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TITLE: Ruxolitinib for refractory LGL leukemia.

Aline Moignet¹MD, Cédric Pastoret^{2,3}MD, Guillaume Cartron⁴MD-PhD, Paul Coppo^{5,6}MD-PhD, Thierry Lamy^{1,3}MD-PhD

SHORT TITLE: Ruxolitinib in LGL Leukemia

Affiliations :

¹Centre Hospitalier Universitaire de Rennes, Service d'Hématologie Clinique, Rennes, France

²Centre Hospitalier Universitaire de Rennes, Laboratoire d'Hématologie, Rennes, France

³Institut national de la santé et de la recherche médicale, Unité mixte de Recherche U1236, Rennes, France

⁴Department of Hematology, CHU Montpellier, UMR 5535, Université de Montpellier, Montpellier, France

⁵Service d'Hématologie, centre de référence des microangiopathies thrombotiques (CNR-MAT), Hôpital Saint-Antoine, AP-HP – Sorbonne - Université, Paris, France.

⁶INSERM UMRS1138, Centre de Recherche des Cordeliers, Paris

Corresponding author

Thierry Lamy: thierry.lamy@univ-rennes1.fr

Corresponding authors:

Thierry Lamy (thierry.lamy@univ-rennes1.fr)

Hematology Department, CHU Pontchaillou, 2 rue Henri Le Guilloux, F-35033 Rennes cedex 9, France.

Tel: +33-299-284-291; Fax: +33-299-284-161

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Letter to Editor

Large Granular Lymphocyte (LGL) leukemia is a T or NK cell clonal disorder characterized by tissue invasion of marrow, spleen, and liver. Clinical presentation is dominated by recurrent infections associated with neutropenia, anemia, splenomegaly and auto-immune diseases, particularly rheumatoid arthritis (RA). It accounts for 2-5% of chronic lymphoproliferative disorders. Indications for treatment are severe or infections related neutropenia, symptomatic or transfusion-dependent anemia or associated autoimmune diseases requiring therapy.¹ There is no standard treatment for patients with LGL leukemia. Immunosuppressive therapy remains the foundation of first line treatment including single agents i.e. methotrexate, oral cyclophosphamide or cyclosporine. Usually, refractory patients may be treated with purine analogs, Bendamustine or alemtuzumab while polychemotherapy does not provide any good results. There is a clear unmet medical need for such patients whose prognosis is poor.

Before moving to targeted therapy, it is important to better understand the pathogenesis of LGL leukemia. Constitutive activation of STAT3 pathway in all LGL leukemia patients has been demonstrated in 2001, while common somatic gain-of-function *STAT3* mutations was reported in 28% to 60 % of T-LGL leukemia and 30% to 48% of NK LGL lymphocytosis in 2012. Whether or not *STAT3* mutation acts as an initial trigger or a late event in LGL leukemia proliferation is still debated. Dysregulations of several signaling pathways including MAPK, PI3K-AKT, NF- κ B, and JAK/STATs constitute a hallmark of the pathogenesis of LGL leukemia. However, the landscape of mutational events includes also epigenetic and DNA methylation mutated genes.¹ We and others have recently reported TET2 mutations in 30% of NK LGL leukemia.² All these findings open a new window to explore targeted therapy in LGL leukemia. JAK inhibitors are indeed of potential interest in the treatment of the disease. JAK3 specific inhibitor tofacitinib has shown clinical efficacy in a series of 9 RA patients presenting with refractory T-LGL leukemia.³ Hematologic response was observed in 6 patients with neutropenia improvement in 5 patients. One patient experienced an increase of hemoglobin level.

JAK2 inhibitor ruxolitinib is commonly used in myeloproliferative disorders. Interestingly, its effectiveness is not dependent on *JAK2*^{V617F} mutation status. We therefore evaluated the use of ruxolitinib in two cases of refractory T-LGL leukemia. The initial diagnosis was based on a chronic LGL-T cell expansion (> 1G/l) with a typical phenotype (CD3+/CD5dim/CD8+/CD57+) and TCR γ clonal rearrangement. Both patients had a long term medical history of transfusion-dependent anemia and neutropenia, failing or partially responding to immunosuppressive or chemotherapeutic agents. Informed consent was obtained in both cases according to IRB protocol.

Case 1: A 36-year-old female was diagnosed with pure red cell aplasia associated to *STAT3* mutated T-LGL leukemia. From 2009 to 2017, she successively received high dose immunoglobulin, prednisone, methotrexate, ciclosporin and cytoxan leading to transitory and partial remission. In 2018, one course of 2CDA (cladribin) was administered due to recurrence of severe anemia and neutropenia without any hematological improvement. The patient was transfusion dependent and experienced recurrent infections. In July 2019, sixth line therapy with ruxolitinib was then introduced at oral dose of 15 mg twice per day and resulted in rapid improvement of anemia and neutropenia with complete hematological response. At months 20, patient had hematologic complete response with normalization of blood cell count: Hb 11.3g/dl, neutrophils 1.78 G/L, platelets 335 G/L (Fig 1A). After 12 months of therapy, bone marrow biopsy evidenced a slight persistence of LGL infiltration (Fig 1B). Flow cytometric and molecular analyses showed a drastic and stable reduction of clonal LGL expansion in serial blood samples (Fig 1C). At month 20, patient showed a persistent hematologic complete response with normalization of blood cell count: Hb 11.3g/dl, neutrophils 1.78 G/L, platelets 335 G/L.

Case 2: The second case was related to 70 year female with severe pancytopenia and splenomegaly related to *STAT3* un-mutated T-LGL leukemia diagnosed in 1990. She failed methotrexate, ciclosporin and Cytoxan and 2CDA (cladribin). The patient was transfusion dependent despite 4 months EPO delivery before starting ruxolitinib. In march 2020, ruxolitinib was administered at a dose of 10 mg taken orally twice per day and induced a very good partial remission: the patient became transfusion independent by the third month of therapy. In February 2021, complete blood cell count showed: hemoglobin 10.4g/dl (EPO not stopped), neutrophils 1.5 G/L (G-CSF once a week), Platelets 110 G/L. Large spleen was no longer palpable. Both patients did not present any adverse event secondary to ruxolitinib.

JAK inhibitors may be considered as relevant targeting agents for the treatment of cytopenic LGL leukemia patients.^{4,5} Different compounds targeting JAK/STAT3 signaling pathway have demonstrated *in vitro* efficacy on leukemic samples from T-LGL leukemic and aggressive NK cell leukemia patients, depending on the basal activity of mutant *STAT3*. It has been shown that IL6/IL15 promoted T/NK LGL leukemic expansion through *STAT/JAK* pathway activation. The ability of *STAT3* to promote IL6 gene expression then results in a feed forward autocrine loop. Therefore, we hypothesize that JAK inhibition could induce LGL clone apoptosis through a blockade of a feedback IL6 activation. Clinical efficacy of Ruxolitinib was recently reported in a case of refractory severe enterocolitis harboring a *STAT3* gene mutation.⁶ In the two present cases, ruxolitinib was able to induce durable complete and very good partial response (lasting more than one year) in two

refractory LGL patients. These results make ruxolitinib a potential and promising alternative therapeutic agent in LGL leukemia. This option needs to be further explored in prospective clinical trials.

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Conflict of interest

The authors report no conflict of interest

Legends for figure 1

Figure 1A: Course of treatment in a patient with a refractory T-LGL leukemia treated successfully with ruxolitinib.

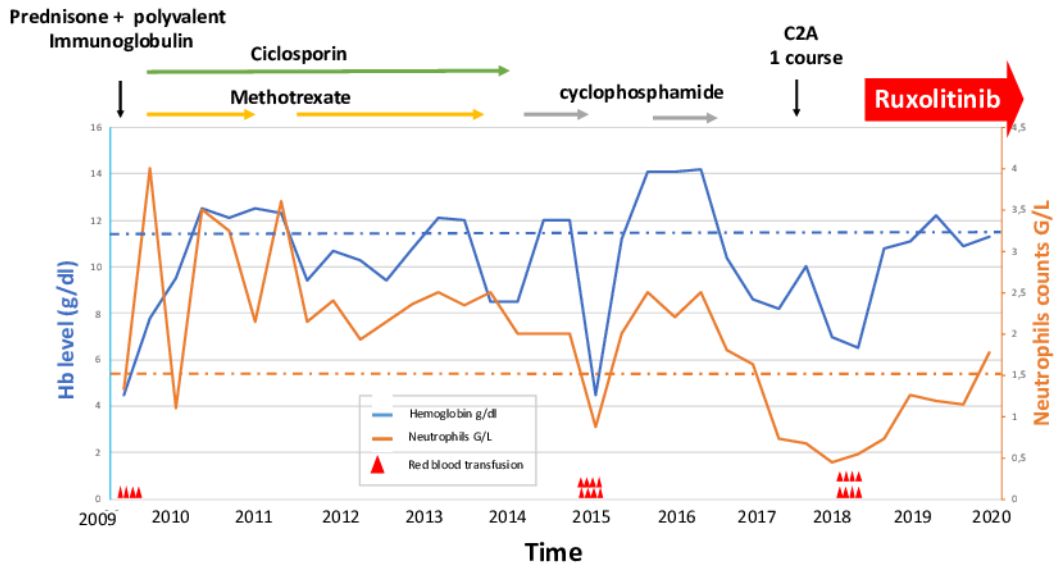
Figure 1B: Bone marrow histology and flow cytometry quantification of LGL in blood samples during the course of ruxolitinib. Bone marrow biopsy performed before ruxolitinib showed a left shift of erythroid precursors and CD8+/granzyme B+ intrasinusoidal lymphocytes, with several linear arrays of cells, and clusters. After 12 months of ruxolitinib, erythroid precursors were normally distributed and immunohistochemical analysis revealed a significant decrease of CD8+/granzymeB+ intrasinusoidal lymphocytes (MGG: May-Grünwald-Giemsa staining, original magnification; CD8 and Granzyme B immunohistochemistry, original magnification x200).

T-cell LGL defined as CD3^{pos}, CD8^{pos}, CD5^{low}, CD57^{pos} cells expressing Vβ7.1 accounted for 77% of lymphocytes before Ruxolitinib initiation and significantly decreased to 16% after 12 months of treatment.

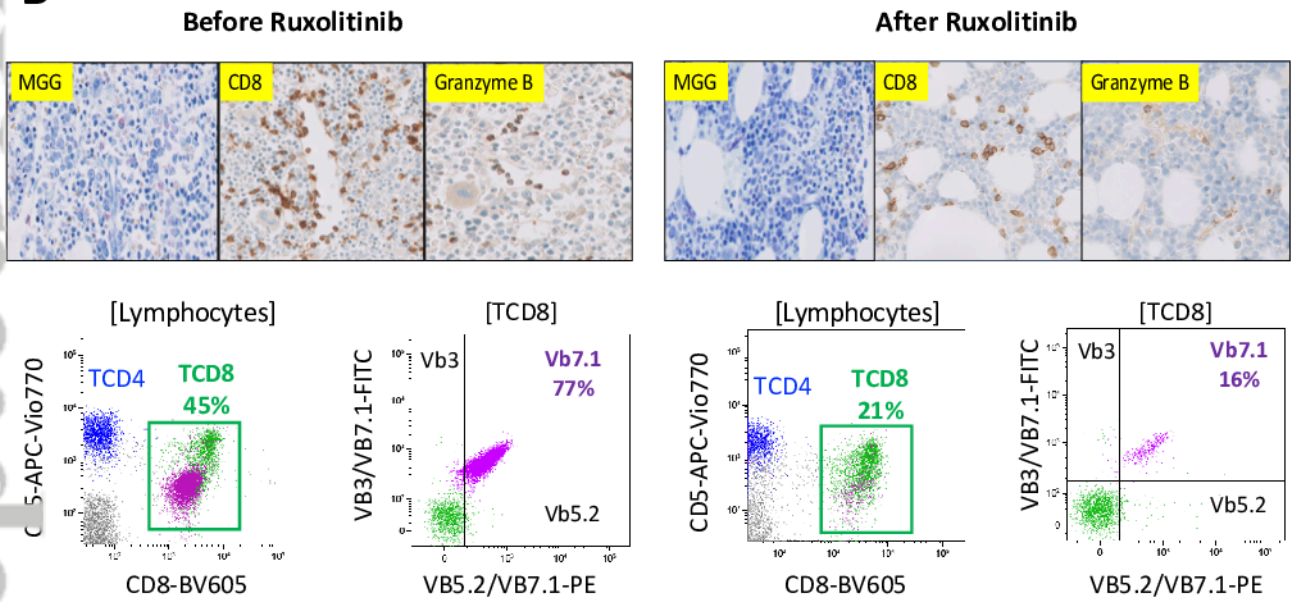
Figure 1C: After 12 months of ruxolitinib, absolute LGL count (defined by the total number of peripheral lymphocytes x % of CD8+/Vβ7.1 cells) decreased from 1.2 G/L to 0.08 G/L correlating with a significant reduction of STAT3 variance allelic frequency from 25 to 4%.

Figure 1

A



B



C

