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**Tumor necrosis factor-α inhibitors and chronic hepatitis C: A comprehensive literature review**

Pompili M *et al* TNF-α Inhibitors and HCV

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**Abstract**

Tumor necrosis factor-α (TNF-α) inhibitors are known to increase reactivation of concurrent chronic hepatitis B, but their impact on the hepatitis C virus (HCV) is controversial. Some conditions of immunosuppression, such as liver transplantation, typically cause an increase in the rate of HCV evolution. Inhibition of TNF-α, a cytokine involved in the apoptotic signaling pathway of hepatocytes infected by HCV, could potentially increase viral replication. Currently available clinical data appear to contradict this hypothesis. A review of medical literature revealed that a total of 216 patients with HCV were exposed to one or more treatments with TNF-α inhibitors, with a median observation time of 1.2 years and 260 cumulative patient-years of exposure. Only three cases of drug withdrawal due to suspected HCV liver disease recrudescence were reported. Treatment with TNF-α inhibitors in patients with HCV infection appears to be safe in the short term, but there are insufficient data to assess their long-term safety. Universal screening for HCV before beginning treatment with TNF-α inhibitors is currently controversial. The presence of HCV is not a contraindication to therapy with TNF-α inhibitors, with the exception of cirrhotic patients. In cases of cirrhosis, the benefit/risk ratio should be evaluated at the individual level. Prior to treatment with TNF-α inhibitors, patients with HCV should be referred to a hepatologist to determine the necessity of hepatic disease assessment, using liver biopsy or non-invasive methods, and the potential indication for antiviral therapy. In patients with HCV infection who are treated with TNF-α inhibitors, liver function monitoring every three months is advised.

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**Key words:** Infliximab; Etanercept; Adalimumab; Hepatitis C virus; Rheumatoid arthritis; Inflammatory bowel disease; Psoriasis

**Core tip:** Our review summarizes data on patients with hepatitis C exposed to tumor necrosis factor-α (TNF-α) inhibitors, thus building a stronger safety profile than previously reported. A comprehensive paragraph on the pathway of TNF-α in hepatitis C virus (HCV) and an overview on immune-mediated damage induced by TNF-α inhibitors (cryoglobulins, autoimmune hepatitis) have been also included. Some controversies regarding the universal screening and monitoring of HCV-RNA were also addressed.

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**INTRODUCTION**

Tumor necrosis factor-α (TNF-α) is a cytokine involved in the pathogenesis of inflammatory diseases and in the immune-mediated response to infections, especially against intracellular pathogens. Drugs targeting and inhibiting the biological activity of TNF-α, such as infliximab, etanercept and adalimumab, are increasingly used for the treatment of immune-mediated diseases such as rheumatoid arthritis, inflammatory bowel diseases and psoriasis[1]. TNF-α inhibitors increase susceptibility to new or reactivation of concurrent infections. Thus, before its use for therapy, a screening for tuberculosis (with chest radiography and an interferon-gamma release assay) and certain viral infections such as hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus, and herpes virus is recommended[2].

The potential risk of reactivation of HBV infection during TNF-α inhibitor therapy is well established. Animal studies have demonstrated that TNF-α plays a key role in clearing HBV from infected hepatocytes by synergizing with interferons (INFs) in the suppression of viral replication[3,4]. TNF-α inhibitors can increase HBV replication and reactivate chronic hepatitis, both during and after discontinuation of treatment. It is worth noting that many patients receiving TNF-α inhibitors have been previously or simultaneously treated, even for long periods, with other immunosuppressant agents that further increase the risk of HBV reactivation[5]. Hepatitis reactivation has been reported in twenty-three hepatitis B surface antigen (HBsAg)-positive patients treated with TNF-α inhibitors in the absence of prophylaxis (inactive carriers or with unrecognized HBsAg seropositivity), including 9 cases of fulminant hepatitis, 4 deaths and 1 liver transplantation. Furthermore, three HBsAg-negative, hepatitis B core antibody (Anti-HBc)-positive patients presented HBsAg seroreversion followed by a hepatitis flare-up after administration of TNF-α inhibitors[6]. The protocol that is currently recommended, borrowed from other clinical situations of pharmacologically induced immunosuppression, includes prophylaxis with lamivudine of all inactive carriers during and for 6-12 mo following therapy with TNF-α inhibitors and quarterly monitoring of HBsAg in HBsAg-negative anti-HBc positive patients[7,8].

In the context of HCV infection, the potential risk of reactivation of infection during therapy with TNF-α inhibitors is controversial. Several clinical reports have shown that chronic hepatitis C usually evolves rapidly in some conditions associated with immunosuppression, such as co-infection with human immunodeficiency virus, hypogammaglobulinemia, and after bone marrow transplantation and, above all, liver transplantation[9]. In various other circumstances, *e.g.,* following chemotherapy, hepatitis flare-up does not occur during immunosuppression or after its suspension[10]. The inhibition of TNF-α, a cytokine involved in the apoptotic signaling pathway of hepatocytes infected by HCV, could potentially increase viral replication and worsen the course of chronic hepatitis[11]. In this review, we present an overview of the relationship between the TNF-α pathway and HCV, summarize the available evidence regarding the safety of TNF-α inhibitor usage in patients with HCV and provide suggestions for the management of therapy in this clinical setting.

**TNF-**α **PATHWAY IN CHRONIC HCV INFECTION**

The role of TNF-α in chronic HCV infection is not well understood. Serum levels of TNF-α and its soluble receptors (sTNF-R55 and sTNF-R75) are significantly higher in HCV-infected patients than in healthy subjects[12]. Serum levels of TNF-α correlate with serum transaminase levels, histological activity and fibrosis, but not with serum HCV RNA levels or viral genotype[13,14]. Laboratory studies have indicated that the HCV core protein has the potential to inhibit the TNF-α-mediated apoptotic signaling pathway, providing a selective advantage for HCV replication and avoidance of the host antiviral defense mechanism[15]. Thus, further suppression of TNF-α by biological drugs may pose a potential threat of excessive viral replication and worsening of chronic HCV infection. In contrast, some studies have postulated that the baseline overexpression of TNF-α is associated with reduced cell capability to respond to INF signaling and, consequently, to reduced viral clearance[16]. Zein *et al*[17] conducted a controlled, double-blind, randomized, placebo trial assessing the effects of etanercept as adjuvant therapy to INF alfa-2b for 24 wk plus ribavirin in patients with chronic hepatitis C. The 19 patients treated with etanercept achieved sustained virologic response at a significantly higher rate compared to the 25 controls, and treatment was associated with decreased incidence of the most common side effects associated with INF and ribavirin. This phase II study supported the assumption that etanercept may restore TNF-induced CD4+ cell impairment and enhance antiviral effects of INF and ribavirin combination therapy. Large studies of the effects of adjuvant etanercept on therapy with pegylated INF and ribavirin are currently lacking.

Infliximab is a recombinant human-murine chimeric immunoglobulin-G1 (IgG1) antibody that specifically binds both soluble and membrane-bound precursor forms of TNF-α. Etanercept is a dimeric fusion protein that consists of the extracellular ligand-binding portion of the human 75 kDa TNF receptor linked to the Fc portion of the human IgG1, and binds only soluble TNF-α. Adalimumab is a human-derived recombinant IgG1 monoclonal antibody that binds to TNF-α and blocks the interaction between soluble TNF-α and cell-surface TNF receptors[18]. The limited data that are currently available are not sufficient for the assessment of the potential specific differences between the drugs regarding the effect on viral replication.

**CLINICAL EVIDENCE OF THE SAFETY OF TNF-Α INHIBITORS IN PATIENTS WITH HCV**

We performed a comprehensive review of reports published in English between January 2000 and August 2013; patients were evaluated for the following variables: disease, comorbidities, TNF-α inhibitors, previous HCV treatment, concomitant immunosuppressive drugs, liver function tests, HCV-ribonucleic acid (HCV-RNA), histopathological liver findings (when available), complications and outcomes. Patients with HCV are excluded from participation in controlled clinical trials with TNF-α inhibitors. Next, available data regarding the safety of TNF-α inhibitors in patients with hepatitis C, as derived from several case reports and small retrospective cohort studies in the field of rheumatology, dermatology and gastroenterology, in addition to the already mentioned trial of Zein *et al*[17], were evaluated. These findings come from various clinical contexts, in terms of differing uses of concomitant immunosuppressive drugs (in most cases dermatologists tend to employ TNF-α inhibitors in monotherapy, while gastroenterologists and rheumatologists prescribe them in combination with other immunosuppressants), pre-treatment selection of HCV patients, monitoring protocols and differences in the threshold used for discontinuing treatment with TNF-α inhibitors. Furthermore, most of the evidence concerns the measurement of transaminases and viral load, with few reports including a histological evaluation before and after treatment.

 total of 216 patients with hepatitis C were treated with one or more TNF-α inhibitors, with a median observation time of 1.2 years and 260 cumulative patient-years of treatment, a measure of exposure that includes all patients treated and normalizes the different durations of treatment to one year (Table 1)[19-58]. The majority of the available safety data concern etanercept. Clinical evidence suggests that the role of TNF-α in the control of HCV replication is modest. Currently, only three cases of drug withdrawal due to clinical suspicion of a worsening of HCV liver disease have been reported. The viral load in most cases remains stable or decreases, and it is difficult to confidently attribute the few cases of serum HCV-RNA increase > 1 log above the baseline value to treatment with TNF-α inhibitors, considering the well-known virological profile of HCV, which shows spontaneous fluctuations > 1 log of HCV-RNA level in 5%-10% of patients[59]. Overall, TNF-α inhibitors do not increase transaminase levels or viral load in the short term in patients with hepatitis C. Furthermore, the administration of these drugs has allowed the concomitant use of INF in some patients with hepatitis C in whom INF had been previously discontinued due of a worsening of concurrent immunomediated diseases such as psoriasis, rheumatoid arthritis or other arthritis. In regard to the long-term safety of TNF-α inhibitors and their impact on the progression of liver fibrosis, the limited available data do not allow for the assessment of this issue. Another area of uncertainty is related to their use in cirrhotic patients; only two cases of patients with cirrhosis who received TNF-α inhibitors have been reported, by Zein and Abdelmalek, and both cases were without significant side effects.

Another potential concern is the possibility of immune-mediated liver damage induced by TNF-α inhibitors. Emergence of serum auto-antibodies is a common observation in patients treated with TNF-α inhibitors and presents an additional concern in patients with hepatitis C. In the absence of HCV infection, the auto-antibodies induced by such treatments are usually non-organ specific [anti-double-stranded-DNA (dsDNA), rheumatoid factors, anti-cardiolipin] and belong to the IgM class[60,61]. Vauloup *et al*[62] prospectively evaluated the induction of circulating auto-antibodies during therapy with TNF-α inhibitors in patients with HCV and observed induction of anti-nuclear and anti-dsDNA antibodies, but no induction of anti-tissue antibodies (anti-smooth muscle and anti-liver/kidney/microsome type 1), even in patients with actively replicating chronic hepatitis C. Induction of cryoglobulinemia was also a possibility, and HCV-related mixed cryoglobulinemia usually includes an IgM component. Auto-antibodies emerging during treatment with TNF-α inhibitors are usually clinically silent, possibly due to the low avidity of antibodies to their antigen. Seventeen cases of TNF-α-induced hepatitis without known past history of liver disease have been reported in the literature[63-78]. The majority of these cases are secondary to infliximab and resemble autoimmune hepatitis type 1 due to an increased prevalence among females, the more common elevation of autoantibodies related to autoimmune hepatitis type 1 (anti-nuclear, anti-smooth-muscle or anti-dsDNA), the presence of interface hepatitis at liver biopsy, and the strong response to steroid therapy. Some of these patients were subsequently able to tolerate etanercept, suggesting a different potential of the two drugs in inducing immune-mediated liver damage. Indeed, among patients with HCV infection, only one case of granulomatous hepatitis not associated to a rise of serum HCV-RNA, diagnosed after 7 mo of therapy with etanercept, has been reported[79]. A TNF-α blockade induces a cytokine imbalance that is rarely responsible for inducing pulmonary, cutaneous, eye and even hepatic sarcoidosis. Overall, the incidence of autoimmune hepatitis induced by TNF-α inhibitors appears to be low and does not represent a contraindication in the treatment of patients with chronic hepatitis C.

Although observations of transaminase elevation have been documented in the package inserts of TNF-α inhibitors, no direct link between these drugs and liver toxicity has been established to date, with the exception of one single case of acute hepatitis during infliximab treatment, in which the liver biopsy showed signs of toxic damage (intralobular necrosis, ceroid-containing Kupffer cells)[80]. For this reason, TNF-α inhibitors present an attractive alternative therapy in some patients with autoimmune diseases, such as psoriasis or rheumatoid arthritis, which are routinely treated with other drugs with well established, likely more severe liver toxicity profiles cyclosporine, acitretin, methotrexate, leflunomide).

**CLINICAL MANAGEMENT OF TNF-Α INHIBITORS IN PATIENTS WITH HCV**

Many guidelines recommend screening by means of serum anti-HCV antibodies in all patients undergoing therapy with TNF-α inhibitors, emphasizing that a definitive decision on the safety of TNF-α inhibitors in cases of chronic HCV infection has not been made[81-83]. A study conducted in Ireland, a country with a low prevalence of HCV (< 1%), including 215 patients with psoriasis treated with TNF-α inhibitors documented a single case of positivity for antibodies to HCV with undetectable serum HCV-RNA. The authors concluded that, in areas with low prevalence of HCV infection, universal screening should be replaced by targeted screening based on the individual risk factors of each patient[84]. Other guidelines state that universal screening should not be definitively recommended, as the risk of HCV reactivation under immunosuppressive drugs appears to be very low[85,86]. Before beginning treatment with TNF-α inhibitors, assays for serum alanine aminotransferase (ALT), gamma-glutamyl-transferase and total bilirubin are recommended, bearing in mind that approximately 30% of patients with chronic HCV infection show persistently normal ALT levels[87]. In cases of anti-HCV positivity, assessment of HCV-RNA, HCV genotype, cryoglobulins, complete blood count, total protein, albumin, total cholesterol, prothrombin time, creatinin, and urine exam, as well as a liver ultrasound, are also recommended.

TNF-α inhibitors in patients with HCV are not contraindicated, provided that monitoring of liver function tests is performed every three months during treatment. Currently, there is uncertainty in the standards for viral load monitoring (quarterly or only in case of serum transaminase increase). Due to the absence of data regarding cirrhotic patients, TNF-α inhibitors should be used with caution in compensated patients, while they are contraindicated in patients with decompensated liver disease, considering the extremely high risk of potentially fatal severe infections. In cases of reactivation of hepatitis, patients should be referred to a hepatologist for a differential diagnosis and to consider the potential for TNF-α inhibitor treatment withdrawal.

**CONCLUSION**

TNF-α inhibitor treatment in patients with HCV appears to be safe in the short term, but there are insufficient data to assess their long-term safety. A potential concern related to the administration of these drugs is the induction of immune-mediated reactions that potentially involve the liver (cryoglobulinemic syndrome or autoimmune hepatitis), but the incidence of such reactions appears to be low. Universal screening for HCV before beginning treatment with TNF-α inhibitors is currently controversial. The presence of HCV is not a contraindication to therapy with TNF-α inhibitors, except in cirrhotic patients, in whom the benefit/risk ratio should be evaluated at the individual level before treatment is initiated. Before administration of TNF-α inhibitors, patients with HCV should be referred to a hepatologist for the evaluation of the liver disease stage through liver biopsy or non-invasive methods and the potential for antiviral therapy. Liver function tests are advised for patients with HCV at a frequency of every three months during treatment with TNF-α inhibitors.

**REFERENCES**

1 **Nielsen OH**, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. *N Engl J Med* 2013; **369**: 754-762 [PMID: 23964937 DOI: 10.1056/NEJMct1209614]

2 **Nathan DM**, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti-tumor necrosis factor-α therapy: guidelines for clinical approach. *J Gastroenterol Hepatol* 2006; **21**: 1366-1371 [PMID: 16911678 DOI: 10.1111/j.1440-1746.2006.04559.x]

3 **Guidotti LG**, Ishikawa T, Hobbs MV, Matzke B, Schreiber R, Chisari FV. Intracellular inactivation of the hepatitis B virus by cytotoxic T lymphocytes. *Immunity* 1996; **4**: 25-36 [PMID: 8574849 DOI: 10.1016/S1074-7613(00)80295-2]

4 **Kasahara S**, Ando K, Saito K, Sekikawa K, Ito H, Ishikawa T, Ohnishi H, Seishima M, Kakumu S, Moriwaki H. Lack of tumor necrosis factor α induces impaired proliferation of hepatitis B virus-specific cytotoxic T lymphocytes. *J Virol* 2003; **77**: 2469-2476 [PMID: 12551985 DOI: 10.1128/JVI.77.4.2469-2476.2003]

5 **Papa A**, Mocci G, Bonizzi M, Felice C, Andrisani G, De Vitis I, Guidi L, Gasbarrini A. Use of infliximab in particular clinical settings: management based on current evidence. *Am J Gastroenterol* 2009; **104**: 1575-1586 [PMID: 19491875 DOI: 10.1038/ajg.2009.162]

6 **Viganò M**, Degasperi E, Aghemo A, Lampertico P, Colombo M. Anti-TNF drugs in patients with hepatitis B or C virus infection: safety and clinical management. *Expert Opin Biol Ther* 2012; **12**: 193-207 [PMID: 22188392 DOI: 10.1517/14712598.2012.646986]

7 **Lok AS**, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]

8 **European Association For The Study Of The Liver.** EASL Clinical Practice Guidelines: management of chronic hepatitis B. *J Hepatol* 2009; **50**: 227-242 [PMID: 19054588 DOI: 10.1016/j.jhep.2008.10.001]

9 **Zignego AL**, Giannini C, Gragnani L, Piluso A, Fognani E. Hepatitis C virus infection in the immunocompromised host: a complex scenario with variable clinical impact. *J Transl Med* 2012; **10**: 158 [PMID: 22863056 DOI: 10.1186/1479-5876-10-158]

10 **Zuckerman E**, Zuckerman T, Douer D, Qian D, Levine AM. Liver dysfunction in patients infected with hepatitis C virus undergoing chemotherapy for hematologic malignancies. *Cancer* 1998; **83**: 1224-1230 [PMID: 9740089 DOI: 10.1002/(SICI)1097-0142(19980915)83: 6<1224]

11 **Marusawa H**, Hijikata M, Chiba T, Shimotohno K. Hepatitis C virus core protein inhibits Fas- and tumor necrosis factor α-mediated apoptosis via NF-kappaB activation. *J Virol* 1999; **73**: 4713-4720 [PMID: 10233931 DOI: 0022-538X/99/$04.0010]

12 **Tilg H**, Wilmer A, Vogel W, Herold M, Nölchen B, Judmaier G, Huber C. Serum levels of cytokines in chronic liver diseases. *Gastroenterology* 1992; **103**: 264-274 [PMID: 1612333 DOI: 0016-5085/92/$3.00]

13 **Nelson DR**, Lim HL, Marousis CG, Fang JW, Davis GL, Shen L, Urdea MS, Kolberg JA, Lau JY. Activation of tumor necrosis factor-α system in chronic hepatitis C virus infection. *Dig Dis Sci* 1997; **42**: 2487-2494 [PMID: 9440625 DOI: 0163-2116/97/1200-2487$12.50/0]

14 **Zylberberg H**, Rimaniol AC, Pol S, Masson A, De Groote D, Berthelot P, Bach JF, Bréchot C, Zavala F. Soluble tumor necrosis factor receptors in chronic hepatitis C: a correlation with histological fibrosis and activity. *J Hepatol* 1999; **30**: 185-191 [PMID: 10068094 DOI: 10.1016/S0168-8278(99)80060-9]

15 **Ray RB**, Meyer K, Steele R, Shrivastava A, Aggarwal BB, Ray R. Inhibition of tumor necrosis factor (TNF-α)-mediated apoptosis by hepatitis C virus core protein. *J Biol Chem* 1998; **273**: 2256-2259 [PMID: 9442069 DOI: 10.1074/jbc.273.4.2256]

16 **Larrea E**, Garcia N, Qian C, Civeira MP, Prieto J. Tumor necrosis factor α gene expression and the response to interferon in chronic hepatitis C. *Hepatology* 1996; **23**: 210-217 [PMID: 8591843 DOI: 10/S0270913996000365]

17 **Zein NN**; Etanercept Study Group. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. *J Hepatol* 2005; **42**: 315-322 [PMID: 15791697 DOI: 10.1016/j.jhep.2004.11.025]

18 **Croft M**, Benedict CA, Ware CF. Clinical targeting of the TNF and TNFR superfamilies. *Nat Rev Drug Discov* 2013; **12**: 147-168 [PMID: 23334208 DOI: 10.1038/nrd3930]

19 **Oniankitan O**, Duvoux C, Challine D, Mallat A, Chevalier X, Pawlotsky JM, Claudepierre P. Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. *J Rheumatol* 2004; **31**: 107-109 [PMID: 14705228 DOI: unavailable]

20 **Parke FA**, Reveille JD. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. *Arthritis Rheum* 2004; **51**: 800-804 [PMID: 15478165 DOI: 10.1002/art.20702]

21 **Holtmann MH**, Galle PR, Neurath MF. Treatment of patients with Crohn's disease and concomitant chronic hepatitis C with a chimeric monoclonal antibody to TNF. *Am J Gastroenterol* 2003; **98**: 504-505 [PMID: 12591081 DOI: 10.1111/j.1572-0241.2003.07245.x]

22 **Campbell S**, Ghosh S. Infliximab therapy for Crohn's disease in the presence of chronic hepatitis C infection. *Eur J Gastroenterol Hepatol* 2001; **13**: 191-192 [PMID: 11246620 DOI: 00042737/200102000-00016.]

23 **Magliocco MA**, Gottlieb AB. Etanercept therapy for patients with psoriatic arthritis and concurrent hepatitis C virus infection: report of 3 cases. *J Am Acad Dermatol* 2004; **51**: 580-584 [PMID: 15389194 DOI: 10.1016/j.jaad.2004.05.013]

24 **De Simone C**, Paradisi A, Capizzi R, Carbone A, Siciliano M, Amerio PL. Etanercept therapy in two patients with psoriasis and concomitant hepatitis C. *J Am Acad Dermatol* 2006; **54**: 1102-1104 [PMID: 16713482 DOI: 10.1016/j.jaad.2005.11.1035]

25 **Paradisi A**, Caldarola G, Capizzi R, Siciliano M, Annichiarico E, Vecchio FM, Amerio PL, De Simone C. Safety of etanercept in patients with psoriasis and hepatitis C virus assessed by liver histopathology: preliminary data. *J Am Acad Dermatol* 2010; **62**: 1067-1069 [PMID: 20466184 DOI: 10.1016/j.jaad.2009.07.010]

26 **Peterson JR**, Hsu FC, Simkin PA, Wener MH. Effect of tumour necrosis factor α antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. *Ann Rheum Dis* 2003; **62**: 1078-1082 [PMID: 14583571 DOI: 10.1136/ard.62.11.1078]

27 **Ferri C**, Ferraccioli G, Ferrari D, Galeazzi M, Lapadula G, Montecucco C, Triolo G, Valentini G, Valesini G. Safety of anti-tumor necrosis factor-α therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. *J Rheumatol* 2008; **35**: 1944-1949 [PMID: 18688917]

28 **Cavazzana I**, Ceribelli A, Cattaneo R, Franceschini F. Treatment with etanercept in six patients with chronic hepatitis C infection and systemic autoimmune diseases. *Autoimmun Rev* 2008; **8**: 104-106 [PMID: 19014870 DOI: 10.1016/j.autrev.2008.05.002]

29 **Niewold TB**, Gibofsky A. Concomitant interferon-α therapy and tumor necrosis factor α inhibition for rheumatoid arthritis and hepatitis C. *Arthritis Rheum* 2006; **54**: 2335-2337 [PMID: 16802375 DOI: 10.1002/art.21949]

30 **Rokhsar C**, Rabhan N, Cohen SR. Etanercept monotherapy for a patient with psoriasis, psoriatic arthritis, and concomitant hepatitis C infection. *J Am Acad Dermatol* 2006; **54**: 361-362 [PMID: 16443079 DOI: 10.1016/j.jaad.2005.05.043]

31 **Bellisai F**, Giannitti C, Donvito A, Galeazzi M. Combination therapy with cyclosporine A and anti-TNF-α agents in the treatment of rheumatoid arthritis and concomitant hepatitis C virus infection. *Clin Rheumatol* 2007; **26**: 1127-1129 [PMID: 17143590 DOI: 10.1007/s10067-006-0412-1]

32 **Roux CH**, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Safety of anti-TNF-α therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. *Rheumatology (Oxford)* 2006; **45**: 1294-1297 [PMID: 16603583 DOI: 10.1093/rheumatology/kel123]

33 **Marotte H**, Fontanges E, Bailly F, Zoulim F, Trepo C, Miossec P. Etanercept treatment for three months is safe in patients with rheumatological manifestations associated with hepatitis C virus. *Rheumatology (Oxford)* 2007; **46**: 97-99 [PMID: 16720634 DOI: 10.1093/rheumatology/kel191]

34 **Cecchi R**, Bartoli L. Psoriasis and hepatitis C treated with anti-TNF α therapy (etanercept). *Dermatol Online J* 2006; **12**: 4 [PMID: 17459290]

35 **Alcaide AJ**, Barrera MV, Habicheyn S, López N, Mendiola MV, Herrera E. Safety of etanercept therapy in a patient with psoriasis, Down's syndrome and concomitant hepatitis C virus infection. *J Eur Acad Dermatol Venereol* 2008; **22**: 1514-1516 [PMID: 18355196 DOI: 10.1111/j.1468-3083.2008.02693.x]

36 **Abdelmalek MF**, Liu C, Valentine JF. Successful treatment of chronic hepatitis C with pegylated interferon, ribavirin, and infliximab in a patient with Crohn's disease. *Am J Gastroenterol* 2007; **102**: 1333-1334 [PMID: 17531027 DOI: 10.1111/j.1572-0241.2007.01131.x]

37 **Linardaki G**, Katsarou O, Ioannidou P, Karafoulidou A, Boki K. Effective etanercept treatment for psoriatic arthritis complicating concomitant human immunodeficiency virus and hepatitis C virus infection. *J Rheumatol* 2007; **34**: 1353-1355 [PMID: 17552060]

38 **Cansu DU**, Kalifoglu T, Korkmaz C. Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease modifying antirheumatic drugs without antiviral prophylaxis. *J Rheumatol* 2008; **35**: 421-424 [PMID: 18203328]

39 **Di Lernia V**, Zoboli G, Ficarelli E. Long-term management of HIV/hepatitis C virus associated psoriasis with etanercept. *Indian J Dermatol Venereol Leprol* 2013; **79**: 444 [PMID: 23619459 DOI: 10.4103/0378-6323.110807]

40 **Li S**, Kaur PP, Chan V, Berney S. Use of tumor necrosis factor-α (TNF-α) antagonists infliximab, etanercept, and adalimumab in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: a retrospective record review of 11 patients. *Clin Rheumatol* 2009; **28**: 787-791 [PMID: 19291350 DOI: 10.1007/s10067-009-1149-4]

41 **Lin MV**, Blonski W, Buchner AM, Reddy KR, Lichtenstein GR. The influence of anti-TNF therapy on the course of chronic hepatitis C virus infection in patients with inflammatory bowel disease. *Dig Dis Sci* 2013; **58**: 1149-1156 [PMID: 23179145 DOI: 10.1007/s10620-012-2457-0]

42 **Bartalesi F**, Salomoni E, Cavallo A, Corti G, Pimpinelli N, Bartoloni A, Taliani G. Chronic hepatitis C virus hepatitis and psoriasis: no longer a contraindication to interferon use in the era of biological agents? *Scand J Infect Dis* 2013; **45**: 320-323 [PMID: 23113733 DOI: 10.3109/00365548.2012.720026]

43 **Zanni M**, Missale G, Santilli D, Di Nuzzo S. Etanercept in the treatment of psoriasis and psoriatic arthritis with concomitant hepatitis C virus infection: clinical and virological study in three patients. *Eur J Dermatol* 2011; **21**: 564-567 [PMID: 21543290 DOI: 10.1684/ejd.2011.1318]

44 **Navarro R**, Vilarrasa E, Herranz P, Puig L, Bordas X, Carrascosa JM, Taberner R, Ferrán M, García-Bustinduy M, Romero-Maté A, Pedragosa R, García-Diez A, Daudén E. Safety and effectiveness of ustekinumab and antitumour necrosis factor therapy in patients with psoriasis and chronic viral hepatitis B or C: a retrospective, multicentre study in a clinical setting. *Br J Dermatol* 2013; **168**: 609-616 [PMID: 22985451 DOI: 10.1111/bjd.12045]

45 **Prignano F**, Ricceri F, Pescitelli L, Zanieri F, Lotti T. Tumour necrosis factor-α antagonists in patients with concurrent psoriasis and hepatitis B or hepatitis C: a retrospective analysis of 17 patients. *Br J Dermatol* 2011; **164**: 645-647 [PMID: 21375517 DOI: 10.1111/j.1365-2133.2010.10140.x]

46 **Mederacke I**, Witte T, Wedemeyer H, Meyer-Olson D. Successful clearance of hepatitis C virus with pegylated interferon α-2a and ribavirin in an etanercept-treated patient with psoriatic arthritis, hepatitis B virus coinfection and latent tuberculosis. *Ann Rheum Dis* 2011; **70**: 1343-1344 [PMID: 21131645 DOI: 10.1136/ard.2010.139824]

47 **Katsanos KH**, Tsianos VE, Zois CD, Zioga H, Vagias I, Zervou E, Christodoulou DK, Tsianos EV; Northwest Greece IBD Study Group. Inflammatory bowel disease and hepatitis B and C in Western Balkans: a referral centre study and review of the literature. *J Crohns Colitis* 2010; **4**: 450-465 [PMID: 21122543 DOI: 10.1016/j.crohns.2010.03.001]

48 **Gandhi RK**, Pickup T, Sheth PB. Is etanercept safe for treating plaque psoriasis in a patient with chronic hepatitis C virus infection? *Arch Dermatol* 2010; **146**: 1151-1152 [PMID: 20956650 DOI: 10.1001/archdermatol.2010.253]

49 **Garavaglia MC**, Altomare G. Etanercept therapy in patients with psoriasis and concomitant HCV infection. *Int J Immunopathol Pharmacol* 2010; **23**: 965-969 [PMID: 20943071]

50 **Ventura F**, Gomes J, Duarte Mda L, Fernandes JC, Brito C. Efficacy and safety of etanercept in patients with psoriasis and hepatitis C. *Eur J Dermatol* 2010; **20**: 808-809 [PMID: 20923749 DOI: 10.1684/ejd.2010.1065]

51 **Di Lernia V**, Guareschi E. Successful treatment of hand and foot psoriasis with infliximab. *Dermatol Online J* 2010; **16**: 8 [PMID: 20673536]

52 **Behnam SE**, Hindiyeh R, Fife DJ, Jeffes EW, Wu JJ. Etanercept as prophylactic psoriatic therapy before interferon-α and ribavirin treatment for active hepatitis C infection. *Clin Exp Dermatol* 2010; **35**: 397-398 [PMID: 19663835 DOI: 10.1111/j.1365-2230.2009.03476.x]

53 **Uda H**, Kuhara M, Nishimoto N, Saiki O. Progression of viraemia during treatment with infliximab in a patient with rheumatoid arthritis and chronic hepatitis C infection. *BMJ Case Rep* 2009; **2009**: [PMID: 21829428 DOI: 10.1136/bcr.04.2009.1732]

54 **Dufour C**, Giacchino R, Ghezzi P, Tonelli R, Ferretti E, Pitto A, Pistoia V, Lanza T, Svahn J. Etanercept as a salvage treatment for refractory aplastic anemia. *Pediatr Blood Cancer* 2009; **52**: 522-525 [PMID: 19061218 DOI: 10.1002/pbc.21886]

55 **Cassano N**, Vena GA. Etanercept treatment in a hemodialysis patient with severe cyclosporine-resistant psoriasis and hepatitis C virus infection. *Int J Dermatol* 2008; **47**: 980-981 [PMID: 18937672 DOI: 10.1111/j.1365-4632.2008.03619.x]

56 **Piccolo D**, Di Cesare A, Fargnoli MC, Paoloni M, Vecchiotti S, Peris K. Effective control of psoriasis by etanercept in a patient with HCV-related diseases. *Eur J Dermatol* 2008; **18**: 459-460 [PMID: 18573723 DOI: 10.1684/ejd.2008.0443]

57 **Kaur PP**, Chan VC, Berney SN. Histological evaluation of liver in two rheumatoid arthritis patients with chronic hepatitis B and C treated with TNF-α blockade: case reports. *Clin Rheumatol* 2008; **27**: 1069-1071 [PMID: 18521652 DOI: 10.1007/s10067-008-0896-y]

58 **Costa L**, Caso F, Atteno M, Giannitti C, Spadaro A, Ramonda R, Vezzù M, Del Puente A, Morisco F, Fiocco U, Galeazzi M, Punzi L, Scarpa R. Long-term safety of anti-TNF-α in PsA patients with concomitant HCV infection: a retrospective observational multicenter study on 15 patients. *Clin Rheumatol* 2013; Epub ahead of print [PMID: 23975363 DOI: 10.1007/s10067-013-2378-0]

59 **Arase Y**, Ikeda K, Chayama K, Murashima N, Tsubota A, Suzuki Y, Saitoh S, Kobayashi M, Kobayashi M, Suzuki F, Kumada H. Fluctuation patterns of HCV-RNA serum level in patients with chronic hepatitis C. *J Gastroenterol* 2000; **35**: 221-225 [PMID: 10755692]

60 **Vermeire S**, Noman M, Van Assche G, Baert F, Van Steen K, Esters N, Joossens S, Bossuyt X, Rutgeerts P. Autoimmunity associated with anti-tumor necrosis factor α treatment in Crohn's disease: a prospective cohort study. *Gastroenterology* 2003; **125**: 32-39 [PMID: 12851868 DOI: 10.1016/S0016-5085(03)00701-7]

61 **Elkayam O**, Burke M, Vardinon N, Zakut V, Yitzhak RB, Paran D, Levartovsky D, Litinsky I, Caspi D. Autoantibodies profile of rheumatoid arthritis patients during treatment with infliximab. *Autoimmunity* 2005; **38**: 155-160 [PMID: 16040336 DOI: 10.1080/08916930400021378]

62 **Vauloup C**, Krzysiek R, Greangeot-Keros L, Wendling D, Goupille P, Brault R, Brousse C, Mariette X, Emilie D. Effects of tumor necrosis factor antagonist treatment on hepatitis C-related immunological abnormalities. *Eur Cytokine Netw* 2006; **17**: 290-293 [PMID: 17353164 DOI: 10.1684/ecn.2006.0046]

63 **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]

64 **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]

65 **Ierardi E**, Valle ND, Nacchiero MC, De Francesco V, Stoppino G, Panella C. Onset of liver damage after a single administration of infliximab in a patient with refractory ulcerative colitis. *Clin Drug Investig* 2006; **26**: 673-676 [PMID: 17163303 DOI: 10.2165/00044011-200626110-00008]

66 **Soto-Fernández S**, González-Carro P, De Pedro-Esteban A, Legaz-Huidobro ML, Pérez-Roldán F, Roncero García-Escribano O, Valbuena-González M, Ruiz-Carrillo F. [Infliximab-induced hepatitis in a patient with Crohn's disease]. *Gastroenterol Hepatol* 2006; **29**: 321-322 [PMID: 16733041]

67 **Wahie S**, Alexandroff A, Reynolds NJ. Hepatitis: a rare, but important, complication of infliximab therapy for psoriasis. *Clin Exp Dermatol* 2006; **31**: 460-461 [PMID: 16681606 DOI: 10.1111/j.1365-2230.2006.02086.x]

68 **Kluger N**, Girard C, Guillot B, Bessis D. Efficiency and safety of etanercept after acute hepatitis induced by infliximab for psoriasis. *Acta Derm Venereol* 2009; **89**: 332-334 [PMID: 19479148 DOI: 10.2340/00015555-0619]

69 **Mancini S**, Amorotti E, Vecchio S, Ponz de Leon M, Roncucci L. Infliximab-related hepatitis: discussion of a case and review of the literature. *Intern Emerg Med* 2010; **5**: 193-200 [PMID: 20107930 DOI: 10.1007/s11739-009-0342-4]

70 **Menghini VV**, Arora AS. Infliximab-associated reversible cholestatic liver disease. *Mayo Clin Proc* 2001; **76**: 84-86 [PMID: 11155419 DOI: 10.4065/76.1.84]

71 **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 DOI: 3.0.CO; 2-3]']

72 **Germano V**, Picchianti Diamanti A, Baccano G, Natale E, Onetti Muda A, Priori R, Valesini G. Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis. *Ann Rheum Dis* 2005; **64**: 1519-1520 [PMID: 16162908 DOI: 10.1136/ard.2004.032821]

73 **Thiéfin G**, Morelet A, Heurgué A, Diebold MD, Eschard JP. Infliximab-induced hepatitis: absence of cross-toxicity with etanercept. *Joint Bone Spine* 2008; **75**: 737-739 [PMID: 18693125 DOI: 10.1016/j.jbspin.2007.12.009]

74 **Tobon GJ**, Cañas C, Jaller JJ, 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]

75 **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]

76 **Becker H**, Willeke P, Domschke W, Gaubitz M. Etanercept tolerance in a patient with previous infliximab-induced hepatitis. *Clin Rheumatol* 2008; **27**: 1597-1598 [PMID: 18795397 DOI: 10.1007/s10067-008-1000-3]

77 **Fairhurst DA**, Sheehan-Dare R. Autoimmune hepatitis associated with infliximab in a patient with palmoplantar pustular psoriaisis. *Clin Exp Dermatol* 2009; **34**: 421-422 [PMID: 19309375 DOI: 10.1111/j.1365-2230.2008.03088.x]

78 **Coffin CS**, Fraser HF, Panaccione R, Ghosh S. Liver diseases associated with anti-tumor necrosis factor-α (TNF-α) use for inflammatory bowel disease. *Inflamm Bowel Dis* 2011; **17**: 479-484 [PMID: 20848520 DOI: 10.1002/ibd.21336]

79 **Cuchacovich R**, Hagan J, Khan T, Richert A, Espinoza LR. Tumor necrosis factor-α (TNF-α)-blockade-induced hepatic sarcoidosis in psoriatic arthritis (PsA): case report and review of the literature. *Clin Rheumatol* 2011; **30**: 133-137 [PMID: 20886249 DOI: 10.1007/s10067-010-1577-1]

80 **Carlsen KM**, Riis L, Madsen OR. Toxic hepatitis induced by infliximab in a patient with rheumatoid arthritis with no relapse after switching to etanercept. *Clin Rheumatol* 2009; **28**: 1001-1003 [PMID: 19370307 DOI: 10.1007/s10067-009-1179-y]

81 **Smith CH**, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, Finlay AY, Griffiths CE, Jackson K, McHugh NJ, McKenna KE, Reynolds NJ, Ormerod AD. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol* 2009; **161**: 987-1019 [PMID: 19857207 DOI: 10.1111/j.1365-2133.2009.09505.x]

82 **Brunasso AM**, Puntoni M, Gulia A, Massone C. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. *Rheumatology (Oxford)* 2011; **50**: 1700-1711 [PMID: 21690185 DOI: 10.1093/rheumatology/ker190]

83 **Menter A**, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, Lebwohl M, Koo JY, Elmets CA, Korman NJ, Beutner KR, Bhushan R. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol* 2008; **58**: 826-850 [PMID: 18423260 DOI: 10.1016/j.jaad.2008.02.039]

84 **Reid CT**, De Gascun C, Hall W, Collins P, Lally A, Kirby B. Is universal screening for hepatitis C infection (HCV) prior to commencing anti-TNF-α therapy necessary? *Br J Dermatol* 2013; Epub ahead of print [PMID: 24032395 DOI: 10.1111/bjd.12598]

85 **Gisbert JP**, Chaparro M, Esteve M. Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **33**: 619-633 [PMID: 21416659 DOI: 10.1111/j.1365-2036.2010.04570.x]

86 **Rahier JF**, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, Domènech E, Eliakim R, Eser A, Frater J, Gassull M, Giladi M, Kaser A, Lémann M, Moreels T, Moschen A, Pollok R, Reinisch W, Schunter M, Stange EF, Tilg H, Van Assche G, Viget N, Vucelic B, Walsh A, Weiss G, Yazdanpanah Y, Zabana Y, Travis SP, Colombel JF. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009; **3**: 47-91 [PMID: 21172250 DOI: 10.1016/j.crohns.2009.02.010]

87 **Puoti C**, Magrini A, Stati T, Rigato P, Montagnese F, Rossi P, Aldegheri L, Resta S. Clinical, histological, and virological features of hepatitis C virus carriers with persistently normal or abnormal alanine transaminase levels. *Hepatology* 1997; **26**: 1393-1398 [PMID: 9397976 DOI: 10/S0270-9139(97)00521-1]

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**Table 1 Safety of tumor necrosis factor-α inhibitors in patients with hepatitis C virus**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **Patients with HCV infection (*n*)** | **Mean follow-up (yr)** | **Patients/yr exposure** | **Elevation in AST/ALT serum level > 3 ULN** | **Elevation in HCV-RNA (> 1 log above baseline)** | **Drug withdrawal due to liver toxicity** |
| Etanercept | 153 | 1.14 | 174.49 | 31 | 5 | 2 |
| Infliximab | 40 | 1.59 | 63.64 | 2 | 4 | 1 |
| Adalimumab | 23 | 0.97 | 22.43 | 0 | 0 | 0 |

1Elevation of transaminases without concomitant increase of HCV viremia in two cases. TNF-α: Tumor necrosis factor-α; HCV: Hepatitis C virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HCV-RNA: Hepatitis C virus-ribonucleic acid; ULN: Upper limit of normal.