Infliximab-Associated Hepatic Injury in Crohn's Disease

Sura A. Abdulsattar[1], Raghd A.Y. Alkhader[2], Haider Ridha Mohammed Saeed[3], Fatin F. AlKazazz[4]

[1]Professor, [2]Assistant Tutor, [3]Assistant Tutor, Department of Chemistry and Biochemistry, College of Medicine, Mustansiriyah University, Baghdad, Iraq, [4]Professor, Department of Chemistry, College of Science, Mustansiriyah University, Baghdad, Iraq

Abstract

Hepatotoxicity disorders are relatively common in patients with inflammatory bowel disease that includes ulcerative colitis and Crohn's disease. Abnormal serum liver functions tests can develop during treatment with (TNF-α) blocking agents, such as, Infliximab. The aim of this review is to clarify the role of infliximab in the development of liver enzyme abnormalities in patients with Crohn's disease. The most common presentation of infliximab -associated liver injury is a hepatocellular type with auto-immune features, marked by increased serum aminotransferases levels. Cholestatic injury is much less common, and marked by jaundice and increased serum ALP and bilirubin levels,with elevations of serum ALT and AST. Abnormalities of liver function tests in sera of patients with Crohn's disease typically resolve after discontinuation of infliximab, although sever liver injury leading to liver transplant cannot be ruled out.

Keywords: *Aminotransferase, autoimmune hepatitis, Cholestatic, Crohn's, hepatocellular, inflammatory bowel disease, Infliximab, liver.*

Introduction

Crohn's Disease: Crohn's disease (CD) is a chronic inflammatory condition characterized by discontinuous skip lesions affecting any part of the gastrointestinal tract from the mouth to the anus. It is encompassed in the term "inflammatory bowel disease (IBD)", which includes ulcerative colitis (UC) and CD [1]. Crohn disease is a chronic disease with an annual incidence ranging from 3 to 20 cases per 100,000. The median onset of disease is age 30 years and it has 2 peaks, first between age 20 and 30 years and then a smaller peak around age 50 years[2]. The origin of the disease is not entirely clear however several involved mechanisms have been postulated such as genetic predisposition and disruption of homeostasis regulation in the gastrointestinal tract [3]. The diagnosis and management of Crohn's disease is based on clinical signs and symptoms in addition to laboratory tests, endoscopy and imaging techniques[4]. Medical treatment for IBD typically targets inflammatory mediators including aminosalicylates, corticosteroids, immunomodulators such as methotrexate, and the biological therapies including anti-tumor necrosis factor (TNF) therapies[5]. The aim of this review is to clarify the role of infliximab in the development of liver enzyme abnormalities in patients with CD and its relationship to drug-induced liver injury (DILI).

Anti-Tumor Necrosis Factor Alpha Therapy: Biologic therapy with anti-TNF medication has been effective in treating inflammation and reducing complications in CD[6]. Infliximab, adalimumab, and certolizumab have been shown to be effective as both induction and maintenance therapy in moderate to severe CD[7]. In systematic review of Singh S et.al. It has been suggested through indirect comparisons that infliximab or adalimumab may be preferred as the first line agents, while ustekinumab preferred as the second line agent, for induction of remission in patients with moderate-severe CD[8]. In (Robbins L. et al.) study, anti-TNF alpha therapy successfully treated denovo CD in 28 out of 38 (74%) patients. Out of seventeen patients with CD who had failed to response to anti-TNF alpha agents before surgery and were treated with anti-TNF alpha therapy after surgery, twelve patients (71%) responded to the treatment[9]. A study of Buhl S et.al. reported that in total, 376 Crohn's disease patients had received infliximab. After 1 year of therapy 76 (20%) among them were classified as having response but non-remission. While it was found that there was no additional therapeutic

benefit after another year of treatment maintenance of infliximab for (n = 54; 71%), thus still having response but non-remission. Nineteen patients (25%) obtained remission during continued infliximab, whereas only 4% (n = 3) experienced treatment failure[10]. Loss of response LOR) to biologics in Crohn's disease is a significant clinical problem [11]. The rates of LOR are reported to be 50–54% in CD patients during 1 year of continuous IFX treatment [12] The rates of LOR are reported to be 50–54% in CD patients during 1 year of continuous IFX treatment [13,14]. While in other study indicated by meta-analysis that the incidence of LOR among adult CD patients undergoing IFX therapy is 34% [15]. Study by de Bruyn JR et.al reported that the failure to Infliximab therapy is associated with subclinical fibrosis in Crohn's disease [16].

There are numerous complications which have been described with the use of infliximab such as instances of cholestasis or hepatitis [45,47,50], induction of auto-immune/ immuno-mediated hepatitis [51-54], acute liver failure [55,56] and the need for liver transplantation [57,58]. In the earlier controlled trial of Infliximab in Crohn's disease minor elevation in levels of the liver enzymes weredescribed, but extreme elevations were rare, and no cases of liver failure or jaundice were found [21]. Cholestatic liver injury was described in one case report of a patient treated with IFX. The patient developed jaundice after the infliximab infusion, with high alkaline phosphatase levels accompanied by elevations in bilirubin, ALT and AST. The patient underwent liver biopsy which revealed "bland cholestasis". Cholestatic injury resolved within 4 weeks with supportive therapy and cessation of IFX [47]. Cases of AIH have also been demonstrated in patients with IBD receiving treatment [38]. Several cases have been reported AIH in CD patients who received infliximab therapy [51-54,59]. In one of these cases, Cravo *et al.*[51] reported a 38-year-old female suffering from Crohn's disease who required IFX. At the beginning of therapy, LFTs were normal, furthermore ANA as well as Anti-ds-DNA were negative. Importantly, 2 years into treatment with IFX, the patient developed transaminases and hypergammaglobulinemia. Serology results for viral infections were negative, moreover ANA, Anti-ds-DNA, in addition to antihistone antibodies were positive. ''Liver biopsy showed chronic hepatitis with inflammatory plasmocytic infiltrate in the portal tracts, interface hepatitis, and mild periportal fibrosis.''. So, the patient met the criteria for a definitive autoimmune hepatitis. During three-months period, after discontinuing IFX therapy, ANA titers reduced with normalization of LFTs [51]. In most reported cases of IFX-induced autoimmune hepatitis, the hepatitis resolved with discontinuation of infliximab and steroid treatment. Interestingly, in two of these reported cases, AIH resolved when switched to another biologic agent for exampleadalimumab (ADA) implying an absence of cross-reactivity [51,5 3]. This phenomenon can be related to IFX being a chimeric (part mouse, part human) monoclonal antibody, while ADA is a fully human antibody [22, 51]. In this regard, Rodrigues*et al.,*[60] described 8 cases of TNF-α blocking agents-induced hepatitis which was defined as ALTlevels (>10× ULN) out of a cohortincluding 600 patients, with seven cases related to infliximab(3/7 patients with Crohn's disease). These 3 patients with Crohn's disease showed an autoimmune type of liver injury, with elevated levels ofaminotransferases. Twopatients responded favourably to steroids with normalization of LFTs after the suspension of IFX.In one female patient, IFX therapy was restarted within three months after discontinuation of this agent, with no recurrence of the liver injury [60]. In the case reports of van Casteren-Messidoro *et al*[59] two females patients suffering from IBD developed AIH while receiving IFX. One case with Crohn's disease, developed AIH after the third infusion of IFX, with elevated serum transaminase levels up to (25 × ULN). During five-months period, after discontinuing IFX, and receiving azathioprine along with steroids, her transaminases normalized [59]. Crohn's disease, chronic inflammatory granulomatous condition of gastrointestinal tract, can rarely have extra-intestinal complications. Involvement of the vulva in CD is very uncommon [61].Caussé *et al.,* [56] reported a case of IFX-induced acute hepatitis in a patient suffering from severe vulvar Crohn's disease. Her LFTs showed ten times the normal value of ALT, twice the normal value of AST, 1.5 times the normal value of ALP and three times the normal value of GGT. Due to the hepatitis, the IFX therapy was withdrawn [56]. Importantly, the latest case reports have described two rare cases of IFX-induced autoimmune hepatitis in patients with Crohn's disease that led to liver failure necessitating liver transplantation. One well-documented case by Estes et al., [57] described markedly elevated levels ofaminotransferases and bilirubin, 5 months after starting IFX. Similarly, in another report by Wong *et al.,*[58]one such case developed 3 months after starting infliximab, with abnormal LFTs, low albumin level and jaundice.

Conclusion

Infliximab -associated liver injury is still a potential concern in patients with Crohn's disease. The most common presentation is a hepatocellular pattern of injury with auto-immune features, involving histologic changes which are similar to autoimmune hepatitis. This pattern marked by increased serum and AST levels. Cholestatic injury due to Infliximab is much less common, and marked by increased serum ALP and bilirubin levels,with elevations of serum ALT and AST. Symptoms generally include jaundice. In most cases, these patterns of injury improve and abnormalities in liver function tests typically resolve after discontinuation of infliximab, although sever liver injury leading to liver transplant cannot be ruled out.

Conflict of Interest: We declare that we have no conflict of interest.

Source of Funding: Self

Ethical Clearance: Ethics committee approval obtained from Mustansiriyah University/College of medicine and college of science.

References

1. Mohammad F.A, Alkazazz F.F, Abdlusattar S.A. Zinc Deficiency is Associated with Meprin a in Iraqi Patients with Crohn's Disease. Medico-legal Update, January-March 2020, Vol.20(1):1097-1102.
2. J. D. Feuerstein and A. S. Cheifetz, "Crohn disease: epidemiology, diagnosis, and management," Mayo Clinic Proceedings, vol. 92, no. 7, pp. 1088–1103, 2017.
3. Kúsulas-Delint D, González-Regueiro JA, Rodríguez-Aldama JC, García-Miranda FS, García-Santos RA, Lizardo AE, Gutiérrez-Grobe Y. Crohn's disease. Review and current concepts. Rev Invest Med Sur Mex, 2016; 23 (1): 10-20 11.
4. Cosima Schiavone, Marcello Romano. Diagnosis and management of Crohn's disease. J Ultrasound. 2015 Mar; 18(1): 1–2.
5. Mohammad F.A, Alkazazz F.F, Abdlusattar S.A. Risk of Osteoporosis in Patients with Crohn's Disease Not Respond to Infliximab Therapy Undergoing Surgical Intervention. Indian Journal of Forensic Medicine & Toxicology.2020 Vol. 14 (1): 968-973.
6. Razvi M, Lazarev M .Optimization of biologic therapy in Crohn's disease. Expert Opin Biol Ther. 2018 Mar; 8(3):263-272. doi: 10.1080/14712598.2018.1410131
7. Adegbola SO, Pisani A, Sahnan K, Tozer P, Ellul P, Warusavitarne J. Medical and surgical management of perianal Crohn's disease. Ann Gastroenterol. 2018 Mar-Apr;31(2):129-139.
8. Singh S, Fumery M, Sandborn WJ, Murad MH.Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. Aliment PharmacolTher. 2018 Aug;48(4):394-409.
9. Robbins L, Zaghiyan K, Melmed G., et al. Outcomes with anti-tumour necrosis factor-alpha therapy and serology in patients with de novo Crohn's disease after ileal pouch anal anastomosis. J Crohn's Colitis 2017; 11 (01) 77-83.
10. Buhl S, Kristina Borghede M, Brynskov J, Steenholdt C, Rasmussen M, Andrew Ainsworth M.Outcome of Continued Infliximab Therapy in Crohn's Disease Patients With Response but Without Remission After One Year of Infliximab - A Retrospective Cohort Study. Scand J Gastroenterol. 2018 Aug; 53(8):930-937.
11. Boneh R, SarbagiliShabat C, Yanai H, Chermesh I, Ben Avraham S, Boaz M, Levine A.J .Dietary Therapy With the Crohn's Disease Exclusion Diet Is a Successful Strategy for Induction of Remission in Children and Adults Failing Biological Therapy Sigall Crohns Colitis. 2017 Oct 1;11(10):1205-1212.
12. Papamichael K, Gils A, Rutgeerts P, Levesque BG, Vermeire S, Sandborn WJ, VandeCasteele N .Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse Inflamm Bowel Dis. 2015 Jan; 21(1):182-97.
13. Romero-Cara P, Torres-Moreno D, Pedregosa J, Vílchez JA, García-Simón MS, Ruiz-Merino G, et al. A FCGR3A polymorphism predicts anti-drug antibodies in chronic inflammatory bowel disease patients treated with anti-TNF. Int J Med Sci. 2018;15(1): 10–15.
14. Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, et al. Incidence and importance of antibody responses to infliximab after maintenance

or episodic treatment in Crohn's disease. Clin Gstroenterol Hepatol. 2004;2: 542–553.

15. Zhang QW, Shen J, Zheng Q, Ran ZH Loss of Response to Scheduled Infliximab Therapy for Crohn's Disease in Adults: A Systematic Review and Meta-Analysis. .J Dig Dis. 2019 Feb; 20(2):65-72.
16. de Bruyn JR, Becker MA, Steenkamer J, Wildenberg ME, Meijer SL, Buskens CJ, Bemelman WA, Löwenberg M, Ponsioen CY, van den Brink GR, D'Haens GR. Intestinal Fibrosis Is Associated With Lack of Response to Infliximab Therapy in Crohn's Disease.PLoS One. 2018 Jan 24;13(1):e0190999.
17. Billiet, T, Rutgeerts, P, Ferrante, M. Targeting TNF-α for the treatment of inflammatory bowel disease. Expert Opin Biol Ther 2014; 14: 75–101.
18. Papamichael, K., Lin, S., Moore, M., Papaioannou, G., Sattler, L., & Cheifetz, A. S. (2019). Infliximab in inflammatory bowel disease. Therapeutic Advances in Chronic Disease.
19. Atreya R, Zimmer M, Bartsch B, Waldner MJ, Atreya I, Neumann H, et al. Antibodies against tumor necrosis factor (TNF) induce T-cell apoptosis in patients with inflammatory bowel diseases via TNF receptor 2 and intestinal CD14(+) macrophages. Gastroenterology. 2011;141(6):2026–38.
20. Matsuoka K, Hamada S, Shimizu M, Nanki K, Mizuno S, Kiyohara H, Arai M, Sugimoto S, Iwao Y, Ogata H, Hisamatsu T, Naganuma M, Kanai T, Mochizuki M, Hashiguchi M. Factors predicting the therapeutic response to infliximab during maintenance therapy in Japanese patients with Crohn's disease. PLoS One. 2018 Oct 4;13(10):e0204632.
21. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet (London, England). 2002;359(9317):1541–9.
22. Parekh R, and Kaur N. Liver Injury Secondary to Anti-TNF-Alpha Therapy in Inflammatory Bowel Disease: A Case Series and Review of the Literature. Case Rep Gastrointest Med. 2014; 2014: 956463.
23. Jonas, M. M., and Lee, C. Review. Gastroenterol Hepatol (N Y). 2006 Feb;2(2):90.
24. French JB, Bonacini M, Ghabril M, Foureau D, Bonkovsky HL. Hepatotoxicity associated with the use of anti-TNF-α agents. Drug Saf. 2016;39(3):199–208.
25. Harding FA, Stickler MM, Razo J, DuBridge RB. The immunogenicity of humanized and fully human antibodies: residual immunogenicity resides in the CDR regions. MonoclonAntib. 2010;2(3):256–265.
26. Eriksson, C.; Engstrand, S.; Sundqvist, K.G.; Rantapaa-Dahlqvist, S. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. Ann. Rheum. Dis. 2005, 64, 403–407.
27. Tobon, G.J.; Canas, C.; Jaller, J.J.; Restrepo, J.C.; Anaya, J.M. Serious liver disease induced by infliximab. Clin. Rheumatol. 2007, 26, 578–581.
28. Diehl, A.M. Cytokine regulation of liver injury and repair. Immunol. Rev. 2000, 174, 160–171.
29. Chen, X.; Oppenheim, J.J. Contrasting effects of TNF and anti-TNF on the activation of effector t cells and regulatory t cells in autoimmunity. FEBS Lett. 2011, 585, 3611–3618.
30. Lopetuso LR, Mocci G, Marzo M, D'aversa F, Rapaccini GL, Guidi L, Armuzzi A, Gasbarrini A, Papa A. Harmful effects and potential benefits of anti-tumor necrosis factor (TNF)-α on the liver. International journal of molecular sciences. 2018 Aug;19(8):2199.
31. Papamichael, K., Mantzaris, G. J., and Peyrin-Biroulet, L. A safety assessment of anti-tumor necrosis factor alpha therapy for treatment of Crohn's disease, Expert Opinion on Drug Safety.2016, 15:4, 493-501.
32. Lichtenstein, GR, Feagan, BG, Cohen, RD. Infliximab for Crohn's Disease: More Than 13 Years of Real-world Experience Inflamm Bowel Dis. 2018 Mar; 24(3): 490–501.
33. United States Departement of Health and Human Services F. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Drug Saf 2009; 28. Availablefrom: https://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.
34. Shelton E, Chaudrey K, Sauk J, Khalili H, Masia R, Nguyen DD, Yajnik V, Ananthakrishnan AN. New onset idiosyncratic liver enzyme elevations with biological therapy in inflammatory bowel disease. AlimentPharmacolTher. 2015 May;41(10):972-9. doi: 10.1111/apt.13159. Epub 2015 Mar 10
35. Parisi I, O'Beirne J, Rossi RE, Tsochatzis E, Manousou P, Theocharidou E, Hamilton M,

Murray C, Epstein O, Burroughs AK. Elevated liver enzymes in inflammatory bowel disease: the role and safety of infliximab.Eur J Gastroenterol Hepatol. 2016 Jul;28(7):786-91. doi:10.1097/MEG.0000000000000624.

36. Koller T, Galambosova M, Filakovska S, Kubincova M, Hlavaty T, Toth J, Krajcovicova A, Payer J.Drug-induced liver injury in inflammatory bowel disease: 1-year prospective observational study. World J Gastroenterol. 2017 Jun 14;23(22):4102-4111.
37. US Department of Health and Human Services. (2010) Common terminology criteria for adverse events (CTCAE) version 4.03. USA: National Institutes of Health, National Cancer Institute.
38. Rojas-Feria M1, Castro M, Suárez E, Ampuero J, Romero-Gómez M.Hepatobiliary manifestations in inflammatory bowel disease: the gut, the drugs and the liver. World J Gastroenterol. 2013 Nov 14;19(42):7327-40. 39.
39. Björnsson ES, Gunnarsson BI, Gröndal G, et al. Risk of drug-induced liver injury from tumor necrosis factor antagonists. Clin Gastroenterol Hepatol 2015; 3: 602–8.
40. Kok B, Lester ELW, Lee WM, Hanje AJ, Stravitz RT, Girgis S, Patel V, Peck JR, Esber C, Karvellas CJ; United States Acute Liver Failure Study Group. Acute Liver Failure from Tumor Necrosis Factor-α Antagonists: Report of Four Cases and Literature Review. Dig Dis Sci. 2018 Jun;63(6):1654-1666.
41. Kim JM, Cheon JH. Pathogenesis and clinical perspectives of extraintestinal manifestations in inflammatory bowel diseases. Intestinal Research. 2020 Apr 18.
42. Khan N, Abbas AM, Whang N, et al. Incidence of liver toxicity ininflammatory bowel disease patients treated with methotrexate: a meta-analysis of clinical trials. Inflamm Bowel Dis 2012;18:359–67.
43. Colina F, Molero A, Casis B, et al. Infliximab-related hepatitis: a casestudy and literature review. Dig Dis Sci 2013;58:3362–7.
44. Saubermann LJ, Deneau M, Falcone RA, Murray KF, Ali S, Kohli R, Ekong UD, Valentino PL, Grossman AB, Rand EB, Jonas MM. Hepatic issues and complications associated with inflammatory bowel disease: a clinical report from the NASPGHAN inflammatory bowel disease and hepatology committees. Journal of pediatric gastroenterology and nutrition. 2017 Apr 1;64(4):639-52.
45. Ghabril M, Bonkovsky HL, Kum C, et al. Liver injury from tumornecrosis factor-alpha antagonists: analysis of thirty-four cases. Clin Gastroenterol Hepatol 2013;11:558.e3–64.e3.
46. Mancini S, Amorotti E, Vecchio S, et al. Infliximab-related hepatitis: discussion of a case and review of the literature. Intern Emerg Med 2010;5:193–200.
47. Menghini VV, Arora AS. Infliximab-associated reversible choles- tatic liver disease. Mayo Clin Proc 2001;76:84-86.
48. Soto-Fernández S, González-Carro P, De Pedro-Esteban A, Legaz-Huidobro ML, Pérez-Roldán F, RonceroGarcíaEscribano O, et al. Infliximab-induced hepatitis in a patient with Crohn's disease [in Spanish]. Gastroenterol Hepatol 2006;29:321-322.
49. Moum B, Konopski Z, Tufteland KF, Jahnsen J. Occurrence of hepatoxicicty and elevated liver enzymes in a Crohn's disease patient treated with infliximab. Inflamm Bowel Dis 2007;13: 1584-1586.
50. Rossi RE, Parisi I, Despott EJ, Burroughs AK, O'Beirne J, Conte D, et al. Anti-tumour necrosis factor agent and liver injury: literature review, recommendations for management. World J Gastroenterol 2014;20:17352-17359.
51. 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.
52. 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.
53. Goldfeld DA, Verna EC, Lefkowitch J, Swaminath A. Infliximab- induced autoimmune hepatitis with successful switch to adalimumab in a patient with Crohn's disease: the index case. Dig Dis Sci 2011;56:3386-3388.
54. Subramaniam K, Chitturi S, Brown M, Pavli P. Infliximab- induced autoimmune hepatitis in Crohn's disease treated with budesonide and mycophenolate. Inflamm Bowel Dis 2011;17:E149-E150.
55. Haennig A, Bonnet D, Thebault S, Alric L.

Infliximabinduced acute hepatitis during Crohn's disease therapy: absence of cross-toxicity with adalimumab. Gastroenterol Clin Biol 2010; 34:e7-e8.

56. Caussé S, Bouquin R, Wylomanski S, Flamant M, Joubert M, Dréno B, et al. Infliximab-induced hepatitis during treatment of vulvar Crohn's disease [in French]. Ann Dermatol Venereol2013;140:46-51.
57. Estes DJ, Szeto W, Kingsley M, Poveda JC, Beduschi T, Deshpande AR. Unique Immediate Postoperative Management of Crohn's Disease in a Patient with Autoimmune Hepatitis-Like Drug-Induced Liver Injury from Infliximab Requiring Liver Transplantation. American Journal of Medical Case Reports. 2020;8(1):11-3.
58. Wong F, Al Ibrahim B, Walsh J, Qumosani K. Infliximab-induced autoimmune hepatitis requiring liver transplantation. Clinical Case Reports. 2019 Nov;7(11):2135-9.
59. Van Casteren-Messidoro C, Prins G, van Tilburg A, ZelinkovaZ,Schouten J, de Man R. Autoimmune hepatitis following treatment with infliximab for inflammatory bowel disease. J Crohns Colitis. 2012;6:630–631.
60. Rodrigues, S., Lopes, S., Magro, F., Cardoso, H., e Vale, A.M.H., Marques, M., Mariz, E., Bernardes, M., Lopes, J., Carneiro, F. and Macedo, G., 2015. Autoimmune hepatitis and anti-tumor necrosis factor alpha therapy: a single center report of 8 cases. World journal of gastroenterology: WJG, 21(24), p.7584.
61. Batra J, Goraya SK, Grewal S, Singh A. Metastatic Crohn's disease of the vulva: A rare presentation. Indian Dermatology Online Journal. 2020 May 1;11(3):416.