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## ORIGINAL PAPER

Haematological Malignancy – Clinical

# Efficacy of ruxolitinib in the treatment of relapsed/refractory large granular lymphocytic leukaemia

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## Summary

Large granular lymphocytic (LGL) leukaemia is a rare chronic lymphoproliferative disorder characterized by an expansion of cytotoxic T or NK cells. Despite a usually indolent evolution, most patients will require a treatment over the course of the disease because of cytopenia or symptomatic associated autoimmune disorders. First-line treatment is based on immunosuppressive agents, namely cyclophosphamide, methotrexate and ciclosporin. However, relapses are frequent, and there is no consensus on the management of relapsed/refractory patients. The implication of the JAK/STAT pathway in the pathogenesis of this disease has prompted our group to propose treatment with ruxolitinib. A series of 21 patients who received this regimen is reported here. Ten patients (47.6%) were refractory to the three main immunosuppressive drugs at the time of ruxolitinib initiation. Ruxolitinib yielded an overall response rate of 86% ( $n = 18/21$ ), including 3 complete responses and 15 partial responses. With a median follow-up of 9 months, the median response duration was 4 months. One-year event-free survival and 1-year overall survival were 57% and 83% respectively. Mild side effects were observed. Biological parameters, notably neutropenia and anaemia, improved significantly, and complete molecular responses were evidenced. This study supports ruxolitinib as a valid option for the treatment of relapsed/refractory LGL leukaemia.

## KEY WORDS

chronic T cell leukaemia, clinical studies, lymphoproliferative disease, molecular biology, T-cell lymphoma

## INTRODUCTION

Large granular lymphocytic (LGL) leukaemia is characterized by the expansion of clonal cytotoxic T or natural killer (NK) cells and accounts for 2%–5% of lymphoproliferative disorders, with an estimated incidence of 0.2–0.7 per million individuals each year.<sup>1</sup> The clinical presentation

is dominated by recurrent infections associated with neutropenia, anaemia and splenomegaly.<sup>2,3</sup> Interestingly, LGL leukaemia is frequently associated with various autoimmune diseases.<sup>4</sup> Despite a classically indolent evolution, more than 70% of the patients will eventually require treatment. First-line therapy is based on immunosuppressive agents such as methotrexate, cyclophosphamide and/or

For affiliations refer to page 922.

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ciclosporin.<sup>5–7</sup> However, the overall response rate (ORR) is less than 50%, and the response duration is usually short, with frequent relapses. Several strategies have been tried in relapsed/refractory (R/R) patients. Alemtuzumab has shown some promising results, with a reported ORR of 56% in a series of 25 patients, but was associated with significant toxicity and high treatment-related mortality.<sup>8</sup> Other strategies have been reported, mostly in small retrospective studies, including bendamustine and purine analogues such as cladribine and fludarabine.<sup>9,10</sup> Autologous and allogeneic haematopoietic stem cell transplantation have been proposed in rare cases of highly pretreated patients.<sup>11</sup> Some results have been observed with anti-thymocyte globulins associated or not with ciclosporin in LGL leukaemia patients with associated aplastic anaemia.<sup>7</sup> However, results with these treatments have been disappointing, with inconstant responses, frequent relapses, and significant toxicities. Therefore, R/R LGL leukaemia represents an unmet medical need.

Deregulation of the JAK/STAT pathway is a hallmark of LGL leukaemia pathogenesis.<sup>12–14</sup> Somatic *STAT3* gain-of-function mutations are found in up to 60% of T-cell LGL leukaemia and 30% of NK-cell LGL leukaemia.<sup>15,16</sup> Activation of the JAK/STAT pathway has been demonstrated even in the absence of *STAT3* mutation, due to mutations in alternative genes, epigenetic modifications or dysregulations of the cytokine network.<sup>16–18</sup> Therefore, JAK/STAT inhibitors represent a potential option for the treatment of LGL leukaemia. The JAK3-specific inhibitor tofacitinib has shown clinical efficacy in a small series of refractory T-cell LGL leukaemia patients with associated rheumatoid arthritis.<sup>19</sup> Ruxolitinib, a JAK1 and JAK2 inhibitor, was initially developed to treat *JAK2*-mutated myeloproliferative neoplasms and graft-versus-host disease.<sup>20,21</sup> We and others have previously reported the efficacy of ruxolitinib in LGL leukaemia through seven clinical observations.<sup>22,23</sup> Here, the efficacy and safety profile of ruxolitinib are reported in a series of 21 R/R LGL leukaemia patients treated in a compassionate protocol.

## METHODS

### Study population

This multicentre international retrospective study included 21 consecutive adult patients who received ruxolitinib for R/R LGL leukaemia. Ruxolitinib compassionate use was granted due to relapsed/refractory disease without any suitable therapeutic option available. Patients had been previously treated with at least one drug among cyclophosphamide, methotrexate or ciclosporin in 10 French hospitals, one Argentinian and one Swedish centre. The study was approved by the Rennes University Hospital ethics committee, and all patients provided informed consent.

### Response assessment

Treatment response was assessed through clinical examination, full blood count and LGL number assessment in both flow cytometry and *STAT3*-targeted digital polymerase chain reaction (PCR). Complete remission (CR) was defined as the resolution of initial symptoms and complete normalization of blood counts (haemoglobin [Hb]  $\geq 12$  g/dL, absolute neutrophil count [ANC]  $\geq 1.5 \times 10^9$ /L, platelet count  $\geq 150 \times 10^9$ /L and the absence of circulating LGLs). Haematological partial response (PR) was defined as an improvement in blood counts that did not meet the criteria for CR in two different situations. First, in case of previous neutropenia, PR was considered for an ANC increase of more than 50% from baseline, reaching at least  $0.5 \times 10^9$ /L but lower than  $1.5 \times 10^9$ /L with no recurrence of infections. Second, PR was reached, in case of previous anaemia, for an increase in Hb of more than 2 g/dL from baseline but still lower than 12 g/dL, without transfusion requirement. ORR was defined as the sum of patients in CR or PR. Progressive disease was defined as the worsening of cytopenia, organomegaly or an increased incidence of infections related to persistent neutropenia, regardless of the severity.

### Flow cytometry

LGL quantification was performed by flow cytometry on a BD FACSLyric™ Lyric instrument (BD Biosciences, Franklin Lakes, NJ), with a T-cell panel including the cytotoxic markers CD16, CD56 and CD57, as well as the V-beta T-cell receptor (TCR) repertoire (IOTest Beta Mark Kit, Beckman Coulter, Miami, FL).

### Molecular analysis

We sequenced a 74-gene panel on diagnostic samples and at follow-up when available molecular targets were identified. Libraries were generated in duplicate from 125 ng of DNA. Targeted regions were amplified using the Advanta NGS Library Prep reagents on the 48.48 Integrated Fluidic Circuit loaded in the Juno system (Standard Biotech, San Francisco, CA), then sequenced on a NextSeq550 system (Illumina, San Diego, CA). The data were analysed with an in-house bioinformatic pipeline. Non-synonymous variants with an allelic frequency above 2%, not recognized as a polymorphism (MAF  $< 0.1$  in gnomad database), were investigated in this study.

Furthermore, the level of *STAT3* mutation allelic fraction was assessed by double drop-off digital PCR.<sup>24</sup> Briefly, 20 ng of DNA were added to Naica PCR mix (Stilla Technologies, Villejuif, France), primers and two fluorescent probes designed for the detection of Y640 and D661 hotspots, then loaded in a Sapphire chip (Stilla Technologies). Partitioning and amplification were performed on the Geode instrument.

Then, the chip was read on a Naica Prism6 system with Crystal Minner software (Stilla Technologies).

## Statistical analyses

Comparisons of biological data between time points were performed using paired Wilcoxon tests or Fisher exact test. Survivals were estimated using the log rank test with Kaplan–Meier graphical representations. Progression-free (PFS) and overall (OS) survivals were both calculated from the day of ruxolitinib treatment initiation, to relapse, death or date of last follow-up for PFS, and to death or date of last follow-up for OS. Statistical analyses used the Medcalc software (Ostend, Belgium). *p* values lower than 0.05 were considered statistically significant.

## RESULTS

### Patient characteristics

Twenty-one patients were identified with R/R LGL leukaemia in the participating hospitals in France (*n* = 17), Argentina (*n* = 3) and Sweden (*n* = 1). All the patients fulfilled the diagnosis criteria for LGL leukaemia.<sup>3</sup> The main patient characteristics at diagnosis are indicated in Table S1. Eleven men and ten women were included, with a median age of 60 years [interquartile range (IQR): 46–63]. Eighteen patients (86%) presented with T-LGL leukaemia and three with NK-LGL leukaemia. At diagnosis, splenomegaly was detected in nine patients. None of the patients had rheumatoid arthritis, while one had a Sjögren syndrome. Among the 18 patients with available absolute LGL counts, the median value was  $0.93 \times 10^9/L$  [0.31–6.02]. Six patients had an LGL count lower than the  $0.5 \times 10^9/L$  threshold, but were classified as LGL leukaemia due to the presence of cytopenia with TCR clonality and/or *STAT3* mutation, in the absence of an alternative diagnosis. Neutropenia was observed in 18 patients (86%), including eight patients with severe neutropenia (ANC  $< 0.5 \times 10^9/L$ ) (38%) and seven who experienced recurrent infections (33%). The median ANC was  $0.67 \times 10^9/L$  [0.18–0.90]. Anaemia, defined as Hb  $< 11.5$  g/dL, was present in five patients, three of them being transfusion-dependent. The median Hb level was 12.0 g/dL [11.3–13.4]. Ten patients had thrombocytopenia below  $150 \times 10^9/L$ , while the median platelet count was  $140 \times 10^9/L$  [72–247].

Ruxolitinib treatment was initiated with a median time of 29 months [19–88] and 25 months [13.4–79] after diagnosis and first-line treatment respectively. The median number of previous lines of treatment was 3 (range 1–6) and included a variety of schedules (Figure 1; Table S2). Cyclophosphamide, methotrexate and ciclosporin were given to 12 (57%), 14 (67%) and 18 (86%) patients respectively. Of note, 10 patients (48%) were refractory to the three immunosuppressive drugs at the time of ruxolitinib initiation. Other therapeutic agents given before ruxolitinib included cladribine, pentostatin,

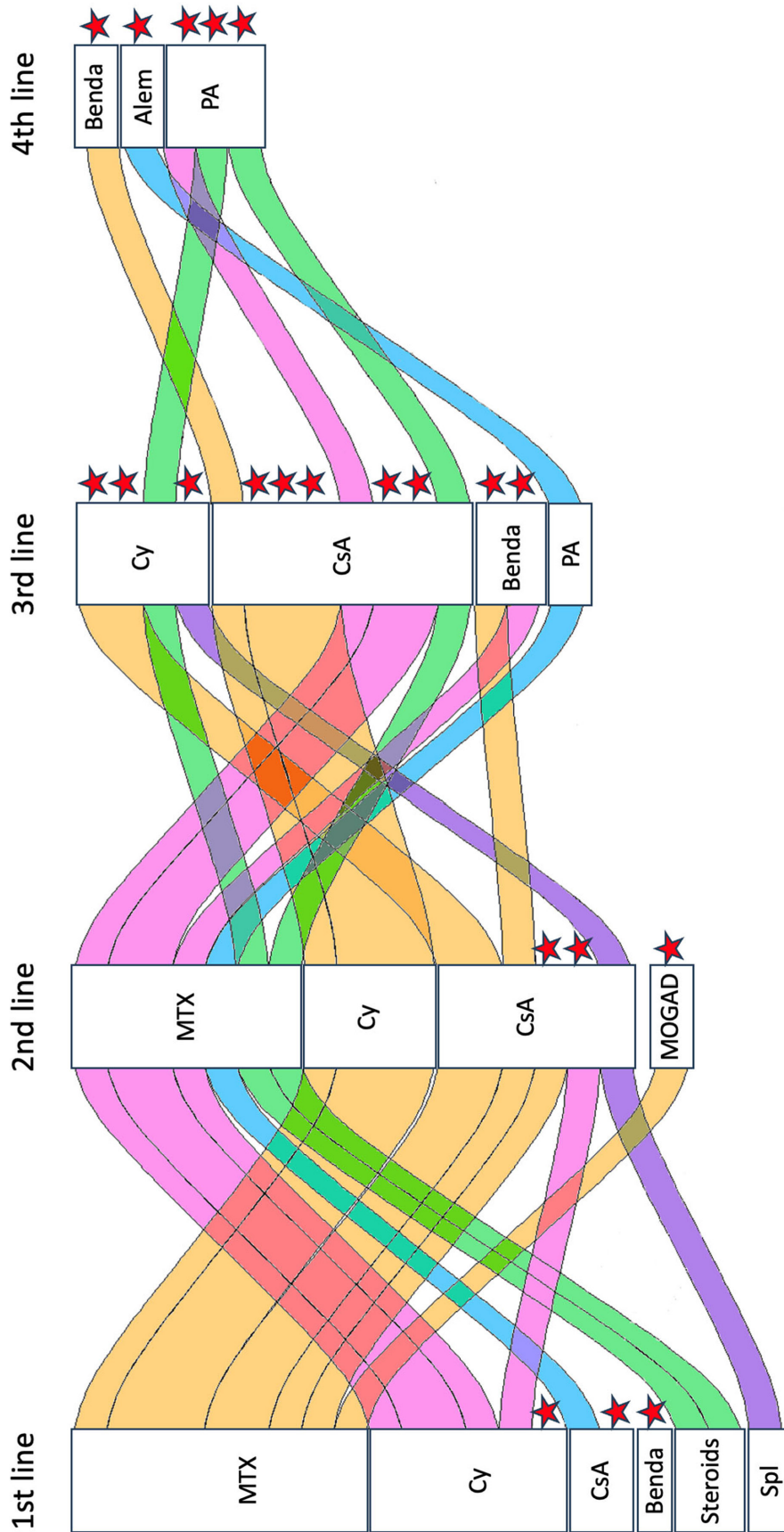
bendamustine, corticosteroids, erythropoietin, granulocyte-stimulating factors and polychemotherapy. The best response to first-line treatment was CR for three patients and PR for another three. Fourteen patients showed no response or progress. Patient characteristics at inclusion for ruxolitinib therapy are indicated in Table 1. Compared to diagnosis, the median lymphocyte count was significantly lower at that time ( $1.10 \times 10^9/L$ , [0.81–1.82], *p* = 0.006), with median absolute LGL counts, available for comparison in 10 patients, of  $0.70 \times 10^9/L$  ([0.15–1.74], *p* = 0.02). Haemoglobin levels were significantly lower (9.9 g/dL, [8.8–11.4], *p* = 0.016). Median ANC ( $0.44 \times 10^9/L$ , [0.11–0.81], NS) and platelets ( $145 \times 10^9/L$ , [72–247], NS) were not significantly different from diagnosis. Clinical features had worsened, with hepatomegaly reported in six patients (28.6%), B symptoms in 5 (23.8%) and infections in 10 (47.6%). Mutational status, obtained for 17 patients, evidenced mutations of *STAT3* in 14 patients (82%), of *STAT5B* in one patient (6%), of *TNFAIP* and *SETD2* in two patients each (12%) and of *DNMT3A* and *IDH2* in one patient each (6%). Most patients (*n* = 13) received the drug at 15 mg twice daily (bid), while other dosages were 10 mg bid (*n* = 3), 20 mg once a day (*n* = 2) and 20 mg bid (*n* = 2). A dose increase from 20 mg to 40 mg was proposed to one patient. Ruxolitinib was given for a median duration of 7 months [1–56]. Ruxolitinib was pursued until progression or unacceptable toxicity. The drug was not restarted in the event of a relapse.

### Efficacy of ruxolitinib

The ORR for ruxolitinib therapy was 85.7%. Fifteen patients reached PR (71.4%) and 3 CR (14.3%). Only three patients (14.3%) remained refractory. The median time to response was 3.5 months, ranging from 1 to 21 months. Notably, among the 11 patients with LGL leukaemia refractory to immunosuppressive drugs, the ORR was 73%, with one patient reaching CR and eight reaching PR. The ORR was 86.7% in patients with the *STAT3/STAT5b* mutation, with 2/15 and 11/15 reaching CR and PR respectively.

Ruxolitinib was associated with a significant improvement in haemoglobin level, ANC count and platelet count (Figure 2; Table S3). The best median haemoglobin level was 11.9 g/dL [10.4–12.7] compared with 9.8 g/dL [8.7–11.3] (*p* = 0.02), the ANC count reached  $1.30 \times 10^9/L$  [0.88–2.45] compared with  $0.44 \times 10^9/L$  [0.11–0.81] (*p* = 0.002) and the platelet count was  $203 \times 10^9/L$  [109–281] compared with  $145 \times 10^9/L$  [56.7–191] (*p* = 0.004) before ruxolitinib treatment. However, lymphocyte counts, although much less dispersed, did not differ significantly ( $1.5 \times 10^9/L$ , [1.0–2.84], *p* = 0.33). Importantly, among the eight transfusion-dependent patients, five patients (62%) became transfusion-independent. It is noteworthy that, neutropenia showed significant improvement (*p* = 0.007) compared to diagnostic parameters, while lymphocyte counts were lower (*p* = 0.007).

To evaluate the specific anti-tumoral effect of ruxolitinib on LGL, 22 samples were collected at treatment initiation



**FIGURE 1** Alluvial chart of consecutive treatment lines before ruxolitinib. Red stars show ruxolitinib initiation. Alem, alemtuzumab; Benda, bendamustine; Cs, ciclosporin; Cy, cyclophosphamide; MOGAD: polychemotherapy (MTX, oxaliplatin, gemcitabine, asparaginase, dexamethasone); MTX, methotrexate; PA, purine analogues; Spl, splenectomy; Steroids, corticosteroids.



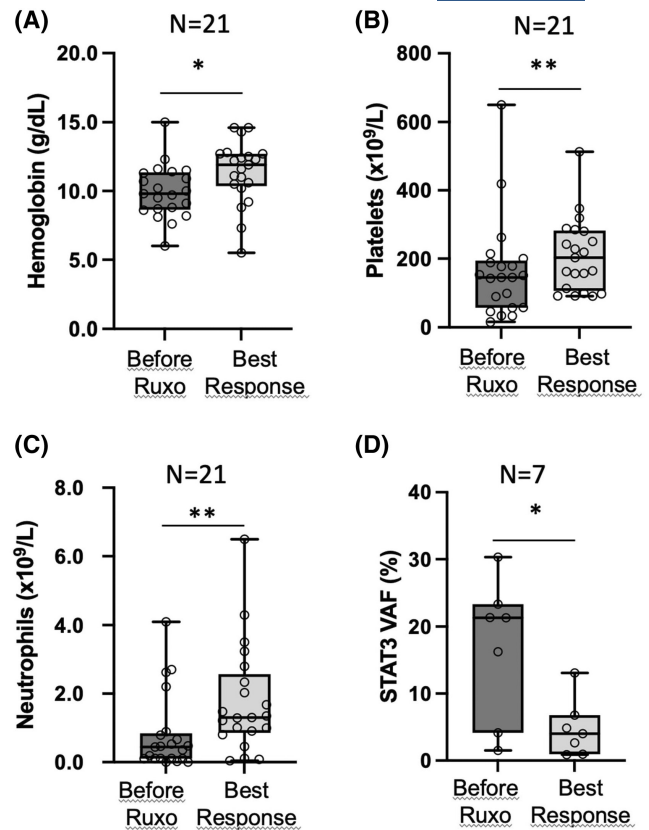
**TABLE 1** Patient characteristics at ruxolitinib initiation.

Variable	N=21
Age (years)	64.4 [51.5–70]
Time from diagnosis to ruxolitinib (months)	29 [18.7–87.5]
Time from first line (months)	24.7 [13.4–79]
Blood parameters	
Haemoglobin level (g/dL)	9.8 [8.7–11.3]
Transfusion dependency	8 (38%)
Platelet count ( $10^9/L$ )	145 [57–191]
Absolute neutrophil count ( $10^9/L$ )	0.44 [0.11–0.81]
Lymphocyte count ( $10^9/L$ )	1.10 [0.81–1.82]
Mutations, N (%/tested)	
STAT3	14 (82%)
STAT5	1 (6%)
TNFAIP	2 (12%)
SETD2	2 (12%)
IDH2 R140Q	1 (6%)
DNMT3A	1 (6%)
No molecular analysis performed	4 (24%)
Clinical parameters	
Splenomegaly, N (%)	9 (43%)
Hepatomegaly, N (%)	7 (33%)
B symptoms, N (%)	6 (28%)
Infections, N (%)	10 (48%)
Associated autoimmune disease, N (%)	1 (5%)
Prior therapy (median 3 lines; range 1–6)	
Cyclophosphamide (Cy), N (%)	13 (62%)
Methotrexate (MTX), N (%)	15 (71%)
Ciclosporin (Cs), N (%)	19 (90%)
Failure to Cy, MTX and Cs, N (%)	11 (52%)
Cladribine, N (%)	3 (14%)
Bendamustine, N (%)	4 (19%)
Corticosteroids, N (%)	3 (14%)
Erythropoietin, N (%)	3 (14%)
G-CSF, N (%)	3 (14%)
Polychemotherapy, N (%)	1 (5%)

Note: Continuous variable are reported as median [interquartile range]; discrete or qualitative variables as number of cases (percentage among tested cases).

( $n=7$ ) and after ruxolitinib ( $n=15$ ), and analysed by digital PCR. The median allelic frequency of STAT3 before ruxolitinib initiation was 21.3% (range 1.5–30.3) and dropped down to 4.1% (range 0.9–13.1) at best response (Figure 2D). No complete molecular response was observed, but three patients showed a reduction of the STAT3 burden to below 1%.

After a median follow-up of 9 months [6–22] since ruxolitinib initiation, 18 patients responded to treatment. However, 10 of these patients relapsed, five died and only two remained in CR. The median duration of response was 4 months (range: 1–52). The three non-responders are still alive. PFS and OS survival curves are shown in Figure 3A,B



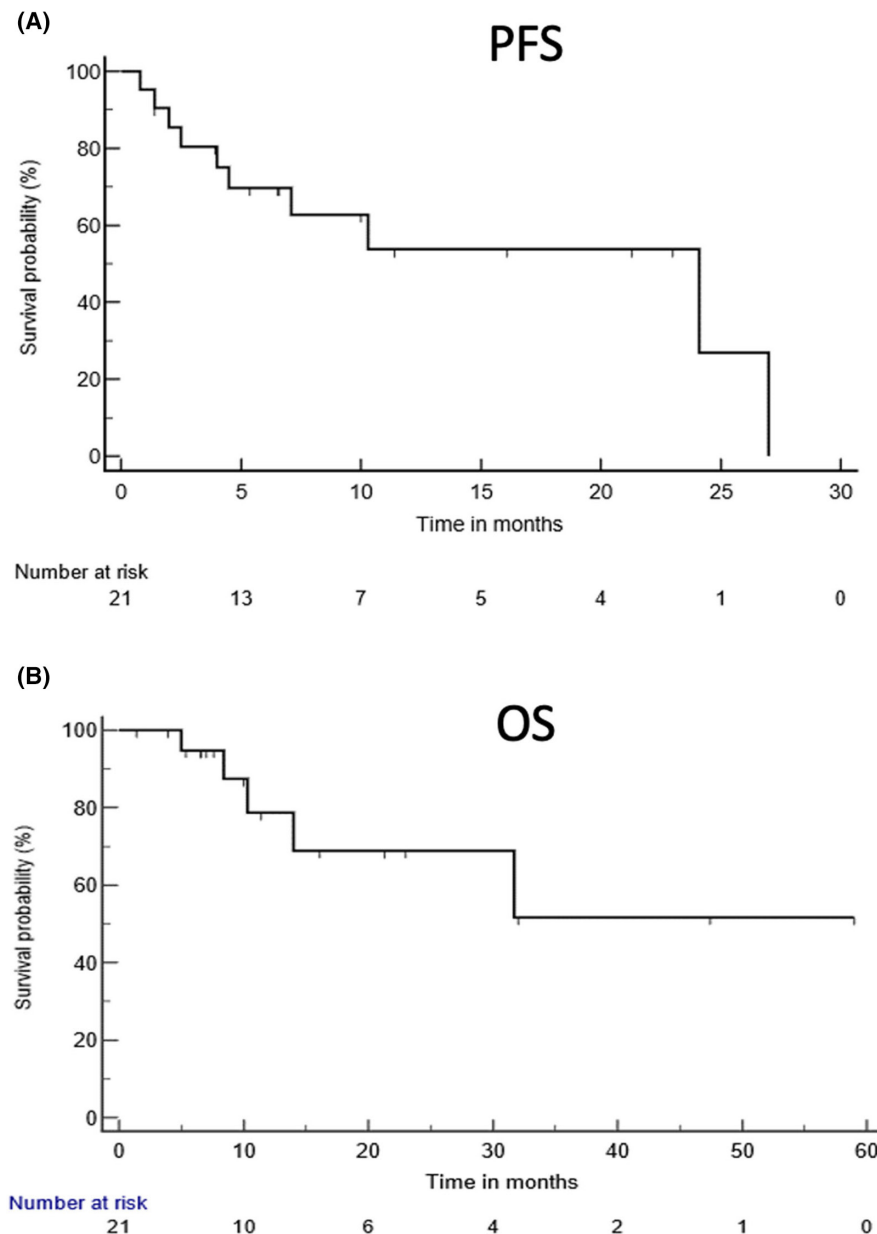
**FIGURE 2** Efficacy of ruxolitinib treatment on blood parameters and on large granular lymphocytic clone. Evolution of (A) haemoglobin (g/dL), (B) platelets ( $10^9/L$ ) and (C) neutrophils ( $10^9/L$ ), at the time of ruxolitinib initiation (dark plots) and at the time of best response after ruxolitinib (light plots). (D) Evolution of STAT3 variant allele frequency before and after ruxolitinib in seven patients. Wilcoxon paired  $t$ -test ( $*p < 0.05$ ,  $**p < 0.01$ ).

respectively. The median PFS was 24.1 months (95% confidence interval [CI] 4–27), with a 1-year PFS of  $53.8\% \pm 12.9\%$ . The median OS has not been reached, with a 1-year OS of  $78.7\% \pm 11.0\%$ . A separate analysis was conducted on the 14 patients with mutated STAT3, revealing a slightly higher median PFS compared to the 3 STAT3<sup>wt</sup> patients (27 months, CI not reached) and a 100% OS ( $p = ns$ ).

Among the 10 patients who experienced relapse after ruxolitinib, four died, three of them from infections, including one sepsis, following allogeneic stem cell transplantation. One additional patient died because of a progressive disease associated with an infection. Among the six remaining patients who experienced relapse, three were switched to azacitidine, one received a thrombopoietin agonist and G-CSF and one is currently treated with tofacitinib.

## Safety

Six patients (30%) experienced side effects while on ruxolitinib. Fatigue was the most frequent side effect, reported in three patients (15%). Musculoskeletal pain was reported in two patients. Gastrointestinal disorders, headache and



**FIGURE 3** Outcomes of large granular lymphocytic leukaemia patients treated with ruxolitinib. (A) Progression-free survival. (B) Overall survival.

cholangitis were less frequent, reported in one patient each. Infections, including one VZV reactivation, occurred in six patients (30%), all but one in those with pre-existing neutropenia. Only one patient had to stop ruxolitinib prematurely because of an adverse reaction (extreme fatigue). Only one patient died while still on ruxolitinib. This patient was admitted to the hospital with respiratory distress associated with significant ascites and, in the end, cardiorespiratory arrest. The death was not considered to be related to ruxolitinib.

## DISCUSSION

Advances in the understanding of LGL leukaemia pathogenesis and the identification of recurrent mutations have

opened the way to the development of targeted therapy for this condition.<sup>16</sup> Of particular interest are mutations affecting directly or indirectly the JAK-STAT pathway. Indeed, hyper-activation of JAK-STAT signalling has been observed in the vast majority of LGL leukaemia patients. Moreover, inhibition of STAT3 using different therapeutic compounds has been shown to restore apoptosis in vitro.<sup>25,26</sup> Therefore, ruxolitinib, a potent orally available JAK1 and JAK2 inhibitor with a well-known safety profile, represents a promising option in this disease. With a median of 3 previous lines and 50% of the cohort refractory to the three immunosuppressive drugs classically used in LGL leukaemia, patients included in the present study were highly pretreated. Response rates observed in this situation with conventional approaches rarely exceed 50%.<sup>6,27</sup> Indeed, even if LGL leukaemia is

characterized by an indolent evolution, the prognosis for relapsed/refractory patients remains poor. The results obtained with ruxolitinib show an ORR of 85.7%, which is remarkably high. Only three patients (14%) were refractory to this treatment. This response rate is higher than that reported in a prospective ECOG study where cyclophosphamide, proposed as a second-line treatment in patients refractory to methotrexate, yielded an ORR of 64%.<sup>28</sup> Here, ruxolitinib was effective on all blood parameters, and responses were obtained in less than 3 months in 13/18 responding patients (72%). However, it is worth mentioning that, as observed in other indications such as graft-versus-host disease, late responses were observed in two patients who reached CR after 12 and 21 months following ruxolitinib initiation.<sup>21</sup> This suggests that, in the absence of toxicity or progression, ruxolitinib treatment should be pursued for at least several months before considering a patient refractory. None of the three CR patients relapsed, as opposed to 10 patients out of 15 partial responders. It can be speculated that these relapses were in part the consequence of subclonal evolution, since clonal heterogeneity has been recently highlighted in LGL leukaemia.<sup>29</sup> The good response rate observed in our cohort compares favourably with results recently reported in a series of 20 evaluable patients with R/R LGL proliferation who received ruxolitinib 20 mg bid after a median number of 2 previous lines of therapy.<sup>30</sup> In this series, five reached CR and six PR, while four remained in stable disease (ORR 55%) and five progressed. Notably, in the Moskowitz study, only 54% of patients were found to have a mutation in the STAT3 gene, compared to 82% of patients in our study with available mutation profiles. This discrepancy in STAT3 mutation frequency could potentially explain the difference in treatment response observed between the two studies. Due to the retrospective nature of our study, we cannot rule out the possibility that this difference in response is related to selection bias.

STAT3 gain-of-function mutations are found in 30%–60% of patients with NK or T-LGL leukaemia, respectively, at diagnosis. The differences in STAT3 mutation frequency reported across the studies are related to the selection criteria of LGL cohorts, to the timing between diagnosis and genomic analysis, and to the sensitivity of the used techniques, varying from 15% with Sanger sequencing to less than 1% with high-throughput sequencing or digital PCR. Interestingly, we observed a higher proportion of STAT3 mutation in our cohort. Of the 17 patients with a molecular testing available in this series, 14 patients (82%) carried a STAT3 mutation, suggesting that most patients with R/R LGL leukaemia are mutated for the STAT3 gene. This offers the opportunity to track the leukaemic clone with sensitive techniques such as digital PCR or flow cytometry, positioned as reference tools for MRD evaluation in this new area of targeted therapy for LGL leukaemia. In our cohort, the STAT3 mutation was associated with a slightly better survival as compared to that observed in STAT3<sup>wt</sup> patients, with a median PFS of 27 months (CI not reached) and a 100% OS. This observation is consistent with the series

reported by Moskowitz et al. in which the STAT3 mutation status was associated with a better event-free survival (14-month EFS 100% vs. 40%,  $p=0.007$ ).<sup>30</sup> These authors suggested that activation of the JAK/STAT pathway in LGL leukaemia could be responsible for a paracrine myelosuppression efficiently cancelled by ruxolitinib. The authors found that the clinical improvement in patients with T-LGL was associated with a significant reduction in the number of circulating myeloid cells, a significant downregulation of the JAK–STAT signalling pathway in myeloid cells, and a decreased production of several myeloid-derived cytokines such as CXCL9, CXCL10 and CCL19. In line with this hypothesis, an improvement in ANC was observed in our cohort after treatment. Further studies are required to better characterize the mechanism of action of ruxolitinib in LGL leukaemia. The ongoing phase II study (NCT05592015) will provide additional information on the optimal dosage and mechanism of action of the drug in this context. Ruxolitinib was well tolerated, with only one patient discontinuing the treatment because of side effects. This contrasts sharply with the therapeutic strategy generally proposed in this setting, including splenectomy, purine analogues or alemtuzumab.<sup>8–11,19</sup> These agents are associated with potentially lethal neurotoxicity, nephrotoxicity and severe opportunistic infections, which limit their use in an indolent disease.<sup>31–33</sup> Additionally, even if high response rates have been reported, caution is needed since most data are issued from case reports and small-sized series.<sup>34–36</sup>

Targeted therapy for R/R LGL leukaemia will have to be clarified in the future.<sup>37</sup> Tofacitinib, a JAK3 inhibitor, has been proposed in refractory LGL leukaemia associated with rheumatoid arthritis, with some haematological responses.<sup>19</sup> However, cardiovascular and cancer risks associated with this drug are likely to limit its use.<sup>38,39</sup> Inhibition of cytokines such as IL-15, which are involved in LGL leukaemia clonal expansion, is an interesting option, as recently shown with BNZ-1, a peptide specifically inhibiting IL-15 and other gamma chain cytokines binding to their cellular receptor.<sup>40,41</sup> However, the reported ORR with this drug used as monotherapy was only 20%. Targeting the CD94 lectin is currently being tested in a clinical trial (NCT05475925). Another phase Ia/Ib trial is testing a STAT3 degrader, KT-333 (NCT05225584). Given the excellent safety profile of ruxolitinib, therapeutic associations could be considered with immunosuppressive or hypomethylating agents. In fact, since several mutations affecting epigenetic mechanisms have recently been reported, orally available azacitidine could represent a promising candidate with an ongoing study (NCT05141682).<sup>15–17,42,43</sup> A phase II clinical trial evaluating ruxolitinib in R/R LGL leukaemia is ongoing (NCT05592015).

## CONCLUSION

Despite the well-demonstrated role of the JAK–STAT pathway in LGL leukaemia, there is limited literature regarding



the efficacy and safety profile of ruxolitinib in this rare disease. In the present study, ruxolitinib in monotherapy led to a high remission rate in highly pretreated R/R LGL leukaemia patients, paving the way for prospective studies as the one currently recruiting.

## AUTHOR CONTRIBUTIONS

TM and TL designed the study, enrolled patients, analysed the data and wrote the manuscript. CP performed molecular analyses. GD, AL, CH, AM, MP, AP, AB, ME, VL, PL, AS, CN, MO and JP enrolled patients and provided data. All authors approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data from this study will be provided upon reasonable request to the corresponding author.

## ETHICS STATEMENT

The study was approved by the Rennes University Hospital ethic committee.

## PATIENT CONSENT STATEMENT

All patients provided informed consent.


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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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