World Journal of Dermatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5314/wjd.v3.i4.76

World J Dermatol 2014 November 2; 3(4): 76-85
ISSN 2218-6190 (online)

REVIEW

Psoriasis: Biologic treatment and liver disease

Eva Vilarrasa, Luis Puig

Eva Vilarrasa, Luis Puig, Psoriasis Unit, Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, 08025 Barcelona, Spain
Author contributions: All authors contributed to this paper; Vilarrasa E designed and wrote the paper; Puig L reviewed the manuscript.
Correspondence to: Eva Vilarrasa, MD, Physician Staff, Psoriasis Unit, Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, C/ Sant Antoni Maria Claret 167, 08025 Barcelona, Spain. evilarrasa@santpau.cat
Telephone: +34-93-5537007 Fax: +34-93-5537008
Received: December 29, 2013 Revised: August 28, 2014
Accepted: September 16, 2014
Published online: November 2, 2014

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 hepatitis B virus (HBV), anti-TNF-α treatments carry a high risk of HBV reactivation. Anti-interleukin-12/23 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 potential 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.

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-interleukin-12/23 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. Data collected and revised up to December 2013.

Vilarrasa E, Puig L. Psoriasis: Biologic treatment and liver disease. *World J Dermatol* 2014; 3(4): 76-85 Available from: URL: http://www.wjgnet.com/2218-6190/full/v3/i4/76.htm DOI: http://dx.doi.org/10.5314/wjd.v3.i4.76

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. Ultraviolet B 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 hepatitis B virus (HBV) infection, anti-TNF-α treatments carry a high risk of HBV reactivation[23-38].

Regarding anti-interleukin (IL)-12/23 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 potential 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 human immunodeficiency virus 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 up-regulation 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-α blocking agents[1,3,62].

In a phase Ⅱ randomized, double-blind, placebo-controlled study, Zein *et al*[56] 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 etanercept[2-4,6-9]. 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 psoria-

sis (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 HCV-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 in 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-α plays 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, Navarro *et al*[4] and Pérez-Alvarez *et al*[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-IL-12/23: 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 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 diseases are 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 ILs (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 *vs* 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 psoralen and UVA light (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[101]. 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)[102].

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[101].

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[102,103]. 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 alcoholic liver disease[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[101]. 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]. Anyway, 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 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[97,101,105,106]. Both infliximab and etanercept carry an increased risk of infections and even mortality in these patients[97,101,105,106]. 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].

REFERENCES

1 **Frankel AJ**, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF, Gottlieb AB; National Psoriasis Foundation. Treatment of psoriasis in patients with hepatitis C: from the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol* 2009; **61**: 1044-1055 [PMID: 19811848 DOI: 10.1016/j.jaad.2009.03.044]

2 **Alter MJ**. Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 2007; **13**: 2436-2441 [PMID: 17552026]
3 **Domm S**, Cinatl J, Mrowietz U. The impact of treatment with tumour necrosis factor-alpha antagonists on the course of chronic viral infections: a review of the literature. *Br J Dermatol* 2008; **159**: 1217-1228 [PMID: 18945310 DOI: 10.1111/j.1365-2133.2008.08851.x]
4 **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]
5 **Efe C**. Drug induced autoimmune hepatitis and TNF-α blocking agents: is there a real relationship? *Autoimmun Rev* 2013; **12**: 337-339 [PMID: 22841985 DOI: 10.1016/j.autrev.2012.03.010]
6 **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]
7 **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]
8 **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]
9 **Cecchi R**, Bartoli L. Psoriasis and hepatitis C treated with anti-TNF alpha therapy (etanercept). *Dermatol Online J* 2006; **12**: 4 [PMID: 17459290]
10 **Gisondi P**, Prignano F, Grossi P, Lotti T, Girolomoni G. Treatment of psoriasis with efalizumab in patients with hepatitis C viral infection: report of five cases. *Dermatology* 2009; **219**: 158-161 [PMID: 19506351 DOI: 10.1159/000224433]
11 **Prignano F**, Zanieri F, Milani S, Lotti T. Switch from etanercept to efalizumab in a psoriatic patient with HCV infection: a case report. *Dermatol Ther* 2009; **22**: 386-390 [PMID: 19580583 DOI: 10.1111/j.1529-8019.2009.01251.x]
12 **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]
13 **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]
14 **Behnam SE**, Hindiyeh R, Fife DJ, Jeffes EW, Wu JJ. Etanercept as prophylactic psoriatic therapy before interferon-alpha 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]
15 **Peterson JR**, Hsu FC, Simkin PA, Wener MH. Effect of tumour necrosis factor alpha 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]
16 **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]
17 **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]
18 **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]
19 **Aslanidis S**, Vassiliadis T, Pyrpasopoulou A, Douloumpakas I, Zamboulis C. Inhibition of TNFalpha does not induce viral reactivation in patients with chronic hepatitis C infection: two cases. *Clin Rheumatol* 2007; **26**: 261-264 [PMID: 16924392 DOI: 10.1007/s10067-006-0394-z]
20 **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]
21 **Khanna M**, Shirodkar MA, Gottlieb AB. Etanercept therapy in patients with autoimmunity and hepatitis C. *J Dermatolog Treat* 2003; **14**: 229-232 [PMID: 14660270 DOI: 10.1080/09546630310020470]
22 **Di Lernia V**. Treatment of psoriasis in patients with hepatitis C virus infection. *Clin Exp Dermatol* 2011; **36**: 417 [PMID: 21070334 DOI: 10.1111/j.1365-2230.2010.03951.x]
23 **Esteve M**, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004; **53**: 1363-1365 [PMID: 15306601 DOI: 10.1136/gut.2004.040675]
24 **Ostuni P**, Botsios C, Punzi L, Sfriso P, Todesco S. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. *Ann Rheum Dis* 2003; **62**: 686-687 [PMID: 12810441 DOI: 10.1136/ard.62.7.686]
25 **Michel M**, Duvoux C, Hezode C, Cherqui D. Fulminant hepatitis after infliximab in a patient with hepatitis B virus treated for an adult onset still's disease. *J Rheumatol* 2003; **30**: 1624-1625 [PMID: 12858469]
26 **Lee YH**, Bae SC, Song GG. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. *Int J Rheum Dis* 2013; **16**: 527-531 [PMID: 24164839 DOI: 10.1111/1756-185X.12154]
27 **Anelli MG**, Torres DD, Manno C, Scioscia C, Iannone F, Covelli M, Schena FP, Lapadula G. Improvement of renal function and disappearance of hepatitis B virus DNA in a patient with rheumatoid arthritis and renal amyloidosis following treatment with infliximab. *Arthritis Rheum* 2005; **52**: 2519-2520 [PMID: 16052569 DOI: 10.1002/art.21216]
28 **Millonig G**, Kern M, Ludwiczek O, Nachbaur K, Vogel W. Subfulminant hepatitis B after infliximab in Crohn's disease: need for HBV-screening? *World J Gastroenterol* 2006; **12**: 974-976 [PMID: 16521231]
29 **Montiel PM**, Solis JA, Chirinos JA, a Casis B, Sánchez F, Rodríguez S. Hepatitis B virus reactivation during therapy with etanercept in an HBsAg-negative and anti-HBs-positive patient. *Liver Int* 2008; **28**: 718-720 [PMID: 18433400 DOI: 10.1111/j.1478-3231.2007.01665.x]
30 **Carroll MB**, Bond MI. Use of tumor necrosis factor-alpha inhibitors in patients with chronic hepatitis B infection. *Semin Arthritis Rheum* 2008; **38**: 208-217 [PMID: 18221983 DOI: 10.1016/j.semarthrit.2007.10.011]
31 **Pérez-Alvarez R**, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, Retamozo S, Bové A, Bosch X, Sanchez-Tapias JM, Forns X, Ramos-Casals M. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. *Medicine* (Baltimore) 2011; **90**: 359-371 [PMID: 22033451 DOI: 10.1097/MD.0b013e3182380a76]
32 **Núñez-Rodríguez MH**, Santamaría-Martínez A, Mata-Román L, Caro-Patón A. [Reactivation of hepatitis B treated with adefovir after infliximab administration]. *Med Clin* (Barc) 2006; **126**: 558-559 [PMID: 16756915 DOI: 10.1157/13087150]

33 **Fotiadou C**, Lazaridou E, Ioannides D. Safety of anti-tumour necrosis factor-α agents in psoriasis patients who were chronic hepatitis B carriers: a retrospective report of seven patients and brief review of the literature. *J Eur Acad Dermatol Venereol* 2011; **25**: 471-474 [PMID: 20561122 DOI: 10.1111/j.1468-3083.2010.03754.x]

34 **Bordas X**, Martín-Sala S. [Etanercept and chronic infection by HCV and HBV]. *Actas Dermosifiliogr* 2010; **101** Suppl 1: 82-87 [PMID: 20492886 DOI: 10.1016/S0001-7310(10)70014-4]

35 **Navarro R**, Ibañes S, Llamas M, Sotomayor E, García-Martín P, Daudén E. Awareness about possible reactivation of HBsAg-negative patients when prescribing biological therapy. *J Eur Acad Dermatol Venereol* 2011; **25**: 1232-1233 [PMID: 20726937 DOI: 10.1111/j.1468-3083.2010.03833.x]

36 **Abramson A**, Menter A, Perrillo R. Psoriasis, hepatitis B, and the tumor necrosis factor-alpha inhibitory agents: a review and recommendations for management. *J Am Acad Dermatol* 2012; **67**: 1349-1361 [PMID: 22727462 DOI: 10.1016/j.jaad.2012.04.036]

37 **Cho YT**, Chen CH, Chiu HY, Tsai TF. Use of anti-tumor necrosis factor-α therapy in hepatitis B virus carriers with psoriasis or psoriatic arthritis: a case series in Taiwan. *J Dermatol* 2012; **39**: 269-273 [PMID: 22077677 DOI: 10.1111/j.1346-8138.2011.01434.x]

38 **Cassano N**, Mastrandrea V, Principi M, Loconsole F, De Tullio N, Di Leo A, Vena GA. Anti-tumor necrosis factor treatment in occult hepatitis B virus infection: a retrospective analysis of 62 patients with psoriatic disease. *J Biol Regul Homeost Agents* 2011; **25**: 285-289 [PMID: 21880218]

39 **Abuchar A**, Vitiello M, Kerdel FA. Psoriasis treated with ustekinumab in a patient with hepatitis C. *Int J Dermatol* 2013; **52**: 381-382 [PMID: 23414168 DOI: 10.1111/j.1365-4632.2011.04876.x]

40 **Chiu HY**, Chen CH, Wu MS, Cheng YP, Tsai TF. The safety profile of ustekinumab in the treatment of patients with psoriasis and concurrent hepatitis B or C. *Br J Dermatol* 2013; **169**: 1295-1303 [PMID: 23746170 DOI: 10.1111/bjd.12461]

41 **Warren RB**, Al-Rifai A. Treatment of severe psoriasis with biological therapies in patients with viral hepatitis B and C. *Br J Dermatol* 2013; **168**: 461-462 [PMID: 23445306 DOI: 10.1111/bjd.12227]

42 **Opel D**, Economidi A, Chan D, Wasfi Y, Mistry S, Vergou T, Antoniou C, Sofen H. Two cases of hepatitis B in patients with moderate to severe psoriasis with ustekinumab. *J Drugs Dermatol* 2012; **11**: 1498-1501 [PMID: 23377523]

43 **Koskinas J**, Tampaki M, Doumba PP, Rallis E. Hepatitis B virus reactivation during therapy with ustekinumab for psoriasis in a hepatitis B surface-antigen-negative anti-HBs-positive patient. *Br J Dermatol* 2013; **168**: 679-680 [PMID: 23121260 DOI: 10.1111/bjd.12120]

44 **Purnak S**, Purnak T. Hepatitis B virus reactivation after ustekinumab treatment. *Br J Dermatol* 2014; **170**: 477-478 [PMID: 24032639 DOI: 10.1111/bjd.12612]

45 **Tsai TF**. Hepatitis B virus reactivation after ustekinumab treatment: reply from authors. *Br J Dermatol* 2014; **170**: 478-479 [PMID: 24028547 DOI: 10.1111/bjd.12613]

46 **Motaparthi K**, Stanisic V, Van Voorhees AS, Lebwohl MG, Hsu S. From the Medical Board of the National Psoriasis Foundation: Recommendations for screening for hepatitis B infection prior to initiating anti-tumor necrosis factor-alfa inhibitors or other immunosuppressive agents in patients with psoriasis. *J Am Acad Dermatol* 2014; **70**: 178-186 [PMID: 24220724 DOI: 10.1016/j.jaad.2013.08.049]

47 **Ohtsuki M**, Terui T, Ozawa A, Morita A, Sano S, Takahashi H, Komine M, Etoh T, Igarashi A, Torii H, Asahina A, Nemoto O, Nakagawa H. Japanese guidance for use of biologics for psoriasis (the 2013 version). *J Dermatol* 2013; **40**: 683-695 [PMID: 24033880 DOI: 10.1111/1346-8138.12239]

48 **Reich K**. The concept of psoriasis as a systemic inflammation: implications for disease management. *J Eur Acad Dermatol Venereol* 2012; **26** Suppl 2: 3-11 [PMID: 22356630 DOI: 10.1111/j.1468-3083.2011.04410.x]

49 **Channual J**, Wu JJ, Dann FJ. Effects of tumor necrosis factor-alpha blockade on metabolic syndrome components in psoriasis and psoriatic arthritis and additional lessons learned from rheumatoid arthritis. *Dermatol Ther* 2009; **22**: 61-73 [PMID: 19222518 DOI: 10.1111/j.1529-8019.2008.01217.x]

50 **Campanati A**, Ganzetti G, Di Sario A, Damiani A, Sandroni L, Rosa L, Benedetti A, Offidani A. The effect of etanercept on hepatic fibrosis risk in patients with non-alcoholic fatty liver disease, metabolic syndrome, and psoriasis. *J Gastroenterol* 2013; **48**: 839-846 [PMID: 23065020 DOI: 10.1007/s00535-012-0678-9]

51 **Kanada KN**, Schupp CW, Armstrong AW. Association between psoriasis and viral infections in the United States: focusing on hepatitis B, hepatitis C and human immunodeficiency virus. *J Eur Acad Dermatol Venereol* 2013; **27**: 1312-1316 [PMID: 22564047]

52 **Tsai TF**, Wang TS, Hung ST, Tsai PI, Schenkel B, Zhang M, Tang CH. Epidemiology and comorbidities of psoriasis patients in a national database in Taiwan. *J Dermatol Sci* 2011; **63**: 40-46 [PMID: 21543188 DOI: 10.1016/j.jdermsci.2011.03.002]

53 **Imafuku S**, Naito R, Nakayama J. Possible association of hepatitis C virus infection with late-onset psoriasis: a hospital-based observational study. *J Dermatol* 2013; **40**: 813-818 [PMID: 23961783]

54 **Andrade DL**, de Oliveira Mde F, de Souza TF, Lima RA, Bomfim EA, Rêgo VR, Paraná R, Schinoni MI. [A study about hepatitis C virus infection in patients with psoriasis in a Brazilian reference center]. *Acta Gastroenterol Latinoam* 2012; **42**: 285-290 [PMID: 23383522]

55 **Brazzelli V**, Carugno A, Alborghetti A, Cananzi R, Sangiovanni L, Barbarini G, De Silvestri A, Borroni RG. Hepatitis C infection in Italian psoriatic patients: prevalence and correlation with patient age and psoriasis severity. *J Eur Acad Dermatol Venereol* 2012; **26**: 1581-1582 [PMID: 22142565]

56 **Zein NN**. 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]

57 **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]

58 **Fukuda R**, Ishimura N, Ishihara S, Chowdhury A, Morlyama N, Nogami C, Miyake T, Niigaki M, Tokuda A, Satoh S, Sakai S, Akagi S, Watanabe M, Fukumoto S. Intrahepatic expression of pro-inflammatory cytokine mRNAs and interferon efficacy in chronic hepatitis C. *Liver* 1996; **16**: 390-399 [PMID: 9021719 DOI: 10.1111/j.1600-0676.1996.tb00768.x]

59 **Zhu N**, Khoshnan A, Schneider R, Matsumoto M, Dennert G, Ware C, Lai MM. Hepatitis C virus core protein binds to the cytoplasmic domain of tumor necrosis factor (TNF) receptor 1 and enhances TNF-induced apoptosis. *J Virol* 1998; **72**: 3691-3697 [PMID: 9557650]

60 **Moura AS**, Carmo RA, Teixeira AL, Rocha MO. Soluble inflammatory markers as predictors of hepatocellular damage and therapeutic response in chronic hepatitis C. *Braz J Infect Dis* 2009; **13**: 375-382 [PMID: 20428640 DOI: 10.1590/S1413-86702009000500013]

61 **Moura AS**, Carmo RA, Teixeira AL, Leite VH, Rocha MO. Soluble inflammatory markers as predictors of liver histological changes in patients with chronic hepatitis C virus infection. *Eur J Clin Microbiol Infect Dis* 2010; **29**: 1153-1161 [PMID: 20559676 DOI: 10.1007/s10096-010-0981-4]

62 **Downs AM**, Dunnill MG. Exacerbation of psoriasis by inter-

feron-alpha therapy for hepatitis C. *Clin Exp Dermatol* 2000; **25**: 351-352 [PMID: 10971502 DOI: 10.1046/j.1365-2230.2000.00655-4.x]
63 **Quiroga JA**, Martín J, Navas S, Carreño V. Induction of interleukin-12 production in chronic hepatitis C virus infection correlates with the hepatocellular damage. *J Infect Dis* 1998; **178**: 247-251 [PMID: 9652448 DOI: 10.1086/517446]
64 **Shiina M**, Kobayashi K, Satoh H, Niitsuma H, Ueno Y, Shimosegawa T. Ribavirin upregulates interleukin-12 receptor and induces T cell differentiation towards type 1 in chronic hepatitis C. *J Gastroenterol Hepatol* 2004; **19**: 558-564 [PMID: 15086600 DOI: 10.1111/j.1440-1746.2003.03329.x]
65 **Zeuzem S**, Carreño V. Interleukin-12 in the treatment of chronic hepatitis B and C. *Antiviral Res* 2001; **52**: 181-188 [PMID: 11672828 DOI: 10.1016/S0166-3542(01)00183-8]
66 **Teuber G**, Rossol S, Lee JH, Dietrich CF, Zeuzem S. TH1/TH2 serum cytokine profiles and soluble TNF-receptor response in patients with chronic hepatitis C during recombinant human interleukin-12 (rHuIL-12) treatment. *Z Gastroenterol* 2002; **40**: 487-495 [PMID: 12122596 DOI: 10.1055/s-2002-32804]
67 **O'Brien CB**, Moonka DK, Henzel BS, Caufield M, DeBruin MF. A pilot trial of recombinant interleukin-12 in patients with chronic hepatitis C who previously failed treatment with interferon-alpha. *Am J Gastroenterol* 2001; **96**: 2473-2479 [PMID: 11513193]
68 **Pockros PJ**, Patel K, O'Brien C, Tong M, Smith C, Rustgi V, Carithers RL, McHutchison JG, Olek E, Debruin MF. A multicenter study of recombinant human interleukin 12 for the treatment of chronic hepatitis C virus infection in patients nonresponsive to previous therapy. *Hepatology* 2003; **37**: 1368-1374 [PMID: 12774016 DOI: 10.1053/jhep.2003.50242]
69 **Lee WM**. Hepatitis B virus infection. *N Engl J Med* 1997; **337**: 1733-1745 [PMID: 9392700 DOI: 10.1056/NEJM199712113372406]
70 **Lavanchy D**. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004; **11**: 97-107 [PMID: 14996343 DOI: 10.1046/j.1365-2893.2003.00487.x]
71 **Thiers V**, Nakajima E, Kremsdorf D, Mack D, Schellekens H, Driss F, Goudeau A, Wands J, Sninsky J, Tiollais P. Transmission of hepatitis B from hepatitis-B-seronegative subjects. *Lancet* 1988; **2**: 1273-1276 [PMID: 2904005 DOI: 10.1016/S0140-6736(88)92891-7]
72 **Wang JT**, Wang TH, Sheu JC, Shih LN, Lin JT, Chen DS. Detection of hepatitis B virus DNA by polymerase chain reaction in plasma of volunteer blood donors negative for hepatitis B surface antigen. *J Infect Dis* 1991; **163**: 397-399 [PMID: 1988524 DOI: 10.1093/infdis/163.2.397]
73 **de la Fuente RA**, Gutiérrez ML, Garcia-Samaniego J, Fernández-Rodriguez C, Lledó JL, Castellano G. Pathogenesis of occult chronic hepatitis B virus infection. *World J Gastroenterol* 2011; **17**: 1543-1548 [PMID: 21472118 DOI: 10.3748/wjg.v17.i12.1543]
74 **Yang YW**, Keller JJ, Lin HC. Medical comorbidity associated with psoriasis in adults: a population-based study. *Br J Dermatol* 2011; **165**: 1037-1043 [PMID: 21711339 DOI: 10.1111/j.1365-2133.2011.10494.x]
75 **Schlaak JF**, Tully G, Löhr HF, Gerken G, Meyer zum Büschenfelde KH. HBV-specific immune defect in chronic hepatitis B (CHB) is correlated with a dysregulation of pro- and anti-inflammatory cytokines. *Clin Exp Immunol* 1999; **115**: 508-514 [PMID: 10193426 DOI: 10.1046/j.1365-2249.1999.00812.x]
76 **Guidotti LG**, Chisari FV. Noncytolytic control of viral infections by the innate and adaptive immune response. *Annu Rev Immunol* 2001; **19**: 65-91 [PMID: 11244031 DOI: 10.1146/annurev.immunol.19.1.65]
77 **Herbein G**, O'Brien WA. Tumor necrosis factor (TNF)-alpha and TNF receptors in viral pathogenesis. *Proc Soc Exp Biol Med* 2000; **223**: 241-257 [PMID: 10719836 DOI: 10.1046/j.1525-1373.2000.22335.x]
78 **Lok AS**, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]
79 **Hatzakis A**, Wait S, Bruix J, Buti M, Carballo M, Cavaleri M, Colombo M, Delarocque-Astagneau E, Dusheiko G, Esmat G, Esteban R, Goldberg D, Gore C, Lok AS, Manns M, Marcellin P, Papatheodoridis G, Peterle A, Prati D, Piorkowsky N, Rizzetto M, Roudot-Thoraval F, Soriano V, Thomas HC, Thursz M, Valla D, van Damme P, Veldhuijzen IK, Wedemeyer H, Wiessing L, Zanetti AR, Janssen HL. The state of hepatitis B and C in Europe: report from the hepatitis B and C summit conference*. *J Viral Hepat* 2011; **18** Suppl 1: 1-16 [PMID: 21824223 DOI: 10.1111/j.1365-2893.2011.01499.x]
80 **López-Serrano P**, Pérez-Calle JL, Sánchez-Tembleque MD. Hepatitis B and inflammatory bowel disease: role of antiviral prophylaxis. *World J Gastroenterol* 2013; **19**: 1342-1348 [PMID: 23538480 DOI: 10.3748/wjg.v19.i9.1342]
81 **Ayoub WS**, Keeffe EB. Review article: current antiviral therapy of chronic hepatitis B. *Aliment Pharmacol Ther* 2011; **34**: 1145-1158 [PMID: 21978243 DOI: 10.1111/j.1365-2036.2011.04869.x]
82 **Naoumov NV**, Rossol S. Studies of interleukin-12 in chronic hepatitis B virus infection. *J Viral Hepat* 1997; **4** Suppl 2: 87-91 [PMID: 9429215 DOI: 10.1111/j.1365-2893.1997.tb00185.x]
83 **Rossol S**, Marinos G, Carucci P, Singer MV, Williams R, Naoumov NV. Interleukin-12 induction of Th1 cytokines is important for viral clearance in chronic hepatitis B. *J Clin Invest* 1997; **99**: 3025-3033 [PMID: 9185527 DOI: 10.1172/JCI119498]
84 **Carreño V**, Zeuzem S, Hopf U, Marcellin P, Cooksley WG, Fevery J, Diago M, Reddy R, Peters M, Rittweger K, Rakhit A, Pardo M. A phase I/II study of recombinant human interleukin-12 in patients with chronic hepatitis B. *J Hepatol* 2000; **32**: 317-324 [PMID: 10707873 DOI: 10.1016/S0168-8278(00)80078-1]
85 **Rigopoulou EI**, Suri D, Chokshi S, Mullerova I, Rice S, Tedder RS, Williams R, Naoumov NV. Lamivudine plus interleukin-12 combination therapy in chronic hepatitis B: antiviral and immunological activity. *Hepatology* 2005; **42**: 1028-1036 [PMID: 16250037 DOI: 10.1002/hep.20888]
86 **Iwakura Y**, Ishigame H. The IL-23/IL-17 axis in inflammation. *J Clin Invest* 2006; **116**: 1218-1222 [PMID: 16670765 DOI: 10.1172/JCI28508]
87 **Mitsdoerffer M**, Lee Y, Jäger A, Kim HJ, Korn T, Kolls JK, Cantor H, Bettelli E, Kuchroo VK. Proinflammatory T helper type 17 cells are effective B-cell helpers. *Proc Natl Acad Sci USA* 2010; **107**: 14292-14297 [PMID: 20660725 DOI: 10.1073/pnas.1009234107]
88 **Bordignon M**, Viel G, Peserico A, Alaibac M. Non-alcoholic fatty liver disease, alcohol intake and psoriasis. *J Hepatol* 2010; **53**: 587 [PMID: 20561701 DOI: 10.1016/j.jhep.2010.04.012]
89 **Gisondi P**, Del Giglio M, Cozzi A, Girolomoni G. Psoriasis, the liver, and the gastrointestinal tract. *Dermatol Ther* 2010; **23**: 155-159 [PMID: 20415823 DOI: 10.1111/j.1529-8019.2010.01310.x]
90 **Miele L**, Vallone S, Cefalo C, La Torre G, Di Stasi C, Vecchio FM, D'Agostino M, Gabrieli ML, Vero V, Biolato M, Pompili M, Gasbarrini G, Rapaccini G, Amerio P, De Simone C, Grieco A. Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. *J Hepatol* 2009; **51**: 778-786 [PMID: 19664838 DOI: 10.1016/j.jhep.2009.06.008]
91 **Wenk KS**, Arrington KC, Ehrlich A. Psoriasis and non-alcoholic fatty liver disease. *J Eur Acad Dermatol Venereol* 2011; **25**: 383-391 [PMID: 20840346 DOI: 10.1111/j.1468-3083.2010.03841.x]
92 **Rivera R**, Vanaclocha F. [Nonalcoholic fatty liver disease and psoriasis]. *Actas Dermosifiliogr* 2010; **101**: 657-658 [PMID: 20965008 DOI: 10.1016/j.ad.2010.06.004]
93 **Christophers E**. Comorbidities in psoriasis. *Clin Dermatol*

2007; **25**: 529-534 [PMID: 18021889 DOI: 10.1016/j.clindermatol.2007.08.006]
94 **Sommer DM**, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. *Arch Dermatol Res* 2006; **298**: 321-328 [PMID: 17021763 DOI: 10.1007/s00403-006-0703-z]
95 **Adams LA**, Angulo P, Lindor KD. Nonalcoholic fatty liver disease. *CMAJ* 2005; **172**: 899-905 [PMID: 15795412 DOI: 10.1503/cmaj.045232]
96 **Adams LA**, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol* 2005; **42**: 132-138 [PMID: 15629518 DOI: 10.1016/j.jhep.2004.09.012]
97 **Pietrzak A**, Jastrzębska I, Chodorowska G, Maciejewski R, Mosiewicz J, Krupski W, Prystupa A, Szubstarski F, Szepietowski JC, Hercogova J. Psoriasis and unreported excessive alcohol intake--a simple screening approach. *J Eur Acad Dermatol Venereol* 2011; **25**: 1261-1268 [PMID: 21564326 DOI: 10.1111/j.1468-3083.2011.04101.x]
98 **Kirby B**, Richards HL, Mason DL, Fortune DG, Main CJ, Griffiths CE. Alcohol consumption and psychological distress in patients with psoriasis. *Br J Dermatol* 2008; **158**: 138-140 [PMID: 17999698]
99 **McAleer MA**, Mason DL, Cunningham S, O'Shea SJ, McCormick PA, Stone C, Collins P, Rogers S, Kirby B. Alcohol misuse in patients with psoriasis: identification and relationship to disease severity and psychological distress. *Br J Dermatol* 2011; **164**: 1256-1261 [PMID: 21457207 DOI: 10.1111/j.1365-2133.2011.10345.x]
100 **Brenaut E**, Horreau C, Pouplard C, Barnetche T, Paul C, Richard MA, Joly P, Le Maître M, Aractingi S, Aubin F, Cribier B, Jullien D, Ortonne JP, Misery L. Alcohol consumption and psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol* 2013; **27** Suppl 3: 30-35 [PMID: 23845150 DOI: 10.1111/jdv.12164]
101 **Gao B**, Seki E, Brenner DA, Friedman S, Cohen JI, Nagy L, Szabo G, Zakhari S. Innate immunity in alcoholic liver disease. *Am J Physiol Gastrointest Liver Physiol* 2011; **300**: G516-G525 [PMID: 21252049 DOI: 10.1152/ajpgi.00537.2010]
102 **O'Shea RS**, Dasarathy S, McCullough AJ. Alcoholic liver disease. *Hepatology* 2010; **51**: 307-328 [PMID: 20034030 DOI: 10.1002/hep.23258]
103 **Menon KV**, Gores GJ, Shah VH. Pathogenesis, diagnosis, and treatment of alcoholic liver disease. *Mayo Clin Proc* 2001; **76**: 1021-1029 [PMID: 11605686 DOI: 10.4065/76.10.1021]
104 **Gao B**, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology* 2011; **141**: 1572-1585 [PMID: 21920463 DOI: 10.1053/j.gastro.2011.09.002]
105 **Valenti L**, Fracanzani AL, Fargion S. The immunopathogenesis of alcoholic and nonalcoholic steatohepatitis: two triggers for one disease? *Semin Immunopathol* 2009; **31**: 359-369 [PMID: 19440711 DOI: 10.1007/s00281-009-0152-9]
106 **Cassano N**, Vestita M, Apruzzi D, Vena GA. Alcohol, psoriasis, liver disease, and anti-psoriasis drugs. *Int J Dermatol* 2011; **50**: 1323-1331 [PMID: 22004481 DOI: 10.1111/j.1365-4632.2011.05100.x]
107 **Spahr L**, Rubbia-Brandt L, Frossard JL, Giostra E, Rougemont AL, Pugin J, Fischer M, Egger H, Hadengue A. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis: a randomized controlled pilot study. *J Hepatol* 2002; **37**: 448-455 [PMID: 12217597 DOI: 10.1016/S0168-8278(02)00230-1]
108 **Naveau S**, Chollet-Martin S, Dharancy S, Mathurin P, Jouet P, Piquet MA, Davion T, Oberti F, Broët P, Emilie D. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. *Hepatology* 2004; **39**: 1390-1397 [PMID: 15122768 DOI: 10.1002/hep.20206]
109 **Boetticher NC**, Peine CJ, Kwo P, Abrams GA, Patel T, Aqel B, Boardman L, Gores GJ, Harmsen WS, McClain CJ, Kamath PS, Shah VH. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. *Gastroenterology* 2008; **135**: 1953-1960 [PMID: 18848937 DOI: 10.1053/j.gastro.2008.08.057]
110 **Boursier J**, Bertrais S, Oberti F, Gallois Y, Fouchard-Hubert I, Rousselet MC, Zarski JP, Calès P. Comparison of accuracy of fibrosis degree classifications by liver biopsy and non-invasive tests in chronic hepatitis C. *BMC Gastroenterol* 2011; **11**: 132 [PMID: 22129438 DOI: 10.1186/1471-230X-11-132]

P- Reviewer: Aksoy B, Chen GS, Husein-ElAhmed H, Manolache L
S- Editor: Song XX **L- Editor**: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com