual events were COPD worsening and cough, both of which occurred more frequently with placebo than with indacaterol.

In INSURE study,[14] adverse events were reported in 3/86 (3.5%), 3/87 (3.4%), 4/86 (4.7%), 6/88 (6.8%), and 4/87 (4.6%) patients taking indacaterol 150 μg, indacaterol 300 μg, salbutamol 200 μg, salmeterol–fluticasone 50/500 μg, and placebo, respectively. All reported adverse events were mild or moderate in severity. There were no deaths and no patient discontinued from the study due to adverse events.

Another study[15] has already demonstrated an acceptable tolerability and safety profile of indacaterol even with the above-therapeutic 600 μg doses given for up to 1 year, compared with placebo.

In phase III clinical studies,[15,16] health care providers observed that at clinic visits on average 17–20% of patients experienced sporadic cough that occurred usually within 15 s following inhalation and typically lasted for 5 s. This cough experienced post-inhalation was generally well tolerated and did not lead to any patient discontinuing the studies at the recommended doses. There is no evidence that cough experienced post-inhalation is associated with bronchospasm, exacerbations, deteriorations of disease or loss of efficacy. In the phase III trials, the incidence of cough spontaneously reported by patients as an adverse event was approximately 7% for indacaterol with no clear dose response versus 5% for placebo. This compares to 6% on tiotropium and 4% on formoterol.

The patient reports on cough were fewer than health care professionals have noticed, which shows the lack of importance patients gave to this episode.

Work[16] was carried out to identify the aetiology of cough experienced following inhalation, but so far has not provided conclusive results and further research is ongoing to elucidate its mechanism.

Finally, a word about Breezhaler®. It is a new capsule based dry-powder inhaler with low resistance ($0.07\ cm\ H_2O^{1/2}/l/min$), specially created to be used with indacaterol.[19,20] This low resistance device is therefore suitable for use by patients with a wide range of COPD severities (including GOLD IV patients), making it possible to deliver a consistent fine particle dose irrespective of disease severity and age.[19,20]

There are no reports about device failures in clinical trials.[19]

Furthermore, it is a small and very portable device preferred by many patients as their continued daily use inhaler.[21] In an open-label, randomized, cross-over study, patients found Breezhaler® more comfortable to inhale through and simpler to use than Handihaler®.[21] Patients were also more confident that the medication had been taken correctly using this inhaler[21] because they could hear the capsule spinning when inhaling, taste the lactose and see that the capsule, which is transparent, was empty after the procedure.[21] So, this device has additional security mechanisms to assure patients a correct drug delivery.

To summarize, indacaterol is rapid onset action, ultra-long acting, effective, safe and well-tolerated therapy for COPD patients. It is provided in a very portable, low resistance device, already preferred by many patients.

These characteristics may make the difference in achieving better rates of therapy adherence in these chronic patients. So, in my opinion this therapy tool should be considered when prescribing bronchodilators to COPD patients.

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