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Title page

Title: Rituximab for rheumatoid arthritis-associated large granular lymphocytic leukemia, a retrospective case series.

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Highlights

- 1°. Rituximab is effective and safe in RA-associated LGLL.
- 2°. Repeated rituximab infusion seems to be effective in LGLL relapse.
- 3°. Potentials mechanisms include: decreased inflammatory cytokine production, reduced T-cell stimulation and direct T-cell depletion.

Abstract:

Objectives: To assess the efficacy and tolerance profile of rituximab in rheumatoid arthritis (RA)-associated large granular lymphocyte leukemia (LGLL).

Methods: Multicenter retrospective case series. Inclusion criteria were RA defined by the ACR/EULAR 2010 criteria and LGLL defined by absolute LGL count $\geq 0.3 \times 10^9/L$ with evidence of an expanded clonal LGL population (flow cytometry, TCR- γ polymerase chain reaction, or *Stat3* mutation).

Results: Fourteen patients (10 women, mean age 55.2 ± 14.2 years) included; 13 were seropositive for anti-cyclic citrullinated peptides (n = 11) or rheumatoid factor (n = 10). LGLL diagnosis was made 9.5 [IQR: 3.25;15.5] years after RA diagnosis. Thirteen patients had T-LGLL. Rituximab was the first-line therapy for LGLL for 4 patients. Previous treatment lines included methotrexate (n = 7), cyclophosphamide (n = 2), cyclosporin A (n = 1), or granulocyte colony-stimulating factor (n = 4). Rituximab was used in monotherapy (n = 8) or associated to methotrexate (n = 3), granulocyte colony-stimulating factor (n = 2), or alkylating agents (n = 1). The number of rituximab cycles ranged from 1 to 11 (median 6), with high heterogeneity in dosing regimens. Median duration response after rituximab initiation was 35 [IQR: 23.5;41] months. The overall response rate was 100%: 8 patients experienced complete response (normalization of blood count and $LGL \leq 0.3 \times 10^9/L$) and 6 experienced partial responses (improvement in blood counts without complete normalization). The tolerance profile was good, with no infectious complications.

Conclusion: rituximab appears as a valuable therapeutic option for RA-associated LGLL.

Keywords: Rheumatoid arthritis. Large Granular Lymphocyte Leukemia. Rituximab.

1. Introduction:

Large granular lymphocytic leukemia (LGLL) is a rare mature lymphoproliferative disorder characterized by chronic proliferation of T or NK mature cells with an estimated incidence of 0.72 per 10^7 person-per year [1]. LGLL is frequently asymptomatic but can be responsible for cytopenia and recurrent infections [2] in a third of cases. LGLL can be associated to hematological disorders such as monoclonal gammopathy and to autoimmune disease. Rheumatoid arthritis (RA) is described in up to 30% of LGLL patients [3]; this condition is also called pseudo-Felty syndrome. Indications for LGLL treatment include severe neutropenia (neutrophil $< 0.5 \times 10^9/L$), mild neutropenia with recurrent infections, and associated autoimmune conditions. To date, there has been no large clinical trial for LGLL: as such, immunosuppressive therapy use is based on retrospective series. Methotrexate, cyclophosphamide and cyclosporine A are the most common options, with an overall response rate of 50%, and a complete response (CR) rate ranging from 5 to 33% [4].

Rituximab is a monoclonal antibody targeting CD20 cells, approved for the treatment of [5] with better efficacy in seropositive patients [6]. Seven patients treated by rituximab for RA-associated LGLL experienced significant improvement in blood count and good response for RA [7–10]. These cases reflect noticeable discrepancy between rheumatologists and hematologists or oncologists therapeutic strategy that might be due to the difference in clinical manifestations and treatment indications. The rarity of reported cases contrasts with the wide use of rituximab in RA: therefore, we conducted a nationwide retrospective registry to describe the efficacy and tolerance of rituximab in RA-associated LGLL.

ANC: Absolute Neutrophil Count; CR: complete response; DLBCL: diffuse large B cell lymphoma; DMARD: disease-modifying-anti-rheumatic-drug; G-CSF: Granular colony stimulating factor; LGLL: large granular lymphocyte leukemia; PR: partial response; RA: rheumatoid arthritis; TCR: T-cell Receptor; TF: treatment failure; TNF: Tumor Necrosis Factor.

2. Patients and methods:

2.1 Patients:

We conducted a multicenter retrospective case series study. French internal, rheumatology and hematology units were invited to take part in this study with the support of two French scientific medical associations (CRI: Club Rhumatismes et Inflammation, and SNFMI: Société Nationale Française de Médecine Interne).

Inclusion criteria were as follows:

- Age \geq 18 years old;
- A diagnosis of RA according to the ACR/EULAR-2010 criteria [11];
- A diagnosis of LGLL supported by the evidence of an expanded clonal T or NK LGL population, as defined by Lamy et al. [2]: assessed by flow cytometry, TCR- γ polymerase chain reaction, or mutation of *Stat 3*.

2.2 Methods:

Written informed consent was obtained from each patient. We collected the following data from standardized medical forms: age, sex, medical history, disease duration and therapeutic modalities for RA and LGLL, disease course after LGLL treatment, and reported side effects of rituximab use. Data were centrally collected and analyzed by one of the author (HL).

In line with French regulations, ethical approval was obtained from the International Review Board “CPP Sud-Est VI” (ref. 2019/CE44). The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Recommendations.

LGLL hematologic response to therapy was defined according to the review by *Lamy et al* [4] as follows:

- Complete response (CR) fulfilling both criteria:
 - o Complete normalization of blood count: hemoglobin > 120 g/L, platelets > 150 × 10⁹/L, absolute neutrophil count (ANC) > 1.5 × 10⁹/L, lymphocyte count < 4 × 10⁹/L.
 - o Circulating LGL count in the normal range ($\leq 0.3 \times 10^9/L$).
- Partial response (PR): improvement in blood counts not fulfilling the criteria for CR: for example, decrease of red blood cells or platelets transfusion or ANC > 0.5 × 10⁹/L but < 1.5 × 10⁹/L.
- Treatment failure (TF): any response not meeting criteria for CR or PR within 4 months after treatment initiation.
- Progressive disease: worsening of cytopenia or organomegaly despite treatment.

3. Results:

We included 14 patients from four French tertiary medical centers. Their characteristics are shown in Table I. Five of them were included in previous case series [8,12]: we updated the follow-up data for each of them. The male-to-female ratio was 0.4. Mean age was 55.2 ± 14.2 years at RA diagnosis and 64 ± 10.2 years at LGLL diagnosis. LGLL diagnosis was made after RA diagnosis for 13 patients with a median delay of 9.5 [IQR: 3.25;15.5] years.

3.1 RA therapy.

Of the 14 patients, 13 had seropositive RA with elevated rheumatoid factor (n = 10, median 211 Units/mL [IQR: 116;417]) and positive tests for anti-cyclic citrullinated peptides (n = 11, median 338 Units/mL, [IQR: 180;545]). Five patients had positive tests for antinuclear antibodies (> 1/160). Four patients were active smokers and one patient reported excessive alcohol consumption. Four patients had bone erosions at RA diagnosis; and 11 patients received prednisone as first- or second-line therapy. Every patient received at least one conventional

disease-modifying-anti-rheumatic-drug (DMARD), including methotrexate (n = 13), hydroxychloroquine (n = 5), sulfasalazine (n = 5), or leflunomide (n = 4). Six patients received biological DMARDs, including anti-TNF α (n = 5), interleukin-6 receptor antagonist (tocilizumab, n= 1) and interleukin-1 receptor antagonist (anakinra, n = 1). The median number of prior treatment lines before LGLL diagnosis was 3 (minimum 1, maximum 6).

3.2 LGLL therapy before rituximab: table 1.

Thirteen patients exhibited asthenia at LGLL diagnosis; none had organomegaly or recurrent infections. Thirteen had T-LGLL and one patient had NK-LGLL. At LGLL diagnosis, the median absolute LGL count was $1.4 \times 10^9/L$ [IQR: 0.6;2.7] and the median ANC was 0.9 [IQR: 0.6;1.4]. The median number of prior treatment lines before rituximab therapy was 1 (minimum 0, maximum 3). Five patients received rituximab as first-line therapy after LGLL diagnosis. Nine patients received other treatment before rituximab therapy, including methotrexate (n = 8), cyclophosphamide (n = 2), cyclosporin A (n = 1), or granulocyte colony-stimulating factor (n = 4).

3.3 LGLL course under rituximab therapy: table 2.

One patient (patient 1) had a diagnosis of diffuse large B cell lymphoma (DLBCL) 6 years after LGLL diagnosis. She received 6 cycles of chemotherapy: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone every 3 weeks. After 1 cycle, LGL were no longer detectable and CR was achieved after the second cycle.

Two patients who were in CR after cyclophosphamide treatment received rituximab therapy because of high RA activity:

- Patient 2 received rituximab 1 month after cyclophosphamide discontinuation when she was in CR. She received 3 infusions (1 g) every 6 months with no relapse of LGLL.

Because of uncontrolled RA, rituximab was stopped and replaced by etanercept: LGLL relapsed 34 months later (ANC $1.2 \times 10^9/L$ and bone marrow invasion of LGL $\geq 20\%$). She received one more infusion of rituximab and achieved PR 5 months later (no further bone marrow exploration was performed).

- Patient 3 was previously treated with methotrexate (with PR) and cyclophosphamide (with CR). She received 5 infusions of rituximab in monotherapy and showed CR for 52 months. Twenty-two months after the last rituximab infusion, LGLL relapsed: she received two more rituximab infusions and experienced PR.

Six patients were in PR after methotrexate therapy when rituximab was initiated. Median LGL count before rituximab was $0.65 \times 10^9/L$ [0.6;1.6] (range $0.09-3.6 \times 10^9/L$) and median ANC was $1.15 \times 10^9/L$ [0.54;1.35].

- Patient 4 was receiving methotrexate monotherapy. Rituximab was initiated because RA and LGLL were not controlled while methotrexate was discontinued. He received 3 cycles of rituximab and showed CR for 14 months. He relapsed 8 months after the third infusion and received two more infusions, but ANC remained below $0.5 \times 10^9/L$; as RA activity was low, he received no more treatment until June 2019 when his RA relapsed. After a multidisciplinary team meeting, he received an infusion of twice 1000 mg rituximab and weekly infusions of G-CSF and experienced PR again.
- Four patients were receiving methotrexate associated to G-CSF. Rituximab was initiated because of persistent neutropenia while RA activity was low. G-CSF was discontinued for every patient. Responses to rituximab therapy were as follows:
 - o PR for patient 5 who received 7 infusions of rituximab. LGL were in the normal range ($0.3 \times 10^9/L$) but she remained mildly neutropenic (ANC $0.58 \times 10^9/L$) even after G-CSF infusions weekly after the 4th cycle of rituximab.

- CR for patients 6, 7, and 8 after 1 to 4 cycles of rituximab. The response duration ranged from 21 to 41 months.
- Patient 9 was previously treated with methotrexate (NR), cyclosporine A (PR), and G-CSF (PR). She received 2 infusions of rituximab and showed CR but relapsed 3 years after the second infusion. After two more cycles of rituximab, she again showed CR.

Five patients received rituximab as first-line therapy for LGLL with no additional treatment.

- Three patients (10, 11 and 12) showed CR. They received one to six cycles of rituximab therapy. The response duration ranged from 7 to 36 months..
- Two patients showed PR. They received 6 (patient 13) and 3 (patient 14) cycles of rituximab therapy. Response duration was 54 and 12 months respectively.

4. Discussion:

We report here the largest case series to date of patients suffering from RA-associated LGLL who received rituximab therapy. Due to its retrospective design, our population was heterogeneous. However, a controlled trial appears to be inappropriate in such a rare disease (annual incidence of 0.2 per 1 000 000 individuals [13]). We report an excellent response rate with good tolerance profile, but these data should be interpreted cautiously because of the short follow-up for some patients.

Although the use of rituximab in LGLL might appear counterintuitive, evidence of rituximab's effects on T-cell functions is increasing. The first step of LGLL pathogenesis could be the activation and proliferation of an oligoclonal population of large granular lymphocytes (LGL) after antigen stimulation. This step requires STAT3 activation [2], which is dependent on interleukin-10, whose production might be reduced with rituximab treatment [14]. This shift from oligoclonal to monoclonal dominance is supported by swift modifications in T-cell repertoires in patients with T-LGLL [15]. However, this step occurs at a very early stage in

LGLL pathogenesis, and thus, it cannot be the central mechanism underlying rituximab efficacy: indeed, in clonal LGL populations, STAT3 is constitutively activated. Rituximab treatment was shown to be associated with reduced T-cell activation and reduced T-cell responsiveness to professional antigen-presenting cells (dendritic cells). Furthermore, B cells also act as efficient antigen-presenting cells and play a crucial role in initiating antigen-specific CD4+ T-cell responses [16]. Indeed, in patients with RA, repeated rituximab infusions reduced the number of CD4+ T-cells [17] and induced the depletion of functionally active CD20+ T cells [18]. Finally, rituximab impaired antigen presentation, due to B-cell depletion; this might have contributed to the polarization of T cells toward the regulatory phenotype observed with the rituximab regimen [19]. Interestingly, discontinuation of rituximab therapy restores normal proliferation and stimulation of T cells: this could explain the relapses observed in our case series. Nevertheless, the exact mechanism of rituximab efficacy in LGLL currently remains unclear and will require further investigation.

Only one patient (patient 14) was seronegative in our case series. This woman received successive sulfasalazine, methotrexate, and anti-TNF α treatments over a period of 24 years after the RA diagnosis, before LGLL was diagnosed. She received rituximab as the first-line treatment, experienced PR in LGLL, and achieved low RA disease activity. The RA diagnosis could be questioned: she fulfilled the ACR/EULAR criteria for RA, because she experienced numerous simultaneous synovitis but she did not display joint erosions. Information on the level of anti-carbamylated antibodies could have strengthened the diagnosis [20]. Additionally, both the achievement of low RA activity and the PR of LGLL were particularly interesting: indeed, it has been shown that rituximab was more effective in patients with seropositive RA [6]. The definitive LGLL diagnosis for this patient was strongly supported by the flow cytometry results and the TCR γ rearrangement. These observations suggested that part of the mechanism that underlies rituximab efficacy in LGLL might also underlie its efficacy in seronegative RA.

Our report suggests that rituximab might be effective in RA-associated LGLL, both as an initial treatment and after conventional LGLL (cyclophosphamide or methotrexate) treatment. Given the wide interest in rituximab as a biological DMARD and its good tolerance profile, we suggest it could be a reasonable option before treatment with cyclophosphamide or cyclosporin A in RA-associated LGLL.

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Table 1: Patients baseline characteristics.

Sex and age at RA diagnosis (y) ⁽¹⁾		ACPA/RF	Bone erosion	RA duration at LGLL diagnosis (year)	LGLL characterization	LGL count at LGLL diagnosis	ANC at LGLL diagnosis	Treatment for LGLL before RTX	Hematologic response to treatment
1	Female, 37	+/+	-	9	T LGL: CD3+CD8+CD57+	6.1	0.88	MTX	PR
2	Female, 72	+/+	-	4	T LGL: CD3+CD4+/-CD8-CD57+ TCR γ rearrangement	0.73	0.29	CYC	CR
3	Female, 39	+/+	-	15	T LGL: CD3+CD5+CD8+	0.3	0.25	MTX CYC	PR (hepatic toxicity) CR
4	Male, 37	+/+	+	26	T LGL: CD3+CD8+CD57	ND	0.6	MTX	PR
5	Female, 78	+/-	-	1	T LGL: CD3+CD7+CD56	0.38	0.6	MTX and G-CSF	PR
6	Female, 42	+/+	-	17	T LGL: CD3+CD8+CD57+	5.4	1	MTX and G-CSF	PR (hepatic toxicity)
7 [#]	Female, 78	+/+	+	1	T LGL: CD3+CD8+CD57+	0.6	6.8	MTX and G-CSF	PR
8 [*]	Male, 63	+/+	+	Simultaneous	T LGL: CD3+CD8+CD57+	3.6	1.16	MTX and G-CSF	PR
9 [*]	Female, 65	+/+	-	1	T LGL: CD3+CD8+CD16+	2.4	1.5	MTX CsA G-CSF	NR PR PR
10 [#]	Female, 51	+/+	-	11	T LGL: CD3+CD8+CD56+ TCR γ rearrangement	0.6	0.7	None	
11	Male, 49	-/+	-	10	T LGL: CD3+CD7+CD51 ^{low} /CD5-	1.4	1.6	None	
12	Male, 56	+/+	+	4	T LGL: CD3+CD8+CD56- TCR γ rearrangement	ND	0.27	None	

13 [#]	Female, 53	-/+	-	1	NK LGL: CD4-CD8-CD56+ TCR γ rearrangement	1.4	4.9	None
14	Female, 54	-/-	-	24	T LGL: CD3+CD8+CD57+	1.5	1.1	None

(1) Age at RA diagnosis. DLBCL: diffuse large B-cell lymphoma; LGL: large granular lymphocyte. Treatment: CsA: cyclosporine A; CYC: cyclophosphamide; MTX: methotrexate; RTX, rituximab. Evaluation of response: CR: complete response; NR: no response; PR: partial response. [#] Patients previously described by Verhoeven et al. [8]. * Patients previously described by Cornec et al. [12].

Table 2 Large granular lymphocyte course after rituximab therapy.

Patient	Rituximab schedule	Associated treatment	Hematologic response	Duration of response (months)	Relapse	Relapse treatment	Response after relapse
1	6 cycles of weekly infusions of rituximab 375 mg.m ⁻² associated to chemotherapy	Chemotherapy [†]	CR	37	No		
2	3 infusions of 1000 mg every 6 months	None	CR	34	Yes	One infusion of 1 g	PR, 5 months
3	5 cycles of twice [⊛] 1000 mg every 6 months	None	CR	52	Yes	Twice [⊛] 1000 mg	PR, 3 months
4	3 cycles of twice [⊛] 1000 mg every 6 months	None	CR	14	Yes	Twice [⊛] 1000 mg and G-CSF	PR, 3 months
5	1 infusion of twice [⊛] 1000 mg then 6 infusions of 1000 mg every 6 months	G-CSF after the 4 th infusion	PR	32	No		
6	4 cycles of twice [⊛] 1000 mg; on-demand retreatment [§]	G-CSF stopped after the first infusion	CR	41	No		
7 [#]	3 cycles of twice [⊛] 500 mg; on-demand retreatment [§]	G-CSF stopped after the first infusion	CR	21	No		
8*	11 infusions of 1000 mg; on-demand retreatment [§]	G-CSF stopped after the first infusion	CR	41	No		
9*	4 cycles weekly 375 mg.m ⁻² then 1 infusion of twice [⊛] 1000 mg 2 years later because of RA clinical relapse	G-CSF stopped after the first infusion	CR	63	Yes	Twice [⊛] 500 mg and 1000 mg 14 months later	CR, 45 months
10 [#]	6 cycles of twice [⊛] 1000 mg; on-demand retreatment [§]	None	CR	36	No		
11	1 infusion of twice [⊛] 1000 mg	None	CR	31	No		
12	2 infusions of 1000 mg every 6 months	None	CR	7	No		
13 [#]	6 cycles of twice [⊛] 1000 mg; on-demand retreatment [§]	None	PR	54	No		
14	1 cycle of twice [⊛] 1000 mg then 2 infusions of 1000 mg; on demand retreatment [§]	None	PR	12	No		

Evaluation of response: CR: complete response; NR: no response; PR: partial response. G-CSF: granulocyte colony-stimulating factor. Delay to response is defined as the time between first rituximab infusion and hematologic response (months). Duration of response is defined as the time between treatment response and relapse or last follow-up visit (months).

Patients previously described by Verhoeven et al. [8]. * Patients previously described by Cornec et al. [12].

α chemotherapy: cyclophosphamide, doxorubicin, vincristine, prednisone.

☼ two infusions, on day 0 and day 15.

§ on-demand treatment: patients received rituximab because of rheumatoid arthritis clinical relapse.

Patients previously described by Verhoeven et al. [8]. * Patients previously described by Cornec et al. [12].