RUXOLITINIB FOR TREATMENT OF VEXAS SYNDROME

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Please find following a summary of a literature search and relevant results.

QUESTION

Is Ruxolitinib the best agent for treatment of VEXAS syndrome?

SEARCH LIMITS

English-language, last 10 years.

SEARCH METHODOLOGY

A systematic search was conducted for literature. The results were screened by one librarian using Covidence. See the Appendix for the PRISMA chart, search terms, and Medline search strategy.

DATABASES SEARCHED

- Medline – index of peer reviewed articles across health sciences and medicine.
- Embase – index of biomed and pharmacological peer reviewed journal articles.
- Emcare – index of nursing, allied health, critical-care medicine and more.
- Cochrane Library – collection of databases containing high-quality independent evidence.

LITERATURE RESULTS

All articles can be provided in full text – click on the link for each citation or email library@monashhealth.org with a list of articles you require.

PEER-REVIEWED LITERATURE - IN REVERSE CHRONOLOGICAL ORDER

Articles are grouped by theme:

- Janus kinase inhibitors and VEXAS –cohort or case studies
- Janus kinase inhibitors and VEXAS – general
- Janus kinase inhibitors and VEXAS – single case study or reference to JAKs with little detail
- Janus kinase inhibitors and VEXAS – grey literature

Each article summary contains excerpts from the abstract or article, and an online link.

JANUS KINASE INHIBITORS AND VEXAS – COHORT OR CASE STUDIES

Sujobert, P. et al. (2023) **VEXAS: where do we stand 2 years later?** *Current Opinion in Hematology*, 30(2), 64-69. Request full-text.

Recent findings: Among the nearly 150 articles published about VEXAS, some have provided determinant insights into VEXAS pathophysiology and treatment. Clinical data from retrospective series support the JAK inhibitor ruxolitinib as the most efficient strategy to control inflammation, and interesting results were also described with azacytidine. Allogeneic stem cell transplantation remains the only curative option, but should be proposed to carefully selected patients. Summary: Although waiting for more robust evidence from prospective clinical trials, therapeutic options emerge from retrospective studies. We propose a set of criteria that should be systematically reported to harmonize the evaluation of therapeutic outcomes. This will allow the collection of high-quality data and facilitate their subsequent meta-analysis with the overall aim of improving the management of VEXAS patients.

Borie, R. et al. (2023) **Pleuropulmonary Manifestations of Vacuoles, E1 Enzyme, X-Linked, Autoinflammatory, Somatic (VEXAS) Syndrome**. *Chest*, 163(3), 575-585. Request full-text.

Background: The vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a newly identified autoinflammatory disorder related to somatic UBA1 mutations. Up to 72% of patients may show lung involvement. Research Question: What are the pleuropulmonary manifestations in VEXAS syndrome? Study Design and Methods: One hundred fourteen patients were included in the French cohort of VEXAS syndrome between November 2020 and May 2021…. All 45 patients eventually demonstrated at least one flare that required high-dose glucocorticosteroids of > 20 mg/d prednisone, and 40 patients received at least one other immunosuppressive drug, at a median of 3 drugs (IQR, 1-13 drugs) (Table 4). Janus kinase inhibitors and IL-1 antagonists yielded a good response rate, but the clinical, radiologic, and biological evaluation was not standardized, and IL-1 antagonist treatment was associated with skin reaction and neutropenia, without reported pulmonary reaction….

Muratore, F. et. Al. (2022) **VEXAS Syndrome: A Case Series From a Single-Center Cohort of Italian Patients With Vasculitis**. *Arthritis and Rheumatology*, 74(4), 665-670. Click for full-text.

Objective: To identify patients with VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome) from a single-center cohort of Italian patients with vasculitis, using a clinically oriented phenotype-first approach. Methods: We retrospectively reviewed the clinical records of 147 consecutive male patients followed up in our vasculitis clinic from 2013 to date. All patients with a diagnosis of vasculitis and treatment-resistant manifestations of inflammation, persistently elevated inflammation markers, and hematologic abnormalities were identified. Bone marrow aspirates were examined for the presence of vacuoles. Sequencing of ubiquitin-activating enzyme E1 (UBA-1) was performed using genomic DNA from peripheral blood leukocytes or bone marrow tissue.
Discussion mentions treating 7 patients with '… the selective JAK1 inhibitor upadacitinib. The drug showed a steroid-sparing effect and a good safety profile. Further studies evaluating the efficacy and safety of JAK inhibitors in the treatment of patients with VEXAS syndrome are needed.'

Heiblig, M. et al. (2022) **Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: a retrospective multicenter study**. *Blood*, 140(8), 927-931. Request full-text.

Letter to the editor. VEXAS syndrome (vacuoles in myeloid progenitors, E1 ubiquitin-activating enzyme, X-linked, autoinflammatory manifestations, and somatic) is the consequence of the expansion of hematopoietic stem and/or progenitor cells with somatically acquired UBA1 (ubiquitin-like modifier activating enzyme 1) mutations. Patients present with a variety of autoinflammatory manifestations, and approximately half of them have an associated hematological malignancy, mainly myelodysplastic syndrome (MDS) and/or monoclonal gammopathy. Long-term use of high doses in this steroid-dependent disease is often associated with unacceptable side effects. Retrospective studies have underlined the poor response of VEXAS patients to a variety of therapeutic strategies, except for a few patients exposed to Janus kinase inhibitors (JAKi). Here, we present the results of a multicenter international retrospective analysis of VEXAS patients treated with different JAKi to better characterize safety and efficacy profiles… Thirty patients with genetically proven VEXAS syndrome treated with JAKi (ruxolitinib [n 5 12], tofacitinib [n 5 11], baricitinib [n 5 4], or upadacitinib [n 5 3]) between April 2018 and February 2022 were included in 10 hospitals from France, the United States, and Portugal.

Conway, R. (2022) **Ruxolitinib takes center stage for VEXAS syndrome**. *Blood*, 140(8), 807-808. Click for full-text.
In this issue of Blood, Heiblig et al report on the efficacy of Janus kinase (JAK) inhibition in treating patients who have VEXAS (vacuoles in myeloid progenitors, E1 ubiquitin–activating enzyme, X-linked, autoinflammatory manifestations, somatic) syndrome. VEXAS syndrome is a recently described disorder consequent to somatic mutation in the UBA1 gene.

Georgin-Lavialle, S. et al. (2022) **Further characterization of clinical and laboratory features in VEXAS syndrome: large-scale analysis of a multicentre case series of 116 French patients*.** British Journal of Dermatology, 186(3), 564-574. Request full-text.

Objectives To describe clinical characteristics, laboratory findings and outcomes of VEXAS syndrome. Methods One hundred and sixteen patients with VEXAS syndrome were referred to a

French multicentre registry between November 2020 and May 2021. The frequency and median of parameters and vital status, from diagnosis to the end of the follow-up, were recorded… Treatments, especially the use of glucocorticoids, conventional DMARDs, targeted biological drugs, azacytidine, JAK inhibitors and allogeneic haematopoietic stem cell transplantation, were recorded during follow-up..

Bourbon, E. et al. (2021) **Therapeutic options in VEXAS syndrome: insights from a retrospective series**. *Blood*, 137(26)), 3682-3684. Click for full-text.

Letter to the editor. 'We identified 19 male patients with myeloid dysplasia and autoinflammatory disease such as relapsing polychondritis or Sweet syndrome… We collected data to evaluate the response to immunosuppressive drugs such as corticosteroids (n = 10) and methotrexate (n = 3), cytokine-targeting agents such as anti-tumor necrosis factor α (anti-TNF-α) (adalimumab, n = 3) or anti-interleukin-6 (anti-IL-6) receptor (tocilizumab, n = 4), signaling inhibitors such as calcineurin inhibitor (cyclosporine, n = 3) and JAK inhibitors (ruxolitinib, n = 2; tofacitinib, n = 1), and the hypomethylating agent azacytidine (n = 4). Details of individual patient responses to each therapeutic line are presented in supplemental Table 4. As illustrated in Figure 1, most treatments were only transiently effective; the median time to next treatment was 3.4 months for adalimumab, 3.9 months for corticosteroids, 7.4 months for methotrexate, and 8 months for tocilizumab.

Heiblig, M. et al. (2021) **Clinical efficacy of JAK inhibitors in patients with vexas syndrome: A multicenter retrospective study**. *Blood*, 138 (Supplement 1), 2608. Click for full-text.

In this multicenter retrospective study, we report some clinical efficacy of JAK inhibitors (JAKi) in VEXAS patients. Patients: We analyzed retrospectively 24 UBA1 mutated patients (Met41 or previously reported alternative splicing site) treated with JAKi (11 with ruxolitinib (RUXO), 11 with tofacitinib (TOFA), 1 with baricitinib, 1 with upadicitinib) in 7 French, 1 Portugese and 2 US centers. Complete clinical (CCR) and complete biological response (CBR) were defined as complete resolution of clinical symptoms and normalization of inflammation markers (C reactive protein, CRP) respectively. Partial clinical (PCR) and biological (PBR) response were defined by reduction of at least 50% of clinical or inflammation markers, respectively…. Conclusion: Ruxolitinib (and less often other JAK inhibitors used in this study) provides rapid response in most VEXAS patients, allowing in two third of the cases corticosteroid dose reduction/withdrawal and RBC transfusion independence in 4/6 patients with MN who were initially transfusion dependent. Those retrospective preliminary results, with limited follow up, must be interpreted with caution and will be updated at the meeting. The effect of RUXO on VEXAS patients with concomitant MN will soon be studied prospectively in a Groupe Francophone des Myélodysplasies (GFM) clinical study.

JANUS KINASE INHIBITORS AND VEXAS - GENERAL

Petric, D. (2023) **VEXAS syndrome: is there an effective treatment?** *Precision Medicine Research*, 5(1), 1. Click for full-text.

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) is an acronym for a monogenic disease of adulthood caused by somatic mutations in UBA1 gene (which translates into the ubiquitin-activating enzyme E1, that is necessary for the normal functioning of the ubiquitin-proteasome system) in hematopoietic progenitor cells and stands for: Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic… Here author summarizes available evidence on treatment options for VEXASS… There was a significant clinical improvement of cutaneous lesions after the introduction of ruxolitinib (JAK inhibitor) as monotherapy following azacytidine in one patient. However, no improvement of cytopenia, especially anemia, as well as no changes in myelodisplastic features, was observed in any of the treatments used in this study, including corticosteroids, methotrexate, adalimumab (anti-tumor necrosis factor α agent), tocilizumab (anti-interleukin-6 receptor agent), cyclosporine (signaling inhibitor), ruxolitinib and tofacitinib (JAK inhibitors), and azacytidine.

Al-Hakim, A., & Savic, S. (2023). **An update on VEXAS syndrome**. *Expert Review of Clinical Immunology*, *19*(2), 203-215. Click for full-text.

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a recently described, late-onset, acquired autoinflammatory disorder caused by mutations in the UBA1 gene. The various clinical manifestations of VEXAS broadly divided into inflammatory or haematological. VEXAS defines a new disease category – the hematoinflammatory disorders triggered by somatic mutations restricted to blood but causing systemic inflammation with multi-organ involvement and associated with aberrant bone marrow status. VEXAS causes significant morbidity and reduced life expectancy, but the optimum standard of care remains undefined… VEXAS causes significant morbidity and reduced life expectancy, but the optimum standard of care remains undefined… In patients manifesting mostly inflammatory and rheumatological disease, therapeutic options include anti-interleukin (IL)1 (anakinra & canakinumab), anti-IL6 (tocilizumab) and JAK-inhibitors (e.g. baricititinib & ruxolitinib)…. In a recent retrospective case series of 30 patients assessing the efficacy of different JAK inhibitors (JAKi) in VEXAS, with ruxolitinib (n = 12), tofacitinib (n = 11), baricitinib (n = 4) and upadacitinib (n = 3) all compared.

Long, A. et al. (2023). **Immune dysregulation**. *Journal of Allergy and Clinical Immunology*, 151(1), 70-80. Click for full-text.

This review focuses on recent advances in the understanding of immune dysregulation and describes potential key factors that may function as biomarkers for disease or targets for therapeutic interventions… Autoinflammatory disorders: In a multicenter retrospective cohort of VEXAS patients treated with JAK inhibitors, ruxolitinib was significantly more effective than other JAK inhibitors, with complete response at 6 months 87% versus 11% (P = .002). VEXAS may also respond to treatment for myelodysplastic syndrome, such as stem cell transplantation and azacytidine.

van Leeuwen-Kerkhoff, N. et al. (2022) **Case report: Up-front allogeneic stem cell transplantation in a patient with the VEXAS syndrome**. *British Journal of Haematology*, 199(3), e12-e15. Click for full-text.

Letter to the editor. Recently, Beck et al. reported a novel monogenic autoinflammatory syndrome called the VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome)… In the reported cohorts, patients showed high steroid dependency and responded poorly to multiple (biologic) disease-modifying anti-rheumatic drugs. The most optimal results were achieved using monotherapy, or corticosteroids combination therapy, of the hypomethylating agent azacytidine, tocilizumab, JAK-inhibitors (ruxolitinib and tofacitinib) or ciclosporin A.

Koster, M. J. et al. (2022) **VEXAS Syndrome: A Review of Pathophysiology, Presentation, and Prognosis**. *Journal of Clinical Rheumatology: Practical Reports on Rhematic & Musculoskeletal Diseases* (in press). Click for full-text.

EXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is a newly identified disease caused by somatic mutations in the UBA1 gene resulting in refractory autoinflammatory features, frequently accompanied by cytopenias. Although the prevalence of this syndrome is yet unknown, understanding the clinical phenotype can assist clinicians in prompt recognition of cases among patients with glucocorticoid-responsive but immunosuppressive-resistant inflammatory symptoms. The pathophysiology, clinical presentation, diagnostic methods, treatment, and prognosis of VEXAS are herein reviewed….Although the prevalence of this syndrome is yet unknown, understanding the clinical phenotype can assist clinicians in prompt recognition of cases among patients with glucocorticoid-responsive but immunosuppressive-resistant inflammatory symptoms. The pathophysiology, clinical presentation, diagnostic methods, treatment, and prognosis of VEXAS are herein reviewed…. Given the multiple upregulated inflammatory pathways involved, interest has grown in the use of Janus kinase signal transducer and activator of transcription (JAK-STAT) inhibitors. Ruxolitinib has shown early signals of potential efficacy in a small group of patients with VEXAS and MDS,7,60 but nonruxolitinib JAK-STAT inhibitors (tofacitinib, baricitinib) have not provided consistent benefit and are generally not recommended….

Guilpain, P. (2022). **JAK inhibitors in autoinflammatory syndromes? The long road from drug development to daily clinical use**. *Rheumatology*, in press. Request full-text.

Editorial. This editorial refers to the article 'JAK inhibitors in difficult-to-treat adult-onset Still's disease and systemic-onset juvenile idiopathic arthritis', published by Gillard L et al. The study by Gillard and colleagues describes the use of Janus kinase (JAK) inhibitors (JAKi) for difficult-to-treat adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (sJIA), which are both systemic autoinflammatory diseases (SAID)… Interestingly, JAKi could be useful for the treatment of VEXAS syndrome (vacuoles, E1, X-linked, autoinflammatory manifestations, somatic), presenting with various inflammatory features (including polychondritis) and hematological diseases (mainly myelodysplastic syndrome and monoclonal gammopathy). Recently, ruxolitinib was reported to induce a clinical response in about 50% of patients, independently of the presence of myeloid neoplasm, and may exhibit better efficacy over other JAKi in this context [10]. Notably, the safety of JAKi is difficult to establish, as VEXAS syndrome itself can also lead to infectious and thromboembolic events.

Nguyen, K. K. et. al (2022) **VEXAS syndrome: A dermatological perspective**. Australasian Journal of Dermatology, 63(4), 488-492. Click for full-text.

Case study. Here, we report on two patients with treatment-resistant neutrophilic dermatosis and myelodysplastic syndrome, who were subsequently diagnosed with VEXAS syndrome. Our cases highlight the need for dermatologists' awareness of this novel condition and to initiate early referral to haematologists for appropriate multidisciplinary care. Discussion… Refers to Bourbon et al… therapeutic approaches for 11 patients with VEXAS syndrome using time-to-next steroid-sparing agent as a marker of efficacy. In this cohort, the best outcomes were observed with JAK inhibitors (next treatment not reached, median follow- up 25.1 months), azacitidine (21.9 months) and ciclosporin (12.7 months), although most treatment strategies were only transiently effective for cutaneous lesions, and had limited effect on cytopenias or myelo-dysplastic changes.

Gurnari, C., & McLornan, D. P. (2022). **Update on VEXAS and role of allogeneic bone marrow transplant: Considerations on behalf of the Chronic Malignancies Working Party of the EBMT**. *Bone Marrow Transplantation*, *57*(11), 1642-1648. Request full-text.

Since its discovery, several groups have documented pleomorphic clinical phenotypes, in addition to a plethora of therapeutic options (e.g., JAK inhibitors, hypomethylating agents, and allogeneic stem cell transplant, allo-HCT) in retrospective case series. However, no treatment guidelines have been validated to date, VEXAS patients are typically steroid-dependent and may manifest life-threatening inflammatory symptoms refractory to multiple lines of therapy…. In a retrospective study, Heiblig reported on 30 VEXAS patients (median age 68 years) treated with JAKi [41]. Of note, 14 patients had an associated myeloid neoplasm (MN). JAKi choice included ruxolitinib (n = 12), tofacitinib (n = 11), baricitinib (n = 4) and upadacitinib (n = 3)…. Other small case series have reported variable degrees of responses following JAKI exposure…

Islam, S. et al. (2022) **VEXAS syndrome: lessons learnt from an early Australian case series**. Internal Medicine Journal, 52(4), 658-662. Click for full-text.

Refers to: A recent retrospective series evaluating therapeutic options in VEXAS syndrome suggested a role for JAK inhibitors in attaining a durable treatment response, although only short-term follow up was reported for the three patients.

Fabian, L. et al. (2021) **Case report: genetic double strike: VEXAS and TET2 positive myelodysplastic syndrome in a patient with long-standing refractory autoinflammatory disease**. *Swiss Medical Weekly*, 151(SUPPL 252), 5S. Click for full-text.

We present a patient, who suffered from a long-standing refractory adult-onset autoinflammatory syndrome (AIS), previously interpreted as various distinct rheumatic disorders. … Our case illustrates that the triad of an unresponsive multisystemic autoinflammatory disease, hematological abnormalities and vacuoles in myeloid- and erythroid progenitors in the bone marrow biopsy should prompt screening for the VEXAS syndrome…. A French center described a promising response to JAK-inhibitor therapy: 2 patients were treated with the JAK1/2 inhibitor ruxolitinib, and 1 patient with the JAK1/3 inhibitor tofacitinib. The IFN-signature of our patient as indicated by Siglec-1-positivity as well as the option to target multiple cytokines prompted us to follow this approach. In our patient, however, tofacitinib did not prove beneficial. This might be due to the concomitant MDS with TET2 mutation, the late stage of the disease or the choice of the JAK-inhibitor…

Heiblig, M. et al. (2021) **Toward a pathophysiology inspired treatment of VEXAS syndrome**. *Seminars in Hematology*, 58(4), 239-246. Request full-text.

VEXAS syndrome has an unmet need for therapeutic interventions. Even if few data exist regarding the treatment of this newly described syndrome, different options can be proposed given the unique pathophysiological consequences of the clonal dominance of UBA1 mutated hematopoietic stem cells. To date, allogeneic transplantation is the only curative option, but many questions remain regarding the selection of eligible patients, the conditioning regimen or management of toxicities that may be unique to VEXAS patients. Alternatively, drugs used in myelodysplastic syndrome such as hypomethylating agents or lenalidomide are interesting candidates, which could theoretically have also an effect on the clone. Another strategy is to target the inflammatory cascade, by inhibiting proinflammatory cytokines (such as TNFα, IL1, IL6) or effector cells, for example with JAK inhibitors… Drugs targeting cytokines (IL1, IL6, TNFα) and the effector cells signaling pathways (JAK inhibitors, calcineurin inhibitors, corticosteroids, and other immunosuppressive medications) have been used empirically in VEXAS patients prior to the identification of their underlying UBA1 mutation. Retrospective analysis of a small series of patients having received these drugs suggested that most of them had a transient effect, though prolonged responses were observed in some patients…'

Grayson, P. C. et al. (2021) **VEXAS Syndrome**. *Blood,* 137(26), 3591–3594. Click for full-text.

VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a monogenic disease of adulthood caused by somatic mutations in UBA1 in hematopoietic progenitor cells. Patients develop inflammatory and hematologic symptoms. Myeloid-driven autoinflammation and progressive bone marrow failure lead to substantial morbidity and mortality. Effective medical treatments need to be identified. Reports in the current issue of Blood describe novel UBA1 genetic variants, treatment options, and insight into disease pathophysiology. VEXAS syndrome represents a prototype for a new class of diseases… Treatment of VEXAS syndrome… Janus kinase inhibitors were effective for some features of systemic inflammatory disease, particularly skin involvement. Prospective evaluation of treatment efficacy is needed to define optimal clinical management.

JANUS KINASE INHIBITORS AND VEXAS – SINGLE CASE STUDY OR REFERENCE TO JAKS WITH LITTLE DETAIL

Collantes-Rodríguez, C. et al. (2023) **Vexas syndrome successfully treated with canakinumab**. JDDG: Journal of the German Society of Dermatology, 21(1):69-70. Request full-text.

Clinical letter. Refers to use of Janus kinase inhibitors in VEXAS syndrome with varying success.

Ziaee, V. et al. (2023) **Update of monogenic vasculitis: DADA2 and VEXAS syndrome**. International Journal of Rheumatic Diseases, 26(Supplement 1), 4. Request full-text.

Abstract only. Various treatments have been proposed as effective in the two disorders; TNF inhibitors and hematopoietic stem cell transplantation (HSCT) stand as the most effective treatments in DADA2, and Janus Kinase inhibitors and HSCT are suggested as the potential treatments in VEXAS.

Moura, M. C. et al (2022). **Lung Involvement in VEXAS Syndrome**. *Arthritis and Rheumatology*, *74*(Supplement 9), 3103-3104. Click for full-text.
Abstract only. Objectives: To describe lung involvement in VEXAS syndrome. Methods: A retrospective cohort study was conducted of all patients identified at the Mayo Clinic with VEXAS syndrome since October 2020. Clinical records and chest high resolution computed tomography (HRCT) scans were reviewed.... All patients received glucocorticoids (GC) (median duration of treatment was 2.6 years); 21 (96%) received conventional immunosuppressive agents (methotrexate, azathioprine, mycophenolate, leflunomide, cyclosporin, hydroxychloroquine, tofacitinib, ruxolitinib) and 9 (41%) received biologic agents (rituximab, tocilizumab, infliximab, etanercept, adalimumab, golimumab, abatacept).

Ciferska H. et al. (2022) **VEXAS syndrome: a report of three cases**. Clinical and Experimental Rheumatology, 40(7):1449 Request full-text.

Letters to the editor… The optimal therapy of VEXAS syndrome is not yet known, but the beneficial role of various immunosuppressants including azacytidine and janus kinase inhibitors has been reported.

Tozaki, N. et al. (2022) **A case of VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) with decreased oxidative stress levels after oral prednisone and tocilizumab treatment**. Frontiers in medicine, 9. Request full-text.

We report the case of a 64-year-old Japanese man with VEXAS syndrome. At age 63, he was referred to us with a recurrent erythema on the hands associated with a general fever of 38–40°C that had persisted for 4 or 5 days and had recurred about once a month for a year. The skin rash appeared 2 or 3 days after the onset of each fever episode… Discussion…Targeted agents, including anti-IL-1 (anakinra and canakinumab), anti-IL-6 (tocilizumab), anti-tumor necrosis factor α (TNF-α) (adalimumab, infliximab, and etanercept), and Janus kinase inhibitors, have been proposed as possible treatments for VEXAS syndrome.

Delplanque, M. et al. (2022) **Diagnostic and therapeutic algorithms for monogenic autoinflammatory diseases presenting with recurrent fevers among adults**. Rheumatology, in press. Request full-text.

The most important discovery for adult patients is VEXAS syndrome associated with somatic UBA1 mutations leading to an AID affecting mostly elderly men. Diagnosis of monogenic AIDs is based on personal and family history and detailed analysis of symptoms associated with febrile attacks in the context of elevated peripheral inflammatory markers. This review proposes a practical approach for the diagnosis of the main monogenic AIDs among adult patients…. For VEXAS syndrome, the treatment is not yet codified, but it seems that Janus kinase (JAK) inhibitors, in particular ruxolitinib, seem to be more effective than anti-cytokine biotherapy. Azacytidine has also shown some effectiveness. Nevertheless, more data are required.

Kao, R. L. et. al. (2022) **A case of VEXAS syndrome associated with EBV-associated hemophagocytic lymphohistiocytosis**. *Blood Cells, Molecules, and Diseases*, 93. Request full-text.

Case study of 1 patient. Refers to use of ruxolitinib. Vacuoles, E1, X-linked, autoimmunity, somatic (VEXAS) syndrome is characterized by a pathogenic mutation in UBA1, which leads to protean complications including autoimmunity and myelodysplasia. A 56-year-old man with

steroid-dependent, later steroid-refractory cutaneous polyarteritis nodosa and Sweet syndrome developed recurrent daily fever, macrocytic anemia, thrombocytopenia, acute hypoxic respiratory failure, and anasarca. He was eventually diagnosed with Epstein-Barr virus (EBV) viremia and hemophagocytic lymphohistiocytosis (HLH). He improved clinically with rituximab, ruxolitinib, and increased glucocorticoids before expiring from Pseudomonas sepsis. UBA1 exon 3 mutational analysis in myeloid enriched peripheral blood revealed a c.122T>C (p.Met41Thr) pathogenic variant, consistent with VEXAS syndrome. We describe the first case of EBV-associated HLH in a patient diagnosed with VEXAS syndrome. Early identification of this syndrome will be important in order to offer potential therapies before life-threatening complications arise.

Patel, B. A. et al. (2022)). **Towards treatments for VEXAS**. *British Journal of Haematology*, *196*(4), 804-805. Click for full-text.

There are two major approaches to therapeutics in VEXAS: to target and eradicate the etiologic UBA1 clone and/or inhibit inflammatory pathways and cytokines. VEXAS results in high morbidity and mortality. Effective therapeutics and development of a treatment algorithm are immediate goals. In addition to azacytidine, anti-IL6 (tocilizumab), JAK inhibitors (ruxolitinib), and hematopoietic stem cell transplantation have been effective in small cohorts and case reports. The current article describes three patients who showed hematologic improvement without improved inflammatory symptoms, indicating that azacytidine might also serve as a bridge to hematopoietic stem cell transplant in VEXAS.

Guerrero-Bermudez, C. A. et al. (2022) **Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome (VEXAS syndrome) with prominent supraglottic larynx involvement: a case-based review**. *Clinical Rheumatology*, 41(11), 3565-3572. Click for full-text.

Case study. We describe a case of a 72-year-old male patient with VEXAS syndrome with p.Met41Val mutation of the UBA1 gene, prominent supraglottic larynx involvement, and costochondritis. Discussion: Mentions JAK inhibitors, specially ruxolitinib, as 'associated with a dramatic regression of cutaneous lesions and are currently being tested in a larger cohort with a longer follow-up time to provide efficacy and security data.'

Habershon, C. et al. (2022) **VEXAS syndrome: a case treatment refractory, severe autoinflammatory disease**. Internal Medicine Journal, 52(Supplement 5), 26. Click for full-text.

Abstract only. Case study. Mentions that patient commenced tofacitinib but no information about outcome.

Beecher, M. et al. (2022) **Recurrent dacryoadenitis associated with VEXAS syndrome.** Clinical & Experimental Ophthalmology, 50(8), 934. Click for abstract.

Abstract only. Poster. This case will describe an atypical presentation of recurrent dacryoadenitis associated with VEXAS syndrome…. Tofacitinib, a JAK inhibitor, was commenced with resolution of inflammatory symptoms.

Beecher M. et al. (2022) **Recurrent orbital inflammation associated with VEXAS syndrome**. Clinical and Experimental Ophthalmology, 50(8), 934. Request full-text.

This report describes an atypical presentation of recurrent dacryoadenitis associated with VEXAS syndrome and provides a review of the literature. A 68-year-old male presented with three episodes of unilateral alternating dacryoadenitis followed by bilateral involvement over a 4-year

period… Genetic testing established the diagnosis of VEXAS syndrome and tofacitinib, a JAK inhibitor, was commenced with resolution of inflammatory symptoms… Tofacitinib provided significant benefits to this patient, reducing the frequency and severity of flares, with no further periorbital or facial inflammation. In a case series, tofacitinib use was associated with a complete or partial resolution of symptoms at three months in only a minority of 11 patients. In contrast, ruxolitinib, another JAK inhibitor, provided complete resolution of symptoms in all 11 patients.

Euvrard, R. (2022) **VEXAS syndrome-related AA amyloidosis: a case report**. Rheumatology, 61(1), E15-E16. Click for full-text.

We report herein the case of a systemic AA amyloidosis revealing a VEXAS syndrome and responding favourably to anti-IL-1 therapy …There is a need for the development of effective therapeutic interventions to target this inflammation and prevent AA amyloidosis development [6]. Because of the pathogenesis and similarities with other inflammatory conditions, anti-IL-17, anti-IL-6, Janus kinase inhibitors and anti-IL-1 therapies are the best candidates to treat VEXAS syndrome.

Goyal, A. et al. (2022) **Tocilizumab for treatment of cutaneous and systemic manifestations of vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome without myelodysplastic syndrome**. JAAD Case Reports, 23, 15-19. Click for full-text.

Systemic corticosteroids and supportive care are the first-line treatment for the inflammatory symptoms and cytopenias of VEXAS. However, identification of nonsteroidal therapies is necessary for long-term management. The steroid-sparing treatments that have been reported in the literature with some success are methotrexate, mycophenolate, azathioprine, cyclophosphamide, and cyclosporine.4 Targeted agents, including anti–IL-1 therapy (anakinra and canakinumab), IL-6 blockade (tocilizumab), tumor necrosis factor α blockade (adalimumab, infliximab, and etanercept), and Janus kinase inhibitors, have been proposed as possible treatments for VEXAS.

Vitale, A. (2022) **Development and Implementation of the AIDA International Registry for Patients With VEXAS Syndrome**. Frontiers in medicine, 9 Click for full-text.

Objective: The aim of this paper is to present the AutoInflammatory Disease Alliance (AIDA) international Registry dedicated to Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic (VEXAS) syndrome, describing its design, construction, and modalities of dissemination… The Registry includes 4,952 fields organized into 18 instruments designed to fully describe patient's details about demographics, clinical manifestations, symptoms, histologic details about skin and bone marrow biopsies and aspirate, laboratory features, complications, comorbidities, therapies, and healthcare access. Conclusion: This international Registry for patients with VEXAS syndrome will allow the achievement of a comprehensive knowledge about this new disease, with the final goal to obtain real-world evidence for daily clinical practice, especially in relation to the comprehension of this disease about the natural history and the possible therapeutic approaches… If VEXAS syndrome is only little known as a whole, the lesser-known aspect is the proper therapeutic approach. Many treatments have been tested in VEXAS syndrome, including glucocorticoids, conventional disease-modifying antirheumatic drugs (cDMARDs), azacytidine, biologically targeted agents and janus kinase (JAK) inhibitors. Except for corticosteroids, which are especially useful at high dosage, preliminary data show a significant interindividual variability in the effectiveness of these therapeutic strategies. Therefore, identifying the better treatment approach based on the patient's features could allow the optimal treatment in the perspective of

a personalized medicine. Similarly, the identification of the best dosages and the assessment of long-term safety profile represent indispensable goals to ensure a correct management.

Habershon C. et al. (2022) **VEXAS syndrome: a case of treatment refractory, severe autoinflammatory disease**. *Internal Medicine Journal*, 52(supplement 5), 26. Click for full-text.

Abstract only. Reports on the case of a 71-year-old gentleman with a recent diagnosis of VEXAS syndrome. Mentions commencing Tofacitinib 5 mg.

Hochman M.J. et al. (2022) **Myelodysplastic syndrome and autoimmune disorders: two sides of the same coin?** *The Lancet Haematology* 9(7), e523-e534. Click for full-text.

Mentions ruxolitnib being under investigation for the treatment of VEXAS syndrome. (Heibling 2022)

JANUS KINASE INHIBITORS AND VEXAS – GREY LITERATURE

ASH Clinical News. (2022) **Ruxolitinib Most Effective JAK Inhibitor for VEXAS Syndrome**. *ASH Clinical News*. Aug. Click for full-text.

Treatment with Janus kinase (JAK) inhibitors, especially ruxolitinib, was an effective therapeutic option for patients with vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome, according to a retrospective analysis published in Blood.

Goring, S. et. Al. (2022) **CADTH Health Technology Review: Treatment options for VEXAS syndrome**. *Canadian Journal of Health Technologies*, 2(11). Click for full-text.

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a disorder caused by a genetic mutation, and is characterized by hematologic and autoinflammatory symptoms that are severe and progressive. It is typically seen in older men and is considered to be rare. Proposed treatments for VEXAS syndrome include DNA hypomethylating agents such as azacitidine, anti-IL6 monoclonal antibodies such as tocilizumab, and Janus kinase inhibitors such as ruxolitinib. We found 5 non-randomized studies on the effectiveness of the proposed treatments — 4 on azacitidine; 1 on ruxolitinib; and 1 on azacitidine, ruxolitinib, and tocilizumab. There are several limitations to the research studies, most notably that they included a small number of patients who were retrospectively identified as having VEXAS syndrome. Therefore, the effectiveness of tocilizumab, ruxolitinib, and azacitidine for treating VEXAS syndrome is uncertain. We did not find any evidence-based guidelines on the management of VEXAS syndrome.

MEDLINE SEARCH STRATEGY

Ovid MEDLINE(R) ALL <1946 to March 14, 2023>

1 (vacuoles and E1 and X-linked and autoinflammatory and somatic).tw. 75

2 vexas.mp. 192

3 1 or 2 193

4 Janus Kinase Inhibitors/ 1389

5 (Ruxolitinib or Jakavi or Jakafi or Janus Kinase Inhibitor* or JAKinibs or (JAK adj3 inhibitor*)).mp. 7007

6 Pharmacology, Clinical/ or therapeutics/ or exp drug therapy/ or (therap* or medicat* or pharma* or drug* or treatment*).tw. 9053650

7 adalimumab/ or (tocilizumab or tofacitinib or adalimumab or actemra or Xeljanz or AURO?Tofacitinib or PMS?Tofacitinib or TARO?Tofacitinib or Amjevita or Humira or Abrilada or Amgevita or Hadlima or Hulio or Humira or Hyrimoz or Idacio or Simlandi or Yuflyma).tw,kw. 18213

8 4 or 5 or 6 or 7 9057027

9 3 and 8 70

10 limit 9 to english language 66

11 limit 10 to yr="2013 -Current" 66

SEARCH TERMS

Concept	MeSH headings	Keywords
VEXAS syndrome	NA	vacuoles E1 X-linked autoinflammatory somatic, VEXAS
Ruxolitinib / Janus kinase inhibitors / Drug therapy	Janus kinase inhibitors, Pharmacology, Clinical, Therapeutics, Drug therapy, Adalimumab	Ruxolitinib, Jakavi, Jakafi, Janus Kinase Inhibitors, JAKinibs, JAK inhibitors, Tocilizumab, tofacitinib, adalimumab, actemra, Xeljanz, AUROTofacitinib, PMSTofacitinib, TAROTofacitinib, Amjevita, Humira, Abrilada, Amgevita, Hadlima, Hulio, Humira, Hyrimoz, Idacio, Simlandi, Yuflyma, therapy, medication, pharmacology, drugs, treatment