To the editor:

Variability in the efficacy of the IL1 receptor antagonist anakinra for treating Erdheim-Chester disease

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Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis characterized by foamy histiocytes, sometimes associated with central nervous system (CNS) and cardiac infiltration.[1] Several reports have suggested that an interleukin (IL)1 receptor antagonist, anakinra, is effective in treating ECD.[2-8]

Twelve patients (7 men and 5 women; median age, 70 years; range, 22-80 years) with biopsy-proven ECD[9] and previous failure (cases 2, 3, 4, 9, and 11), poor tolerance, or contraindication (cases 1, 2, 5, 6, 7, 8, 10, and 12) to interferon-α (IFN-α) therapy received alternative treatment with daily subcutaneous injection of 100 mg anakinra. Data collection and analysis were performed retrospectively. Three patients rapidly stopped the treatment (2 for failure and 1 for pain at the injection site). Table 1 shows the characteristics of the 12 initial and the 9 remaining patients at baseline. Eight patients had long bone involvement, 8 had cardiac disease (4 with a pericardial effusion or thickening and 8 with a pseudomass in the right atrium), 3 had retro-orbital infiltration, 1 had a pseudo-meningioma of the spine, and 1 had pachymeningitis. The median duration of ECD disease when anakinra was started was 5 years (range, 1-12 years). Ten of the 12 patients were treated prior to inclusion with IFN-α (pegylated or not). For 5 of them, anakinra was given just after IFN-α treatment.

The median duration of anakinra treatment (always given as a monotherapy) among the 9 patients was 22 months (range, 3-34 months). Clinical symptoms improved in 50% of the patients (3 of 7 for fatigue, among them 2 stopped IFN-α just before, 1 of 1 for fever, 2 of 6 for bone pain, 1 of 2 for sinus disturbance). The median C-reactive protein (CRP) value at baseline was 10 mg/L (range, 4-30 mg/L) and at the end of the treatment was 10 mg/L (range, 4-43 mg/L), which was not significantly different. All patients had a positron emission tomography (PET) evaluation at baseline and at the end of follow-up. Five had progression of the disease, 2 had stable disease, 1 had a partial response, and 1 had a complete metabolic response. Among the 6 patients who had cardiac involvement, 5 underwent baseline and final cardiac magnetic resonance imaging (MRI), which displayed stability in 3 and progression in 2 (among them, 1 had tamponade). Retro-orbital infiltration evaluated by cerebral MRI was stable in 1 of 1 patients and CNS infiltration appeared in 1 patient free of CNS involvement at the beginning of the treatment.

Tolerance was variable. Four of the 9 patients included in the long-term analysis had side effects, including pain at the injection site (n = 4), edema (n = 1), severe sepsis (n = 1), and headache (n = 1). Overall, anakinra was stopped in 11 of 12 patients because of poor tolerance (n = 4) or progression of disease (n = 7).

Proinflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor-α, are strongly increased in ECD lesions. Whether IL-1 blood levels are increased is still controversial; this finding has been reported in isolated cases but not in a larger series of 37 patients.[10] Altogether, these findings suggested that inhibition of the IL-1 pathway could be a promising therapeutic area for ECD treatment.

Here, we report a series of 12 patients with ECD exhibiting multisystem histiocyte infiltration treated with anakinra. Tolerance was variable and led to discontinuation of the treatment in 33% of patients. In contrast with 6 of 8 previous case reports, we did not observe an improvement in CRP levels. This may be due to IFN-α therapy, which may have lowered basal CRP levels in 4 patients who received this treatment just before receiving anakinra. The efficacy of anakinra assessed by fluorodeoxyglucose (FDG)-PET was variable. The extent of the disease evaluated by computed tomography or MRI imaging was not improved in our patients receiving anakinra, regardless of the site (retro-orbital, cardiac, spine, brain, pleura, or retroperitoneal). Conversely, CNS infiltration and tamponade occurred during treatment in 1 patient each.

Aouba et al[2] first reported the dramatic efficacy of anakinra in 2 ECD patients with a dramatic improvement in retroperitoneal infiltration and regression of hydronephrosis. Since then, the use of IL-1 blockade in ECD has been reported in 6 additional reports[3-8] (Table 2), which did not mention any changes in bone lesions or retroperitoneal infiltration. Killu et al[5] described a patient with a right atrial mass in which FDG uptake decreased under anakinra treatment, although there was no MRI evaluation of the cardiac infiltration. Some of our patients, conversely to several previous reports including the one by Aouba et al, were refractory to IFN-α therapy, which could be the hallmark of more severe disease and can explain the different responses to treatment.

Altogether, these results show that anakinra displays a variable efficacy in ECD sometimes, with progression of cardiac or CNS involvement.

In conclusion, anakinra is possibly effective for treating constitutional symptoms, has variable efficacy in organs as measured by FDG-PET scan, and did not lead to measurable regression of tumors. For ECD patients with cardiac or CNS infiltration, other treatments, such as IFN-α or B-Raf inhibitors, should be considered first. Increasing the anakinra dose should also be considered in the future, as has been proposed in other inflammatory conditions.

Table 1. Demographic and clinical characteristics of the 12 patients at baseline and of the 9 (1-9) patients included in the analysis of long-term outcome

	Sex, age at anakinra treatment (years)	Age at ECD diagnosis (years) and BRAF status	ECD localizations	Previous treatments	Biopsy site	Treatment duration	Anakinra failure, progression of disease	Anakinra efficacy
1	M, 64	52 WT	Retroperitoneal, bones, aorta, pericardium, atrial pseudomass, sinus, spine	SteroidsIFN, PEG-IFN	Pericardium, perirenal	22 mo	Heart, pleura	Spine
2	M, 68	60 ND	Retroperitoneal, bones, aorta, atrial pseudomass	Steroids, IFN, PEG-IFN, imatinib	Perirenal	31 mo	Pleura, lung, spine	
3	M, 76	72 V600E	Retroperitoneal, Bones, aorta, pericardium, atrial pseudomass	IFN, PEG-IFN	Perirenal	26 mo	Aorta, heart	Pleura
4	F, 80	72 V600E	Retroperitoneal, bones, aorta, pericardium, atrial pseudomass, lung	Steroids, IFN	Perirenal	7 mo	Stable	
5	F, 58	52 ND	Bones	IFN, PEG-IFN	Bone	28 mo		Bones
6	M, 75	72 ND	Bones	None	Bone	11 mo	CNS	
7	F, 22	16 ND	DI, lung, sinus, retroperitoneal	Steroids, IFN, PEG-IFN, vinblastine	Sinus	3 mo	Stable	
8	M, 71	65 V600E	Retroperitoneal, bones, lung, aorta, atrial pseudomass, CNS	IFN, PEG-IFN	Perirenal	5 mo	Bones, pleura, CNS	
9	M, 70	69 V600E	Aorta, bones, retroperitoneal, atrial pseudomass, retroorbital, xanthelasma	Steroids, PEG-IFN	Perirenal	34 mo	Heart	
10	M, 72	71 ND	Aorta, bones, pericardium, atrial pseudomass, hydronephrosis, retroorbital	PEG-IFN	Perirenal	3 wk	NA	NA
11	F60	59 V600E	Aorta, bones, atrial pseudomass, skin, bones, retroorbital, DI	Steroids, PEG-IFN	Perirenal	3 wk	NA	NA
12	F70	69 ND	Aorta, DI, bones	None	Bones	1 wk	NA	NA

DI, diabetes insipidus; NA, not available; ND, not determined; PEG, pegylated; V600E, presence of mutation BRAF V600E; WT, wild type.

Table 2. Previous reported cases of anakinra treatment of ECD

	Sex, age (years)	ECD localizations and previous treatments	ECD duration (years)	Anakinra duration (months)	CRP	Tolerance	Efficacy
Aouba 1[13]	F, 46	Bones, retroperitoneal, hydronephrosis, xanthelasma Steroids Zoledronic acid Cladribine	7	25	Normalized	Pruritus	Disappearance of bone pain and fever Regression of hydronephrosis and retroperitoneal infiltration Normalization of bone scintigraphy
Aouba 2[13]	M, 55	Bones, coated aorta and renal artery stenosis, retroperitoneal, hydronephrosis Steroids IFN-α	9	26	Normalized	Pain at injection sites	Disappearance of bone pain and fever Regression of hydronephrosis No improvement of scintigraphic bone uptake
Tran[14]	F, 10	Bones, retroperitoneal Vinblastine Steroids IFN-α	?	10	Normalized	Pain at injection sites	Disappearance of bone pain and fever No changes in bone lesions nor retroperitoneal infiltration
Aubert[20]	F, 32	Bones, retroperitoneal, adrenal infiltration Steroids Vesanoid	10	12	Normalized	Slight injection sites reaction	Disappearance of bone pain and fever Improvement of bone hypermetabolism in PET No change in retroperitoneal infiltration
Killu[22]	M, 71	Right atrial mass, bilateral pleura infiltration, temporal artery infiltration No prior treatment	0	6	?	?	Improvement of 18 FDG uptake in right atrial mass Heart MRI evaluation not done
Courcoul[23]	M, 57	Bones Steroids Pamidronate IFN-α	1	12	Normalized	No side effects	Disappearance of bone pain No changes in 18 FDG uptake, bone scan and bone MRI
Darstein[24]	M, 48	Bones, retroperitoneal, hydronephrosis, CNS No prior treatment	3	5	Rapid decrease	Gram-negative urosepsis controlled under antibiotics	Improvement of neurological symptoms (not assessed by MRI)
Cohen[25]	F, 43	Bones, pituitary involvement, sinuses, lichen planus	4	3	NA	Injection site reaction	Cutaneous lesions, desmopressin need and bone pain improvement

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Contribution: F.C.-A., J.H., and Z.A. designed the study and analyzed the data; F.C.-A., D.S., F.C., Z.A., and J.H. wrote the manuscript; P.M. reviewed and analyzed the PET imaging; A.D. and P.C. reviewed the cerebral and cardiac imaging; and all authors approved the final manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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DOI 10.1182/blood-2015-09-672667

To the editor:

Uncompromised 10-year survival of oldest old carrying somatic mutations in *DNMT3A* and *TET2*

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Recent large-scale sequencing studies report recurrent somatic mutations in the blood of elderly individuals in genes previously linked to clonal expansion of hematopoietic stem cells.[1-4] Particularly for *DNMT3A* and *TET2*, a steep age-associated increase in the prevalence of somatic mutations is observed from middle age onward.[2-4] In addition, prospective analyses performed in predominantly middle-aged individuals show an increased risk for all-cause mortality for carriers of such mutations as compared with noncarriers.[3,4] Jointly, these data suggest a rapidly increasing vulnerability among the elderly for adverse health effects associated with clonal expansion of hematopoietic stem cells. However, prospective data on elderly somatic mutations carriers are scarce. We therefore investigated the association between all-cause mortality and carriership of somatic mutations in genes linked to clonal expansion of hematopoietic stem cells in a large elderly subsample (N = 864, 80 years and older) derived from 2 large-scale community-dwelling Dutch cohort studies.[5,6]

For the present study, we investigated whole-blood–derived genomes of 646 individuals of 80 years and older from the Rotterdam Study[5] (RS; mean age at inclusion, 84.6 years; range, 80.0-105.8 years; supplemental Appendix 2, available on the *Blood* Web site) and 218 individuals of 89 years and older from the Leiden Longevity Study[6] (LLS; mean age at inclusion, 94.0 years; range, 88.9-103.4 years; supplemental Appendix 2). Jointly, this elderly subsample consists of 597 participants aged 80 to 89 years and 267 participants aged over 90 years, which is twice the number of participants for the respective age categories as compared with any other study previously conducted on this topic.[2-4] Selected elderly participants of the RS and LLS were followed for all-cause mortality for a median 8.7 and 9.2 years, respectively, which was sufficiently long to identify the age at death of 81.3% and 93.6% of the respective study subsamples. Methods of DNA sequencing and analysis are described in supplemental Appendix 3. The ethical committees of the involved institutes approved both studies, and written informed consent was obtained from all study participants.

Using this unique cohort of sequenced oldest old, we first set out to confirm the recurrent acquisition of somatic mutations in genes linked to clonal hematopoiesis in the blood of highly aged individuals. For this, we curated a list of 15 genes (supplemental Appendix 4) reported to harbor recurrent somatic mutations in the blood of normal individuals in any of the large-scale sequencing studies conducted to date.[2-4] Thus, identified genes were analyzed for putative somatic mutations according to the gene-specific inclusion criteria set by Jaiswal et al (supplemental Appendix 4).[4]

The mutational analysis identified 39 (6.0%) and 40 (18.3%) unique carriers of, respectively, 42 and 46 mutations for the RS and