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Original Article

Pooled analysis of two large randomised phase III inhaled mannitol studies in cystic fibrosis☆,☆☆

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Abstract

Background: To evaluate safety and efficacy of inhaled mannitol treatment in subgroups of a large global CF population.
Methods: Data were pooled from two multicentre, double-blind, randomised, controlled, parallel group phase III studies in which 600 patients inhaled either mannitol (400 mg) or control (mannitol 50 mg) twice a day for 26 weeks.
Results: Both the mean absolute change in FEV_1 (mL) and relative change in FEV_1 by % predicted from baseline for mannitol (400 mg) versus control were statistically significant (73.42 mL, 3.56%, both $p<0.001$). Increases in FEV_1 were observed irrespective of rhDNase use. Significant improvements in FEV_1 occurred in adults but not children (6–11) or adolescents (aged 12–17). Pulmonary exacerbation incidence was reduced by 29% ($p=0.039$) in the mannitol (400 mg) group.

Abbreviations: AE, adverse event; ASL, airway surface liquid; BID, twice a day; BMI, body mass index; CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator; CI, confidence interval; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GRAS, generally recognised as safe; HS, hypertonic saline; ITT, intent to treat; MCC, mucociliary clearance; MedDRA, medical dictionary for regulatory activities; MMRM, Mixed-effects model for repeated measures; MTT, mannitol tolerance test; PA, *Pseudomonas aeruginosa*; PDPE, protocol defined pulmonary exacerbation; PE, pulmonary exacerbation; SAE, serious adverse event; SD, standard deviation

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Conclusions: Sustained six-month improvements in lung function and decreased pulmonary exacerbation incidence indicate that inhaled mannitol is an important additional drug in the treatment of CF.

Keywords: Cystic fibrosis; Mannitol dry powder; FEV_1; Airway mucociliary clearance; Clinical study; Dry powder inhalers

1. Introduction

Morbidity and mortality of cystic fibrosis (CF) are mostly related to deterioration of lung function. Many processes contribute, including chronic bacterial infection, excessive inflammation, production of abnormally viscid phlegm, and defective clearance of airway secretions. All of these factors lead to airway remodelling and progressive parenchymal disease [1].

In addition, there are episodes of acute worsening of signs and symptoms, often called pulmonary exacerbations (PE), which are clinically important events that have recently been shown to be associated with accelerated and irreversible loss of lung function [2].

Most CF treatments work downstream in the pathophysiological process and not on the fundamental abnormalities. The underlying defect in the airways stems from malfunction of the CF transmembrane conductance regulator (CFTR), which controls the homeostasis of airway surface liquid (ASL), which is shallow in CF. Adequate ASL depth is critical for normal airway defences, as is optimal ciliary movement and maintenance of mucus hydration, both of which are necessary for normal MCC. Restoration of ASL depth is a strategy to address an underlying defect in CF and can be achieved either by restoring CFTR function or by directly increasing ASL with airway luminal application of osmotic agents.

Mannitol is a naturally occurring polyol (sugar alcohol) and is a generally recognised as safe (GRAS) excipient for food substances at intakes of up to 20 g/day. It is also approved for oral, intravenous and ocular products [3]. When examined in a number of acute [4–9], short [10–12], and long-term studies [13–15], inhaled dry powder mannitol improved airway surface hydration and increased MCC and cough clearance in patients with asthma, bronchiectasis and CF [4–17]. Use in those conditions also contributed to improved lung function [10,11] and a reduction in PEs. Based on its mechanism of action as an osmotic agent, mannitol should be complementary to existing therapies.

Two phase III randomised double-blind controlled studies, referred to as CF301 and CF302 in this article, with nearly identical protocols have been conducted with inhaled mannitol in CF patients with mild to severe pulmonary impairment [14,15]. We present the integrated data from these studies and evaluate the safety and efficacy of inhaled mannitol in a large population of CF patients in order to optimise subgroup analyses by age group and PE outcome measures.

2. Methods

Data have been integrated from two six-month phase III studies examining the safety and efficacy of inhaled mannitol in patients with CF. The primary focus of the studies is on FEV_1 because its decline correlates with survival in CF [18–20].

2.1. Study design, setting

Detailed methodologies of the individual studies have been published elsewhere [14,15]. The study protocols and consent were approved by the institutional review board or research ethics committee at each participating centre, and informed written consent was obtained. Both studies were performed in accordance with good clinical practices and the principles expressed in the Declaration of Helsinki.

These were multicentre, randomised, double-blind, controlled, parallel group phase III clinical trials of very similar design. The minimum FEV_1 inclusion threshold was higher in CF302 ($\geq$40% predicted versus $\geq$30% in CF301), and quantitative sputum microbiology and historic PE over the preceding 12 months was gathered only in CF302.

Prior to randomisation, a mannitol initiation dose was administered to exclude patients with airway hyperresponsiveness, as previously described [14,15]. Eligible patients were randomised 3:2 to receive 26 weeks of 400 mg inhaled mannitol or control (mannitol 50 mg) twice a day. The randomisation schema included rhDNase users and non-users.

Data captured at baseline and all 3 subsequent visits to Week 26 included lung function tests, concomitant medication use, PEs, adverse events (AEs), physical examination, and blood and sputum microbiology assessments. Sputum weight from samples obtained within 30 min of study drug administration, was assessed in both studies after the administration of the first dose at visit 1 and repeated at visit 3 (Week 14).

Subjects were pre-medicated with 400 μg of salbutamol 5–15 min before each study drug dosing. Mannitol (Bronchitol™, Pharmaxis Ltd., Frenchs Forest NSW, Australia) was supplied in blister-packed 40 mg capsules (control, 5 mg capsules), together with an inhaler device (RS01, Monodose Inhaler Model 7, Plastiape, Milan, Italy).

2.2. Study population

Eligible patients had a diagnosis of CF, were aged $\geq$6 years, and had a baseline FEV_1 $\geq$30% ($\geq$40% for CF302) and <90% predicted. They were permitted to continue all CF therapies including rhDNase and inhaled antibiotics but not hypertonic saline (HS). Patients were categorised by age and rhDNase use at screening as follows: children (6 to 11 years), adolescents (12 to 17 years), and adults (>18 years); and rhDNase users and non-users.