Etanercept and Chronic Infection by HCV and HBV

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Abstract

Both psoriasis and chronic infections by HBV and HCV have high prevalence. Thus, it is relatively easy for them to coincide in the same patient. If the psoriasis requires systemic treatment, the dermatologist should consider the hepatic comorbidity when selecting an appropriate treatment. Cyclosporine, in addition to other well-known side effects, is an immunosuppressant that may condition worse evolution of the viral hepatitis. On the other hand, retinoids, psoralens and, above all, methotrexate may worsen the liver function. The anti-TNF-α biological agents are not hepatotoxic and their theoretical contraindication in this context would be because of their action on the immune response and risk of reactivation of the hepatic infection. However, several studies have demonstrated that neither the viral load nor the hepatic inflammation parameters are generally modified negatively when they are used in hepatitis due to HCV. Their use in this context, with correct monitoring, seems, therefore, very reasonable. On the contrary, in chronic hepatitis B virus, there are cases of worsening, even with fatal outcome in some cases, and the use of these biological agents should be reserved for cases having greater need, and always be associated to antiviral treatment and strict monitoring. The review of the recent literature seems to allow the conclusion that the concomitant use of lamivudine would greatly reduce the risk of viral reactivation and, with this condition, the use of etanercept in some HBV+ patients may also be contemplated.

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KEYWORDS
Anti-TNF-α agents; Etanercept; Hepatitis HBV; Hepatitis HCV

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ralenos y, sobre todo, metotrexato pueden empeorar la función hepática. Los agentes biológicos anti-factor de necrosis tumoral alfa (TNF-α) no son hepatotóxicos, y su teórica contraindicación en este contexto vendría dada por su acción sobre la respuesta inmune y el eventual riesgo de reactivación de la infección hepática. Sin embargo, diversos estudios han demostrado que ni la carga viral ni los parámetros de inflamación hepática suelen modificarse negativamente cuando se utilizan en hepatitis por el VHC. Su uso en este contexto, con una correcta monitorización, parece por tanto muy razonable. En cambio, en la hepatitis crónica por el VHB, sí existen casos de agravamiento, incluso con desenlace fatal en alguna ocasión, y el uso de estos agentes biológicos debe reservaarse para casos de mayor necesidad, siempre asociados a tratamiento antiviral y monitorización estricta. La revisión de la literatura reciente parece permitir la conclusión de que el uso concomitante de lamivudina reduciría mucho el riesgo de reactivación viral y, con esta condición, puede también contemplarse el uso de etanercept en ciertos pacientes positivos para el VHB.

**Introduction**

The development of the so-called biological agents has led to a very significant change in the therapeutic approach to psoriasis. Previously, many patients with severe forms of the disease and with comorbid conditions, such as liver disease, had very limited management options due to the contraindications, adverse effects, and potential long-term toxicity of conventional systemic therapy (phototherapy, retinoids, methotrexate, and cyclosporine). The possible hepatotoxicity of the retinoids, oxoralen, and, in particular, methotrexate, can limit the therapeutic options to narrowband UV-B phototherapy or cyclosporine. However, if the patient has chronic viral hepatitis, cyclosporine also appears inappropriate because the immunosuppression leads to a risk of viral reactivation or worsening of the hepatitis. Even in the absence of liver disease, it must be remembered that the long-term use of cyclosporine is limited by its nephrotoxicity. Furthermore, in the patients with psoriasis and psoriatic arthritis, neither cyclosporine nor phototherapy are ideal options as they have little or no effect on the joint component.

Like cyclosporine, tumor necrosis factor-alpha (TNF-α) antagonists are not particularly hepatotoxic; however, it is known that TNF-α plays an important role in the immune response to certain infectious conditions and, in the early years of its use, special care was therefore taken when the patient was a carrier of hepatitis B (HBV) or hepatitis C (HCV) virus. Furthermore, the Enbrel Summary of Product Characteristics and Prescribing Information state, “Treatment with Enbrel should not be initiated in patients with active infections including chronic or localized infections” and “Whether treatment with Enbrel might influence the development and course of malignancies in adults is unknown.”

Given that TNF-α antagonists have been used successfully in a number of immune-mediated inflammatory diseases—inflammatory bowel disease, rheumatoid arthritis, and psoriatic arthritis—dermatologists, who received approval for its use in psoriasis much more recently, can take advantage of the information accumulated in other specialties. A large proportion of the references cited in this paper thus refer to HBV or HCV carriers in the context of inflammatory rheumatic diseases.

**Case Description**

The patient was a 55-year-old woman with a history of systemic hypertension, noninsulin-dependent diabetes mellitus, morbid obesity (BMI, 41.5), pulmonary tuberculosis in childhood, and severe psoriasis that had developed 12 years earlier. She came to our clinic for psoriatic erythroderma. She had been treated with phototherapy, acitretin, methotrexate, and cyclosporine with no significant improvement; a year earlier treatment had therefore been started with efalizumab, with only moderate results. Due to an episode of influenza, the treatment with efalizumab was interrupted and the patient developed erythroderma, which was the reason for her consultation.

Treatment with etanercept was considered, given that all other therapeutic options had failed, but a blood test performed at our hospital revealed chronic HBV hepatitis with an undetectable viral load. The case was discussed with the gastroenterology department, and it was decided to start etanercept with the addition of lamivudine to avoid a possible reactivation of the HBV; treatment with etanercept was commenced some months after starting lamivudine. The tuberculin and QuantiFERON-TB tests were also performed prior to starting treatment with etanercept; the results were positive and therefore, after excluding an active form of tuberculosis, a 9-month course of isoniazid prophylaxis was initiated.

Three months after the initiation of treatment with etanercept, the patient presented a marked improvement in her psoriasis, with a reduction in the Psoriasis Area Severity Index (PASI) from 25.2 to 7.8; during certain periods she required adjuvant treatment with cyclosporine.

Liver function (transaminases, alkaline phosphatase, γ-glutamyltransferase) and viral load were monitored every 3 months. During the 24 months of treatment with etanercept and lamivudine, the liver biochemistry and the viral load remained stable, with no significant variations with respect to the results prior to starting treatment, and she achieved a sustained improvement equivalent to a 50% reduction in PASI score (PASI 50), which had reduced from 25.2 to 11 at her last follow-up.

As will be discussed below, TNF-α antagonists can reactivate HBV replication. However, treatment in...
combination with lamivudine appears to reduce this risk considerably, making the TNF-α antagonists a treatment to be considered in patients for whom there are no other therapeutic options, as long as close monitoring of liver function and the HBV viral load is performed.

Importance of TNF-α in Viral Infections

TNF-α is a proinflammatory cytokine involved in the immune response to certain infections. The TNF-α antagonists increase the risk of acquiring certain infections and of reactivating latent infections, particularly intracellular bacterial infections such as Mycobacterium tuberculosis. However, there is much less information or evidence available on the role of this cytokine and its antagonists in viral infections such as herpes simplex, cytomegalovirus, varicella-zoster, and human immunodeficiency virus (HIV). The same is true of the impact of the use of TNF-α antagonists on the course of HBV or HCV hepatitis. In view of the high prevalence of these infections, it is essential to know whether, when they coexist with disorders amenable to treatment with TNF-α antagonists, we are assuming a risk, and what is the magnitude of that risk if we consider using this therapeutic option.

Viral hepatitis is considered to be an inflammatory disorder caused by a T-lymphocyte-mediated cellular immune response. This immune response, directed against hepatocytes that contain the viral antigen, causes the inflammatory phenomena, though it is also essential for the elimination of the virus. Thus, the impact of the TNF-α antagonists on viral hepatitis can be contemplated from 2 opposing viewpoints: on the one hand, the risk that these agents could produce an increase in the viral load and, therefore, a worsening of the disease, and on the other, the fact that they could have a positive effect on the hepatic necroinflammatory phenomena.

The risk of an exacerbation of this type of hepatitis with the use of TNF-α antagonists has mainly been observed in the context of chronic hepatitis B virus, as TNF-α has a beneficial action in these patients, controlling viral replication. However, there is evidence that TNF-α plays a central role in the liver damage induced by specific Th-1 lymphocytes directed against the HBV surface antigen (HBsAg) in antigen-specific fulminant hepatitis. Ohta et al. developed an animal model of severe hepatitis by injecting C57BL/6 mice with HBsAg in combination with Th-1 lymphocytes specific for that surface antigen. Histological analysis of these animals demonstrated widespread severe necroinflammatory liver damage. However, this liver damage did not occur when the mice were pretreated with anti-TNF-α monoclonal antibodies. The authors concluded that TNF-α produced by Th-1 cells specific for HBsAg in the effector phase of the cellular immune response is an essential factor in the pathogenesis of this model of fulminant hepatitis.

In patients with chronic hepatitis C infection, the increase in TNF-α levels correlates with elevated alanine aminotransferase levels, such that, in those patients, treatment with TNF-α antagonists would be beneficial. The levels of the soluble TNF-α receptor, which compete with the cell-surface receptor to bind TNF-α, correlate with the severity of the disease, but not with the levels of TNF-α or with virological parameters such as the viral load. In contrast, in hepatitis B, both TNF-α and its soluble receptor (p75) are elevated in the serum and in liver tissue, and it appears that they are involved not only in the liver damage but also in the elimination of the virus.

Use of TNF-α Antagonists in Viral Hepatitis

There is a clear consensus that, before starting treatment with TNF-α antagonists, patients with bacterial infections must be excluded and cases of latent tuberculosis must be detected in order for chemoprophylaxis to be given. Much less is known and there is much less agreement about the risks associated with the use of these agents in viral infections such as HBV, HCV, and even HIV. Thus, for example, in the 2005 British Association of Dermatologists guidelines for the use of biological agents in the management of psoriasis patients, these viral infections were described as “relative contraindications”. In view of these initial doubts, patients with viral hepatitis have been excluded from clinical trials with TNF-α antagonists. However, publications have been appearing that suggest that, in the case of chronic HCV infections, the use of TNF-α antagonists seems not just safe, but even beneficial. In contrast, in chronic HBV hepatitis, these agents can increase the risk of reactivation of the infection, although, as we indicate below, this apparent evidence does not mean that TNF-α antagonists cannot be used in certain situations, with adequate monitoring, even in the case of chronic HBV hepatitis.

Use of TNF-α Antagonists in Chronic HCV Infection, Focusing on Etanercept

Analysis of the evidence suggests that inflammatory cytokines such as TNF-α play an important role in the pathogenesis of hepatocyte destruction in chronic HCV infection, and a clear correlation has been reported between TNF-α levels (which are elevated in HCV hepatitis) and the fibrotic and inflammatory histological changes in the liver. Furthermore, some studies appear to confirm that in addition to favoring hepatocyte destruction, TNF-α may be responsible for a poorer response to the treatment of hepatitis C with interferon alfa-2b. In 2005, the results of a study of patients with chronic hepatitis C treated with etanercept as adjuvant therapy for interferon and ribavirin, with another group that received placebo, interferon, and ribavirin, with another group that received etanercept responded better, achieving clearance of the HCV RNA in 63% of cases compared to 32% with placebo. With regard to safety, the patients who received etanercept presented a lower incidence of adverse effects than was observed with the conventional antiviral treatment. Despite the reservations that come from a lack of larger studies, we can conclude that the use of etanercept not only is not contraindicated in hepatitis C infection, but that it can even be beneficial.
importance of performing prospective long-term studies on transaminase levels. This observation indicates the presence of inflammation, necrosis, and fibrosis despite normal values of the transaminases from patients with chronic HCV infection can show signs of liver inflammation. An absence of elevation of the transaminases does not necessarily exclude active liver disease. Liver biopsies from patients with chronic HCV infection can show signs of inflammation, necrosis, and fibrosis despite normal transaminase levels. This observation indicates the importance of performing prospective long-term studies using histological data in addition to information on the serum markers of liver inflammation.

Marotte et al.11 used etanercept over a short period of time (3 months) to treat 9 patients with various rheumatic disorders and concomitant HCV infection. No increase in the viral load and no signs of liver inflammation were observed in any of the patients.

Peterson et al.12 (with 24 cases) and Parke and Reveille13 (with 5 cases) published their experience with the use of infliximab and etanercept in patients with HCV and rheumatoid arthritis. Both groups reported that there were no negative effects on liver function parameters in any case. The viral load only increased in 2 of the 24 patients in the first study and in 1 of the 5 patients in the second. Roux et al.14 published a series of 6 patients, one of whom was given infliximab for ankylosing spondylitis in the context of hepatitis B infection. The other 5 patients suffered from rheumatoid arthritis and all received treatment with etanercept despite 2 of them being positive for HBV and 3 positive for HCV. The HBV-positive patients were treated simultaneously with lamivudine. There were no alterations of the clinical state of any of the patients, no elevation of the transaminases, and no significant changes in the viral load. However, the authors recommended periodic monitoring during treatment.

Cansu et al.15 used etanercept to treat 5 patients with rheumatoid arthritis or ankylosing spondylitis and who were positive for HVB and/or HCV; they also detected no increase in the transaminases. In 2 of the 5 patients, the viral load remained undetectable, it decreased in one, and there was a nonsignificant increase in 2 patients.

As we have stated above, much of the accumulated experience concerning the safety of etanercept and other TNF-α antagonists in the context of HCV infection comes from patients with rheumatic diseases. However, there are also a few publications involving patients with psoriasis, though the patient numbers have often been very small. Rokhsar et al.16 (1 case), de Simone et al.17 (2 cases), and Magliocco and Gottlieb18 (3 cases) have published reports of HCV-positive patients with psoriasis treated with etanercept. The 3 groups concluded that, with correct monitoring of the viral load and of the liver enzymes, etanercept is an acceptable alternative in these patients. In the report by Rokhsar et al.,16 the patient was treated with etanercept for a severe form of psoriasis and arthritis mutilans; he had a cumulative dose of methotrexate of 3.5 g, liver biopsies that showed progression of liver fibrosis from stage II to stage IIIb, and a viral load greater than 1,000,000 copies/mL of HCV RNA. Anti-TNF-α therapy produced a marked improvement in the skin and joint disease and there was no change in the viral load after 5 and 12 months of treatment.

Cecchi and Bartoli19 have also published the case of an HCV-positive patient with plaque psoriasis who was treated with etanercept over a 12-month period; no deterioration was detected in the baseline viral load or liver function.

Other authors have drawn attention to the fact that an absence of elevation of the transaminases does not necessarily exclude active liver disease. Liver biopsies from patients with chronic HCV infection can show signs of inflammation, necrosis, and fibrosis despite normal transaminase levels. This observation indicates the importance of performing prospective long-term studies using histological data in addition to information on the serum markers of liver inflammation.20

Use of TNF-α Antagonists in Chronic HVB Infection, Focusing on Etanercept

In contrast to what has been discussed above regarding HCV infection, TNF-α appears to play an important role in the suppression of viral replication in chronic HVB hepatitis, and the use of antagonists of this cytokine could theoretically lead to HBV reactivation with a deterioration in the liver disease.21 A number of publications have reported this situation, which appears to be more likely to occur with infliximab than with etanercept. Esteve et al.22 used infliximab to treat 3 HVB-positive patients with Crohn disease; 2 of them developed reactivation of the hepatitis, with a fatal outcome in 1 case. Another HVB-positive patient with Crohn disease treated using infliximab developed subfulminant hepatitis that responded to treatment with lamivudine.23 Other diseases, such as rheumatoid arthritis or Still disease, have also been treated with infliximab, including in HVB-positive patients. In a case of rheumatoid arthritis, the patient developed acute hepatitis due to viral reactivation24; complete recovery was achieved after the administration of lamivudine, despite maintaining the anti-TNF-α treatment. A patient with Still disease developed fulminant hepatitis that required liver transplant.25

Carroll and Bond26 suggested that the risk of HBV reactivation was lower with etanercept than with infliximab, probably because of the pharmacological and biochemical differences between the 2 agents: infliximab neutralizes soluble and membrane-bound TNF-α, whereas etanercept only binds the soluble molecule. Despite the fact that etanercept appears to be safer in these patients, there have also been occasional reports of HBV reactivation. Montiel et al.27 published the case of a patient with ankylosing spondylitis who presented viral reactivation after 14 months of treatment with etanercept, and who responded very well to treatment with lamivudine, with no deterioration after the reintroduction of etanercept in association with the antiviral treatment.

Lamivudine is a reverse-transcriptase inhibitor that has been employed successfully in the prevention of the HBV reactivation that can occur secondary to treatments in transplant recipients, lymphomas, or other malignant diseases. In patients with chronic HBV infection and who are receiving treatment with infliximab, it has also been possible to prevent HBV reactivation and the possible deterioration in liver function by administering lamivudine.28 Roux et al.29 described 3 patients with chronic HVB hepatitis in whom the use of lamivudine controlled the hepatitis without complications. One patient had rheumatoid arthritis treated with etanercept and subsequently with adalimumab for a total of 21 months; during this period the increase in the viral load was insignificant. The second patient, who also had rheumatoid arthritis, received etanercept for 26 months and there was a fall in the viral load. The final patient had ankylosing spondylitis treated with infliximab for 7 months and there was no change in the viral load.

Antiviral treatment for HBV should be started 2 to 4 weeks before administering an immunosuppressive agent.30 Treatment with lamivudine must be continued for 3 to 6 months after the final withdrawal of the TNF-α antagonist.31 The use of lamivudine over very long periods can induce mutations in HIV that lead to resistance to the...
In Cases With Chronic HCV Hepatitis

- Although the long-term safety of etanercept is not fully defined, the presence of HCV should not be considered an absolute contraindication.  
- It is advisable to obtain the opinion of a gastroenterologist or hepatologist before starting treatment with TNF-\( \alpha \) antagonists.  
- When etanercept is administered in chronic HCV hepatitis, the transaminases and the viral load must be monitored periodically.  
- If the viral load increases, interruption of the anti-TNF-\( \alpha \) therapy should be considered.  
- The absence of elevated transaminases does not necessarily rule out active liver disease. Patients with chronic HCV infection can present inflammation, necrosis, and fibrosis in the liver biopsy despite normal transaminase levels.  
- Although the use of TNF-\( \alpha \) antagonists appears to be safe in patients with chronic HCV hepatitis, larger, longer-term studies that include histopathological data are required as these would be more reliable than simple stability of the transaminase levels.  

In Cases With Chronic HBV Hepatitis

- In contrast to the situation with HCV infection, the use of TNF-\( \alpha \) antagonists in chronic HBV hepatitis can lead to an increase in the viral load and a deterioration in the liver disease if simultaneous antiviral therapy is not administered.  
- In patients with chronic HBV infection, with or without active viral replication, specific treatment of the HBV infection (for example, lamivudine or adefovir) should always be considered before it is decided to use a TNF-\( \alpha \) antagonist.  
- A hepatologist should be consulted to select the most appropriate antiviral treatment and to decide whether a liver biopsy should be performed before starting anti-TNF-\( \alpha \) therapy.  
- In all cases, including those in which lamivudine is administered, the viral load and the serum indicators of reactivation of the hepatitis must be monitored periodically.  
- HBV reactivation is very likely in patients treated with infliximab not combined with lamivudine.  
- The risk of HBV reactivation appears to be lower with etanercept than with infliximab, probably because of the difference in the mechanism of TNF-\( \alpha \) inhibition.  
- The risk of reactivation appears to be lower in patients with a history of hepatitis B and who are HBsAg negative, though it cannot be completely ruled out.  

References