Development of a Consensus Definition of VEXAS Flare for Use in Clinical Research

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CONCLUSIONS

- This consensus definition of VEXAS (Vacuoles, E1 ubiquitin-activating enzyme, X-linked, Autoinflammatory, Somatic) flare provides uniform criteria for defining and characterizing VEXAS disease activity
- This consensus definition of VEXAS flare supports the Overall Clinical Response primary endpoint in the randomized, placebo-controlled PAXIS trial (Beck DB, et al. Oral 2663)[1]
- As a binary measure, this flare definition may fail to capture low levels of disease activity, and it does not differentiate between flares based on severity. Development of a VEXAS Disease Activity Index is underway to address these limitations (Byram K, et al. Oral 0777)[2]
- This unified approach is essential for comparing therapeutic outcomes and advancing care for patients with VEXAS

INTRODUCTION

- VEXAS syndrome is a severe systemic hemato-inflammatory disease with complex and heterogeneous clinical presentations[3]
- VEXAS syndrome is associated with significant morbidity and mortality, as patients experience recurrent inflammatory flares despite receiving anti-inflammatory therapy

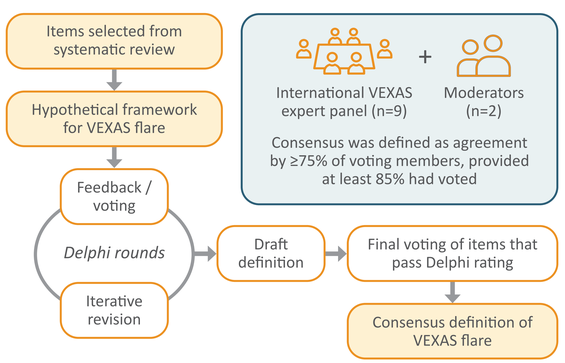
OBJECTIVE

- Development of a consensus definition of a VEXAS flare to advance clinical trial design and conduct in VEXAS syndrome

METHODS

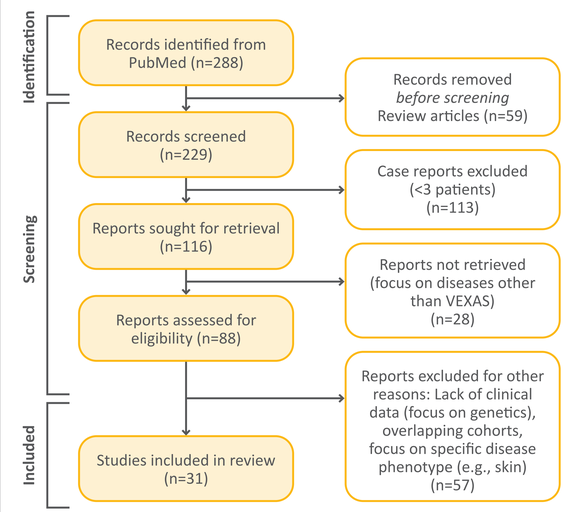
- A Delphi panel was established to develop a hypothetical framework for and a consensus definition of VEXAS flare (**Figure 1**)

Figure 1. Delphi review process



VEXAS, Vacuoles, E1 ubiquitin-activating enzyme, X-linked, Autoinflammatory, Somatic.

Figure 2. PRISMA flow diagram for systematic review



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

- Clinical manifestations of VEXAS syndrome were identified based on systematic literature review of publications (performed January 2024) including ≥3 VEXAS patients (**Figure 2**)[3–33]
- These manifestations were considered by the Delphi panel for inclusion in the flare definition

RESULTS

- 19 categories of inflammatory involvement were obtained from systematic review (**Table 1**)
- Panel members agreed upon a hypothetical framework, based on categorization of flares into 3 categories (**Table 2**):
  - Recurrence of a prior manifestation (Category A)
  - New VEXAS-defining manifestation (Category B)
  - New manifestation that is not VEXAS-defining (Category C): Panel recommended independent adjudication of such flares

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Disclosures

LDW: Consultant: Abbvie, Vertex, Sobi; **DH:** None; **SS:** Speakers Bureau: Pharming, Takeda; Consultant: Novartis, Sobi, Takeda, KalVista, Celldex, Phraming, CSL Behring, Phavaris; Grant: CSL Behring, Novartis; **MH:** Consultant: BMS/Celgene, Blueprint, Servier, Jazz Pharmaceuticals, ABBVIE, Astellas; **OC:** Speakers Bureau: Novartis, Jazz; **AM:** None; **CG:** Grants: Alexion; Consulting fees: Genesis Therapeutics; **RR:** Speakers Bureau: GSK; Consultant: Sobi, Incyte, Curis; **SG-L:** Consultant: Sobi, Novartis; **MAF:** None; **SAB, BGH:** Employee: Sobi Inc.; **SG:** Employee (former): Sobi Inc.; **DBB:** Consultant: Sobi, GSK, Novartis, Alexion, Montage bio; **MJK:** Consultant: Amgen.

Table 1. Inflammatory manifestations of VEXAS syndrome based on literature review

Systemic involvement and examples	
Fatigue	Reduced ability to perform physical or mental activities
Constitutional	Fever, chills, night sweats, unintended weight loss
Thrombosis	Venous or arterial thrombosis/thromboembolism
Organomegaly	Lymphadenopathy, splenomegaly
Systemic vasculitis	Polyarteritis nodosa, large vessel arteritis
End-organ involvement and examples	
Cutaneous	Neutrophilic dermatosis, leukocytoclastic vasculitis
Pulmonary	Pulmonary infiltrates, pleural effusion, cough
Joint	Arthritis, joint effusion, arthralgia
Cartilage	Relapsing polychondritis
Cardiac	Myocarditis, pericarditis, pericardial effusion
Ocular	Uveitis, scleritis, episcleritis
Periorbital	Periorbital edema, facial swelling
Nervous system	Demyelinating polyneuropathy, sensory neuropathy
Gonadal	Orchitis, epididymitis, testicular pain
Gastrointestinal	Peritonitis
Musculoskeletal	Myalgia, polymyalgia rheumatica
Renal	Tubulointerstitial nephritis
Oropharyngeal	Odynophagia, aphthous ulcers
Inner ear	Labyrinthitis, hearing loss

VEXAS, Vacuoles, E1 ubiquitin-activating enzyme, X-linked, Autoinflammatory, Somatic.

- A total of 4 revision rounds were conducted from May to July of 2024, and consensus was reached on the definition of VEXAS flare as an active inflammatory manifestation of VEXAS syndrome requiring escalation in glucocorticoid therapy
- Consensus was reached on items that do not constitute a flare: isolated thrombosis, chronic organ damage, inflammation not requiring an increase in glucocorticoids, and isolated elevation of C-reactive protein levels
- Consensus was not reached on whether the following items without other inflammatory manifestations should constitute a flare: isolated cytopenia(s), isolated fatigue, and isolated weight loss

Table 2. VEXAS flare consensus definition

Definition of VEXAS flare
A VEXAS flare is defined as an active inflammatory manifestation of VEXAS syndrome fulfilling at least one of the criteria below, for which an escalation in glucocorticoid therapy is indicated*,†
Category A
Recurrence of one or more of the patient's prior documented VEXAS-related inflammatory manifestations
Category B
Development of one or more of the following inflammatory signs considered by the Investigator to be directly attributable to VEXAS syndrome: a) Skin rash with biopsy-proven diagnosis of neutrophilic dermatosis, erythema nodosum, leukocytoclastic vasculitis, panniculitis, or neutrophilic urticarial dermatosis b) Auricular and/or nasal chondritis c) Biopsy- or imaging-proven vasculitis of any caliber vessel d) Ocular inflammation, including orbital inflammation, dacryoadenitis, uveitis, scleritis, or episcleritis e) Persistent periorbital edema
Category C‡
Development of any of the following inflammatory manifestations directly attributable to VEXAS syndrome per an independent adjudication committee§: a) Recurrent or persistent fevers >38.0°C documented on at least two occasions within the span of at least 2 weeks in the absence of infection or alternative etiology evident after comprehensive clinical investigation a) Night sweats on multiple occasions over at least 2 weeks in the absence of infection or alternative etiology after comprehensive clinical investigation a) Arthritis, arthralgias, or myalgias a) New onset non-infectious cough or clinically significant dyspnea in the setting of pulmonary infiltrates lasting at least 1 week without an alternative etiology a) Other inflammatory end-organ involvement that is considered directly attributable to VEXAS syndrome and that does not meet Category B criteria

*Chronic organ damage or impairment resulting from VEXAS syndrome does not constitute evidence of a disease flare; †While arterial or venous thrombosis may occur in the setting of a disease flare, the isolated diagnosis of new thrombosis is insufficient to constitute a VEXAS syndrome flare; ‡Independent adjudication committee recommended; §Documentation of the relevant manifestations and results of clinical, laboratory, and radiographic investigations undertaken to exclude alternative etiologies (including infection), accompanied by longitudinal C-reactive protein, erythrocyte sedimentation rate (where available), and ferritin values (including values drawn while the manifestation is active) must be provided to the adjudication committee.

VEXAS, Vacuoles, E1 ubiquitin-activating enzyme, X-linked, Autoinflammatory, Somatic.

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