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Original Article

Efficacy and tolerability of a new nasal spray formulation containing hyaluronate and tobramycin in cystic fibrosis patients with bacterial rhinosinusitis

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Abstract

Background: Chronic rhinosinusitis is common in cystic fibrosis (CF), as CFTR defects equally affect the airway and sinonasal mucosa. However, therapeutic strategies for CF-associated chronic rhinosinusitis lag behind current approaches for pulmonary disease.
Objective: To assess the tolerability and efficacy of a nasal spray formulation containing 0.2% sodium hyaluronate and 3% tobramycin compared to a control formulation containing 0.2% sodium hyaluronate alone in the treatment of bacterial rhinosinusitis in patients with CF.
Methods: In a double-blind controlled study, 27 patients with an established diagnosis of CF and a documented nasal infection with *Pseudomonas aeruginosa* and/or *Staphylococcus aureus* [22 males (81%), median age of 15 years (range 5–26 yrs)], were randomized to receive the nasal spray formulation containing hyaluronate and tobramycin ($N = 14$) or hyaluronate alone ($N = 13$) for 14 days. Efficacy and local tolerability of the treatments were assessed by ear, nose and throat (ENT) examination and related symptoms.
Results: The formulation containing hyaluronate and tobramycin was more effective than hyaluronate alone in improving the status of the nasal mucosa, in reducing the mucopurulent secretion at the level of the osteomeatal complex and in improving ENT symptoms (hyposmia/anosmia and headache/facial pain). The treatment was well tolerated without relevant side effects.
Conclusions: The present study suggests that the combination therapy with hyaluronate plus tobramycin was more effective than hyaluronate alone in the treatment of bacterial rhinosinusitis in CF. Trial registration number: EudraCT 2007-003628-39.

Keywords: Cystic fibrosis; Bacterial rhinosinusitis; Nasal spray formulation; Hyaluronic acid; Tobramycin

1. Introduction

Chronic rhinosinusitis is very common in cystic fibrosis (CF), being reported in 30–67% of affected patients over all age groups [1,2], with classic and atypical form of the disease [3]. It is associated with a wide spectrum of clinical symptoms (including nasal obstruction, impaired olfactive function and facial pain) that have a significant impact on quality of life [4].

Recently, the influence of the upper airways on the general health of CF patients has been the object of investigation to verify the hypothesis that sinonasal involvement may function as a reservoir for pulmonary infection. Several studies have documented concordance between microorganisms isolated in the upper and lower airways, supporting the unified airway

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concept and also the idea that colonization of the upper airways may precede spread to the lower airways [5–8].

In a group of 16 CF patients who underwent endonasal endoscopic sinus surgery, a significant association was found between bronchoalveolar lavages and sinus cultures [5]. More recently, a cross-sectional study in adult CF patients also comparing upper and lower cultures has shown one or more concordant microorganism in 50% of the patients [8]. *Pseudomonas aeruginosa* was frequently cultured from upper airways and this also occurred after eradication therapy.

Treatment strategies for CF-associated chronic rhinosinusitis vary but usually include a combination of endoscopic sinus surgery, systemic and topical antibiotics/steroids and nasal irrigations [9]. In consideration of the unified airway concept, other therapeutic interventions currently used for pulmonary disease provide potential benefits.

Hyaluronic acid (HA) has been shown to exert beneficial effects in experimental models of chronic respiratory diseases [10]. Due to its water-retaining properties, it humidifies and protects the respiratory airways against injury and is also provided of anti-inflammatory properties [11]. More recently, nebulized HA has been shown to be effective in controlling inflammation in vivo in mice CF airways and in vitro in human airway epithelial cells, thus providing the proof of concept for its use as a potential anti-inflammatory drug in CF therapy [12]. HA inhalation has also been shown to be effective and safe in CF patients with lung disease [13]. However, the inhalation of HA alone does not decrease bacterial load in these patients. Therefore, a nasal spray formulation of HA plus tobramycin was developed to provide the benefits of HA together with the bacteriostatic and bactericidal (at high concentration) effects of tobramycin.

In this study, we compared the efficacy and tolerability of this new formulation with a nasal spray formulation containing HA alone, in the treatment of bacterial rhinosinusitis in patients with CF.

2. Materials and methods

2.1. Study design

We carried out a randomized, double-blind controlled parallel-group pilot study aimed to test the tolerability and efficacy of a 2-week treatment of a nasal spray formulation containing 0.2% sodium hyaluronate and 3% tobramycin compared to a control formulation containing 0.2% sodium hyaluronate alone in CF-associated bacterial rhinosinusitis. The study was carried out at the CF Centre, Fondazione IRCSS, Ca' Granda Ospedale Maggiore Policlinico of Milan in compliance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice. The institutional ethics committee approved the study, and all patients or their guardians provided written informed consent prior to undergoing any study procedures. The trial registration number is EudraCT 2007-003628-39.

Patients older than 6 years with an established diagnosis of CF (sweat chloride >60 mEq/L and/or presence of two CF causing mutations), symptoms of rhinosinusitis and a forced expiratory volume in one second (FEV 1) of at least 30% of the predicted value were considered for the enrolment. Exclusion criteria were a history of hypersensitivity to aminoglycosides, a negative sinus culture for both *P. aeruginosa* and *Staphylococcus aureus*, pregnancy or breastfeeding and the use of systemic antibiotics within 30 days before enrolment in the study. Patients colonized by *Burkholderia cepacia* were also excluded because of the multidrug resistance of the bacterium. Finally, in consideration of the nasal route of administration, patients with deviation of nasal septum totally obstructing one nasal cavity or suffering from allergic rhinitis or sinonasal polyposis, those with ongoing or recurrent epistaxis or with a history of endoscopic sinus surgery in the 6 months preceding enrolment were excluded from the study.

During the study period, patients were allowed to take their usual treatments or to take drugs for any concomitant diseases. However, systemic antibiotic treatment or local nasal treatments with anti-inflammatory drugs were not allowed for the duration of the study.

In all eligible patients, swab cultures obtained from osteomeatal complex were taken under endoscopic control for the identification of pathogens (*P. aeruginosa* and/or *S. aureus* bacteria). We considered the middle meatus representative for the upper airways as a concordance of cultures obtained by middle meatal swab with maxillary sinus aspirate has been confirmed by a meta-analysis [14]. The nasal swabs were placed into 1 mL of 0.9% sodium chloride for processing. After 20 min, the samples were vortexed and 0.1 mL was cultured on different agar plates to detect Gram-positive and Gram-negative bacteria. All samples were incubated aerobically at 37 °C and were analysed for growth of bacteria after 18 h and then every 24 h during 7 consecutive days. Each microorganism isolated was identified by a standardized and automated method (Microscan System Siemens HD). A sputum culture was also performed at the same day visit. Enrolled patients were randomly assigned to one of the two treatment groups using a computer generated randomization code. The test nasal spray formulation consisted of a 10-mL aqueous solution containing 0.2% sodium hyaluronate (MW 0.3–0.5 Mda, obtained by fermentation from *Streptococcus equi* bacterial strain; CPN Spol Dolni Dobrouc 401, 561 02) and 3% tobramycin sulphate. The control nasal spray formulation was identical in presentation but contained only 0.2% sodium hyaluronate. The two test products were packed in identical containers. Each patient nebulized 100 μL of the assigned product into each nostril 3 times a day for 14 days.

The study participants, investigators and study monitors were blind to the treatment assigned to the patients. However, the investigator had access to a sealed envelope containing the randomisation code of each patient to be opened in case of a medical emergency. Data entry and data analysis were also performed in a blind manner, i.e., before the codes were broken.

At baseline (Visit 1, Day 1) and at the end of the study (Visit 2, Day 14), patients underwent nasal endoscopy using the 2.2 flexible optical scope from Olympus NF XP (Olympus