

Therapeutic strategies in chronic lymphocytic leukemia: efficacy and safety of zanubrutinib in patients with arrhythmias and hemorrhagic risk. Report of two cases

Estrategias terapéuticas en LLC: eficacia y seguridad de zanubrutinib en pacientes con arritmias y riesgo hemorrágico. Informe de dos casos

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Abstract

The management of chronic lymphocytic leukemia (CLL) has evolved significantly with the introduction of Bruton's tyrosine kinase inhibitors (BTKis). Zanubrutinib, a next-generation BTKi, was engineered to provide greater selectivity and reduce "off-target" effects, owing to its pharmacokinetic/pharmacodynamic profile, which offers an improved safety and efficacy profile. This report presents two illustrative cases from the ALPINE study (NCT03734016), highlighting the safety profile of zanubrutinib in CLL patients with high cardiovascular and bleeding risk. The first, a 67-year-old male with a history of atrial flutter and autoimmune hemolytic anemia, showed a sustained response without recurrence of arrhythmias or significant bleeding events despite baseline hypertension and concomitant medications. The second, a 61-year-old male with Factor V Leiden-associated thrombophilia, previous thrombotic events, and multiple comorbidities, experienced effective control of CLL without hemorrhagic complications after appropriate management of anticoagulant medication. These cases underscore the efficacy and tolerability of next-generation BTKi zanubrutinib, reinforcing its potential as a therapeutic option in complex patients with cardiovascular risk.

Keywords: Chronic lymphocytic leukemia. Safety. Zanubrutinib. Case report. Cardiovascular risk.

Resumen

El manejo de la leucemia linfocítica crónica (LLC) ha cambiado con los inhibidores de la tirosina quinasa de Bruton (BTKi). Zanubrutinib, BTKi de última generación, se diseñó para ser más selectivo y minimizar efectos "off-target"; su perfil farmacocinético/farmacodinámico se traduce en un mejor balance de eficacia y seguridad. En este documento presentamos dos casos del estudio ALPINE (NCT03734016) que ponen de relieve el perfil de seguridad de zanubrutinib en pacientes con LLC y alto riesgo cardiovascular y hemorrágico. El primer caso es el de un varón de 67 años, con aleteo auricular y anemia hemolítica autoinmune, que mantuvo una respuesta clínica sin recurrencia de arritmias ni sangrados relevantes, pese a la hipertensión basal y la medicación concomitante. En el segundo caso se presenta un varón de 61 años con trombofilia por Factor V Leiden, antecedentes trombóticos y múltiples comorbilidades, con control eficaz de la LLC y ausencia de complicaciones hemorrágicas tras un ajuste adecuado de la anticoagulación. Estos casos apoyan la eficacia y la tolerabilidad de zanubrutinib y refuerzan su utilidad como opción terapéutica en pacientes complejos con riesgo cardiovascular.

Palabras clave: Leucemia linfocítica crónica. Seguridad. Zanubrutinib. Informe de casos. Riesgo cardiovascular.

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Introduction

Chronic lymphocytic leukemia (CLL) management has been revolutionized by Bruton's tyrosine kinase inhibitors (BTKis). Zanubrutinib is a potent and highly selective next-generation BTKi, uniquely designed to offer enhanced BTK specificity and potency compared to ibrutinib and acalabrutinib.^{1,2} Its pharmacokinetic/pharmacodynamic (PK/PD) profile, along with its increased selectivity and reduced off-target effects, may account for its distinctive safety profile, which potentially entails a lower risk of cardiovascular disorders compared to earlier agents.³ Here, we discuss its safety profile through two illustrative cases of patients diagnosed with CLL and high-risk cardiovascular factors treated with zanubrutinib from the ALPINE study (NCT03734016). This phase 3 randomized trial that established the superiority of zanubrutinib over ibrutinib in patients with relapsed/refractory CLL and small lymphocytic lymphoma (SLL). A summary of the clinical features of both cases is shown in [table 1](#).

Case 1

A 56-year-old male was diagnosed with CLL in 2008 (Rai A, Binet I), which was associated with autoimmune hemolytic anemia (AIHA). The patient also had a history of hypertension and surgically resolved atrial flutter (AF). After 3 years with a stable white blood cell (WBC) count, no CLL-related symptoms, and a good quality of life, the patient showed a decrease in hemoglobin (Hb) and platelet levels. Computed tomography scan (CT) showed lymphadenopathies up to 30 mm and splenomegaly up to 160 mm. Genetic studies detected *ATM* deletion (11q22) in 90% of the nuclei, unmutated *IGHV*, and no *TP53* gene aberrations. Due to disease progression in 2011, the patient received five cycles of fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy. Despite achieving a complete response, the patient developed a febrile syndrome accompanied by a decline in Hb and platelet levels. After excluding disease progression and treatment-related toxicity, Coombs-negative AIHA was suspected. Empiric steroid therapy was initiated, resulting in a favorable clinical response.

In 2019, at 67 years of age, the patient presented with multiple adenopathies, in addition to splenomegaly of 180 mm. Blood examination showed WBC $345 \times 10^3/\text{mm}^3$ (98% Lym), Hb 5.7 g/dL, and platelets $50,000/\mu\text{L}$. Genetic studies remained unchanged. Given the progression of CLL, the patient was enrolled

in the ALPINE study. He was randomized to receive zanubrutinib 160 mg twice daily (BID), exhibiting a favorable response. After four months of treatment, the patient reported persistent discomfort in the right hypochondrium, and CT showed splenomegaly of 221 mm. Splenic hematoma was diagnosed, and splenectomy was performed due to symptomatic anemia requiring continuous transfusions. The drug was not discontinued, and it remains unclear whether the hematoma had a traumatic origin.

At the latest follow-up in late 2025, the patient remains on zanubrutinib treatment, showing progressive improvement in Hb and platelet levels and a reduction in lymphocyte count, achieving a complete response. Despite the high-risk profile, the recent splenic hematoma, the concomitant use of enalapril and baseline hypertension, the patient did not have bleeding or cardiovascular complications. No arrhythmias or serious infections were observed throughout the entire follow-up period, and no new episodes of hemolysis were reported.

Case 2

A 46-year-old male with a medical history of thrombophilia associated with Factor V Leiden, deep vein thrombosis (DVT), and inguinal adenopathies was diagnosed with CLL. The patient received chemotherapy treatment with fludarabine plus cyclophosphamide. He also underwent anticoagulation therapy, initially with heparin, followed by acenocoumarol for three months. The patient achieved a complete response. At the age of 61, he presented with several comorbidities, including benign prostatic hypertrophy, atherosclerosis, obesity, type 2 diabetes mellitus, and hypertension. He was being treated with metformin, rosuvastatin, enalapril, and diltiazem. The patient also had a history of a new DVT 1 year earlier, which was managed with indefinite oral anticoagulation (acenocoumarol). The blood count showed persistent lymphocytosis (Lym $33 \times 10^3/\text{mm}^3$), with the rest of the parameters showing no significant alterations. Bone marrow aspirate presented an 83% infiltration by CLL. CT showed lymphadenopathy in all areas, including an inguinal node of up to 30 mm, and genetic studies showed deletion of 13q and unmutated *IGHV*, and no *TP53* mutation.

Due to disease progression, the patient was offered to participate in the ALPINE study and randomized to receive zanubrutinib 160 mg BID. Apixaban (5 mg every 12 h) was initiated as an alternative anticoagulant

Table 1. Summary of clinical characteristics and follow-up of cases 1 and 2

Characteristics	Case 1	Case 2
Clinical history	Resolved atrial fibrillation, autoimmune hemolytic anemia episode	Recurrent DVT
Highlighted comorbidities	Hypertension, atrial flutter	Factor V Leiden thrombophilia, type 2 diabetes, hypertension, atherosclerosis, and obesity
Genetic mutations	ATM deletion (90%) Non-mutated IGHV Non-mutated p53 gene variants and del17p	13q deletion Non-mutated IGHV Non-mutated p53 gene variants and del17p
Concomitant treatment	Erythropoietin, allopurinol, and enalapril	Apixaban, metformin, rosuvastatin, and enalapril
Zanubrutinib start date	Jul-2019	Oct-2018
Age at zanubrutinib start	67 years	61 years
Stage at baseline	Rai IV/Binet C	Rai III/Binet B
Analytics at baseline:		
WBC	$346 \times 10^3/\text{mm}^3$	$33 \times 10^6/\text{mm}^3$
Lym	98% ($339 \times 10^3/\text{mm}^3$)	
Hb	5.7 g/dL	13.1 g/dL $120 \times 10^3/\text{mm}^3$
Plt	$50 \times 10^3/\text{mm}^3$ 263U/L (135-250)	Within normal range
LDH	Splenomegaly (180 mm)	No splenomegaly
CT scan	Multiple lymphadenopathies in all areas (up to 30 mm)	Multiple lymphadenopathies in all areas (up to 30 mm)
Analytics at follow-up (to 2023):		
WBC	$33.0 \times 10^3/\text{mm}^3$	$< 5.0 \times 10^3/\text{mm}^3$
Lym	$27.4 \times 10^3/\text{mm}^3$	$1.9 \times 10^3/\text{mm}^3$
Hb	16.2 g/dL	13.5 g/dL
Plt	$219 \times 10^3/\text{mm}^3$	$140 \times 10^3/\text{mm}^3$
CT scan	No lymphadenopathy or splenomegaly	Residual lymph nodes (≤ 16 mm)
Response	Complete remission	Partial remission

ATM: ataxia telangiectasia mutated gene; CT: computerized tomography; DVP: deep vein thrombosis; DVT: deep vein thrombosis; Hb: hemoglobin; IGHV: immunoglobulin heavy-chain variable region gene; Lym: lymphocyte; Plt: platelet cells; WBC: white blood cells.

therapy due to the high risk of bleeding associated with BTKi use and the concomitant administration of cytochrome P450 CYP3A4 inhibitors.

From 2018 to the latest follow-up in 2025, a favorable clinical response to treatment was observed (the adenopathies decreased to a maximum size of 16 mm and Lym under $2 \times 10^3/\text{mm}^3$), despite the patient's poor prognostic profile. Similarly, although the patient had a history of hypertension and other comorbidities, the appropriate management of concomitant medications enabled the patient to remain free from hemorrhagic episodes and cardiovascular complications. No interactions between zanubrutinib and antiplatelet therapy were reported until the end of follow-up. No drug side effects were reported either.

Discussion

The first case describes a 67-year-old male with CLL and a high-risk genetic profile who responded well to zanubrutinib, achieving complete remission without cardiovascular complications despite a medical history of arrhythmia and hypertension. The second case is about a 61-year-old male with CLL and several comorbidities, including hypertension, who experienced a favorable clinical response to zanubrutinib, with no hemorrhagic episodes despite concomitant use of anti-coagulation. Both cases illustrate how zanubrutinib can lead to safe and favorable hematological response in CLL patients with a poor prognostic genetic profile, hazardous comorbidities including cardiovascular and hemorrhagic risks, as well as concomitant treatments

with a substantial potential for drug interactions, upon the implementation of appropriate pharmacological management.

Elderly patients with CLL have an increased risk of hemorrhage, which can potentially increase with BTKi treatment.⁴ In addition, the risk is heightened when BTKis are combined with anticoagulant or antiplatelet drugs.⁴ BTKi-related hemostatic defects involve effects on platelet pathways, including von Willebrand factor-GPIIb and collagen-GPVI, mediated by BTK and TEC inhibition.¹ Other comorbidities such as hypertension and atrial fibrillation (AF) are more common in elderly patients. Furthermore, it is important to note that the management of atrial fibrillation (AF) in CLL patients is complicated by the potential for drug interactions between BTKis and anticoagulants.⁵

Zanubrutinib is a next-generation BTKi designed to maximize BTK occupancy and minimize off-target kinase inhibition.^{1,6} This orally administered drug has demonstrated proven efficacy in CLL, marginal zone lymphoma (MZL), Waldenström's macroglobulinemia (WM), follicular lymphoma (FL), conditions with European Medicines Agency approval, as well as mantle cell lymphoma, which has received approval from the U.S. Food and Drug Administration. Zanubrutinib has demonstrated superior efficacy in relapsed/refractory CLL compared to first-generation BTKi, ibrutinib,^{3,7} maintaining a favorable cardiovascular safety profile.⁸

The greater selectivity of zanubrutinib, as well as its PK/PD profile, translates into clinically impactful benefits, including improved dosing flexibility, safety, and efficacy.^{1,2} Potentially, reduced off-target inhibition of Src-family kinases compared with ibrutinib may contribute to the lower incidence of cardiac arrhythmias observed with zanubrutinib.

Although the literature shows lower TEC inhibition with zanubrutinib,² the rates of major bleeding or any bleeding appear to be similar across covalent BTK inhibitors, with 44.8% any grade and 4% grade ≥ 3 bleeding reported with zanubrutinib treatment in the ALPINE study.³ In other diseases, such as MZL, twenty-three patients (33.8%) were administered concomitant antithrombotic agents during zanubrutinib therapy, with no incidence of major hemorrhage observed.⁸ In addition, in those clinical trials, whether zanubrutinib was compared to other drugs such as bendamustine-rituximab, the inclusion of patients with concurrent use of warfarin was allowed.^{8,9}

Zanubrutinib is the only BTKi that has shown fewer treatment discontinuations due to both disease progression and adverse events in CLL compared to

ibrutinib, as well as a lower incidence of grade 3 AF.^{10,11} In the ALPINE study, after a median follow-up of 42.5 months, zanubrutinib compared with ibrutinib showed lower rates of serious cardiac events (25.9% vs. 35.5%), fatal cardiac events (0% vs. 1.9%), atrial fibrillation (AF) (7.1% vs. 17%), despite similar rates of hypertension (27.2% vs. 25.3%).^{3,7} Furthermore, 6 deaths due to cardiac disorders were reported in patients treated with ibrutinib and none with zanubrutinib.³ The lower incidence of AF with zanubrutinib may reduce the need for anticoagulants, which could aid the pharmacological management to prevent major bleeding complications.^{10,12}

A recent systematic review and network meta-analysis in patients with B-cell malignancies demonstrated that the rates of AF, with zanubrutinib, were low and generally occurred less frequently than with other BTKis.¹³ Another pooled analysis showed that zanubrutinib is a well-tolerated BTKi that causes significantly lower exposure-adjusted incidence rates of AF, hypertension, and ventricular arrhythmias compared to ibrutinib.⁷ Notably, and unlike acalabrutinib, the cumulative AF rate curve for zanubrutinib did not align and exhibits statistically significant divergence from that of ibrutinib.¹⁴

Lastly, both patients have maintained remission after initiating zanubrutinib to the date of this publication, despite high-risk features, including del(11q) and unmutated *IGHV*.¹⁵ These findings align with the overall SEQUOIA and ALPINE trial results, which support that zanubrutinib is a valuable treatment option in both treatment-naïve and relapsed/refractory patients with CLL/SLL.^{8,9}

Conclusion

Effective management of CLL patients with complex baseline profiles due to multiple comorbidities and concomitant medications is needed to facilitate the continuation of therapy and to achieve long-term full benefits of available treatments. Both cases underscore zanubrutinib's efficacy and safety in CLL patients regardless of baseline risk status. Its lower "off-target" adverse event rates make it a compelling choice for patients with cardiovascular and hemorrhagic risks, considering that, in addition, zanubrutinib has proven in the ALPINE trial that efficacy is independent of *IGHV* or other mutational status.

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Conflicts of interest

J. Marquet has received honoraria for participation in sponsored events and/or advisory boards for BeOne and AbbVie. Conference attendance: Janssen, AstraZeneca, BeOne, AbbVie, and Takeda. J. López has received honoraria for participation in sponsored events and/or advisory boards for BeOne, AbbVie, Janssen, AstraZeneca, and Eli Lilly. Research funding: BeOne, Janssen, and AbbVie. S. Moreno has received honoraria for participation in sponsored events and/or advisory boards for: Amgen, Sanofi, AstraZeneca, Novonordisk, and BeOne. Conference attendance: Janssen, AstraZeneca, Novartis, Pfizer, GSK, and BeOne. L.F. Casado has received honoraria for participation in sponsored events and/or advisory boards for: Janssen, Roche, Novartis, BMS, Amgen, Takeda, Pfizer, Incyte, AbbVie, GSK, Sanofi, and BeOne. Research funding: Janssen, Roche, Novartis, BMS, Amgen, Takeda, Pfizer, Incyte, AbbVie, GSK, Sanofi, BeOne, and Loxo.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's

confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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