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УДК 616.24-036.12-085.234(048.8) DOI: 10.20969/VSKM.2017.10(1).7-14

PROGRESS AND PROSPECTS FOR LONG-ACTING β_2-AGONISTS IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Abstract. ***Aim.*** The treatment of chronic obstructive pulmonary disease (COPD) is generally based on the assumption of drug combinations in which β_2-agonists are commonly included. Ultra-LABAs were developed to induce a greater adherence to the treatment as a result of the simplification of treatment with the reduction of the daily dose to be taken. ***Material and methods.*** We analyzed the current literature data on β2-adrenergic agonists. The potential positioning of ultra-LABAs in the treatment of COPD and their cardiovascular safety is discussed according to the new information on the topics. ***Results and discussion.*** The novel fixed-dose combinations of ultra-LABAs with LAMAs and/or ICSs are examined, as well as the novel ultra-LABAs under clinical development and the ultra-LABAs in preclinical development. ***Conclusion.*** The huge interest in developing new ultra-LABAs has apparently declined progressively in recent times. Nevertheless, ultra-LABAs are considered a fundamental component of the combinations with other classes of drugs (LAMAs and ICSs) that are central for treating COPD and now are administered on oncedaily basis.
Key words: Cardiovascular safety; combination therapy; COPD; monotherapy; ultra-LABAs.
For reference: Puxxedu E, Ora J, Calzetta L, Cazzola M. Progress and prospects for long-acting β_2-agonists in the treatment of COPD**.** The Bulletin of Contemporary Clinical Medicine. 2017; 10 (1): 7—14. ***DOI:*** 10.20969/VSKM.2017.10(1).7-14.

ДОСТИЖЕНИЯ И ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ β_2-АГОНИСТОВ ДЛИТЕЛЬНОГО ДЕЙСТВИЯ В ЛЕЧЕНИИ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЕГКИХ (ХОБЛ)

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Реферат. ***Цель.*** Лечение хронической обструктивной болезни легких (ХОБЛ), как правило, предполагает назначение комбинации лекарственных препаратов, одним из которых зачастую является агонист β_2-адренорецепторов. Данная статья написана с целью представления информации об агонистах β_2-адренорецепторов длительного действия (ultra-LABAs) — современной форме препаратов, обеспечивающей высокую приверженность пациентов лечению благодаря упрощенной схеме приема 1 раз в сутки. ***Материал и методы.*** Проанализированы современные литературные данные об агонистах β_2-адренорецепторов. В частности, новейшие данные о применении ultra-LABAs в лечении ХОБЛ, а также вопросы безопасности препарата для сердечно-сосудистой системы. ***Результаты и их обсуждение.*** Рассматривается инновационный метод назначения фиксированных доз LABAs в комбинации с антихолинергическими препаратами длительного действия (LAMAs) и/или с ингаляционными кортикостероидами, а также новейших препаратов ultra-LABAs, находящихся на этапах клинического исследования и доклинической разработки. ***Заключение.*** Интерес к разработке новых агонистов β_2-адренорецепторов длительного действия значительно снизился за последние годы. Тем не менее ultra-LABAs считаются одним из основных компонентов лечения ХОБЛ в комбинации с другими классами препаратов (LAMAs и ингаляционными кортикостероидами), которые в настоящее время находятся на этапе внедрения для регулярного использования.

Ключевые слова: безопасность сердечно-сосудистой системы, комбинированная терапия, ХОБЛ, монотерапия, ultra-LABAs.
Для ссылки: Progress and prospects for long-acting β_2-agonists in the treatment of COPD / E. Puxxedu, J. Ora, L. Calzetta, M. Cazzola // Вестник современной клинической медицины. — 2017. — Т. 10, вып. 1. — С.7—14. ***DOI:*** 10.20969/VSKM.2017.10(1).7-14.

Introduction. In 2005, we coined the term ultra long-acting β_2-agonists (ultra LABAs) to identify the novel β_2-agonists that, at least from the pharmacological point of view, seemed able of inducing bronchodilation for 24 hours or more [1]. We pointed out that «the oncedaily dosing of a LABA would be a significant convenience and probably a compliance-enhancing advantage, leading to improved overall clinical outcomes in patients with asthma and COPD». Apparently, at that time several ultra LABAs (arformoterol, carmoterol, indacaterol, GSK-159797 (milveterol), GSK-597901, GSK-159802, GSK-642444 (vilanterol) and GSK-678007) were under development.

In 2007, we highlighted that arformoterol was not a real once daily LABA and also stressed that «Any company planning to develop a new ultra-LABA must consider very carefully the pharmacological characteristics of the β_2-adrenoceptor agonist component to understand how it will fit into current treatment strategies and whether it should be used only in combination with other drugs» [2].

In 2009, we included in the list of new β_2-agonists under development BI-1744-CL (olodaterol), and LAS100977 (abediterol) [3]. Furthermore, we illustrated the possible development of saligenin- or indole-containing and adamantyl-derived β_2-agonists and highlighted that despite this interesting profile of milveterol, it was likely that it would be developed only as a back-up because of the greater therapeutic index of vilanterol, and also the great delay in the development of carmoterol, although it was the oldest of the ultra-LABAs under investigation.

In 2011, considering the great interest within the pharmaceutical industry in the discovery of effective ultra LABAs, we described what we considered the mandatory pharmacological characteristics of any new LABA [4]. They included longer duration of action (compared with existing LABAs) with a true 24 h sustained bronchodilator efficacy allowing once daily dosing, fast onset of action, superior efficacy compared with existing LABAs, and favourable safety and tolerability profile.

At that time, indacaterol had already received European regulatory approval and been launched in several countries, whereas olodaterol, vilanterol, carmoterol, LAS100977 (abediterol) and PF-610355 were apparently under development.

In the 2012, in a review paper mainly focuses on bronchodilators that were in Phase I and II clinical trials, we described AZD3199, abediterol, and PF-610355 and pointed out that further development of this last ultra-LABA had been stopped [5].

In the 2013, in a further revision of the literature focused on β_2-agonist treatment in lung disease [6], we highlighted that it was likely that the also the development of AZD3199had been discontinued for strategic and regulatory reasons.

In the last three years, apart from the publication of some of our original contributions focused primarily on understanding the value of dual bronchodilation [7-12], in which surely β_2-agonists play a fundamental role, we examined and described the development of single ultra-LABAs now entered into the daily practice as monotherapy or in combination with a long-acting muscarinic antagonist (LAMA) or an inhaled corticosteroid (ICS) [13-21].

In this article, we aim to describe the novelties that have emerged in recent years on the use of β_2-agonists in the treatment of COPD and illustrate the possible further development of this class of bronchodilators.

Positioning ultra-LABAs in the treatment of COPD

Basically, almost all the new information on the topic has been obtained with indacaterol, which is the archetype of this new group of β_2-agonists and is the first ultra-LABA approved for the treatment of COPD.

Since in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report no distinction is made as to which class of bronchodilators, either LABAs or LAMAs, should be considered first, but they only recommend the use of long-acting bronchodilator agents [22], Kerstjens and colleagues [23] examined the effectiveness of indacaterol and other bronchodilators compared with placebo in patients across the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 categories A to D through a post-hoc, subgroup pooled analysis of 6-month efficacy data from three randomized, placebo-controlled, parallel-group studies involving 3862 patients. The results indicated that indacaterol was effective in improving lung function, dyspnoea, and rescue medication use across all four GOLD categories. Furthermore, a pooled analysis of two randomized, parallel-group trials showed that in patients in GOLD categories A and B indacaterol improved lung function and provided a greater benefit in terms of dyspnoea and health status compared with placebo [24]. However, a post hoc pooled analysis of four trials suggested that concomitant COPD therapies and COPD severity influenced the magnitude of the bronchodilatory effect of another ultra-LABA, olodaterol, in a subgroup of patients with moderate to severe disease (GOLD 2-3) [25]. In particular, of the patients who had not received concomitant therapy, those who were GOLD stage 2 had FEV_1 AUC_{0-3} and trough FEV_1 responses with olodaterol that were 1.2- and 1.9-fold, respectively, higher than in, GOLD 3 patients. Anotherpost-hoc analysis of pooled data from clinical studies compared the efficacy of once daily inhaled bronchodilators indacaterol (150 and 300μg) and tiotropium (18μg) according to baseline breathlessness severity in patients with COPD documented that, while all treatments were equally effective in patients with less dyspnoea, indacaterol 300 μg was preferable for patients with COPD who suffered from more severe dyspnoea [26].

The crucial Indacaterol: Switching Non-exacerbating Patients with Moderate COPD From Salmeterol/ Fluticasone to Indacaterol (INSTEAD) trial, which enrolled COPD patients with moderate airflow limitation and without a history of exacerbations in the previous year, but on treatment with ICS/LABA combination therapy for ≥3 months, documented that these patients can be switched from ICS/LABA to indacaterol 150 μg with no efficacy loss [27].

Interestingly, a single-centre audit of a primary care COPD cohort comprising all patients treated with indacaterol for a minimum of 12 months, showed that indacaterol was an effective LABA as an escalation or switch medication from a LABA/ICS combination significantly reducing the number of exacerbations in patients with moderate-to-severe COPD [28].

This is an intriguing finding, but it must be admitted that to determine whether a treatment with ultra-LABAs is sufficient to prevent, or at least delay, exacerbations of COPD is quite difficult. In a pooled analysis of data from three randomized, double blind, placebo-controlled studies, both indacaterol doses, 150 and 300 μg, were associated with significant reductions in exacerbations versus placebo [29]. However, the Indacaterol: providing opportunity to re-engage patients with life (INVIGORATE) study showed that tiotropium offered greater protection from exacerbations than indacaterol [30], but the absolute number of events was small and the difference between treatments was of uncertain clinical importance.

A post hoc analysis has shown that blood eosinophil count ≥2%, which is a promising biomarker of response to ICSs in patients with COPD [31], does not appear to predict bronchodilator response to β_2-agonists in either ICS users or non-users [32].

It is remarkable to point out that a UK-based cost-utility analysis of indacateroldemonstrated that indacaterol can produce better outcomes at a lower cost to the healthcare system compared with both tiotropium and salmeterol and is likely to remain cost-effective under a range of assumptions [33]. In particular, the proportion of patients in each of the COPD stages and the mortality rate associated with very severe COPD are the variables with the largest impact on the results.

Cardiovascular safety of ultra-LABAs

All inhaled β_2-agonists have a potential to increase heart rate and the incidence of ventricular arrhythmias in patients with COPD [6] because some of the β_2-adrenoceptors in the atria and ventricles are β_2, and thus even selective β_2-agonists can provoke direct simulation of the heart [34, 35]. Furthermore, they can also induce vasodilation and reflex tachycardia as a consequence of the β_2-adrenoceptors stimulation [34, 35].

A meta-analysis of randomized, double-blind, parallel-group, placebo-controlled trials for ultra-LABAs (and also formoterol and salmeterol) treatment of COPD with at least 3 months of follow-up suggested that inhaled LABAs significantly reduced the rate of fatal cardiovascular events in COPD patients compared with placebo and were able to significantly decrease fatal cardiovascular events in long-term, but not in the short-term, trials and in studies in which the predicted FEV_1 of the participants were less than 50% [36].

Unsurprisingly, COPD patients with cardiac report a higher incidence of cardiovascular adverse events versus those with no history, but fortunately, no increase in risk estimates of fatal or any major adverse cardiac event (MACE) end points is observed in this subgroup and also in those who are taking β-blockers [37].

A recent study, which has investigated the ability of a chronic treatment with indacaterol to reverse cardiac remodelling and its effects on myocardial infarction in a rat model of heart failure, demonstrated that this ultra-LABA significantly reduced the infarct size in heart failure rats and BNP levels [38]. Intriguingly, the results of the study showed an additive interaction between indacaterol and metoprolol, a selective β_1-adrenoceptor antagonist, in normalizing and reversing cardiac remodelling in this experimental model of heart failure. This emerging information suggests the need for more extensive studies with the combination of an ultra-LABA and a selective β_1-adrenoceptor antagonist in patients suffering from both heart failure and COPD, considering that pharmacological modulation of β-adrenoceptor function is one of the critical issues in the treatment of these patients [39].

There is documentation that ultra-LABAs are able to induce a rapid reduction in BNP levels in patients admitted to emergency department for AECOPD [40]. It is not easy to explain why ultra-LABAs decrease BNP levels. The most plausible hypothesis is that they are able to directly influence the pulmonary hemodynamics. Alternatively, it has been suggested that ultra-LABAs are able to cause an attenuation of air trapping, leading to a reduction of intrathoracic pressure, including pressure on the whole heart, and, consequently, to an improvement of right ventricular overload and left ventricular diastolic dysfunction. In effect, it has been shown that indacaterol significantly reduces lung hyperinflation in acute conditions [41]. This reduction is associated with a significant increase of the right ventricular compliance indexes and may have a role in improving left ventricular preload leading to a reduction in cardiac frequency.

Ultra-LABAs and combination therapies

Three fixed-dose combination formulations (FDCs) containing an ultra-LABA and a LAMA have been developed indacaterol/glycopyrronium [15], vilanterol/ umeclidinium [20], and olodaterol/tiotropium [18]. Addition of an ultra-LABA to a LAMA not only induces a larger bronchodilation than that obtained with the LAMA as monotherapy, but also significantly improves many patient reported outcomes. In fact, a systematic review with meta-analysis that incorporated the data from trials lasting at least 3 months [12] has shown that these three ultra-LABA/LAMA combinations are always more effective than the LAMA or ultra-LABA alone in terms of the improvement not only in trough FEV_1, but also in transitional dyspnoea index and St. George' s Respiratory Questionnaire scores.

This finding is nor surprising because there is recent preclinical documentation that combining an ultra-LABA with a LAMAat lower concentrations than those used in therapy provides a pharmacological synergistic benefit on airway smooth muscle relaxation [8], which may have major implications for the use of ultra-LABA/

LAMA FDCs in the treatment COPD [11]. Unfortunately, the synergistic effect is difficult to be documented in patientssuffering from COPD, although it can be shown after acute administration of the two bronchodilators [9], mainly because the choice of the doses to be used in the clinical development of ultra-LABA/LAMA FDCs has always been done without having previously performed studies to determine the optimal concentrations able to induce synergism in human isolated airways and we strongly believe that this is a mistake because, as already mentioned in the past "the doses extrapolated from ex vivo studies may provide a translational approach to design clinical trials that would promptly offer information on the optimal doses of LAMA/LABA combination inducing synergistic bronchodilation in COPD patients" [12].

In any case, the results of the already mentioned meta-analysis [12] have documented that the twice-daily indacaterol/glycopyrrolate 27.5/15.6 μg FDC (glycopyrrolate 15.6 μg, excluding the bromide salt, is equivalent to 12.5 μg glycopyrronium), which hasbeen developed in the United States, is as effective as the -daily indacaterol/glycopyrronium 110/50 μg FDC, a finding that fully supports our opinion.

The innovative information generated by the use of ultra-LABA/LAMA FDCs is that at least indacaterol/glycopyrronium FDC seems to be more effective than salmeterol/fluticasone FDC in preventing COPD exacerbations in patients with a history of exacerbation during the previous year [42]. It is well known that non-neuronal acetylcholine (ACh) has inflammatory properties and the multitude of cells in the airways, including bronchial epithelial cells, neutrophils, lymphocytes, macrophages and fibroblasts, involved in exacerbations of COPD, have muscarinic receptors [43]. There is evidence that co-administration of indacaterol and glycopyrronium reduces the release of non-neuronal ACh, ACh that is released from the epithelium but not from bronchi [8].

The important role of combination therapy with an ICS and a LABA in the treatment of severe COPD patients with frequent exacerbations [22]reveals major marketing chances. Consequently, the pharmaceutical industry has a real interest in also developing anultra-LABA/once daily ICSFDC, in an attempt to simplify the treatment and, consequently, increase adherence to the prescribed therapy, and likely also to overcome the loss of patent protection [4].

At present time, vilanterol/fluticasone furoate is the only ultra-LABA/once daily ICS FDC approved for the long-term, once daily, maintenancetreatment of airflow obstruction in COPD patients,including chronic bronchitis and/or emphysema and toreduce exacerbations of COPD in patients with a history ofexacerbations [19].

The growing body of evidence suggests that triple therapy with LABAs, LAMAs, and ICS is efficacious making it an attractive combination in COPD. Therefore, a variety of triple combinations are currently under development [44]. However, the vilanterol/umeclidinium/fluticasone furoate combination is the only triple therapy under development that includes an ultra-LABA.Two recent randomized studies evaluated the efficacy and safety of umeclidinium added to vilanterol/fluticasone furoate in patients with moderate-to-very-severe COPD. The results of these studies documented that the addition of umeclidinium to vilanterol/fluticasone furoate resulted in significant improvements in lung function compared with vilanterol/fluticasone furoate, with similar safety profiles, though the impact on quality of life was inconsistent [45].The InforMing the PAthway of COPD Treatment (IMPACT) study will evaluate the efficacy and safety of this triple combination versus vilanterol/fluticasone furoate or vilanterol/umeclidinium over a 52-week treatment period [46]. The study aims to recruit 10000 symptomatic advanced COPD patients (Global initiative for chronic Obstructive Lung Disease (GOLD) group D) with an exacerbation in the previous 12 months.The anticipated completion date is July 2017.

It is likely that also a fixed dose combination with indacaterol/glycopyrronium/mometasone will be developed on a once-daily basis. However, there is still no available information although apparently it is under development only in patients with asthma.

Novel ultra-LABAsstill
under clinical development

Abediterol (AZD0548) is a new ultra-LABA that in preclinical setting showed superior bronchodilatory potency and similar or superior selectivity for β_2-adrenoreceptors over β_1-adrenoreceptors but a reduced effect on heart rate compared with formoterol, indacaterol, salmeterol, vilanterol and olodaterol [47, 48].Furthermore, this new ultra-LABAexhibited a long residence time at the human β_2-adrenoceptor, with a much slower dissociation half-life than indacaterol, olodaterol and vilanterol [49].

A Phase II, randomized study has documented that abediterol 0.625-2.5 μg provided dose-dependent, clinically and statistically significant bronchodilation versus placebo in 62 patients with mild-to-moderate asthma who were also receiving an ICS, with a peak effect similar to salbutamol and duration of action compatible with once daily dosing [50]. All doses of abediterol were well tolerated. Also in 70 COPD patients who were GOLD stage 2/3, all doses of abediterol (0.625-10 μg) provided clinically and statistically significant, dose-dependent improvements in bronchodilation versus placebo, and were well tolerated [51]. Interestingly abediterol 2.5, 5 and 10 μg gave significant improvements versus indacaterol.

PF-610355 is a member of a series of potent and selective sulfonamide derived β_2-adrenoceptor agonists [52]. In healthy subjects, duration of action of PF-610355 450 μg on airways determined by plethysmography was superior to salmeterol 50 μg by 9.77 h indicating the potential for sustained pharmacological effect in the lung [53]. A preliminary trial documented that PF-610355 induced a clear 24 h bronchodilator effect in asthmatic patients [54].In patients with COPD, it has been estimated that once daily fine-particle dose of 28.1 μg versus placebo has a moderate probability of providing an average improvement above 100 mL at trough [55]. The 50 μg fine-particle dose, on the other hand, has a greater than 0.78 probability of achieving a 120 mL improvement versus placebo at trough.A pharmacokinetic/pharmacodynamic analysis suggested

that no relevant effects of PF-610355 on heart rate in COPD patients should be expected for doses up to 280 µg once daily [56]. Although this interesting profile, in 2011 the development of the compound for the treatment of asthma and COPD was discontinuedlikely for strategic and regulatory reasons. We are confident that the interesting pharmacological and clinical profile of PF-610355 will induce the further development of this ultra-LABA.

AZD3199 is another novel inhaled, selective ultra-LABA**.** It has been selected froma new series of dibasic C-1 des-hydroxy 7-hydroxy benzthiazolone β_2-adrenoreceptor agonists and is highly selective (>1500-fold) for the human β_2-adrenoreceptors (pEC_{50} 7.9 ± 0.12 (*n* = 8)) over human β_1- and β_3-adrenoreceptors s [57].AZD3199 plasma exposure in healthy volunteers and patients suggested linear pharmacokinetics and a long half-life [58]. Systemic availability was similar in healthy subjects and patients with asthma, but was lower in patients with COPD. In asthmatic patients, AZD3199 480 µg and 1920 µg produced 24-hour bronchodilation [59]. At comparable peak bronchodilator effect, AZD3199 was associated with a lower level of systemic side effects than formoterol. In COPDthree different doses of AZD3199 (200, 400 or 800 µg o.d.) produced effective bronchodilation with 24-hour duration of action that was comparable to, or greater than, that achieved with formoterol twice daily [60]. However, no clear dose–response was observed for the bronchodilatory effects of AZD3199 at either peak or trough effects

A network meta-analysis that included >200 randomised trials showed that AZD3199 was the most effective agent in having a reduced risk of mortality in COPD patients (OR 0.45, 95%CI 0.02-10.32) [61].

Milveterol is being developed as an ultra-LABA for use in patients with asthma and COPD. Preclinical studies demonstrated high potency in vitro and long duration of action in a guinea pig model of bronchoprotection [62].The currently available information about its clinic efficacy is scarce and has not been presented or published yet.

Ultra-LABAs in preclinical development

The optimisation of two series of 4-hydroxybenzo-thiazolone derived β_2-agonists, bearing α-substituted cyclopentyl and β-phenethyl amino-substituentshas led to identification of the α-substituted cyclopentyl analogue 2 as the optimal compound [63]. It combines a rapid onset of action, with a comparable intrinsic duration of action to indacaterol, and has a favourable tolerability profile with respect to the systemic β_2-adrenoceptor mediated side effects that are associated with the targeted levels of bronchodilation.

Sulfone 10b was identifiedfrom series of novel, potent, and selective human β_2-agonists incorporating a sulfone moiety on the terminal right-hand-side phenyl ring of (R)-salmeterol [64]. Although it showed a salmeterol-like potency and selectivity profile, it had longer duration of action than salmeterol in guinea pig in vivo, suitable for once daily dosing. Furthermore, it displayed lower than salmeterol oral absorption in rat, lower bioavailability in rat and dog, and a high turnover in human hepatocytes with metabolites that would be expected to have reduced or no β_2 activity. Being free of any genetic toxicity issues, it was considered as a backup to vilanterol.

TD-5471, a potent and selective full agonist of the human β_2- adrenoceptor, was identified as the most promising agent of a series of potent β_2-agonists incorporating a biarylamine secondary binding group [65].

Amines are known to have a high affinity for lung tissue (possibly through lysosomal partitioning) and their addition to the neutral secondary binding group of an existing β_2-agonist series was found to provide improved in vivo efficacy, but also led to the formation of biologically active aldehyde metabolites [66]. The introduction of basic secondary binding groups to the salmeterol scaffold and blocking the site of metabolism to prevent aldehyde formation generated TD-4306, a β_2-agonist with superior duration of action relative to salmeterol. In the guinea pig model of in vivo bronchoprotection, bronchoprotection at 72 h was dose-dependent and was significantly greater than salmeterol at nebulizer concentrations of ≥30 µg/m.

Expert Commentary

The huge interest in developing new ultra-LABAs in the last decade has apparently declined progressively in recent times. Although, as already mentioned,indacaterol is cost-effective compared to tiotropium and salmeterol [33] and notwithstanding what we have previously illustrated on the potential positioning of ultra-LABAs in the treatment of COPD, no guideline indicates ultra-LABAs as first choice drugs compared to LAMAs. In effect, there is not published evidence that ultra-LABAs are definitely more effective than LAMAs as monotherapy. In particular, in the INVIGORATE study tiotropium produced a small (absolute difference 11 ml) and likely not of clinical significance, but statistically greater, improvement in trough FEV_1 than indacaterol. Even though indacaterol reduced the rescue medication use, numerically fewer exacerbations occurred among the participants taking tiotropium [67].

On the other hand, in general even the prescribing behaviour of specialists does not seem to favour the use of LABAs as monotherapy in the treatment of COPD. The Adelphi Respiratory Disease Specific Programme, a cross-sectional survey of consulting patients in five European countries and in the US, showed a conflict between the current real-world practice and the GOLD 2011 updated treatment recommendations, documenting that even large proportions of patients in the low risk groups were currently receiving ICS/LABA, either alone or in combination with a LAMA [68]. Furthermore, LABAs as monotherapy were only prescribed in a small percentage of patients in GOLD group A and B.

The documentation that in real life, the switch from LAMA to LABA and also the step downs of ICS/LABA to LABA or LAMA are infrequent [69] is interesting to understand the progressive decline in interest in developing new ultra-LABAs as monotherapy.

In any case, it is possible that the safety warning released by the U.S. Food and Drug Administration (FDA) in 2010 for the use of inhaled LABAs [70] has reduced the interest in this class of bronchodilators

and, actually, vilanterol has not been introduced into the market as a single agent.On the other hand, an emphasized contraindication to LABA monotherapy without another controller medicationat least in asthma [70] and the documented best pharmacological effect that is achieved by combining a LABA with a LAMA [11] with a larger bronchodilation and a better improvement in patient-reported outcomes and a better improvement in some patient-reported outcomes in patients with COPD [12] are strong arguments against the use the ultra-LABAs as monotherapy. This contrasts with the evidence that at least in US new LABA starts have been significantly reduced over time among those with a diagnosis of asthma, but they are largely unchanged in those without such a diagnosis [71].

Nevertheless, ultra-LABAs remain extremely useful drugs because they guarantee a greater adherence to the treatment as a result of the simplification of treatment with the reduction of the daily dose to be taken [72]. Nonadherence to prescribed medications is one of the major obstacles to successful management of COPD [73], but, inexcusably, adherence to COPD prescribed therapy is generally very poor [74]. Furthermore, ultra-LABAs also allow the combination with other classes of drugs, such as LAMAs and ICSs, that are fundamental for treating COPD and now are administered on a once daily basis [4]. In fact, as already mentioned, the treatment of COPD is generally based on the assumption of drug combinations (LABA/LAMA and ICS/LABA) in which β_2-agonists are commonly included.

Five-year view

It is likely that over the next 5 years there will be less and less interest in the use of ultra-LABAs as monotherapy in COPD. The apparent lack of commercial success of indacaterol, the fact that olodaterol has only a single dose irrespective of COPD severity and the evidence that vilanterol will not be used as monotherapy provide a strong presumption that physicians will move always more their attention to LAMAs if they will prefer to prescribe a long-acting bronchodilator as monotherapy. Alternatively, we can suppose the possibility of starting the treatment of COPD patients administering low doses of LABA/LAMA combinations in order to optimize the bronchodilation [75]. This alternative approach would provide a patient-tailored therapy, with the further relevant advantage of reducing the risk of potential adverse events that characterize both LABAs and LAMAs, especially when inhaled at the full doses currently approved for the treatment of COPD [11].

This will mean that we should have available different doses of LABA/LAMA FDCs, a nonirrational eventuality considering that, as already mentioned, the twice-daily indacaterol/glycopyrrolate 27.5/15.6 μg seems to be as effective the once daily indacaterol/glycopyrronium110/50 μg FDC [12].

Transparency. *The study did not have sponsorship. The authors are fully responsible for the submission of the final version of the manuscript.*

Financial and other relationships declaration*. All authors participated in concept and design of the article and manuscript writing. The final version of the manuscript was approved by all authors. Authors did not receive fees for research.*

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УДК 616.24-004(048.8) DOI: 10.20969/VSKM.2017.10(1).14-21

ИДИОПАТИЧЕСКИЙ ЛЕГОЧНЫЙ ФИБРОЗ: СОСТОЯНИЕ ПРОБЛЕМЫ

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Реферат. ***Цель исследования*** — провести анализ публикаций и подготовить обзор работ, посвященных современному пониманию идиопатического легочного фиброза и его лечению. ***Материал и методы.*** Изучены публикации отечественных и зарубежных авторов. ***Результаты и их обсуждение.*** Идиопатический легочный фиброз является особой формой хронической прогрессирующей фиброзирующей интерстициальной пневмонии неизвестной этиологии, которая возникает преимущественно у людей старшего возраста, поражает только легкие и связана с гистологическим и/или рентгенологическим паттерном обычной интерстициальной пневмонии. Прогноз течения идиопатического легочного фиброза хуже, чем у ряда онкологических заболеваний. Диагностика идиопатического легочного фиброза основана на результате мультидисциплинарного заключения пульмонолога, рентгенолога и морфолога. Ведущим диагностическим критерием является совокупность данных рентгеновской компьютерной томографии высокого разрешения: преобладание изменений в базальных, кортикальных отделах легких; диффузные ретикулярные изменения; сотовое легкое с тракционными бронхоэктазами и без них; отсутствие любых признаков, противоречащих данной патологии. Функциональная оценка состояния больных основана на измерении жизненной емкости легких и диффузионной способности. Хирургические методы получения образцов тканей рекомендуются только при несоответствии лучевых признаков идиопатического легочного