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Expert Opinion on Emerging Drugs

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EDITORIAL



# Expert opinion on emerging drugs for lung chronic graft-versus-host disease

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## 1. Introduction

Lung chronic graft-versus-host disease (cGVHD) is a rare, severe complication after allogeneic hematopoietic stem cell transplantation (HSCT), with high morbidity and mortality rates. Early recognition and treatment, which still represent an unmet need in the field, are the key to preventing permanent airways obstruction and lung fibrosis.

National Institute of Health (NIH) recognized bronchiolitis obliterans (BO) and bronchiolitis obliterans syndrome (BOS) as the only accepted diagnostic or distinctive forms of lung cGVHD. The incidence may vary from 3% to 10% among HSCT recipients and 14% among patients with other signs of cGVHD [1]. Clinical manifestations of overt BOS include cough, dyspnea, and wheezing, although in its early phases many patients could be asymptomatic; indeed, screening with pulmonary function test (PFT) is highly recommended beginning on day +100 post-HSCT. A 6 minute walking test (6MWT) can play an important role in defining the functional status of patients and in measuring the response to therapeutic interventions in patients with BOS [2].

BO/BOS is characterized by irreversible narrowing and obliteration of the small airways [1], due to intraluminal connective tissue and chronic inflammation. Distal mucostasis, aggregates of macrophages and bronchiectasis may develop late. Studies on HSCT murine models showed the pathogenic role of thymic injury, macrophages recruitment, aberrant activation of T- and B-cells with local antibody production in airway damage [1,3]. Different pathways have been recognized leading to biological-driven therapeutic approaches. Although the definitive diagnosis of BO/BOS requires histologic demonstration of pulmonary fibroproliferative disorder, lung biopsy is seldom feasible in HSCT recipients. Thus, clinical diagnosis is largely based on PFT, as defined by the 2014 NIH criteria [4]: briefly, FEV1/vital capacity < .7 or the fifth percentile of predicted, FEV1 < 75% of predicted with ≥10% decline over less than 2 years, not corrected with albuterol, and absence of documented infection in the respiratory tract. High-resolution chest computed tomography (HRCT) is useful in better defining airways obstruction and air trapping, but also in the differential diagnosis of pulmonary infections [4,5]. Likewise, bronchoscopy with bronchoalveolar lavage, nasal wash, and viral screening are also recommended to rule out infections [4–6].

In parallel with CT-documented air trapping, evidence of air trapping by PFT, defined by residual volume/total lung capacity (RV/TLC) elevated outside the 90% confidence interval or RV >120% of predicted, supports the diagnosis of BOS [4]. However, not all post-HSCT lung impairment disorders fulfill the NIH criteria for lung cGVHD.

A PFT restrictive pattern (namely a consensual reduction of FEV1 and FVC, reflecting air trapping by small airway obstruction) is not currently recognized as a chronic GVHD manifestation, as it may be due to interstitial lung impairment but can also be caused by extra parenchymal processes [1,4,5]. Moreover, other forms of post-transplant lung impairment such as bronchiolitis obliterans organizing pneumonia, cryptogenic organizing pneumonia, interstitial pneumonia are considered as potentially associated with cGVHD but not diagnostic.

Plethysmography is the preferred means to measure TLC to further define the emergence of a restrictive ventilatory defect. But, as in the lung transplantation setting, serial TLC monitoring is not routinely performed in HSCT recipients [7].

## 2. Emerging treatment

Recent advances in the management of HSCT recipients have led to better transplant outcomes. However, the prognosis of patients with lung cGVHD remains poor, with a 3-years mortality rate after transplantation ranging from 25% to 65%. Early diagnosis and treatment are considered essential [1,4,5].

Prednisone 0.5 to 1 mg/kg represents the current standard of care for first-line systemic treatment of cGVHD. Although no statistically significant benefit from the combination of other agents has been demonstrated in randomized trials, prednisone is often associated with immunosuppressants (calcineurin inhibitors, mycophenolate mofetil, azathioprine, and antithymocyte globulin) aiming at reducing steroid use and

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minimizing toxicity caused by prolonged treatment [6,8]. In case of acute flare-up of respiratory distress, pulses of high dose methylprednisolone might be used [5,9]

Inhaled steroids have been tested in small clinical trials of patients with BOS after HSCT, with the rationale of reducing local lung inflammation. Long-acting bronchodilator might be considered if there are symptoms of airway obstruction and FEV1 ≥ 70% [6]. The addition of azithromycin and montelukast leads to a reduction in neutrophilia, local interleukin-8 levels and impairment of leukotriene activity. The Fluticasone-Azytromicin-Montelukast regimen (FAM) has proved efficacy, it is well tolerated, and it allows to reduce the systemic steroid exposure [9]. Nowadays, it is recommended as an initial treatment of BOS [8].

Promising preclinical results of ruxolitinib have been confirmed in clinical studies [10]. In the phase III trial, the JAK inhibitor led to a higher overall response rate than control therapy at week 24 (49.7% vs. 25.6%) regardless of the organs involved, a higher best overall response (76.4% vs. 60.4%), longer duration of response and failure-free survival. Furthermore, a steroid-sparing effect was seen with ruxolitinib. However, pulmonary responses were low in both groups (8,6% vs 6,1%) [10]. Zhao et al. showed promising results in patients with steroid-refractory BOS in real-life study: the best overall response rate was 66,7% at a median duration of ruxolitinib therapy of 9,25 months, with FEV1 improvement and a steroid-sparing effect [11]. Due to the high incidence of opportunistic infections observed with ruxolitinib, antimicrobial prophylaxis, including fungal, is recommended together with thorough infection monitoring.

Recently, a significant reduction of lung and skin fibrosis has been observed with belumosudil, an oral selective ROCK2 inhibitor, in cGVHD animal models. These results were confirmed by phase II studies, leading to belumosudil being granted Breakthrough Therapy Designation by the US Food and Drug Administration (FDA) in 2018 and approved in 2021 as a third-line treatment. Partial responses (PR) were the best obtained in patients; PR was also achieved in lung cGVHD and it was associated with a corticosteroid-sparing effect [12]. Conflicting data emerged from the use of imatinib in pulmonary cGVHD. Olivieri et al. observed a similar response rate in lung and skin cGVHD [13], not confirmed in a retrospective real-life analysis where only a slight decrease of the daily corticosteroid dose was observed [14].

Ibrutinib was approved by FDA in 2017 for the treatment of cGVHD (II line or more). Despite an overall response rate of 67% [15], the high rate of adverse events limits its use in a real-life setting; however, a phase III placebo-controlled trial is ongoing (NCT02959944).

Extra-corporeal photopheresis, rituximab, etanercept have been evaluated as a treatment of BOS without evidence of sustainable improvement of pulmonary function [5,8]. Finally, lung transplantation might be indicated as the *ultima ratio* in young fit patients in complete remission with severe progressive functional deterioration despite at least 3–6 months of medical treatments. Due to the limited availability of lung donors and the risk of relapse, infections and second malignancies, lung transplantation should be carefully evaluated [5].

## 3. Expert opinion

Despite recent therapeutic advances, treatment of lung cGVHD is still an unmet medical need. As easy definitive tests are lacking, diagnoses of cGVHD can be extremely tricky. Clinical symptoms and signs should be routinely investigated and serial PFTs are recommended starting from day +100. Functional impairment detection should be followed by a lung CT examination, and all other possible causes should be ruled out (i.e. infections). Furthermore, the feasibility of a lung biopsy should be at least considered. Early recognition and diagnosis are essential for the management of lung HSCT complications, and a multidisciplinary team approach is strongly recommended.

According to the NIH criteria, a significant FEV1 or FEV1/vital capacity reduction should be followed by proper treatment. When only a mild decline in FEV1 occurred, topical treatment with a combination of steroids and long-acting bronchodilator might be considered [6]. Systemic steroid together with FAM regimen is recommended as first-line systemic treatment for mild to severe forms, with appropriate antifungal prophylaxis including mold-active agents. Steroid tapering schedule provides for a dose reduction of 20–30% every 2 weeks, reaching an alternate-day regimen and discontinuing after a minimum of 4 weeks of treatment at a dose of 0.10 mg/kg every other day. If a cGVHD exacerbation occurs, the taper should be interrupted, and prednisone dose increased by two levels. Treatment should then be continued for at least 3 months before attempting to resume the taper [6], which could be slower. We suggest the execution of 6MWT at baseline and follow-up since it is a rapid and useful tool to assess the response to treatment, whereas PFTs should be repeated every 3 months.

In case of lack of response within a month, of worsening cGVHD manifestation or development of cGVHD signs and symptoms in a previously unaffected organ, second-line treatment should be started. No consensus has been reached regarding the optimal choice of second-line agents, and this is the second pitfall of lung cGVHD. Indeed, many of the published studies on steroid-refractory cGVHD are small and retrospective, particularly if they focus on lung cGVHD. Furthermore, results are often reported as overall responses, with no single organ data, despite the widespread of NIH grading. For these reasons, we strongly suggest addressing patients to clinical trials whenever available.

In absence of clinical trial and based on recently published studies, ruxolitinib might be a promising second-line treatment of cGVHD, but conclusive results for patients predominantly affected by lung cGVHD are still lacking. While ruxolitinib seems the candidate drug in multi-organ cGVHD, imatinib could be an option in case of near-exclusive pulmonary (± skin) involvement. At the same time, the high rate of adverse events limits ibrutinib use in real-life setting.

Following the FDA approval for cGVHD treatment after failure of at least two prior systemic therapies, belumosudil might be a valuable third-line option, as it was associated with FEV1 improvement and reduction of NIH lung symptom score irrespective of previous ruxolitinib or ibrutinib treatment.

In conclusion, early detection of lung impairment and initiation of effective therapy are the key elements to interrupt the pathological process and avert the fibrotic evolution of cGVHD. Early intervention clinical trials for the evaluation of targeted agents are needed to obtain better responses after the first-line treatment and reduce morbidity and mortality. A longitudinal prospective cohort is the optimal substrate for conducting such studies. Finally, given the complexity of manifestations, a multidisciplinary approach is mandatory.

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## References

1. Wolff D, Radojcic V, Lafyatis R, et al. National Institutes of Health Consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2020 highly morbid forms report. Transplant Cell Ther. 2021;27(10):817–835.
2. Hayakawa J, Miyamura D, Kimura S-I, et al. Negative impact of chronic graft-versus-host disease and glucocorticoid on the recovery of physical function after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2019;54(7):994–1003.
3. Socié G, Kean LS, Zeiser R, et al. Insights from integrating clinical and preclinical studies advance understanding of graft-versus-host disease. J Clin Invest. 2021;131(12):e149296.
4. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus development project on criteria for clinical trials in chronic graft-versus-host disease: i. The 2014 diagnosis and staging working group report. Biol Blood Marrow Transplant. 2015;21(3):389–401.e1.
5. Hildebrandt GC, Fazekas T, Lawitschka A, et al. Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD. Bone Marrow Transplant. 2011;46(10):1283–1295.
6. Flowers MED, Martin PJ. How we treat chronic graft-versus-host disease. Blood. 2015;125(4):606–615.
7. Glanville AR, Verleden GM, Todd JL, et al. Chronic lung allograft dysfunction: definition and update of restrictive allograft syndrome–a consensus report from the pulmonary council of the ISHLT. J Heart Lung Transplant. 2019;38(5):483–492.
8. Penack O, Marchetti M, Ruutu T, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol. 2020;7(2):e157–e167.
9. Williams KM, Cheng G-S, Pusic I, et al. Fluticasone, azithromycin, and montelukast treatment for new-onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2016;22(4):710–716.
10. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. N Engl J Med. 2021;385(3):228–238.
11. Zhao Y, OuYang G, Shi J, et al. Salvage therapy with low-dose ruxolitinib leads to a significant improvement in bronchiolitis obliterans syndrome in patients with cGVHD after allogeneic hematopoietic stem cell transplantation. Front Pharmacol. 2021;12:668825.
12. Jagasia M, Lazaryan A, Bachier CR, et al. ROCK2 inhibition with belumosudil (KD025) for the treatment of chronic graft-versus-host disease. J Clin Oncol. 2021;39(17):1888–1898.
13. Olivieri A, Cimminiello M, Corradini P, et al. Long-term outcome and prospective validation of NIH response criteria in 39 patients receiving imatinib for steroid-refractory chronic GVHD. Blood. 2013;122(25):4111–4118.
14. Parra Salinas I, Bermudez A, López Corral L, et al. Treatment of steroid-refractory chronic graft-versus-host disease with imatinib: real-life experience of the Spanish group of hematopoietic transplantation (GETH). Clin Transplant. 2021;35(5):e14255.
15. Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood. 2017;130(21):2243–2250.