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Treatment Options for Bronchiolitis Obliterans After Hematopoietic Stem Cell Transplant: A Systematic Review of Clinical Trials in the Last 10 Years

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INTRODUCTION

One of the severe manifestations of chronic graft-versus-host-disease (cGVHD) is bronchiolitis obliterans syndrome (BOS), which occurs as progressive airway fibrosis after hematopoietic stem cell transplantation (HSCT). Due to the higher morbidity and mortality, multiple treatment studies are still done without clear standard therapy of care.

AIM

This systematic review aims to assess the efficacy of different treatment options for BOS after hematopoietic stem cell transplant.

METHOD

A literature search was conducted on PubMed and Embase with keywords "Bronchiolitis Obliterans" and "Stem Cell Transplant" from 1/1/2012 to 2/10/2023. 635 articles were screened, and we included 2 randomized clinical trials (RCTs, N=54) and 6 non-randomized clinical trials (nRCTs, N=187). Data was extracted for baseline characteristics and efficacy outcomes using Microsoft excel software. PRISMA guidelines were followed while conducting this systematic review.

RESULTS

In an RCT by Lam et al. (N=22), the mean FEV1% change was -1.21±13.09 with azithromycin compared to the placebo change of +0.74±10.79. In an nRCT by Brownback et al. (N=13), corticosteroids + azithromycin + montelukast showed an FEV1 decline slope of -5.12 cc/month without and +2.27 cc/month with rituximab. In an RCT (N=32) by Bergeron et al., budesonide/formoterol showed an absolute FEV1 change of 267.5±69.28 vs. 17.5±135.6 (p=0.012) with placebo. In an nRCT by Kim et al. (N=61), budesonide + formoterol + montelukast + N-acetylcysteine showed an FEV 1 change of 6.36%±12.72 (p=<0.001) after 3 months of treatment. In an RCT by Zhao et al. (N=30), ruxolitinib showed a predicted change of 11%(p=0.029) in mean FEV1. In an RCT by Matthieu et al. (N=22), pirfenidone showed mean rate of change in FEV 1 %slope +0.59%/month(p=0.046). In an nRCT by Williams et al. (N=25), montelukast alone showed a median FEV1 % predicted change of -2 (-5 to-3%) with median FEV1 slope after 2 years Rx +1.32 (p<0.0001). In a study by Williams et al. (N=36), fluticasone + azithromycin + montelukast showed absolute improvement in %predicted FEV1 5-10% in 24% and >10% in 10% of the patients.

Study	Patients	Treatment	N	Efficacy
Lam et al. 2011	Adults with BO after HSCT	Azithromycin	10	Mean FEV_1 % change: -1.21 ± 13.09 Mean FVC change: +2.79 ± 8.88 Mean FEF $_{25-75}$% change: -9.11 ± 33.17
		Placebo	12	Mean FEV_1 % change: +0.74 ± 10.79 (p = 0.711) Mean FVC change: -0.37 ± 5.62 (p = 0.345) Mean FEF $_{25-75}$% change: +9.2 ± 26.85 (p = 0.178)
Beregeron et al. 2015	Adults with BO after HSCT	Budesonide/ formoterol	16	Absolute FEV_1 change= 267.5 ± 69.28 Variation in FEV_1 relative to baseline (%) =13 ± 4.04 Variation in FVC: 346.25 ± 119.8 Variation in MEF 25-75%: 127.5 ± 118.3
		Placebo	16	Absolute FEV_1 change= 17.5 ± 135.6 (p = 0.012) Variation in FEV_1 relative to baseline (%) = 0 ± 7.79 (p = 0.019) Variation in FVC= 10 ± 80.84 (p = 0.021) Variation in MEF 25-75%= 174.06 ± 166.36 (p=0.84)
Kim et al. 2016	Adults with BO after HST	Budesonide/formetrol + montelukast + N-acetylcysteine	61	FEV1 change after treatment=0.22 ± 0.43 (p= <0.001) FEV1 % change after treatment=6.36±12.72 (p=<0.001) FVC change after treatment = 0.23 ± 0.43 (p=<0.001)
Williams et al. 2016	Adults with BO after HST	Fluticasone+ Montelukast + Azithromycin	36 (29 completed PFT and 23 had treatment success)	Absolute improvement in % predicted FEV1>10%= 3 (10%) of 23 patients Absolute improvement in % predicted FEV1 5-10%= 7 (24%) of 23 patients Absolute improvement in % predicted FEV1 < 5%= 5(17%) of 23 patients Absolute deterioration of % predicted FEV1 1-10%= 8 (28%) of 23 patients % change in absolute FEV1 volume ≥10%= 31% Stable absolute FEV1 volume= 41% % decline in absolute FEV1 volume<10%= 28%
Brownback et al. 2017	BO due to GVHD after HSCT	Rituximab+ ICS + Azithromycin+Montelukast + immunosuppression	13	Average FEV1 slope prior to Rituximab infusion= -5.12 cc/mo Average FEV1 slope 12 months after Rituximab infusion= +2.27 cc/mo Average FVC slope prior to Rituximab Infusion= -4.15 cc/mo Average FVC slope 12 months after Riruximab infusion= -0.77 cc/mo
Zhao et al. 2021	BO in adolescents and adults after HSCT	Ruxolitinib	30 (20 responded)	Change in mean FEV1% predicted after 6 months in 20 responders= 11 (p=0.029)
Matthaiou et al. 2022	Adults with BO after HSCT	Pirfenidone	22	Mean rate of change in FEV1% slope= +0.59%/month (p=0.046)
Williams et al. 2022	BO in pediatric and adult patients after HSCT	Montelukast	25	Median FEV1% predicted change was –2.0 (-5% - -3%) Median baseline FEV1 slope prior to treatment= -1.36 Median FEV1 slope after 2 yrs treatment= +1.32 (p<0.0001)

CONCLUSIONS

Combination of budesonide with formoterol significantly improved lung functions as compared to placebo. Results were similar after treatment with azithromycin vs. placebo. In single-arm trials, lung function tests significantly improved after treatment with rituximab, ruxolitinib, pirfenidone, and montelukast. Randomized phase 3 trials are needed to confirm the efficacy of these drugs.

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