Background

Tumor necrosis factor-alpha (TNF-alpha), a basic cytokine is an immunosuppressive agent used intensively in the treatment of systemic diseases. Some studies have demonstrated that TNF-α inhibitors may be safe in patients with chronic viral infection. However, various side effects have been reported with the use of these powerful immunosuppressive drugs [1]. The most important of these are an increase in latent infection (especially tuberculosis) and malignity risk. That’s why it is important to do many exams to be sure of the absence of any contraindication [2]. A rise in hepatic enzymes is still frequently observed. It is not a significant side effect because it can be transitory. In some cohort studies, transaminase elevation due to TNF-alpha is not common and was significantly affected by use of background methotrexate treatment [3-5]. Hepatic insufficiency has been reported in phase studies on the drugs. However, once the drugs entered into use, we didn’t note this effect. In this case we report an autoimmune hepatitis an uncommon side effect of infliximab perfusion.

Case report

A 41-year-old man living with HIV without previous history of liver disease, transfusion, intravenous drug or alcohol abuse was referred for persistent increase in aminotransferase levels during infliximab therapy. He was on emtricitabine tenofovir and efavirenz for 6 years with good tolerance and undetectable viral load. After the 3rd infusion, serum aspartate Aminotransferase (AST) and alanine Aminotransferase (ALT) raised to 75 and 136 IU/L. After exhaustive etiological exams we retained autoimmune hepatitis. Two months after stopping infliximab aminotransferases were normal.

Conclusion: Infliximab induced autoimmune hepatitis is an uncommon side effect. Clinicians should be aware of this risk and should perform aminotransferase level control when infliximab use.

Abstract

Background: Tumor necrosis factor-alpha (TNF-alpha), a basic cytokine is an immunosuppressive agent used intensively in the treatment of systemic diseases. Various side effects have been reported with the use of these powerful immunosuppressive drugs. In this case we report an autoimmune hepatitis an uncommon side effect of infliximab perfusion.

Case: A 41-year-old man living with HIV on emtricitabine tenofovir and efavirenz for 6 years with good tolerance and undetectable viral load had been diagnosed as having a Crohn disease. He was referred for persistent increase in aminotransferase levels during infliximab therapy. After the 3rd infusion, serum aspartate Aminotransferase (AST) and alanine Aminotransferase (ALT) raised to 75 and 136 IU/L. After exhaustive etiological exams we retained autoimmune hepatitis. Two months after stopping infliximab aminotransferases were normal.

Conclusion: Infliximab induced autoimmune hepatitis is an uncommon side effect. Clinicians should be aware of this risk and should perform aminotransferase level control when infliximab use.
disease 3 month previously. It was an ileal Crohn disease with epigastric localization. This disease will be discovered after investigations for weight loss. The first line treatment was infliximab, because the risk of lymphoma with Azathioprine use. The decision was made to start a treatment with infliximab at a dose of 5 mg/kg. Prior to the first infusion,aminotransferases were normal; Hepatitis B surface (HBs) antigen and hepatitis C serology was normal. After the 3rd infusion, serum aspartate aminotransferase (AST) and alanine Aminotransferase (ALT) raised to 75 and 136 IU/L. AST and ALT still raised to 240 and 323 IU/L after the 4th infusion of infliximab and then to 226 and 317 IU/L two weeks later. Serologies for hepatitis C and hepatitis B were negative. Other autoantibodies, including anti-smooth muscle antibody, antiliver-kidney-microsomal antibody, antimitochondrial antibody, anti-double stranded DNA and anti-nuclear antibodies were negative. The patient denied alcohol use. HIV viral load was maintained undetectable. Liver biopsy showed chronic hepatitis with portal tracts showing a prominent inflammatory cellular infiltrate composed of lymphocytes, scattered eosinophils, and numerous plasma cells with interface hepatitis.

The overall presentation corresponded Autoimmune Hepatitis (AIH). A decision was made to stop anti-TNF therapy and observe the liver enzymes as the serum level of IFX declined. Two month later aminotransferases were normal. Because of this perfusion stop, the patient had an outbreak of his Crohn’s disease. He was put on corticosteroid and azathioprine with favorable outcome.

Discussion

In our case we reported a rare case of autoimmune hepatitis, a side effect on infliximab. The role of infliximab in our observation is suggested by the temporal relationship between exposure to the drug and appearance of hepatic abnormalities and by the complete normalization after treatment withdrawal. Our patient was a person living with HIV and was treated for Crohn’s diseases.

Using infliximab for PLHIV is uncommon because they were considered immuno compromised. But actually, after introducing Antiretroviral Treatment (ARV), HIV is a chronic infection and PLHIV have many comorbidities and systemic diseases like arthritis that’s need infliximab use [6]. For this population infliximab use was safe. Anti TNF use can be considered even when $\text{CD}_4$ count are stable and $>200$/mm$^3$.

Anti-TNF therapy, infliximab, was successfully used in Crohn’s Disease (CD) treatment. Tumour necrosis factor $\alpha$ (TNF$\alpha$) antibodies have been proven to be efficient in inducing and maintaining clinical remission in patients with active CD [7].

Many side effects were reported after using infliximab. They were secondary to immunodepression induced by this treatment. So, the most one was infections like tuberculosis. In our case it was an uncommon side effect: autoimmune hepatitis. Liver injuries was seen for children. Therefore, it appears rare. Alternate etiologies included antibiotics, concomitant thiopurines or methotrexate, viral illnesses, Inflammatory Bowel Disease (IBD) flares, and chronic liver diseases like Primary Sclerosing Cholangitis (PSC) and Nonalcoholic Fatty Liver Disease (NAFLD) that were uncovered during the work-up prompted by the raised liver enzymes [8].

Infliximab was considered to be a safe medication in terms of liver impairment, even though it is known to cause an asymptomatic elevation of liver enzymes [9]. In a cohort study elevation of liver enzyme was frequent when CD and it is not associated to infliximab use. In these cases, these elevations are usually not severe and they resolve spontaneously in the majority of cases, thus rarely requiring specific management [10].

Ghabril et al. Describe cases of drug induced injuries by infliximab use having autoimmunity background and resolve after stopping treatment [11].

The pathophysiology of anti-TNF-related AIH is poorly understood. The association between anti-TNF use and autoantibody development, especially ANA, has long been known, but the pathogenic role of these antibodies, if any, remains unclear. Several possible mechanisms may be postulated. Fc receptor-mediated clearance mechanisms could lead to local hepatocyte damage and transient release of liver enzymes. Hepatic sinusoids are recognised as a major location for clearance of immune complexes from erythrocytes and bind IgG immune complexes via Fc receptor-mediated interactions. These, in turn, can activate Kupffer cells to produce reactive oxygen metabolites. In vitro, monoclonal antibodies more readily form immune complexes than soluble receptors, potentially resulting in differential effects on hepatocyte activation. Lastly, a direct effect on hepatocytes cannot be excluded [12]. Autoantibodies have not been shown to have a pathogenic role in classical AIH, but rather serve as disease markers. For our patient, the ANA was negative and the diagnostic was be on anatomopathological examination.

Conclusion

Physicians should be aware of the risk of infliximab-induced autoimmune hepatitis. Hepatic enzyme increasing can be seen with infliximab use. Many etiologies may cause this side effect. That’s why investigations should be performed to identify the exact diagnosis: Hepatitis B, C, E serology, antibodies. A liver biopsy can establish the diagnosis in patients with persistent unexplained transaminase elevation and guide further therapeutic decisions, particularly in terms of the continuation of infliximab.

References

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