Review

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Comparative effectiveness of indacaterol/glycopyrronium in the treatment of chronic obstructive pulmonary disease

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Summary: Indacaterol/glycopyrronium has been the first long-acting β_2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) fixed-dose combination to be approved as a maintenance treatment in chronic obstructive pulmonary disease patients. Comparative effectiveness studies indicate that it is constantly superior to a LAMA or a LABA alone or even a LABA/inhaled corticosteroid combination, regardless of the drugs used. However, definitive data documenting the benefit of indacaterol/glycopyrronium fixed-dose combination over these consolidated therapies are still absent in a real-world setting, although the results of pivotal randomized controlled trials show that this is the case. Therefore, in addition to the large body of evidence already available supporting the use of indacaterol/glycopyrronium, pragmatic observational studies or *ad hoc* designed trials should be planned to collect data that could confirm the high effectiveness of indacaterol/glycopyrronium even in the real-life clinical practice.

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Current guidelines and recommendations of the management of chronic obstructive pulmonary disease (COPD) indicate that inhaled bronchodilators are fundamental in the treatment at each stage of the disease [1–3]. Nevertheless, they do not specify if it is preferable to start treatment with a β-agonist or an antimuscarinic agent in patients with mild/moderate stable COPD, and if the once-daily regimen is more effective than the twice-daily dosing or vice versa [4]. Moreover, it is still not known when two bronchodilators with different mechanisms of action must be combined [4], although the most recent GOLD Strategy recommends the use of the dual bronchodilation (a combination of a long-acting muscarinic antagonist [LAMA] with a long-acting β_2-agonist [LABA]) for patients with persistent breathlessness on monotherapy, and as initial therapy for patients with severe breathlessness [1].

Indacaterol/glycopyrronium fixed-dose combination

Indacaterol/glycopyrronium has been the first LABA/LAMA fixed-dose combination (FDC) to be developed [5]. It has been approved for sale and marketing by many regulatory authorities worldwide as a maintenance bronchodilator treatment to alleviate symptoms in COPD patients based on results from the pivotal Phase III programs IGNITE, which investigated indacaterol/glycopyrronium 110/50 μg once-daily across 52 countries and enrolled >10,000 patients, and EXPEDITION, which explored indacaterol/glycopyrronium 27.5/15.6 μg twice-daily in the USA [5].

The results of the IGNITE program and the QUANTIFY trial showed that once-daily indacaterol/glycopyrronium 110/50 μg once-daily causes faster and more sustained bronchodilation than indacaterol, glycopyrronium, tiotropium, salmeterol/fluticasone FDC and the free-dose combination of tiotropium plus formoterol, larger improvements in patient-reported dyspnea than tiotropium, salmeterol/fluticasone FDC, and the free-dose combination of tiotropium plus formoterol, greater control of daytime and also nighttime COPD symptoms than glycopyrronium, tiotropium and salmeterol/fluticasone FDC, and health related quality of life (HRQoL) improvements greater than those induced by glycopyrronium, and tiotropium [5]. The LANTERN [6]

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and, mainly, the FLAME studies [7] documented that indacaterol/glycopyrronium 110/50 μg once-daily is also more effective than salmeterol/fluticasone 50/500 μg FDC twice daily in preventing acute exacerbations of COPD.

Need for comparative effectiveness research

All this information has been generated by randomized controlled trials (RCTs). However, RCTs, sometimes called 'efficacy' research, fulfill established regulatory rules, are focused on a specific primary end point and explore whether the experimental intervention is statistically more effective than placebo or an active comparator on this end point. To make this determination, RCTs are conducted under standardized conditions, with strict enrollment criteria to avoid variables unrelated to the intervention. In this way, it is possible to better define the effectiveness of the intervention [8]. However, the patients recruited do not necessarily represent those encountered in everyday life. Those who are enrolled in RCTs are inclined to be less symptomatic than general patient populations. Furthermore, RCTs tend to exclude patients who may derive the maximum benefit from the treatment, as they are able to benefit the most sooner. Also, most symptomatic patients among those included in the control arms may withdraw from the study to obtain greater symptom relief [9].

Consequently, RCTs, which are mandatory to have a drug approved by regulatory authorities, often do not provide answers of the fundamental question "Which interventions, when translated into practice, improve care and increase the likelihood of health benefits?" [10]. In fact, large and rigorous inclusion/exclusion criteria of RCTs may substantially diminish generalizability or application of evidence [11].

Clearly, there is a need for more evidence on effectiveness of the intervention in everyday practice of typical healthcare clinicians from comparative effectiveness research, which utilizes observational and clinical trials or conventional meta-analyses to compare different therapeutic strategies, in order to overcome limits of RCTs and also to help make decisions that can really be more generalizable [12]. Actually, comparative effectiveness studies seem to be fundamental in addressing questions about the best existing therapies in individual patients and the most effective method to deliver this care [13].

Evidence from COPD RCTs

A systematic review and meta-analysis of RCTs that assessed the efficacy and safety of indacaterol tried to give a possible answer to a critical question "Does the addition of indacaterol to tiotropium offer additional benefits to patients" [14]. Two RCTs that enrolled 2239 patients described adjusted FEV_1 changes at 12 weeks. The pooled additional benefit from indacaterol on top of tiotropium treatment was 0.07 l (95% CI: 0.05–0.10 l, $I^2 = 0\%$). Remarkably, the upper 95% CI of the effect size approached the minimally important difference threshold.

We performed a systematic review and synthesis on the available clinical evidence to assess the effectiveness and cardiac safety of indacaterol/glycopyrronium FDC administered via the dry powder inhaler (DPI) Breezhaler/Neohaler for COPD treatment using the data from all trials lasting at least 3 months [15]. Indacaterol/glycopyrronium FDC increased the trough FEV_1 by 89.44 ml (95% CI: 76.04–102.85) versus monocomponents ($p < 0.001$). The efficacy was independent of the regimen of administration (once-daily +91.77 ml, 95% CI: 73.09–110.45; twice-daily +90.60 ml, 95% CI: 65.63–115.17) [14]. It also improved transition dyspnea index (TDI) score compared with monocomponents (mean difference: 0.52; 95% CI: 0.20–075) and increased the proportion of responder patients according to baseline value (Odd Ratio [OR]: 1.41; 95% CI: 1.19–1.66). The mean difference versus monocomponents in St. George's Respiratory Questionnaire (SGRQ) total score was -1.55 (95% CI: -2.08 to -1.02) and its OR versus monocomponents for the increase in the proportion of responder patients was 1.25 (95% CI: 1.12–1.40). Intriguingly, indacaterol/glycopyrronium FDC significantly ($p < 0.05$) protected against cardiac serious adverse events versus monocomponents (OR vs monocomponents: once-daily 0.39, 95% CI: 0.08–1.86; twice-daily 0.79, 95% CI: 0.25–2.49).

Other LABA/LAMA FDCs have recently become available or are under clinical development [4]. Regrettably, none of the newer combinations have been studied in a head-to-head comparative pragmatic trial with indacaterol/glycopyrronium FDC, which is the LABA/LAMA FDC that has shown to date the vast majority of evidences supporting the entire LABA/LAMA class. We strongly believe that such a type of trials will not be executed because of their cost and, mainly, because pharmaceutical companies have no interest in producing data that might be potentially bad for them. The choice of the combination to be used is difficult and empiric because of this lacking information, but at present indacaterol/glycopyrronium is the LABA/LAMA FDC supported by the strongest evidences of favorable effects on lung function and patient reported outcomes in comparison with other COPD well-established therapies (LABA, LAMA and LABA/inhaled corticosteroid [ICS]).

It is appreciated that all conventional meta-analyses only provide effective estimates for comparisons of two treatments simultaneously. Therefore, a ranking of competing treatments does not exist [16]. Nevertheless, valid investigations of whether interventions work differently in different subgroups involve comparing the subgroups with each other and, in this context, the nonoverlap of the CIs of the summary estimates in the groups can be considered [17].

In the already mentioned meta-analysis, we also evaluated the effectiveness and cardiac safety of four currently available LABA/LAMA FDCs for COPD treatment, always using data from all LABA/LAMA FDC trials lasting at least 3 months [15]. Although our results showed overlap of the CIs, which indicates no significant difference between treatments, the FEV_1 summary estimates regarding the approved doses of LABA/LAMA FDCs identified the following gradient of effectiveness in comparison with monocomponents: vilanterol/umeclidinium 62.5/25 μg (reference effectiveness) ≅ indacaterol/glycopyrronium 15.6/27.5 μg (-3 ml) > indacaterol/glycopyrronium 50/110 μg (-12 ml) > olodaterol/tiotropium 5/5 μg (-30 ml) > formoterol/aclidinium 400/12 μg (-49 ml). However, these differences were related to each monocomponent of the LABA/LAMA FDC. Consequently, no definitive conclusion regarding the relative efficacy could be obtained from this comparison also considering the substantial differences in the effect on FEV_1 showed by any single bronchodilator, especially if a LABA [18].

In any case, in a study that assessed the relative clinical benefit of all currently available LABA/LAMA FDCs using a Bayesian network meta-analysis [19], indacaterol/glycopyrronium was found to be associated with an increase in trough FEV_1 of 42 ml (95% CI: 7–77) compared with formoterol/aclidinium, a change that was statistically significant, 3 ml (95% CI: -24–31) compared with olodaterol/tiotropium and -22 ml (95% CI: -50–7) compared with vilanterol/umeclidinium at 24/26 weeks when using a fixed effects model. When the impact of concomitant ICS use at baseline was assessed, increases in trough FEV_1 were -23 ml (95% CI: -175–133) versus formoterol/aclidinium, 1 ml (95% CI: -38–43) versus olodaterol/tiotropium and -28 ml (95% CI: -66–14) versus vilanterol/umeclidinium, respectively. For the analysis of SGRQ or TDI percentage of responders at 24/26 weeks, no statistically significant results were seen in any of the LABA/LAMA FDC treatment comparisons. We must point out that the authors of this study acknowledged that differences in patients population, time points and exacerbation history could have biased the results of the analysis.

A meta-analysis compared the pooled efficacy data on prospectively collected COPD exacerbation rates from trials of LABA/LAMA FDCs with the two most commonly prescribed first-line treatments: LAMAs and LABA/ICS combinations [20]. An analysis on the effect of treatment with LABA/LAMA FDCs versus LAMA was not carried out because of data scarcity. Actually, only one study compared indacaterol/glycopyrronium versus glycopyrronium and documented that indacaterol/glycopyrronium was better in preventing moderate to severe COPD exacerbations [21]. However, indacaterol/glycopyrronium significantly decreased the annualized rate of moderate and/or severe exacerbations (risk ratio: 0.82; 95% CI: 0.75–0.91; $p < 0.00$) when compared with LABA/ICS treatment.

A Cochrane review with meta-analysis not only has confirmed that, compared with LABA+ICS, participants who were treated with indacaterol/glycopyrronium had fewer exacerbations (OR: 0.72; 95% CI: 0.63–0.83) but also has shown that, in contrast, vilanterol/umeclidinium (OR: 1.15; 95% CI: 0.64–2.06) and the other LABA+LAMA subgroups (OR: 1.02; 95% CI: 0.78–1.34) were not related to reduced risk of exacerbation [22]. Interestingly, the article highlighted that it is still not clear whether only indacaterol/glycopyrronium is able to prevent COPD exacerbations or all LAMA+LABA combinations are able to exert such type of effect. The same Cochrane review showed that all LABA/LAMA FDCs induced a significant increase in trough FEV_1 from the baseline. The mean difference versus LABA+ICS was: 0.08 l (95% CI: 0.44–0.12) for indacaterol/glycopyrronium, 0.09 l (95% CI: 0.07–0.11) for vilanterol/umeclidinium and 0.05 l (95% CI: 0.02–0.08) for the other LABA+LAMA subgroups, respectively. There was a significant decrease in SGRQ total scores in participants treated with indacaterol/glycopyrronium (mean difference: -1.29; 95% CI: -2.08 to -0.50) and the other LABA+LAMA subgroups (mean difference: -5.00; 95% CI: -7.35 to -2.65), but not with vilanterol/umeclidinium (mean difference: -0.08; 95% CI: -1.34–1.18) compared with participants treated with LABA+ICS.

Another very recent network meta-analysis has compared indacaterol/glycopyrronium with LABA/ICS combinations [23]. Both indacaterol/glycopyrronium once- and twice-daily caused a statistically significant greater improvement in trough FEV_1 at 3 months than both formulations of salmeterol/fluticasone propionate (50/250 and 50/500 μg) and vilanterol/fluticasone furoate 25/100 μg. At 6 months indacaterol/glycopyrronium once-daily showed statistically significant greater improvement in trough FEV_1 compared with salmeterol/fluticasone propionate 50/500 μg. Indacaterol/glycopyrronium twice-daily also showed statistically significant greater reduction of rescue medication use at 3 months than salmeterol/fluticasone propionate 50/250 μg.

Anzueto *et al.* [24] described the effect of indacaterol/glycopyrronium versus both tiotropium and salmeterol/fluticasone on the risk of clinically important deterioration (CID) in COPD using patient data from three large RCTs with a 26 weeks' duration and conducted in patients with moderate-to-severe COPD. The risks of the first CID and a sustained CID were evaluated using two definitions. The first definition included a ≥100 ml decrease in FEV_1, a ≥4-unit increase in SGRQ, and a moderate-to-severe COPD exacerbation, whereas in the second definition a ≥1-unit decrease in TDI replaced FEV_1. Indacaterol/glycopyrronium significantly reduced the risk of first or sustained CID versus either tiotropium (hazard ratio [HR]: 0.72; 95% CI: 0.61–0.86; p = 0.0003; and 0.73 95% CI: 0.61–0.89, p = 0.001) or salmeterol/fluticasone (HR: 0.67; 95% CI: 0.57–0.80; and HR: 0.63; 95% CI: 0.52–0.77, both p < 0.0001) using the first definition. On the contrary, it significantly reduced the risk of first, but not sustained, CID versus tiotropium (HR: 0.80; 95% CI: 0.64–0.99, p = 0.0359; and HR: 0.85; 95% CI: 0.66–1.10, p = 0.2208) and both first and sustained CID versus salmeterol/fluticasone (HR: 0.73; 95% CI: 0.61–0.88, p = 0.001; and HR: 0.72; 95% CI: 0.58–0.90, p = 0.0036) when the second definition was used.

All these findings are interesting and suggest that the use of indacaterol/glycopyrronium FDC should always be preferred to that of single monocomponents and also to the use of LABA/ICS if exacerbations are the primary end point of the treatment. However, they have been generated by the analysis of data produced by RCTs. We have already pointed out that the efficacy and safety data from RCTs are important. However, they do not always reflect in a precise way the outcomes observed in routine clinical practice due to their study designs and rigorous inclusion/exclusion criteria, and frequently do not take into account local prescribing habits that are often influenced by cultural and economic factors.

Evidence from trials mimicking the clinical practice

In contrast to RCTs, changes to new treatments in clinical practice occur without any washout period. In the CRYSTAL trial [25], a prospective, multicenter, 12-week, randomized, pragmatic, open-label trial designed to mimic clinical practice in which patients with symptomatic, nonfrequently exacerbating, moderate COPD treated with various drugs were directly switched to glycopyrronium 50 μg or indacaterol/glycopyrronium 110/50 μg, indacaterol/glycopyrronium FDC provided superior improvement in trough FEV_1 at week 12 versus LABA+ICS (treatment difference (Δ) = 71 ml, p < 0.0001) and LABA or LAMA (Δ = 101 ml, p < 0.0001). Indacaterol/glycopyrronium also improved TDI versus LABA+ICS (Δ = 1.10 units, p < 0.0001) and versus LABA or LAMA (Δ = 1.26 units, p < 0.0001). Significantly more patients on indacaterol/glycopyrronium reached the minimally clinically important difference of 100 ml for trough FEV_1 and 1 point for TDI versus comparators.

Evidence from COPD real-world observational studies

Observational studies are more useful than RCTs in performing opportune comparisons in diverse populations and in real-world settings [26]. In addition, they can help to characterize actual practice in real-life settings and are very useful in identifying study questions and design trials that better reflect patients' healthcare preferences and experiences. Furthermore, they likely produce results that can lead to changes of care [27]. Observational studies include a wider selection of patients and focus on balancing the risks and benefits of treatments [28].

At present time, there are some real-life studies, the GLARE [29] and the INFLOW [30], which support the effectiveness of both indacaterol and glycopyrronium as monotherapies in real-world clinical practice.

The POWE study is evaluating the effectiveness of indacaterol/glycopyrronium in Canada. It is enrolling patients that have not responded to their current treatment with tiotropium alone, or who are on the salmeterol/fluticasone FDC. The study is enrolling only patients for whom the physician has chosen to change treatment because it is ineffective. Currently only an abstract [31] addressing results on less than 20% of sample size has been presented, showing that indacaterol/glycopyrronium is effective in improving respiratory and functional outcomes in patients with COPD that have failed previous treatment with salmeterol/fluticasone FDC or tiotropium. These preliminary results confirm that in a real-world setting those patients with COPD who are at low risk of exacerbations and remain symptomatic although receiving a mono-bronchodilator or inappropriately a LABA/ICS FDC, can benefit from a switch to indacaterol/glycopyrronium FDC.

This fits very well with the already discussed documentation that indacaterol/glycopyrronium FDC is preferable to other therapies. However, a retrospective, observational study of COPD patients in the USA treated with LABA/LAMA or LABA/ICS combination that used insurance claims from January 1, 2004 through December 31, 2014 as the data source demonstrated that patients had similar rates of exacerbations for the LABA/LAMA cohort compared with the LABA/ICS cohort (rate ratio: 0.98; 95% CI: 0.95–1.01), although patients greater

than or equal to 65 years of age had a small but significantly lower rate of exacerbations in the LABA/LAMA cohort compared with the LABA/ICS cohort (rate ratio: 0.96; 95% CI: 0.92–0.99) [32]. Conversely, no difference was seen between cohorts among patients less than 65 years of age. Although this study is not focalized on indacaterol/glycopyrronium and data from this study were captured primarily when the LABA/LAMA FDCs were not yet available, it would suggest that effectiveness is comparable with both combinations. However, the study had fundamental biases: data were obtained from a health insurance claims database that usually contain limited information on patient-specific characteristics and disease severity, there was a real possibility of misclassified or uncaptured exacerbations, and most of the patients in the LABA/LAMA cohort took them as separate medications.

Discussion

Current evidence, based almost exclusively on RCTs data, indicates that indacaterol/glycopyrronium FDC is able to elicit a significant improvement in lung function and patient-reported outcomes, including breathlessness, rescue medication use, and HRQoL, and to reduce rates of COPD exacerbations, when compared with the current standard of care. Consequently, although GOLD strategy recommends a single long-acting bronchodilator as the initial treatment in mild COPD, with LABA/LAMA therapy indicated for patients who continue to experience symptoms despite bronchodilator treatment, or for those who have more severe COPD [1], the results of comparative effective research present in the literature suggest that it is appropriate to consider that indacaterol/glycopyrronium FDC is always better than a LAMA or a LABA alone or even a LABA/ICS combination, regardless of the drugs used. In other words, an earlier start of the treatment could be useful in many COPD patients.

Unfortunately we still do not know whether it is preferable to use indacaterol/glycopyrronium on a once- and twice-daily basis. Actually, there is meta-analytical evidence of a substantial therapeutic overlap between indacaterol/glycopyrronium once- and twice-daily [15]. Furthermore, it has now been ascertained from the results of RCTs that the safety of once- and twice-daily schedules is similar to that of placebo [33]. It is clear that results from head-to-head equivalence trials comparing indacaterol/glycopyrronium once- and twice-daily are needed to document conclusively which of the two treatment schedules, if any, is more effective in reducing symptoms, and improving HRQoL. We also believe that an *ad hoc* designed real-world trial, which could document possible differences in adherence to the prescribed regimens, is needed.

Although the various comparative analyses apparently indicate a significant advantage in using indacaterol/glycopyrronium FDC, we cannot ignore the contrasting data generated by the network meta-analysis of Schlueter *et al.* [19]. However, in the past we already questioned the real value of this meta-analysis and highlighted that it was affected by major weaknesses that may have led to biased results and conclusions [15]. We believe that the lack of an adequate evaluation of the RCT quality and of the publication bias assessment, the absence of the PRISMA statement, and, mainly, the omission of data from more than 1800 patients, are all factors that greatly limit its scientific value [15].

Rather, it is more important to evaluate the efficacy of indacaterol/glycopyrronium against scientifically consolidated therapies. In this case, large-scale RCTs can produce the best evidence on the effect of a treatment because they are less prone to bias than observational studies [26].

The Institute for Quality and Efficiency in Healthcare in Germany [34], in accordance with §35a Social Code Book (SGB) V, wished to assess the added benefit in relieving symptoms of indacaterol/glycopyrronium in comparison with the appropriate comparator therapy according to the recommendations of the German National Care Guideline COPD in stable COPD of the severity stages II to IV [35]. In view of the wide usage of tiotropium and formoterol free-dose combination, a standard-of-care treatment in Germany, the health-status QUANTIFY trial randomized patients aged ≥40 years with moderate-to-severe COPD (postbronchodilator FEV_1) ≥30% to <80% predicted to indacaterol/glycopyrronium 110/50 μg once-daily or tiotropium 18 μg once-daily + formoterol 12 μg twice daily for 26 weeks [36].

The percentage of patients achieving ≥1 point improvement in the TDI was higher on the indacaterol/glycopyrronium arm (49.6%) than in the tiotropium + formoterol arm (42.4%, $p = 0.033$). It was also associated with favorable results concerning SGRQ for COPD patients (difference: -0.69 units; 95% CI: -2.31–0.92; $p = 0.399$), but the change did not reach statistical significance. Indacaterol/glycopyrronium significantly increased predose FEV_1 (+68 ml, 95% CI: 37–100; $p < 0.001$) and FVC (+74 ml, 95% CI: 24–125; $p = 0.004$) compared with tiotropium + formoterol. Finally, the percentage of patients experiencing at least one moderate or severe exacerbation and the time to first moderate or severe exacerbation were similar in the two treatment groups. The noninferiority results from this trial suggest that treatment with indacaterol/glycopyrronium

is a simpler alternative to improve patients' adherence and compliance compared with the free combination of tiotropium + formoterol.

Based on the results of this trial, the Institute concluded that there are some minor added benefits of indacaterol/glycopyrronium compared with the tiotropium + formoterol free combination for patients with COPD stage II and III with no more than two exacerbations per year [34].

As already mentioned, conclusive data on a greater benefit of indacaterol/glycopyrronium FDC over LAMAs, and also LABAs, in real-life still do not exist, but the results of pivotal RCTs suggest that this is possible. Therefore, it is crucial to define how useful it is to start the treatment of COPD patients with this LABA/LAMA FDC immediately, until the time of diagnosis, in order to optimize bronchodilation [5]. Moreover, considering the documented improvement in lung function and the lower exacerbation rates, it is important to establish if it makes sense to switch all patients from a LABA/ICS treatment to indacaterol/glycopyrronium FDC or there is a subgroup of COPD patients who may benefit the most from dual bronchodilation [5].

The first question is very insidious. Pragmatic observational studies or an *ad hoc* designed real-world trial could likely give an answer. It is our opinion that the documented synergistic interaction between indacaterol and glycopyrronium [37] supports the possibility of an early intervention with this LABA/LAMA combination in order to let patients perceiving benefits coming from fast relieving of symptoms, and a potential increase in the adherence to COPD treatment [5].

Relatively to the second question, we must point out that the comparative effectiveness research that we have described suggests that the use of indacaterol/glycopyrronium FDC should always be preferred to the use of LABA/ICS if exacerbations are the primary end point of the treatment. However, although other trials (SPARK [38] and LANTERN [6]) have explored the efficacy of indacaterol/glycopyrronium on exacerbation rates, much of the evidence comes from FLAME study [7]. We already highlighted that regrettably this trial does not allow determining whether dual bronchodilation is actually capable of preventing COPD exacerbations if patients are treated according to the severity of exacerbations [39]. However, a post hoc analysis of a subset of GOLD Group D COPD patients with a history of $\geq$2 exacerbations or one hospitalization documented that indacaterol/glycopyrronium was better than salmeterol/fluticasone in reducing the rate (RR, 0.86) and risk (-19%) of moderate or severe exacerbations, and in delaying the time-to-first moderate or severe exacerbation (median days: 291 vs 215) [40]. Interestingly, indacaterol/glycopyrronium significantly reduced the risk of moderate/severe exacerbations versus salmeterol/fluticasone in COPD patients with/without prior triple therapy [41].

Although GOLD strategy suggests that 'high' blood eosinophils is a parameter supporting ICS use in GOLD D patients [1], the analysis of FLAME data found that indacaterol/glycopyrronium was significantly better than salmeterol/fluticasone in reducing exacerbation rate, irrespective of blood eosinophil count [42]. Actually, there were minimal differences in favor of indacaterol/glycopyrronium in the RRs for moderate or severe exacerbations among the <2, <3 and <5% subgroups (RR, 0.80, 0.81 and 0.81, respectively), but these differences did not reach statistical significance. The two treatments appeared approximately similar (RR, 0.94) when a rather high cut-off ($\geq$5%) was used [42]. Furthermore, the increase of baseline blood eosinophils did not influence the rate of moderate or severe exacerbations.

Anyway, regardless of any other consideration, we strongly believe that a comprehensive assessment of any therapeutic strategy requires evaluation of both its efficacy under optimum conditions (high internal validity), which means well designed RCTs, and effectiveness in real-life populations and situations (high external validity). In fact, we fully share the general opinion that even though an RCT with a large number of patients demonstrates a high statistical significance for a drug over another, this does not automatically mean that results can be extrapolated to a larger and less selected population [43,44]. This means that in addition to the large body of evidence already available supporting the use of indacaterol/glycopyrronium FDC, more data from other pragmatic observational studies or *ad hoc* designed trials should be collected to confirm the apparently high effectiveness of indacaterol/glycopyrronium FDC even in the real-world clinical practice.

We have repeatedly pointed out that there are still several general questions to be addressed to optimize use of bronchodilators in COPD [4,45]. Regarding especially indacaterol/glycopyrronium FDC we must highlight that there is no evidence to suggest which patients should initially receive indacaterol/glycopyrronium FDC, or more generally a LABA/LAMA combination. As suggested by Singh *et al.* [46] this could be investigated in patients who have not received long-acting bronchodilator treatments previously, unlike the majority of patients in published studies. A prospective, population-based, observational study should be performed in adult COPD patients initiating a 12-month treatment with indacaterol/glycopyrronium FDC or a LAMA in monotherapy

prescribed by a general practitioner or pulmonologist as initial therapy according to his/her choice. It could allow to collect data describing patient characteristics and treatment modalities in this population, and to analyze clinical outcomes at the end of treatment.

Although indacaterol, glycopyrronium and indacaterol/glycopyrronium FDC seem to be safe from a cardiovascular point of view, since both LABAs and LAMAs have the potential to cause cardiac-related adverse events [47], at least hypothetically the possibility of a cardiovascular adverse effect cannot be excluded in patients with COPD and heightened cardiovascular risk. In this context, we must mention that the results of our systematic review with a meta-analysis indicated a protective role of indacaterol/glycopyrronium FDC against cardiac adverse events when compared with monotherapies [15]. This signal looks very promising, but since it comes from RCTs, confirmations in unselected COPD patients are needed. Therefore, a population-based retrospective cohort study to compare the cardiovascular and cerebrovascular risks of indacaterol alone, glycopyrronium alone, and indacaterol/glycopyrronium FDC among patients with COPD, could be extremely useful. Alternatively, a pragmatic real-world RCT that enrolls COPD patients with heightened cardiovascular risk could compare indacaterol/glycopyrronium with standard therapy in order to confirm the safety profile showed in RCTs.

Conclusion

Current evidence, based almost exclusively on randomized controlled trials data, indicates that indacaterol/glycopyrronium FDC is able to elicit a significant improvement in lung function and patient-reported outcomes, including breathlessness, rescue medication use, and health-related quality of life, and to reduce rates of chronic obstructive pulmonary disease exacerbations, when compared with the current standard of care. The results of comparative effective research available in the literature, which utilized observational and clinical trials or conventional meta-analyses, suggest that it is appropriate to consider that indacaterol/glycopyrronium FDC is always better than a LAMA or a LABA alone or even a LABA/inhaled corticosteroid (ICS) combination, regardless of the drugs used.

Future perspective

The critical assessment of the available documentation indicates that indacaterol/glycopyrronium FDC, also because of the documented pharmacological synergy between indacaterol and glycopyrronium [37] in addition to the convenience of the Breezhaler device [5], shows a clear superiority on different outcomes relevant for COPD patients in comparison with standard COPD treatment (LABA, LAMA and LABA/ICS FDC).

Nevertheless, considering what suggested by the 2017 GOLD report [1], it is crucial to establish whether indacaterol/glycopyrronium FDC is preferred over triple therapy (LABA/LAMA/ICS), and whether addition of an ICS to indacaterol/glycopyrronium FDC provides any additional clinical benefit. In any case, at present no trials have shown the superiority of triple therapy FDC over indacaterol/glycopyrronium FDC.

More generally, we strongly believe that it is now time to perform pragmatic RCTs conducted in real-world settings that must be well designed and implemented to offer a concrete evidence of risks and benefits in real-life clinical practice [48]. These pragmatic RCTs could help us in giving the right answer to all the already discussed fundamental questions regarding the use of indacaterol/glycopyrronium FDC that still require clarification to optimize utilization of this FDC.

Financial & competing interests disclosure

M Cazzola acted as a consultant and is a member of the Speaker Bureau for Novartis. P Rogliani is a member of the Speaker Bureau for Novartis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Executive summary

- Indacaterol/glycopyrronium has been the first long-acting β_2-agonist/long-acting muscarinic antagonist (LABA/LAMA) fixed-dose combination (FDC) to be developed and approved as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease.
- Current evidence, based almost exclusively on randomized controlled trials data, indicates that indacaterol/glycopyrronium FDC is able to elicit a significant improvement in lung function and patient-reported outcomes, including breathlessness, rescue medication use, and health-related quality of life, and to reduce rates of chronic obstructive pulmonary disease exacerbations, when compared with the current standard of care.
- The general opinion is that even though a large randomized controlled trial, containing a large number of patients, provides highly statistical significances in favor of a drug over another, this does not necessarily imply that the results can be extrapolated to a larger, less selected patient population.
- The results of comparative effective research available in the literature, which utilized observational and clinical trials or conventional meta-analyses, suggest that it is appropriate to consider that indacaterol/glycopyrronium FDC is always better than a LAMA or a LABA alone or even a LABA/inhaled corticosteroid (ICS) combination, regardless of the drugs used.
- We must still establish whether indacaterol/glycopyrronium FDC is preferred over triple therapy (LABA/LAMA/ICS), and whether addition of an ICS to indacaterol/glycopyrronium FDC provides any additional clinical benefit.

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