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Fluticasone, Azithromycin, and Montelukast Treatment for New-Onset Bronchiolitis Obliterans Syndrome after Hematopoietic Cell Transplantation

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A B S T R A C T

Bronchiolitis obliterans syndrome (BOS) after allogeneic hematopoietic cell transplantation (HCT) is associated with high mortality. We hypothesized that inhaled fluticasone, azithromycin, and montelukast (FAM) with a brief steroid pulse could avert progression of new-onset BOS. We tested this in a phase II, single-arm, open-label, multicenter study (NCT01307462). Thirty-six patients were enrolled within 6 months of BOS diagnosis. The primary endpoint was treatment failure, defined as 10% or greater forced expiratory volume in 1 second decline at 3 months. At 3 months, 6% (2 of 36, 95% confidence interval, 1% to 19%) had treatment failure (versus 40% in historical controls, $P < .001$). FAM was well tolerated. Steroid dose was reduced by 50% or more at 3 months in 48% of patients who could be evaluated (n = 27). Patient-reported outcomes at 3 months were statistically significantly improved for Short-Form 36 social functioning score and mental component score, Functional Assessment of Cancer Therapies emotional well-being, and Lee symptom scores in lung, skin, mouth, and the overall summary score compared to enrollment (n = 24). At 6 months, 36% had treatment failure (95% confidence interval, 21% to 54%, n = 13 of 36, with 6 documented failures, 7 missing pulmonary function tests). Overall survival was 97% (95% confidence interval, 84% to 100%) at 6 months. These data suggest that FAM was well tolerated and that treatment with FAM and steroid pulse may halt pulmonary decline in new-onset BOS in the majority of patients and permit reductions in systemic steroid exposure, which collectively may improve quality of life. However, additional treatments are needed for progressive BOS despite FAM.

INTRODUCTION

Bronchiolitis obliterans syndrome (BOS) after hematopoietic cell transplantation (HCT), also known as lung chronic graft-versus host disease (GVHD), is an insidious disease with poor outcomes where the donor immune system attacks the small airways in the lungs, leading to

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obstructive pulmonary disease and air trapping [1,2]. Although BOS is rare, affecting only 5% to 12% of HCT recipients, it is a significant problem after HCT because of the high attributed morbidity and mortality [1,3-7]. Patients with early BOS are often asymptomatic, with symptoms developing later in the course of the disease, such as dyspnea on exertion or a chronic cough, followed by dyspnea at rest, and finally inability to accomplish activities of daily living because of progressive pulmonary compromise and attributed weakness [4]. BOS is caused by an immune response to antigens expressed by bronchiolar epithelia, causing inflammation and epithelial disruption, followed by progressive intraluminal fibrosis of the small terminal airways [8-12]. Multiple studies have linked decline in lung function to poor survival after chronic GVHD diagnosis, and historically only 44% of BOS patients are expected to survive 2 years [13-15]. Here, we present the first prospective study to evaluate the efficacy of the combination therapy of inhaled fluticasone, azithromycin, and montelukast (FAM) to treat new-onset BOS after HCT.

Historically, there have been no effective therapies for BOS after HCT. Prior retrospective series have evaluated response of BOS to corticosteroids, cyclosporine, azathioprine, antithymocyte globulin, and extracorporeal photopheresis, and have been limited not only by patient numbers and retrospective evaluations, but also by differences in diagnostic criteria for BOS [15-17]. However, consensus criteria developed in 2005 and revised in 2014 have permitted standardization of diagnostic criteria, which were used for this study [1,4,18,19]. More recently, prospective studies enrolling patients with restrictive pulmonary disease after HCT have evaluated etanercept [20] and azithromycin [21] and have included responses in some patients meeting the definition of BOS. A recent study of inhaled budesonide/formoterol in a prospective, randomized, placebo-controlled, cross-over trial of 32 patients showed benefit for 62% of patients in the treated arm versus 25% in the placebo arm, with a greater than 12% increase in absolute value of forced expiratory volume in 1 second (FEV1) at 1 month. However, only 56% completed the 6-month primary endpoint and 37% required unblinding because of nonimprovement after 1 month of therapy [22].

The FAM regimen was based on encouraging preliminary data with single-agent montelukast reported for the treatment of BOS after HCT and other prior work that had suggested possible benefit with the use of inhaled fluticasone and oral azithromycin for BOS after HCT [1,23-26]. Mechanisms of action for these agents could include a decrease in local lung inflammation (inhaled fluticasone), a reduction in local interleukin-8 levels and neutrophilia (azithromycin), and impairment of leukotriene activity (montelukast). Together, these agents may work by interrupting the cellular homing signals of activated cells trafficking to the lungs and decreasing fibroblast activity that results in the fibrotic constriction of the bronchiole lumen [1,25-35]. Therefore, we undertook a prospective study to evaluate this novel combination of agents (FAM) for the treatment of newly diagnosed BOS after HCT [24,26,36]. Because of the rarity of disease, associated morbidity, and reluctance of investigators to randomize patients to placebo, we conducted an open-label, single-arm study.

MATERIALS AND METHODS

Participants

The trial was limited to patients with *new-onset BOS*, defined as diagnosis within 6 months of enrollment. Inclusion criteria included: (1) BOS, per the National Institutes of Health (NIH) modified criteria: FEV1 $< 75\%$ predicted, FEV1/vital capacity (VC) $< .7$, and an absolute decline of the percent of predicted FEV1 by $\geq 10\%$ from before HCT without evidence of infection or pathologic diagnosis [1,4,18,19]. Pulmonary function testing (PFT) was performed with and without bronchodilators at enrollment to confirm that post-bronchodilator values still met diagnostic criteria; and (2) prior or current diagnosis of chronic GVHD per NIH criteria.

Exclusion criteria included the following: (1) known history of intolerance or allergy to any FAM component; (2) recurrent or progressive malignancy requiring anticancer treatment; (3) serum transaminases concentrations $> 5 \times$ upper limit of normal or total bilirubin $> 3 \times$ upper limit of normal; (4) treatment with inhaled steroid or montelukast or zafirlukast for greater than 1 month during the past 3 months; (5) current treatment with prednisone at > 1.2 mg/kg/day (or equivalent steroid) on the enrollment evaluation; (6) treatment with rifampin or phenobarbital, aspirin at doses > 325 mg/day, or ibuprofen at doses > 1200 mg/day; (7) treatment with any non–Food and Drug Administration–approved medication within the past 4 weeks; (8) evidence of any viral, bacterial, or fungal infection involving the lung and not responding to appropriate treatment; (9) chronic oxygen therapy; (10) clinical asthma; (11) baseline post-bronchodilator FEV1 $< 20\%$ of predicted normal; (12) inability to reliably perform PFT; (13) patient age < 6 years; (14) life expectancy < 6 months at the time of enrollment as judged by the enrolling investigator; (15) any condition that, in the opinion of the enrolling investigator, would interfere with the subject's ability to comply with the study requirements; or (16) pregnancy or nursing.

Central review confirmed PFT eligibility before study entry. Patients were typically referred at the first PFT that showed BOS, though several months may have elapsed between pulmonary visit and primary HCT visit whereby patients would be diagnosed with BOS and referred for study. The Crapo calculation was used to convert FEV1 volume to percent predicted FEV1 [37]. All institutions obtained institutional review board approval, and all participants provided written informed consent. The study is registered at Clinicaltrials.gov as NCT01307462.

Study Design

This was a phase II, single-arm, open-label study. The primary endpoint was *treatment failure* by 3 months, defined as an absolute decline of the percent of predicted FEV1 by $\geq 10\%$ from before enrollment (eg, 40% to 30% predicted FEV1), confirmed by 2 PFTs performed at least 2 weeks apart. The selection of 3 months for the primary endpoint and 6 months for study completion was based on data published with similar evaluation periods in lung dysfunction after HCT and preliminary data showing that this timeframe was predictive of changes for the subsequent 1.5 years [22,23,38]. If the 3-month PFT were missing, the 2- or 6-month PFT was used for endpoint assessment, with the worst test included in the analysis. If no 2- or 6-month test were available, the patient was considered a treatment failure in the primary analysis. A minimum of a 10% decline was used to define treatment failure because a decline of 8% over a 6- to 12-month period is clinically important [39]. *Treatment success* was defined as lack of failure, ie, less than 10% decline in absolute FEV1 percent predicted. Secondary endpoints include the safety of FAM and change in other PFT parameters, non-pulmonary chronic GVHD, 6-minute walk test, and patient-reported outcomes.

Upon study entry, all participants taking prednisone at < 1 mg/kg/day increased their dose to 1 mg/kg/day orally for 2 weeks, unless contraindicated by other comorbidities. This brief steroid pulse was included because of the prevailing treatment recommendation of prednisone for newly diagnosed BOS; however, the intention of the study was to test the efficacy of FAM and intolerance of high-dose prednisone was not an exclusion criteria. After 2 weeks, participants started a taper of .25 mg/kg/day per week with a goal of attaining an equivalent dose of .25 mg/kg/day by 5 weeks after enrollment or the dose of corticosteroids at study entry, whichever was greater, unless higher doses were required by other chronic GVHD manifestations. This tapering schedule is much faster than usually used for BOS to attempt to minimize infectious complications and test the efficacy of FAM. Otherwise, steroids were tapered at the investigator's discretion, taking into consideration other chronic GVHD manifestation severity. Corticosteroids could be tapered faster in cases of uncontrollable toxicity.

FAM Treatment

Fluticasone (inhaled fluticasone propionate) was given at 440 mcg twice a day (ages, 12 to 99 years) or 220 mcg twice a day (ages, 6 to 11 years) and was provided by GlaxoSmithKline to each participant for 6 months under grant 113611. Azithromycin was given at 250 mg orally for adults (19 to 99 years) and 5 mg/kg orally (max 250 mg) for children (6 to 18 years) taken 3 days per week was prescribed commercially. Montelukast, 10 mg oral