CASE REPORT | LIVER

Anakinra Hepatotoxicity in a Patient With Adult-Onset Still’s Disease

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Abstract
We report a 46-year-old white woman with adult-onset Still’s disease (AOSD) treated with anakinra, a IL-1B receptor antagonist. Within weeks, her liver enzymes deteriorated; subsequent cessation and rechallenge confirmed anakinra-related drug-induced liver injury (DILI). Although AOSD has been associated with liver involvement, little is known about the hepatotoxicity of anakinra. Heightened awareness by gastroenterologists and hepatologists is warranted.

Introduction
Adult-onset Still’s disease (AOSD) is a rare disorder mediated by an autoimmune inflammatory response. It manifests with fever, arthritis, rash, leukocytosis, hyperferritinemia, and abnormal liver enzymes,¹ and diagnosis is made using the Yamaguchi criteria.² Although the mainstay of treatment has been non-steroidal anti-inflammatory drugs (NSAIDs) and high-dose steroids, there has been a recent growth in the use of IL-1B receptor antagonists.³ Anakinra is one such drug with growing evidence of efficacy to improve liver disease secondary to AOSD.⁴,⁵ However, the data on anakinra causing drug-induced liver injury (DILI) is not well described, with only 1 previous case report of a suspected DILI that resolved with discontinuation of anakinra.⁶

Case Report
A 46-year-old white woman presented with a 3-week history of a maculopapular rash, episodic fevers, and arthritis. She had no significant medical history and was not on any medications. She had no family history of liver disease and did not acknowledge any high-risk behavior (tattoos, intravenous drug abuse, high-risk sexual behavior, or previous blood transfusions). She had an average alcohol intake of 2-3 units per week. Laboratory tests demonstrated ferritin >6000 μg/L and C-reactive protein (CRP) 124 mg/L. Her liver enzymes at presentation were unremarkable. She was diagnosed with AOSD and was started on prednisone 50 mg daily with improvement of her clinical symptoms. Three months later, she was started on anakinra 100 mg subcutaneously every other day with a concurrent decrease of prednisone to 45 mg daily.

Two weeks after initiation of anakinra, her clinical symptoms had resolved; however, laboratory tests showed an elevation in AST from 26 to 927 IU/L and ALT from 19 to 1414 IU/L. Her CRP had fallen to 61 mg/L. An ultrasound with Doppler revealed a normal liver and gallbladder. She had no signs of liver failure. Anakinra was discontinued; 1 week after discontinuation, her liver enzymes stabilized, but were persistently high with AST 818...
IUI/L, ALT 1202 IU/L, GGT 586 IU/L, and total bilirubin 20 µmol/L, but CRP decreased to 8.7 mg/L. Unfortunately, her clinical symptoms returned with arthralgias of her hands and knees, raising the possibility of AOSD as the cause for hepatotoxicity. We felt that the patient benefited from anakinra, and the liver abnormalities were better explained by AOSD. Thus, we restarted anakinra.

After a week of therapy, she was hospitalized for jaundice with AST 1543 IU/L, ALT 1945 IU/L, GGT 696 IU/L, and total bilirubin 114 µmol/L. Tests were negative for viral hepatitis, HIV, ANA, anti-mitochondrial (AMA), anti-smooth muscle antibodies (ASMA), ceruloplasmin, immunoglobulins, alpha-1-fetoprotein, and alpha-1 anti-trypsin. Acetaminophen and alcohol levels were normal. Anakinra was discontinued again. She was started on etanercept 50 mg once weekly and her liver abnormalities gradually resolved. On follow-up, she continued to do well on etanercept with normal liver enzymes.

Discussion
The case demonstrates a link between anakinra and DILI. Liver abnormalities are commonly seen in patients with AOSD, with literature suggesting up to 65% of patients having mild-to-moderate elevations in their aminotransferases.7 Recent DILI guidelines suggest the first step to determining DILI is a detailed history and physical examination, including time of onset and latency, exposures to other medications, co-morbidities, and symptoms.8 Physical exam findings of note are hepatomegaly and signs of chronic liver disease.1 Laboratory investigations should include inflammatory markers such as CRP, which can help differentiate between disease and DILI. Imaging of the abdomen is also recommended to rule out vascular causes of injury.6 In our patient, symptoms and physical exam findings were thought to be associated with AOSD, which subsided with the use of anakinra and reappeared with discontinuation of anakinra.

Common validated scoring systems to determine whether liver injury is secondary to drug exposure include the RUCAM score and the Maria and Victorino system.9 Our patient’s RUCAM score was 10 (“highly probable”).8 A liver biopsy can be helpful in differentiating drug-induced and disease-associated liver injury, but it is not always necessary. Current guidelines recommend pursuing a biopsy in cases of suspected autoimmune liver disease or if liver enzymes remain high even after discontinuation of suspected offending drugs.8 If anakinra-induced drug injury is suspected, it is important to discontinue the medication as soon as possible. Supportive care is usually sufficient, with ongoing monitoring of liver enzymes and liver function tests, and avoidance of the drug.8

Disclosures
Author contributions: O. Ahmed drafted the manuscript and performed the literature review. M. Brahmania edited and revised the manuscript, performed the literature review, and is the article guarantor. S. Alkhowaiter, M. Alsahafi, and S. Erb edited and revised the manuscript.

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References
1. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Seve P. Adult-onset Still’s disease. Autoimmun Rev. 2014;13(7):708–22.
2. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still’s disease. J Rheumatol. 1992;19(3):424–30.
3. Efthimiou P, Paik PK, Bieylo L. Diagnosis and management of adult onset Still's disease. Ann Rheum Dis. 2006;65(5):564–72.
4. Nordström D, Knight A, Luukkainen R, et al. Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still’s disease. An open, randomized, multicenter study. J Rheumatol. 2012;39(10):2008–11.
5. Mylona E, Golfinopoulou S, Samarkos M, et al. Acute hepatitis in adult Still’s disease during corticosteroid treatment successfully treated with anakinra. Clin Rheumatol. 2008;27(5):659–61.
6. Diallo A, Mekinian A, Boukari L, et al. Severe hepatitis in a patient with adult-onset Still’s disease treated with anakinra [Article in French]. Rev Med Interne. 2013;34(3):168–70.
7. Zhu G, Liu G, Liu Y, et al. Liver abnormalities in adult onset Still’s disease: A retrospective study of 77 Chinese patients. J Clin Rheumatol. 2009;15(6):284–8.
8. Chalasani NP, Hayashi PH, Bonkovsky HL, et al. ACG clinical guideline: The diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2014;109(7):950–66; quiz 67.
9. Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. Hepatology. 1997;26(3):664–9.

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