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Autoimmune hepatitis in a patient with rheumatoid arthritis treated with etanercept

Adrian Mitroi[1,2]*; Ana M Ionescu[1,2]

[1]Faculty of Medicine, "Ovidius" University of Constanța, Romania.

[2]Clinical Railway Hospital Constanta, Romania.

***Corresponding Author: Mitroi Adrian**

Faculty of Medicine, "Ovidius" University of Constanța, Romania.

Tel: +40-0241-583-355;

E-mail: MITROI_74@yahoo.com

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Abstract

Introduction: Etanercept is a Tumor Necrosis Factor-A (TNF-alpha) blocking agent used in Rheumatoid Arthritis (RA). It is a well-tolerated drug, but during treatment with it may occur increases in liver enzymes, the formation of autoantibodies and very rarely autoimmune hepatitis.

Case presentation: We present a case of RA which after 3 years of treatment with etanercept it detects increases in transaminases of up to twice normal values and a year later (after 4 years of treatment with etanercept) is diagnosed with Autoimmune Hepatitis (AIH) already in the stage of decompensated liver cirrhosis.

Conclusion: In a patient with rheumatoid arthritis who is being treated with anti-TNF alpha, the increase in liver enzymes can have multiple causes, so an exhaustive approach in which the autoimmune etiology is not overlooked is desirable.

Keywords: autoimmune hepatitis; etanercept; drug induced autoimmune hepatitis; rheumatoid arthritis.

Abbreviations: RA: Rheumatoid Arthritis; AIH: Autoimmune Hepatitis; TNF-Alpha: Tumor Necrosis Factor-Alpha; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; AST: Aspartate Transaminase; ALT: Alanine Transaminase; Hbs-Ag : Hepatitis B Surface Antigen; HCV-Ab: Hepatitis C Virus Antibody; TB: Tuberculosis; LAP: Serum Alkaline Phosphatase; γ-GTP: Gamma-Glutamyl Transpeptidase; ASMA: Anti Smooth Muscle Antibody; ANA: Antinuclear Antibodies; Ig: Immunoglobulin; DILI: Drug Induced Liver Disease; DIAIH: Drug Induced Auto-Immune Hepatitis.

Introduction

Etanercept is a TNF-alpha blocking agent used in RA. It is a well-tolerated drug, but a number of severe side effects can occur: Infections, reactivation of viral hepatitis B, worsening of viral hepatitis C, malignancies, lymphoproliferative disorders, haematological disorders (aplastic anemia, pancytopenia), disorders of the nervous system by demyelination, aggravation heart failure, etc. During treatment with etanercept, increases in liver enzymes were observed with a frequency of 4.18% and the formation of antinuclear antibodies in titer > 1:40 in 11% of patients. Autoimmune hepatitis associated with etanercept had an incidence of 0.24% [1]. This article presents a case of autoimmune hepatitis in a patient with RA who is being treated with etanercept.

Case presentation

A 52-year-old man is being treated with etanercept for stage 3 rheumatoid arthritis because there has been no response to methotrexate given for 1 year. He also uses Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) at the same time as etanercept, if needed. At the start of treatment with etanercept performed laboratory tests: Complete blood counts, Aspartate Transaminase (AST), Alanine Transaminase (ALT), Hepatitis B Surface Antigen (Hbs-Ag), Hepatitis C Virus Antibody (HCV-Ab), Quantiferon Tuberculosis (TB), creatinine - all within normal limits. The patient presents to periodic evaluation, RA being in remission and laboratory tests within normal limits - without changes in liver tests.

The patient does not smoke, does not consume alcohol and has not used any medications other than those mentioned, has no history of exposure to liver damage or family liver disease.

After 3 years of treatment with etanercept it detects increases in transaminases of up to twice normal values (ALT 60 U/L; AST 58 U/L), Serum Alkaline Phosphatase (LAP) and Gamma-Glutamyl Transpeptidase (γ-GTP) being normal; investigations for hepatitis B and C are normal, and abdominal ultrasonography revealed only hepatic steatosis. The patient is asymptomatic. Slight growth of liver enzymes is constant and is considered to be caused by nonalcoholic hepatic steatosis and intermittent NSAIDs treatment. Continue treatment with etanercept.

One year after the detection of hepatic cytolysis syndrome, respectively after 4 years of treatment with etanercept, the patient becomes symptomatic and is admitted to our hospital for jaundice, fatigue and abdominal enlargement, symptoms that have installed insidiously during a month.

At the physical examination the patient was afebrile, brady psychic, tempo spatial oriented, present jaundice, palmar erythema, spider angioma, blood pressure 135/80 mmHg, heart rate 100 / minute, no heart murmurs, respiratory rate 16/ minute, painless abdomen and increased in volume by fluid of ascites, hepatomegaly, splenomegaly.

The blood test results were shown in Table 1. It is found: Inflammatory syndrome, prolongation of prothrombin time, increase in transaminases (ALT * 7.5 times the normal value), liver cholestasis (total bilirubin 20.6 mg/dl). Serological analysis for viral causes of hepatitis, including the hepatitis A, B and C viruses, the herpes simplex virus and the Epstein Barr virus, were negative. Serum Anti-Smooth Muscle Antibody (ASMA) was positive in a titer of 1: 160 and serum Antinuclear Antibodies (ANA) were positive in a titer of 1: 320 and with a fine speckled pattern.

Other relevant data included the following: Immunoglobulin (Ig) G 2514 mg/dL; IgA 450 mg/dL; Liver-kidney microsomal autoantibody type 1 and mitochondrial M2 antibody were negative. Liver biopsy was performed and liver histology is compatible with autoimmune hepatitis and cirrrosis. Abdominopelvic computed tomography and abdominal ultrasonography were suggestive of decompensated liver cirrhosis (cirrhotic liver, signs of portal hypertension, splenomegaly, moderate ascites) and ruled out mechanical jaundice (without gallstones, intrahepatic and extrahepatic biliary tract were normal).

Table 1: Laboratory findings of patient.

Complete blood counts		Blood chemistry		Serology	
Hemoglobin	13.7 g/dl	Glucose	105 mg/dl	CRP	5.9 mg/dl
Hematocrit	41.2%	AST	271 U/L	IgG	2514 mg/dl
White blood cells	9800/µL	ALT	301 U/L	IgA	450 mg/dl
Neutrophils	62%	BUN	28 mg/dl	ANA	1:320
Monocytes	6%	Creatinine	0,8 mg/dl	ASMA	1:160
Lymphocytes	28%	LAP	506 U/L	LKM1	negative
Platelets	242000/µL	γ-GTP	260 U/L	AMA	negative
ESR	126 mm/h	Total bilirubin	20.6 mg/dl	HAV-IgM	negative
		Direct bilirubin	16,4 mg/dl	Hbs-Ag	negative
		Total protein	7,8mg/dl	HCV-Ab	negative
		Albumin	3.8 g/dL	EBV-VCA IgM	negative
		Prothrombin time	16,5 seconds	EBV-VCA IgG	negative
		Sodium	129 mmol/L	CMV-IgM	negative
		Potassium	4.3mmol/L	CMV-IgG	negative
		Fibrinogen	268 mg/dl	RF	82 IU/L
		Total cholesterol	258 mg/dl		
		Triglyceride	260 mg/dl		

ESR: Erythrocyte Sedimentation Rate; AST: Aspartate Transaminase; ALT: Alanine Transaminase; BUN: Blood Urea Nitrogen; LAP: Serum Alkaline Phosphatase; CRP: C-Reactive Protein; ANA: Antinuclear Antibody; ASMA: Antismooth Muscle Antibody; LKM1: Anti Liver-Kidney Microsome Type 1 Antibody; AMA: Antimitochondrial Antibody; HAV: Hepatitis A Virus; Hbs-Ag: Hepatitis B Surface Antigen; HCV-Ab: Hepatitis C Virus Antibody; EBV-VCA: Epstein-Barr Virus–Viral Capsid Antigen; CMV: Cytomegalovirus; RF: Rheumatoid Factor.

Diagnosis of definite autoimmune hepatitis was made according to simplified diagnostic criteria of the International Autoimmune Hepatitis Group [2].

The patient was treated with oral glucocorticoid (prednisone 60 mg/day) and discontinued etanercept. After one month of treatment, the levels of transaminases and bilirubin decrease, but do not return to normal (ALT 160 U/L; AST 140 U/L; total bilirubin 5.01 mg/dl; direct bilirubin 3.79 mg/dl). Ascites is controlled under diuretic treatment. The patient dies at home from a respiratory infection.

Discussions

Drug-Induced Liver Disease (DILI) causes a wide range of manifestations, from asymptomatic biological abnormalities to liver failure. According to the mechanisms of hepatotoxicity, there are two types of damage: intrinsic or predictable (dose-dependent) and idiosyncratic or unpredictable (dose-independent). Etanercept can cause drug induced auto-immune hepatitis (DIAIH) by an idiosyncratic mechanism. In a study published in 2020 Vollmer et. al identified 389 new cases of DIAIH associated with infliximab, adalimumab and etanercept [3].

Anti-TNF alpha induced pattern of hepatic injury can be hepatocellular, cholestatic, or mixed, but hepatocellular injury is predominant. In a cohort of 34 AIH patients the most clinically common presentation of anti-TNF hepatotoxicity is an acute hepatocellular injury, serum aminotransferases ranged from 140 to 2000 U/L, bilirubin was significantly elevated (>3 mg/dL, peak value 34.2 mg/dl) in 37% of cases and autoantibodies detected were represented by ANA and ASMA. [4]

The duration of time from the initiation of anti-TNF alpha treatment to the onset of DIAIH varies, the latency being between 2 and 104 weeks [4-6]. A higher latency (of ~156 weeks) was described by Rösner et al. [7]

In idiopathic Autoimmune Hepatitis (AIH), transaminases are invariably elevated, but their level varies from values slightly above the upper limit to values 50 times normal. The degree of increase in transaminases does not correlate with the severity of histological lesions of AIH. Transaminases can even normalize despite the histological evidence of persistent inflammatory activity and thus can delay the diagnosis of AIH. This feature could explain the initial diagnosis of AIH already in the stage of cirrhosis in almost one third of patients at the time of initial diagnosis [8]. 28% [9] to 33% [10] of patients with AIH are diagnosed directly in the stage of liver cirrhosis. The time required for HAI to develop cirrhosis varies between 52 months [9] and 7.2 years [11].

AIH and DIAIH show similar paraclinical and histological changes and are difficult to differentiate. The evolution of hepatitis after discontinuation of anti-TNF alpha and administration of immunosuppressive therapy may point to one of the two etiologies. In DIAIH remission is complete and no relapses occur [12], however in HAI remissions do not occur in all patients and relapses are common after discontinuation of corticosteroid therapy or immunosuppressive medication.

The case presented by us is of a patient with RA who after 3 years of treatment with etanercept shows small increases in liver enzymes (up to 2 times the normal value) that allow the continuation of treatment with etanercept. One year after the onset of liver injury, respectively after 4 years of treatment with etanercept, he is diagnosed with decompensated liver cirrhosis. Diagnosis of definite AIH was made according to simplified diagnostic criteria of the International Autoimmune Hepatitis Group. After initiating oral corticosteroid treatment, the evolution is favorable - it significantly decreases the level of liver enzymes and bilirubin, but the patient dies due to an infection.

In view of the above, it is likely that the patient had DIAIH secondary to etanercept treatment given the 3-year latency between etanercept initiation and hepatic injury, only one case with a latency of 156 weeks was described [7].

The diagnosis of AIH already in the cirrhosis stage allows, according to data from the literature, an estimate of the duration of liver injury of at least 4 years [9]. It is unlikely that the patient had a subclinical AIH and the initiation of etanercept treatment may have been a trigger for AIH relapse.

Because the patient died, we did not have data on the progression of hepatitis after discontinuation of etanercept and initiation of corticosteroid therapy, the progression of hepatitis in these circumstances being the strongest argument for separating AIH from DIAIH.

Conclusion

In a patient with RA who is being treated with anti-TNF alpha, the increase in liver enzymes can have multiple causes, so an exhaustive approach in which the autoimmune etiology is not overlooked is desirable.

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