Effect of bronchodilators in healthy individuals receiving lumacaftor/ivacaftor combination therapy

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Abstract

In an open-label, single-center phase 1 pharmacokinetic study in healthy subjects who received lumacaftor (LUM) in combination with ivacaftor (IVA), review of spirometry data showed a transient decline in percent predicted forced expiratory volume in 1 s (ppFEV1) within 4 h of drug administration. An additional cohort of healthy subjects with normal baseline ppFEV1 values was studied to evaluate the ppFEV1 response to LUM/IVA administration and assess the effect of long-acting bronchodilators (LABDs) and short-acting bronchodilators (SABDs) on ppFEV1 response. The ppFEV1 decline observed at 4 h was attenuated following administration of an LABD and reversed following administration of an SABD. Concomitant administration of LUM/IVA with bronchodilators was well tolerated. These data show that a transient decline in ppFEV1 was observed in healthy subjects following administration of LUM/IVA combination therapy, which can be ameliorated with LABDs or SABDs.

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1. Introduction

In 2 phase 3 studies, treatment with the combination of lumacaftor (LUM) and ivacaftor (IVA) resulted in clinically meaningful improvements in lung function, rate of pulmonary exacerbations and nutritional status in patients aged 12 years or older with cystic fibrosis (CF) who were homozygous for the F508del-CFTR mutation [1]. LUM/IVA was generally well tolerated; however, the incidence of certain respiratory adverse events (AEs), including dyspnea and chest tightness, was higher in LUM/IVA-treated patients than placebo-treated patients. These AEs were often associated with initiation of therapy and generally resolved within the first few weeks of treatment [1]. In a phase 2 study of patients with CF who had an F508del-CFTR mutation, dose-dependent reductions in percent predicted forced expiratory volume in 1 s (ppFEV1) were observed during the 28-day period of LUM monotherapy [2]. Review of spirometry data from an open-label, single-center phase 1 pharmacokinetic study in healthy volunteers [3] revealed a transient decline in ppFEV1 within 4 h of administration of LUM/IVA combination therapy. To better understand this decline, a cohort was added to the latter study to evaluate ppFEV1 response within 4 h of LUM/IVA administration and assess the effect of long-acting bronchodilators (LABDs) and short-acting bronchodilators (SABDs) on ppFEV1 response.

2. Methods

Healthy male and female volunteers aged 18 to 55 years with ppFEV1 80 or higher, body mass index 18 to 31 kg/m² and body weight more than 50 kg were eligible; those with a history of regular alcohol consumption, smoking and bronchodilator use within the previous 28 days were excluded. Participants were randomized to 1 of 4 dosing sequences (1:1:1:1), each of which included 3 dosing periods (period 1: days −2 to 2; period 2: days 6 to 9; period 3: days 13 to 16). Once during each dosing period on days 1, 8 and 15, LUM 200 mg was administered in combination with IVA 250 mg orally in the morning. The peak concentrations in healthy subjects administered LUM 200 mg/IVA 250 mg were projected to be comparable to the peak concentrations in patients...
with CF administered LUM 400 mg/IVA 250 mg. As shown in Figs. 1 and 2, an SABD (albuterol 2.5 mg or ipratropium 0.5 mg) was administered by inhalation via nebulizer during each dosing period (after the 4-h spirometry assessment) and an LABD (indacaterol 75 μg or tiotropium 18 μg) was administered via inhalation in dosing periods 2 and 3 (12 h prior to and 12 h after LUM/IVA administration); spirometry assessments were performed throughout the study.

The primary outcome measure was the absolute change in ppFEV₁ from before to 4 h after LUM/IVA administration. Safety was assessed by the incidence of treatment emergent AEs, vital signs, clinical laboratory tests, electrocardiograms, spirometry and physical examinations. A mixed model for repeated measures was used to evaluate the overall effect of LABDs by comparing the absolute change in ppFEV₁ from before LUM/IVA to 4 h post LUM/IVA in the presence and absence of LABDs. The model included sequence and treatment (albuterol + ipratropium, indacaterol, tiotropium) as fixed effects, period baseline ppFEV₁ as a covariate and subject nested within sequence as a random effect. Data for ppFEV₁ were pooled for administration of an SABD (albuterol, ipratropium) and an LABD (indacaterol, tiotropium).

3. Results

A total of 26 participants was enrolled; 24 (92.3%) completed the study and 2 (7.7%) withdrew consent and were discontinued after dosing period 1. Baseline characteristics were well balanced for participants in each dosing sequence. The mean age (SD) was 36.5 (10.5) years and mean ppFEV₁ (SD) was 96.6 (14.8).

We observed a transient decline in ppFEV₁ after a single dose of LUM/IVA (mean absolute change [SD] on day 1 at 4 h was −4.1 [5.6] percentage points). The absolute change in ppFEV₁ for each individual subject is shown in Fig. 3. The decline in ppFEV₁ was rapidly reversed following administration of an SABD (Fig. 1). The mean (SD) difference in absolute change in ppFEV₁ from 4 h to 5 h post LUM/IVA following administration of an SABD in the absence of an LABD was 3.8 (5.8) percentage points (p = 0.003); similar results were observed with beta agonists and anticholinergics (4.0 [5.5] percentage points for albuterol and 3.5 [6.3] percentage points for ipratropium). Moreover, when an LABD was administered 12 h before LUM/IVA, the decline in ppFEV₁ was attenuated (Fig. 2). The mean absolute change (SD) was −1.4 (4.1) percentage points on days 8 and 15 (average) at 4 h post LUM/IVA. The least squares (LS) mean (SE) difference for attenuation of the decline in ppFEV₁ in the presence of all LABDs vs in the absence of LABDs was 2.9 (1.4) percentage points (p = 0.046); findings were similar for beta agonists and anticholinergics (LS mean [SE]: 3.1 [1.6] percentage points for indacaterol and 2.8 [1.6] percentage points for tiotropium). As shown in Fig. 2, an SABD administered 4 h post LUM/IVA in the presence of an LABD led to further improvement in ppFEV₁.

Overall, 11 participants (42.3%) reported AEs, all of which were mild (n = 9) or moderate (n = 2) in severity. AEs occurring in more than one participant included oropharyngeal...

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Fig. 1. Percent predicted FEV₁ before and after LUM/IVA administration in the absence of LABD (period 1). Data are mean ppFEV₁ during period 1 and error bars indicate standard error. FEV₁, forced expiratory volume in 1 s; LUM/IVA, lumacaftor/ivacaftor; SABD, short-acting bronchodilator; SE, standard error.

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pain in 3 (11.5%), cough in 2 (7.7%) and viral infection in 2 (7.7%). One AE of dyspnea was reported and considered possibly related to study drug; it occurred within 1 day of initiating treatment, was mild in severity and resolved. The transient decline in ppFEV₁ observed after LUM/IVA administration was not reported as an AE. No clinically relevant trends were observed in laboratory tests or vital signs.

4. Discussion

Our findings reveal that administration of LUM/IVA resulted in a transient decline in ppFEV₁ in healthy subjects with normal baseline ppFEV₁ values, a response attenuated by pre-treatment with an LABD and reversed with an SABD. These results suggest that bronchoconstriction could contribute to the occurrence of
certain respiratory AEs (i.e., dyspnea and chest tightness) observed in some CF patients upon initiation of LUM/IVA [1]. Recent evidence suggests that loss of CF transmembrane conductance regulator (CFTR) function may play a role in the airway smooth muscle dysfunction that is common in patients with CF [4]; however, it appears that CFTR modulation may ameliorate this. Using a porcine model, CFTR was found to localize to the sarcoplasmic reticulum compartment of airway smooth muscle, where it regulates Ca\textsuperscript{2+} reuptake and airway smooth muscle basal tone. Loss of CFTR was found to increase basal tone, while CFTR potentiation with IVA was found to reduce airway reactivity in that study [4]. Furthermore, in a phase 3 clinical study in patients with CF and the G551D-CFTR mutation, there was not an increased incidence of respiratory AEs (i.e., dyspnea and chest tightness) with IVA monotherapy [5]. These findings suggest that a potential bronchoconstrictive response does not occur with IVA monotherapy. The apparent bronchoconstrictive effect with LUM is thus likely an off-target effect.

Importantly, LUM/IVA was well tolerated when administered concomitantly with bronchodilators in this study. Future studies to evaluate whether bronchodilator pre-treatment would ameliorate the occurrence of dyspnea and/or chest tightness in some CF patients beginning treatment with LUM/IVA may be warranted.

Declaration of interests

GM, FL and DW are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company.

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