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Received 1st December 2020

Accepted 29 December 2020
Available online 6 January 2021

https://doi.org/10.1016/j.idnow.2020.12.010

Jaundice in a patient treated with Anakinra in a context of Covid-19

1. Introduction

Anakinra, IL-1 receptor antagonist, is being used in the treatment of acute severe distress syndrome due to SARS-Cov-2 [1]. Although this drug is associated with moderate elevation in transaminases, increased bilirubin is not documented as one of its adverse effects. We report a case of 87 years old woman with moderate COVID-19 infection treated by Anakinra. She had an elevation of the conjugated bilirubin 5 days after Anakinra treatment with clinical improvement and symptoms resolution one week after drug withdrawal. The pathophysiology behind Anakinra and an elevation of conjugated bilirubin is still not fully understood.

2. Case presentation

An 87 year old female patient presented on April 2 to our hospital and was evaluated for a period of two weeks with upper respiratory symptoms, myalgia, headache, and worsening dyspnea over 3 days. Medical history is significant for longstanding hyperlipidemia treated with Fenofibrate and hypertension treated with indapamide and propranolol. She had no history of alcohol abuse or chronic liver disease.

On presentation, the patient was afebrile and severely hypoxemic (oxygen saturation was 80% on room air). Her physical exam was notable only for basilar crackles with no signs of cardiac decompensation. Initial laboratory evaluation showed elevated CRP (280 mg/L). No abnormalities were shown on liver, kidney, and hematological biological tests.

Hepatitis B virus surface antigen was not detected. Serology for hepatitis C virus (HCV), and human immunodeficiency virus (HIV) were negative. She had HAV-specific IgG positive antibody in the serum. Autoimmune antibodies were negative especially ANA, anti-smooth muscle antibody (SMA), anti-liver kidney microsomal antibodies (LKM-1, LKM-2, LKM-3), and anti-mitochondrial antibody (AMA).

Chest CT without contrast was compatible with COVID-19 infection with extensive involvement estimated at 45%.

The patient's hypoxemia resolved with 15L/min oxygen therapy reaching 95% saturation. Initial regimen treatment was composed of lopinavir/ritonavir (10 days), Dexamethasone (6 days), and Ceftriaxone (total course of 7 days). Anakinra (Interleukin 1 receptor antagonist) was added to the initial regimen on April 4 for a total of 5 days.

Since April 5, the patient had been clinically improving. Her oxygen requirements decreased and the inflammatory marker (CRP) was trending down to 16 mg/L on April 7.

On April 8, the patient became suddenly icteric with elevated total and direct bilirubin (179 and 150 μmol/L respectively) on lab test of April 9. Her liver function tests were normal except for elevated GGT (481 U/L) as shown in the Table 1.

A repeat chest CT on April 8 showed a right proximal pulmonary embolism and stability of the pulmonary lesions typical of COVID-19 with no dilation of the biliary tract.

Over a week, total bilirubin rapidly declined to reach 22 μmol/L on April 16. On the other hand, the patient's condition was clinically and gradually re-deteriorating. She had a recurrence of fever and an increase in oxygen requirements. Laboratory evaluation showed leukocytosis (WBC 16500/mm^3 with PMN 14300/mm^3 and Lymphocyte 660/mm^3) and an increase in inflammatory markers (CRP 175 mg/L and ferritin 1711 μg/L). Liver tests showed a gradual increase in GGT (645 U/L) (Table 1).

In the light of her clinical deterioration, a repeat CT on April 16 showed an increase in pulmonary condensations of COVID-19, no dilation of the biliary tract, and no abdominal abnormalities.

Table 1
Liver tests of case report.

Date	AST (U/L)	ALT (U/L)	GGT (U/L)	ALP (U/L)	Total bilirubin (μmol/L)	Direct bilirubin (μmol/L)	INR	CRP (mg/L)
02/04: before Anakinra	51	31	30	52	8		1.18	280
09/04: 5 days after starting Anakinra	61	46	481	51	179	150	1.05	16
16/04: 8 days after the end of Anakinra	51	80	645	174	22		NA	175
22/04	22	38	467	173	18		1.36	260
29/04	37	26	654	297	10		NA	111
04/05	21	35	548	221	7		NA	91

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-Reactive protein; DBIL: direct bilirubin; GGT: gamma-glutamyl transpeptidase; INR: International Normalized Ratio; NA: not available; TBIL: total bilirubin

In the context of new imaging findings, Pseudomonas aeruginosa in urine culture, dyspnea, and elevated CRP level (250 mg/L), the patient was started on piperacillin-tazobactam on April 18 for suspicion of urinary or pulmonary infection. To note, the bilirubin level was stable (24 μmol/L).

One week later, the patient's clinical status had improved dramatically. Her oxygen requirements decreased along with resolution of fever and respiratory symptoms. Her inflammatory markers and bilirubin trended down (Table 1).

Afterwards, the patient was sent to a rehabilitation center on oxygen 1L/min to attain full recovery before going home.

3. Discussion

In this report, we present a case of bilirubin elevation after 5 days of Anakinra treatment. There was no disturbance in either transaminases (AST/ALT) or in the activity of alkaline phosphatase (ALP). At the onset of this disturbance, the patient's clinical condition was improving, and her inflammatory markers were trending down. Therefore, the etiology of this perturbation is most likely related to the Anakinra treatment rather than the inflammatory syndrome.

Even though the patient was on fenofibrate, her baseline liver enzymes were normal. She also received steroids for six days only, in addition to ceftriaxone for seven days and lopinavir/ritonavir for ten days, but none of these medications give jaundice without acute hepatitis after a short duration of treatment [2]. No history of chronic or active viral infection (HBV, HCV, HAV), no autoantibodies found, and no morphological abnormalities in the biliary tract.

An isolated increase of conjugated bilirubin has to be related to change in bilirubin secretion. Conjugated bilirubin is secreted by the multidrug resistance protein 2 (MRP2, gene ABCC2), through the canalicular membrane into bile [3]. Two nuclear receptors, the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR) supervise bilirubin metabolism [4]. Proinflammatory cytokine IL-1β leads to CAR downregulation and hyperbilirubinemia [5]. Therefore, an increase of bilirubin during Anakinra administration is not expected as Anakinra is the recombinant human IL-1Ra which inhibits the action of IL-1α and IL-1β.

A delicate equilibrium exists between pro-inflammatory cytokines (IL-1, IL-12, IL-18, TNF-α, IFNγ, and GM-CSF) and anti-inflammatory cytokines (interleukin -1 receptor antagonist, IL-4, IL-6, IL-10, IL-13, IL-19, and IL-35). It is known that MRP2/ABCC2 is significantly down-regulated by TNF-α, IL-6, and IL-1β [6]. During COVID, the cytokine's equilibrium is disrupted by excessive elevation of pro-inflammatory cytokines [7]. When pro-inflammatory cytokines are released, anti-inflammatory cytokines are subsequently secreted to restore the balance. This equilibrium between early pro-inflammatory and late anti-inflammatory cytokines is disturbed through Anakinra administration. So even if Anakinra-induced liver injury is reported as mild elevations in aminotransferase levels except for some case reports [8–10]. This report, with isolated hyperbilirubinemia, suggests a modulation of MRP2 expression or function. This observation should prompt assessment of MRP2 polymorphism to fully understand the regulatory mechanism underlying such a change.

Disclosure of interest

The authors declare that they have no competing interest.

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Received 8 August 2020

Accepted 24 September 2020
Available online 30 September 2020

https://doi.org/10.1016/j.medmal.2020.09.011