Effective treatment of late-onset noninfectious pulmonary complication with ruxolitinib in an 8-year-old boy

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To the Editor:

Haematopoietic stem cell transplantation (HSCT) is an effective treatment for many malignant and nonmalignant diseases both in adults and children, but this procedure can be burdened by the so-called "late-onset non-infectious pulmonary complications" (LONIPCs), which are characterised by significant morbidity and mortality [1]. LONIPCs include different forms of inflammatory lung involvement, occurring after 100 days and within 2–3 years following HSCT [2]. They have a variable incidence, with similar rates in adults and children [3], and uncertain pathogenesis, even if a strict relationship with chronic graft-*versus*-host disease (GVHD) has been reported. Pneumonia before 100 days after HSCT is considered as a risk factor [4, 5]. In these patients, unspecific signs and symptoms, such as dry cough or exercise-induced dyspnoea, frequently appear 8–12 months after HSCT [6]. Lung biopsy is considered the gold standard to establish a specific diagnosis; however, it is not always feasible in clinical practice, especially in children. Therefore, the diagnosis of LONIPCs relies upon clinical manifestations, lung imaging, spirometry, and the exclusion of infections [2]. First-line treatment is based on high-dose corticosteroids, while second-line treatment includes immunosuppressive agents such as calcineurin inhibitors [2]. Inhaled corticosteroids and short/long-acting bronchodilators may be slightly effective [7]. Ruxolitinib is a selective inhibitor of JAK1/2 approved for acute GVHD (in patients >12 years of age) [8], which has recently been proposed for chronic GVHD and LONIPCs [9].

Here, we report a case of LONIPCs effectively treated with ruxolitinib in an 8-year-old boy, referred in April 2020 due to dry cough and increasing exercise-induced dyspnoea for 10 days. The patient had a history of B-cell acute lymphoblastic leukaemia diagnosed in August 2015 at 3 years of age, treated accordingly to the AIEOP-BFM-2009 protocol [10]. He obtained a first complete remission and then relapsed in March 2018. He then received additional chemotherapy achieving a second remission and a subsequent haploidentical HSCT from his mother with a peripheral graft and a busulfan-based regimen in November 2018. Neutrophil and platelet engraftment was unremarkable and GVHD prophylaxis included post-transplantation cyclophosphamide, cyclosporin and mycophenolate-mofetil. Early post-HSCT complications were represented by pneumonia treated with empiric therapy. The patient was discharged on cyclosporin and antimicrobial prophylaxis. Within the first year after HSCT, after a persistent increase in liver function tests (LFTs), namely alanine aminotransferase, aspartate aminotransferases and γ-glutamyltransferase, worsened by corticosteroid therapy and nonresponsive to immunosuppression, a liver biopsy showed a vanishing bile-duct syndrome related to drug toxicity with only mild signs of GVHD. Therefore, we tapered immunosuppression with a full suspension of cyclosporin in March 2020. 1 month later, on evaluation the boy was slightly tachypnoeic (respiratory rate 48 breaths per min), chest auscultation showed slightly decreased breathing sounds and oxygen saturation measured by pulse oximetry (S_{pO_2}) was 90%. Spirometry showed a restrictive pattern with severe reduction of all the parameters and normal forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio (FEV_1 48%, z-score −4.25; FVC 48%, z-score −4.35) (figure 1), and a chest computed tomography (CT) showed bilateral multiple peribronchial consolidations associated with bronchiectasis with a peri-lobular distribution. Nasopharyngeal swabs were negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), blood examination showed an increase in LFTs, and bronchoalveolar lavage (BAL) cytology showed a predominance of neutrophils. Microbiological testing, including cultures and molecular testing for bacteria, fungi and viruses, were negative on BAL and blood samples, so we suspected a

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Ruxolitinib could be considered as an option in the treatment of LONIPCs in children when other treatments are ineffective. Spirometry is a valuable tool for both diagnosis and follow-up of LONIPCs in children. https://bit.ly/3BmOYfb

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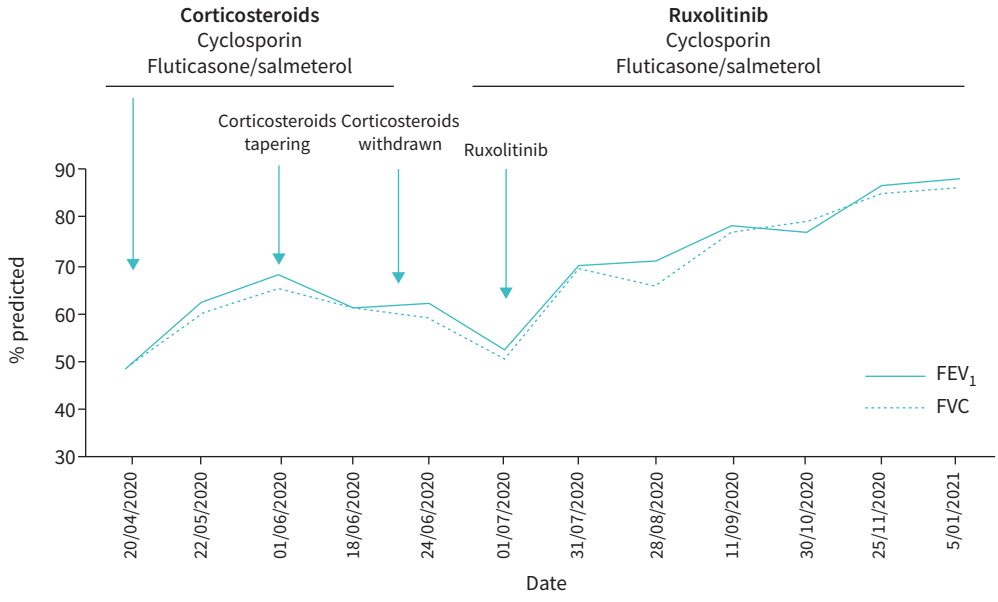

FIGURE 1 Lung function testing trend by means of forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) values.

LONIPC. The patient required low-flow oxygen, while cyclosporin, high-dose prednisone and inhaled salmeterol/fluticasone were initiated, with a gradual improvement of both symptoms and spirometry (FEV_1 62%, z-score −3.12, FVC 60%, z-score −3.32). 1 month later, chest CT showed a reduction of the parenchymal consolidations, but fibrotic bands were observed in the same areas and were associated with traction bronchiectasis, suggesting a fibrotic evolution. On tapering the steroids, the patient worsened again both clinically (dyspnoea on exertion, S_{pO_2} 94%) and at spirometry (FEV_1 52%, z-score −3.95). Prednisone was increased again, but it had to be stopped due to a further increase in LFTs. Then, ruxolitinib was introduced (10 mg per day), with subsequent gradual improvement. Remarkably, 7 months later both LFTs and spirometry were normal (FEV_1 88%, z-score −1.05; FVC 86%, z-score −1.18) (figure 1). To further characterise the pulmonary damage and in the attempt to avoid additional radiation exposure, lung magnetic resonance imaging (MRI) was performed in February 2021, revealing a reduction of the parenchymal bands and striae. T2-weighted sequences were consistent with chronic inflammatory involvement and initial fibrosis.

To our knowledge, this is the first reported effective treatment of LONIPCs with ruxolitinib in a child younger than 12 years with complete normalisation of lung function testing. LONIPCs is a generic definition including different subtypes of inflammatory lung involvement, potentially leading to aberrant tissue repair [11]. Among them, interstitial disease, bronchiolitis obliterans syndrome (BOS), and cryptogenic organising pneumonia (COP), are the most common [12]. According to the American Thoracic Society/European Respiratory Society guidelines [13], in LONIPCs the flow–volume curve may show an obstructive pattern (BOS), a restrictive pattern (interstitial disease), or even a mixed pattern [4]. CT may show geographic hypoattenuation and air trapping with a subpleural predominance in BOS, airspace consolidation along the bronchovascular bundle or in the subpleural area in COP, or ground-glass areas with reticulation and crazy paving pattern with predominantly peribronchovascular traction bronchiectasis in interstitial disease [14]. In our case, respiratory signs and symptoms appeared more than 1 year after transplantation, when cyclosporin was discontinued, and without any relationship with hepatic toxicity, suggesting the presence of an underlying alloreactive status that was exacerbated by the removal of immunosuppression. Moreover, lung infections were excluded, a restrictive pattern was identified on spirometry, and interstitial damage together with bronchiectasis was shown at CT, while MRI confirmed the presence of chronic inflammatory damage with fibrosis. In the absence of a diriment histological finding, while neither the BOS nor COP criteria were met, interstitial lung disease was a reasonable diagnosis.

Ruxolitinib can control alloreactivity through: 1) suppression of pro-inflammatory cytokines, 2) increase in regulatory T-cells, and 3) decrease in memory T-cells [15]. However, its safety and efficacy in children is

still uncertain. Data on the effects of ruxolitinib on lung function in LONIPCs are lacking and only one study included five children with BOS showing that steroids were reduced in four patients, a full suspension was achieved in three patients and a 24% increase in FEV_1 was observed [16]. Our patient responded to high-dose steroids, but the treatment was discontinued due to hepatic toxicity; since cyclosporin was not sufficient to control lung involvement, ruxolitinib was a valuable and effective option, providing a clinical response and a definite improvement of lung function. We also observed an improvement of lung involvement at the MRI. Our case shows that spirometry is a valuable tool for both diagnosis and follow-up of LONIPCs in children since lung auscultation may be unremarkable. Our case report suggests that ruxolitinib should be considered as an effective option in the treatment of LONIPCs in children when other treatments are not effective nor feasible. However, more studies are needed to further investigate its efficacy and long-term safety in this age group.

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References

1 Patriarca F, Skert C, Sperotto A, *et al.* Incidence, outcome, and risk factors of late-onset noninfectious pulmonary complications after unrelated donor stem cell transplantation. *Bone Marrow Transplant* 2004; 33: 751–758.
2 Carreras E, Cooke KR. Noninfectious pulmonary complications. *In:* Carreras E, Dufour C, Mohty M, *et al.*, eds. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. 7th Edn. Cham, Springer, 2019; pp. 393–407.
3 Palmas A, Tefferi A, Myers JL, *et al.* Late-onset noninfectious pulmonary complications after allogeneic bone marrow transplantation. *Br J Haematol* 1998; 100: 680–687.
4 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: 1283–1295.
5 Bergeron A, Chevret S, Peffault de Latour R, *et al.* Noninfectious lung complications after allogeneic haematopoietic stem cell transplantation. *Eur Respir J* 2018; 51: 1702617.
6 Trisolini R, Bandini G, Stanzani M, *et al.* Morphologic changes leading to bronchiolitis obliterans in a patient with delayed non-infectious lung disease after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2001; 28: 1167–1170.
7 De Soyza A, Fisher AJ, Small T, *et al.* Inhaled corticosteroids and the treatment of lymphocytic bronchiolitis following lung transplantation. *Am J Respir Crit Care Med* 2001; 164: 1209–1212.
8 Przepiorka D, Luo L, Subramaniam S, *et al.* FDA approval summary: ruxolitinib for treatment of steroid-refractory acute graft-versus-host disease. *Oncologist* 2020; 25: e328–e334.
9 Streiler C, Shaikh F, Davis C, *et al.* Ruxolitinib is an effective steroid sparing agent in bronchiolitis obliterans due to chronic graft-versus-host-disease. *Bone Marrow Transplant* 2020; 55: 1194–1196.

10 clinicaltrials.gov. International Collaborative Treatment Protocol For Children And Adolescents With Acute Lymphoblastic Leukemia (Phase III). ClinicalTrials.gov Identifier: NCT01117441. https://clinicaltrials.gov/ct2/show/study/NCT01117441 Date last accessed: 6 July 2021.
11 Barker AF, Bergeron A, Rom WN, *et al.* Obliterative bronchiolitis. *N Engl J Med* 2014; 370: 1820–1828.
12 Nishio N, Yagasaki H, Takahashi Y, *et al.* Late-onset non-infectious pulmonary complications following allogeneic hematopoietic stem cell transplantation in children. *Bone Marrow Transplant* 2009; 44: 303–308.
13 Pellegrino R, Viegi G, Brusasco V, *et al*. Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.
14 Merlini L, Borzani IMO, Anooshiravani M, *et al.* Correlation of lung abnormalities on high-resolution CT with clinical graft-versus-host disease after allogeneic versus autologous bone marrow transplantation in children. *Pediatr Radiol* 2008; 38: 1201–1209.
15 Spoerl S, Mathew NR, Bscheider M, *et al.* Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. *Blood* 2014; 123: 3832–3842.
16 Schoettler M, Duncan C, Lehmann L, *et al.* Ruxolitinib is an effective steroid sparing agent in children with steroid refractory/dependent bronchiolitis obliterans syndrome after allogenic hematopoietic cell transplantation. *Bone Marrow Transplant* 2019; 54: 1158–1160.