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RESEARCH LETTER

Safety and effectiveness of the combination of 5-azacitidine and ruxolitinib in VEXAS syndrome: A single-centre experience

To the Editor,

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is an adult-onset haemato-inflammatory disorder caused by somatic mutations in the *UBA1* gene in chromosome X.[1] Clinically, VEXAS syndrome presents a broad-spectrum of autoinflammatory symptoms[1,2] and haematological involvement, with myelodysplastic syndrome (MDS)[3] in up to 50% of patients.[4] The management of VEXAS syndrome remains challenging due to its dual inflammatory and haematological nature. A recently published consensus guidance[5] has provided considerations about VEXAS treatment, including steroid-sparing disease-modifying anti-rheumatic drugs (DMARDs), that are frequently transiently beneficial.[6] Ruxolitinib, a Janus kinase (JAK) 1/2 inhibitor, has shown efficacy in controlling inflammation but does not impact clonal haematopoiesis or disease progression.[7,8] In contrast, 5-azacitidine (AZA), a hypomethylating agent used to treat MDS, targets the clonal myeloid population and has shown promise in VEXAS patients.[9] However, its anti-inflammatory effect typically appears only after the fourth to sixth treatment cycle,[9] so acute inflammation management without increased steroid dependence remains an unmet clinical need. The treatment of refractory patients remains challenging due to uncontrolled inflammation, cytopenias and infections.

This monocentric experience included patients with genetically confirmed VEXAS syndrome and concomitant lower risk MDS, who received standard dose AZA (75 mg/m^2 for 7 non-consecutive days) as a strategy to target the mutated clone, in combination with ruxolitinib as a steroid-sparing approach to control systemic inflammation in steroid-dependent patients who were refractory to previous lines of treatment. Off-label treatment with AZA and ruxolitinib was authorized by the Regional Rare Disease Fund—in the absence of approved therapies and available clinical trials—and initiated following the signing of the informed consent form. Patients received anti-infective prophylaxis with trimethoprim/sulfamethoxazole and acyclovir and vaccinations against Influenza virus, SARS-CoV-2, *Streptococcus pneumoniae* and Varicella-Zoster Virus.

Demographic and clinical data at diagnosis, including sex, age and *UBA1* mutation status, were analysed. Laboratory parameters, including levels of haemoglobin (Hb), platelets (PLT) and C-reactive protein (CRP), were analysed at baseline and during follow-up, specifically prior to the initiation of treatment with either ruxolitinib or AZA and every 3 months following the start of AZA therapy as per our local clinical practice (Table S1). Variant allele frequency (VAF) of *UBA1* mutations was assessed using droplet digital PCR (ddPCR) at baseline and during treatment.[9,10] Criteria for MDS diagnosis and risk stratification and for assessment of responses are discussed in Supporting Information: Methods S1.

Quantitative variables were described as median and interquartile range. Qualitative variables were described as cardinal number and percentage where necessary. Graphical representations were performed using GraphPad Prism version 10.5.0 (GraphPad Software, San Diego, CA, USA).

Four male patients with VEXAS syndrome were included. Median age at VEXAS diagnosis was 70 [67.5–72] years. Clinical and demographic data at baseline are summarized in Table 1. All patients were diagnosed with lower risk MDS. In two cases, the MDS diagnosis preceded that of VEXAS by 3 and 5 years respectively. In the other two cases, MDS was diagnosed subsequently—after 2 months in one case and after 2 years in the other. Cytogenetic and molecular biology data are shown in Table 1.

At the time of ruxolitinib initiation, all patients were on glucocorticoid therapy. Three out of four patients received at least one line of steroid-sparing therapy before ruxolitinib (Table 1). In all patients, ruxolitinib was initiated prior to AZA. The maximum daily dose of ruxolitinib was 25 mg in one patient, 20 mg in two patients and 15 mg in the other patient. One patient experienced a VEXAS syndrome flare during ruxolitinib treatment, which required a transient increase in glucocorticoid dosage, leading to the resolution of symptoms. No clinically significant infections were observed during treatment with ruxolitinib and glucocorticoids.

After a median delay of 109 [90–130] days, AZA was added for a median of 8.5 [5–11.25] cycles. One patient was still receiving AZA at the time of the last follow-up, having completed 11 cycles. One patient completed an initial full cycle of AZA; however, two subsequent cycles were discontinued prematurely due to a twofold event of fever, desaturation and increased CRP levels occurring in the days immediately following AZA therapy, attributed to hypersensitivity pneumonitis probably related to AZA (Naranjo score 5). The remaining two patients discontinued all treatments (AZA, ruxolitinib and steroids) after 12 and 6 cycles, respectively, following the achievement of a complete inflammatory, haematological and

TABLE 1 Main demographic, clinical and haematological features of four patients with VEXAS treated with the combination of 5-AZA and ruxolitinib.

Patient (UPN)	Age at diagnosis (years)	*UBA1* mutation	Inflammatory manifestations at diagnosis	Haematological conditions at start of 5-azacitidine	Karyotype	Concomitant CH mutations (VAF % at first detection)	Previous lines of DMARDs
UPN1	71	Met41Thr	Fever, joint pain, pulmonary infiltrates	MDS-LB (IPSS-R low, IPSS-M moderate-low)	46,XY	None	Anakinra, tocilizumab, ciclosporin, canakinumab
UPN2	66	Met41Val	Fever, joint pain, peri-orbital oedema	MDS-LB (IPSS-R low, IPSS-M moderate-low)	46,XY	*ZRSR2* (3.79%), *DNMT3A* (38%)	Ciclosporin, canakinumab
UPN3	73	Met41Val	Fever, joint pain, ocular involvement	MDS-LB (IPSS-R low, IPSS-M low)	46,XY,t(1;12)(p?22;q?15)	None	None
UPN4	69	Met41Leu	Fever, joint pain, chondritis, skin involvement	MDS-LB (IPSS-R very-low, IPSS-M low)	46,XY	None	Azathioprine

Abbreviations: CH, clonal haematopoiesis; DMARDs, disease-modifying anti-rheumatic drugs; IPSS-M, International Prognostic Scoring System–Molecular; IPSS-R, International Prognostic Scoring System–Revised; MDS-LB, myelodysplastic syndrome with low blasts; p.Met41Leu, methionine on location 41 is substituted by leucine; p.Met41Thr, methionine on location 41 is substituted by threonine; p.Met41Val, methionine on location 41 is substituted by valine; VAF, variant allele frequency.

molecular response. Of note, no cases of VEXAS syndrome flare were reported after the initiation of azacitidine.

Regarding safety, two of four patients experienced a clinically relevant infectious episode during the combined treatment, after one and five cycles respectively. The infectious rate was in keeping with previous data reported for VEXAS patients treated with AZA monotherapy.[9] One case involved febrile neutropenia, which required hospitalization, while the other patient developed upper respiratory tract symptoms, followed by uvular and soft palate oedema treated with antibiotics and increased steroid dose. No events of deep vein thrombosis were observed during the administration of ruxolitinib and/or AZA.

Overall, four of four patients achieved HI-E and transfusion independence after a median time of 19.5 [16.25–22.75] weeks since AZA introduction. Median haemoglobin levels were 104 [94–115] g/L prior to ruxolitinib initiation, 97.5 [89.25–102.5] g/L before AZA and 121.5 [108.5–137.5] g/L at the end of the final AZA cycle (Figure 1A). All four patients achieved HI-P after a median of 9 [6.5–11.5] weeks. Median platelet counts were 64.5 [53–91.5] $\times 10^9$/L before ruxolitinib, 115 [106.25–141.5] $\times 10^9$/L after ruxolitinib but prior to AZA and 166 [141.25–188] $\times 10^9$/L at the end of the last AZA cycle (Figure 1B). Moreover, all patients could successfully reduce their median daily prednisone dose: from 15 [13.8–15.7] mg/day prior to ruxolitinib, to 8.75 [6.9–10.7] mg/day before AZA, to 3.75 [0–8.1] mg/day after the final AZA cycle (Figure 1C). Similarly, CRP levels showed a progressive decrease, from a median value of 2.85 [0.95–30.45] mg/L before ruxolitinib to 1.25 [0.53–4.18] mg/L after the final cycle of AZA (Figure 1D). Longitudinal monitoring of the mutant *UBA1* clones revealed an overall decline in VAF, with three patients achieving a complete molecular response after a median of 6 [4–7] cycles, including two with a VAF below 1% (Figure 1E). The other patient did not show a reduction in *UBA1* VAF and is continuing treatment with azacitidine. In addition to *UBA1*, concurrent myeloid clonal alterations were studied in patients UPN2 and UPN4. The results of these analyses are presented in Figure S1.

None of the patients showed leukaemic transformation and all were alive at the time of last follow-up, with a median follow-up duration of 31.5 [18.6–44.6] months since diagnosis.

This study is the first to focus on the combination of AZA and ruxolitinib in VEXAS syndrome. Despite the small cohort, our clinical and molecular findings provide meaningful insights into the potential of combined haemorheumatological therapy for VEXAS. The biological rationale is supported by emerging evidence that chronic inflammation plays a central role not only in driving systemic manifestations but also in promoting clonal haematopoiesis through sustained stress on the haematopoietic stem cell compartment.[4] Indeed, AZA primarily acts through global DNA hypomethylation, which may modulate the dynamics of the *UBA1*-mutant clone,[11] while ruxolitinib inhibits JAK1/2-mediated cytokine signalling, reducing inflammation.

In our cohort, ruxolitinib was introduced as a steroid-sparing agent to achieve rapid and effective control of

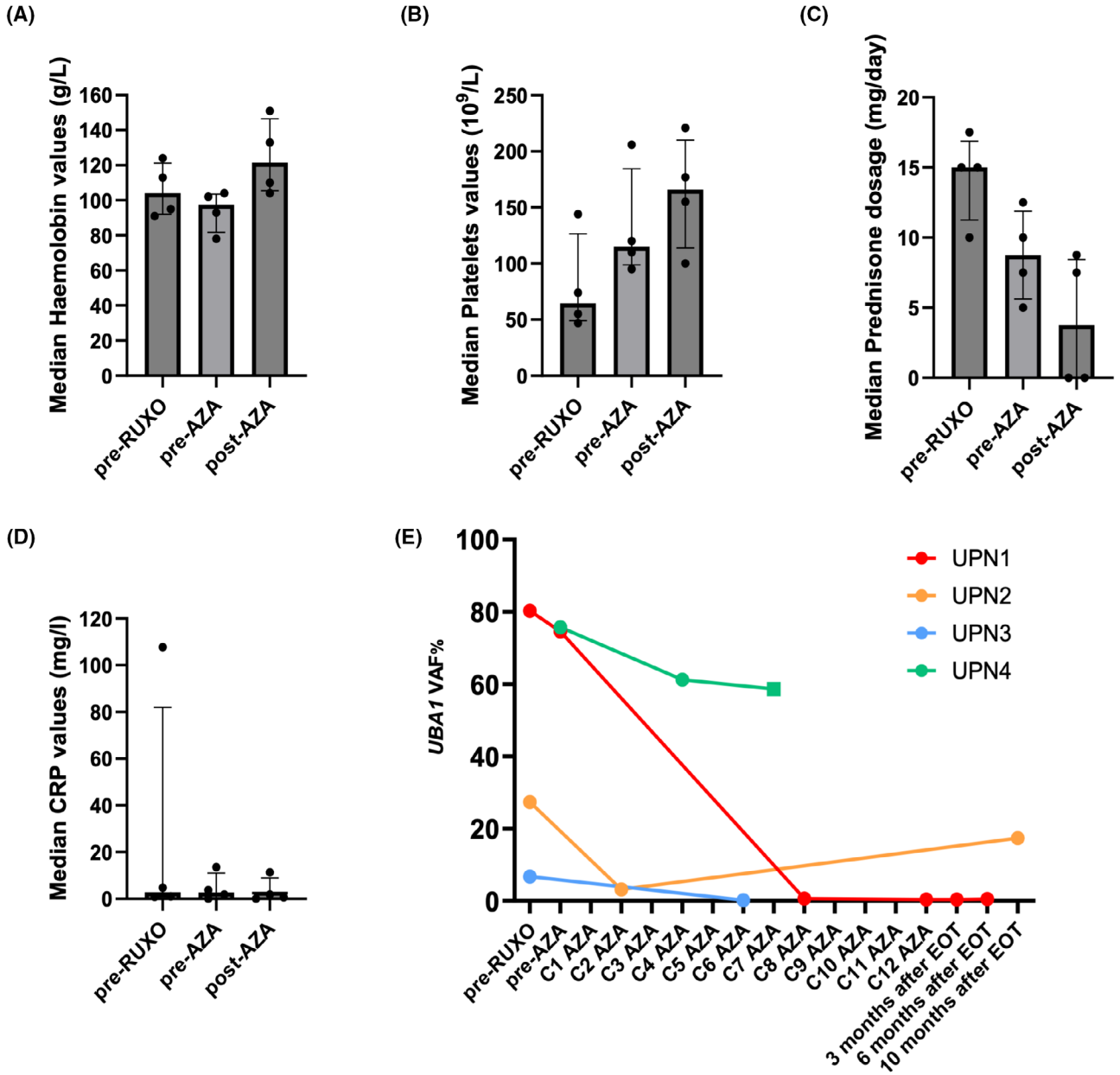

FIGURE 1 Haematological, inflammatory and molecular responses to combined ruxolitinib and 5-azacitidine therapy in patients with VEXAS syndrome. (A) Haemoglobin levels measured at three key time points: Prior to ruxolitinib initiation (pre-Ruxo), immediately before 5-azacitidine initiation (pre-AZA) and at 5-azacitidine discontinuation or at last follow-up (post-AZA). (B) Platelet counts assessed at the same time points. (C) Daily prednisone dosage over the treatment course, illustrating corticosteroid tapering. (D) Serum C-reactive protein (CRP) levels, reflecting the inflammatory burden, recorded at the same time points. (E) Variant allele frequency (VAF) of *UBA1* mutations, as determined by digital droplet PCR (ddPCR), shown longitudinally across multiple treatment time points, indicating molecular response dynamics. [Colour figure can be viewed at wileyonlinelibrary.com]

inflammatory manifestations in heavily pretreated and steroid-dependent patients. AZA was added with the aim of further consolidating the control of inflammation and improving severe cytopenias.[9] Following AZA administration, *UBA1* VAF decreased, indicating a disease-modifying effect on the clonal burden, and there was improvement in haematological parameters, suggesting partial restoration of haematopoiesis.[9] Inflammatory markers like CRP decreased, and all the patients achieved complete inflammatory response, along with a reduction in glucocorticoid requirement, supporting the role of JAK–STAT inhibition in controlling inflammation. Notably, the early increase in platelet counts might also be attributable to ruxolitinib treatment, since platelets can behave as acute-phase reactants and their rise may reflect an early anti-inflammatory effect rather than a direct consequence of azacitidine.

However, given the limited number of cases that are currently in 'treatment-free remission', definitive conclusions about the underlying mechanisms or predictive factors cannot be drawn; by now, persistent UBA1 negativity on ddPCR

may represent the most relevant prognostic marker, but this remains speculative and requires validation in larger, controlled cohorts.

Another key finding is the favourable safety profile of the combination therapy, which is relevant given the patients' advanced age and immunodeficiency resulting from intrinsic disease-related factors and the concomitant immunosuppressive treatments.[12] Considering the very limited cohort, the infection rate appeared acceptable, with 50% of patients experiencing infections as adverse events, compared to 34%,[9] 36.7%[13] and 23%[14] in other cohorts of patients treated with azacitidine or ruxolitinib. However, the absence of severe infectious complications, along with the observed reduction in glucocorticoid therapy, represents a highly encouraging starting point for the broader clinical application of this combination therapy.

In conclusion, our results highlight the need for integrated therapeutic approaches in VEXAS syndrome, reflecting its complex pathogenesis. Larger prospective studies are needed to validate these findings and optimize treatment regimens.

AUTHOR CONTRIBUTIONS

GMB, EC, AT, CC and ED designed the study, interpreted data and wrote the manuscript; GMB and EC performed the statistical analysis; CG and FR performed molecular analysis; GMB, AT, CP, GS, CC and ED took care of patients. All authors accepted the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Original data may be available upon reasonable request to the corresponding author.

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SUPPORTING INFORMATION

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