

CASE REPORT OPEN ACCESS

Momelotinib Is Effective in Treatment for VEXAS Syndrome: Two Cases Within the AGMT Austrian Myeloid Registry

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ABSTRACT

VEXAS syndrome is caused by somatic mutations in the UBA1 gene and includes features of both autoinflammatory and myeloid diseases. Among several treatment options, JAK inhibitors have proven effective, especially ruxolitinib. However, anemia is often present in VEXAS syndrome. The novel JAK inhibitor momelotinib is approved for myelofibrosis with anemia. Here, we report of two patients within the Austrian Myeloid Registry of the Austrian Group Medical Tumor Therapy (AGMT), with newly diagnosed VEXAS syndrome and anemia, who were treated with momelotinib. Both patients experienced an improvement in anemia, a decrease in inflammation, and the treatment was well tolerated. VEXAS syndrome (acronym for: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is an autoinflammatory disease caused by somatic mutations in the ubiquitin-like modifier activating enzyme 1 (UBA1) gene. Key clinical features comprise hematological as well as rheumatological, features. Associated hematological conditions include cytopenia, bone marrow failure, myelodysplastic syndrome, increased risk for thromboembolic events, and prominent vacuolization of myeloid and erythroid precursor cells in the bone marrow.

Involvement of multiple organs is possible, most commonly skin and connective tissue, lung, or blood vessels, and classical features include polychondritis, neutrophilic dermatosis, or vasculitis [1, 2]. Several hot-spot mutations of UBA1 have been described, most prominently involving methionine 41.

Treatment with high-dose glucocorticoids is effective, and steroid-sparing approaches mainly include hypomethylating agents, Janus kinase (JAK) inhibitors, or IL-1 or IL-6 directed approaches [3]. Many patients benefit from glucocorticoid treatment, especially concerning inflammatory manifestations. As

a glucocorticoid-sparing strategy, tocilizumab is of benefit in most patients. Due to their capability to target multiple inflammatory pathways, JAK inhibitors have emerged as an effective treatment option [4]. Regarding JAK inhibitors, often ruxolitinib is chosen and is considered most effective [5]. However, moderate to severe anemia is a well-known adverse effect of RUX, reported in 35%–45% of patients within the clinical trials for myelofibrosis, COMFORT I&II and JUMP [6]. For VEXAS syndrome with leading cytopenias, HMAs (azacitidine, decitabine) are considered standard therapies, and allogeneic stem cell transplantation can be discussed [4, 7].

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We present two cases of patients with VEXAS syndrome within the Austrian Myeloid Registry of the Austrian Group Medical Tumor Therapy (AGMT), who, to our knowledge, present the first experiences of treatment with the novel JAK2 inhibitor momelotinib (MMB). MMB was chosen as first-line treatment for these patients due to baseline anemia below 10g/dL at the start of treatment.

MMB is a newer generation JAK inhibitor and its major targets include JAK1, JAK2, JAK3, and TYK2 inhibitor [8]. Due to its additional inhibition of Activin A Receptor type 1 gene (ACRV1), it leads to hepcidin downregulation, thereby increasing iron availability and ultimately to improvement of anemia [9]. MMB has already received approval for higher-risk myelofibrosis with anemia (Sep 2023 FDA, Apr 2024 EMA).

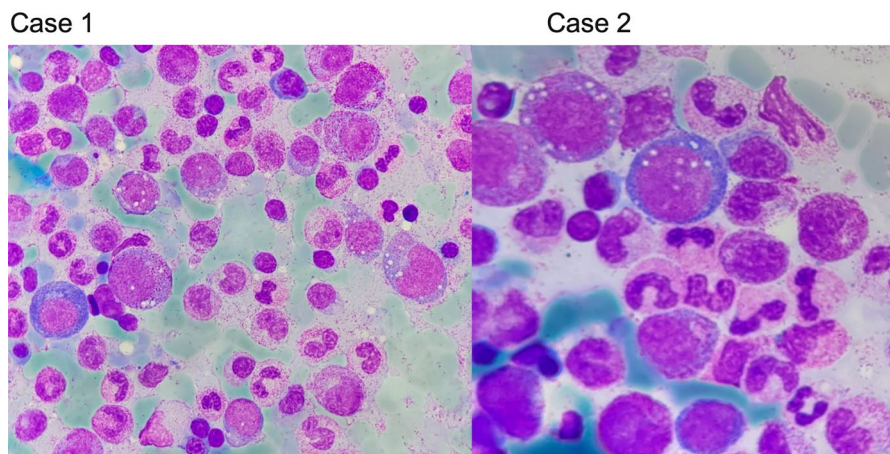
1 | Case 1

Patient 1 is an 82-year-old male who presented with B-symptoms including night sweats and elevated inflammatory parameters (CRP initially undulating between 5 and 10 mg/dL). There was no clinically apparent infectious focus, and an initial CT scan was negative apart from discrete interstitial pulmonary infiltrates. Shortly after, a thrombosis of the external jugular vein was diagnosed despite ongoing anticoagulation with phenprocoumon within therapeutic range. A screening for antiphospholipid antibodies was negative, and the patient was started on

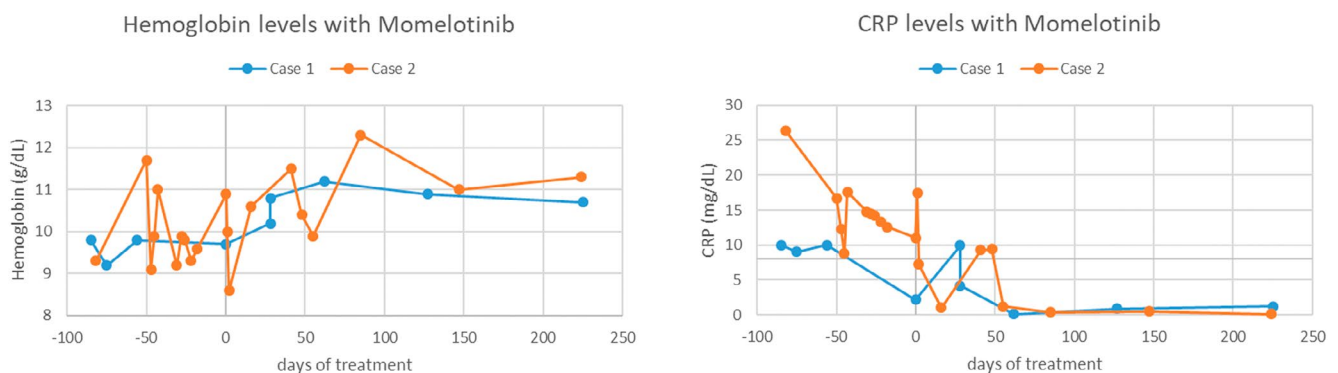
apixaban. A further diagnostic assessment with a PET scan did not reveal additional findings.

Due to macrocytic anemia with hemoglobin levels of around 10g/dL and mild neutropenia, a bone marrow biopsy was performed, where trilinear dysplasia was described, along with prominent cellular vacuolization (Graph 1). The molecular workup revealed a UBA1 (GlyMet40AlaLe—involving hotspot Met41) alteration, along with a ZRSR2 and TET2 mutations. The diagnosis of VEXAS syndrome was made, with associated MDS (with revised IPSS very low risk and molecular IPSS low risk).

Specific therapy for the MDS was not indicated, and therefore, the decision for initiation of a JAK inhibitor therapy was made, due to significant inflammation with persistent CRP of 10 mg/dL and ESR 80–100 mm/h. With hemoglobin levels below 10g/dL (9,7g/dL), the patient started on MMB within the Austrian early access program. After 4 weeks of treatment, the night sweats that had been ongoing for almost 6 months had vanished. CRP levels declined to normal values within the first 2 months of treatment and have remained below 1,5 mg/dL for the subsequent months (Graph 2). The hemoglobin values have increased to stable values around 11 g/dL (Graph 2). Treatment with MMB 200 mg once daily is ongoing and tolerated well without adverse events within the first 9 months of treatment.



GRAPH 1 | Bone marrow cytology with typical features of VEXAS syndrome, including vacuolization of the erythroid and myeloid precursors.



GRAPH 2 | Changes in hemoglobin and CRP levels before and during treatment with momelotinib.

2 | Case 2

The second patient is an 81-year-old male. He experienced relapsing fevers without clinically apparent infectious symptoms over the course of several months. A PETscan displayed multiple pathologically enlarged lymph nodes and chronic inflammatory changes of the lung parenchyma. The initial histology of a lymph node was without evidence of malignancy but inconclusive regarding the cause of inflammation. An empiric course of corticosteroid transiently improved symptoms, but subsequent a pancreatitis, as part of an IgG4-associated disorder, was diagnosed.

After the diagnosis of a perichondritis, and due to anemia and mild thrombocytopenia, in conjunction with the given history, a bone marrow biopsy was performed. On cytology, prominent vacuoles within hematopoietic cells were observed, and an UBA1 mutation was found (pMet41Thr) (Graph 1). Bone marrow histology was without myelodysplastic changes, and an additional TET2 mutation was also found. There were no signs of hemophagocytosis.

Initially, the dose of corticosteroids was increased, and simultaneously treatment with the JAK inhibitor MMB was started. The patient's condition improved rapidly, and inflammatory parameters markedly declined from CRP 15–20 mg/dL to 1 mg/dL within 10 days and remained normal within the first five months of treatment (apart for one episode of accidental therapy pause by the patient), along with normalization of previously elevated ferritin values and a decline in ESR (Graph 2). Hemoglobin increased from below 10 g/dL to above 11 g/dL. Corticosteroids were tapered (Graph 2). VEXAS syndrome has remained in remission for 6 months after initiation of MMB treatment, which is ongoing. The initial dose of 200 mg once daily was decreased to 100 mg daily at around 6 months due to grade IV neutropenia, which was likely attributed to MMB.

3 | Discussion

Here, we report on two patients who had typical signs and symptoms of VEXAS syndrome including constitutional symptoms, inflammatory pulmonary changes, myelodysplastic syndrome in one of the patients, and cytopenia, perichondritis, and thrombosis.

We observed a decline in inflammation as apparent by improved symptoms and lab parameters, and importantly, MMB was also able to alleviate anemia.

Interestingly, it could be speculated that the activity of MMB against ACVR1 might add anti-inflammatory properties. Even though current data on MMB mainly stem from clinical data on myelofibrosis, preclinical observations overall suggest an increased iron availability due to the impact of MMB on iron availability due to its negative regulation on hepcidin (via ACVR1) overall in chronic inflammation. This effect appears to be additional to the anti-inflammatory effect on JAK1/2 [10]. Moreover, limited data (mainly in context of human heterotopic ossification) attribute ACVR1 a role in increasing proinflammatory signatures including cytokines and M1 macrophage polarization,

for example, via NFκB activation [11, 12]. In fact, previously, a theoretical advantage for MMB and pacritinib compared to ruxolitinib in the mitigation of inflammation due to targeting ACVR1 has been discussed [4].

To our knowledge, we describe the first experiences of the JAK inhibitor MMB as a safe and effective treatment option for VEXAS syndrome, especially in patients with anemia.

The Austrian Myeloid Registry of the Austrian Group for Medical Tumor Therapy (AGMT) Study Group is a registered noninterventional study (NCT04438889) and was approved by the ethics committee 415-E/2581/9–2020. Patients were included within the registry and provided written consent.

Author Contributions

Conceptualization: D.K. and T.M. Data analysis: D.K. Visualization: D.K. and T.M. Cytology images: M.L. Directly involved in patient treatment: D.K., M.L., I.T., A.E., T.M. Original draft: D.K. and T.M. Critical review and editing: all authors. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

T.M. received honoraria from GSK. The Austrian Myeloid Registry of the Arbeitsgemeinschaft Medikamentöse Tumorthherapie (AGMT) Study Group received research funding from GSK.

Data Availability Statement

Data available on request from the authors.

References

1. P. C. Grayson, B. A. Patel, and N. S. Young, "VEXAS Syndrome," *Blood* 137, no. 26 (2021): 3591–3594, <https://doi.org/10.1182/blood.2021011455>.
2. D. B. Beck, D. L. Bodian, V. Shah, et al., "Estimated Prevalence and Clinical Manifestations of UBA1 Variants Associated With VEXAS Syndrome in a Clinical Population," *Journal of the American Medical Association* 329, no. 4 (2023): 318–324, <https://doi.org/10.1001/jama.2022.24836>.
3. A. Al-Hakim and S. Savic, "An Update on VEXAS Syndrome," *Expert Review of Clinical Immunology* 19, no. 2 (2023): 203–215, <https://doi.org/10.1080/1744666X.2023.2157262>.
4. M. J. Koster, T. L. Lasho, H. Olteanu, et al., "VEXAS Syndrome: Clinical, Hematologic Features and a Practical Approach to Diagnosis and Management," *American Journal of Hematology* 99, no. 2 (2024): 284–299, <https://doi.org/10.1002/ajh.27156>.
5. M. Heiblig, M. A. Ferrada, M. J. Koster, et al., "Ruxolitinib Is More Effective Than Other JAK Inhibitors to Treat VEXAS Syndrome: A Retrospective Multicenter Study," *Blood* 140, no. 8 (2022): 927–931, <https://doi.org/10.1182/blood.2022016642>.
6. S. Verstovsek, R. A. Mesa, R. A. Livingston, W. Hu, and J. Mascarenhas, "Ten Years of Treatment With Ruxolitinib for Myelofibrosis: A Review of Safety," *Journal of Hematology & Oncology* 16, no. 1 (2023): 82, <https://doi.org/10.1186/s13045-023-01471-z>.

7. K. Sockel, K. Götze, C. Ganster, et al., “VEXAS Syndrome: Complete Molecular Remission After Hypomethylating Therapy,” *Annals of Hematology* 103, no. 3 (2024): 993–997, <https://doi.org/10.1007/s00277-023-05611-w>.
8. A. Tefferi and A. Pardanani, “Momelotinib for Myelofibrosis: Our 14 Years of Experience With 100 Clinical Trial Patients and Recent FDA Approval,” *Blood Cancer Journal* 14, no. 1 (2024): 47, <https://doi.org/10.1038/s41408-024-01029-3>.
9. A. Tefferi, A. Pardanani, and N. Gangat, “Momelotinib (JAK1/JAK2/ACVR1 Inhibitor): Mechanism of Action, Clinical Trial Reports, and Therapeutic Prospects Beyond Myelofibrosis,” *Haematologica* 108, no. 11 (2023): 2919–2932, <https://doi.org/10.3324/haematol.2022.282612>.
10. M. Asshoff, V. Petzer, M. R. Warr, et al., “Momelotinib Inhibits ACVR1/ALK2, Decreases Hepcidin Production, and Ameliorates Anemia of Chronic Disease in Rodents,” *Blood* 129, no. 13 (2017): 1823–1830, <https://doi.org/10.1182/blood-2016-09-740092>.
11. K. Matsuo, A. Lepinski, R. D. Chavez, et al., “ACVR1^{R206H} Extends Inflammatory Responses in Human Induced Pluripotent Stem Cell-Derived Macrophages,” *Bone* 153 (2021): 116129, <https://doi.org/10.1016/j.bone.2021.116129>.
12. E. Barruet, B. M. Morales, C. J. Cain, et al., “NF- κ B/MAPK Activation Underlies ACVR1-Mediated Inflammation in Human Heterotopic Ossification,” *JCI Insight* 3, no. 22 (2018): e122958, <https://doi.org/10.1172/jci.insight.122958>.