ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Advances in the treatment of bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation: a scoping review

Avanços no tratamento da Síndrome da Bronquiolite Obliterante pós-transplante de células-tronco hematopoiéticas - uma revisão de escopo

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ABSTRACT

Hematopoietic Stem Cell Transplantation (HSCT) is the treatment of choice for a variety of neoplastic and non-neoplastic diseases in children. However, respiratory complications in the post-transplant period are common and result in increased morbidity and mortality rates. Graft-versus-Host Disease (GVHD) is among the major complications in the late phase, with bronchiolitis obliterans syndrome (BOS) being the most frequent clinical syndrome. It is characterized by an obstructive pattern and progressive nature, caused by the obliteration of the small airway. This is a challenging condition as there is no specific treatment with proven efficacy, coupled with a scarcity of data in the pediatric population. The aim of this article is to review studies highlighting the effectiveness of existing treatments for this condition, across different modalities ranging from conventional therapies to the most recent approaches, aiming to inform attending physicians involved in the care of this patient group. Precise and effective management of BOS is crucial to halt the impairment of pulmonary function in the medium and long term, promoting increased survival for patients post-HSCT.

Keywords: Bronchiolitis obliterans, transplantation, treatment, pulmonary complications.

RESUMO

O Transplante de Células-Tronco Hematopoiéticas (TCTH) é o tratamento de escolha para uma variedade de doenças neoplásicas e não neoplásicas em crianças. No entanto, complicações respiratórias no pós-transplante são comuns e resultam em aumento dos índices de morbidade e mortalidade. A Doença Enxerto Contra Hospedeiro (DECH) está entre as principais complicações na fase tardia, sendo a síndrome da bronquiolite obliterante (BOS), a síndrome clínica mais frequente. Caracteriza-se pelo padrão obstrutivo e de caráter progressivo, ocasionado pela obliteração da pequena via aérea. É uma condição desafiadora, uma vez que não existe tratamento específico com eficácia comprovada, além da escassez de dados na população pediátrica. O objetivo deste artigo é revisar estudos que apontam a efetividade dos tratamentos existentes para esta condição, nas diferentes modalidades, desde as terapias convencionais até as abordagens mais atuais, buscando informar os médicos assistentes envolvidos no atendimento deste grupo de pacientes. O manejo preciso e eficaz da BOS é fundamental para interromper o comprometimento da função pulmonar em médio e longo prazo, favorecendo uma maior sobrevida para os pacientes no pós-TCTH.

Descritores: Bronquiolite obliterante, transplante, tratamento, complicações pulmonares.

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Introduction

Hematopoietic stem cell transplantation (HSCT) represents a potentially curative treatment option for several diseases, including hematological malignancies, inborn errors of immunity, and non-neoplastic conditions. Among the possible complications of HSCT, pulmonary graft-versus-host disease (GVHD) can contribute significantly to post-transplant morbidity and mortality.[1,2]

Pulmonary complications affect 25–50% of HSCT recipients, presenting either as acute manifestations, defined as those occurring within the first 120 days after the procedure, or in subacute/chronic form, with onset approximately 6 months after transplantation. Acute complications are associated with a high mortality rate, with viral and fungal infections, as well as non-infectious complications such as pulmonary edema, diffuse alveolar hemorrhage, and idiopathic pneumonia syndrome, being most common. Subacute/chronic complications have a more insidious course and include pulmonary chronic GVHD, a term which covers two distinct syndromes: bronchiolitis obliterans syndrome (BOS), characterized by an obstructive pattern on pulmonary function tests, and cryptogenic organizing pneumonia (COP), characterized by a restrictive pattern.[1]

BOS is the pulmonary manifestation of GVHD and is characterized by airway obstruction secondary to a fibroproliferative inflammatory process. Collagen deposition occurs in the subepithelial layer, causing partial or complete fibrosis and lymphocyte infiltration associated with hyperplasia or squamous metaplasia of the epithelium, leading to obliteration of the small airways.[3]

The underlying pathophysiological process is complex and multifactorial. Damage to the host bronchiolar epithelium occurs through both immune and non-immune mechanisms. Macrophages and neutrophils play an important role, resulting in the release of inflammatory, chemotactic, and profibrotic mediators. Studies that examined the bronchoalveolar lavage fluid of patients with BOS found increased neutrophils, interleukin (IL)-8, IL-1ra, transforming growth factor beta (TGF-β), monocyte chemotactic protein-1 (MCP-1), and tumor necrosis factor alpha (TNF-α).[4]

The disease is usually asymptomatic, developing insidiously within the first two years after HSCT. Diagnostic suspicion is raised by a progressive decline in lung function in the absence of other etiologies.[5] The recommended criteria are those of the 2014 National Institutes of Health (NIH) Consensus modifications: FEV_1 < 75% or below the fifth percentile of predicted or a ≥ 10% decrease in FEV_1 the last 2 years; FEV_1/FVC ratio < 0.70 or below the fifth percentile of predicted; evidence of air trapping on CT scan with bronchi al thickening or bronchiectasis or due to an increase in residual volume > 120% of predicted in pulmonary function tests; and absence of respiratory tract infection. Nevertheless, biopsy with histopathological analysis remains the gold standard for diagnostic confirmation.[6]

Despite the modifications, the aforementioned criteria may fail to identify early declines in lung function, given their use of an absolute cutoff point for FEV_1. Therefore, the NIH recommends that pulmonary function tests be performed every 3 months for the first 2 years after HSCT, especially in high-risk patients, such as those with extrapulmonary GVHD.[7,8]

Risk factors related to the development of BOS include decreased serum IgG levels, a history of acute GVHD, advanced recipient or donor age, a lower pre-transplant FEV_1/FVC ratio, viral respiratory infections in the first 100 days post-HSCT, conditioning with busulfan or high-intensity conditioning, female-donor-to-male-recipient gender discordance, and a previous episode of interstitial pneumonitis.[1] A pre-transplant history of lung disease and cytomegalovirus (CMV) seropositivity are also associated with an increased risk of BOS.[9]

This is a particularly challenging condition, since no combination of therapeutic agents studied has been completely effective to date; furthermore, many patients may remain asymptomatic for long periods even when evidence of moderate to severe obstruction is already present on pulmonary function tests. BOS is associated with significant impairment of quality of life and increased mortality after HSCT.[1,6,10]

Objectives and methods

To address our main research question (the approach to treatment of BOS after HSCT in adults and children), we chose to conduct a scoping review, seeking to synthesize relevant studies on the subject through a broad literature search of electronic databases, using the keywords bronchiolitis obliterans, transplantation, treatment, and pulmonary complications. The review followed the steps described in the Joanna Briggs Institute method.[11]

Table 1 provides a detailed description of this review (guiding questions, objectives, inclusion and exclusion criteria, source of evidence, characteristics, and instrument used to extract results), ensuring greater rigor and transparency.[11]

Figure 1 shows a flow diagram of article selection, including the final number of records selected for review.

Results

First-line therapies

Corticosteroids

Based on the theory that immune dysregulation might be implicated in GVHD and possibly in BOS as well, immunosuppression with systemic corticosteroids is a common approach to management of such cases. Prolonged therapy with high-dose corticosteroids is the most traditional and widely described approach for treatment of GVHD and some acute post-transplant complications, such as idiopathic pneumonia syndrome and diffuse alveolar hemorrhage; in BOS, however, it has limited impact and is associated with adverse effects.[12]

A study conducted by Ratjen et al. (2005) sought to evaluate the effectiveness of corticosteroids, in the form of methylprednisolone pulse therapy, in children undergoing HSCT who developed BOS as a complication. The sample included a total of 9 patients. The protocol consisted of a 3-day course of methylprednisolone at a dosage of 10 mg/kg/day. This treatment regimen was flexible insofar as it could be repeated monthly, if symptoms persisted, for up to 6 cycles. All patients also received inhaled budesonide for the duration of pulse steroid therapy.[13]

The investigators found a significant increase in oxygen saturation in the patients, with normalization

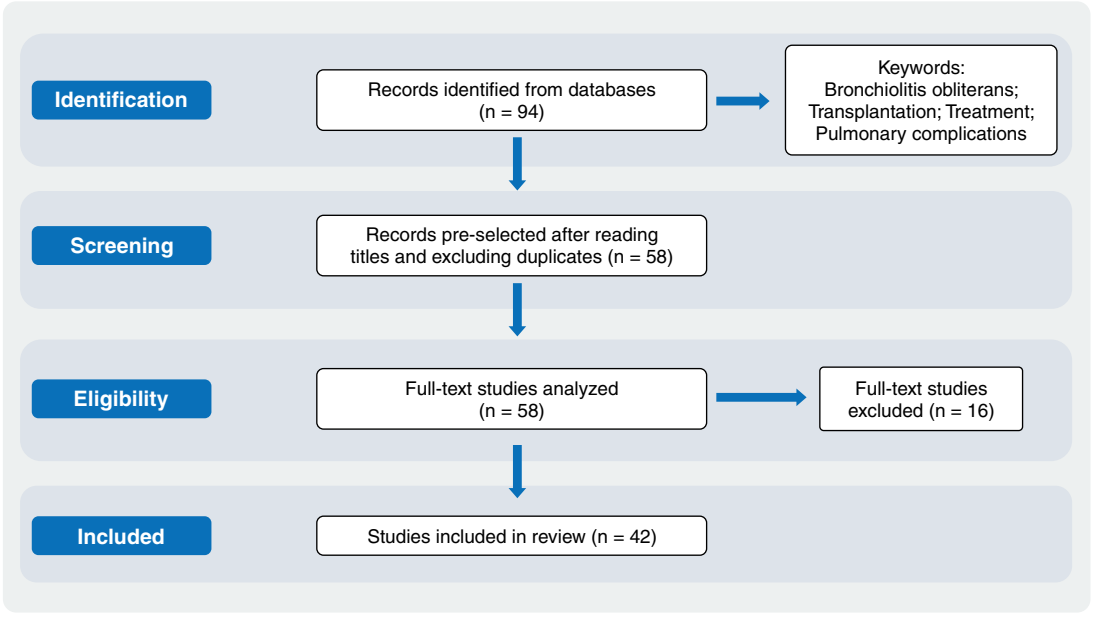

Figure 1
Selection of studies included in the review

Table 1
Detailed description of scoping review

Title of scoping review: Therapeutic approaches to post-transplant bronchiolitis obliterans syndrome (BOS)
Objectives of the review: – to review pharmacological and non-pharmacological treatments for post-transplant bronchiolitis obliterans syndrome (BOS); – to review treatments considered as first-line and second-line therapies; – to review details of the use of these treatments in adults and children, data providing confirmatory evidence of efficacy, and the main adverse events reported; and – to research innovations in the treatment of BOS.
Review questions: – what are the most commonly described current treatments for BOS? – which treatments have shown the greatest efficacy in controlling the disease in adults and children? – which treatments have the fewest adverse events?
Inclusion/Exclusion criteria ***Population:*** adults and children with a diagnosis of post-HSCT BOS. ***Inclusion:*** original articles reporting on treatments for post-HSCT BOS in adults and children (controlled trials, case reports, case-control studies), systematic reviews and meta-analyses with appropriate methodologies, and review articles supported by reference scientific societies. ***Exclusion:*** studies with unclear methodology, studies based on unscientific opinions, and studies with conflicts of interest with the pharmaceutical industry.
Concept: treatments for BOS which demonstrate effectiveness in disease control (improving patients' symptoms and preventing loss of pulmonary function) in adults and children.
Context: studies that address treatments for BOS in children and adults and that have been published in reputable journals.
Types of sources of evidence ***For review articles:*** methodology previously described for meta-analyses and systematic reviews (PROSPERO, PICO, PRISMA, SPIDER registry) and quality assessment of included studies (STROBE, GRADE, CONSORT, Newcastle–Ottawa, etc.). ***For non-systematic reviews:*** only those supported by leading scientific societies, such as the U.S. National Institutes of Health (NIH) or European Society for Blood and Marrow Transplantation, are accepted. ***Case reports or case-control studies:*** those presenting clear data and documenting the diagnostic workup.
Details and characteristics of the source of evidence ***Citation details (e.g., author(s), date, title, journal, volume, number, pages):*** throughout the text and tables. ***Country:*** all countries. ***Context:*** as described above. ***Participants (details, e.g., age/sex and number):*** all ages (children and adults), all sexes, no restriction on number of participants.
Details/results extracted from the source of evidence (regarding the concept of the scoping review) – Treatments for post-HSCT BOS most cited in the literature in recent decades; – Those considered first-line treatments and evidence of their efficacy; – Those considered second-line treatments and evidence of their efficacy; – Treatments under investigation.

of this parameter at the end of therapy. Notably, seven of the nine patients remained clinically stable throughout the follow-up period, with no further deterioration in pulmonary function.[13] These positive findings notwithstanding, this study lacked a control group, a key methodological limitation which precludes any more assertive conclusions regarding the effectiveness of the treatment regimen. Therefore, despite providing valuable insights, the Ratjen study must be interpreted with caution.

Prolonged treatment with high doses of prednisone is associated with several complications and a high risk of morbidity. Patients may experience weight gain, hypertension, infections, osteoporosis, glucose intolerance and, in children, impaired growth. Given this, much research has focused on the possibility of corticosteroid-sparing regimens, which combine other medications aiming for better efficacy and reduced toxicity from chronic corticosteroid use.[14]

Current recommendations on post-HSCT BOS from the two largest relevant international scientific societies, the 2020 European Society for Blood and Marrow Transplantation consensus[15] and the 2021 National Institutes of Health Workshop,[6] do not impose choices on clinicians. Both comment on low-dose systemic corticosteroid therapy in combination with other drugs—fluticasone, azithromycin, and montelukast (FAM), etanercept, among others—and express concern about the need for therapies that can effectively slow or halt the development of functional impairment in post-HSCT BOS.[6,15]

Azithromycin

Azithromycin is frequently used in the treatment of BOS due to its prophylactic and immunomodulatory effect, and may halt or reverse the decline in pulmonary function in some patients.[16]

In 2011, Lam et al. compared patients who received azithromycin versus a placebo group for 12 weeks, analyzing a symptom questionnaire and spirometry before treatment and at 1, 2, 3, and 4 months (with the last assessment performed 1 month after the end of treatment). Ten patients received azithromycin, and 12 patients were in the control group. The study found no significant changes in respiratory symptom scores or FEV_1 measurements between groups.[17] However, a 2005 study by Khalid et al. evaluated 8 patients with post-HSCT BOS who received azithromycin every other day for 12 weeks, comparing pre- and post-treatment pulmonary function tests as well as a respiratory symptom questionnaire. All patients tolerated the treatment well; 7 showed significant improvement in FVC and FEV_1 after treatment, for a response rate of 87%. The mean increase in parameters was 21.57% in FVC ($p < 0.052$) and 20.58% in FEV_1 ($p < 0.067$).[18]

Since 2017, long-term azithromycin therapy has been a matter of debate, even though most studies reported promising findings. In the ALLOZITHRO trial, which was terminated early in 2017, Bergeron et al. found an increased rate of hematological relapse and lower survival in the azithromycin group.[19] In response to this study, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issued warnings, as did the Brazilian Health Regulatory Agency (Anvisa), which also recommended against long-term off-label use of azithromycin for BOS prophylaxis in patients who have undergone HSCT.

Another study conducted by Cheng et al. in 2020 investigated the use of azithromycin in 227 patients with BOS and its relationship with cancer risk (recurrence of the same cancer or another neoplasm), regardless of the time elapsed since HSCT.[20] The study found that exposure to azithromycin after a diagnosis of BOS was associated with an increased incidence of subsequent neoplasms, but not of relapse of the original malignancy.[20] The study also showed that patients who used azithromycin had a lower risk of death free of neoplasm (i.e., from non-cancer causes). These adverse effects of azithromycin are potentially related to its inhibitory effect on various cell types, altering inflammatory pathways and modulating the immune system.[20]

Further reinforcing the latest studies, the 2020 European Society for Blood and Marrow Transplantation consensus stressed that prolonged use of azithromycin in patients with BOS is not recommended due to the risk of hematological relapse.[15]

These findings highlight the importance of a careful assessment of the benefits and risks of this medication in the setting of post-HSCT BOS, a process which should include evaluation of the BOS phenotype, in order to assess its potential effectiveness.

FAM therapy

The combination of fluticasone, azithromycin, and montelukast is known as FAM therapy. To this day, it is still used in many centers that treat patients with

post-HSCT BOS. In 2011, Norman et al., seeking to assess the effectiveness of alternatives to systemic immunosuppressant therapy, tested the FAM regimen in light of its anti-inflammatory and/or antifibrotic properties.[21] A group of 8 patients was followed for 6 months, receiving FAM therapy alone or in combination with systemic corticosteroids, compared to 14 controls who received corticosteroids alone. Both groups had their corticosteroid doses reduced according to the institution's tapering protocol. In most patients, pulmonary function remained stable throughout this period, with no between-group difference. A rapid reduction in prednisone doses was achieved in the group treated with FAM therapy, as well as a lower mean cumulative corticosteroid dose.[21] Despite these positive results, the study had limitations, mainly due to its small number of patients, its retrospective and uncontrolled design, and the fact that some patients in the FAM group (3 cases) did not receive corticosteroids at all, which may have introduced confounding in data analysis.

In 2016, Williams et al. assessed 36 adult patients in the first 6 months after diagnosis of BOS who had received prednisone 1 mg/kg/day for 2 weeks in combination with FAM therapy.[22] The FAM regimen consisted of inhaled fluticasone (220 to 440 µg twice daily), montelukast (5 to 10 mg daily), and azithromycin (5 mg/kg up to a maximum of 250 mg every other day). After 15 days, systemic corticosteroid therapy was tapered by 0.25 mg/kg/day per week. Of the 36 patients, 6 (17%) had no response and 23 (63%) achieved some response (3 with > 10% improvement in FEV_1 from baseline, 7 with > 5% improvement in FEV_1 from baseline, 5 with stable FEV_1, and 8 with a 1–10% decline in FEV_1). Regarding corticosteroid withdrawal, 48% of patients achieved a 50% reduction in corticosteroids within 3 months, and 71% achieved a 50% reduction within 6 months. These findings suggest that FAM therapy was well tolerated, corticosteroid-sparing, and associated with a reduced decline in pulmonary function.[22]

The two studies described above demonstrated good tolerability of this therapeutic regimen and its importance in reducing chronic corticosteroid exposure. However, for optimal results and to inform recommendations for clinical use in the management of these patients, ideally each medication should be studied independently, in separate clinical trials; studies with a larger number of participants are also necessary.

Inhaled budesonide/formoterol

A study conducted by Bergeron et al. in 2015 evaluated the efficacy and tolerability of the fixed-dose combination of inhaled budesonide and formoterol as an alternative treatment for post-HSCT BOS. The study was double-blind, randomized, and placebo-controlled, and included 32 patients allocated into two groups (one received budesonide/formoterol and the other placebo, for 6 months).[23] The primary outcome was change in FEV_1 from baseline after one month of treatment. Patients who received budesonide/formoterol experienced an increase in FEV_1 of 260 mL on average, versus a 5-mL increase in the placebo group ($p = 0.012$).[23] Furthermore, the change in FEV_1 from baseline was greater in the treatment group, with a median difference of 1240 mL after 1 month of treatment ($p = 0.0001$), with the effect maintained in all 13 patients who completed 6 months of treatment. The administered dosage was 800 µg budesonide and 24 µg formoterol twice daily for 1 month, followed by a maintenance dose of 400 µg budesonide and 12 µg formoterol twice daily for 6 months.[23] This double-blind, randomized, placebo-controlled study showed promising results, with a significant improvement in FEV_1 in the group receiving the budesonide/formoterol combination. Considering the effectiveness, safety, and wide availability of this medication at an affordable cost, it is a promising option and, above all, a truly systemic corticosteroid-sparing treatment, which should be considered in the management of patients with BOS.

Budesonide/formoterol, montelukast, and N-acetylcysteine

Additional drug combinations have been studied with the primary goal of reducing the role of systemic corticosteroids in the treatment of BOS. In 2016, Kim et al. assessed a combination of budesonide/formoterol, montelukast, and N-acetylcysteine.[24] In this study, 61 patients diagnosed with BOS received this drug combination and were reassessed after 3 months. Pulmonary function tests and respiratory symptom scores were administered at baseline and after therapy. The results showed a response rate of 82%, an average increase in FEV_1 of 220 mL ($p < 0.001$), and a decrease in residual volume of 200 mL ($p = 0.005$).[24] The authors concluded that combination therapy with budesonide/formoterol, montelukast, and N-acetylcysteine improved pulmonary function and respiratory symptoms, with no significant adverse effects.[24]

Budesonide/formoterol and tiotropium

One treatment option being studied is the use of inhaled tiotropium bromide. Tiotropium is a long-acting anticholinergic administered via a proprietary device that produces a fine mist, causing bronchodilation. In a study published in 2023, Lim Ju et al. evaluated whether the addition of inhaled tiotropium bromide to the budesonide/formoterol regimen would improve pulmonary function in patients with post-HSCT BOS.[25] The study included 86 patients diagnosed with post-BMT BOS according to the modified NIH criteria (2014), who were already on budesonide/formoterol, subsequently had tiotropium added to their regimen and used it for at least 2 months. Pulmonary function tests were compared before and after addition of tiotropium. FEV_1 increased significantly: from 1.47 to 1.53 in absolute values ($p = 0.023$) and from 45% to 46.8% of predicted ($p = 0.031$). Furthermore, 41.7% of patients experienced an increase in $FEV_1 > 100$ mL and improvement in diffusion capacity of the lungs for carbon monoxide.[25] A score for assessment of respiratory symptoms was administered; however, no significant difference was found. The study concluded that adding tiotropium to the budesonide/formoterol combination significantly improved pulmonary function, but not respiratory symptoms, in post-HSCT BOS.[25]

Given that bronchiolitis obliterans is a disease characterized by irreversible airway obstruction, the effect of bronchodilators is expected to be less effective than in other airway diseases in which reversibility is somewhat preserved. However, the study above provides an important reflection on the effect of bronchodilators in BOS, since the addition of tiotropium improved lung function in patients who were already on a bronchodilator-containing regimen. Perhaps this effect can be explained by the findings of studies conducted in patients with chronic obstructive pulmonary disease (COPD), in which the combination of a long-acting beta-agonist and a long-acting antimuscarinic resulted in a more pronounced improvement in bronchodilation than either drug alone.[25,26]

Despite its limitations, such as its retrospective design, lack of a control group, and short-term follow-up, this study is notable for the positive effect observed with addition of a long-acting antimuscarinic; considering the safety of tiotropium and experience with its use in other diseases, it can be considered as a treatment option for these patients.

Second-line and alternative therapies

Extracorporeal photopheresis

Extracorporeal photopheresis (ECP) has demonstrated effectiveness in the treatment of GVHD in clinical trials. However, its utility in the setting of BOS remains uncertain. In 2011, Lucid et al. conducted a prospective study investigating the use of ECP in 9 patients with symptomatic BOS refractory to conventional treatment (azithromycin, inhaled corticosteroids, and montelukast).[27] Adding ECP to the patients' current treatment regimen resulted in faster improvement of BOS symptoms and pulmonary function tests, with 67% of patients responding to treatment and 2 of the 3 patients who did not qualify as responders still showing improvement in symptoms and stable or declining FEV_1. These findings suggest that ECP can be an effective alternative for patients with BOS refractory to conventional treatment.[27]

Although ECP has demonstrated efficacy and safety in autoimmune diseases, including GVHD, few centers are able to perform this procedure. Specific equipment is required for extracorporeal cell apheresis and UV exposure, as well as a specialized, specifically trained team, and the procedure is extremely costly.[28]

Cytokine modulators (TNF-α inhibitors and rituximab)

TNF-α inhibitors (etanercept and infliximab)

Insight into the role of proinflammatory cytokines in the pathogenesis of BOS led to the investigation of TNF-α inhibitors as potential treatment alternatives. In 2012, Yanik et al. conducted a study in 34 patients (aged 8 to 65 years) with chronic pulmonary GVHD; 25 had an obstructive pattern and 9 had a restrictive pattern. All received etanercept (a dimeric fusion protein which binds TNF-α) at a dose of 0.4 mg/kg subcutaneously, twice weekly, for 4 to 12 weeks. Of the 34 participants, 33 were already on corticosteroids, which were continued throughout. The overall response rate was 32%; 5-year survival was 61% for all patients and 90% for those who responded to therapy. Etanercept was well tolerated, with no treatment-emergent infectious complications. Despite some limitations, such as the lack of a control group for comparison, the toxicity profile of etanercept supports the conduct of larger, randomized trials to further investigate its role in the treatment of patients with pulmonary GVHD.[29]

Infliximab, a monoclonal antibody against TNF-α, has also been studied as a treatment option for BOS, considering the key role of TNF-α in inflammation. In 2005, Fullmer et al. reported the case of an 8-year-old child with BOS, diagnosed 5 months after HSCT, who received infliximab after failure of corticosteroid therapy. Infliximab was administered at 10 mg/kg twice a week for 4 doses, then weekly for a further 4 doses, then once every 2 weeks for 2 months. One month after the end of treatment, there was a response to therapy, with cessation of cough, resolution of obstructive pulmonary disease as measured by spirometry, and improvement in chest CT findings. The use of infliximab and other immunosuppressive therapies aims to reduce progression of inflammation and improve pulmonary function, but further research is still needed to confirm its effectiveness in the specific setting of post-transplant BOS.[30]

Rituximab

Although GVHD has traditionally been considered a process driven by donor-derived alloreactive T cells, there is growing evidence implicating B cells in the pathogenesis of chronic GVHD. Rituximab, an anti-CD20 monoclonal antibody, is used to suppress B-cell function and has been studied in the treatment of post-HSCT BOS.[31]

In 2017, Brownback et al. evaluated pulmonary function tests in patients with steroid-refractory post-HSCT BOS, seeking to determine the effect of rituximab on corticosteroid dosage in these patients and whether combining rituximab with other treatment modalities could improve clinical response. Thirteen patients, aged 19 to 65 years, were evaluated for 12 months after rituximab therapy. The rate of decline in pulmonary function was seen to improve, from -5.12 mL/month before rituximab infusion to -0.31 mL/month after 3 months and -2.27 mL/month 12 months later. Seven of the 13 patients experienced increases in FEV_1 after rituximab treatment. Furthermore, the average daily dose of prednisone decreased from 27 mg before treatment with rituximab to 11 mg 12 months after treatment. There were no complications associated with rituximab infusions. Five of the 13 patients died: 4 from complications of GVHD and 1 due to disease recurrence.[31] All patients were on inhaled corticosteroids, azithromycin, and montelukast. The patients who showed improvement in FEV_1 were receiving concomitant ECP, and most were also being treated with ruxolitinib. This may represent a synergistic effect of combination therapies leading to improvement of pulmonary function in patients with post-HSCT BOS. The role of rituximab in immunosuppression and modulation of GVHD makes it an interesting option for the management of post-HSCT pulmonary complications, as a safe therapy which can be used to supplement current BOS treatment regimens.[31]

Mesenchymal stem cells

Given the complexity of managing BOS, studies have been conducted seeking effective and safe alternative treatment approaches. One of these studies, conducted by Chen et al. in 2019, assessed the efficacy of mesenchymal stem cells (MSCs).[29] In this prospective, multicenter cohort study, 81 patients with BOS received MSC infusions in combination with prednisone and azithromycin or in isolation. Significant improvements in FEV_1 and reductions in corticosteroid doses were achieved. Furthermore, MSC therapy proved to be more effective than treatment with steroids and azithromycin alone, with a response rate of 71% in the group that received cell therapy compared to 44% in the group that did not receive it.[32]

MSCs have an immunomodulatory effect on both adaptive and innate immunity, and may be a promising avenue for treatment in the context of BOS.[32] This study reported interesting results, but it has limitations. The study design did not include blinding, randomization or a placebo group, and results were assessed at only 3 months of therapy; the duration of response after this period was not considered. Consequently, these findings should be interpreted with caution, and the effects of MSCs require more in-depth evaluation in larger, randomized studies with long-term outcome assessment.

Inhaled ciclosporin

A phase 2 trial evaluated inhaled ciclosporin in 20 patients diagnosed with BOS, aged 14 to 71 years. Response was evaluated by pulmonary function tests after 18 weeks of ciclosporin therapy. Cytology and inflammatory mediators in bronchoalveolar lavage fluid were evaluated at baseline and after 18 weeks. The study was completed with only 11 patients, as nine discontinued treatment due to side effects (cough and bronchospasm), worsening FEV_1, or recurrence of primary disease. Among those who completed the

trial, 4 showed improvement in FEV_1 (10% increase from baseline), 5 achieved disease stabilization (smaller increase in FEV_1 or decline in FEV_1 <10% from baseline), and 2 did not respond to therapy. Bronchoalveolar lavage showed a predominance of neutrophils at baseline and at the end of treatment, with an increase in matrix metalloproteinase-9 and a reduction in PD-L1 protein at 18 weeks.[33]

Inhaled ciclosporin led to improvement or stabilization of pulmonary function tests and/or a decrease in systemic immunosuppression in 9 of the 11 patients who completed the trial. However, the small sample size, absence of a control group, and significant number of treatment-related adverse effects must be noted.[33]

Imatinib and belimumab

Imatinib

Imatinib mesylate, an antineoplastic tyrosine kinase inhibitor, has recently been studied in GVHD. In 2020, Faraci et al. evaluated 26 cases of bronchiolitis obliterans in a series of 293 children who had undergone bone-marrow transplantation. This retrospective observational study compared patients who received imatinib and those who did not (n=13 in each group). Imatinib was given at doses of 100 to 300 mg/day (mean, 100 mg). It was well tolerated, with no adverse effects. In addition to imatinib, patients were on a range of other medications, including azithromycin, montelukast, methylprednisolone (50% of patients), ciclosporin (53.8%), tacrolimus (15.4%), and ciclosporin plus methylprednisolone (15.4%).[34]

The estimated 1-year survival rate was 71.9% (95% CI, 47.6±86.49) in the group that did not receive imatinib versus 83.3% (95% CI, 27.3±97.5) in the imatinib-treated group. At 4 years, overall survival had decreased in the non-imatinib group (42.6%) but remained stable in the imatinib group (83.3%). Mortality was also significantly lower in the group that received imatinib (7.7% vs. 84.6%; $p < 0.001$). Pulmonary function was also monitored. Improvement in FEV_1 over time was observed in the imatinib group, whereas this parameter worsened in the non-imatinib group.[34]

Despite the positive survival difference among patients who received imatinib, this was a retrospective, observational study of a very small group of patients, and further prospective studies are needed to confirm these findings.

Belimumab

B-cell activating factor (BAFF), a member of the tumor necrosis factor family, has been extensively studied since its discovery in 1999, particularly in the field of autoimmunity, where it plays a crucial role. Patients with chronic GVHD have been found to have increased serum levels of BAFF, strongly suggesting a role for B cells in the pathogenesis of GVHD. The combination of high serum BAFF levels and CD19+ CD21lo cell counts has been used successfully to assess the risk of BOS in HSCT recipients.[35,36]

Belimumab is a fully human recombinant IgG1-λ monoclonal antibody that inhibits the binding of BAFF to its receptors on B cells, thereby reducing the survival of autoreactive B cells. While its efficacy is well established in autoimmune diseases, such as systemic lupus erythematosus and active lupus nephritis, ongoing studies are currently evaluating its potential use in other conditions associated with B-cell dysregulation, including post-HSCT BOS.[35,36]

A single-center, phase 1 study conducted by Pusic et al. in 2021 evaluated whether targeting BAFF early after allogeneic HSCT would have a favorable effect on the incidence or severity of chronic GVHD. The included patients were all adults in complete remission who tested negative for minimal residual disease 30 days after transplantation. Patients received belimumab at a dose of 10 mg/kg every 2 weeks for 3 doses, followed by 4 more doses at monthly intervals. Treatment began 50 to 80 days after transplant. Patients who received at least 1 dose were evaluated for safety, and those who received at least 2 doses were evaluated for efficacy. Eight of the 9 patients successfully received all 7 planned doses of belimumab. After more than 20 months of follow-up, 5 were alive with no evidence of chronic GVHD. Two patients developed moderate to severe GVHD of the skin, eyes, mouth, and liver, and 2 patients experienced disease recurrence, but both had high-risk malignancies. No adverse events of grade 3 or higher were reported. There were also no significant infections or myelosuppression.[37] This was the first trial to describe the use of belimumab for prophylaxis of chronic GVHD. Results were encouraging, as it was well tolerated and there was no increased rate of serious infections. Nevertheless, further studies with larger sample sizes are needed for a more in-depth assessment of the impact of belimumab on the incidence of GVHD.[37]

Antifibrotic therapies (nintedanib and pirfenidone)

In 2020, Tang et al. reported the case of an 18-year-old patient who began experiencing cough and dyspnea approximately 1 year after HSCT. The CT scan showed bronchiectasis, thickening of septa, and interstitial involvement. Pulmonary function tests showed an FVC of 36.9%, an FEV_1 of 38.7%, and a residual volume of 125% of predicted. The patient had received montelukast, azithromycin, and inhaled budesonide/formoterol, as well as methylprednisolone, with no improvement. The authors suggested a trial of nintedanib, an intracellular tyrosine kinase inhibitor which affects vascular endothelial growth factor and fibroblasts and has been approved for the treatment of idiopathic pulmonary fibrosis, hypothesizing that it might thus be useful in post-HSCT BOS as well. Cough and dyspnea improved after 2 weeks of treatment. After 1 month of therapy, improvements in pulmonary function tests and CT scan findings were also observed.[38]

Following the same rationale, pirfenidone, a compound with anti-inflammatory and antifibrotic properties, acts by downregulating collagen synthesis stimulated by TGF-β, thus reducing fibroblast proliferation. In a 2022 non-randomized phase 1 trial, Matthaiou et al. evaluated the tolerability of pirfenidone and its impact on pulmonary function tests over 1 year of follow-up in patients diagnosed with post-HSCT BOS. Twenty-two patients were evaluated, of whom 13 (59%) tolerated therapy. There was a 7% mean annual increase in FEV_1, as well as patient-reported improvements in physical capacity and dyspnea.[39]

In this phase 1 trial, treatment with pirfenidone was safe. Stabilization of pulmonary function tests and improvements in patient-reported outcomes suggest pirfenidone has potential for the management of post-HSCT BOS and supports the conduct of a randomized controlled trial to evaluate its efficacy in this setting.[39]

Lung transplantation

In cases of severe lung disease with high morbidity and mortality and poor response to therapy, lung transplantation can be a viable treatment option. In 2005, Sano et al. reported the case of a 29-year-old woman who developed post-HSCT BOS refractory to all attempted treatment options (ciclosporin, prednisone, methotrexate, tacrolimus, and home oxygen therapy).[40] Given her clinical deterioration, with spontaneous pneumothorax and progression to frank respiratory failure, the decision was made to pursue living-donor lung transplantation. Thirty-eight months after the transplant, at the time of writing the case report, the patient was in good health, with no evidence of acute rejection, infection, or BOS.[40]

In 2001, Rabitsch et al. documented the case of a 37-year-old patient who developed BOS refractory to corticosteroids, extracorporeal phototherapy, and ciclosporin.[41] One year after HSCT, she underwent lung transplantation. Twenty-three months after the transplant, when the report was written, there was no evidence of rejection and pulmonary function tests were within normal range.[41]

Isolated case reports with satisfactory results, demonstrating improvements in quality of life and survival for patients with advanced post-HSCT BOS, suggest this treatment modality can be an option for severely ill patients. However, further studies are needed to assess the effectiveness of this procedure more comprehensively, considering that lung transplant is a complex, high-risk intervention with very specific indications, requiring careful patient selection.

Investigational therapies

An ongoing phase 1b/2 trial is evaluating alvelestat (MPH966), an oral neutrophil elastase inhibitor, for the treatment of patients with GVHD and post-HSCT BOS.[42]

In addition to drugs specifically targeting BOS, proper management of comorbidities and exacerbation triggers, control and treatment of infections, proper management of post-transplant immunosuppression, and pulmonary rehabilitation are all essential.[9]

Individualized nutritional monitoring, ensuring adequate intake of macro and micronutrients, is also essential in slowing the progression of pulmonary disease, especially in patients with weight loss.[5]

The results of the key studies covered in this review are shown in Table 2.

Conclusion

Pulmonary complications, such as BOS, are common after HSCT and represent an important cause of morbidity and mortality in adults and children alike. Early detection and appropriate treatment are key prognostic factors for these patients.

Individually varied responses are expected. The relentless search for drugs, alone or in combination, that can spare these patients prolonged use of high-dose systemic corticosteroids remains a noble goal, particularly for the pediatric population.

The treatment of post-HSCT BOS continues to pose a challenge for specialists worldwide. Studies that thoroughly elucidate bronchiolar inflammation and other factors involved in post-HSCT BOS are needed to achieve a better understanding of the pathophysiology of this condition and serve as a starting point for the development of effective, precise treatments.

Table 2
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
			First-line therapies		
High-dose corticosteroid therapy	High-dose corticosteroid therapy for bronchiolitis obliterans after bone marrow transplantation in children	Ratjen et al. (2005)	Retrospective pediatric study. Case series of methylprednisolone pulse therapy	9 patients aged 1 to 17 years with a diagnosis of post-HCST BOS	Increased oxygen saturation and normalization of pulmonary function at the end of treatment; absence of functional deterioration in children with BOS (improvement of FEV_1 after 2 months of therapy)
Azithromycin	Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study	Khalid et al. (2005)	Observational study investigating the potential effect of azithromycin on pulmonary function tests in patients with post-HSCT BOS	8 out of 153 patients with post-HSCT BOS, aged 18 to 63 years	Significant improvement in FVC and FEV_1 after treatment; response rate 87%. The mean increase in parameters was 21.57% in FVC ($p < 0.052$) and 20.58% in FEV_1 ($p < 0.067$)
	Effects of azithromycin in bronchiolitis obliterans syndrome after HCT—a randomized double-blinded placebo-controlled study	Lam et al. (2011)	Randomized, double-blind, placebo-controlled clinical trial of azithromycin therapy	Patients aged > 18 years with post-HSCT BOS (age range, 24-57 years)	No significant changes in respiratory symptom scores or in FEV_1 measurements between groups

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

Table 2 *(continued)*
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
			First-line therapies		
	Effect of Azithromycin on Airflow Decline–Free Survival After Allogeneic Hematopoietic Stem Cell Transplant: The ALLOZITHRO Randomized Clinical Trial	Bergeron et al. (2017)	Randomized, multicenter, double-blind, placebo-controlled clinical trial assessing whether early administration of azithromycin can improve airflow decline-free survival after allogeneic HSCT	Patients aged > 16 years with post-HSCT BOS. Assessment of pulmonary function, disease-free survival, and post-BMT BOS for a period of 2 years of disease recurrence.	There was no difference in FEV_1 or other pulmonary function tests or post-BMT BOS throughout the study period between groups. The authors conclude it is unlikely that azithromycin may reduce the risk of post-BMT BOS. Study interrupted due to increased disease recurrence. FDA, EMA, and ANVISA issued warnings recommending against off-label prescribing of azithromycin
	Azithromycin use and increased cancer risk among patients with bronchiolitis obliterans after hematopoietic cell transplantation	Cheng et al. (2020)	Retrospective study. Assess the impact of azithromycin exposure on the occurrence of recurrent or subsequent (new) neoplasm in patients with post-HSCT BOS treated with azithromycin alone or in combination with other agents	Patients with post-HSCT BOS, aged > 18 years, with at least 6 months elapsed since HSCT. 316 patients with BOS included, 277 on azithromycin	In the azithromycin group, there was an increased incidence of subsequent neoplasms, but not recurrence of the original malignancy; however, there was a reduction in mortality from other non-cancer causes
FAM therapy	Fluticasone, Azithromycin, and Montelukast (FAM) Therapy in reducing corticosteroid exposure in BOS after allogeneic HSCT. A case series of 8 patients	Norman et al. (2011)	Retrospective case series. Assess whether corticosteroid exposure can be reduced in post-HSCT BOS patients who received FAM therapy	Adult patients, aged > 20 years, with post-HSCT BOS	Rapid reduction in prednisone doses in patients treated with FAM therapy who were on corticosteroids. Stable pulmonary function throughout study period, with no between-group difference

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

Table 2 *(continued)*
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
			First-line therapies		
	FAM treatment for new onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation	Williams et al. (2016)	Open-label, single-arm, multicenter study. Assess the effectiveness of FAM, combination therapy to treat BOS of recent onset in post-HSCT patients	Adult patients aged 23 to 72 years with recent-onset post-HSCT BOS (up to 6 months since diagnosis)	FAM therapy was well tolerated. Less decline in lung function; allowed for a reduction in systemic corticosteroid therapy
Budesonide/ formoterol	Budesonide/ formoterol for bronchiolitis obliterans after hematopoietic stem cell transplantation	Bergeron et al. (2015)	Randomized, double-blind, placebo-controlled, multicenter trial. Assess efficacy and tolerability of budesonide/ formoterol as an alternative treatment for post-HSCT BOS	Patients aged ≥ 16 years with post-HSCT BOS	Significant increase in average FEV_1 in the group that received budesonide/formoterol and increase in FEV_1 from baseline
Budesonide/ formoterol + montelukast + N-acetylcysteine	Therapeutic effect of budesonide/formoterol, montelukast and N-acetylcysteine for bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation	Kim et al. (2016)	Retrospective study. Assess therapeutic effect of budesonide/ formoterol, montelukast, and N-acetylcysteine as a treatment option for post-HSCT BOS	61 patients with post-HSCT BOS (mean age 46.5 years)	Response rate 82%. Improvement in FEV_1 and respiratory symptoms
Budesonide/ formoterol + tiotropium	Efficacy of inhaled tiotropium add-on to budesonide/formoterol in patients with bronchiolitis obliterans developing after hematopoietic stem cell transplantation	Lim JU et al. (2023)	Retrospective cohort study. Patients with post-HSCT BOS who were already on budesonide/ formoterol and had tiotropium added to their regimen	86 patients with post-HSCT BOS, mean age 45.9 years	Increased FEV_1. Improvement in carbon monoxide diffusion capacity and pulmonary function, but no improvement in respiratory symptom scores

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

Table 2 *(continued)*
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
Second-line and alternative therapies					
Extracorporeal photopheresis	Extracorporeal photopheresis in patients with refractory bronchiolitis obliterans developing after allo-SCT	Lucid et al. (2011)	Prospective study. Determine the clinical efficacy of extracorporeal photopheresis in the treatment of BOS through assessment of clinical improvement and pulmonary function tests	Patients with post-BMT BOS aged 21 to 54 years (mean of 38 years), with failure of conventional therapies	The addition of extracorporeal phototherapy resulted in faster improvement of symptoms and pulmonary function tests. Response rate 67%
Etanercept	Soluble Tumor Necrosis Factor Receptor: Enbrel (Etanercept) for Subacute Pulmonary Dysfunction Following Allogeneic Stem Cell Transplantation	Yanik et al. (2012)	Open-label, prospective study. Assess the response rate to etanercept added to prednisone in patients with pulmonary GVHD	34 patients aged 8 to 65 years with pulmonary GVHD, 25 of whom had an obstructive pattern and 9 had a restrictive pattern	Response rate 32%; 5-year survival: 61% overall and 90% for those who responded to therapy. No treatment-emergent infectious complications
Infliximab	Successful Treatment of Bronchiolitis Obliterans in a Bone Marrow Transplant Patient with Tumor Necrosis Factor - Blockade	Fullmer et al. (2005)	Case report. Report the case of a pediatric patient with post-HSCT BOS who received infliximab after failure of corticosteroid therapy	8-year-old patient with post-HSCT BOS, confirmed by biopsy 5 months after transplantation	Response to therapy with resolution of respiratory symptoms, improved spirometry, and CT changes
Rituximab	Effect of Rituximab on Pulmonary Function in Bronchiolitis Obliterans Syndrome due to Graft-Versus-Host Disease	Brownback et al. (2017)	Prospective, non-randomized study. Determine the effects of treatment with rituximab on pulmonary function in patients with post-HSCT BOS	13 patients, aged 19 to 65, evaluated over 12 months of treatment with rituximab	Improvement in the rate of decline in pulmonary function. Increased FEV_1 in 7 of 13 patients
Mesenchymal stem cells	The efficacy of mesenchymal stem cells in bronchiolitis obliterans syndrome after allogeneic HSCT: A multicenter prospective cohort study	Chen et al. (2019)	Multicenter, prospective cohort study. Assess the efficacy and safety of mesenchymal stem cells in patients with post-BMT BOS	81 patients with post-BMT BOS, aged 18 to 59 years, received infusions of mesenchymal stem cells alone or in combination with prednisone and azithromycin	Significant improvements in FEV_1 and dose reduction of corticosteroids; furthermore, mesenchymal stem cell therapy proved more effective than treatment with steroids and azithromycin alone

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

Table 2 *(continued)*
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
			Second-line and alternative therapies		
Inhaled ciclosporin	Effect of cyclosporine inhalation solution (CIS) on lung function and inflammatory biomarkers in patients with hematopoietic stem cell transplant (HSCT) associated bronchiolitis obliterans syndrome (BOS)	Athale et al. (2019)	Phase 2 trial. Assess response to treatment with inhaled ciclosporin in patients with post-HSCT BOS through pulmonary function tests at 18 weeks of therapy. Cytology and proinflammatory mediators in bronchoalveolar lavage fluid assessed at baseline and after 18 weeks	20 patients with post-HSCT BOS, aged 14 to 71 years	Improvement or stabilization of pulmonary function tests. Among those who completed the trial, 4 exhibited improvements in FEV_1, 5 achieved stable disease, and 2 did not respond. New-onset cough and bronchospasm in 9 patients
Imatinib mesylate	Imatinib mesylate as second-line treatment of bronchiolitis obliterans after allogenic hematopoietic stem cell transplantation in children	Faraci et al. (2020)	Observational and retrospective pediatric study. Assess overall survival in children with post-HSCT BOS treated with imatinib mesylate	26 cases of BOS in a series of 293 children who underwent BMT mean age 8.3 years (3.5–12.5 years)	Lower mortality rate and higher survival rate in the imatinib group
Belimumab	Use of belimumab for prophylaxis of chronic graft-versus-host disease	Pusic et al. (2021)	Single-center phase 1 trial. Assess the use of belimumab after allogeneic HSCT and its effect on the incidence or severity of chronic GVHD	9 adult patients who received belimumab 50–80 days after transplantation	No ≥ Grade 3 adverse events reported. No significant infections or myelosuppression; 5 patients alive and without chronic GVHD after 20 months of follow-up
Nintedanib	Nintedanib in Bronchiolitis Obliterans Syndrome After Allogeneic Hematopoietic Stem Cell Transplantation	Tang et al. (2020)	Case report. Describe the case of a patient with post-HSCT BOS who was treated with nintedanib, a drug approved for idiopathic pulmonary fibrosis	18-year-old patient with post-HSCT BOS who received nintedanib	Improvement in respiratory symptoms, pulmonary function tests, and chest CT scan findings

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

Table 2 *(continued)*
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
Second-line and alternative therapies					
Pirfenidone	The Safety and Tolerability of Pirfenidone for Bronchiolitis Obliterans Syndrome after Hematopoietic Cell Transplant (STOP-BOS) trial	Matthaiou et al. (2022)	Phase 1, non-randomized, single-center trial. Assess the tolerability of pirfenidone and pulmonary function tests over 1 year in patients diagnosed with post-HSCT BOS	22 patients diagnosed with post-HSCT BOS, mean age 53.8 years	Drug was well tolerated. Stabilization of pulmonary function tests. Improvement in patient-reported outcomes (physical capacity and dyspnea)
Lung transplantation	Living-donor lobar lung transplantation for bronchiolitis obliterans after bone marrow transplantation	Sano et al. (2005)	Case report of a patient with post-HSCT BOS who underwent lung transplantation	29-year-old woman with BOS refractory to treatment with ciclosporin, prednisone, methotrexate, and tacrolimus	Patient doing well 38 months after transplant
	Successful lung transplantation for bronchiolitis obliterans after allogeneic marrow transplantation	Rabitsch et al. (2001)	Case report of a patient with post-HSCT BOS who underwent lung transplantation	37-year-old woman underwent lung transplantation 1 year after BMT due to BOS refractory to corticosteroids and extracorporeal photopheresis	Patient doing well 23 months after transplant

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

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