Treatment outcomes in patients with VEXAS syndrome: a retrospective cohort study

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Summary

Background Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a recently described autoinflammatory disorder with little therapeutic evidence. We compared treatment outcomes of targeted therapies versus prednisolone alone in the largest UK cohort of patients with VEXAS syndrome to date.

Methods In this retrospective cohort study, we analysed the outcomes of targeted therapies in patients with VEXAS syndrome in six tertiary referral centres across the UK between July 22, 2014, and Oct 19, 2024. The inclusion criteria were genetically confirmed VEXAS syndrome and receipt of at least one targeted therapy or prednisolone alone. Patients without clinical information at all timepoints after baseline were excluded. Data collection forms were used to record clinical and biochemical data at the following timepoints: time of diagnosis, initiation of treatment, and follow-up at 3 months, 6 months, and 12 months from the initiation of treatment (±28 days). Laboratory parameters, including C-reactive protein (CRP) and haemoglobin, and glucocorticoid doses were collected at each timepoint and compared between timepoints. Primary outcomes were complete response (ie, clinical remission, CRP ≤10 mg/L, and prednisolone ≤10 mg per day) and partial response (ie, clinical remission with ≥50% reductions in both CRP and glucocorticoid dose from baseline) to treatment. Treatment discontinuation and adverse events were documented for each treatment. Due to the high prevalence of cytopenias in VEXAS syndrome, these were only recorded as adverse events when necessitating treatment change. People with lived experience were not involved in the study.

Findings We analysed 71 targeted therapies in 59 patients with genetically confirmed VEXAS syndrome. Of the 59 patients, 58 (98%) were male and one (2%) was female, with a mean age of 71 years (SD 8), and 27 (46%) had myelodysplastic syndrome. The treatments included tocilizumab (n=19), anakinra (n=13), azacitidine (n=13), baricitinib (n=11), and prednisolone only (n=10). At 6 months, in those who continued therapy, ten (91%) of 11 patients receiving azacitidine showed a response (three [27%] complete responses), as well as did seven (64%) of 11 receiving tocilizumab (four [36%] complete responses), three (100%) of three receiving anakinra (one [33%] complete response), and two (40%) of five receiving baricitinib (no complete responses). Although all patients who tolerated anakinra had a response, the discontinuation rate was high (eight [62%] of 13), mostly due to severe injection-site reactions (n=5). Patients were more likely to respond to azacitidine than to other therapies at 6 months (risk ratio 2·47, 95% CI 1·18–5·20; p=0·018). Absence of fever or thromboembolism at diagnosis was associated with better outcomes. By 6 months, median CRP concentrations had decreased in patients receiving tocilizumab (from 30 mg/L [IQR 13–45] to 4 mg/L [3–37]) or anakinra (from 18 mg/L [11–52] to 2 mg/L [1–28]), whereas azacitidine showed the greatest increase in haemoglobin (from mean concentration 104 g/L [SD 17·5] to 120 g/L [14·4]). 28 (39%) of 71 treatments were discontinued, most commonly due to serious adverse events (12 [17%]) and death (nine [13%]). Infections were most frequent with azacitidine (eight [62%] of 13) and tocilizumab (nine [47%] of 19).

Interpretation In this UK cohort of patients with VEXAS syndrome, azacitidine and tocilizumab showed superior effectiveness compared with anakinra, baricitinib, and prednisolone only. Treatment selection should consider individual risk factors and tolerability. Prospective studies are needed to confirm optimal treatment strategies and develop standardised protocols.

Funding None.

Introduction

The first description of vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome in 2020 highlighted the emerging field of haematoinflammatory disorders and the paucity of effective treatments. A large retrospective study[1] demonstrated an unexpectedly high prevalence of around one in 4000 men older than 50 years, suggesting that about 3000 men in the UK are living with the disease, with most probably undiagnosed and untreated.[1,2] Therapies are inconsistently available

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Research in context

Evidence before this study

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a rare condition, first described in 2020 as an autoinflammatory disorder predominantly affecting men older than 50 years. We conducted a systematic search of MEDLINE, PubMed, Embase, and Web of Science from Dec 31, 2020 (when VEXAS syndrome was first described), to May 25, 2024, without language restrictions. Search terms combined disease-specific keywords ("VEXAS syndrome" OR "Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic" OR "somatic" AND "UBA1 mutation") with treatment-related terms ("treatment" OR "therapy" OR "azacitidine" OR "tocilizumab" OR "baricitinib" OR "JAK inhibitor" OR "IL-1 inhibitor" OR "IL-6 inhibitor" OR "steroids" OR "prednisolone" OR "management"). Studies were included if they reported treatment outcomes in (three or more) patients with genetically confirmed VEXAS syndrome. Case reports, non-peer reviewed articles, and studies without outcome data were excluded. There are still no agreed recommendations for treating VEXAS syndrome. Treatment options to date have been largely empirical, guided by patients' symptoms and the biological plausibility of the condition. Treatment outcomes have been reported in some case series, one of which is a large study (based on the French national registry of patients with VEXAS syndrome) reporting outcomes from several biological therapies (194 treatment courses), whereas others largely focus on a single agent in a small number of patients. Collectively, these studies have shown superior efficacy for ruxolitinib compared with other Janus kinase (JAK) inhibitors, with preliminary data on azacitidine suggesting both symptomatic benefit and potential for achieving clonal responses. Additionally, allogeneic stem cell transplantation emerged as a potential curative option in selected patients. However, treatment algorithms remained undefined, with little comparison of therapeutic approaches and incomplete understanding of predictive factors for response. We aimed to address the lack of comparative evidence on treatment efficacy in VEXAS syndrome and establish the effectiveness of various therapeutic options in a real-world UK cohort.

Added value of this study

To our knowledge, this study presents the first comprehensive analysis of VEXAS syndrome treatment outcomes in the UK health-care system, examining 71 treatment courses across 59 genetically confirmed patients. It provides several important insights. Azacitidine showed promising effectiveness, improved blood counts, and favourable steroid-sparing effects in patients, suggesting a potential disease-modifying role beyond symptom control. The study confirms the effectiveness of tocilizumab in selected patients and reports use of baricitinib, with this drug showing lower effectiveness than other JAK inhibitors for patients with VEXAS syndrome—important, given that baricitinib might be the only available agent in some countries. By mirroring the methods used in the reporting of the French national registry, this study enables robust comparisons between health-care systems, identifying important differences in mutation profiles and treatment patterns between populations.

Implications of all the available evidence

The combined evidence supports a stratified approach to therapy for patients with VEXAS syndrome, with early consideration of azacitidine for those with clinically significant cytopenias or myelodysplastic syndrome, and a balanced effectiveness–safety profile offered by tocilizumab as an alternative first-line therapy. The identification of clinical predictors of response provides a framework for risk stratification and treatment selection. The marked differences in outcomes for different JAK inhibitors highlight the need for prospective trials comparing specific agents within therapeutic classes. Future research priorities should include standardised response criteria, investigation of predictive biomarkers, and optimal timing of definitive therapies such as stem cell transplantation. The substantial diagnostic delays even after disease discovery underscore the need for increased disease awareness and development of streamlined diagnostic pathways.

throughout the UK and often suboptimal, with persisting disease burden common, and glucocorticoid toxicity.[3]

Patients with VEXAS syndrome have a substantial burden of disease, with recurrent episodes of inflammation, progressive cytopenias, and reduced life expectancy. The disease course is marked by progressive deterioration, with many patients developing treatment-refractory inflammation and haematological complications. The mortality rate is high, with a median survival of 10 years from symptom onset.[3]

Management of VEXAS syndrome is challenging due to the complex nature of the disease and the sparse evidence base for specific therapies. Treatment strategies fall into three broad categories: suppression of systemic inflammation, elimination of mutated stem cells, and amelioration of haematological dysfunction.[4] High-dose glucocorticoids, typically prednisolone, are often used as first-line therapy and can be rapidly effective; however, many patients develop glucocorticoid dependence and associated toxicity, despite the use of additional immunomodulatory agents.

Targeted therapies, such as inhibitors of interleukin (IL)-1, IL-6, and Janus kinase (JAK), have shown promise in managing refractory inflammation. Azacitidine is a DNA-hypomethylating agent that improves bone marrow function and is the established standard of care in some groups of patients with myelodysplastic syndrome, showing promise in VEXAS syndrome. For patients with

severe, treatment-refractory disease, allogeneic haematopoietic stem cell transplantation is a potentially curative option, although the optimal timing and patient selection for this approach remain uncertain.[5–8] Other supportive care measures include erythropoiesis-stimulating agents, transfusion support, antimicrobial prophylaxis, and thrombosis prophylaxis.

Since the initial description of VEXAS syndrome in 2020, several retrospective studies have evaluated the use of targeted therapies for this condition, although evidence remains sparse. The largest analysis to date examined 194 treatments in 110 patients in France, showing superior effectiveness for JAK inhibitors and IL-6 blockade compared with other biological therapies.[9] These findings were further supported by a focused international analysis of 30 patients with VEXAS syndrome treated with JAK inhibitors, which found that ruxolitinib had superior response rates (83% at 3 months) compared with other JAK inhibitors (18% at 3 months).[10] More recently, hypomethylating therapy with azacitidine has shown promise in patients with concurrent myelodysplastic syndrome, with reports of both symptom control and, unexpectedly, clonal responses.[11–13] However, the retrospective nature of current evidence, heterogeneous response definitions, and paucity of head-to-head comparisons limit definitive conclusions about optimal therapeutic strategies.

In this Article, we present the first reported UK cohort of patients with VEXAS syndrome and delineate their responses to various targeted therapies or prednisolone alone.

Methods

Study design and participants

This multicentre retrospective cohort study (a collaborative effort by the UK VEXAS interest [VEXNET] group) included patients identified through clinical attendance at six major tertiary referral centres in the UK between July, 2014, and October, 2024: Leeds Teaching Hospitals National Health Service (NHS) Trust, King's College Hospital (London), Royal Free Hospital (London), Cambridge University Hospitals, Oxford University Hospitals, and St George's University Hospitals (London). These centres are the primary diagnostic and treatment hubs within the broader VEXNET UK collaboration.

Inclusion criteria were genetically confirmed VEXAS syndrome (pathogenic *UBA1* mutation) and receipt of at least one targeted therapy or prednisolone alone. Exclusion criteria included absence of relevant clinical information and patients not receiving targeted therapy for treatment of their VEXAS syndrome. Ethnicity data were not collected in this study because complete and standardised ethnicity records were not consistently available. People with lived experience were not involved in the study. The UK VEXAS registry data used for this study were collected under ethical approval granted by the Leeds East Research Ethics Committee (18/YH/0070 and 07/Q1206/47). Written informed consent from all patients was provided.

Procedures

A data collection form was sent to each participating centre in the UK for the recording of clinical and biochemical data at the following timepoints: time of diagnosis; treatment initiation (±28 days); 3 months, 6 months, and 12 months from treatment initiation (±28 days for each timepoint); and a final recorded follow-up. If data for any timepoints were missing, they were omitted from the calculations for that timepoint.

Laboratory parameters (including C-reactive protein [CRP] and haemoglobin) and glucocorticoid doses were compared between timepoints. Two patients were on dexamethasone with targeted therapies; dexamethasone was converted to prednisolone equivalent for analysis. All glucocorticoid doses are presented as prednisolone throughout. Reasons for discontinuation and adverse events were documented for each therapy. Adverse events were defined as any undesirable event considered related to the study drug. Due to the high prevalence of cytopenias in VEXAS syndrome, these were recorded as adverse events only when necessitating temporary or permanent treatment discontinuation. Serious adverse events were defined as events requiring permanent treatment discontinuation; additionally, infections were classified as serious adverse events if they were recurrent, atypical, or necessitated hospital admission.

In this study, myelodysplastic syndrome was defined as a diagnosis from a patient's treating centre or haematologist, as established by morphological analysis of bone marrow aspirate and trephine. Due to the retrospective nature of data collection from historical clinical records, detailed characterisation of infectious complications beyond the primary classification was not feasible while maintaining data quality standards.

To enable international data comparison, we followed the core methods established by Hadjadj and colleagues[9] for the French national VEXAS registry (ie, timepoints, response definitions, and statistical analysis), adapting only the statistical reporting format. This approach facilitated direct comparison between cohorts of patients with VEXAS syndrome in the UK and France while maintaining consistency with current statistical best practice. All data for comparison were extracted from the study by Hadjadj and colleagues.[9]

Disease duration was not included in this analysis given the substantial diagnostic delays and evolving disease recognition of this newly described syndrome. Treatment continuation periods were not analysed separately given the wide temporal spread of diagnoses (2011–24) and small numbers in each treatment group. Instead, the standardised timepoints enabled robust cross-treatment comparisons while maintaining analytical clarity and statistical power.

Outcomes

Primary outcomes were complete response (ie, clinical remission, CRP ≤10 mg/L, and prednisolone ≤10 mg per day) and partial response (ie, clinical remission with ≥50% reductions in both CRP and glucocorticoid dose from baseline) to treatment. Treatment failure was defined according to ongoing symptoms, persistent inflammation, or inability to reduce glucocorticoids. Response without withdrawal, response without transfusion, and survival without treatment withdrawal were evaluated as additional outcomes.

Statistical analysis

No formal sample size calculation was done; instead, all eligible patients with genetically confirmed VEXAS syndrome were included in this retrospective analysis. Quantitative variables were assessed for normality using ratio of the standard deviation to the mean; variables with a mean to SD ratio >2 (indicating normal distribution) were reported as mean (SD), whereas those with a mean to SD ratio ≤2 (indicating skewed distribution) were reported as median (IQR). To facilitate comparison, some parameters were also reported as median (range) when being directly compared with data from the French cohort.

See Online for appendix

Baseline characteristics, including clinical features, mutations, and laboratory parameters were recorded. Treatment responses were assessed at the 3, 6, and 12 month timepoints for each therapy class. Patients who discontinued treatment were considered non-responders in the analysis.

Statistical analyses were conducted using R version 4.4.0. We fitted mixed-effects Poisson models to identify clinical and treatment-related factors associated with therapeutic response. Variables examined included demographic characteristics, clinical manifestations, laboratory parameters, and specific therapies. There were few missing data for baseline factors (range 0–17% missingness). We applied multiple imputation by chained equations with 20 imputed datasets for missing baseline factors. Missing outcome variables were allowed for by the analysis approach, under a missing at random assumption.

Each variable was assessed for its association with response outcomes at 6 months and 12 months. The mixed-effects models were fitted using the glmer function in the lme4 package in R. Each model included a normally distributed random effect for each patient, together with two dummy parameters representing the effect of the variable on the 6-month response and the effect on 12-month response. The model was fitted to each imputed dataset and results combined using Rubin's rules. This process was done for each combination of variable and response outcome considered. Results are presented as risk ratios (RRs) with 95% CIs and corresponding p values. RRs were rounded to two significant figures for reporting. Statistical significance was set at p values lower than 0·05. For continuous variables, we tested the assumption of linearity by using a likelihood ratio test to compare the fit of the model assuming linearity to a similar model with a spline with two knots. In all cases, there was no significant evidence against the linearity assumption being valid, so we only present the linear models. Survival without treatment withdrawal up to 24 months after treatment initiation was analysed using a Kaplan-Meier plot and log-rank test. Multivariable analyses to assess differential treatment responses by *UBA1* variant or haematological phenotype (including myelodysplastic syndrome and paraproteinemia) were not done due to insufficient numbers in these subgroups to reach adequate statistical power.

Role of the funding source

There was no funding source for this study.

Results

As of October, 2024, the UK VEXAS registry includes 82 genetically confirmed patients. Of these 82 patients (appendix pp 2–3), 81 (99%) are male and one (1%) is female; the only female patient has Turner's syndrome (commonly known as 45,X). The mean age at first disease manifestation was 69 years (SD 8). There was a median diagnostic delay of 16 months (IQR 7–29) from symptom onset to diagnosis in patients presenting after disease discovery in 2020. *UBA1* mutations were shown to have a distinct distribution, with pMet41Thr being the most predominant mutation (36 [49%] of 74 for whom genetic information was available) followed by pMet41Leu and pMet41Val (15 [20%] each). Amongst the studied population, in the 40 individuals in whom comprehensive genetic profiling was reported, mutations in the following additional genes were identified: *DNMT3A* (six patients), *TP53* (two patients), *TET2* (two patients), *NPM1*, *WT1*, *TNFAIP3*, patients, *ASXL1*, *CSF3R*, *MPL*, *GATA2*, *SRSF2*, and *STAT5B*, along with chromosomal abnormalities, including deletions at 8q22.2 and 13q14.2. 38 (46%) of 82 patients had concurrent myelodysplastic syndrome, and 54 (79%) of 68 had macrocytic anaemia. Before receiving targeted therapy, most patients had received glucocorticoids (75 [94%] of 80).

In this study, we included 59 patients with genetically confirmed VEXAS syndrome who had received 71 targeted therapies between July 22, 2014, and Oct 19, 2024 (table 1). 23 patients from the VEXAS registry were excluded from the analysis as they did not meet the inclusion criteria of either being treated with a targeted therapy or having sufficient data to contribute meaningfully to the study. 58 (98%) of 59 participants were male and one (2%) was female, with a mean age of 71 years (SD 7) at treatment initiation (table 1). The proportions of *UBA1* mutations were similar to those reported in the general UK population, and the mean variant allele frequency was 68% (SD 20), suggesting

that the *UBA1* mutation typically represents a major clonal population.

Associated haematological disorders were common, with myelodysplastic syndrome present in 27 (46%) of 59 patients and monoclonal gammopathy in ten (17%). At baseline, macrocytic anaemia was present in 40 (74%) of 54 patients (mean haemoglobin 101 g/L [SD 19·3]) and thrombocytopenia in 25 (45%) of 55 patients. Mean corpuscular volume was 105 fL (SD 9·1; table 1). Transfusion dependency (defined as at least three red blood cell units across two transfusion episodes over 16 weeks) was considerable, with 25 (43%) of 58 patients

	All patients (N=59)	Tocilizumab (N=19)	Anakinra (N=13)	Azacitidine (N=13)	Baricitinib (N=11)	Prednisolone only (N=10)
Age, years						
At first VEXAS manifestation	68 (8)	66 (8)	66 (10)	69 (8)	67 (9)	70 (5)
At treatment initiation	71 (7)	68 (8)	70 (10)	72 (8)	70 (8)	73 (5)
Sex						
Male	58 (98%)	19 (100%)	12 (92%)	13 (100%)	11 (100%)	10 (100%)
Female	1 (2%)	0	1 (8%)	0	0	0
VEXAS syndrome clinical manifestations						
Constitutional symptoms	58 (98%)	19 (100%)	13 (100%)	13 (100%)	10 (91%)	10%
Unexplained fevers	44 (75%)	14 (74%)	11 (85%)	12 (92%)	9 (82%)	5 (50%)
Periorbital oedema	21 (36%)	10 (53%)	3 (23%)	4 (31%)	4 (36%)	3 (30%)
Skin involvement	50 (85%)	15 (79%)	12 (92%)	12 (92%)	10 (91%)	8 (80%)
Inflammatory arthritis	24 (41%)	10 (53%)	6 (46%)	4 (31%)	4 (36%)	3 (30%)
Ear or nose chondritis	23 (39%)	7 (37%)	8 (62%)	5 (38%)	2 (18%)	2 (20%)
Pulmonary infiltrate	26 (44%)	9 (47%)	6 (46%)	7 (54%)	2 (18%)	6 (60%)
Ocular manifestations	22 (37%)	7 (37%)	5 (38%)	6 (46%)	4 (36%)	2 (20%)
Venous thromboembolism	15 (25%)	6 (32%)	2 (15%)	3 (23%)	3 (27%)	2 (20%)
Vasculitis	18 (31%)	7 (37%)	5 (38%)	5 (38%)	5 (45%)	2 (20%)
Previous rheumatological diagnoses						
Relapsing polychondritis	11 (19%)	3 (16%)	5 (38%)	2 (15%)	1 (9%)	2 (20%)
Sweet's syndrome	10 (17%)	1 (5%)	3 (23%)	6 (46%)	2 (18%)	1 (10%)
Adult-onset Still's disease	4 (7%)	1 (5%)	1 (8%)	1 (8%)	1 (9%)	2 (20%)
Schnitzlers syndrome	4 (7%)	0	4 (31%)	0	0	0
UBA1 mutation						
c122T>C (pMet41Thr)	25/54 (46%)	11/17 (65%)	6/12 (50%)	5/11 (45%)	5/11 (45%)	3/9 (33%)
c121A>C (pMet41Leu)	10/54 (19%)	1/17 (6%)	3/12 (25%)	3/11 (27%)	2/11 (18%)	1/9 (11%)
c121A>G (pMet41Val)	12/54 (22%)	5/17 (29%)	1/12 (8%)	2/11 (18%)	4 /11 (36%)	2/9 (22%)
Splice site	4/54 (7%)	0/17	2/12 (17%)	1/11 (9%)	0/11	1/9 (11%)
c167C>T (pSer56Phe)	2/54 (4%)	0/17	0/12	0/11	0/11	2/9 (22%)
Other	1/54 (2%)	0/17	0/12	0/11	0/11	0/9
Mean variant allele frequency	68% (20)	76% (9)	61% (23)	61% (22)	75% (15)	68% (19)
Other associated haematological diseases						
Myelodysplastic syndrome	27 (46%)	8 (42%)	4 (31%)	10 (77%)	3 (27%)	5 (50%)
Monoclonal gammopathy	10 (17%)	3 (16%)	2 (15%)	0	2 (18%)	2 (20%)
CRP, mg/L	35 (13–62)	30 (13–45)	18 (11–52)	9 (5–23)	45 (13–60)	104 (53–145)
Haemoglobin, g/L	101·4 (18·8)	106·4 (21·4)	102·1 (24·7)	103·8 (17·5)	101·9 (12·7)	92·0 (16·7)
Mean corpuscular volume, fL	105·6 (9·4)	105·6 (8·5)	103·8 (12·5)	106·7 (8·8)	105·9 (10·4)	103·5 (6·3)
Macrocytic anaemia	40/54 (74%)	14 (74%)	6/11 (55%)	10/11 (91%)	9 (82%)	5/9 (56%)
Thrombocytopenia	25/55 (45%)	5 (26%)	4/11 (36%)	5/12 (42%)	7 (64%)	5/9 (56%)
Concomitant glucocorticoids at targeted therapy initiation	NA	19 (100%)	12/13 (92%)	13 (100%)	11 (100%)	NA
Prednisolone (or equivalent) dose, mg per day	17·5 (12·5–25·0)	20 (12·5–21·3)	15 (7·5–15·0)	15 (7·5–27·5)	15 (12·0–20·0)	22·5 (15·0–30·0)
Previous immunosuppressive treatment						
Methotrexate	17 (29%)	9 (47%)	7 (54%)	1 (8%)	4 (36%)	1 (10%)
Azathioprine	8 (14%)	2 (11%)	3 (23%)	1 (8%)	2 (18%)	0
Mycophenolate mofetil	7 (12%)	3 (16%)	4 (31%)	0	2 (18%)	0

(Table 1 continues on next page)

	All patients (N=59)	Tocilizumab (N=19)	Anakinra (N=13)	Azacitidine (N=13)	Baricitinib (N=11)	Prednisolone only (N=10)
(Continued from previous page)						
Indication for targeted therapy						
Relapsing disease	4/52 (8%)	0/18	2/13 (15%)	0/11	1/11(9%)	1/8 (13%)
Refractory disease	22/52 (42%)	6/18 (33%)	8/13 (62%)	1/11 (9%)	5/11 (45%)	6/8 (75%)
Refractory to glucocorticoids	24/52 (46%)	12/18 (67%)	2/13 (15%)	10/11 (91%)	5/11 (45%)	NA
Other	2/52 (4%)	0/18	0/13	0/11	0/11	1/8 (13%)
Therapeutic line						
First line	31/39 (79%)	8/11 (73%)	9/11 (82%)	7/11 (64%)	7/9 (78%)	NA
Second line	5/39 (13%)	2/11 (18%)	2/11 (18%)	3/11 (27%)	1/9 (11%)	NA
Third line	1/39 (3%)	1/11 (9%)	0/11	0/11	1/9 (11%)	NA
Fourth line	0/39	0/11	0/11	1/11 (9%)	0/9	NA

Data are n (%), n/N (%), % (SD), median (IQR), or mean (SD). CRP=C-reactive protein. NA=not applicable. VEXAS=Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

Table 1: **Baseline characteristics of patients with VEXAS syndrome at initiation of targeted therapy**

requiring regular red blood cell transfusions (appendix p 4).[14]

Among the 71 therapies received overall, patients received five main categories of targeted therapy: tocilizumab (n=19, 27%), anakinra (n=13, 18%), azacitidine (n=13, 18%), baricitinib (n=11, 15%), and glucocorticoids (prednisolone) alone (n=10, 14%). Tocilizumab was given intravenously with a weight-based dosage (n=7) on varying schedules or as a weekly 162 mg subcutaneous injection (n=12). Anakinra was given as 100 mg subcutaneously once daily to all patients except for one who was on a haemophagocytic lymphohistiocytosis protocol (200 mg anakinra twice daily with subsequent variation depending on clinical outcome) and who died within 3 months. Baricitinib was given orally as 4 mg daily. Azacitidine was administered by subcutaneous injection.

Although treatment groups shared broadly similar baseline characteristics, several notable differences were observed between cohorts (table 1). Compared with patients receiving other therapies, the group receiving azacitidine had a higher prevalence of myelodysplastic syndrome and lower median CRP at initiation. The distribution of *UBA1* mutations also varied: the pMet41Thr variant was found in 11 (65%) of 17 patients in the tocilizumab group, six (50%) of 12 in the anakinra group, five (45%) of 11 in the azacitidine group, five (45%) of 11 in the baricitinib group, and three (33%) of nine patients in the prednisolone alone group. The pMet41Val variant was less frequent in the anakinra group than in the other groups. At initiation, 55 (98%) of 56 patients treated with the main targeted therapies were also receiving glucocorticoids, with a median prednisolone dose of 17·5 mg per day (IQR 12·5–20·0).

The analysis revealed distinct patterns of therapeutic effectiveness across different treatment modalities (figure 1 and appendix pp 4–7). At 3 months, patients receiving azacitidine and anakinra showed the most promising initial responses, with a response in nine (90%) of ten patients receiving azacitidine and seven (88%) of eight patients receiving anakinra, although complete responses remained relatively modest (none in patients receiving azacitidine and two in patients receiving anakinra). Eight (62%) of 13 patients receiving tocilizumab showed a response, with a complete response in three (23%), whereas baricitinib was less effective, with partial responses in five (56%) of nine patients and no complete responses.

At 6 months, azacitidine showed encouraging results in patients maintaining therapy (figure 1 and appendix pp 4–7), with a response in ten (91%) of 11 patients, including a complete response in three (27%). Notably, prednisolone reduction was favourable in patients treated with azacitidine, with only three (30%) of ten requiring more than 10 mg per day at 6 months versus higher requirements in other treatment groups. Anakinra appeared similarly effective at 6 months, with a response in all three of the patients continuing to receive this drug (complete response in one patient) and a promising glucocorticoid reduction rate (with only one of three patients on >10 mg prednisolone per day); however, the high discontinuation rate by 6 months (eight of 13 patients), mostly due to severe injection-site skin reactions (n=5), should be noted. Furthermore, subsequent switching to canakinumab (n=2) resulted in early discontinuation in both cases, suggesting that switching from one IL-1 inhibitor to another might not be particularly effective. Tocilizumab also showed good effectiveness, with a response in seven (64%) of 11 patients, including four (36%) with a complete response, whereas results for baricitinib were more modest, with two (40%) of five patients responding and no complete responses.

12-month data (figure 1), although limited by patient attrition, suggest a sustained benefit in those continuing to receive azacitidine (responses in all five patients, with three complete responses) or anakinra (responses in all four patients, with two complete responses). The effectiveness of tocilizumab was maintained in some

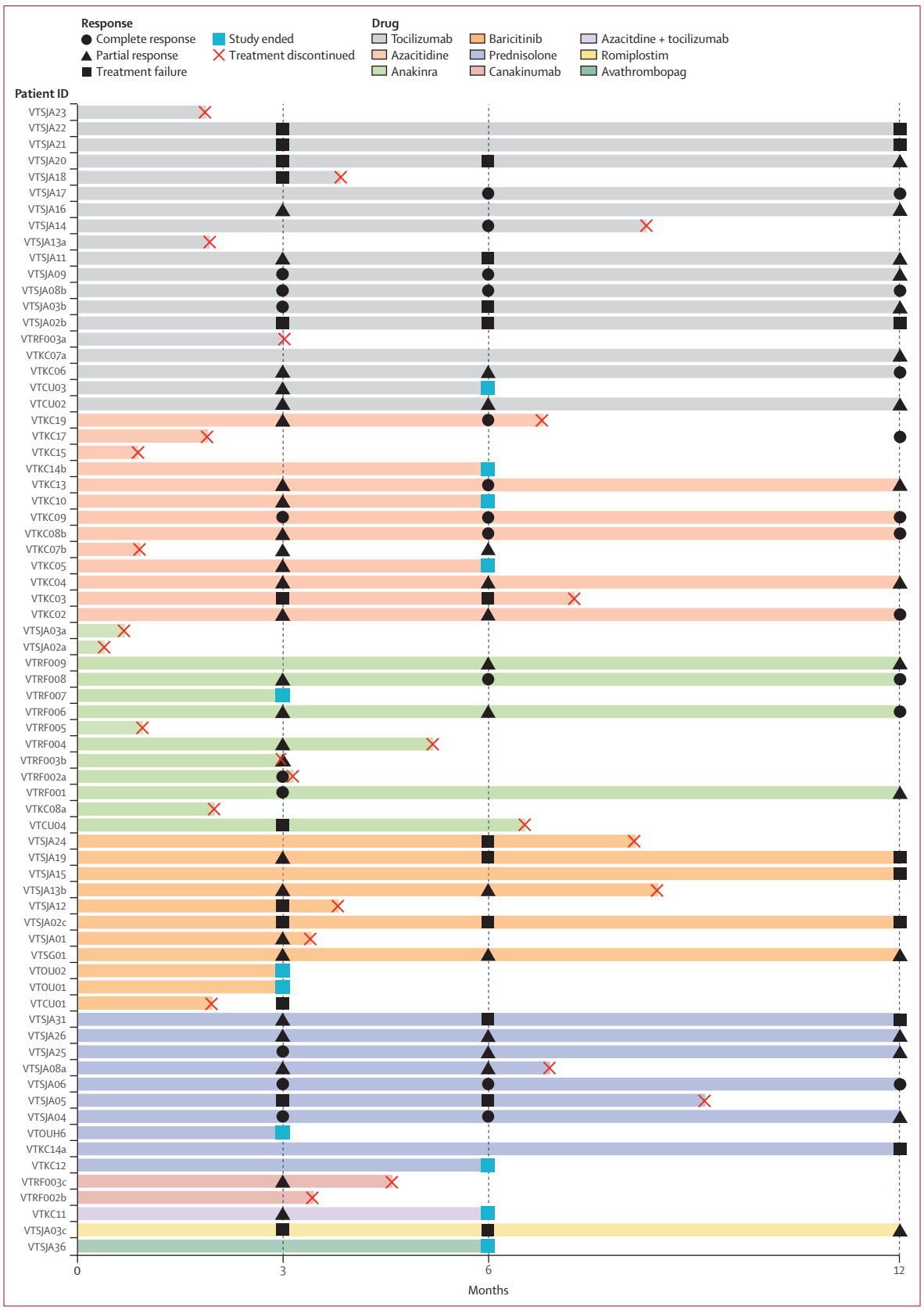

Figure 1: **Individual patient responses to different therapeutic agents**
Each horizontal line in the swimmer plot represents an individual patient, with response status indicated by symbols. Timepoints were 3, 6, and 12 months from the date of initiation (± 28 days).

	Overall (N=71)	Tocilizumab (N=19)	Anakinra (N=13)	Azacitidine (N=13)	Baricitinib (N=11)	Prednisolone only (N=10)
Treatment discontinuation	28 (39%)	5 (26%)	8 (62%)	5 (38%)	5 (45%)	3 (30%)
Reason for treatment discontinuation						
Primary failure	2 (3%)	0	1 (8%)	0	0	0
Switched therapy or insufficient control	5 (7%)	1 (5%)	1 (8%)	0	1 (9%)	2 (20%)
Serious adverse event	12 (17%)	2 (11%)	6 (46%)	3 (23%)	1 (9%)	0
Death	9 (13%)	2 (11%)	0	2 (15%)	3 (27%)	1 (10%)
Median time to discontinuation, months	3·4 (0·4–11·4)	3·0 (1·9–8·3)	2·5 (0·4–6·5)	1·9 (0·9–7·3)	3·8 (2·0 –8·5)	9·2 (6·9 –11·4)
Total adverse events	38 (54%)	11 (58%)	9 (69%)	10 (77%)	2 (18%)	3 (30%)
Most common adverse events						
Infection	25 (35%)	9 (47%)	2 (15%)	8 (62%)	2 (18%)	1 (10%)
Cytopenia	4 (6%)	1 (5%)	1 (8%)	1 (8%)	1 (9%)	0
Thrombosis	2 (3%)	0	0	1 (8%)	0	1 (10%)
Acute kidney injury	2 (3%)	1 (5%)	1 (8%)	0	0	0
Severe injection-site reaction	6 (8%)	0	6 (46%)	0	0	0
Other	5 (7%)	2 (11%)	0	2 (15%)	0	1 (10%)

Data are n (%) or median (IQR). Data are shown for 71 treatment courses in 59 patients with genetically confirmed VEXAS syndrome. Adverse events were events considered related to study drug. Cytopenias were recorded only when requiring treatment modification. Serious adverse events were events requiring permanent treatment discontinuation. Multiple adverse events could occur in individual patients. VEXAS=Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

Table 2: **Safety outcomes during the first 12 months of targeted therapy in patients with VEXAS syndrome (2014–24)**

patients (responses in ten [77%] of 13 patients, with two [15%] complete responses), but baricitinib's lower therapeutic benefit persisted, with a partial response in one (25%) of the four patients continuing to receive this drug and no complete responses. These findings highlight important differences in both the initial response rates and long-term durability of different therapeutic approaches.

Glucocorticoid-sparing effects were most pronounced in the azacitidine and anakinra groups at 12 months, with daily prednisolone doses reduced to 5 mg or less in three (60%) of patients on azacitidine and two (50%) of four patients on anakinra, compared with one (25%) of four patients receiving baricitinib and two (15%) of 13 patients receiving tocilizumab.

Within the first 12 months, 28 (39%) of 71 treatments were discontinued (table 2). Median time to discontinuation differed markedly between therapies: treatment duration was longest for prednisolone alone (9·2 months [IQR 6·9–11·4]), whereas targeted agents showed shorter treatment retention: 3·8 months (2·0–8·5) for baricitinib, 3·0 months (1·9–8·3) for tocilizumab, 2·5 months (0·4–6·5) for anakinra, and 1·9 months (0·9–7·3) for azacitidine. Primary reasons for discontinuation included serious adverse events (12 [17%] of 71), death (nine [13%]), and insufficient disease control or switching of therapy (five [7%]). Mortality was highest with baricitinib (three [27%] of 11 patients]), followed by azacitidine (two [15%] of 13). Notably, anakinra had the highest rate of discontinuation due to adverse events (six [46%] of 13]), mostly due to severe injection-site reactions (n=5). Survival analysis in patients without treatment discontinuation showed no significant differences between treatments (appendix pp 18–19).

The safety profiles differed between therapeutic agents (table 2). Adverse events were documented for 38 (54%) of the 71 therapies received overall, with infections representing the most frequent adverse event (25 [35%]). Infections were particularly common with azacitidine (eight [62%] of 13 patients]) and tocilizumab (nine [47%] of 19), whereas baricitinib had a lower infection burden (two [18%] of 11). Cytopenias requiring treatment discontinuation occurred during four (6%) of the 71 treatments, with one in each targeted therapy group. Severe injection-site reactions were observed exclusively with anakinra.Thrombotic complications and acute kidney injury were uncommon across all treatment modalities, with two (3%) instances of each.

Analysis of sequential therapy showed that seven (12%) of 59 patients required multiple lines of targeted therapy, with one patient requiring three sequential therapies. Treatment sequences included switching from anakinra to tocilizumab (n=2), tocilizumab to baricitinib (n=2), anakinra to canakinumab (n=2), and either tocilizumab or anakinra to azacitidine (n=2). 6-month treatment responses were variable, with switches to azacitidine showing the most success (one complete response and one partial response), whereas switching to baricitinib (one partial response and one treatment failure) or tocilizumab (two treatment failures) was less effective. Notably, both instances of switching IL-1 inhibition from anakinra to canakinumab resulted in discontinuation within 6 months (figure 1).

Longitudinal monitoring of clonal burden in two patients receiving azacitidine showed substantial

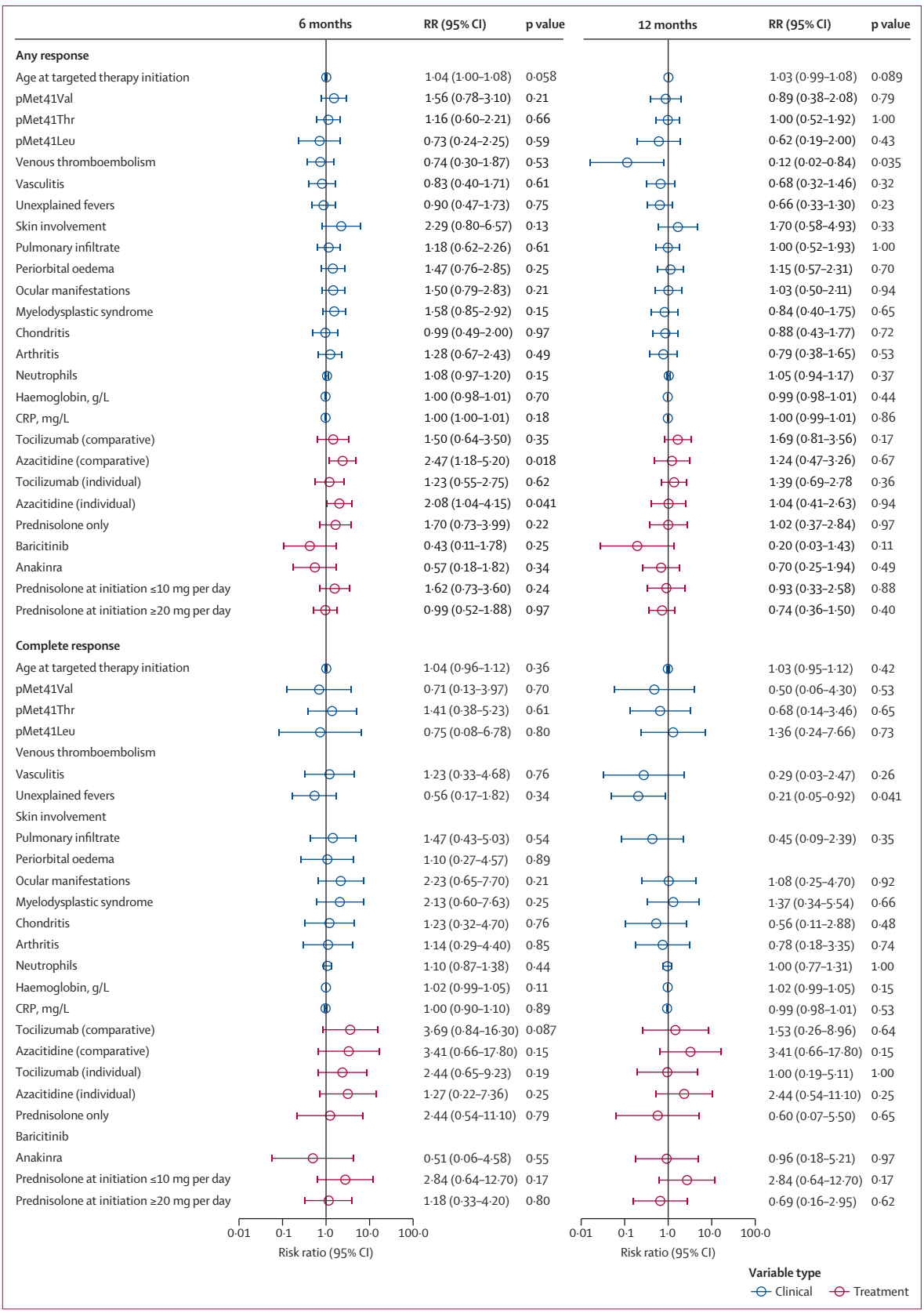

Figure 2: **Treatment response at 6 months and 12 months**
Forest plot showing RRs with 95% CIs for clinical variables (blue) and treatment-related factors (red) associated with any response (top; defined as either partial response or complete response) and complete response (bottom). Variables are ordered by category and significance. Comparative refers to a model whereby tocilizumab and azacitidine are separately compared against a reference group comprising all other drugs in the study. Individual means that each drug is compared against the rest of the drugs. CRP=C-reactive protein. RR=risk ratio. *RR per 1 unit increase.

	UK cohort (N=59)	French national VEXAS registry[9] (N=110)
Age (range) at first manifestation, years	70 (49–79)	74 (68–79)
Male sex	58 (98%)	109 (99%)
Female sex	1 (2%)	1 (1%)
Clinical manifestations of VEXAS syndrome		
Constitutional symptoms	58 (98%)	90 (82%)
Skin involvement	50 (85%)	84 (76%)
Inflammatory arthritis with synovitis	24 (41%)	..
Undifferentiated arthritis	NA	65 (60%)
Chondritis	23 (39%)	37 (34%)
Pulmonary involvement	26 (44%)	40 (37%)
Ocular manifestations	22 (37%)	36 (33%)
Venous thromboembolism	15 (25%)	38 (36%)
UBA1 mutations		
pMet41Thr	25/54 (46%)	32 (31%)
pMet41Leu	10/54 (19%)	22 (21%)
pMet41Val	12/54 (22%)	35 (34%)
Other mutations	7/54 (13%)	15 (14%)
Associated conditions		
Myelodysplastic syndrome	27 (46%)	31 (29%)
Monoclonal gammopathy	10 (17%)	11 (10%)
Laboratory features at treatment initiation		
CRP, mg/L	35 (13–62)	60 (30–130)
Haemoglobin (range), g/L	98 (64–137)	100 (74–114)
Mean corpuscular volume, fL	107 (100–113)	103 (94–107)
Macrocytic anaemia	40/54 (74%)	..
Treatment		
Concomitant glucocorticoids	48 (98%)†	102 (94%)
Previous methotrexate exposure	17 (29%)	21 (19%)
Previous azathioprine exposure	8 (14%)	5 (5%)
Previous mycophenolate mofetil exposure	7 (12%)	4 (4%)
Targeted therapies		
JAK inhibitors	11/71 (15%)	78/194 (40%)
IL-6 inhibitors	19/71 (27%)	51/194 (26%)
IL-1 inhibitors*	15/71 (21%)	33/194 (17%)
Azacitidine	13/71 (18%)	Not reported separately
TNF inhibitors	NA	20/194 (10%)
Other	13/71 (18%)	12/194 (6%)
	(Table 3 continues in next column)	
(Continued from previous column)		
6-month outcomes		
JAK inhibitors: complete response and partial response	2/5 (40%)	44/57 (77%)
JAK inhibitors: complete response	0/5	26/57 (46%)
IL-6 inhibitors: complete response and partial response	7/11 (64%)	20/44 (45%)
IL-6 inhibitors: complete response	4/11 (36%)	13/44 (30%)
IL-1 inhibitors: complete response and partial response	3/3 (100%)	5/24 (21%)
IL-1 inhibitors: complete response	1/3 (33%)	1/24 (4%)
TNF inhibitors: complete response and partial response	NA	3/20 (15%)
TNF inhibitors: complete response	NA	1/20 (5%)
Azacitidine inhibitors: complete response and partial response	10/11 (91%)	..
Azacitidine inhibitors: complete response	4/11 (36%)	..

Data are n (%), n/N (%), and median (IQR [unless range is specified]). UK cohort data are presented to match the data in the study by Hadjadj and colleagues[9] of the French national registry of patients with VEXAS; data for the French national registry study are as originally presented (denominators for percentage calculations were not provided). VEXAS=Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic. CRP=C-reactive protein. IL=interleukin. JAK=Janus kinase. NA=not applicable. TNF=tumour necrosis factor. *Including two patients receiving canakinumab. †Excluding ten patients receiving prednisolone only.

Table 3: **Comparison of demographics, clinical features and treatment outcomes between UK and French VEXAS cohorts**

reductions in *UBA1* variant allele frequency (from 71% to 33% in one patient and from 81% to 7% in another), occurring in parallel with clinical improvement. This improvement was not observed in a patient receiving tocilizumab, for whom variant allele frequency showed little change (86% to 82%) during their treatment.

Univariable analysis (figure 2 and appendix p 8–11) identified several clinical and treatment-related factors associated with response. The presence of unexplained fevers at diagnosis was associated with poorer outcomes (complete response at 12 months RR 0·21, 95% CI 0·05–0·92; p=0·041) compared with those without fevers, suggesting that they might require more intensive initial therapy. Venous thromboembolis was also associated with treatment failure (any response at 12 months RR 0·12, 95% CI 0·02–0·84; p=0·035) compared with those without thrombosis. Additionally, at 6 months, patients receiving azacitidine were more likely to respond than those receiving other therapies (RR 2·47, 95% CI 1·18–5·20; p=0·018). These findings should be interpreted with caution given the wide CIs, reflecting the small size of the cohort and potential confounding factors in this real-world dataset.

At treatment initiation, CRP concentrations were elevated across all groups (median 30 mg/L [IQR 13–60]), with baseline concentrations highest in patients receiving prednisolone only (104 mg/L [53–145]) and lowest in patients receiving azacitidine (9 mg/L [5–23]; appendix p 12–13). By 6 months, patients receiving tocilizumab or anakinra showed the most consistent improvements in median CRP concentrations (from 30 mg/L [IQR 13–45] to 4 mg/L [3–37] for tocilizumab and from 18 mg/L

[11–52] to 2 mg/L [1–28] for anakinra). Haemoglobin responses were most pronounced in the azacitidine group, improving from a mean concentration of 104 (SD 17·5) at baseline to 120 g/L (14·4) at 6 months and with the improvement maintained at 12 months (133 g/L [12·4). Lymphocyte counts remained fairly stable across all treatment groups, whereas neutrophil counts showed a reduction towards the normal range, particularly in the tocilizumab group (from median $6·50\times10^9$ cells per L [IQR 3·71–8·58] at baseline to $2·33\times10^9$ cells per L [1·77–7·54] at 6 months).

Apart from the five main treatment categories, there were two instances of canakinumab treatment after anakinra, one combination of tocilizumab and azacitidine, one patient receiving romiplostim, and one patient receiving avathrombopag. Canakinumab was discontinued in both patients before 6 months—in one case because the patient died from Legionnaire's disease (a known infectious risk in VEXAS syndrome).[15] Notably, both romiplostim and avathrombopag are thrombopoietin receptor agonists, and we have previously reported on a patient who had complete resolution of cytopenias and florid inflammatory symptoms while receiving romiplostim.[16] The patient receiving avathrombopag showed improvement in haemoglobin (from 68 g/L to 137 g/L) and CRP (from 118 mg/L to 1 mg/L), albeit with stable low platelets and lymphocytes, after 6 months of avathrombopag and prednisolone.

Comparison of this UK cohort with the French registry of patients with VEXAS (n=110)[9] revealed notable demographic and phenotypic similarities, albeit with several distinct differences in disease manifestations and treatment patterns (table 3). Although median age was similar in both cohorts, as was the predominance of male sex, the UK cohort had a higher proportion of myelodysplastic syndrome than the French cohort. The genetic landscape differed markedly, with pMet41Thr variants more prevalent and pMet41Val less frequent in the UK cohort. Median CRP concentrations at treatment initiation were lower in the UK cohort than in the French cohort, although the two cohorts had similar baseline haemoglobin concentrations and macrocytic indices. Treatment strategies showed distinct patterns, with greater use of azacitidine and lower use of JAK inhibitors in the UK cohort. Additionally, response rates to IL-6 inhibition were higher and JAK inhibitor responses were notably lower in the UK cohort than in the French cohort.

Discussion

This study presents the first comprehensive analysis of VEXAS syndrome treatment outcomes in a UK cohort, building on existing international evidence. A key finding was the effectiveness of azacitidine in this cohort, with high response rates and a possible disease-modifying role beyond symptom control supported by sustained haematological improvements, potential for reaching transfusion independence, and robust glucocorticoid-sparing effect. However, these findings should be interpreted cautiously given the small sample size and treatment attrition. The changes in clonal burden we observed in two patients receiving azacitidine align with recent reports showing azacitidine's potential to reduce clonal burden in patients with VEXAS syndrome.[11] Larger studies, with comparator therapies, are needed to validate these observations, assess the persistence of changes, and evaluate their clinical significance.

Results in patients receiving IL-6 inhibitors were encouraging, with complete response rates at 6 months similar to those in the French cohort.[9] It should be noted that tocilizumab could plausibly inflate response rates through direct suppression of CRP production via IL-6 blockade. Nonetheless, our biochemical data showed that patients receiving the IL-1 inhibitor anakinra reached similar CRP reductions, and the composite outcome measure also required a substantial reduction in glucocorticoid doses, which would be difficult to reach without genuine control of underlying inflammatory manifestations.

Treatment with anakinra showed good effectiveness in those who tolerated therapy, but the substantial rate of early discontinuation, mostly due to severe injection-site reactions, substantially limits its practicality as a sustainable therapeutic option. Notably, attempts to salvage IL-1 pathway blockade through switching to canakinumab proved unsuccessful. These results suggest that anakinra might be best suited for short-term management of disease flares—eg, when intravenous delivery could be considered in the acute setting.

JAK inhibition showed low effectiveness in this cohort, especially when compared with its effectiveness in the French cohort.[9] These results were compounded by the high discontinuation rate of baricitinib in this study, driven by the highest mortality rate. The disparity between this UK cohort and the French cohort probably reflects important differences in JAK inhibitor selection; the UK cohort exclusively used baricitinib, whereas the French study[9] reported superior outcomes with ruxolitinib, potentially due to its more potent JAK2 inhibition or varied dosing regimen.[17,18] The group of ten patients in this study is the largest reported group treated with baricitinib—a retrospective study by Heiblig and colleagues[10] included four patients treated with baricitinib, and the French cohort study included two.[9] These findings support growing evidence that different JAK inhibitors have variable efficacy in VEXAS syndrome.

Safety profiles indicated important considerations for clinical practice. Although infection rates were similar overall, we observed higher rates of severe injection-site reactions with anakinra than with the other therapies, leading to frequent discontinuation. The number of infections in the azacitidine and tocilizumab groups highlight the need for careful monitoring and pre-emptive management strategies. Although thrombosis is

a known complication of VEXAS, only two patients had a thrombotic event during treatment, and neither were in the reportedly pro-thrombotic baricitinib group, suggesting that suppression of inflammation outweighs iatrogenic risk in this group.

These findings have several practical implications. Treatment algorithms should consider early use of azacitidine in patients with clinically significant cytopenias or co-existing myelodysplastic syndrome, whereas tocilizumab offers a balanced efficacy–safety profile as an alternative first-line therapy. Anakinra could be considered for patients with severe flares who require admission to hospital as it can be delivered intravenously and has a short half-life. Development of standardised monitoring protocols, particularly for infection risk, and the establishment of a specialist centre network could help optimise outcomes.

The UK VEXAS registry of 82 patients provides important context for interpreting these treatment outcomes. The registry shows that the UK population of patients with VEXAS has several distinctive features, including a higher prevalence of myelodysplastic syndrome and pMet41Thr mutations than is found in international cohorts. This difference in rates of myelodysplastic syndrome might reflect diagnostic uncertainty, as many patients with VEXAS syndrome have bone marrow changes that fall between non-diagnostic dysplasia and low-risk myelodysplastic syndrome, with neither classification adequately capturing their risk of adverse outcomes. Of particular interest is the substantial diagnostic delay even after disease discovery, with a median of 16·1 months (IQR 7–29) from symptom onset to diagnosis in patients presenting after 2020, highlighting ongoing challenges in recognition and referral patterns. The presence of other mutations on myeloid panel testing of patients with VEXAS syndrome (including mutations in *DNMT3A*, *TET2*, and *TP53*) suggests complex genetic landscapes that might influence treatment responses and deserves further investigation.

Future research priorities should include prospective trials comparing different therapeutic strategies, particularly early intervention with azacitidine versus conventional immunosuppression in patients with concurrent myelodysplastic syndrome. Investigation of clonal evolution patterns, development of predictive biomarkers, and establishment of harmonised international response criteria will be crucial for advancing the field. Lastly, questions remain about the potential role of thrombopoietin receptor agonists in managing cytopenias in patients with VEXAS syndrome and whether these agents can lead to improvement in inflammatory sequelae through a yet uncharacterised pathogenic mechanism.

This study has several limitations, including its retrospective design, potential selection bias in treatment allocation, and small subgroups, limiting statistical power. The extreme RR values and wide CIs seen in some analyses (eg, RR <0·2 for fevers and thromboembolism) probably reflect sparse-data bias due to our small sample size, suggesting that the magnitude of these effects should be interpreted cautiously. Furthermore, due to our sample size, we were unable to conduct multivariable analyses to adjust for potential confounding factors, which could have affected our assessment of treatment effectiveness. Moreover, patients in this study were assigned a clinical response on the basis of the physician's clinical opinion, increasing the likelihood of reporting bias and variance among physicians and treating centres. The absence of standardised prednisolone tapering protocols introduces potential physician-dependent variations in glucocorticoid reduction strategies, which could influence response assessments across treatment groups.

Future prospective studies should implement standardised tapering approaches to enhance comparative analyses. Furthermore, a standardised clinical score using a VEXAS syndrome-disease activity score and patient-reported outcome measures would be fundamental for better design and implementation of prospective trials. Nevertheless, the findings of this study provide important real-world evidence to guide clinical practice and future research directions in the management of patients with VEXAS syndrome.

Contributors

AA-H, AK, HJL, and SS conceived the study. AA-H, RT, EEPH, OC, AC, AK, SA, JAP, CC, SG, and CAM collected the data. AA-H and JMSW analysed the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. AA-H and JMSW directly accessed and verified the underlying data reported in the manuscript. All authors read, edited and approved the manuscript.

Declaration of interests

SS has received honoraria for consulting services from AstraZeneca, Takeda, Sobi, KalVista, Pharming, Novartis, Celldex and Phavaris; grants from CSL Behring; and travel support from Novartis. HJL has received consulting fees from Sobi and Novartis and serves as President of the International Society of Systemic Auto-inflammatory Diseases. AC received an honorarium from Servier for a regional meeting presentation. AK received speaker fees from Lilly and travel support from AbbVie for British Society for Rheumatology attendance. CC received honoraria from Novartis and Astellas. EMP received consulting fees from AbbVie and serves as an unpaid lead for UK Myelodysplastic Syndrome Research network. JG received honoraria for lecture presentations from AbbVie, Alfasigma, Pfizer, Janssen, UCB and Lilly; grants from AbbVie, Kinevant, Gilead, Pfizer, Janssen, and Sobi. SJ has received support from CSL Behring (for projects, meetings, advisory boards, and clinical trials), Pharming (for projects, meetings, and advisory boards), Octapharma (for projects, meetings, and advisory boards), UCB Pharma (for projects, meetings, and advisory boards), LFB (for projects, meetings, advisory boards, drug safety monitoring boards, and clinical trials), Biocryst (projects, meetings, and advisory boards), Kedrion (meetings), Biotest (projects, meetings, and advisory boards), Sobi (projects), Grifols (meetings and advisory boards), Takeda (projects, meetings, and advisory boards), Sanofi advisory boards), GSK (meetings), Binding Site (projects), Stratech (projects), and Health and Care Research Wales (research project). OC serves on the Sobi advisory board for VEXAS. TY received consulting fees from AbbVie and is Treasurer of the UK and Ireland Vasculitis Rare Disease Group. All other authors declare no competing interests.

Data sharing

De-identified individual participant data that support the findings of this study are available from the corresponding author upon reasonable request.

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References

1 Beck DB, Bodian DL, Shah V, et al. Estimated prevalence and clinical manifestations of UBA1 variants associated with VEXAS Syndrome in a clinical population. *JAMA* 2023; **329:** 318–24

2 UK Office for National Statistics. Population estimates for the UK, England, Wales, Scotland, and Northern Ireland: mid-2022. 2022. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2022#:~:text=At%20mid%2D2022%2C%20there%20were,of%20males%20since%20mid%2D2011 (accessed April 15, 2025).

3 Ferrada MA, Savic S, Cardona DO, et al. Translation of cytoplasmic UBA1 contributes to VEXAS syndrome pathogenesis. *Blood* 2022; **140:** 1496–506.

4 Al-Hakim A, Savic S. An update on VEXAS syndrome. *Expert Rev Clin Immunol* 2023; **19:** 203–15.

5 Al-Hakim A, Poulter JA, Mahmoud D, et al. Allogeneic haematopoietic stem cell transplantation for VEXAS syndrome: UK experience. *Br J Haematol* 2022; **199:** 777–81.

6 Gurnari C, Koster L, Baaij L, et al. Allogeneic hematopoietic cell transplantation for VEXAS syndrome: results of a multicenter study of the EBMT. *Blood Adv* 2024; **8:** 1444–48.

7 Mohty R, Reljic T, Abdel-Razeq N, et al. Assessing the efficacy of allogeneic hematopoietic cell transplantation in VEXAS syndrome: results of a systematic review and meta-analysis. *Bone Marrow Transplant* 2024; **59:** 1423–27.

8 Mangaonkar AA, Langer KJ, Lasho TL, et al. Reduced intensity conditioning allogeneic hematopoietic stem cell transplantation in VEXAS syndrome: data from a prospective series of patients. *Am J Hematol* 2023; **98:** E28–31.

9 Hadjadj J, Nguyen Y, Mouloudj D, et al. Efficacy and safety of targeted therapies in VEXAS syndrome: retrospective study from the FRENVEX. *Ann Rheum Dis* 2024; **83:** 1358–67.

10 Heiblig M, Ferrada MA, Koster MJ, et al. Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: a retrospective multicenter study. *Blood* 2022; **140:** 927–31.

11 Trikha R, Kong KL, Galloway J, et al. De-escalation of corticosteroids and clonal remission in UBA1 mutation-driven VEXAS syndrome with 5-azacytidine. *Haematologica* 2024; **109:** 3431–34.

12 Jachiet V, Olivier K, Guedon AF, et al. OP0231 efficacy and safety of azacitidine for patients with vexas syndrome: retrospective study from the FRENVEX. *Ann Rheum Dis* 2024; **83** (suppl 1)**:** 62 LP–63 (abstr).

13 Nannya Y, Tobiasson M, Sato S, et al. Postazacitidine clone size predicts long-term outcome of patients with myelodysplastic syndromes and related myeloid neoplasms. *Blood Adv* 2023; **7:** 3624–36.

14 Platzbecker U, Fenaux P, Adès L, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood* 2019; **133:** 1020–30.

15 de Valence B, Delaune M, Nguyen Y, et al. Serious infections in patients with VEXAS syndrome: data from the French VEXAS registry. *Ann Rheum Dis* 2024; **83:** 372–81.

16 Al-Hakim A, Cull A, Topping J, et al. Recovery of bone marrow function in VEXAS Syndrome—potential role for romiplostim. *HemaSphere* 2023; **7:** e934.

17 Shawky AM, Almalki FA, Abdalla AN, Abdelazeem AH, Gouda AM. A comprehensive overview of globally approved JAK inhibitors. *Pharmaceutics* 2022; **14:** 1001.

18 Assadiasl S, Fatahi Y, Mosharmovahed B, Mohebbi B, Nicknam MH. Baricitinib: from rheumatoid arthritis to COVID-19. *J Clin Pharmacol* 2021; **61:** 1274–85.