



WJG 20th Anniversary Special Issues (2): Hepatitis C virus

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

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Author contributions: Pompili M and Biolato M designed the study, wrote the manuscript, and revised the final version of the article; Miele L and Grieco A contributed to the literature search and writing the manuscript.

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Received: September 27, 2013 Revised: October 31, 2013

Accepted: November 12, 2013

Published online: November 28, 2013

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 pa-

tients. 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.

Pompili M, Biolato M, Miele L, Grieco A. Tumor necrosis factor- α inhibitors and chronic hepatitis C: A comprehensive literature review. *World J Gastroenterol* 2013; 19(44): 7867-7873 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v19/i44/7867.htm> DOI: <http://dx.doi.org/10.3748/wjg.v19.i44.7867>

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 (IFNs) 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 inhibi-

tor 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 IFN 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 IFN 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 IFN and ribavirin. This phase II study supported the assumption that etanercept may restore TNF-induced CD4⁺ cell impairment and enhance antiviral effects of IFN and ribavirin combination therapy. Large studies of the effects of adjuvant etanercept on therapy with pegylated IFN 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 pub-

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

Drug	Patients with HCV infection (<i>n</i>)	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	3 ¹	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. HCV: Hepatitis C virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ULN: Upper limit of normal.

lished 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 IFN in some patients with hepatitis C in whom IFN had been previously discontinued due of a worsening of concur-

rent 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^[17,36], 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, creatinine, 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.

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P-Reviewers: Liu CJ, Slomiany BL, Takaki A **S-Editor:** Gou SX
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ISSN 1007-9327



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