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VEXAS syndrome

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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VEXAS syndrome

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1 Summary

Hematological-inflammatory disorders were long anticipated and have been described as clinical syndromes rather than genetically defined disorders. With the description of VEXAS syndrome (**v**acuoles, **E**1 enzyme, **X**-linked, **a**utoinflammatory, **s**omatic) in 2020, a clearly genetically defined, clonal hematologic-inflammatory entity was identified, which has since been regarded as the prototype of this disease group [1].

The condition is caused by an acquired mutation in the UBA1 gene of hematopoietic progenitor cells. The clinical inflammatory manifestations are heterogeneous and can affect multiple organ systems. Concurrently, there is clonally expanded hematopoiesis with variable hematological manifestations, ranging from CHIP and CCUS to myelodysplastic neoplasms (see Onkopedia Guideline on MDS) and transformation into acute myeloid leukemia (see Onkopedia Guideline on AML); associations with plasma cell disorders (see Onkopedia Guidelines on MGUS (German only) and Multiple Myeloma (German only)) have also been described. In addition to mild forms of the disease, severe, complication-prone courses are frequently observed, characterized by refractory fever, pronounced inflammatory manifestations, and complications such as thromboembolic events, infections, and the need for treatment in an intensive care unit [2].

Standardized treatment regimens or approved medications are not yet available, and results from prospective studies are also not yet available. Treatment is currently based on case series and expert consensus, often following an approach analogous to that used for known hyperinflammatory diseases such as Still's disease. Various therapeutic approaches—including corticosteroids, IL-6 inhibitors [3], JAK inhibitors [3, 4], azacitidine [5, 6], and allogeneic hematopoietic stem cell transplantation (allo-HSCT) [7, 8]—are used. The latter is currently considered the only curative treatment option, although substances such as azacitidine can also induce deep molecular remissions.

2 Basics

2.1 Definition and Basic Information

The acronym VEXAS stands for the key features of the disease [1]:

V: vacuoles in the myeloid progenitor cells of the bone marrow,

E: E1 ubiquitin-activating enzyme, encoded by the *UBA1* gene,

X: X-linked disorder (therefore affecting almost exclusively males),

A: autoinflammatory disease with a systemic inflammatory response, and

S: somatic mutation, i.e., an acquired mutation that typically occurs in later adulthood.

2.2 Epidemiology

With a prevalence of 1:14,000 in the general population [9] and >1:4,000 among men over 50 years of age, the disorder is significantly more common than originally assumed. Since it is an X-linked disorder, men are primarily affected [10]. Women can also be affected [11], but in most cases this is due to concurrent X monosomy (e.g., in Turner syndrome). However, rare cases of the disease in females without X-chromosome loss have also been described, leading to discussion of X-inactivation (lyonization) as a possible mechanism. The median age of onset is 50–71 years [12–14]. The youngest patient described to date is 23 years old [15].

2.3 Pathogenesis

The pathogenesis of VEXAS syndrome is not yet fully understood in all its complexity. According to current knowledge, the disease is caused by an acquired somatic *UBA1* mutation in hematopoietic stem and progenitor cells [1]. *UBA1* encodes the E1 ubiquitin-activating enzyme (E1 enzyme), which initiates the first step of **ubiquitination**. This process marks misfolded or damaged proteins, thereby enabling their degradation.

The inefficient ubiquitination resulting from the *UBA1* mutation leads to an accumulation of misfolded proteins and the activation of the innate immune system. Consequently, there is excessive production of proinflammatory cytokines (IL-1, IL-6, IL-8, interferon, TNF-α) [16, 17], which significantly shape the inflammatory phenotype of VEXAS syndrome and also possess hematopoiesis-suppressing properties.

A distinction is made between the classic *UBA1* mutations in exon 3 at position p.Met41 (M41), which affect the start codon of the cytoplasmic isoform (UBA1b). These mutations lead to reduced translation of this isoform, as well as to the formation of the shorter and catalytically impaired isoform UBA1c [1, 13]. The most common classic mutations in exon 3 are: p.Met41Thr (c.122T>C), p.Met41Val (c.121A>G), and p.Met41Leu (c.121A>C), as well as adjacent splice-site variants; together, they account for approximately two-thirds of VEXAS cases [18]. In addition, an increasing number of atypical “non-M41 mutations” are being described, which are characterized less by loss of function but rather as inducing varying degrees of functional impairment of the nuclear and cytoplasmic UBA1 isoforms [18].

2.4 Risk Factors

VEXAS syndrome is an X-linked disorder and therefore primarily affects males. No exogenous risk factors have been described to date.

3 Prevention and Early Detection

3.1 Prevention

No specific preventive measures are currently known.

3.2 Early Detection

Measures for early detection have not yet been established.

4 Clinical characteristics

The clinical characteristics of VEXAS syndrome are extremely heterogeneous and can affect various organ systems. The severity also varies considerably: While mild courses with little or no inflammatory activity have been described—manifesting exclusively through hematologic changes—at the other end of the spectrum, fulminant, inflammatory disease courses with multiorgan involvement may occur, requiring intensive care management.

Due to the often nonspecific symptoms, diagnosis is frequently delayed. Early recognition therefore requires knowledge of the typical clinical manifestations:

The most common manifestations include fever (64–100%), skin manifestations such as Sweet's syndrome, maculopapular rashes, panniculitis, livedo racemosa, or urticarial lesions (50–90%), as well as predominantly macrocytic anemia (approximately 95%) [1, 12, 14, 19]. Chondritis, particularly of the auricle and nose, is a common feature in patients with VEXAS syndrome and is reported in approximately 40% of cases [20]. Musculoskeletal manifestations such as arthritis or tenosynovitis are also frequently observed. In addition, other organ systems may be affected: pulmonary involvement with radiographic evidence of ground-glass opacities, consolidations, or pleural effusions is found in approximately 50%–87% of patients [21, 22], and ocular involvement in 30–50% [23, 24]. Less commonly, the heart, kidneys, or genital organs (especially orchitis) are affected, as well as the peripheral nervous system and, very rarely, the central nervous system [25].

It is not uncommon for patients to present with rheumatologic diagnoses characterized by atypical clinical courses and an inadequate response to conventional immunosuppressive therapies.

VEXAS patients with atypical non-M41 mutations typically exhibit milder inflammatory symptoms [18, 26] and primarily present with a hematologic phenotype.

In addition to macrocytic anemia, which is the most common hematologic manifestation, VEXAS patients also experience thrombocytopenia and leukopenia. In approximately 50% of affected individuals, myelodysplastic neoplasms (see Onkopedia MDS Guideline) are diagnosed concomitantly; due to their typically mild morphological changes (mild dysplasia, usually without blast proliferation), these are often first recognized through characteristic molecular genetic findings. In addition, plasma cell disorders may occur (see Chapter 5.1.1 Diagnostics).

Table 1: with clinical manifestations

Organ		Symptoms	Evaluation
Skin		Itching, urticaria, maculopapular lesions, livedo racemosa, Sweet's syndrome, leukocytoclastic vasculitis	Dermatology, biopsy if necessary
Cartilage		Pain, swelling in cases of ear and nasal chondritis; hoarseness, dysphagia in cases of epiglottic chondritis	ENT examination
Lungs		Shortness of breath and cough	**Chest CT:** ground-glass opacities, consolidations, pleural effusions **Pulmonary function** with mild restrictive ventilatory impairment, **Bronchoscopy with BAL or biopsy:** neutrophilic alveolitis and parenchymal inflammation [22]
Eyes		Periorbital edema, episcleritis, uveitis, conjunctivitis, blepharitis, orbital myositis	Ophthalmologist
Musculoskeletal		Arthritis, arthralgia, tenosynovitis	Rheumatologist, ultrasound if necessary, MRI, serological markers of inflammation
Kidney		Renal insufficiency	Nephrologist, urine sediment, biopsy: interstitial nephritis
Genital organs		Orchitis	Urologist
Nervous system			
	Central nervous system	Encephalopathy, lacunar cerebral infarcts, posterior reversible encephalopathy syndrome (PRES), optic perineuritis	Neurological examination, cMRI
	Peripheral nervous system	Polyneuropathy, cranial nerve involvement, mononeuropathy	Neurological examination, ENG, EMG
Heart		Myocarditis and pericarditis	Cardiologist, TTE, cardiac MRI if necessary
Thromboembolism		DVT, PE, stroke, myocardial infarction	Duplex ultrasound of the extremities, contrast-enhanced CT cranial imaging, TTE, ECG, cardiac enzymes
Bone marrow		Symptoms related to anemia, thrombocytopenia, or leukopenia; MDS; multiple myeloma	Hematologist, including complete blood count (CBC), differential blood count (DBC), serum electrophoresis, and light chain quantification, and KMP

4.1 Complications

Thromboembolic events are reported in approximately 50% of patients. These are predominantly of venous origin and, less commonly, of arterial origin [27, 28]. They usually occur within the first two years after diagnosis.

Infections are common in patients with VEXAS syndrome and are severe in 40–60% of cases. The lungs are most commonly affected, followed by skin infections and bacteremia. Opportunistic pathogens, such as Pneumocystis jirovecii, Legionella pneumophila, nontuberculous mycobacteria, and varicella-zoster virus, are frequently found [29–31]. Since these pathogens also occur in VEXAS patients not receiving immunosuppressive therapy, it is assumed that VEXAS syndrome is associated with an immunodeficiency per se.

5 Diagnosis

5.1 Diagnostic Approach

The diagnosis is confirmed by detecting the *UBA1* mutation in bone marrow or peripheral blood.

In cases of unexplained inflammatory symptoms combined with (primarily macrocytic) anemia or a paraprotein, molecular genetic testing for a UBA1 mutation should be ordered. Testing should be performed particularly in the following scenarios:

- Men (and women) > 40–50 years of age with unexplained inflammatory symptoms and cytopenias
- Patients with recurrent or treatment-resistant polychondritis/autoinflammation
- Patients with MDS, MGUS, or multiple myeloma and persistent signs of inflammation

Over the past two years, clinical scoring systems have been published that can help to facilitate the selection of patients for *UBA1* mutation analysis. The MAEDA score is based on the following variables: onset of symptoms > 50 years of age, cutaneous lesions, pulmonary involvement, chondritis, and macrocytic anemia. The original study recommended UBA1 testing for a score of ≥3 [32]. The recently published SWIM score, which includes the following four variables—skin involvement, weight loss, inflammation, and macrocytic anemia—shows slightly higher specificity and efficiency [33]. Here, too, UBA1 testing was recommended for a score of ≥2.

5.1.1 Initial Diagnosis

The diagnosis of VEXAS syndrome is based on the detection of a pathogenic *UBA1* mutation (see chapter 5.1.2 Molecular Genetics). In addition, the diagnosis of VEXAS syndrome includes a complete blood count (CBC) with a differential count and a bone marrow examination.

As a rule, patients present not only with clinical signs of inflammation but also with increased inflammatory serum markers such as ESR and CRP.

In some patients with unclear skin lesions, histological examination reveals a picture consistent with Sweet syndrome, characterized by inflammatory infiltrates consisting of immature myeloid cells as well as variable proportions of mature neutrophils, lymphocytes, and histiocytes.

Table 2: Diagnosis of VEXAS Syndrome

Differential blood count	• Cytopenias? (suspected macrocytic anemia, but also neutropenia and thrombocytopenia) • Monocytopenia, lymphocytopenia?
Laboratory parameters	• ESR, CRP • Creatinine, GFR, ALT, AST, LDH, ferritin, vitamin B12, folic acid, protein electrophoresis, immunofixation, • Plasma coagulation
Bone marrow	• Cytology with iron staining: vacuoles? Dysplasia? Blasts? Ring sideroblasts? • Flow cytometry: Blasts, malignant plasma cell clone? • Histology: vacuoles? Dysplasia? Blasts? Fibrosis? Plasma cell proportion? • Cytogenetics: cytogenetic aberrations of a concomitant hematologic neoplasm
Molecular genetics	• *UBA1* mutation analysis (qualitative and quantitative) from bone marrow or peripheral blood: 1. In cases of anemia, a myeloid NGS panel analysis should be used to simultaneously detect mutations typical of MDS (e.g., *DNMT3A, TET2*). 2. If NGS is not available, targeted Sanger sequencing of *UBA1* can be performed as an alternative • Note: In cases of strong clinical suspicion and absence of evidence for classic M41 mutations, sequence the entire *UBA1* gene
Imaging	• Depending on the clinic, abdominal ultrasound, chest CT, or cranial imaging as needed
Other	• Consultation with a specialist depending on symptoms (see Table 1 for clinical manifestations)

5.1.1.1 Complete blood count

Nearly all affected individuals exhibit macrocytic anemia [34]. In addition to anemia, thrombocytopenia and leukopenia also occur in one-third of patients. Cytopenia is often progressive over the course of the disease. Lymphopenia and monocytopenia are also found in approximately 50% of affected individuals.

5.1.1.2 Bone Marrow

A bone marrow aspiration is recommended for all VEXAS patients at the time of initial diagnosis to rule out MDS or other hematologic neoplasms. In fact, a diagnosis of MDS is made concurrently in 30–50% of VEXAS patients, usually in early stages of the disease with a low blast percentage [34]. In addition, plasma cell disorders may also occur; in addition to multiple myeloma, MGUS is occasionally reported.

Typically, the bone marrow shows hypercellularity, an increased G/E index, and mild dysplasia. In the initial description by Beck et al., cytoplasmic vacuoles were observed in myeloid and erythroid progenitor cells in nearly all patients. More recent studies report that vacuoles may be absent, particularly in cases with atypical mutations [35]. It is important to note that vacuoles are not specific to VEXAS syndrome but can also occur in cases of alcohol consumption, copper deficiency, or malnutrition [36, 37].

5.1.2 Molecular Genetics

Detection of a *UBA1* mutation in peripheral blood or bone marrow is essential for the diagnosis of VEXAS syndrome. Various methods are available for this purpose: Most patients have a VAF > 10%, which can be reliably detected using Sanger sequencing [38]. Sanger sequencing thus

remains a robust and cost-effective method for detecting the most common variants (p.M41Thr, p.M41Val, p.M41Leu) [23]. Next-generation sequencing (NGS) also allows for the detection of rare, non-canonical variants, such as splice-site mutations at the junction with exon 3 or mutations outside of exon 3. If Sanger sequencing was initially performed and yielded a negative result, more sensitive methods such as NGS should be used in cases of high clinical suspicion of VEXAS (e.g., SWIM score ≥ 2 or high MAEDA score), as these can reliably detect even mutations with a low VAF (>2%) throughout the entire UBA1 gene.

Since approximately 1% of all MDS patients may also carry a UBA1 mutation without necessarily exhibiting extrahematopoietic manifestations, analysis of the UBA1 gene in MDS patients is advisable, particularly when no typical MDS mutations (see Onkopedia MDS Guideline) are detectable.

Digital droplet PCR (ddPCR) is highly sensitive for “low-level” mutations that were previously identified using NGS. It is therefore particularly suitable for longitudinal therapy monitoring during anti-clonal therapy (e.g., azacitidine or allo-HSCT) [39]. Alternatively, NGS-based methods (ultra-deep NGS) can also be used. This method is particularly suitable for longitudinal monitoring in patients with rare mutations.

The three most common mutations are p.M41Thr (c.122 T > C), p.M41Val (c.121 A > G), and p.M41Leu (c.121 A > C). In approximately one-third of patients, non-canonical mutations are found, such as splice-site mutations (c.118-2A>C, c.118-1G>C, c.118-9_118-2del) [18].

Current evidence suggests that different mutations lead to differences in prognosis and phenotype: Patients with the p.M41Leu mutation often exhibit a milder phenotype and a better 5-year survival rate [12], whereas the p.M41Val mutation is more frequently associated with periorbital edema and undifferentiated inflammatory syndrome, but less frequently with chondritis [13]. In addition, the p.M41Leu mutation is associated with a predisposition to neutrophilic dermatoses. Larger patient cohorts are needed to robustly verify these phenotypes. However, a clear correlation between mutations and phenotype, prognosis, or therapeutic response has not yet been established.

Accompanying mutations are rare, particularly in classic M41 hotspot mutations, and primarily affect epigenetic regulators; the most common are typical mutations associated with clonal hematopoiesis, such as *DNMT3A* and *TET2* [18, 40]. A link between clonal hematopoiesis and autoimmune diseases has been described [41].

5.2 Classification

There is no official classification. VEXAS syndrome is not yet included in current classification systems such as the WHO classification and the ICC. Depending on the mutation type, a distinction is made between so-called canonical mutations affecting codon 41 and non-canonical mutations at other positions in the UBA1 gene [23].

5.3 Remission Criteria

To date, there are no internationally agreed-upon remission criteria for VEXAS syndrome [42]. In retrospective studies, the criteria defined by the French VEXAS study group (FRENVEX) were applied [3, 6]:

Table 3: VEXAS remission criteria, according to [3, 6]

Complete remission	Partial remission
Absence of clinical symptoms	
CRP (≤10 mg/L)	CRP reduction of ≥50%
Glucocorticoid dose ≤10 mg/day	Glucocorticoid reduction of ≥50 %

5.4 Prognostic factors

The median survival time from symptom onset is approximately 10 years [23]. The *UBA1* p.M41Leu mutation was associated with a milder disease course and a better 5-year survival rate compared to p.M41Val and p.M41Thr variants [12].

5.5 Monitoring, Relapse

VEXAS syndrome is a chronically progressive disease. Since both cytopenias and inflammatory symptoms may worsen over time, regular reevaluations of patients (every 1–3 months, depending on disease progression) are necessary. Patients with abnormal blood counts should also undergo frequent hematologic monitoring. If the blood count worsens, a repeat bone marrow aspirate should be performed to rule out a concomitant hematologic neoplasm.

Furthermore, clinical and serological markers of inflammation (CRP, and, if applicable, serum amyloid A) should be monitored regularly (at least every 3 months).

Longitudinal *UBA1* monitoring using the methods described above (see chapter 5.1.2, Molecular Genetics) appears to be appropriate, particularly when using treatment options that can lead to molecular remissions (e.g., hypomethylating agents).

5.6 Differential Diagnosis

The concurrent occurrence of cytopenias and autoimmune or autoinflammatory symptoms is not specific to VEXAS but has also been described in patients with other rheumatologic diseases and hematologic neoplasms. For example, approximately 10–20% of patients with MDS or chronic myelomonocytic leukemia (CMML) also exhibit systemic autoimmune or autoinflammatory manifestations (SAID) [43, 44]. A bone marrow aspiration is therefore essential for differential diagnosis. In these cases, no *UBA1* mutation can be detected. It is important to use a molecular genetic method capable of detecting even atypical *UBA1* mutations.

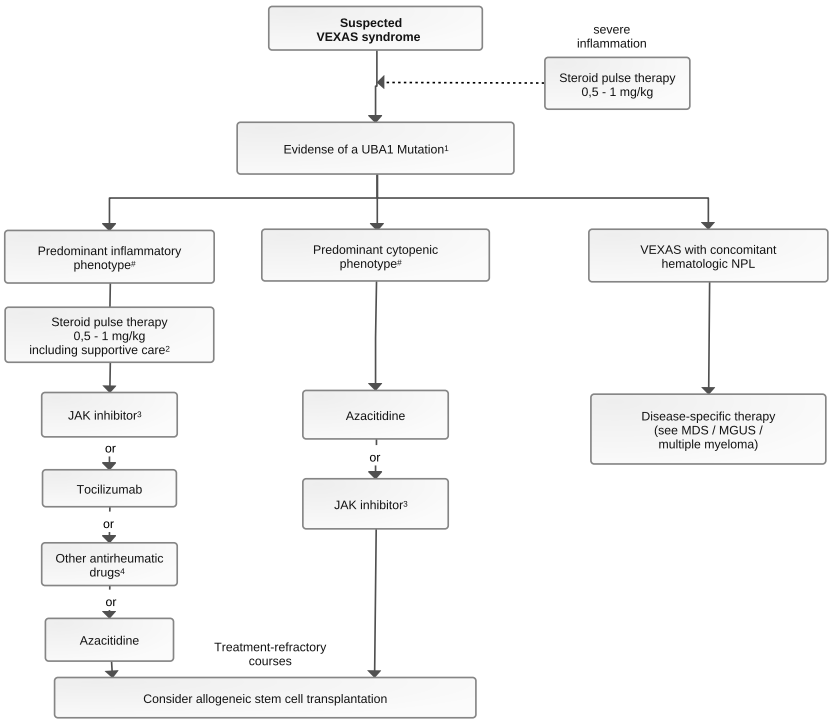
5.7 General Condition and Comorbidities

VEXAS syndrome is associated with high morbidity and mortality due to disease progression and treatment complications. The course of the disease is chronic and progressive, meaning that some patients are in a significantly compromised general condition. In particular, the long-term effects of prolonged and often high-dose steroid therapy contribute to morbidity. Therefore, a central goal of current studies is to reduce the steroid dose (see chapter 6.1.1.).

6 Treatment

Algorithms for the treatment of patients with VEXAS syndrome are shown in Figure 1. Whenever possible, patients should be treated within clinical trials.

Figure 1: Treatment of VEXAS syndrome



Legend:
[1] Molecular diagnostics via NGS or Sanger sequencing
[2] Supportive care: PCJ prophylaxis with Cotrimoxazol 960 3 times per week, HSV prophylaxis, and, if necessary, thrombosis prophylaxis
[3] Therapy within the context of clinical trials; outside of clinical trials, typically ruxolitinib
[4] Classic DMARDs or biologics
 # Inflammatory and hematological manifestations typically coexist in VEXAS syndrome; the predominant symptoms are often fluid and may require therapeutic adjustments as the disease progresses

6.1 Treatment structure

In general, treatment approaches can be divided into three pillars:

1. Anti-inflammatory therapy (suppression of systemic inflammation),
2. Anti-clonal therapy targeting the mutated stem cell clone to improve hematologic function
3. Supportive therapy to prevent complications

6.1.1 Steroid therapy

First-line therapy typically involves high-dose glucocorticoids (e.g., prednisolone 0.5–1 mg/kg), which often lead to rapid stabilization of the patient's general condition. However, many patients develop steroid dependence with associated side effects. Reducing the prednisolone dose below 15–20 mg is often not possible, as this frequently leads to a recurrence of disease activity.

6.1.2 Anti-rheumatic therapies

In general, medications that target signaling pathways of the innate immune system are more effective than those that modulate the adaptive immune system. In addition, therapies that influence the cytokine-based regulation of hyperinflammation (e.g., JAK inhibitors, interleukin-1/6 inhibitors) are more effective than conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate or azathioprine [23].

Cytokine-targeted agents— such as IL-1, IL-6, and JAK inhibitors—may be considered as steroid-sparing second-line therapies. However, the case series-based recommendations in this regard do not allow for an evidence-based recommendation due to variable success rates.

The largest analysis to date of steroid-sparing treatment approaches, conducted on 110 patients in France, showed that JAK and IL-6 inhibitors were more effective than other therapies, such as anti-IL-1 and TNF-α inhibitors [45], even though the overall response rate to IL-6 blockers remained limited, at only 20–26%. In most patients, it was not possible to discontinue steroid therapy [45, 46]. Anti-IL-1 therapies showed low overall response rates (<10% to 32% after three months) [23, 45, 47]. Better remission rates were reported with canakinumab compared to anakinra [47]. Severe cutaneous reactions at the injection site may occur in VEXAS patients treated with anakinra; therefore, this therapy should be used with caution.

6.1.3 JAK Inhibitors

JAK inhibitors have a broad mechanism of action in VEXAS syndrome, as they inhibit several disease-relevant inflammatory cytokines, including IL-6 as well as type I and type II interferons [23]. To date, ruxolitinib has achieved higher response rates (83% after 3 months) than other JAK inhibitors such as tofacitinib, baricitinib, or upadacitinib (18% after 3 months) [4]. The recommended dosage of ruxolitinib ranges from 2×10 mg to 2×20 mg daily and should be determined primarily based on the patient's existing cytopenia. It is known that ruxolitinib can induce not only thrombocytopenia but also worsening anemia during the first few months of therapy, which is why regular blood count monitoring is necessary. Due to the increased risk of viral infections, prophylaxis against alpha-herpesviruses should also be considered. Although ruxolitinib in particular is considered a promising treatment option, no molecular remissions have been reported to date; in isolated cases, the *UBA1* mutation burden increased during therapy [48]. Newer JAK inhibitors such as pacritinib and momelotinib are currently undergoing clinical trials for VEXAS syndrome. Initial positive case reports are available for momelotinib [49].

6.1.4 Hypomethylating agents

Azacitidine, a hypomethylating agent approved for high-risk MDS and long recommended for the treatment of MDS-associated autoinflammatory symptoms [5], has already been successfully used to treat clinical inflammatory symptoms and to induce hematologic remissions in VEXAS syndrome [6, 23, 50]. In addition to clinical and hematologic remissions, complete molecular eradication of the *UBA1*-mutated clone has also been reported. Current data show a response in inflammatory symptoms in approximately 60% of cases, usually with complete clinical remission, as well as hematologic remissions in 60–70% of cases; a reduction in the *UBA1* mutation burden of >25% was observed in two-thirds of patients with clinical remission [6]. Several case reports even document complete molecular remissions [51–54]. Both patients with and without concomitant MDS respond to the therapy.

In addition to direct cytotoxic effects, azacitidine modulates the cytokine profile and influences the bone marrow microenvironment, which could explain the positive effects on autoinflammatory symptoms [55, 56]. However, the exact mechanism by which azacitidine reduces the *UBA1* clonal burden remains unclear; in addition to direct cytotoxicity, synthetic lethality of *UBA1*-mutated cells is suspected [57]. To achieve optimal anti-clonal efficacy in VEXAS syndrome, the standard dose of 75 mg/m²—typically used for MDS—administered subcutaneously on days 1–7 is recommended, at least during the first cycles.

In the context of the described molecular complete remissions, successful attempts to taper the treatment have also been documented [52, 53]. However, reliable long-term data from a larger patient cohort, as well as clear recommendations regarding the required depth and duration of remission prior to attempting to taper the treatment, are currently lacking.

6.1.5 Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation is currently the only potentially curative treatment option for VEXAS syndrome; however, it is known to be associated with significant morbidity and mortality. To date, 39 cases of VEXAS patients who underwent transplantation have been reported [58]. Current data show favorable outcomes, with a 2-year overall survival rate of 74.2% and a transplant-associated mortality rate of 25.8% [59]. Allogeneic stem cell transplantation is particularly indicated for patients with progressive bone marrow failure (e.g., transfusion dependence) or treatment-resistant inflammation. Determining the indication remains challenging due to the patients' generally advanced age, significant comorbidities, and reduced functional capacity—often exacerbated by long-term glucocorticoid therapy.

6.1.6 Supportive Therapy

Especially at the onset of the disease and during high-dose steroid therapy, prophylaxis against infections—such as Pneumocystis jirovecii (e.g., cotrimoxazole) and alpha-herpesviruses (oral valaciclovir or aciclovir)—is recommended [23, 30]. For treatment-refractory skin lesions, a biopsy should be considered to rule out atypical mycobacteriosis.

Due to the secondary immunodeficiency associated with VEXAS syndrome—which is caused both by the disease itself and by the immunosuppressive therapy that is often required—vaccinations against SARS-CoV-2, influenza, pneumococci, and VZV are recommended. In a small study [60], isolated disease flares were observed following SARS-CoV-2 vaccination; therefore, close clinical monitoring is recommended after vaccination.

Given the high risk of thromboembolism, thrombosis prophylaxis is required in high-risk situations—particularly during hospitalization [28] – provided there are no contraindications.

Due to frequent and long-term glucocorticoid exposure, consistent management of steroid-associated complications (including monitoring of blood glucose and blood pressure, as well as DXA scans) is also essential.

For VEXAS patients with primary anemia without pronounced systemic inflammation, treatment may be similar to that for low-risk MDS, using erythropoiesis-stimulating agents (ESAs) or luspatercept. However, in the absence of concomitant low-risk MDS, this remains an off-label use. Patients with non-M41 mutations, in particular, showed a good response to luspatercept in a recently published retrospective patient cohort [61].

7 Rehabilitation

Specialized rehabilitation measures are generally reserved for patients who have undergone curative therapy (allogeneic stem cell transplantation). For most other patients, the condition is considered chronic, requiring long-term treatment.

8 Follow-up Care and Monitoring

Disease monitoring includes regular follow-up examinations, assessment of the treatment response, and detection of new organ manifestations.

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16 Disclosure of Potential Conflicts of Interest

in accordance with the rules of the relevant professional societies.