To the Editor: A 20-year-old man who developed hemophagocytic lymphohistiocytosis (HLH) was treated with methylprednisolone combined with etoposide (VP-16) for 24 weeks. One month after treatment completion, HLH recurred. The patient visited the Hematology Department of the Beijing Friendship Hospital and was diagnosed with primary HLH with PRFI fusion gene mutation. Subsequently, he was treated with a regimen of liposomal doxorubicin, VP-16, and methylprednisolone (DEP) and achieved complete remission. Later, in July 2014, the patient underwent an allogeneic hematopoietic stem cell transplant (allo-HSCT) from an allele human leukocyte antigen (HLA)-5/-10-matched, bone marrow donor. A conditioning protocol of total-body irradiation/cyclophosphamide/VP-16 (TBI/CY/VP-16) was used before the transplant. Additionally, the patient was administered cyclosporine, methotrexate, and mycophenolate mofetil as prophylaxis for graft-versus-host disease (GVHD). However, the patient developed chronic GVHD (cGVHD) in the liver 2 years later and received anti-GVHD treatment with methylprednisolone and tacrolimus (FK506). Despite treatment, 26 months after the HSCT, the patient was re-admitted due to progressive dyspnea. Prior to the HSCT, the patient’s forced expiratory volume in 1 s (FEV1) was 115.2% of the predicted value, and the FEV1/forced vital capacity (FVC) was 87.5%. However, after the HSCT, a pulmonary function test (PFT) demonstrated a reduced FEV1 of 31.7% and a FEV1/FVC of 36.6%. Computerized tomography (CT) examination of the chest revealed multiple bronchiectasis in a columnar shape and air-trapping in both lungs. No evidence was found which suggested lung or other infections, which may further aggravate BOS. GVHD steroids are prone to serious complications, especially lung complications and is recognized as a symptom of cGVHD. The pathogenesis of BOS is unknown, and its clinical presentation is often insidious, with up to 20% of patients remaining asymptomatic.¹ PFT and high-resolution CT scans are the mainstay technologies for BOS diagnosis. The long-term prognosis for BOS is poor, with a 5-year survival rate of 13% to 56%.¹ Currently, the aims of BOS treatment are to prevent progression of airflow obstruction and decline of lung function. Systemic and standard corticosteroids are the first-line therapy for GVHD and may result in disease improvement. However, long-term high-dose corticosteroids are prone to serious complications, especially lung infections, which may further aggravate BOS. GVHD treatment with MSCs has been used for potential immunoregulatory effects. However, after our patient
received treatment with MSCs, the symptoms of dyspnea and FEV1 did not significantly improve.

Ruxolitinib has been proven to be a second-line agent for cGVHD, especially for steroid-dependent or refractory cGVHD. The mechanism of action of ruxolitinib is to suppress proinflammatory signaling by promoting tolerogenic regulatory T cells. In a previous study, Ferreira et al. [4] found that 20 cases of steroid-refractory cGVHD had an overall response rate of 75% after ruxolitinib treatment. Khoury et al. [3] found that 19 patients with steroid-refractory cGVHD showed varied degrees of response in several target organs after ruxolitinib treatment. A partial response (PR) was observed in 18 patients, and one patient had a complete response (CR). [5]

It is reasonable to ask that if BOS is considered to be the main pulmonary symptom of cGVHD, then should ruxolitinib commonly be used to treat BOS? A study by Streiler et al. [6] found that six patients with BOS receiving ruxolitinib as a second-line agent were able to tolerate a significant reduction in prednisone dosing, and one patient was taken off prednisone entirely. They also observed an immediate and marked improvement in FEV1 despite the decreased dosing of prednisone. In addition, Schoettler et al. [3] described five pediatric patients with extensive cGVHD and steroid-refractory BOS treated with ruxolitinib, who had a PR or CR in all organ systems after treatment. Our patient also achieved some degree of improvement in BOS symptoms and FEV1 after ruxolitinib treatment. Previous studies reported that ruxolitinib treatment of BOS was only refractory to steroids. However, the patient in one study had used hormones incorrectly and was also treated with FK506 and MSCs, drugs shown to be ineffective for BOS in our patient, as described above. This suggests that ruxolitinib has a positive therapeutic effect on BOS refractory to steroids, FK506, and MSCs.

In conclusion, this report suggests that ruxolitinib could improve symptoms and FEV1 in patients with BOS refractory to steroids, FK506, and MSCs. However, additional prospective studies are required to confirm this finding.

Declarations of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) or his/her guardian has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients or his/her guardian understand that his/her/their name(s) and initials will not be published and due efforts will be made to conceal his/her/their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

References

1. Gronningsæter IS, Tsykunova G, Lillegard K, Ahmed AB, Bruserud Ø, Rekvam H, et al. Bronchiolitis obliterans syndrome in adults after allogeneic stem cell transplantation: Pathophysiology, diagnostics and treatment. Expert Rev Clin Immunol 2017;13:353–369. doi: 10.1080/1744666X.2017.1279053.

2. Ferreira AM, Pontes da Silva CA, Pereira AD, Szor RS, Medeiros da Fonseca ARB, Serpa MG, et al. Ruxolitinib in steroid-refractory chronic graft-versus-host disease: experience of a single center. Bone Marrow Transplant 2018;53:503–506. doi: 10.1038/s41409-017-0068-2.

3. Khoury HJ, Langston AA, Wilkinson JA, Pusey I, Jillella A, et al. Ruxolitinib: A steroid sparing agent in chronic graft-versus-host disease. Bone Marrow Transplant 2018;53:826–831. doi: 10.1038/s41409-017-0081-5.

4. Streiler C, Shaikh F, Davids C, Abhyankar S, Brownback KR. Ruxolitinib is an effective steroid sparing agent in bronchiolitis obliterans due to chronic graft-versus-host-disease. Bone Marrow Transplant 2018;53:1194–1196. doi: 10.1038/s41409-019-0662-6.

5. Schoettler M, Duncan C, Lehrmann L, Furutani E, Subramaniam M, Margossian S. Ruxolitinib is an effective steroid sparing agent in children with steroid refractory/dependent bronchiolitis obliterans syndrome after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2019;54:1158–1160. doi: 10.1038/s41409-019-0450-3.

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