Accepted: 24 September 2021

LETTER TO THE EDITOR

IL-1 blockade with anakinra for severe inflammatory symptoms during chemotherapy for acute lymphoblastic leukemia

To the Editor:

Anakinra is a recombinant interleukin (IL)-1 receptor antagonist used for several inflammatory conditions including systemic juvenile idiopathic arthritis, recurrent pericarditis, and familial Mediterranean fever (FMF). Its efficacy in blocking IL-1 and its manageable safety profile support its use also in other conditions, such as sepsis, acute myocardial infarction, and COVID-19.[1–4] IL-1 inhibitors, however, have been rarely used in patients with leukemia- or cancer-related inflammatory disorders. We report the use of anakinra therapy for controlling persistent inflammatory symptoms during chemotherapy for acute lymphoblastic leukemia (ALL).

A 17-year-old Iraqi boy with T-cell ALL without cytogenetic abnormalities was treated according to the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) BFM ALL 2009 protocol scheme (observational extension), achieving negative (<0.01%) bone marrow minimal residual disease (MRD) by cytofluorometry at the end of the induction phase. During the first high-dose methotrexate course of the consolidation phase, he developed severe renal toxicity; therefore, it was decided to continue treatment using the high-risk consolidation block HR3 from the same protocol, which does not include methotrexate. Ten days after the completion of this course, he was admitted for febrile neutropenia due to an *Escherichia coli* sepsis. After an initial response to antibiotic therapy, however, spiking fever relapsed, with a marked increase of acute phase reactants and serum ferritin (2077 ng/ml). A full infectious workup was negative, while bone marrow aspirates showed no leukemic blasts but increased histiocytes with signs of hemophagocytosis. The patient did not met all the criteria for hemophagocytic lymphohistiocytosis (HLH)[5]; however, an inflammatory, noninfectious etiology of the fever was suspected and methylprednisolone was started with complete resolution of symptoms. Perforin, SAP, and XIAP expression in lymphocytes was normal, while natural killer cells showed reduced degranulation after incubation with K562 cells compared to a healthy control (CD107a: 3.3% vs. 11.5%), yet this test was performed while already on corticosteroid therapy. Notably, symptoms recurred at steroid tapering; therefore, it was restarted, again with prompt response. Reinduction phase chemotherapy was then started, with oral dexamethasone in place of methylprednisolone. However, fever relapsed at the scheduled steroid tapering, this time associated with elbows, knees, and ankles joint pain and swelling. Notably, at this time cytarabine therapy of the reinduction had not been administered yet. Involved joints ultrasound showed synovial thickening and fluid effusion. An autoimmune workup was negative. Therapy with dexamethasone was restarted with prompt response, yet fever and joint symptoms relapsed immediately at tapering. The patient also started to present significant adverse effects associated with chronic corticosteroid treatment, especially arterial hypertension and disfiguring severe cutaneous striae. A therapeutic trial of subcutaneous anakinra was started (initially 100 mg once daily, then 100 mg twice daily), with prompt resolution of fever and arthritis and normalization of inflammatory markers, thus allowing steroid discontinuation and chemotherapy resumption (Figure 1). Anakinra was continued also throughout the subsequent chemotherapy courses, without evidence of adverse effects. Cytofluorimetric MRD was negative, so maintenance therapy with oral mercaptopurine and methotrexate was started, in association with anakinra. Notably, genetic testing revealed a heterozygous missense mutation in the STX11 gene (c.799G>A, p.V267M), associated with familial HLH in homozygous carriers[6]; and a homozygous E148Q mutation in the MEFV gene, a low-penetrance mutation associated with FMF. After 3 months of maintenance therapy, a combined bone marrow and central nervous system ALL relapse was diagnosed. Second- and third-line therapy with FLAG-Myocet and the TACL consortium 2005-003 scheme[7] was attempted, in association with anakinra, but multiple complications occurred (severe cytopenia, hepatic veno-occlusive disease, sepsis, hemorrhagic cystitis, *Cytomegalovirus* hepatitis, progressive renal and heart failure), eventually leading to patient demise.

Little data are available regarding anakinra therapy in pediatric patients with malignancies and inflammatory symptoms. Demir et al. reported the use of anakinra in association to chemotherapy in a 12-year-old girl with FMF and Hodgkin's lymphoma, without apparent toxicity.[8] Our patient presented with persistent inflammatory symptoms complicating and delaying ALL therapy, requiring prolonged corticosteroid treatment. The cause of inflammatory symptoms in our patient is not fully explained. It was not likely associated with ALL, as it was in remission when these symptoms appeared. Clinical presentation was nonspecific and only partly similar to FMF or systemic juvenile idiopathic arthritis. Notably, our patient harbored two genetic mutations (STX11 and MEFV) that may have predisposed him to the occurrence of inflammatory complications. Heterozygous mutations in genes associated with familial HLH like *STX11* have been identified in patients with secondary HLH.[9–11] FMF is associated with IL-1-dependent inflammation, yet the role of his *MEFV* mutations is unclear, as he had a low penetrance mutation (E148H), which may be associated with no clinical manifestations or mild FMF phenotypes. However,

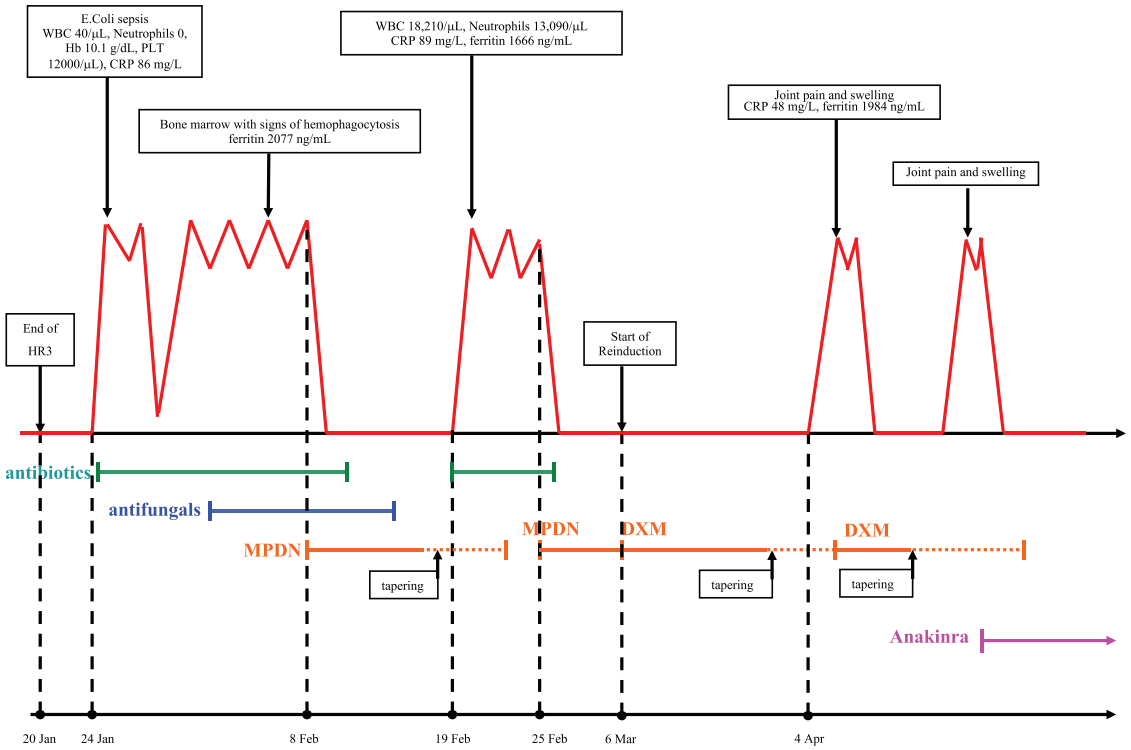

FIGURE 1 Course of fever, selected blood tests and therapeutic management of the patient
Abbreviations: MPDN, methylprednisolone; DXM, dexamethasone, WBC, White Blood Cells; CRP, C- Reactive Protein.

it could be speculated it may have facilitated the occurrence of inflammatory manifestations, possibly in association with other concomitant factors. Interestingly, Awad et al. reported the case of a man with FMF who developed chronic myelomonocytic leukemia associated with an uncontrolled and ultimately fatal inflammatory syndrome.[12] The authors speculate that leukemia and FMF had resulted in increased inflammatory effects, and recommend using IL-1 inhibitors to decrease inflammatory activation.

Despite the absence of a specific diagnosis for our patient's inflammatory syndrome, the empiric introduction of anakinra therapy was immediately useful as it allowed resolution of inflammatory symptoms, sparing of corticosteroids, and prosecution of chemotherapy. We did not observe evidence of increased toxicity during subsequent chemotherapy or delay in the blood cells count recovery; complications occurred after second-line therapy were deemed to be likely due to chemotherapy intensification in a heavily pretreated patient. Anakinra has been reported to have a manageable safety profile, with very few adverse effects; moreover, it has a short half-life, thus it can be readily stopped if necessary. IL-1 blockade does not seem to cause a significant increase in the infectious risk,[13] and has also been tried in patients with sepsis with some benefit.[14] Furthermore, it may allow to stop or reduce corticosteroid therapy, which is definitely associated with an increased infectious risk. IL-1 blockade is also being evaluated as an adjunctive therapy in patients with malignancies, as IL-1 may have tumor-promoting effects in vivo.[15]

In conclusion, we suggest IL-1 blockade with anakinra may represent a useful and manageable strategy in patients with ALL and inflammatory symptoms. An ex juvantibus trial of anakinra may therefore be justified in selected patients with leukemia and persistent, difficult-to-control inflammatory symptoms, possibly allowing control of clinical manifestations, corticosteroid sparing, and prosecution of chemotherapy. Our case also underscores the importance of physicians' awareness of possible genetic predisposition, inborn errors of immunity, and autoinflammatory syndromes in patients with unusual symptoms or complications during chemotherapy for pediatric malignancies, as several factors in these patients may enhance or facilitate their clinical manifestation, especially in a patient from the middle east or areas with high prevalence of inter-familial marriages.

AKNOWLEDGMENTS

Samuele Naviglio and Giada Zanella wrote the manuscript. Samuele Naviglio, Giada Zanella, Nagua Giurici, Valentina Kiren, Federico Verzegnassi, and Marco Rabusin participated in the patient's management. Elena Sieni, Maria Luisa Coniglio, Erica Valencic, and Alberto Tommasini performed genetic, immunological, and functional tests. Alberto Tommasini contributed in reviewing and critically assessing the manuscript. Marco Rabusin is the chair of the unit and revised the draft of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Samuele Naviglio[1]
Giada Zanella[1]

Federico Verzegnassi[1]
Valentina Kiren[1]
Nagua Giurici[1]
Elena Sieni[2]
Maria Luisa Coniglio[2]
Erica Valencic[3]
Alberto Tommasini[3,4]
Marco Rabusin[1]

[1] *Pediatric Hematology-Oncology, Institute for Maternal and Child Health IRCCS "Burlo Garofolo,", Trieste, Italy*
[2] *Pediatric Hematology/Oncology Department, Meyer Children's University Hospital, Florence, Italy*
[3] *Department of Pediatrics, Institute for Maternal and Child Health IRCCS "Burlo Garofolo,", Trieste, Italy*
[4] *Department of Medicine, Surgery, and Health Sciences, University of Trieste, Trieste, Italy*

Correspondence
Giada Zanella, Institute for Maternal and Child Health IRCCS "Burlo Garofolo," Via dell'Istria 65/1, 34137, Trieste, Italy.
Email: giagiada@gmail.com

ORCID

Samuele Naviglio https://orcid.org/0000-0002-1915-9965
Giada Zanella https://orcid.org/0000-0001-8854-814X
Federico Verzegnassi https://orcid.org/0000-0002-8457-2473
Elena Sieni https://orcid.org/0000-0002-6192-9812

REFERENCES

1. Rajasekaran S, Kruse K, Kovey K, et al. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children. *Pediatr Crit Care Med*. 2014;15(5):401-408.
2. Brucato A, Imazio M, Gattorno M, et al. Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: the AIRTRIP randomized clinical trial. *JAMA*. 2016;316(18):1906-1912.
3. Abbate A, Toldo S, Marchetti C, Kron J, Van Tassell BW, Dinarello CA. Interleukin-1 and the inflammasome as therapeutic targets in cardiovascular disease. *Circ Res*. 2020;126(9):1260-1280.
4. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol*. 2020;2(6):e325-e331.
5. Bergsten E, Horne A, Aricó M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood*. 2017;130(25):2728-2738.
6. Ferrari MF, Leinoe E, Rossing M, et al. Germline heterozygous variants in genes associated with familial hemophagocytic lymphohistiocytosis as a cause of increased bleeding. *Platelets*. 2018;29(1):56-64.
7. Messinger YH, Gaynon PS, Sposto R, et al. Bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Study. *Blood*. 2012;120(2):285-290.
8. Demir F, Bahadir A, Mungan S, Çobanoğlu Ü, Kalyoncu M. Systemic amyloidosis in a patient with familial Mediterranean fever and Hodgkin lymphoma: a case report. *J Pediatr Hematol Oncol*. 2020;42(3):234-237.
9. Sieni E, Cetica V, Piccin A, et al. Familial hemophagocytic lymphohistiocytosis may present during adulthood: clinical and genetic features of a small series. *PLoS One*. 2012;7:e44649.
10. Zhang K, Jordan MB, Marsh RA, et al. Hypomorphic mutations in PRF1, MUNC13-4, and STXBP2 are associated with adult-onset familial HLH. *Blood*. 2011;118:5794-5798.
11. Zhizhuo H, Junmei X, Yuelin S, et al. Screening the PRF1, UNC13D, STX11, SH2D1A, XIAP, and ITK gene mutations in Chinese children with Epstein–Barr virus-associated hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2012;58:410-414.
12. Awad F, Georgin-Lavialle S, Brignier A, et al. Chronic myelomonocytic leukemia as a cause of fatal uncontrolled inflammation in familial Mediterranean fever. *Orphanet J Rare Dis*. 2015;10:76.
13. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2009;(1):CD005121. https://doi.org/10.1002/14651858.cd005121.pub3
14. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. *Crit Care Med*. 2016;44(2):275-281.
15. Menu P, Vince JE. The NLRP3 inflammasome in health and disease: the good, the bad and the ugly. *Clin Exp Immunol*. 2011;166(1):1-15. https://doi.org/10.1111/j.1365-2249.2011.04440.x