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**Columns:** **CASE REPORT**

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

Susana R *et al*. Autoimmune hepatitis and anti-TNFα therapy

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**Abstract**

Describe cases of anti-tumor necrosis factor (TNF)  induced autoimmune hepatitis and evaluate the outcome of those patients, relating 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 to 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 unraveling evident autoimmune disease. Liver biopsy is useful in detecting the role of the TNF  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 because most patients with AIH have a relapse after treatment is suspended. Although AIH related to anti-TNF 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****:** Autoimmune hepatitis; Drug-induced liver injury; Inflammatory bowel disease; Anti-tumor necrosis factor antagonist; Infliximab; Adalimumab

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**Core tip:** A total of 8 patients with anti- tumor necrosis factor (TNF)- induced autoimmune hepatitis were detected in a single-center with over 600 patients. The authors raise the question whether most cases represent autoimmune-like drug-induced liver injury (DILI) or defined autoimmune hepatitis (AIH) because the majority of patients responded favorably to steroids and did not require maintenance therapy corresponding to the former. Although anti-TNF-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 to anti-TNF agents have also been increasingly diagnosed. Although psoriasis and lupus-like syndromes are among the most frequent, cases of reported autoimmune hepatitis (AIH) are scarce. A recent review of TNF  antagonist associated drug-induced liver injury (DILI), in the United States, identified 6 subjects and analyzed 28 published cases[1]. One of the major discussions is the importance of the distinction between autoimmune hepatitis and drug-induced autoimmunity because of the long-term repercussions that the disease may hold for these patients.

In our center, we have analyzed the medical records of our patients undergoing anti-TNF therapy (over 600 patients), in order to detect cases of AIH associated to 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 etarnecept. We were able to evaluate eight cases of AIH relating to anti-TNF.

**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 lead 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 LFTs. All of the patients had a complete work-up to exclude other etiologies including viral (anti-HCV, anti-HBs and HBc antibodies and HBs antigen), toxic, metabolic (-1 antitrypsin, iron saturation, ferritin, ceruloplasmin), other autoimmune liver diseases (anti-mitochondrial and ANCA antibodies), in particular those associated to IBD, such as primary sclerosing cholangitis (liver MRI). Liver histology was obtained in all cases and each case showed signs of autoimmune hepatitis (chronic lymphoplasmocytic infiltrate and interface hepatitis). The International Diagnostic Criteria for AIH[2] scores were all above or equal to 19 after treatment allowing for the diagnosis of AIH. In the cases with concomitant medication (immunosuppressants or mesalamine), the patients were under the treatment for over 1 year before starting anti-TNF. 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 presented normal liver function tests after two months following the suspension of anti-TNF drug, two of them requiring 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 was asymptomatic (6/8), underlining the importance of a routine LFT assessment in patients before undergoing anti-TNF.

**DISCUSSION**

The growing number of cases of autoimmune phenomena related to anti-TNF agents has been brought to focus in the last years. A distinction should be made differentiating 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 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, an induction in immune system imbalance due to cytokine blockade, selective effect on T helper cell subsets and immune complex formation, and exposing an underlying disease in a patient with genetic susceptibility.

 In the past 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 drug direct liver toxicity[13-18] not associated to 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 rheumatological patients, most were confounded by concomitant medication, and some did not have histological confirmation of the etiology. In the cases of anti-TNF-induced AIH previously described liver injury was reversible and there was no relapse of AIH, even among the majority of patients that 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 how 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 International Diagnostic Criteria for AIH, and the anti-TNF might 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, in whom 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 of the patients had liver biopsies confirming the diagnosis of AIH and responded rapidly to steroids. Our series includes 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, a presentation of hepatic autoantigens lead to a sustained immune reaction. Following steroid withdrawal, there was a relapse and the patient was maintained on low-dose steroids and azathioprine. These patients have an AIH unmasked by DILI and 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 the previously published cases. We underline that this is the largest series of patients with liver autoimmunity induced by anti-TNF and includes the second report of AIH due to ADA in the literature. This case series, which reports the largest single center experience in this topic, includes a large number of inflammatory bowel disease patients and exemplifies the whole spectrum of AIH and immune-mediated DILI associated to anti-TNF

 Autoimmune diseases and reactions induced by anti-TNF drugs are in fact an increasing concern. Although AIH related to anti-TNF is rare, a baseline immunological panel along with LFTs should be performed in all patients with autoimmune disease in all patients before starting biologics. Considering that most cases are asymptomatic, periodic monitoring of LFTs is necessary for early diagnosis. Steroids should be withdrawn following 3-6 mo, once biochemical remission is achieved, and this may be an important strategy to distinguish between 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) - 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.

***Imaging diagnosis***

Abdominal ultrasound and MRI excluded other causes.

***Pathological diagnosis***

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

***Treatment***

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

***Related reports***

In most cases, anti-TNF- 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 autoimmune panel to detect theses 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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| **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 | 5mg/kg/ 8 | Mesalamine  | No | 13/7 | ANA, High IgG | Interface hepatitis/marginal proliferation bile ducts | 20 | Yes  | Mesalamine 3 g/d POAZA 2.5 mg/kg per day | Controlled on therapy |
| 5 – 43M | AS/30 yr | IFX | 5mg/kg/ 5 | *
 | No | 25/15 | High IgG | Interface hepatitis/cirrhosis | 20 | Yes  | AZA 50 mg, Prednisolone 10mg | Controlled on therapy |
| 6 – 66F | Ileal CD/11 yr | IFX | 5mg/kg/ 13 | Mesalamine, AZA  | No | 2/5 | ANA | Chronic lymphoplasmocytic infiltrate | 19 | Yes  | IFX 5 mg/kg AZA 2.5mg/kg per day | Reversibility |
| 7 – 37M | Ileal CD/2 yr | IFX | 5 mg/kg/ 12 | Mesalamine (suspended INH 2 months prior to IFX) | No | 4/2 | ANA, High IgG | Interface hepatitis | 20 | Yes | Mesalamine 3g/d PO | Reversibility |
| 8 – 69F | Ileal CD/32 yr | IFX | 5 mg/kg/ 4 | Mesalamine  | No | 10/5 | ANA | Interface hepatitis | 19 | Yes | Mesalamine 3g/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: Isoniazide; EOW: Every other week; dsDNA: Double strand DNA; ASMA: Anti smooth muscle antibodies; AMA: Antimitochondrial antibodies.

**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**  |
| 20073 | 56/F | AS | IFX | None  | 5/6 | Yes | Anti-dsDNA, ANA, ASMA | Piecemeal necrosis | Yes  | Reversibility |
| 20054 | 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 |
| 20098 | 22/F | PPP | IFX | None  | 5/3 | No | None | Interface hepatitis | Yes  | Reversibility |
| 201010 | 40/F | PsO, PsA | IFX  | NSAIDS  | 5/5 | Yes | Anti-dsDNA, ANA | Chronic hepatitis with portal+periportal fibrosis | Yes  | Reversibility |
| 20109 | 37/M | PsO | IFX | None  | 5/3 | Yes | Anti-dsDNA, ANA, ASMA Anti-dsDNA, ANA, AMA, anti-cardiolipin | Interface hepatitis | Yes  | Reversibility |
| 20109 | 51/M | PsO | IFX | None  | 5/3 | Yes | Interface hepatitis + PBC Overlap syndrome | Yes  | Reversibility |
| 2001 11 | 36/F | RA | IFX  | PDN 10mg | 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 |
| 201212 | 46/F | CD | IFX | None  | 5/3 | No | ANA, ASMA | Interface hepatitis | Yes  | Reversibility |
| 20085 | 30/F | UC | IFX | AZA | 10 / >15 | No | ANA,Anti-dsDNA | Interface hepatitis | Yes  | Reversibility |

AS: Ankylosing spondilitis; 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 strand DNA; ASMA: Anti smooth muscle antibodies; AMA: Antimitochondrial antibodies.