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

Susana Rodrigues, Susana Lopes, Fernando Magro, Hélder Cardoso, Ana Maria Horta e Vale, Margarida Marques, Eva Mariz, Miguel Bernardes, Joanne Lopes, Fátima Carneiro, Guilherme Macedo

Susana Rodrigues, Susana Lopes, Fernando Magro, Hélder Cardoso, Ana Maria Horta e Vale, Margarida Marques, Guilherme Macedo, Department of Gastroenterology, Centro Hospitalar de São João, 4200-319 Porto, Portugal

Eva Mariz, Miguel Bernardes, Department of Rheumatology, Centro Hospitalar de São João, 4200-319 Porto, Portugal

Joanne Lopes, Fátima Carneiro, Department of Pathology, Centro Hospitalar de São João, 4200-319 Porto, Portugal

Fátima Carneiro, Institute of Molecular Pathology and Immunology at the University of Porto, 4200-319 Porto, Portugal

Author contributions: Rodrigues S study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; Lopes S analysis and interpretation of data; critical revision of the manuscript for important intellectual content; Magro F study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; Cardoso H, Horta e Vale AM, Marques M, Mariz E, Bernardes M and Lopes J analysis and interpretation of data; Carneiro F and Macedo G critical revision of the manuscript for important intellectual content.

Ethics approval: This manuscript is of a case series and not a formal study with a protocol, therefore no submission was made to the Hospital Ethics Review Board.

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.

Conflict-of-interest: None of the authors of this manuscript have any conflicts of interest to declare.

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Correspondence to: Guilherme Macedo, MD, PhD, Department of Gastroenterology, Centro Hospitalar de São João, 4200-319 Porto, Portugal. guilhermemacedo59@gmail.com

Telephone: +351-225-512100
Fax: +351-225-025766

Received: October 6, 2014
Peer-review started: October 6, 2014
First decision: October 29, 2014
Revised: November 24, 2014
Accepted: January 30, 2015
Article in press: January 30, 2015
Published online: June 28, 2015

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

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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.

Rodrigues S, Lopes S, Magro F, Cardoso H, Horta e Vale AM, Marques M, Mariz E, Bernardes M, Lopes J, Carneiro F, Macedo G. Autoimmune hepatitis and anti-tumor necrosis factor alpha therapy: A single center report of 8 cases. World J Gastroenterol 2015; 21(24): 7584-7588 Available from: URL: http://www. wjgnet.com/1007-9327/full/v21/i24/7584.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i24.7584

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 HBe 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 mesalazine), 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...
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 (Table 2). Cases of direct drug liver toxicity 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. 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.

A recent publication 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

| Age/Gender | Disease/Disease duration | Anti-TNF drug | Dose mg/kg/number of infusions/injections | Concomitant drugs | Symptoms | Transamnise levels (ALT/AST - x ULN) | Autoantibodies/ Immunoglobulins | Histology | AIH score | 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 | Aza 50 mg, ETC, Prednisolone 7.5 | 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       | Mesalamine 3 g/d PO | Controlled on therapy          | 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 | Controlled on therapy          | 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       | Mesalamine 3 g/d PO | 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 | Controlled on therapy          | Reversibility |
| 8 - 69F    | Ileal CD/32 yr           | IFX           | 5 mg/kg/4                                | -                  | No       | 10/5                                 | ANA                             | Interface hepatitis             | 19        | Yes       | Mesalamine 3 g/d PO | Reversibility | Reversibility |

AS: Ankylosing spondylitis; PsA: Psoriatic arthritis; ULN: Upper limit of normal; UC: Ulcerative colitis; RA: Rheumatoid arthritis; CD: Crohn’s disease; PPT: Palpomtante 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.
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        | 56/F       | AS      | IFX           | None              | 5/6                    | Yes      | Anti-dsDNA, ANA, ASMA | Piecemeal necrosis | Yes            | Reversibility   |
| 2005        | 53/F       | PsA     | IFX           | MTX               | 3/8                    | No       | Anti-dsDNA, ANA, ASMA | Severe interface hepatitis | Yes            | Reversibility   |
| 2007        | 54/F       | RA      | IFX           | MTX               | 3/12                   | No       | ANA           | Chronic inflammation | Yes            | Reversibility   |
| 2010        | 60/M       | CD      | IFX           | None              | 5/4                    | No       | Anti-dsDNA, ANA, ASMA | Interface hepatitis | Yes            | Reversibility   |
| 2009        | 22/F       | PPP     | IFX           | None              | 5/3                    | No       | None          | Interface hepatitis | Yes            | Reversibility   |
| 2010        | 40/F       | PsO, PsA | IFX           | NSAIDS            | 5/5                    | Yes      | Anti-dsDNA, ANA      | Chronic hepatitis with portal and periportal fibrosis | Yes            | Reversibility   |
| 2001        | 37/M       | PsO     | IFX           | None              | 5/3                    | Yes      | Anti-dsDNA, ANA, ASMA | Interface hepatitis + PBC overlap syndrome | Yes            | Reversibility   |
| 2000        | 51/M       | PsO     | IFX           | None              | 5/3                    | Yes      | Anti-dsDNA, ANA, AMA, anti-cardiolipin | Interface hepatitis | Yes            | Reversibility   |
| 2001        | 36/F       | RA      | IFX           | PDN 10 mg         | 3/3                    | Yes      | Anti-dsDNA, ANA      | Interface hepatitis | Yes            | Reversibility   |
| 2010        | 36/F       | PsA, PsO, CD | ADA          | None              | 40 mg EOW 6th injection | Yes      | Anti-dsDNA, ANA       | Interface hepatitis | Yes            | Reversibility   |
| 2012        | 46/F       | CD      | IFX           | None              | 5/3                    | No       | ANA, ASMA      | Interface hepatitis | Yes            | Reversibility   |
| 2008        | 30/F       | UC      | IFX           | AZA               | 10/15                  | Yes      | 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.

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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 immunology diagnosis in patients with autoimmune-like DILI and not classic AIH.

References

1. Gabril M, Bonkovsky HL, Kung C, Davenport T, Hayashi PH, Kleiner DE, Serrano J, Roche J, Fontana RJ, Bonacini M. Liver injury from tumor necrosis factor-α antagonist: analysis of thirty-four cases. J Gastroenterol Hepatol 2013; 11: 558-564.e3 [PMID: 23333219 DOI: 10.1056/cgh.2012.12.025]

2. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Milici-Vergani G, Vergani D, Vierling JM. Diagnosis and management of autoimmune hepatitis. Hepatology 2010; 11: 2193-2213 [PMID: 20513004 DOI: 10.1002/hep.23584]

3. Ozorio G, McGarity B, Bak H, Jordan AS, Lau H, Marshall C. Autoimmune hepatitis following infliximab therapy for ankylosing spondylitis. Med J Aust 2007; 187: 524-526 [PMID: 17979620 DOI: 10.1097/RHU.0b013e31822bc8e6]

4. Germano V, Picchianti Diamanti A, Baccano G, Natale E, Onetti Muda A, Priori V, Valesini G. Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis. Ann Rheum Dis 2005; 64: 1519-1520 [PMID: 16162008 DOI: 10.1136/ard.2004.023281]

5. Marques M, Magro F, Cardoso H, Carneiro F, Portugal R, Lopes J, Costa Santos C. Infliximab-induced lupus-like syndrome associated with autoimmune hepatitis. Inflamm Bowel Dis 2008; 14: 723-725 [PMID: 17929297 DOI: 10.1002/ibd.20293]

6. Adar T, Mizrahi M, Pappo O, Scheiman-Elazary A, Shibolet O. Adalimumab-induced autoimmune hepatitis. J Clin Gastroenterol 2010; 44: e20-e22 [PMID: 19593165 DOI: 10.1097/MCG.0b013e3181a74e57]

7. Doyle A, Forbes G, Kontorinis N. Autoimmune hepatitis during infliximab therapy for Crohn's disease: a case report. J Crohns Colitis 2011; 5: 253-255 [PMID: 21575891 DOI: 10.1016/j.crohns.2010.12.007]

8. Fairhurst DA, Sheehan-Dare R. Autoimmune hepatitis associated with infliximab in a patient with palmo-neoplastic psoriatic arthritis. Clin Exp Dermatol 2009; 34: 421-422 [PMID: 19309375 DOI: 10.1111/j.1365-2230.2008.03088.x]

9. Goujon C, Dahel K, Bérard F, Guillot I, Gunera-Saad N, Nicolas JF. Autoimmune hepatitis in two psoriasis patients treated with infliximab. J Am Acad Dermatol 2010; 63: e43-e44 [PMID: 20633783 DOI: 10.1016/j.jaad.2009.02.029]

10. Poulin Y, Thérien G. Drug-induced hepatitis and lupus during infliximab treatment for psoriasis: case report and literature review. J Cutan Med Surg 2010; 14: 100-104 [PMID: 20338127]

11. Saleem G, Li SC, MacPherson BR, Cooper SM. Hepatitis with interface inflammation and IgG, IgM, and IgA anti-double-stranded DNA antibodies following infliximab therapy: comment on the article by Charles et al. Arthritis Rheum 2001; 44: 1966-1968 [PMID: 11508453]

12. van Casteren-Messidor C, Pries G, van Tilburg A, Zelinkova E. Autoimmune hepatitis during therapy with infliximab for inflammatory bowel disease. J Crohns Colitis 2012; 6: 630-631 [PMID: 22398075 DOI: 10.1016/j.crohns.2012.01.017]

13. Ierardi E, Della Valle N, Acchieco MC, De Francesco V, Stoppino G, Panella C. Infliximab single administration followed by acute liver injury. Inflamm Bowel Dis 2006; 12: 1089-1091 [PMID: 17075352 DOI: 10.1097/MIB.0b013e3280367873.75573.99]

14. Tobon GJ, Calas J, Jaller J, Restrepo JC, Anaya JM. Serious liver disease induced by infliximab. Clin Rheumatol 2007; 26: 578-581 [PMID: 16547695 DOI: 10.1007/s10067-005-0169-y]

15. Wahle S, Alexandroff A, Reynolds NJ. Hepatitis: a rare, but important, complication of infliximab therapy for psoriasis. Clin Exp Rheumatol 2006; 34: 460-461 [PMID: 16681606 DOI: 10.1111/j.1365-2230.2006.02086.x]

16. García Aparicio AM, Rey JR, Sanz AH, Alvarez JS. Successful treatment with etanercept in a patient with hepatotoxicity closely related to infliximab. Clin Rheumatol 2007; 26: 811-813 [PMID: 16550301 DOI: 10.1007/s10067-006-0253-y]

17. Moun M, Konopski Z, Tuftefeld KE, Jahnens J. Occurrence of hepatotoxicity and elevated liver enzymes in a Crohn’s disease patient treated with infliximab. Inflamm Bowel Dis 2007; 13: 1584-1586 [PMID: 17663423 DOI: 10.1002/ibd.20230]

18. Mancini S, Amorotti E, Vecchio S, Ponz de Leon M, Ronucci L. Infliximab-related hepatitis: discussion of a case and review of the literature. Intern Emerg Med 2010; 5: 193-200 [PMID: 20107900 DOI: 10.1016/j.ijemer.2010.03.042-4]

19. Cravo M, Silva R, Serrano M. Autoimmune hepatitis induced by infliximab in a patient with Crohn’s disease with no relapse after switching to adalimumab. BioDrugs 2010; 24 Suppl 1: 25-27 [PMID: 21175232 DOI: 10.2165/11586210-000000000-00000]

20. Bose KS, Sarma RH. Delimitation of the intimate details of the backbone conformation of pyridine nucleotide coenzymes in aqueous solution. Biochem Biophys Res Commun 1975; 66: 1173-1179 [PMID: 2 DOI: 10.1016/0006-291X(75)90134-8]

21. Haennig A, Bonnet D, Thebault S, Aliche L. Infliximab-induced acute hepatitis during Crohn’s disease therapy: absence of cross-reactivity with adalimumab. Gastroenterol Clin Biol 2010; 34: e7-e8 [PMID: 20189334 DOI: 10.1016/j.cgb.2010.01.016]

22. Weiler-Normann C, Schramm C, Quaes A, Wiegard C, Glahcke B, Pannicke N, Möller S, Lohse AW. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. J Hepatol 2013; 58: 529-534 [PMID: 23178709 DOI: 10.1016/j.jhep.2012.11.010]

23. Weiler-Normann C, Schramm C. Drug induced liver injury and its relationship to autoimmune hepatitis. J Hepatol 2011; 55: 747-749 [PMID: 21396413 DOI: 10.1016/j.jhep.2011.02.024]

P- Reviewer: Mancuso A, Pelcza A, Souza-Mello V
S- Editor: Qi Y
L- Editor: Webster JR
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