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**Psoriasis: Biologic treatment and liver disease**

Vilarrasa E *et al*. Psoriasis: Biologic treatment and liver disease

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**Abstract**

Patients with moderate or severe psoriasis have a high prevalence of chronic liver disease. Chronic liver disease in these patients is related to metabolic syndrome, alcohol abuse or viral infections. Therefore, treatment of these patients is challenging. Classic systemic treatments may be contraindicated because of their immunosuppressive and hepatotoxic potential. First-line therapy in this setting is generally ultraviolet B phototherapy combined with topical treatment, but its feasibility and efficacy are sometimes limited. The therapeutic options are further restricted by concomitant psoriatic arthritis. Biologic treatments have shown to be effective in psoriasis and psoriatic arthritis, and they are largely devoid of liver toxicity. Anti-tumor necrosis factor-alpha (TNF-α) treatments have proven to be effective and safe in patients with chronic hepatitis C virus (HCV) infections and other non-infectious chronic liver disorders, including alcoholic and non-alcoholic liver diseases. However, in chronic HBV, anti-TNF-α treatments carry a high risk of hepatitis B virus (HBV) reactivation. Anti-IL12/23 treatments are also effective in patients with psoriasis, but data regarding their safety in chronic hepatitis infections are still limited. Safety reports in patients with psoriasis and chronic HCV infection are contradictory, and in chronic HBV evidence indicate a high risk of viral reactivation. Moreover, concerns remain about the long-term safety of both TNF-α antagonists and ustekinumab. Non-viral liver diseases such as alcoholic and non-alcoholic liver diseases are more prevalent in patients with psoriasis than in the general population. TNF-α antagonists have also been prescribed in these patients. Although data are still scarce in this setting, results suggest a favorable profile in patients with psoriasis and non-alcoholic liver diseases. We review the literature regarding all these aspects.

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**Key words:** Psoriasis; Liver disease; Biologic; Anti-tumor necrosis factor-alpha; Ustekinumab; Chronic hepatitis C; Chronic hepatitis B; Alcoholic liver disease; Non-alcoholic fatty liver disease

**Core tip:** We review and summarize the published data regarding the efficacy and safety of anti- tumor necrosis factor-alpha and anti-IL12/23 therapies in patients with psoriasis and liver diseases, with special reference to hepatitis C, hepatitis B, non-alcoholic fatty liver disease, and fatty liver disease.

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**INTRODUCTION**

Treatment of moderate and severe psoriasis is challenging in patients with associated chronic liver diseases. Classic systemic treatments such as cyclosporine, methotrexate or acitretin may be contraindicated because of their immunosuppressive and hepatotoxic potential. Ultaviolet B (UVB) phototherapy combined with topicals is considered the first-line therapy in this setting but may not be feasible for many patients, and its efficacy is sometimes limited[1]. Furthermore, the presence of concomitant psoriatic arthritis further restricts the therapeutic options[2].

Biologic treatments have shown to be very effective and largely devoid of liver toxicity in patients with psoriasis and psoriatic arthritis, so they may provide a suitable therapeutic alternative in this particular background[3,4]. Anti-tumor necrosis factor- alpha (TNF-α) treatments may cause acute liver injury, generally related to drug-induced autoimmune hepatitis, but these alterations are usually mild or moderate and reversible with drug discontinuation[5].Nevertheless, biologic treatments are immunosuppressive agents, and some concerns exist about their use in patients with viral hepatitis.

Published data on rheumatoid arthritis, inflammatory bowel disease and psoriasis suggest that anti-TNF-α treatments are effective and safe in patients with chronic hepatitis C virus (HCV) infection[6-22].However, in chronic HBV infection, anti-TNF-α treatments carry a high risk of HBV reactivation[23-38].

Regarding anti-IL12/23 antagonists (ustekinumab), data are still scarce[39-47]. Reports in patients with psoriasis and chronic HCV infection are contradictory[4,39-41], and some evidence in chronic HBV infection suggests a significant risk of viral reactivation[42-47]. Moreover, the long term safety of both TNF-α antagonists and ustekinumab in these patients remains a cause of concern.

TNF-α antagonists have also been prescribed in patients with other chronic liver disorders, such as alcoholic and non-alcoholic liver diseases. These non-infectious liver diseases are more prevalent in patients with moderate and severe psoriasis than in the general population[48-50]. Available data, though still limited, suggests a favorable risk/benefit profile of TNF-α antagonists in patients with psoriasis and non-alcoholic liver diseases[49,50].

This review summarizes the published evidence regarding efficacy and safety of biologic therapies in patients with psoriasis and liver disorders. Special focus is made on chronic HCV and HBV hepatitis, and on alcoholic and non-alcoholic liver diseases due to their high prevalence in patients with psoriasis. Complications in the management of these patients are further compounded by the frequent coexistence of conditions such as metabolic syndrome, alcohol intake, HCV infection, or iron overload.

**VIRAL LIVER DISEASE (HEPATITIS)**

***Hepatitis C***

HCV infection, defined by a positive HCV viral load and detection of antibodies (anti-HCV),is the most common blood-borne infectious disease in the United States, with an estimated seroprevalence of 1.6%[1-3]. The estimated prevalence in Spain is also around 2%[1-3].Psoriasis does not appear to be associated with an increased risk of hepatitis B, hepatitis C, or HIV infection in the United States[51, 52], but the prevalence of HCV infection has been found to be higher in patients with psoriasis than in the general population in other geographical areas, such as Taiwan, Japan, Brazil, Central America and Italy[53-55].

**Hepatitis C and TNF-α antagonists:** TNF-α antagonists, namely infliximab, etanercept and adalimumab, have demonstrated their efficacy in the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease, among others, but their safety in the setting of chronic viral hepatitis is still a matter of debate.

Elevated TNF-α levels have been documented in patients with hepatitis C and are associated with a worse prognosis[56-60].Even though TNF-α appears to play a major role in immune defense against viral infections, in chronic HCV infection TNF-α is an inducer of apoptosis in infected hepatocytes and might also promote damage to adjacent non-infected hepatocytes by cytotoxic T lymphocytes[11].Moreover, serum TNF-α levels are significantly higher in patients with liver cirrhosis than in healthy volunteers, and they are positively associated with serum aminotransferase levels, inflammation, and fibrosis, even in patients with mild liver inflammation[56,57].There is also growing evidence that treatment resistance to interferon alfa-2b in chronic HCV infection may be related to the upregulation of inflammatory cytokines such as TNF-α[8,61,62]. Therefore, anti-TNF-α therapy may be beneficial when used in cases of chronic HCV infection[3,4,6-9,15-21,56].

In addition, standard treatments for chronic hepatitis C, such as interferon alfa and ribavirin, are associated with worsening of psoriasis and psoriatic arthritis, which can be attenuated by the administration of TNF-αblocking agents[1,3,62].

In a phase II randomized, double-blind, placebo-controlled study, Zein *et al*[51] compared the efficacy and safety of etanercept *vs* placebo in patients with chronic HCV infection who were receiving treatment with interferon alfa-2b and ribavirin. In these patients, adjuvant treatment with etanercept significantly improved the response to treatment. Clearance of HCV-RNA was achieved in 63% of patients treated with adjuvant etanercept, compared to 32% of placebo patients. The addition of etanercept was also associated with a decreased incidence of the most common adverse events associated to interferon and ribavirin treatment.

The published case series in a clinical setting also suggest that TNF-α blocking drugs such as etanercept, adalimumab and infliximab are a safe alternative for patients with rheumatic diseases or inflammatory bowel disease and concurrent hepatitis C[3,15-21].However, liver inflammation, necrosis and fibrosis can be observed in liver biopsies of some patients with normal serum liver enzymes[16].

Case series and single case reports have also been published on the safety and efficacy of biologic therapies in patients with concomitant hepatitis C and psoriasis[4,6-9].Most of these publications deal with TNF-α antagonists, the most commonly used being etanercept2-4,6-9].In some reports, etanercept has been prescribed simultaneously with interferon-α to prevent or ameliorate psoriasis flares[14,20].The efficacy of TNF-α blocking agents in psoriasis (and psoriatic arthritis) does not seem to be influenced by the presence of concurrent chronic hepatitis C infection[1-14].

Regarding safety, in most cases, hepatitis C infection has remained asymptomatic, with normal liver function and stable viral loads[1-14].In some cases, there were even decreases in the corresponding values[4].Despite this, in the retrospective multicentric study published by Navarro *et al*[4], two out of 20 patients receiving anti-TNF-α agents presented increases in viral loads that were not accompanied by significant rises in liver enzyme serum levels. Two other patients were diagnosed with hepatocellular carcinoma 9 and 12 mo after the start of etanercept. One of them had a 9-year history of chronic hepatitis C infection and the other one had preexistent cirrhosis related to alcoholism. Three other patients showed either increases in their liver fibrosis or cirrhosis, demonstrated by ultrasonography or Fibroscan. Two of them had a personal history of alcohol intake.

**Hepatitis C and IL-12/23 antagonist:** Ustekinumab is a human monoclonal antibody against p40, a subunit shared by IL-12 and IL-23. It is currently approved for the treatment of psoriasis and psoriatic arthritis.

In contrast with TNF-α antagonists, ustekinumab might theoretically carry a risk of HCV reactivation, since IL-12 has a major role in the immune control of virus replication and elimination[63-65]. Serum levels of IL-12 are higher in HCV chronically infected patients who achieve a normalization of liver enzymes and clearance of viremia at the end of interferon-α therapy than in those who do not[63].Likewise, in patients with chronic hepatitis C infection, ribavirin has been shown to upregulate the IL-12 receptor and induce Th1 polarization of T cells[64].Several studies have also suggested that recombinant human IL-12 is effective in suppressing hepatitis C virus RNA, but the effects are transient and the infection relapses when treatment is stopped[65-68].Furthermore, IL-12 has been shown to be of low efficacy and poorly tolerated when prescribed as monotherapy in patients who have failed prior treatment with interferon plus ribavirin[66,69].

Therefore, some controversy exists regarding the use of ustekinumab in patients with psoriasis and chronic HCV infection, and the efficacy and safety data on the use of ustekinumab in this clinical setting are limited. There is only 1 case report and 2 case series of patients with psoriasis and chronic hepatitis C treated with ustekinumab[4,39,40].The three patients with chronic hepatitis C receiving ustekinumab in the series of Navarro *et al*[4] achieved a 75% improvement in their Psoriasis Area Severity Index (PASI) scores, and their HCV infection remained asymptomatic, with maintenance of normal liver enzymes and stable viral loads.

The case reported by Abuchar *et al*[39] was also characterized by a good clinical response of psoriasis, with normal liver function and an undetectable viral load.

Nevertheless, in the four patients reported by Chiu *et al*[40] the outcomes were less rosy: even though none of them had significant increases in liver enzyme results, the HCV viral count increased in three of them during the course of treatment. One of these patients, who had liver cirrhosis, presented HCV reactivation and a recurrence of a previously removed hepatocellular carcinoma after 1 and 4 mo of ustekinumab treatment, respectively. Moreover, none of the four patients achieved a PASI 75 response during the course of treatment (mean duration, 8 mo).

***Hepatitis B***

HBV infection is a major global health problem. About 350 million of people are infected by HBV worldwide and at least one third of the world population has been exposed to the virus[69-73].

HBV infection is usually diagnosed when circulating hepatitis B surface antigen (HBsAg) is detected, but it can also be present in HBsAg-negative individuals, with or without circulating antibodies to HBsAg (anti-HBs) and/or to hepatitis B core antigen (anti-HBc)[52,74]. These individuals have an “occult” HBV infection, which can be detected by the persistence of viral DNA in the liver. The HBV DNA is sometimes detectable in the sera, but not always[70].

Once a patient has suffered an HBV infection, the HBV DNA becomes integrated in the hepatocyte nucleus forever. Regardless of serological markers, this patient is at risk of developing a reactivation during any immunosuppressive treatment. This risk is higher in HBsAg positive and in hepatitis B e antigen (HBeAg) positive patients. Even though the risk of reactivation in occult HBV infection is low, checking for HBV DNA and close monitoring are recommended[45].

A high prevalence of HBV infection has to be expected patients with psoriasis in endemic areas. Two studies from Taiwan have recently reported a higher prevalence of HBV infection in patients with psoriasis than in the general population[52,74].

**Hepatitis B and TNF-α antagonists:** TNF-α levels are also elevated in patients with chronic HBV infection, but in contrast to HCV infection, TNF-αplays a crucial role against replication of HBV, and promotes its clearance[75-77].Therefore, TNF-α blockade carries a risk of enhanced viral replication and disease reactivation in these patients[77].

There are several case reports regarding the use of TNF-α antagonists in HBV positive patients suffering from either rheumatologic diseases or inflammatory bowel diseases[23-31],and several cases of reactivation or exacerbation of HBV infection have been reported[23-25,28,29,31-33].

In a comprehensive review, Pérez-Alvarez *et al*[4,31] collected 35 cases of HBV reactivation among 257 patients with diverse autoinflammatory diseases who received anti-TNF-α treatments.As has been previously described with other immunosuppressive treatments, the risk of developing liver damage or reactivation of HBV while receiving anti-TNF-α therapy is higher in HBsAg positive carriers than in HBsAg negative patients (with or without positive anti-HBc). These patients are at risk of acute liver failure and death, especially in HBeAg positive patients[30,31].

Infliximab accounts for the majority of cases of HBV reactivation and fulminant hepatitis[23-32], but cases in association with etanercept have also been reported[29,31].This is probably due to the differences in the two molecules and their mechanism of action: infliximab is a monoclonal antibody that neutralizes soluble and membrane-bound TNF-α, while etanercept is a fusion protein that can only bind soluble TNF-α.

Lamivudine has been successfully used to prevent HBV reactivation in patients with chronic HBV infection who are receiving anti-TNF-α treatments[7,35],but its long-term use may result in the appearance of resistance[3].

Similar outcomes have been published regarding the use of anti-TNF-α agents for the treatment of psoriasis and psoriatic arthritis in HBV carriers, either HBsAg positive or HBsAg negative patients (occult carriers)[4,12,33-38]. The available evidence originates from retrospective analysis of single case reports and large case series[4,12,33-38].

The efficacy of TNF-α antagonists in patients with psoriasis does not seem to be influenced by HBV status, and clinical outcomes are similar to those of patients without HBV infection[3,4,12,33-38].

Safety concerns demand a close follow-up of liver enzymes serum levels and viral load, since cases of HBV reactivation have been reported, even in HBsAg negative patients[30-36]. Furthermore, most authors and guidelines recommend antiviral treatment with nucleoside/nucleotide analogues, such as lamivudine, for prevention of HBV reactivation in all HBsAg positive patients (with or without active viral replication) during TNF-α therapy. HBV prophylaxis should be initiated 1 to 3 wk before starting the immunosuppressive therapy and must be prolonged until 3 to 6 mo after discontinuing the biological therapy[3,33-36,78-82]. Nevertheless, resistance to lamivudine may develop with prolonged use in up to 30% of patients after 1 year and in up to 70% after 5 years of treatment[82]. Therefore, when chronic immunosuppressive treatment is required, nucleoside/nucleotide analogues with lower rates of resistance development than lamivudine are preferred, such as tenofovir and entecavir[24,83].

Despite the risks, some authors advocate prevention of HBV reactivation by monitoring HBV viral load, rather than routine anti-HBV prophylaxis therapy regardless of the HBV status (with the exception of HBeAg positive patients)[37,38].In the case series reported by Cho *et al*[37] two patients were inactive HBV carriers but five had chronic hepatitis B. HBV reactivation was observed in three patients, and one required antiviral treatment, but no cases of hepatitis were observed. These authors suggest that monitoring viral load is a cost-effective measure that may prevent the development of drug resistance, especially in endemic areas.

The results of Cassano *et al*[38] also suggest that the use of TNF-α antagonists may be generally safe without simultaneous antiviral treatment in patients with psoriasis who are occult HBV carriers. However, they recommend close monitoring of virological markers to detect viral reactivation at an early stage.

**Hepatitis B and anti-IL12/23:** As in HCV infection, IL-12 plays a crucial role in the control and suppression of HBV[65],and this cytokine has proven to be critical for clearance of HBV[82-85].Pre-clinical data suggest that it inhibits HBV replication by stimulating the production of interferon-gamma[82].Moreover, the production of active IL-12 and Th1 cytokines increases in some patients when HBV infection is cleared and they become anti-HBe positive[83].

Several studies have demonstrated the efficacy of recombinant human IL-12 in the treatment of patients with chronic hepatitis B[65,84,85].In 15 patients with HBeAg-positive chronic hepatitis B who received recombinant human IL-12 with lamivudine, the combination resulted in an enhanced and prolonged suppression of HBV replication in comparison with lamivudine alone[84,85]. But IL-12 did not eradicate HBV replication, and the response did not persist when administered alone[84,85].

IL-23 promotes the differentiation of naive T cells to Th17. Th17 cells stimulate the differentiation of B cells, activating the humoral immune response. Thus, IL-23 blockade may also impair the humoral response to HBV[43,86,87].

The use of ustekinumab in chronic HBV infection is therefore controversial, and clinical experience is still limited. At the moment of writing, only 2 case series and 3 case reports have been published.

Opel *et al*[42] reported the first known cases of acute HBV infection in two patients with psoriasis treated with ustekinumab, during phase III (PHOENIX 1) and phase IV (TRANSIT) studies. Both patients were diagnosed with acute HBV infection during the course of treatment with ustekinumab. One of them was a confirmed case of primary infection, while in the other patient potential reactivation of a preexisting infection could not be absolutely excluded. The administration of ustekinumab was interrupted, and the infection did not require active treatment and was self-limited in both cases. None of the patients progressed to chronic infection. The authors suggest that ustekinumab had no impact on the immune response to acute hepatitis B.

The case series from Navarro *et al*[4] included a patient with chronic HBV infection and severe psoriasis who was treated with ustekinumab for 7 mo. Clinical results were good, the viral load was undetectable, and serum levels of transaminases were normal. This patient was receiving simultaneous antiviral therapy with entecavir.

Koskinas *et al*[43] reported the case of a patient with psoriasis who was HBsAg negative, anti-HBs positive and anti-HBc positive, and who developed HBV reactivation 16 mo after the initiation of ustekinumab treatment. The patient was asymptomatic throughout the whole process. The only sign of reactivation was a moderate increase in alanine transaminase (ALT) levels. Tenofovir was initiated while ustekinumab was continued.

Finally, the study of Chiu *et al*[40] included 14 patients with psoriasis and HBV infection who were treated with ustekinumab. Eleven patients were positive for HBsAg and 3 were HBsAg negative and anti-HBc positive. Two of the seven HBsAg positive patients who did not receive simultaneous antiviral treatment showed HBV reactivations, all of which were classified as very mild. Both had increases in their viral counts but neither of them presented elevation of transaminases. No cases of reactivation were reported among the occult HBV infected patients. The authors suggested that antiviral prophylaxis may minimize the risk of HBV reactivation and that serum levels of liver enzymes may not be good predictors of this reactivation[40].

**NON-VIRAL LIVER DISORDERS**

Alcoholic and non-alcoholic liver diseasesare common causes of liver disease in patients with psoriasis[88-100].Alcoholic liver disease is related to alcohol intake, while non-alcoholic (fatty) liver disease is associated with metabolic syndrome, a frequent comorbidity of psoriasis[88-97].

***Non-alcoholic fatty liver disease***

Fatty liver (simple steatosis), non-alcoholic steatohepatitis (NASH) and fatty cirrhosis are included within the anatomo-clinical spectrum of non-alcoholic fatty liver disease (NAFLD). These liver diseases have shown to be more prevalent in patients with moderate to severe psoriasis, and are likely to be associated with metabolic syndrome and chronic inflammation[48,92,95,96].

NAFLD is the most common cause of increased serum levels of transaminases and the most prevalent form of liver disease in developed countries, affecting approximately one third of the population[95].While individuals with simple steatosis have a low risk of developing terminal liver disease, those with steatohepatitis have a 37% risk of progression to fibrosis in 3.2 years when high body mass index (BMI) and diabetes are also present, and a lower life expectancy than the general population[95,96].

Treatment of fatty liver disease is based on avoidance of alcohol and hepatotoxic drugs and weight loss targeted to normalize BMI[88-92].It has been observed that a certain degree of persistent inflammation, with secretion of pro-inflammatory cytokines such as TNF-α and interleukins (IL-12 and IL-23, among others), favours the development of insulin resistance and metabolic syndrome in patients with psoriasis[48,49].Likewise, elevated serum levels of TNF-α have been associated with hepatic steatosis[93], giving support to the observation that inhibition of TNF-α or IL-12/IL-23 may be helpful in both psoriasis and fatty liver disease[93-96].

In a recent study, Campanati *et al*[50] compared the effect of etanercept versus PUVA on non-alcoholic fatty liver disease and metabolic syndrome in patients with psoriasis. These authors observed significant reductions in aspartate transaminase/alanine transaminase ratios, fasting insulin serum levels, C-reactive protein serum levels and homeostasis model assessment index in patients receiving etanercept, after 24 wk of treatment. These changes were not detected in patients treated with PUVA therapy. They therefore conclude that etanercept can be more efficacious than PUVA therapy to reduce the risk of hepatic fibrosis in patients with NAFLD and psoriasis[50].

Nevertheless, despite the fact that anti-TNF-α treatments can improve fatty liver disease by improving insulin resistance and decreasing systemic inflammation, they can also lead to weight gain and increased BMI in patients with psoriasis[48,49].Therefore, the cornerstone of treatment for fatty liver disease is still weight loss and control of metabolic syndrome risk factors-such as hypertriglyceridemia and hyperglycemia- and systemic inflammation itself.

***Alcoholic liver disease***

The major cause of chronic liver disease in Western countries is excessive alcohol consumption[102].High alcohol consumption is well recognized among patients with psoriasis and has been related to psychological distress[100].Using different measures of alcohol consumption, approximately one third of patients with psoriasis can be classified as having difficulties with alcohol, while 13% and 18% of patients with psoriasis believe that they have a current or past drinking problem, respectively[97-99].

Several studies have investigated the relationship between high alcohol intake and the risk of developing psoriasis. Although alcohol was found to be a risk factor for psoriasis in four out of five studies, there is insufficient evidence to conclude that alcohol consumption is an independent risk factor for psoriasis[100].

Alcoholic fatty liver is an early and reversible consequence of excessive alcohol consumption (> 280 g/wk in men, and > 168 g/wk in women)[101].

Like non-alcoholic fatty liver disease, alcohol-induced liver disease can be classified into 3 groups: alcoholic fatty liver (simple steatosis), alcoholic hepatitis, and alcohol-related cirrhosis. Although fatty liver alone is considered non-progressive and reversible upon cessation of alcohol consumption, patients with alcoholic hepatitis can progress to fibrosis, cirrhosis, and hepatocellular carcinoma in up to 30% of heavy drinkers[102].

Histologically, alcohol-induced hepatitis is similar to NASH (presence of macrovesicular steatosis), but the injury in the former is mainly attributed to a direct toxic effect of alcohol on hepatocytes[101,103].Alcohol produces this direct damage to hepatocytes by oxidative stress and toxic effect of its metabolites, but dysregulation of innate immunity also plays an important role in the pathogenesis of ALD[99,104].Alcohol consumption has been reported to cause activation of the complement system and interact with the Kupffer cells, leading to TNF-α production, which induces hepatocyte damage[102].These mechanisms of liver injury are similar to those observed in fatty liver disease[105].

Moreover, in patients with alcoholic hepatitis, TNF-α levels are higher than in heavy drinkers without liver disease and healthy controls, and these high levels seem to correlate with mortality[106].

Considering the important role of TNF-α in the pathogenesis of ALD, several clinical studies have addressed the potential therapeutic effects of infliximab or etanercept on alcoholic hepatitis[107-109].Anti-TNF-α agents were administered to these patients to improve the outcome of alcoholic hepatitis regardless of whether or not they had concomitant psoriasis (or other conditions responsive to TNF-α blockade). Preliminary studies in patients with alcoholic hepatitis had positive results in terms of survival and safety[107],but increased mortality and risk of infection were associated with these drugs in later-stage clinical trials[108,109].Therefore, anti-TNF-α treatments are not recommended for the treatment of alcoholic hepatitis[108,109].Hence, the mainstay of treatment for alcoholic hepatitis is alcohol abstinence, nutritional support, and corticosteroids when required[102-105].Weight loss and control of the risk factors of metabolic syndrome, such as hypertriglyceridemia and hyperglycemia, can also be helpful if present.

**CONCLUSION**

***Hepatitis C***

Large placebo-controlled trials are needed before clear conclusions can be reached, but TNF-α antagonists appear to be effective and safe in patients with psoriasis and concurrent chronic HCV infection[3-22]. Nevertheless, these patients require close follow up due to their inherent risk of developing cirrhosis or hepatocellular carcinoma, especially in those with longstanding chronic hepatitis[2].In addition, it is important to point out that liver enzyme tests may not sufficiently reliable as predictors of active liver disease, because cases of inflammation and fibrosis have been observed in liver biopsies despite persistently normal alanine transaminase values[16]. Non-invasive explorations such as transient elastography or serological markers of liver fibrosis may therefore be useful to predict structural liver damage and to reduce the need for liver biopsies in these patients[110].

Regarding ustekinumab, its use in the setting of HCV chronic infection is controversial. Cautious use of ustekinumab in patients with psoriasis and chronic hepatitis C is to be recommended, taking into account the role of IL-12 in host defense against HCV infection[62-64].Moreover, the published clinical data are scarce, based only on a few cases, and their results are contradictory[4,39-41].

***Hepatitis B***

Patients with chronic HBV infection are at high risk of developing HBV reactivation during anti-TNF-α treatments[3,32-36].The risk appears to be higher in patients who are HBsAg positive and especially in those who are HBeAg positive[3,30-38].Among the TNF-α antagonists, infliximab apparently carries a higher risk than etanercept[3].Antiviral prophylaxis appears to minimize the risk of viral reactivation in patients with chronic HBV undergoing anti-TNF-α treatments, but it increases the risk of antiviral resistance[3,31].In patients with a low risk of HBV reactivation, such as occult HBV carriers, some authors recommend monitoring the HBV viral load in order to detect viral reactivation early, thus avoiding the need for prophylactic antiviral treatment[37,38]. This approach may prevent the appearance of drug resistance, particularly in endemic areas[37,38].

Since IL-12 and IL-23 appear to play an important role in the control of HBV replication, patients with HBV chronic infection and psoriasis who receive ustekinumab might be placed at high risk of developing HBV reactivation[4,42-45].Even though all the reported cases of reactivation have been considered mild, caution is advised when considering prescription of ustekinumab in patients with HBV infection, and the risk/benefit ratio should be carefully assessed in every case[42-45].In these patients, antiviral prophylaxis may reduce the risk of viral reactivation[4,43,44].Close monitoring of the HBV viral load is also recommended, particularly for patients with high-risk factors, since determination of serum aminotransferase levels may not be useful for early detection of viral reactivation[44].Nevertheless, as the data regarding efficacy and safety of ustekinumab in this setting are still scarce, no definitive conclusions can be made.

***Non-viral liver diseases***

TNF-α plays an important role in the maintenance and progression of liver injury both in alcoholic and non-alcoholic fatty liver disorders[101,102].

In patients with non-alcoholic fatty liver disease and psoriasis, TNF-α antagonists seem to have a positive effect on the inflammation that predisposes to metabolic syndrome and fatty liver progression[48,50].Nonetheless, available data are still limited and treatment should be focused on controlling BMI and other risk factors for fatty liver progression, such as hyperglycemia and alcohol intake[48,49].

Regarding alcoholic liver disease, studies with anti-TNF-α therapies have failed to demonstrate a benefit in patients with moderate or severe alcoholic hepatitis[97,102,105,106].Both infliximab and etanercept carry an increased risk of infections and even mortality in these patients[97,102,105,106].However, the efficacy and safety of TNF-α antagonists in patients with psoriasis and milder forms of alcoholic liver disease have not yet been studied. Nevertheless, the mainstay of treatment for any stage of alcoholic liver disease is alcoholic abstinence[97,102,105,106].

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