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Fluticasone, Azithromycin, And Montelukast (FAM) Therapy In Reducing Corticosteroid Exposure In Bronchiolitis Obliterans Syndrome After Allogeneic Hematopoietic Stem Cell Transplant – A Case Series Of Eight Patients

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Abstract

Backround—Bronchiolitis obliterans syndrome (BOS) is a devastating pulmonary complication affecting long term survivors of allogeneic hematopoietic cell transplantation. Treatment of BOS with prolonged courses of high dose corticosteroids is often associated with significant morbidity. Reducing the exposure to corticosteroids may reduce treatment related morbidity. Our institution has recently begun to treat patients with emerging therapies in an effort to diminish steroid exposure.

Methods—We retrospectively reviewed the 6-month corticosteroid exposure, lung function, and failure rates in 8 patients with newly diagnosed BOS who were treated with a combination of fluticasone, azithromycin and montelukast (FAM) and a rapid corticosteroid taper. These patients were compared to 14 matched historical patients who received high dose corticosteroids followed by a standard taper.

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Results—The median 6-month prednisone exposure in FAM-treated patients was 1819 mg [0 mg to 4036 mg] compared to 7163 mg [6551 mg to 7829 mg] in the control group (p = 0.002). The median FEV_1 change in FAM-treated patients was 2% [−3% to 4%] compared to 1% [−4 to 5%] in the control group (p = 1.0).

Discussion—Prednisone exposure in FAM patients was one quarter that of a retrospective matched group of patients, with minimal change in median FEV_1, suggesting that BOS may be spared of the morbidities associated with long-term corticosteroid use by using alternative agents with less side effects.

Keywords

Bronchiolitis Obliterans Syndrome; Corticosteroids; Steroid Sparing; FAM

INTRODUCTION

Bronchiolitis obliterans syndrome (BOS), defined as new fixed airflow obstruction that develops in the setting of active chronic graft versus host disease (GVHD), is a serious and devastating complication of allogeneic hematopoietic cell transplantation (HCT) (1–4). Although there have been no controlled trials to evaluate the duration and dose of immunosuppressive therapy necessary for treatment of newly diagnosed BOS, the historical clinical approach has been treatment with high dose corticosteroids for extended periods of time, e.g. 12 to 24 months. Unfortunately, such prolonged exposure to even low dose corticosteroids is associated with significant morbidity. Some studies have actually suggested that corticosteroid treatment of BOS may result in poor outcomes and significant infectious complications (5–7). Studies suggest that even modest doses of daily corticosteroids significantly increase risk of developing osteoporosis (8), opportunistic infection (9), and diabetes (10). Because the incidence of corticosteroid related morbidity increases as a function of both total exposure and duration of exposure (11,12), any change in the treatment regimen that can minimize corticosteroid exposure has the potential to significantly reduce corticosteroid related morbidity, as well as suppression of graft function and disease relapse.

Recent reports in both the hematopoietic stem cell and lung transplant literature suggest that inhaled corticosteroids, macrolides, and leukotriene inhibitors may have anti-inflammatory and antifibrotic effects that might be beneficial in the treatment of BOS. Although these agents have never been evaluated prospectively, in an effort to minimize corticosteroid exposure, we recently incorporated these agents into our clinical treatment plan for BOS. We report here a retrospective analysis of these agents in treating eight patients with BOS, and compared their lung function and systemic corticosteroid exposure in the first six months of therapy to a group of retrospectively identified historical BOS patients who received standard care. Because this was not a formal clinical trial, the main goal of this analysis was to evaluate whether corticosteroid exposure may be reduced among patients with BOS.

MATERIALS AND METHODS

Patient Population

Between June 2008 and November 2009, nine patients were evaluated by the pulmonary consultation service at Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care Alliance (SCCA) for new onset airflow obstruction noted on pulmonary function testing. Each patient was clinically determined to have developed BOS according to the National Institutes of Health (NIH) Graft Versus Host Disease Consensus guidelines, characterized by an FEV_1 of < 75% predicted and an FEV_1/SVC ratio of < 0.7, evidence of air trapping as found on high resolution computed tomographic images, and or a residual volume of > 120% and no evidence of respiratory infection (13). Alternative causes of the obstructive pattern (i.e. respiratory infection, asthma, and tobacco related disease) were excluded. All patients were regularly followed for 6 months by their transplant oncologist, a chronic GVHD specialist and/or a pulmonologist. Pulmonary function tests and blood tests (including chemistries, liver function tests, and complete blood counts) were obtained at regular intervals.

FAM Therapy

After confirmation of the BOS diagnosis, all patients were treated throughout the six month period with “FAM” therapy consisting of **F**luticasone Inhaled 440 mcg twice daily, **A**zithromycin 250 mg orally every Monday, Wednesday, and Friday, and **M**ontelukast 10 mg orally every day. Patients on < 1 mg/kg/day of prednisone at the time FAM was initiated had their prednisone dose increased to 1mg/kg/day for the first 2 weeks, followed by a rapid 2 week taper with a goal of 0.25 mg/kg/day equivalence by 4 weeks after enrollment. At this point it was recommended that patients receive every other day dosing. The taper was then directed by the patient’s primary provider, guided by other manifestations of chronic GVHD. Among patients in whom graft-versus leukemia effect was desired or who were at high risk for corticosteroid related complications, FAM was used alone. Patients continued on standard anti-infective prophylaxis agents and any other immunosuppressive agents deemed necessary for management of non-pulmonary chronic GVHD.

Comparison patients were identified from an existing database of BOS patients. Each patient’s clinical data during the first 6 months after BOS diagnosis were obtained for analysis. To be included in the comparison, the historical patients were required to have been diagnosed with BOS based on NIH consensus criteria and needed to have sufficient data from the medical records to document the study outcomes. Patients were not included if they died within 6 months from diagnosis, there was insufficient documentation to obtain 6 month corticosteroid exposure or follow-up pulmonary function testing, or if they received all 3 components of FAM during the follow-up period. The comparison patients had their prednisone tapered at the discretion of their primary providers, guided by our local chronic GVHD taper schedule that recommended 1 mg/kg/day of prednisone for a period of 2 weeks, followed by a 25% per week decrease to 1mg/kg/QOD dose that was maintained for a period of 3 months. If tolerated, a 10–20%/ month taper was then initiated (14). All eligible historical controls were included in the analysis.

Corticosteroid data was obtained using tapering schedules as dictated by pharmacy in conjunction with careful review of clinic notes that documented current prednisone dosage and changes in dosage. Prednisone exposure was calculated by the formula: mg/day × days on that dose. The total exposure over the 6 month period was then summed yielding total mg of prednisone exposure over ~ 180 day period. In the case of alternate day dosing, the number of days was divided by 2 and each particular dose was multiplied by that number, then added together to yield a total mg of exposure over that time frame. For periods without detailed tapering or dosage data, dosing was extrapolated for said period using the standard FHCRC taper schedule as outlined above as long as there was documentation confirming taper at a later date. Average mg/day prednisone dose was then calculated as total mg prednisone/number of days. Inter-quartile values of both total prednisone exposure over 6 months and average prednisone dose per day were calculated.

Pulmonary Function Testing

All pre-transplant and post-transplant PFTs were performed at our Center according to American Thoracic Society guidelines using the Sensormedics V-Max 22 with Autobox 6200 (Sensormedics Co., Yorba Linda, CA). For all PFTs, predicted values were calculated using published equations for children and adults (15, 16). All pulmonary function values, except for the FEV_1/SVC ratio, were expressed as a percentage of predicted values. Pulmonary function tests were performed as previously described and FEV_1 values were recorded at 3 and/or 6-month post diagnosis (+/− 1 month). FEV_1 change was then calculated in both groups by subtracting FEV_1 at BOS diagnosis from the FEV_1 at 6 months or 3 months. Treatment failure was defined as a decrease in absolute predicted FEV_1 of > 10% during the 6 month period of follow-up and worsening of clinical symptoms requiring an increase in corticosteroid dosing. The lung function score (LFS) was calculated according to NIH Consensus Criteria recommendations by scoring the FEV1 and DLCO (>80% = 1, 70–80% = 2, 60–70% = 3, 50–60% = 4, 40–50% = 5, and < 40% = 6), then summing the FEV1 and DLCO scores and dividing them into 4 categories from 0 – 3 (LFS score 2 = category 0, LFS score 3–5 = category 1, LFS score 6–9 = category 2, LFS score 10–12 = category 3) (17). Any change in lung function always prompted a thorough evaluation for a respiratory infection as a potential cause, which included history and physical exam, chest radiograph and computed tomography scan when indicated, and bronchoscopy if indicated.

Statistical Analysis

All analyses were performed using Stata 11.0 software (College Station, TX). Two sided p values <0.05 were considered statistically significant. All categorical variables were compared using Pearson's Chi-Square Test or Fisher's Exact Test and continuous variables were compared using Student's T-test.

RESULTS

A total of 9 patients received FAM therapy as part of their treatment for BOS. One patient was lost to follow-up, thus 8 patients were included in the final analysis. Fourteen comparison patients were identified from the database. Only patient-donor HLA matching was significantly different between the two groups (p = 0.006). Among FAM treated

patients, 3 received matched related donors, 0 received mismatched related donors, and 5 received unrelated donors. Among the comparison group, this distribution was 10, 2, and 0 respectively. Previous studies have shown that patient-donor HLA match was not associated with a statistically significant increase in risk for development of BOS (7,18). There were no significant differences in the distribution of patient age ($p = 0.14$), sex match ($p = 1.0$), race ($p = 0.56$), disease risk ($p = 0.53$), stem cell source, CMV serostatus ($p = 0.53$), conditioning regimen ($p = 0.18$), or chronic GVHD score ($p = 0.23$). (Table 1).There was also no difference in pre-transplantation lung function or lung function at diagnosis as determined by lung chronic GVHD score, LFS, FEV_1, FVC, or FEV/FVC between the 2 groups (Table 2).

In comparison to the non-FAM treated patients, there was no statistically significant difference in the starting prednisone dose ($p=0.868$). Within the comparison group, the median starting daily dose of prednisone was 70 mg, (range 20 mg to 100 mg). Three FAM patients were not started on corticosteroids at the time of initiation of FAM. For two, this was due to active lymphoma or leukemia and the desire to preserve graft-versus-leukemia effect. The third patient had severe underlying osteoporosis due to prior exposure to high dose corticosteroids for other cGVHD manifestations. The median starting dose of prednisone for the remaining 5 FAM treated patients was 70 mg (range 50 mg to 80 mg). All patients treated with FAM tolerated the treatment regimen with no adverse events; no patient had to discontinue any component of FAM therapy during the duration of the observation period. The median 6-month prednisone exposure for the FAM-treated patients was significantly lower than the comparison group: 1819 mg [IQR 0 mg to 4036 mg] versus 7163 mg [IQR 6551 mg to 7827 mg] ($p = 0.002$). The median mg/day prednisone dose for the 6 month period was also significantly lower for the FAM-treated group: 13 mg/day [IQR 0 mg to 23 mg] versus 40 mg/day [IQR 36 mg to 46 mg] ($p = 0.001$). The average prednisone dose at the end of the study period was 9 mg/day (+/− 15 mg) in the FAM group compared to 26 mg/day (+/− 12 mg) in the comparison group.

The median FEV_1 change in the FAM group was 2% [IQR −4 to 5%] compared to 1% [IQR −4% to 5%] in the comparison group over six months, with one patient in each group experiencing treatment failure. There was no statistically significant difference in FEV_1 change between groups ($p = 1.0$). One FAM patient experienced a 17% drop in his FEV_1 by 5 months in the setting of tapering of prednisone and development of Aspergillus fumigatus pneumonia with worsening bronchiectasis. In response, the patient's prednisone dose was increased to 1mg/per/kg/BID for one week, after which a taper was initiated to bring the dose to 1mg/kg every other day at the end of 1 month. This patient's lung function ultimately stabilized after treatment with the higher dose prednisone. A single historical patient also experienced treatment failure characterized by worsening shortness of breath and an FEV_1 decline of 13% with tapering of steroids to 1 mg/kg every other day. These symptoms improved after the prednisone was increased to 1 mg/kg/day for a period of approximately 1 month. Corticosteroids were thereafter very slowly tapered to 1 mg/kg every other day over a period of 4 months. There was no difference in disease relapse rate between the two groups (FAM group: 3 cases comparison group: 2 cases, $p=0.309$). Among the FAM treated patients, there was no significant difference in treatment response between the 5 patients who received systemic corticosteroids versus the 3 patients who had systemic

corticosteroids withheld, as evidenced by similar median FEV_1 change (0% versus 3% respectively). In addition the 3 patients who had corticosteroids withheld experienced no significant decline in functionality, two had ECOG scores of zero and one had an ECOG score of 1.

DISCUSSION

This report provides evidence that challenges two current clinical approaches in the management of new severe airflow obstruction after allogeneic HCT. First, the rapidity with which the FAM patients were able to reduce their prednisone doses or avoid prednisone suggests that BOS patients may not require prolonged corticosteroid tapers that can lead to significant morbidities. Although we observed a significant difference in total 6-month exposure and median daily doses of prednisone, both groups reach every other day corticosteroid dosing within the first 4 to 6 weeks. The observed lower overall corticosteroid exposure among FAM patients is attributable to the absence of a prolonged taper following these initial weeks. While this retrospective analysis is unable to determine whether the FAM regimen facilitated this rapid taper, the observation that the majority of the FAM patients had stable lung function despite this rapid prednisone taper suggests that prolonged corticosteroid tapers may not be necessary for the treatment of BOS, with or without FAM treatment. This observation also suggests that in future trials that consider alternative approaches to treating BOS, corticosteroid exposure represents an important endpoint worth considering.

Second, this report suggests that alternative less toxic therapies should be investigated for the management of BOS. The rationale for FAM combination therapy is based upon their anti-inflammatory and/or anti-fibrotic properties. Inhaled corticosteroids (ICS) have been shown in 2 studies to stabilize FEV_1 and improve symptoms in patients with BOS after allogeneic HCT (19, 20). One small study showed that azithromycin improved FVC and FEV_1 in HCT-related BOS (21). Leukotrienes have been implicated in immune mediated bronchiolitis in animal and human models (22) and have also been implicated as a factor in lung fibrosis (23). A small pilot study also suggested that Montelukast therapy may be beneficial for chronic GVHD (24). These data, along with the minimal side effect profiles of these drugs, provide the motivation for considering their use in this clinical setting. Although ideally, these drugs should be studied independently in separate trials, this is quite challenging given the low prevalence of BOS.

As one considers these data, there are clearly important limitations. The retrospective and uncontrolled nature of this study, as well as the small sample size, is not ideal. In addition, 3 patients receiving FAM did not receive corticosteroids. While this has the potential to bias our corticosteroid dose comparison, an analysis restricted to only FAM patients who did receive prednisone indicate that the total median mg/day prednisone dose for the 6 month period remained lower for the FAM-treated group: 21 mg/day versus 40 mg/day and the total 6 month prednisone exposure remained lower in the FAM treated group: 3620 mg versus 7163 mg. Furthermore, this limitation does not detract from our original goal, to demonstrate that BOS may be effectively treated with less corticosteroid therapy. While these data for FAM are interesting, they do not provide adequate information regarding the

extent of pulmonary function monitoring required and the potential for relapse after 6 months. Although there were essentially no side effects associated with the FAM regimen, one needs to keep in mind that in the event of treatment failure, lung function loss is often irreversible and will likely result in significant loss of quality of life, and possibly death. Thus, we recommend that until FAM therapy has been confirmed to be effective for controlling BOS, this regimen should only be used under intense clinical monitoring or in the setting of a clinical trial.

For orphan diseases such as BOS after allogeneic HCT, where the potential morbidities of current treatment is high, treatment options that can simply help reduce the adverse events profile of current therapies can represent a major step toward improving outcomes. These data suggest for the first time that BOS may be managed using approaches that significantly reduce the total corticosteroid exposure, and that less toxic treatment alternatives are worthy of exploration. If this is proven to be true in clinical trials, this can significantly reduce the number of corticosteroid associated complications encountered in these long-term survivors of allogeneic HCT. Furthermore, these data suggest that it may be possible to shift the risk benefit ratio of treatment for BOS, such that physicians might be more willing to treat new obstructive changes earlier using a less corticosteroid intense approach, when the disease process might be stopped from progressing to more severe stages.

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Abbreviations

BOS	Bronchiolitis Obliterans Sydrome
cGVHD	Chronic Graft Versus Host Disease
FAM	Fluticasone, Azithromycin, Montelukast
FVC	Forced Vital Capacity
FHCRC	Fred Hutchison Cancer Research Center
FEV1	Forced Expiratory Volume in One Second
HCT	Hematopoietic Cell Transplantation
ICS	Inhaled Corticosteroids
LFS	Lung Function Score
PFT	Pulmonary Function Testing
SVC	Sustained Vital Capacity

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Table 1

Demographic Information

	FAM (n=8)	No FAM (n=14)	P-value
Age (yr)			0.143
< 20	0	0	
20–39	1	6	
40–59	3	6	
≥60	4	2	
Sex			0.278
M:M	3	2	
M:F	1	5	
F:F	2	6	
F:M	2	1	
Race			0.798
Caucasian	7	10	
Other	1	2	
Disease Risk @ Tx			0.533
Low	0	2	
Intermediate	4	6	
High	4	6	
HLA Match			0.006
Matched-related	3	10	
Mismatch-related	0	2	
Unrelated	5	0	
Stem Cell Source			-
Bone Marrow	0	0	
Peripheral	8	14	
CMV Status R-D			0.529
Neg-Neg	4	6	
Neg-Pos	1	3	
Pos-Pos	2	5	
Pos-Neg	1	0	
Conditioning Regimen			0.181
Nonmyeloablative	7	7	
Myeloablative: TBI	1	4	
Myeloablative: Non-TBI	0	3	
GVHD Score @ Tx			0.226
2	1	1	
4	3	2	

	FAM (n=8)	No FAM (n=14)	P-value
6	2	1	
7	1	5	
8	0	3	

Table 2

Median post-transplant and at BOS diagnosis spirometric values with Interquartile Intervals.

	Pre-Tx Median [IQR]			BOS Dx Median [IQR]		
	FAM* (n=8)	No FAM (n=14)	P-Values	FAM (n=8)	No FAM (n=14)	P-Values
FEV1	92% [89–92]	92% [89–97]	0.844	52% [33–57]	55% [45–63]	0.343
FVC	95% [84–98]	98% [95–99]	0.923	80% [72–85]	73% [70–80]	0.588
FEV1/FVC	0.74 [0.72–0.8]	0.79 [0.77–0.82]	0.185	0.52 [0.42–0.53]	0.6 [0.52–0.68]	0.094
LFS	1 [1–1]	0 [2–3]	0.272	2 [0–0]	2 [2–2]	0.195

*All values are Pre-HSCT with the exception of one FAM patient whose pre transplant PFTs were not available. Immediate post-transplant PFTs were substituted in this case. IQR=interquartile range.

Table 3

Comparison of prednisone exposure

	FAM (n=8)	No FAM (n=14)	P-Values
Median Cumulative Prednisone Exposure over 180 days (mg)	1819	7163	0.002
Interquartile range	0 – 4036	6551 – 7829	
Median Cumulative (mg/day)	13	40	0.001
Interquartile range	0 – 23	36 – 46	
Median FEV_1 Change	2%	1%	1.0
Interquartile Range	−4% to 5%	−4% to 5%	
Treatment Failure	1	1	1.0