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CASE REPORT

Autoimmune hepatitis and anti-tumor necrosis factor alpha therapy: A single center report of 8 cases

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Informed consent: I hereby declare that all the patients included in the case series were aware that the cases were being submitted for publication in a scientific journal and consented.

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Abstract

This article describes cases of anti-tumor necrosis factor (TNF)-α-induced autoimmune hepatitis and evaluates the outcome of these patients in relation to their immunosuppressive strategy. A retrospective analysis of medical records was performed in our center, in order to detect cases of autoimmune hepatitis (AIH) associated with anti-TNF biologic agents. We describe and analyze eight cases of AIH following anti-TNF therapy, 7 with infliximab and 1 with adalimumab. A distinction should be made between induction of autoimmunity and clinically evident autoimmune disease. Liver biopsy is useful in detecting the role of the TNF-α antagonist in the development of AIH. The lack of relapse after discontinuing immunosuppressive therapy favors, as in this case series, an immune-mediated drug reaction as most patients with AIH have a relapse after treatment is suspended. Although AIH related to anti-TNF therapy is rare, a baseline immunological panel along with liver function tests should be performed in all patients with

autoimmune disease before starting biologics.

Key words: Anti-tumor necrosis factor antagonist; Autoimmune hepatitis; Adalimumab; Drug-induced liver injury; Inflammatory bowel disease; Infliximab

Core tip: A total of 8 patients with anti-tumor necrosis factor (TNF)-α-induced autoimmune hepatitis were detected in a single center with over 600 patients. The authors raise the question as to whether most cases represent autoimmune-like drug-induced liver injury (DILI) or defined autoimmune hepatitis (AIH) as the majority of patients responded favorably to steroids and did not require maintenance therapy corresponding to the former. Although anti-TNF therapy-related AIH is rare, a baseline immunological panel along with liver function tests should be performed in all patients with autoimmune disease before starting biologics, in order to detect undiagnosed AIH or help differentiate between DILI and established AIH.

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INTRODUCTION

The growing use of anti-tumor necrosis factor (TNF) agents in the treatment of autoimmune diseases has increased exponentially in the last decade. As a consequence of the boost in anti-TNF drugs and longer follow-up periods, autoimmune diseases associated with anti-TNF agents have also been increasingly diagnosed. Although psoriasis and lupus-like syndromes are among the most frequently reported, cases of autoimmune hepatitis (AIH) are scarce. A recent review of TNF-α antagonist-associated drug-induced liver injury (DILI) in the United States, identified 6 subjects and analyzed 28 published cases[1]. One of the major findings was the importance of the distinction between AIH and drug-induced autoimmunity due to the long-term repercussions that the disease may hold for these patients.

In our center, we analyzed the medical records of patients undergoing anti-TNF-α therapy (over 600 patients), in order to detect cases of AIH associated with anti-TNF biologic agents. This population included patients with inflammatory bowel disease (IBD) and autoimmune rheumatological (rheumatoid arthritis, ankylosing spondylitis) and dermatological diseases (psoriasis) undergoing treatment with infliximab (IFX), adalimumab (ADA) or etanercept. We were able to evaluate eight cases of AIH relating to anti-TNF biologic agents.

CASE REPORT

We report seven patients who developed AIH during anti-TNF therapy and one patient with previously undiagnosed AIH who experienced a DILI after anti-TNF treatment that led to the diagnosis of cirrhosis (Table 1). IFX was the anti-TNF agent involved in 7 cases and ADA in one. The number of infusions of IFX before the diagnosis of AIH varied between 4 and 13. In six cases, patients were asymptomatic and AIH was diagnosed due to liver function tests (LFTs). All patients had a complete work-up to exclude other etiologies including viral (anti-HCV, anti-HBs and HBc antibodies and HBs antigen), toxic, metabolic (α-1 antitrypsin, iron saturation, ferritin, ceruloplasmin), and other autoimmune liver diseases (anti-mitochondrial and ANCA antibodies), in particular those associated with IBD, such as primary sclerosing cholangitis (liver MRI). Liver histology was obtained in all cases and each case showed signs of AIH (chronic lymphoplasmocytic infiltrate and interface hepatitis). The International Diagnostic Criteria for AIH[2] scores were all above or equal to 19 after treatment allowing the diagnosis of AIH. In the cases with concomitant medication (immunosuppressants or mesalamine), the patients were treated for over 1 year before starting anti-TNF therapy. Only two patients were on combination treatment with an immunosuppressant (azathioprine and methotrexate) at the time of anti-TNF induction and all patients were on scheduled maintenance anti-TNF therapy when liver disease was detected. All patients responded favorably to steroids and had normal LFTs two months after suspension of the anti-TNF drug, and only two required long-term treatment. In one case (6), IFX treatment was cautiously restarted three months after stopping the drug, without recurrence of liver injury. The majority of patients were asymptomatic (6/8), underlining the importance of a routine LFT assessment in patients before undergoing anti-TNF therapy.

DISCUSSION

The growing number of cases of autoimmune phenomena related to anti-TNF agents has been brought into focus in recent years. A distinction should be made between the induction of autoimmunity and clinically evident autoimmune disease. The former does not necessarily imply the latter. The explanation for this difference may lie in host factors such as genetic susceptibility. Those patients who develop overt autoimmune disease may possess genetic features favoring its development. These drugs might reveal

Table 1 Clinical characteristics of the patients in the series

Age/Gender	Disease/Disease duration	Anti-TNF drug	Dose mg/kg/number infusions/injections	Concomitant drugs	Symptoms	Transaminase levels (ALT/AST - x ULN)	Autoantibodies/ Immunoglobulins	Histology	AIH score Post-therapy	Steroid response	Maintenance therapy	Outcome
1 - 36F	Distal UC/ 7 yr	IFX	5 mg/kg/5	Mesalamine	Yes	14/9	Anti-dsDNA, ANA, High IgG	Interface hepatitis	20	Yes	Mesalamine 3 g/d PO	Reversibility
2 - 45F	RA/10 yr	ADA	40 mg EOW/11	MTX NSAIDs	No	4.5/3	ANA, High IgG	Severe interface hepatitis	19	Yes	AZA 50 mg, ETC, Prednisolone 7.5 mg	Reversibility
3 - 34F	Distal UC/ 2 yr	IFX	5 mg/kg/8	Mesalamine	Yes	4.5/3	ANA, High IgG	Interface hepatitis	20	Yes	Mesalamine 3 g/d PO	Reversibility
4 - 35M	Extensive UC/2 yr	IFX	5 mg/kg/8	Mesalamine	No	13/7	ANA, High IgG	Interface hepatitis/ marginal proliferation of bile ducts	20	Yes	Mesalamine 3 g/d PO AZA 2.5 mg/kg per day	Controlled on therapy
5 - 43M	AS/30 yr	IFX	5 mg/kg/5	-	No	25/15	High IgG	Interface hepatitis/ cirrhosis	20	Yes	AZA 50 mg, Prednisolone 10 mg	Controlled on therapy
6 - 66F	Ileal CD/11 yr	IFX	5 mg/kg/13	Mesalamine, AZA	No	2/5	ANA	Chronic lymphoplasmocytic infiltrate	19	Yes	IFX 5 mg/kg AZA 2.5 mg/kg per day	Reversibility
7 - 37M	Ileal CD/2 yr	IFX	5 mg/kg/12	Mesalamine (suspended INH 2 mo prior to IFX)	No	4/2	ANA, High IgG	Interface hepatitis	20	Yes	Mesalamine 3 g/d PO	Reversibility
8 - 69F	Ileal CD/32 yr	IFX	5 mg/kg/4	Mesalamine	No	10/5	ANA	Interface hepatitis	19	Yes	Mesalamine 3 g/d PO	Reversibility

AS: Ankylosing spondylitis; PsA: Psoriatic arthritis; ULN: Upper limit of normal; UC: Ulcerative colitis; RA: Rheumatoid arthritis; CD: Crohn's disease; PPP: Palmoplantar pustular psoriasis; PsO: Psoriasis; IFX: Infliximab; ADA: Adalimumab; ETC: Etanercept; AZA: Azathioprine; MTX: Methotrexate; INH: Isoniazid; EOW: Every other week; dsDNA: Double strand DNA; ASMA: Anti-smooth muscle antibodies; AMA: Anti-mitochondrial antibodies.

subclinical disease or, in fact, induce it in a patient with genetic liability. Some of the mechanisms proposed include: a break in self-tolerance following the exposure of hidden antigens, induction of an immune system imbalance due to cytokine blockade, a selective effect on T helper cell subsets and immune complex formation, and exposing an underlying disease in a patient with genetic susceptibility.

In recent years, the number of case reports of liver toxicity has increased, although cases of AIH induced by anti-TNF agents remain rare[3-12] (Table 2). Cases of direct drug liver toxicity[13-18] not associated with positive autoantibodies, elevated immunoglobulin levels, and liver histology with interface hepatitis, as found in AIH, have been reported (Table 2). These previously published cases were mainly among patients with rheumatological diseases, most were confounded by concomitant medication, and some did not have histological confirmation of the etiology. In cases with anti-TNF-induced AIH, previously described liver injury was reversible and there was no relapse of AIH, even in the majority of patients who did not remain immunosuppressed. Interestingly, in three cases the patients switched treatment to adalimumab without having a relapse of AIH[19-21]. Paradoxically, these patients did not show signs of liver injury after switching to a drug in the same class. Moreover, a recently published paper showed that infliximab was successfully used as rescue therapy in difficult-to-treat AIH[22].

A recent publication[23] established definitions to differentiate between immune-mediated DILI and AIH. This is particularly challenging because there are no pathognomonic features of AIH and the diagnosis is made according to a clinical, biochemical, serological, and histological pattern and the response to immunosuppressants. Some patients may have known/long-standing AIH, according to the International Diagnostic Criteria for AIH, and anti-TNF therapy might

Table 2 Clinical characteristics of patients in published cases

Case - Year	Age/Gender	Disease	Anti-TNF drug	Immunosuppressant	Dose mg/kg/n-infusions	Symptoms	Autoantibodies	Histology	Steroid response	Outcome
2007[3]	56/F	AS	IFX	None	5/6	Yes	Anti-dsDNA, ANA, ASMA	Piecemeal necrosis	Yes	Reversibility
2005[4]	53/F	PsA	IFX	MTX	3/8	No	Anti-dsDNA, ANA, ASMA	Severe interface hepatitis	Yes	Reversibility
2007[12]	54/F	RA	IFX	MTX	3/12	No	ANA	Chronic inflammation	Yes	Reversibility
2010[7]	60/M	CD	IFX	None	5/4	No	Anti-dsDNA, ANA, ASMA	Interface hepatitis	Yes	Reversibility
2009[8]	22/F	PPP	IFX	None	5/3	No	None	Interface hepatitis	Yes	Reversibility
2010[10]	40/F	PsO, PsA	IFX	NSAIDS	5/5	Yes	Anti-dsDNA, ANA	Chronic hepatitis with portal+periportal fibrosis	Yes	Reversibility
2010[9]	37/M	PsO	IFX	None	5/3	Yes	Anti-dsDNA, ANA, ASMA	Interface hepatitis	Yes	Reversibility
2010[9]	51/M	PsO	IFX	None	5/3	Yes	Anti-dsDNA, ANA, AMA, anti-cardiolipin	Interface hepatitis + PBC Overlap syndrome	Yes	Reversibility
2001[11]	36/F	RA	IFX	PDN 10 mg	3/3	Yes	Anti-dsDNA, ANA	Interface hepatitis	Yes	Reversibility
2010[6]	36/F	PsA, PsO, CD	ADA	None	40 mg EOW 6th injection	Yes	Anti-dsDNA, ANA	Interface hepatitis	Yes	Reversibility
2012[12]	46/F	CD	IFX	None	5/3	No	ANA, ASMA	Interface hepatitis	Yes	Reversibility
2008[5]	30/F	UC	IFX	AZA	10/> 15	No	ANA,Anti-dsDNA	Interface hepatitis	Yes	Reversibility

AS: Ankylosing spondylitis; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; CD: Crohn's disease; PPP: Palmoplantar pustular psoriasis; PsO: Psoriasis; IFX: Infliximab; ADA: Adalimumab; MTX: Methotrexate; AZA: Azathioprine; EOW: Every other week; dsDNA: Double stranded DNA; ASMA: Anti-smooth muscle antibodies; AMA: Anti-mitochondrial antibodies; PDN: Prednisolone; NSAIDs: Non-steroidal anti-inflammatory drugs; PBC: Primary biliary cirrhosis.

cause a DILI. A further distinction is made between drug-induced AIH and immune-mediated DILI. Weiler-Normann defined drug-induced AIH as unrecognized AIH or predisposition to AIH, where AIH is unmasked or induced by DILI with a good response to steroids and relapse after withdrawal of immunosuppression with the need for continued immunosuppressive treatment. Immune-mediated DILI was defined as clinical, biochemical, and histological signs similar to AIH, in which eosinophilia and rash may be present. Usually there are no signs of advanced fibrosis with a good response to steroids and sustained remission is maintained after successful withdrawal of steroids.

Some of the distinctive factors of this case series include the predominance of patients with inflammatory bowel disease (6/8), the fact that all the patients had liver biopsies confirming the diagnosis of AIH and responded rapidly to steroids. Our series included patients with long-standing AIH and probable DILI such as, patient 5 (Table 1), who was never diagnosed with AIH, but the fact that cirrhosis was revealed at liver biopsy, leads one to hypothesize that infliximab triggered a DILI in a patient with chronic AIH. Patient 4 (Table 1) is an example of drug-induced AIH, because the course was subclinical, in a genetically predisposed patient (UC) and following this trigger, the presentation of hepatic autoantigens led to a sustained immune reaction. Following steroid withdrawal, there was a relapse and the patient was maintained on low-dose steroids and azathioprine. In these patients AIH was unmasked by DILI and they will permanently need immunosuppression. In immune-mediated DILI, patients usually have no advanced fibrosis, remain in biochemical remission once the immunosuppression is stopped and no maintenance therapy is required, as seen in the majority of our patients, and in previously published cases. We underline that this is the largest series of patients with liver autoimmunity induced by anti-TNF therapy and includes the second report of AIH due to ADA in the literature. This case series, which reports the largest single center experience on this topic, includes a large number of IBD patients and exemplifies the whole spectrum of AIH and immune-mediated DILI associated with anti-TNF therapy.

Autoimmune diseases and reactions induced by anti-TNF drugs are an increasing concern. Although AIH related to anti-TNF therapy is rare, a baseline immunological panel along with LFTs should be performed in all patients with autoimmune disease before starting biologics. Considering that most cases are asymptomatic, periodic monitoring of LFTs is necessary for early diagnosis. Steroids should be withdrawn after 3-6 mo, once biochemical remission is achieved, and this may be an important strategy to distinguish AIH from an immune-mediated DILI. The differential diagnosis between AIH and immune-mediated DILI is essential considering that they diverge significantly in terms of therapeutic approach and long-term prognosis.

COMMENTS

Case characteristics

Eight patients with distinct autoimmune diseases undergoing anti-tumor necrosis factor (TNF)-α antagonist therapy presented with abnormal liver function tests and liver histology suggesting autoimmune hepatitis.

Clinical diagnosis

Most patients were asymptomatic and disease was detected due to abnormal liver tests, positive auto-antibodies and liver histology.

Differential diagnosis

Viral, metabolic, alcoholic liver disease, non-alcoholic steato-hepatitis, other drug-induced liver injury and other causes of autoimmune liver disease were excluded.

Laboratory diagnosis

In most cases, elevated transaminases and positive autoimmune auto-antibodies were observed.

Imaging diagnosis

Abdominal ultrasound and MRI excluded other causes.

Pathological diagnosis

All patients showed typical findings of autoimmune liver disease such as: chronic lymphoplasmocytic infiltrate and interface hepatitis.

Treatment

All patients responded to a standard prednisolone dose for autoimmune hepatitis, and the majority did not require maintenance therapy.

Related reports

In most cases, anti-TNF-α-induced autoimmune hepatitis does not behave like classic autoimmune hepatitis (AIH) and seems to be more of an autoimmune-like drug-induced liver injury (DILI).

Experiences and lessons

This article underlines the need for baseline liver function tests and an autoimmune panel to detect these cases and shows that most cases behave like autoimmune-like DILI and not classic AIH.

Peer-review

Baseline liver function tests and autoimmune panel to detect theses cases are necessary and a distinction between established AIH and autoimmune DILI must be made in these cases because they have disparate disease progression and require different treatment.

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