

This is a repository copy of *Recovery of Bone Marrow Function in VEXAS Syndrome-potential Role for Romiplostim*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/202850/>

Version: Published Version

Article:

Al-Hakim, Adam, Cull, Alyssa, Topping, Joanna et al. (9 more authors) (2023) Recovery of Bone Marrow Function in VEXAS Syndrome-potential Role for Romiplostim. HemaSphere. e934. ISSN: 2572-9241

<https://doi.org/10.1097/HS9.0000000000000934>

Reuse

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can't change the article in any way or use it commercially. More information and the full terms of the licence here: <https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

Letter

Open Access

Recovery of Bone Marrow Function in VEXAS Syndrome-potential Role for Romiplostim

Adam Al-Hakim¹, Alyssa Cull², Joanna Topping³, Fatima Nadat¹, Joanna Milek², Razan Alhefzi², Michael F. McDermott³, Roger Owen⁴, Catherine Cargo⁴, James Poulter⁵, David G. Kent², Sinisa Savic^{1,3}, on behalf of the ImmunAID consortium*

Correspondence: Sinisa Savic (S.Savic@leeds.ac.uk).

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a recently reported late-onset hematoinflammatory disorder occurring predominantly in older men, due to acquired mutations in the X-linked *UBA1* gene.¹ An emerging category of hematoinflammatory disorders are broadly defined as diseases caused by somatic mutations restricted to the blood, but results in systemic inflammation with multiorgan involvement and are associated with abnormal and/or premalignant bone marrow (BM) changes.² The inflammatory manifestations are driven in part by activation of the NLRP3 inflammasome and release of proinflammatory cytokines such as interleukin (IL)-1 β , IL-18, and IL-6.³ The hematological manifestations include vacuoles in erythroid and myeloid precursors, macrocytosis, and multilineage cytopenias. Most patients are diagnosed with clonal cytopenia of unknown significance, with 31%–50% of cases also fulfilling diagnostic criteria for myelodysplastic syndrome (MDS).^{4,5} Typical inflammatory manifestations include fever, weight loss, skin lesions, lung disease, joint involvement, and inflammatory eye disease, while VEXAS can clinically mimic inflammatory syndromes such as Sweet's syndrome (acute febrile neutrophilic dermatosis), relapsing polychondritis, and polyarteritis nodosa.^{4,5}

The best characterized and, to date, most common pathogenic variants lead to substitution of methionine at position 41, (*UBA1* p.Met41 [p.Met41Leu/Thr/Val]), which is the start codon for translation of the cytoplasmic, enzymatically active, isoform of *UBA1* (*UBA1b*). Consequently, there is loss of intracellular homeostasis due to dysregulated ubiquitination. The mutation is found in multipotent hematopoietic progenitors, with putative selection pressure conferred by the mutation driving a high variant allele fraction (VAF) in myeloid cells, while lymphocytes generally do not survive with the mutation.⁶

VEXAS syndrome is associated with significant morbidity, and for the 32% of patients who develop transfusion dependence,

the risk of mortality is increased by 4.5-fold.⁴ Presently, the only potentially curative treatment is allogeneic hematopoietic stem cell transplantation (ASCT), with numerous other medical therapies used for symptomatic control only. Here, we describe a case of VEXAS syndrome, P22 from the original cohort published in 2020,¹ who has undergone spontaneous resolution of their trilineage cytopenia and inflammatory manifestations, despite the persistence of the pathogenic *UBA1* mutation.

The patient is a 76-year-old male who initially presented with macrocytic anemia 10 years earlier. The anemia was later found to be part of his VEXAS syndrome, subsequently diagnosed in 2020. He had a difficult clinical course due to trilineage cytopenia and a variety of inflammatory complications, including suspected polymyalgia rheumatica and relapsing polychondritis (Figure 1). He was not deemed suitable for ASCT due to initial uncertainty about the diagnosis and the presence of significant comorbidities. His treatment has largely been supportive and aimed at controlling inflammatory complications and cytopenia. He became transfusion dependent in June 2015 and subsequently developed severe thrombocytopenia. His anemia and thrombocytopenia were initially presumed to be immune-mediated and he was therefore treated with intravenous immunoglobulin and later rituximab, without success. He had a nondiagnostic BM examination on several occasions. Retrospective investigations showed the presence of the pathogenic *UBA1* Met41Leu mutation with similar VAFs in all BM samples.

In 2020, he was briefly treated with eltrombopag, which was ineffective and subsequently commenced on the thrombopoietin receptor agonist (TPO-RA), romiplostim, for thrombocytopenia. He continues to receive monthly romiplostim (Suppl. Figure S1). The full blood count before his final transfusion in November 2021 showed a hemoglobin (Hb) of 110 g/L, platelets (PLT) 80×10^9 /L, mean corpuscular volume (MCV) 114, lymph 0.67×10^9 /L. Over subsequent months, these have

¹Department of Clinical Immunology and Allergy, St James's University Hospital, Leeds, United Kingdom

²Department of Biology, York Biomedical Research Institute, University of York, United Kingdom

³Leeds Institute of Rheumatic and Musculoskeletal Medicine, St. James's University Hospital, Leeds, United Kingdom

⁴Haematological Malignancy Diagnostic Service, St James's University Hospital, Leeds, United Kingdom

⁵Leeds Institute of Medical Research, St. James's University Hospital, Leeds, United Kingdom

*ImmunAID Consortium is the alias for the list of authors associated with the ImmunAID project (<https://www.immunaid.eu/the-project/consortium>).

Supplemental digital content is available for this article.

Copyright © 2023 the Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Hematology Association. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

HemaSphere (2023) 7:8(e934).

<http://dx.doi.org/10.1097/HS9.0000000000000934>.

Received: April 11, 2023 / Accepted: June 20, 2023

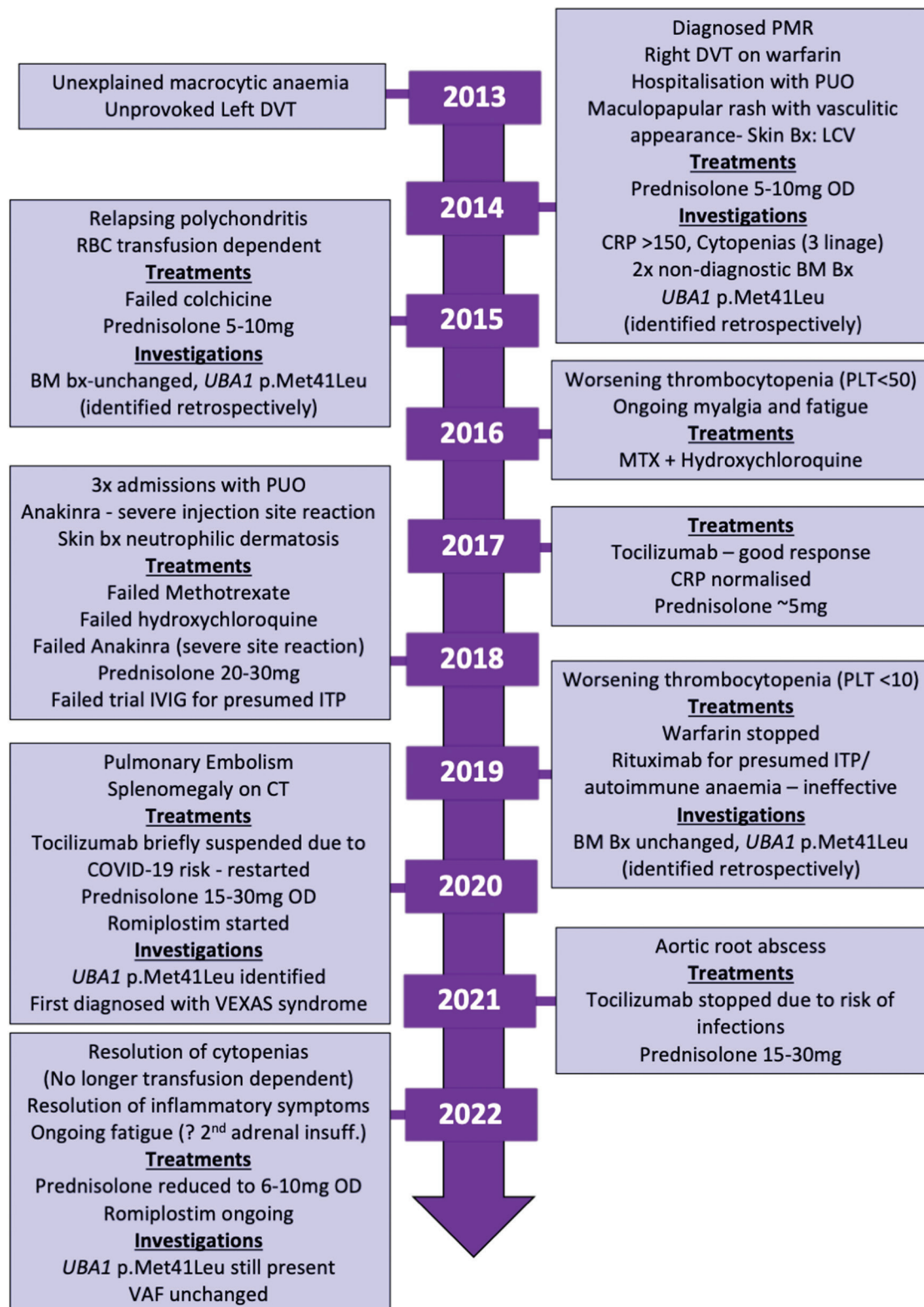


Figure 1. Summary of clinical progress and treatment responses. Timeline of symptoms and complications development, investigations, and treatment responses. BM = bone marrow; Bx = biopsy; CRP = C-reactive protein; CT = computer tomography; DVT = deep vein thrombosis; LCV = leukocytoclastic vasculitis; PLT = platelets; PMR = polymyalgia rheumatica; PUO = pyrexia of unknown origin; RBC = red blood cells.

spontaneously improved to normal levels (Hb 156, PLT 188, and lymph 1.10), although the MCV remains elevated at 110 (Suppl. Figure S1). The patient's inflammatory symptoms are well-controlled despite his prednisolone being weaned down to its current level of 6mg/day. Further reduction is limited by

the patient complaining of severe fatigue. A synacthen test indicated that this is likely due to secondary adrenal insufficiency, but since the test was done while the patient was still receiving 6 mg of prednisolone (<5 mg daily is required for the test to be fully valid), the diagnosis remains unconfirmed. The patient's

latest C-reactive protein (CRP) readings (November 2022 and January 2023) demonstrate well-controlled inflammation with CRP <5 mg/L. These results, along with the clinical picture, confirm that the patient is currently in remission while not receiving any active anti-inflammatory treatment.

We initially postulated that the resolution of his condition was due to spontaneous clearance of the *UBA1* Met41Leu clonal cells, but longitudinal testing of whole blood DNA showed the presence of the same pathogenic *UBA* variant with an unchanged VAF. Additional genetic tests (whole genome sequencing) did not reveal the emergence of any novel mutations, such as *JAK2* V617F mutations, which might be postulated to rescue the phenotype.

To further test if there were any significant differences that might provide some insight into why his hematopoiesis has recovered, we used cell surface marker analysis to investigate the hematopoietic stem and progenitor cell (HSPC) compartment. We compared this case to patients with ongoing manifestations of VEXAS, including macrocytic anemia and thrombocytopenia (VX1, VX2, and VX3); peripheral blood mononuclear cells isolated from the patient (P22) following symptom reversion showed similar frequencies of progenitors (CD34⁺CD38⁺) and hematopoietic stem cell (HSC) enriched fractions (CD34⁺CD38⁺). However, there was a marked difference in the frequency of long-term HSCs (CD34⁺CD38⁺CD90⁺CD45RA⁺), with P22 being 21.2% compared with 0%–4% in the other patients' samples (Figure 2A and 2B).

To determine if there was any evidence of ongoing subclinical inflammation, we compared proinflammatory cytokine profile and the status of the NLRP3 inflammasome activation between the index patient, P22, and 4 other VEXAS patients, matched for sex and age (69–75 years), with active disease (VX-active) who

were treated with similar doses of corticosteroids (between 10 and 15 mg prednisolone daily). Patient 22 had a 7.7-fold reduction in levels of extracellular ASC/NLRP3 protein specks—a readout for NLRP3 inflammasome activation—compared with the 4 active VEXAS patients' sera (mean VX-active group = 76.05 events/μL [range, 34.06–108.93 events/μL], while P22 had only 9.84 events/μL) (Figure 2C). Reductions in IL-6, IL-18, IL-8, IL-23, and MCP-1 levels were detected in P22 compared with VEXAS-active patients (Suppl. Figure S2).

Here, we present a case of a patient with VEXAS syndrome, who appears to have undergone remarkable recovery of BM function, with resolution of the inflammatory complications coinciding with the initiation of romiplostim for his thrombocytopenia. Further investigations have shown that this recovery occurred despite the pathogenic *UBA1* variant still being detectable, but was associated with an increased frequency of long-term HSCs and complete resolution of inflammation. As we did not carry out a simultaneous measurement of the VAF in sorted HSPCs at the time, we cannot distinguish whether the increased HSPC fraction carries the *UBA1* mutation, so this may represent a resurgence of nonmutant HSPCs in response to Romiplostim.

Given the timing of his recovery, we wondered what role romiplostim might have played in the process. Endogenous TPO and its receptor c-MPL are regarded as the main drivers of HSC survival, as evidenced by various murine models.^{7,8} Furthermore, children with functional mutations in TPO or c-MPL tend to develop progressive multilineage cytopenias associated with reduction of HSPCs.⁷ It has recently been shown that IFN-γ inhibits the stimulation of c-MPL by TPO, possibly through the formation of a TPO:IFN-γ heterodimer.⁷ The same study showed that the TPO-RA, eltrombopag, was able to evade this inhibitory mechanism and successfully stimulate

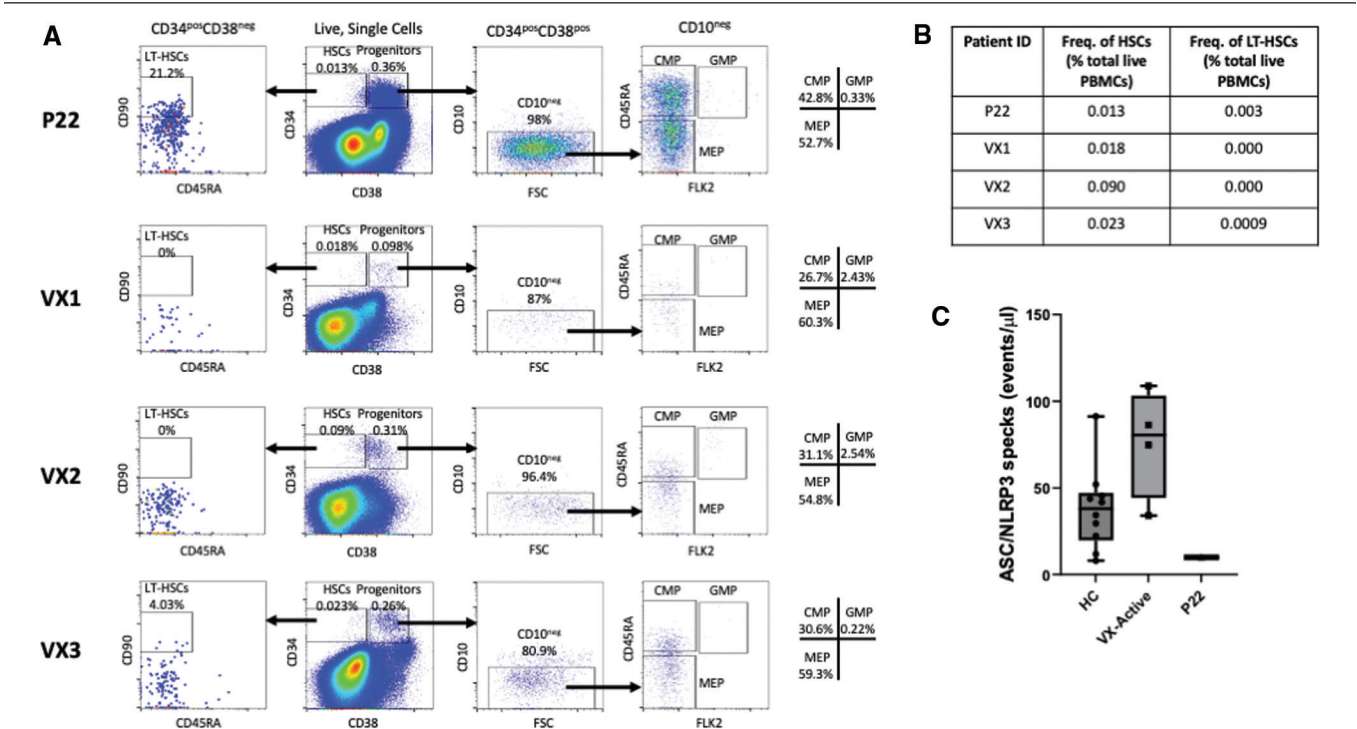


Figure 2. Biological response to romiplostim. (A) Viably frozen PBMCs from 4 patients were thawed and stained with the following antibodies: CD34 PE (clone 561, Biolegend), CD38 FITC (clone HIT2, BD Biosciences), CD90 APC (clone 5E10, BD Biosciences), FLK2 BV650 (clone 4G8, BD Biosciences), CD10 APC-Cy7 (clone HI10a, Biolegend), CD45RA V450 (clone HI100, BD Biosciences), and 7AAD (Thermo-Fisher). Samples were analyzed on a MoFlo Astrios (Beckman Coulter). (C) In-house flow cytometry assay, for quantification of ASC/NLRP3 protein specks in sera. Briefly, 100 μL of patients' sera was incubated in Phycoerythrin conjugated anti-ASC (TMS-1) Antibody (653904, BioLegend) and APC-conjugated NLRP3 Antibody (IC7578A, BioTechne) for 1 hour at room temperature, shaking. Totally 50 μL of sample was measured by using a Cytotex S Flow Cytometer, gating for events 1 μm in size, using Flow Cytometry Submicron Particle Size Reference beads (F13839, Thermo-Fisher Scientific). Results were analyzed using CytExpert software and presented as ASC positive events per microliter. Data are represented in a box and whisker plot of ASC/NLRP3 protein specks. PBMC = peripheral blood mononuclear cells.

the c-MPL receptor. Although only licensed for thrombocytopenia, the 2 TPO-Ras, romiplostim and eltrombopag, have both been shown to restore trilineage hematopoiesis in aplastic anemia (AA) refractory to immunosuppression.^{9,10} Patients with AA show paradoxically elevated levels of endogenous TPO, reinforcing the suggestion that these synthetic agents can evade an underlying inhibitory mechanism.¹¹ IFN- γ levels are known to be increased in VEXAS findings, which have been supported by pathogenic *UBA1* mutations in zebrafish models, and it is plausible that romiplostim has bypassed this mechanism of hematopoietic suppression, thereby allowing restoration of multiple cell lineages.¹ Although this is a plausible explanation for how romiplostim might act to fully restore hematopoiesis, we have no explanation of what mechanisms might be responsible for resolution of the inflammatory complications. Although associations between autoinflammatory complications and MDS have been recognized for a long time, the precise biology underpinning this relationship remains uncertain. For example, it is unclear whether the inflammatory BM milieu, irrespective of the underlying cause, drives the acquisition of somatic mutations leading to MDS, or whether autoinflammatory manifestations are driven by the MDS-causative mutations. In the latter case, any treatment resulting in the cure of MDS would also lead to resolution of the inflammation. In the case described, restoration of BM function, which coincided with use of romiplostim and with resolution of inflammatory complications, was of particular note given the persistence of the pathogenic *UBA1* mutation. It would be premature to recommend routine use of romiplostim in VEXAS based on this anecdotal evidence, but our findings are sufficiently interesting to consider testing the utility of romiplostim in VEXAS in the context of a clinical trial.

ACKNOWLEDGMENTS

Vassili Soumelis (vassili.soumelis@aphp.fr; Inserm, U976, Hôpital Saint Louis, Paris, France); Arturo Hernandez Cervantes (arturo.hernandez-cervantes@inserm.fr; Inserm, U976, Hôpital Saint Louis, Paris, France); Thomas Henry (thomas.henry@inserm.fr; International Center of Infectiology Research (CIRI), University of Lyon, INSERM U1111, Claude Bernard University, Lyon 1, CNRS, UMR5308, ENS of Lyon, Lyon, France); Serge Amsellem (serge.amsellem@inserm.fr; Sorbonne Université, INSERM, UMR_S 933, Assistance Publique Hôpitaux de Paris, Département de Génétique Médicale, Hôpital Trousseau, Paris, F-75012, France); Gilles Hayem (ghayem@ghpsj.fr; Rheumatology Department, Groupe Hospitalier Paris Saint-Joseph, Paris, France); Alexandre Belot (alexandre.belot@chu-lyon.fr; International Center of Infectiology Research [CIRI], University of Lyon, INSERM U1111, Claude Bernard University, Lyon 1, CNRS, UMR5308, ENS of Lyon, Lyon, France); Yvan Jamilloux (yvan.jamilloux@chu-lyon.fr; Department of Internal Medicine, University Hospital Croix-Rousse, Hospices Civils de Lyon, University of Lyon 1, Lyon, France; CIRI, Inserm U1111, ENS/CNRS UMR5308, Lyon, France; Lyon Immunopathology Federation [LIFE], Lyon, France; Centre de Référence des Maladies Auto-Inflammatoires et de l'Amylose inflammatoire [CEREMAIA], Lyon, France); Eric Hachulla (eric.hachulla@chru-lille.fr; Univ. Lille, CHU Lille, Département de Médecine Interne et Immunologie Clinique, Centre de Référence des Maladies Systémiques et Auto-Immunes Rares du Nord-Ouest [CERAINO], LIRIC, INSERM, Lille, France); Thierry Martin (thierry.martin@chru-strasbourg.fr; Strasbourg University Hospital, Clinical Immunology department, RESO reference center, Strasbourg, France); Marie-Elise Truchetet (marie-elise.truchetet@chu-bordeaux.fr; Rheumatology Department, Bordeaux University Hospital and Bordeaux University, Bordeaux, France); Antoine Néel (antoine.neel@chu-nantes.fr; Nantes Université, Internal Medicine Department CHU Nantes, INSERM, Center for Research in Transplantation and Translational Immunology, UMR 1064, F-44000 Nantes, France); Bruno Fautrel (bruno.fautrel@aphp.fr; Sorbonne Universités - AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Rheumatology, Centre de Référence des Maladies Auto-Inflammatoires et de l'Amylose inflammatoire [CEREMAIA], F-75013, Paris, France; INSERM, UMR_S 1136, F-75013; CRI-IMIDATE clinical research network); Nicolas Rosine (nicolas.rosine@aphp.fr; Sorbonne Universités - AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Rheumatology, Centre de Référence des Maladies Auto-Inflammatoires et de l'Amylose inflammatoire [CEREMAIA], F-75013, Paris, France; INSERM, UMR_S 1136, F-75013; CRI-IMIDATE clinical research network); Emna

Chabaane (amna.manfroi@aphp.fr; Département Recherche Clinique et Innovation, Hôpital de La Pitié Salpêtrière, Paris, France); David Saadoun (david.saadoun@aphp.fr; Sorbonne Universités, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, Centre de Référence des Maladies Auto-Inflammatoires et de l'Amylose inflammatoire [CEREMAIA], F-75013, Paris, France; INSERM, UMR_S 959, F-75013; CIC Biothérapie); Matheus Vieira (matheus.vieira@aphp.fr; Sorbonne Universités, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, Centre de Référence des Maladies Auto-Inflammatoires et de l'Amylose inflammatoire [CEREMAIA], F-75013, Paris, France; INSERM, UMR_S 959, F-75013; CIC Biothérapie); Isabelle Koné-Paut (isabelle.kone-paut@aphp.fr; Pediatric rheumatology department and CEREMAIA, Bicêtre hospital APHP, University of Paris Saclay, France); Nasima Matsa (nassima.matsa@aphp.fr; Pediatric rheumatology department and CEREMAIA, Bicêtre hospital APHP, France); Perrine Dusser (perrine.dusser@aphp.fr; Pediatric rheumatology department and CEREMAIA, Bicêtre hospital APHP, University of Paris Saclay, France); Jean-David Bouaziz (jean-david.bouaziz@aphp.fr; APHP, Saint Louis Hospital, Paris Cité University, Paris, France); Thibault Mahevas (thibault.mahevas@aphp.fr; APHP, Saint Louis Hospital, Paris Cité University, Paris, France); Sophie Georgin-Lavialle (sophie.georgin-lavialle@aphp.fr; Sorbonne University, Internal medicine department, Tenon hospital, CEREMAIA, AP-HP, Paris, France); Keshia Koutekissa (keshia.koutekissa@aphp.fr; Sorbonne University, Internal medicine department, Tenon hospital, CEREMAIA, AP-HP, Paris, France); Léa Savey (lea.savey@aphp.fr; Sorbonne University, Internal medicine department, Tenon hospital, CEREMAIA, AP-HP, Paris, France); Pierre Quartier (pierre.quartier@aphp.fr; Université Paris-cité, Paris, France; RAISE reference center for rare diseases, pediatric immunology-hematology and rheumatology unit, Necker hospital, AP-HP, Paris, France); Savvas Savvides (savvas.savvides@irc.vib-ugent.be; VIB Center for Inflammation Research (IRC), Ghent, Belgium); Stephanie Humblet-Baron (tephanie.humbletbaron@kuleuven.be; Laboratory of Adaptive Immunology, Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium); Adrian Liston (al989@cam.ac.uk; Department of Pathology, University of Cambridge, Cambridge, United Kingdom); Jeroen Raes (jeroen.raes@kuleuven.be; [1] Laboratory of Molecular Bacteriology, Department of Microbiology, Immunology and Transplantation, Rega institute, KU Leuven, Leuven, Belgium; [2] VIB Center for Microbiology, Leuven, Belgium); Carine Wouters (carine.wouters@uzleuven.be; Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium; KU Leuven, Department of Microbiology, Immunology and Transplantation, Laboratory of Adaptive Immunology & Immunobiology, Leuven, Belgium); Steven Vanderschueren (steven.vanderschueren@uzleuven.be; Department of General Internal Medicine, University Hospitals Leuven, Leuven, Belgium; KU Leuven, Department of Microbiology, Immunology, and Transplantation, Laboratory of Clinical Infectious and Inflammatory Disorders, Leuven, Belgium); Paul Proost (paul.proost@kuleuven.be; Laboratory of Molecular Immunology, Department of Microbiology, Immunology and Transplantation, Rega Institute, KU Leuven, Leuven, Belgium); Mieke Gouw (mieke.gouw@kuleuven.be; Laboratory of Molecular Immunology, Department of Microbiology, Immunology and Transplantation, Rega Institute, KU Leuven, Leuven, Belgium); Patrick Matthys (patrick.matthys@kuleuven.be; Laboratory of Immunobiology, Department of Microbiology, Immunology and Transplantation, Rega Institute, KU Leuven, Leuven, Belgium); Søren Brunak (soren.brunak@cpr.ku.dk; Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Copenhagen N, Denmark); Isabella Friis Jørgensen (isabella.jorgensen@cpr.ku.dk; Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Copenhagen N, Denmark); Andres Jimenez Kaufmann (andres.kaufmann@cpr.ku.dk; Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Copenhagen N, Denmark); Sara Garcia (sara.garcia@cpr.ku.dk; Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Copenhagen N, Denmark); Philippe Hupé (philippe.hupe@curie.fr; Institut Curie, U900 Inserm, PSL Research University, UMR144 CNRS, Paris, France & Mines Paris Tech, Fontainebleau, France); Fanny Coffin (fanny.coffin@curie.fr; Institut Curie, U900 Inserm, PSL Research University, Paris, France & Mines Paris Tech, Fontainebleau, France); Apolline Gallois (apolline.gallois@curie.fr; Institut Curie, U900 Inserm, PSL Research University, Paris, France & Mines Paris Tech, Fontainebleau, France); Henri de Soyres (henri.de-soyres@curie.fr; Institut Curie, U900 Inserm, PSL Research University, Paris, France & Mines Paris Tech, Fontainebleau, France); Julien Roméjon (julien.romejon@curie.fr; Institut Curie, U900 Inserm, PSL Research University, Paris, France & Mines Paris Tech, Fontainebleau, France); Aura Moreno Vega (aura.moreno-vega@owkin.com; OWKIN, Biotech, Paris, France); Marc Dubourdeau (marc.dubourdeau@ambiotis.com; AMBIOTIS SAS - Toulouse - France); Karoline Krause (Karoline.Krause@charite.de; Charité - Universitätsmedizin Berlin, Institut für

Allergieforschung, 12203 Berlin, Germany); Dirk Foell (dfoell@uni-muenster.de; Department of Pediatric Rheumatology and Immunology, University of Muenster, Muenster, Germany); Christoph Kessel (kesselc@uni-muenster.de; Department of Pediatric Rheumatology and Immunology, University of Muenster, Muenster, Germany); Katerina Laskari (katerina_laskari@yahoo.gr; Rheumatology Unit, 1st Department of Propaedeutic Internal Medicine, Joint Academic Rheumatology Program, University of Athens, Medical School, Athens, Greece); Andreaskos Evangelos (vandreaskos@bioacademy.gr; Laboratory of Immunobiology, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece); Paul Van Daele (p.l.a.vandaele@erasmusmc.nl; Department of internal medicine and department of immunology, Erasmus MC, Rotterdam, The Netherlands); Clementien Vermont (c.vermont@erasmusmc.nl; Department of internal medicine and department of immunology, Erasmus MC, Rotterdam, The Netherlands); Rogier van Wijck (R.vanwijck@erasmusmc.nl; Department of Pathology & Clinical Bioinformatics); Sigrid Swagemakers (S.swagemakers@erasmusmc.nl; Department of Pathology & Clinical Bioinformatics); Peter van der Spek (p.vanderspek@erasmusmc.nl; Department of Pathology & Clinical Bioinformatics); Stefan Erkeland (s.erkeland@erasmusmc.nl; Department of Immunology, Erasmus University Medical Center, Rotterdam, The Netherlands); Harmen van de Werken (h.vandewerken@erasmusmc.nl; Department of Immunology, Erasmus University Medical Center, Rotterdam, The Netherlands); Yvonne Mueller (y.mueller@erasmusmc.nl; Department of Immunology, Erasmus University Medical Center, Rotterdam, The Netherlands); Peter Katsikis (p.katsikis@erasmusmc.nl; Department of Immunology, Erasmus University Medical Center, Rotterdam, The Netherlands); Michael Hofer (michael.hofer@chuv.ch; Pediatric immuno-rheumatology, Dept Pediatrics, CHUV, University Hospital of Lausanne, Lausanne, Switzerland); Cem Gabay (Cem.Gabay@unige.ch; Division of Rheumatology, Department of Medicine & Department of Pathology and Immunology, HUG and University of Geneva, Faculty of Medicine, Switzerland); Helen Lachmann (h.lachmann@ucl.ac.uk; National Amyloidosis Centre, Royal Free London NHS Foundation Trust and University College London, London, UK); Costas Papaloukas (papalouk@uoi.gr; Department of Biological Applications and Technology, University of Ioannina, Greece); Dimitrios I. Fotiadis (fotiadis@uoi.gr; Unit of Medical Technology and Intelligent Information Systems, Department of Materials Science and Engineering, University of Ioannina, Greece); Dominique de Seny (ddeseny@chuliege.be; Laboratory of Rheumatology, GIGA-Research, CHU Liège, University of Liège, 4000 Liège, Belgium); Haner Direskeneli (hanerdir-eskeneli@gmail.com; Department of Internal Medicine, Division of Rheumatology, Marmara University, School of Medicine, Istanbul, Turkey); Seza Ozen (sezaozen@hacettepe.edu.tr; Department of Pediatrics, Division of Rheumatology, Hacettepe University, Faculty of Medicine, Ankara, Turkey); Umut Kalyoncu (umut.kalyoncu@yahoo.com; Division of Rheumatology, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey); Tadej Avcin (tadej.avcin@kclj.si; Department of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia); Jordi Anton (jordi.anton@sjd.es; Pediatric rheumatology. Hospital Sant Joan de Déu. Institut de Recerca Sant Joan de Déu. Universitat de Barcelona, Spain); Violeta Bittermann (violeta.bittermann@sjd.es; Pediatric rheumatology. Hospital Sant Joan de Déu. Institut de Recerca Sant Joan de Déu. Universitat de Barcelona, Spain); Alina Boteanu (al_boter@yahoo.com; Servicio de Reumatología, Hospital Universitario Ramón y Cajal, Madrid, Spain); Fabrizio De Benedetti (fabrizio.debenedetti@opbg.net; Division of Rheumatology, Bambino Gesù Children's Hospital, IRCCS, Roma, Italy); Antonella Insalaco (antonella.insalaco@opbg.net; Division of Rheumatology, Bambino Gesù Children's Hospital, IRCCS, Roma, Italy); Emanuele Bizzi (emanuele.bizzi@asst-fbf-sacco.it; Internal Medicine Ospedale Fatebenefratelli, Milano, Italy); Sonia Caccia (sonia.caccia@unimi.it; Department of biomedical and clinical sciences, University of Milano, Italy);

Luca Cantarini (cantariniluca@hotmail.com; Rheumatology Unit Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy); Paolo Sfriso (paolo.sfriso@unipd.it; Rheumatology Unit, Department of Medicine, University of Padova, Italy); Jean-François Deleuze (deleuze@cng.fr; Centre d'Etude du Polymorphisme Humain, Fondation Jean Dausset, Paris, France); Sarhan Yaiche (Sarhan.YAICHE@ecrin.org; European Clinical Research Infrastructure Network).

AUTHOR CONTRIBUTIONS

AA and SS wrote the first draft of the article. AA, JT, FN, JM, RA, and JP processed the samples and conducted laboratory experiments and analyzed the data. RO, CC, and SS provided clinical details and care of the patient. MFM, DK, and SS provided funding and overall supervision of the study. All authors read and approved the article.

DISCLOSURES

DK is a Scientific Editor for HemaSphere. The remaining authors have no conflicts of interest to disclose.

SOURCES OF FUNDING

This project has received funding from European Union's Horizon 2020 research and innovation programme under grant agreement No 779295 (ImmunAID- Immunome project consortium for Autoinflammatory disorders). SS is supported by Senior fellowship from Kennedy Trust.

REFERENCES

1. Beck DB, Ferrada MA, Sikora KA, et al. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. *N Engl J Med*. 2020;383:2628–2638.
2. Grayson PC, Beck DB, Ferrada MA, et al. VEXAS syndrome and disease taxonomy in rheumatology. *Arthritis Rheumatol (Hoboken, NJ)*. 2022;74:1733–1736.
3. Al-Hakim A, Savic S. An update on VEXAS syndrome. *Expert Rev Clin Immunol*. 2023;19:203–215. doi:10.1080/1744666X.2023.2157262.
4. Ferrada MA, Savic S, Cardona DO, et al. Translation of cytoplasmic UBA1 contributes to VEXAS syndrome pathogenesis. *Blood*. 2022;140:1496–1506.
5. Georgin-Lavialle S, Terrier B, Guedon AF, et al. Further characterization of clinical and laboratory features in VEXAS syndrome: large-scale analysis of a multicentre case series of 116 French patients. *Br J Dermatol*. 2022;186:564–574.
6. Poulter JA, Savic S. Genetics of somatic auto-inflammatory disorders. *Semin Hematol*. 2021;58:212–217.
7. Alvarado LJ, Huntsman HD, Cheng H, et al. Eltrombopag maintains human hematopoietic stem and progenitor cells under inflammatory conditions mediated by IFN- γ . *Blood*. 2019;133:2043–2055.
8. Hitchcock IS, Kaushansky K. Thrombopoietin from beginning to end. *Br J Haematol*. 2014;165:259–268.
9. Desmond R, Townsley DM, Dumitriu B, et al. Eltrombopag restores tri-lineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. *Blood*. 2014;123:1818–1825.
10. Jang JH, Tomiyama Y, Miyazaki K, et al. Efficacy and safety of romiplostim in refractory aplastic anaemia: a Phase II/III, multicentre, open-label study. *Br J Haematol*. 2021;192:190–199.
11. Feng X, Scheinberg P, Wu CO, et al. Cytokine signature profiles in acquired aplastic anemia and myelodysplastic syndromes. *Haematologica*. 2011;96:602–606.