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Interleukin-1 blockade in patients with Wiskott-Aldrich Syndrome: a retrospective multinational case series

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Abstract:
Up to 70% of patients with Wiskott-Aldrich Syndrome (WAS) develop autoimmune and inflammatory manifestations. Dysregulation of interleukin (IL)-1 may be involved in their pathogenesis, yet there is little evidence on treatment with anti-IL-1 agents in these patients. We conducted a multicenter retrospective analysis of nine patients with WAS treated with anti-IL-1 agents (anakinra or canakinumab). All patients had prominent inflammatory manifestations, including systemic, cutaneous, articular, and intestinal symptoms; three patients presented with a severe systemic inflammatory syndrome since the first months of life. Corticosteroid therapy was associated with partial or no response, while treatment with anakinra or canakinumab resulted in prompt, often dramatic, responses in all patients, allowing bridging to gene therapy (four patients) or hematopoietic stem cell transplantation (HSCT, five patients). Treatment was overall well tolerated. Low donor myeloid chimerism developed in four patients after HSCT and was associated with the appearance or the recurrence of inflammatory manifestations. A second HSCT was performed in two patients, achieving full-donor chimerism and resolution of inflammatory manifestation, while the other two patients were treated with prolonged therapy with anti-IL-1 agents. Our experience demonstrates that some inflammatory manifestations of WAS are dependent on IL-1 and respond very well to its pharmacologic blockade.

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Interleukin-1 blockade in patients with Wiskott-Aldrich Syndrome: a retrospective multinational case series

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Key Points

- Patients with Wiskott-Aldrich Syndrome can develop inflammatory manifestations poorly controlled by corticosteroid therapy.
- Treatment with anti-IL-1 agents resulted in dramatic responses, suggesting an autoinflammatory pathogenesis.

Abstract

Up to 70% of patients with Wiskott-Aldrich Syndrome (WAS) develop autoimmune and inflammatory manifestations. Dysregulation of interleukin (IL)-1 may be involved in their pathogenesis, yet there is little evidence on treatment with anti-IL-1 agents in these patients. We conducted a multicenter retrospective analysis of nine patients with WAS treated with anti-IL-1 agents (anakinra or canakinumab). All patients had prominent inflammatory manifestations, including systemic, cutaneous, articular, and intestinal symptoms; three patients presented with a severe systemic inflammatory syndrome since the first months of life. Corticosteroid therapy was associated with partial or no response, while treatment with anakinra or canakinumab resulted in prompt, often dramatic, responses in all patients, allowing bridging to gene therapy (four patients) or hematopoietic stem cell transplantation (HSCT, five patients). Treatment was overall well tolerated. Low donor myeloid chimerism developed in four patients after HSCT and was associated with the appearance or the recurrence of inflammatory manifestations. A second HSCT was performed in two patients, achieving full-donor chimerism and resolution of inflammatory manifestation, while the other two patients were treated with prolonged therapy with anti-IL-1 agents. Our experience demonstrates that some inflammatory manifestations of WAS are dependent on IL-1 and respond very well to its pharmacologic blockade.

Introduction

Wiskott-Aldrich Syndrome (WAS, OMIM 301000) is a rare primary immunodeficiency disorder caused by mutations in the *WAS* gene characterized by immunodeficiency, thrombocytopenia, and eczema.[1] Up to 70% of patients develop autoimmune and inflammatory disorders, including autoimmune cytopenias, arthritis, vasculitis, and inflammatory bowel disease.[2,3] Furthermore, autoimmune and inflammatory disorders complicate allogeneic hematopoietic stem cell transplantation (HSCT) in up to 20% of subjects, particularly when chimerism is low.[4,5] The pathogenesis of autoimmunity in WAS has been shown to be related to defective T and B cell function.[6–8] However, there is increasing evidence for abnormal inflammasome activation and release of proinflammatory cytokines, especially interleukin (IL)-1 and IL-18, in WAS.[9,10] Therapies aimed at IL-1 blockade may, therefore, represent an effective strategy, yet, there is limited clinical information available. Here, we report a cohort of WAS patients treated with anti-IL-1 therapies.

Methods

A retrospective review of clinical records of patients with WAS treated with anti-IL-1 agents (anakinra or canakinumab) was performed at seven pediatric immunology centers. Therapy with anti-IL1 agents was administered off-label after institutional ethical approval and parents/guardians informed consent. All patients were enrolled in locally approved research protocols. The present study has been approved by the Institute for Maternal and Child Health IRCCS “Burlo Garofolo” Institutional Review Board (RC 30/22). Written consent for publication in accordance with the Declaration of Helsinki was obtained from parents or guardians.

Results and discussion

Nine patients were identified; for four patients (patients 5, 6, 8 and 9), partial clinical information had been reported elsewhere.[10–12] Patients' characteristics are summarized in Table 1 (full clinical and therapeutic history in Supplemental data). All patients had prominent inflammatory manifestations (IMs). WAS clinical score, according to Zhu et al.[13], was 5A in all patients. Most commonly reported IMs included systemic, cutaneous, articular, and intestinal signs/symptoms. Inflammatory cutaneous involvement, eczema aside, was present in 8/9 patients and included cutaneous vasculitis (n=5), pyoderma gangrenosum (n=2), recurrent/migrating erysipelas-like lesions (n=2), sterile abscess, pustular psoriasis, and panniculitis (1 patient each) (fig. 1, A-F). Inflammatory joint involvement and inflammatory bowel disease (IBD) were present in four patients each. Three patients (pt 1, 5, and 8) presented with a severe systemic inflammatory syndrome appearing in the first months of life, characterized by prominent fever and systemic symptoms associated with cutaneous inflammatory involvement (rash, vasculitis, and erysipelas-like lesions), failure to thrive, and marked increase of blood inflammatory markers. In the other patients, IMs were not associated with persistent fever and tended to have a more chronic course.

All patients received treatment with systemic corticosteroids, with only partial or no response in most of them. Anti-IL-1 agents (anakinra or canakinumab) led to very good or complete responses in all patients. In most patients, the treatment effect was very rapid (days); this was particularly evident in the three patients presenting with severe systemic inflammatory syndrome in the first months of life, in whom prompt and complete resolution of IMs, fever, and systemic symptoms was observed immediately after the commencement of anakinra. Very good responses were observed also in the other patients, leading to the resolution of IMs often refractory to several other therapies (e.g., pyoderma gangrenosum in pts 4 and 9). Therapy was also associated with normalization or near-normalization of inflammatory markers (supplemental table S2). In all patients, anti-IL-1 agents were used in addition to corticosteroids, allowing their tapering; in five patients, corticosteroids could eventually be discontinued, and IMs were controlled by anti-IL-1 agents alone. Notably, in most patients, treatment with anti-IL-1 agents had to be administered continuously and could not be withheld since symptoms tended to relapse (most evident in pt. 5, in whom symptoms recurred within hours of a delayed dose of

anakinra). Therapy was well tolerated in all patients, even for very long periods (up to 8 years in one patient), allowing successful bridging to definitive treatment. Most commonly reported adverse effects included injection site lipohypertrophy and injection anxiety with anakinra, which improved switching to canakinumab. Two patients developed hypereosinophilia: in one patient (pt 6), this was considered to be related to immune reconstitution post-gene therapy (GT) and resolved spontaneously; in the second patient (pt 8), anakinra was briefly stopped as a precaution, and hypereosinophilia was successfully treated with low-dose corticosteroids; anakinra was then resumed, in association with low-dose corticosteroids, and continued until GT. Colchicine was used in two patients: in one patient, it led to near-complete resolution of cutaneous vasculitis symptoms for more than one year, yet it eventually lost its efficacy; in the second one, it was added to long-standing anakinra, so it was difficult to determine its contribution; nevertheless, colchicine was stopped after five years since it was felt to be not helping.

All patients underwent definitive treatment for WAS, either by GT (4 patients) or HSCT (5 patients; details in supplementary table S1). Treatment with anti-IL-1 agents was discontinued before HSCT/GT in all patients, except in two patients (pt 6 and 9), in whom anakinra was discontinued only after GT. Four out of five patients who underwent HSCT developed low (0-30%) myeloid donor chimerism, with relatively preserved lymphoid chimerism (80-95%). These patients experienced post-HSCT IMs, either for the first time (pt 2 and 3) or as a recurrence of pre-HSCT symptoms (pt 1 and 5). In three patients (pts 1, 2, 5; fig. 1G), loss of myeloid chimerism was temporally associated with the occurrence of IMs, while in pt 3, post-HSCT IMs occurred in the setting of long-standing low myeloid chimerism. Two patients (pt 1 and 2) underwent a second HSCT, resulting in complete donor chimerism and resolution of IMs, while in the other two patients (pt 3 and 5), therapy with anakinra was continued; both patients were eventually switched to canakinumab due to frequent injections intolerance. Patients who underwent GT maintained a stable myeloid correction, and no patient experienced a recurrence of IMs.

The present clinical experience shows that several inflammatory manifestations of WAS are dependent on IL-1 and respond to its pharmacologic blockade, thus suggesting an autoinflammatory contribution to their pathogenesis. While loss of tolerance due to abnormal T and B cell function has been clearly demonstrated in WAS,[3,6,14–16] our experience underlines the role of inflammatory mechanisms in this condition. Wiskott-Aldrich Syndrome protein (WASP) has a major role in

leukocyte chemotaxis/activation,[17,18] autophagy, and inflammasome activity.[9] Furthermore, mutations in several WASP-interacting, cytoskeleton-related, proteins are associated with autoinflammatory disorders that have been included in a new group of immune defects with autoinflammation called “immune actinopathies” (e.g. PSTPIP1, CDC42).[19,20] Notably, similarly to other monogenic autoinflammatory conditions, some of our patients presented with an early-onset, sepsis-like, severe systemic inflammatory syndrome, while in others, IMs appeared at an older age and had a more chronic course. In all cases, IMs responded very well to anti-IL-1 agents, which often could not be discontinued due to the reappearance of symptoms. Incomplete response to corticosteroids, especially if compared to direct IL-1 blockade, is consistent with what is observed in other monogenic autoinflammatory diseases. IL-1 exerts positive feedback on its production; thus its direct blockade can be more effective than reduced transcription by corticosteroids. Furthermore, corticosteroids also suppress IL-1 receptor antagonist synthesis, resulting in reduced overall inhibitory efficacy.[21] Colchicine, a drug that reduces IL-1b release through inhibition of caspase-1 and of NLRP3 inflammasome oligomerization, was also used in two patients, with mixed results; however, our data are too limited to draw conclusions on its efficacy.

The fact that several patients experienced IMs with declining myeloid (but not lymphoid) chimerism after HSCT suggests a central role for myeloid cells in autoinflammation in WAS. WASP-deficient myeloid cells exhibit impaired polarization, migration, and phagocytosis, but also increased activation of the NLRP3 inflammasome and IL-1b release following chemical or bacterial stimulation.[9,22] Furthermore, WASP-deficient neutrophils are prone to spontaneous neutrophil extracellular traps (NETs) release.[23] The role of preserved lymphoid chimerism in this setting is uncertain; however, the fact that IMs occurred both before and after HSCT in patients with loss of myeloid chimerism suggests a more prominent role of defective myeloid cells. No patient experienced a relapse of IMs after GT, possibly due to more stable myeloid correction (supplemental fig. 1).

Therapy with anti-IL-1 agents was very well tolerated in all patients, without severe adverse effects. This is consistent with their overall record of safety from other conditions. Anti-IL-1 therapies do not have direct organ toxicities, and they are not directly immunosuppressive, nor increase the risk of opportunistic infection; however, they may be associated with a slight increase of severe infections, possibly due to a blunting effect on infection signs and symptoms leading to delayed

diagnoses.[24,25] On the other hand, treatment with anti-IL-1 therapies allowed corticosteroid sparing in all patients, therefore reducing their immunosuppressive effect. Overall, we do not suggest adjunctive anti-infectious therapies in patients treated with anti-IL-1 agents, yet the possibility of a more blunted clinical response to infection should be considered.

This study has several limitations, including its retrospective nature, therefore a reporting bias cannot be excluded. We did not study molecular markers that could help identifying patients most likely to benefit from anti-IL-1 agents; therefore, at present, in consideration of its general safety and short half-life, a therapeutic trial of anakinra could represent the most effective strategy in patients presenting with refractory IMs. Overall, our experience encourages further studies on the use of anti-IL-1 agents as first-line treatment for inflammatory manifestation in WAS patients, possibly in lieu of other immunosuppressive drugs often associated with a less favorable safety profile.

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Authors' contribution: S.N. designed the study, cared for patients, collected and analyzed data, and wrote the first draft of the manuscript. M.P.C., E.R., F.F., A.J.T., A.A. designed the study, cared for patients, and critically reviewed the manuscript. C.B., S.C., K.N.C., M.F., S. Giardino, S. Gosh, PPL, PTL, RM, VS, A. Tessitore, A. Tommasini, E.V., T.C.V., S.V., A.J.W., M.R., M.H.A. cared for patients, collected data and critically reviewed the manuscript.

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Table 1. Clinical feat

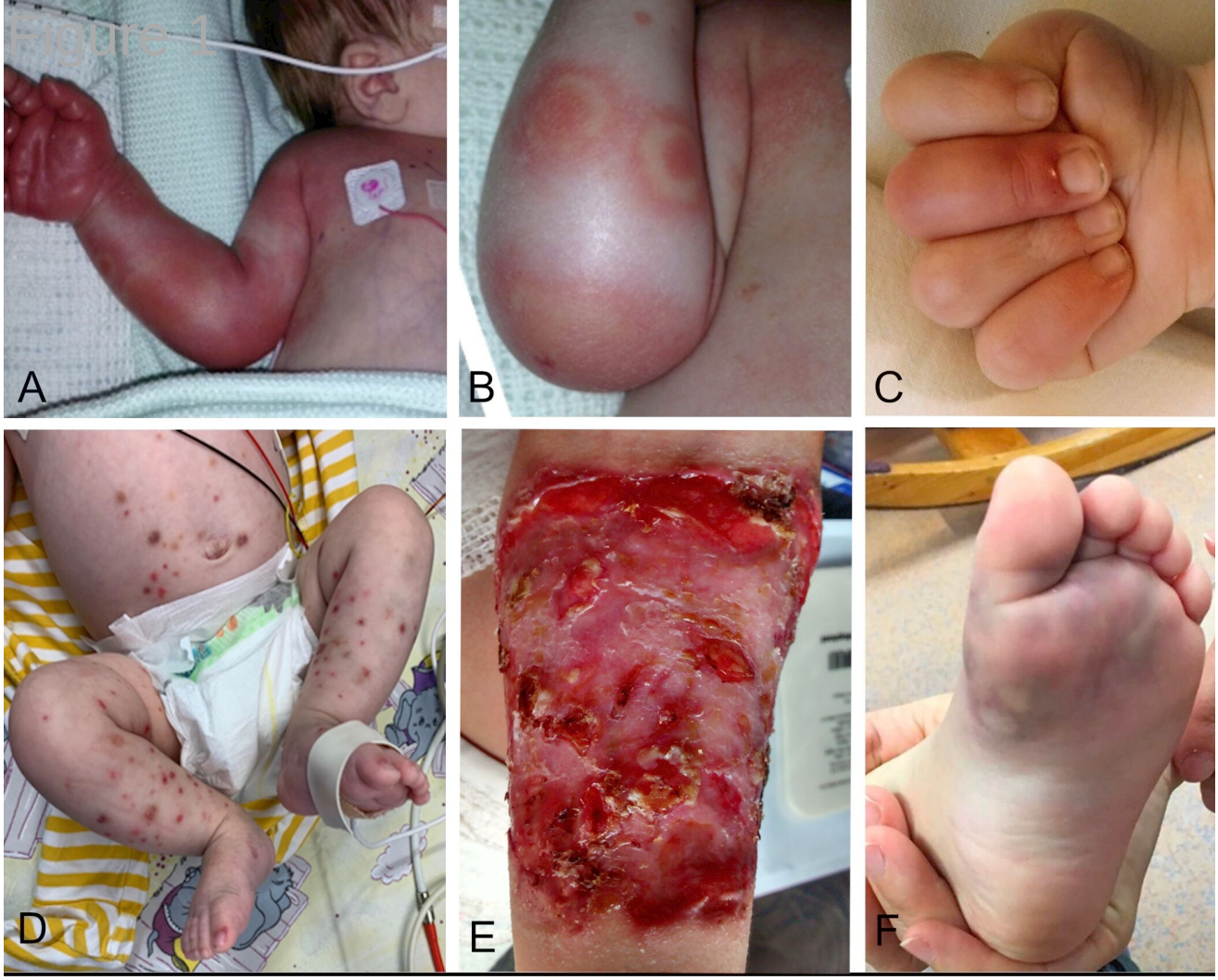
ent c ns	Skin involvement (beside eczema)	Arthritis	IBD	Response to CS	Anti-IL1 drug (age at first use, yrs)	Drug dose	Response to anti-IL1 therapy	Effect of therapy suspension	Adverse effects of therapy	Therapy duration, yrs	Reason for discontinuation	DT	Declining donor chimerism after HSCT (% donor)	IMs after DT ? (% myeloid chimerism at onset)	2nd HSCT	Current statu FU duration last DT
	Vasculitis, erythematous papules, scalp blisters	Hands/ feet	No	Partial	Anakinra (0.25)	3 mg/kg/d	Complete	Not tried	No	0.25	DT	HSCT (twice)	Yes, after 1st HSCT (CD3 85%, CD14 1%)	Yes, recurrence (CD14 1%)	Yes	CR after 2nd full donor chimerism (3 yrs FU)
	Vasculitis-like lesions left foot / hand	Ankle, hands	No	Complete	Colchicine (5)	50 mcg/kg/d	Partial	Not tried	No	1	Loss of efficacy	HSCT (twice)	Yes, after 1st HSCT (CD3 90% CD15 0%)	Yes, 1st appearance (CD15 0%)	Yes	CR after 2nd full donor chimerism (4 yrs FU)
					Anakinra (6)	1.5 mg/kg/d	Complete	Symptoms recurrence	No	2	DT					
	Erysipelas-like inflammation lower limbs	Knees, ankles	No	Partial	Anakinra (14)	3 mg/kg/d	Complete	Not tried	Injection site pain	0.1	Adverse effects	HSCT	Yes, after HSCT (CD3 80%, CD14 30%)	Yes, 1st appearance (CD14 30%)	No	Well-control canakinumab
					Canakinumab (14.2)	2 mg/kg/4 wks	Complete	Not tried	No	1	Ongoing					
	Pyoderma gangrenosum, sterile abscesses	No	No	Partial	Canakinumab (7.5)	4 mg/kg/4 wks	Complete	Symptoms recurrence	No	4	DT	HSCT	No	No	No	CR after HS full donor chimerism (3 yrs FU)
	Necrotizing vasculitis, rash, panniculitis, pustular psoriasis	No	Yes	Partial	Anakinra (0.1)	5 mg/kg/d	Complete	Symptoms recurrence	Lipohypertrophy,injection anxiety	8	Adverse effects	HSCT	Yes, after HSCT (CD3 93%, CD15 15%)	Yes, recurrence (CD15 40%)	No	Well-control canakinumab
					Colchicine (3)	50 mcg/kg/d	ND (given with anakinra)	Yes	No	4	Not effective					
					Canakinumab (8)	3.5 – 5.6 mg/kg/4 wks	Complete	Symptoms recurrence	No	1	Ongoing					
	No	No	Yes	Partial	Anakinra (0.58)	3-4 mg/kg/d	Partial	Not tried	No	0.66	DT	GT	NA	No	No	CR (5 yrs FU
	Cutaneous vasculitis and edema	Ankle	Yes	Partial	Anakinra (1.75)	2 mg/kg/d	Complete	Symptoms recurrence	No	0.3	DT	GT	NA	No	No	CR (4.4 yrs F
	Migrating erysipelas-like lesions; vasculitis	No	No	No	Anakinra (0.3)	5 mg/kg/d	Complete	Symptoms recurrence	Hyper eosinophilia	0.75	DT	GT	NA	No	No	CR (4.1 yrs F
	Pyoderma gangrenosum	No	Yes	Partial	Anakinra (11.8)	3 mg/kg/d	Complete	Symptoms recurrence	No	0.6	DT	GT	NA	No	No	CR (8 yrs FU

d treatments of patients. Abbreviations: IMs, Inflammatory Manifestations; DT, Definitive Therapy; HSCT, Hematopoietic Stem Cell Transplantation; GT, Gene s; NA, Not applicable; ND, Non-determinable; CR, Complete resolution; FU, follow-up.

Figure Legend.

Fig. 1. Panels A-F: inflammatory skin manifestations of patients. A, B: inflammatory skin rash in patient 5 at the onset of systemic inflammatory symptoms at 4 weeks of life (pre-HSCT). C: Cellulitis-like lesions of the third finger in patient 8 (pre-GT). D: Vasculitic lesions of the trunk and the extremities in patient 1 at 2.5 months of age (pre-HSCT). E: Pyoderma gangrenosum in patient 4 (pre-HSCT). F: Vasculitis-like lesions of the foot in patient 2 (post-HSCT; see also panel G). Panel G: Post-HSCT donor chimerism and time course of inflammatory manifestations in patient 2.

Figure 1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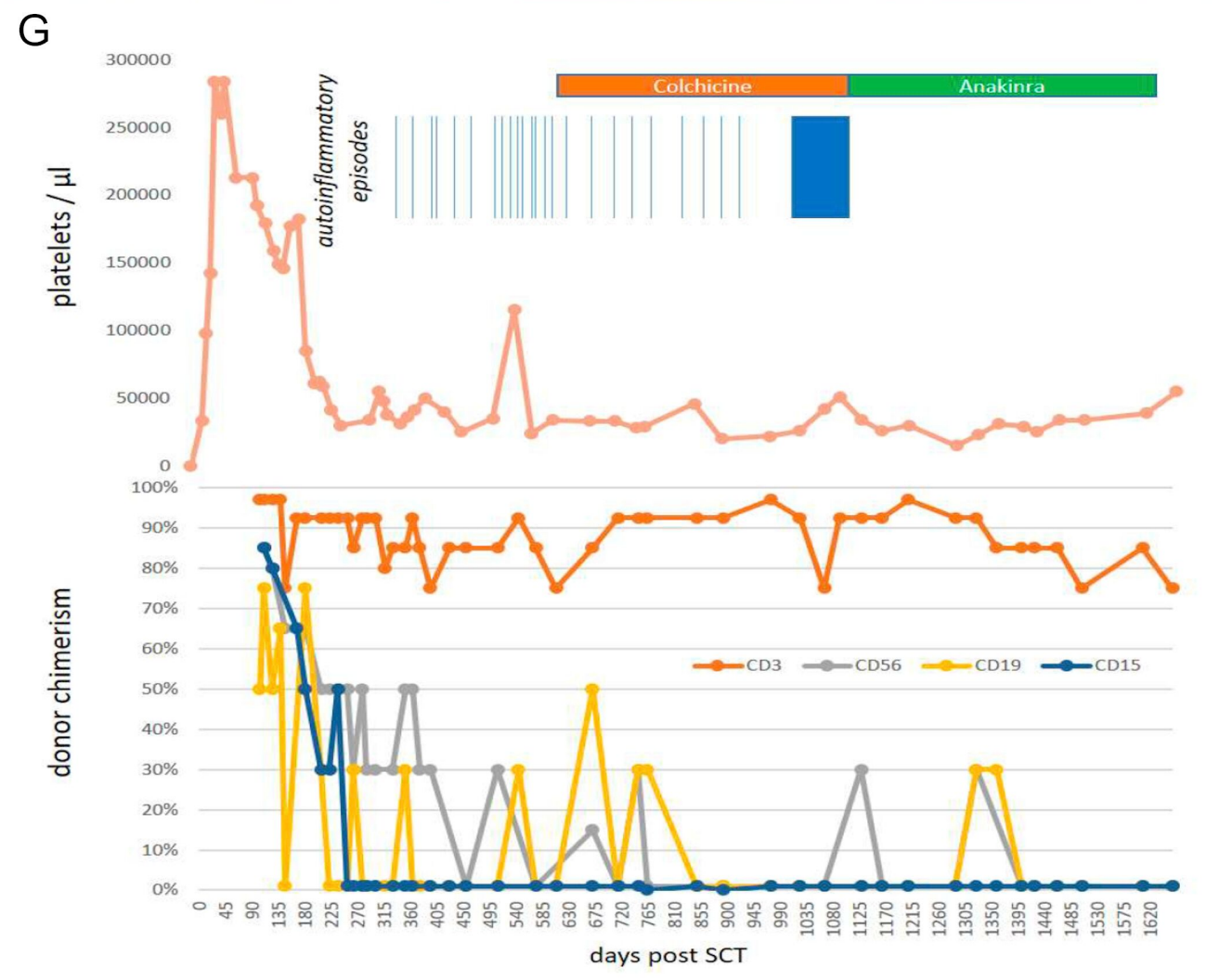
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300000
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200000
150000
100000
50000
0
autoinflammatory episodes
Colchicine
Anakinra
donor chimerism
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
CD3
CD56
CD19
CD15
0
45
90
135
180
225
270
315
360
405
450
495
540
585
630
675
720
765
810
855
900
945
990
1035
1080
1125
1170
1215
1260
1305
1350
1395
1440
1485
1530
1575
1620
days post SCT

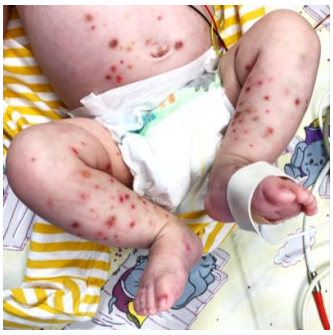
Interleukin-1 Blockade in Patients with Wiskott-Aldrich Syndrome

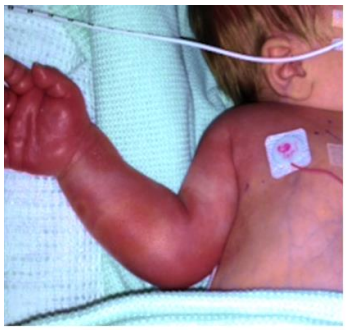
Context of research:

- **Autoimmune and inflammatory manifestations are very common in patients with Wiskott-Aldrich Syndrome (WAS) and their pathogenesis may involve dysregulation of interleukin (IL)-1.**
- **There is little available information on treatment with anti-IL-1 agents (anakinra or canakinumab) in patients with WAS.**

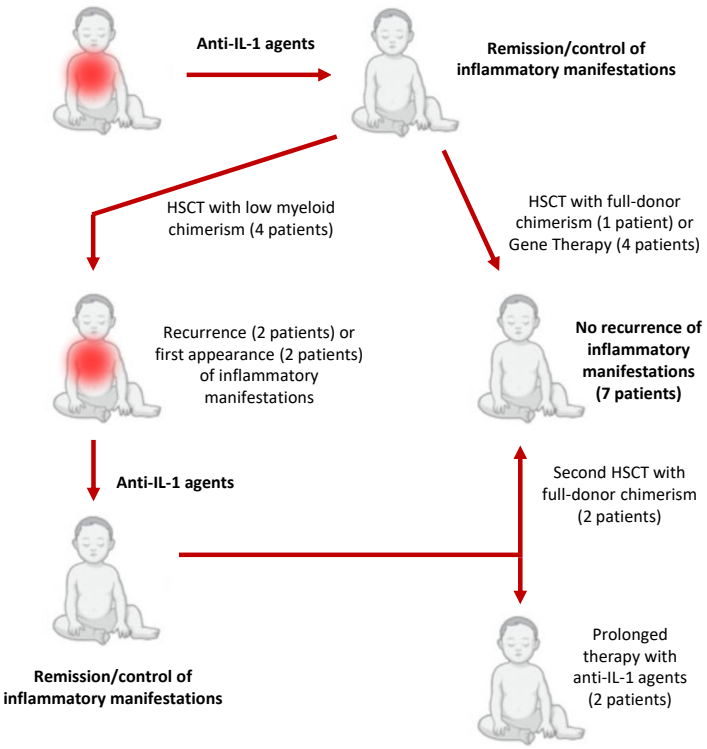
Patients and methods:

- **Retrospective review of 9 children with WAS treated with anti-IL-1 agents (anakinra or canakinumab) for inflammatory manifestations at 7 pediatric centers.**
- **All patients had prominent inflammatory manifestations including systemic, cutaneous, articular, and intestinal symptoms, poorly controlled by systemic corticosteroids.**





Main findings:



Conclusions: 1) Patients with Wiskott-Aldrich Syndrome can develop inflammatory manifestations poorly controlled by corticosteroid therapy. 2) Therapy with anti-IL-1 agents resulted in dramatic responses, allowing successful bridging to definitive therapy.