Effectiveness and safety of ruxolitinib for the treatment of refractory systemic idiopathic juvenile arthritis like associated with interstitial lung disease : a case report

We read with interest the report of a series of 61 patients with systemic juvenile idiopathic arthritis (s-JIA) or s-JIA-like associated with high-fatality lung diseases.¹ Lung disease was associated with digital clubbing, a high frequency of anaphylactic reactions to tocilizumab, and macrophage activation syndrome (MAS). Because of the low 5-year survival probability of 42%, there is an urgent need to identify efficient drugs to treat such patients. Herein we report the effectiveness and safety of ruxolitinib in one patient demonstrating clinical and radiological characteristics consistent to those reported by Saper *et al*

A 2-year-old girl born to non-consanguineous parents presented with s-JIA-like since the age of 12 months, including recurring episodes of unexplained fever, urticaria, arthralgia, poor general health status, leukocytosis and elevated serum C-reactive protein (CRP). The use of corticosteroids resulted in a complete remission but the patient relapsed when prednisone was tapered below 0.5 mg/kg/day. Owing to this corticosteroid dependence, the patient received several lines of biological agents from the age 15–22 months, none of which was either effective nor tolerated. Anakinra had no benefit on the patient's features, and was replaced by canakinumab—but which resulted in a probable drug reaction with eosinophilia and systemic symptoms and a MAS after the third injection. Finally, a third line with tocilizumab led to severe anaphylactic reactions after the second infusion. At age 34 months, the patient developed acute digital clubbing without any respiratory symptoms. Chest CT scan showed a diffuse interstitial disease with interlobular septal thickenings, bronchovascular bundles thickenings, ground glass opacities with a peripheral and lower lobes predominance, and enlargement of mediastinal lymph nodes (figure 1). Bronchoalveolar lavage (BAL) fluid showed 250 000 cells/mL (macrophages: 66%, neutrophils: 27%, lymphocytes: 7%). Microbiological investigations were all negative. A whole exome sequencing did not identify any causal mutation.

The expression of interferon (IFN)-stimulated genes in the whole blood of the patient was normal on two occasions, and increased once while the patient received anti-interleukin-1 treatment. Immunophenotyping showed normal counts of T cell, B cell and natural killer (NK) lymphocytes. Further study showed that, among memory CD4⁺ T cells, the patient had frequencies of Th1 cells well above the control range, and decreased frequencies of Th17 cells (figure 2).

At the age of 4, the patient was treated with the Janus kinase 1/2 selective inhibitor ruxolitinib (1 mg/kg/day) in association with oral prednisone (0.5 mg/kg/day) and 3 monthly intravenous infusions

Figure 1 Radiological response to JAK1/JAK2 blockade with ruxolitinib. (A) Chest CT scan before the initiation of ruxolitinib. (B) Chest CT scan 12 months after the initiation of ruxolitinib.

Figure 2 T helper immunophenotyping. (A) Gating strategy in the patient's peripheral blood mononuclear cells (PBMCs) for T helper immunophenotyping. (B) Representative fluorescence activated cell sorting (FACS) plots are presented. The horizontal bars represent the mean $\pm$ SD. Frequencies of T helper subsets within the CD4⁺ memory compartment in controls and P. Subsets were defined as follows: Th1 (CXCR5⁻CXCR3⁻CCR4⁻CCR6⁻), Th2 (CXCR5⁻CXCR3⁻CCR4⁺CCR6⁻), Th17 (CXCR5⁻CXCR3⁻CCR4⁺CCR6⁺) and Tfh (CXCR5⁺).

of methylprednisolone (600 mg/m²). At last follow-up, 15 months post initiation of ruxolitinib, febrile attacks remitted, CRP value was normal, prednisone was tapered to 0.1 mg/kg/day, and methylprednisolone dosage was progressively decreased to one infusion (300 mg/m²) every 6 weeks. Chest CT scan abnormalities decreased (figure 1). Oxygen saturation increased from 92% to 100%. There was a catch-up growth with an improvement of the height Z-scores from -3 to -2. Ruxolitinib was well tolerated.

Our patient demonstrates features similar to those reported in the series of Saper *et al*. An upregulation of genes related to the IFN γ response both in the (BAL) fluid and lung tissue was demonstrated in some patients from this series.² In line with a putative pathogenic role of IFN γ signaling, a high frequency of MAS was reported. The observation in our patient of (1) elevated frequency of Th1 cells, main producers of IFN γ ,³ and (2) a clinical response to ruxolitinib, blocking the IFN γ signaling, although not selectively,^{4,5} is consistent with this hypothesis. Although no definite conclusion can be drawn from this single case, our report suggests that ruxolitinib may represent a valid therapeutic option to be tested early in patients with s-AJI associated with severe early-onset lung disease.

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