Are Anti-TNF-α Agents Safe for Treating Psoriasis in Hepatitis C Virus Patients with Advanced Liver Disease? Case Reports and Review of the Literature

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Abstract
Tumor necrosis factor-alpha (TNF-α) inhibitors represent an effective treatment for severe psoriasis in hepatitis C virus (HCV) patients. The literature reports mainly on short-term treatment in patients with chronic hepatitis with minimum-to-moderate activity with an acceptable safety profile. We report the first 2 cases of hepatocellular carcinoma (HCC) arising in HCV psoriatic patients with advanced liver disease during long-term treatment with etanercept. Our first patient, known to have had HCV infection for 41 years, developed an HCC after 21 months of therapy with etanercept (50 mg/week). The second patient, HCV+ for 20 years, was treated for 58 months with the same therapy, and despite no signs of liver function impairment was diagnosed with HCC. Both of them presented with cirrhosis, which was diagnosed 9 and 5 years earlier, respectively. It remains to be clarified whether there is any connection between psoriasis treatment with anti-TNF-α agents and the development of HCC in HCV-infected patients. Further long-term, follow-up studies and registries of HCV patients with mild/moderate activity may contribute to clarify this issue.

Introduction
In daily clinical practice, it is not uncommon for psoriatic patients to present psoriasis and hepatitis C virus (HCV) infection in areas where prevalence is high. HCV infection is a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). It has been suggested that tumor necrosis factor-alpha (TNF-α) inhibitors, mainly etanercept, may represent an effective and safe second-line treatment for severe psoriasis in HCV+ patients [1]. Moreover, for patients with concomitant psoriatic arthritis (PsA) such agents may be first-line disease-modifying therapies, as methotrexate is contraindicated. However, the management of these patients is challenging because of the risk of immunosuppressive treatment adversely affecting the outcome of liver disease.

To date, there is no evidence from randomized, controlled trials to support anti-TNF-α therapy for psoriasis in the setting of HCV infection; available data comes from case reports and case series with short-term follow-up. The use of anti-TNF-α agents in HCV+ psoriatic patients has been reported in 26 publications, describing a total of 61 patients (online supplementary e-table 1 and e-references; for all online supplementary material, see www.karger.com/doi/10.1159/000439587). Overall, 49 patients had a plaque-type psoriasis, 2 had erythrodermic psoriasis and for 9 patients the clinical type was not specified. In 20 patients psoriasis was associated with PsA. Of all the patients reported, 53 were treated with a single anti-TNF-α agent (47 with etanercept, 5 with adalimumab and 1 with infliximab). Six patients were treated sequentially with two different anti-TNF-α agents: 1 with infliximab and then adalimumab, 4 with etanercept and then adalimumab and 1 with etanercept and then infliximab. The mean anti-TNF-α treatment duration was 11 months (range 2–48 months). Morphological baseline characterization of liver status by biopsy was available for 15 patients. However, the...
histopathological report after anti-TNF-α treatment, which is the gold standard for assessing changes in activity grade and fibrosis of hepatitis, was presented in only 2 patients, who after 1 year of treatment showed no significant changes compared to pretreatment liver histology. In most studies, serum aminotransferases and viral load were used to monitor hepatic parenchymal inflammation and viral replication, respectively. In the vast majority of patients, the value of aminotransferases and HCV viral load during treatment showed no significant variations. Anti-TNF-α treatment was discontinued in only 2 cases. In 1 patient there was an increase in both transaminases and HCV viral load, both of which decreased following the initiation of peginterferon/ribavirin in combination with the anti-TNF-α agent. The other patient presented an elevation of viral load of more than 1×log10 without any worsening of the liver function. Recently, a retrospective observational multicenter study on 15 HCV+PsA patients, who were followed for a period of 12 months, showed that anti-TNF-α therapy did not modify either the viral load or the values of liver enzyme tests [2].

The safety profile of anti-TNF-α agents, particularly etanercept, appears to be acceptable in the context of psoriasis and concomitant HCV infection. Moreover, a recent review concludes that etanercept, at least in the short term, would appear efficacious and reasonably safe among patients suffering from PsA and concomitant HCV infection [3]. However, considering that the vast majority of patients reported in the literature presented chronic hepatitis with minimum-to-moderate activity, any conclusion must be considered tentative for advanced liver disease.

Case Reports

Case 1

We report a 61-year-old male psoriatic patient with PsA and concomitant HCV infection. His general medical history was notable for atrial fibrillation, severe arterial hypertension and a past history of epidermoid carcinoma of the oral cavity that had been completely removed. The patient was known to have had a genotype 2c HCV infection since 1965, for which he never received therapy. The patient had a previous history of alcohol abuse, and hematological laboratory tests suggested continued alcohol consumption over the subsequent years; however, at that time and thereafter, he denied any alcohol intake. At the time of referral, in August 2006, he presented with liver cirrhosis, which was first diagnosed in 1997. Ultrasonography (US) was consistent with the diagnosis of cirrhosis, with initial signs of portal hypertension. Upper gastrointestinal endoscopy did not reveal any esophageal varices. Laboratory data showed a moderate elevation of alkaline phosphatase and γ-glutamyl transferase. Serological tests for hepatitis B were negative, while HCV-Ab and HCV-RNA were positive (viral load of 4,460,578 copies/ml). Serum levels of aspartate aminotransferase and direct bilirubin were slightly increased. On examination, he showed erythematous, hyperkeratotic plaques of 5–40 cm in diameter, covering 25% of the body surface and predominating on the scalp, axillae, elbows, buttocks, upper part of the legs, and knee. He exhibited pain, tenderness and swelling over the proximal interphalangeal joints of both hands, the left knee and ankles. His major concern was chronic back pain and morning stiffness. The patient had a 7-year history of psoriasis and a 4-year history of PsA. His psoriasis had been previously treated with different topical therapies, including dithranol, corticosteroids, salicylic acid and vitamin-D derivatives, as well as narrow-band ultraviolet-B and bath psoralen ultraviolet-A phototherapies. Systemic therapy with acitretin gave only partial and transient results. Due to hepatic cirrhosis and severe arterial hypertension, methotrexate, leflunomide and cyclosporine were contraindicated. Therapy for articular involvement was limited to nonsteroidal anti-inflammatory drugs and physiotherapy. He came to us for better control of psoriasis and PsA. Given the active peripheral and axial arthritis and psoriasis, the patient was started on 25 mg of etanercept twice weekly. The first 6 months of this therapy yielded a marked improvement in both the psoriasis and the associated arthritis. During treatment, the viral load did not significantly change from the baseline, but aspartate aminotransferase, γ-glutamyl transferase and bilirubin levels progressively increased and led to the discontinuation of etanercept. The patient maintained a good response for about 6 months after treatment withdrawal. However, due to a severe flare-up of arthritis (20 out of 68 joints tender and 10 out of 66 joints swollen) and psoriasis (PASI 22), weekly etanercept (50 mg) was re-introduced 8 months after drug discontinuation. During treatment, the patient achieved remarkable control of both psoriasis and articular involvement. He was evaluated every 3 months by means of laboratory tests and every 6 months by liver US and serum α-fetoprotein measurement. Aspartate aminotransferase and γ-glutamyl transferase levels fluctuated around a value about 3 times the upper normal limit and the bilirubin level ranged between 1.39 and 2.64 mg/dl, while alanine aminotransferase remained normal and HCV viral load decreased to 667,000 copies/ml. Serum α-fetoprotein level was within the normal range at all time points. On June 2009, after 21 months of therapy, 2 HCC nodules were discovered by means of US and confirmed by computed tomography scans. Etanercept was definitively withdrawn and a low-dose systemic corticosteroid, in combination with an analgesic, was given to achieve at least a minimal symptomatic control of psoriasis. The tumor was treated with many cycles of transarterial chemoembolization, percutaneous radiofrequency thermoablation and percutaneous alcoholization, with partial and temporary results. At the time of the last referral, the patient presented with recurrence of HCC with many liver focal lesions, neoplastic thrombosis in the portal vein and severe impairment of liver function that led to his death in August 2011.

Case 2

A 50-year-old Caucasian male patient came to our clinic with psoriasis and concomitant HCV infection. His general medical history reported arterial hypertension, dyslipidemia, nephrolithiasis, and a pylolithotomy with blood transfusion in 1985. Since then, he was known to have had a genotype 1b HCV infection. At the time of referral, laboratory data showed moderate elevation of transaminases and γ-glutamyl transferase; HCV RNA was positive (viral load of 1,190,341 copies/ml) and he had liver cirrhosis. He had a 25-year history of psoriasis and PsA. On skin examination, he showed erythematous, hyperkeratotic confluent plaques over 45% of his body surface, particularly localized on the trunk, elbows, buttocks, upper part of the legs, and knee. He complained of proximal interphalangeal joint pain on awakening and chronic back pain. He had been previously treated with different topical therapies such as corticosteroids, salicylic acid and vitamin-D derivatives, as well as narrow-band ultra-
A patient treated with etanercept for 17 months yielded a marked improvement in both psoriasis and arthritis, the patient was started on monotherapy with etanercept, 25 mg s.c. twice a week. Administration of etanercept for 17 months yielded a marked improvement in both psoriasis and arthritis. During treatment, viral load and transaminases did not significantly change from the baseline. In order to better control the course of his hepatitis he received a treatment with peginterferon-α 2a (Pegasys®) and ribavirin with viral negativization. Therapy with etanercept was continued for the following 58 months. Throughout this time, the patient was checked every 3 months with blood tests and every 6 months with US and α-fetoprotein measurement. Aspartate aminotransferase did not change significantly from the baseline, alanine aminotransferase tripled its basal value and γ-glutamyl transferase reached the peak of 143 U/L. Serum α-fetoprotein level was within the normal range and the viral load was always negative. During follow-up, 2 HCC nodules were discovered by US and confirmed by computed tomography scans. Therefore, etanercept was discontinued and a treatment with low-dose systemic corticosteroid and acitretin was started. The tumor was treated with resections and multiple cycles of transarterial chemoembolization. After 2 years, a new HCC focus was found and treated with percutaneous radiofrequency thermoablation. The patient is now waiting for a liver transplantation.

Discussion

We performed a systematic search of English language databases (PubMed) using the following key words and MeSH terms: [‘Hepatitis C’ (MeSH) AND ‘Psoriasis’ (MeSH)] OR [‘Arthritis, Psoriatic’ (MeSH)] AND [‘adalimumab’ (Supplementary Concept) OR ‘TNFR-Fc fusion protein’ (Supplementary Concept) OR ‘infliximab’ (Supplementary Concept)], as well as [‘Hepatocellular carcinoma’ AND ‘Arthritis, Psoriatic’ (MeSH) OR ‘Psoriasis’ (MeSH)]. No exclusion criteria were applied. The use of anti-TNF-α agents in cirrhotic patients has been reported in 9 publications describing a total of 9 patients [3–11]. Collectively, no significant adverse events were reported in these patients with the notable exception of a retrospective, multicenter case series reporting 2 HCC developed in 20 psoriatic patients suffering from HCV infection. Three reports on treatment with different anti-TNF-α agents in the same psoriatic patient have been published [3–5]. A 52-year-old man with plaque-type psoriasis, PsA and hereditary α1-antitrypsin deficiency resulting in histologically diagnosed micronodular cirrhosis was sequentially treated with infliximab (5 mg/kg every 8 weeks), etanercept (50 mg weekly) and adalimumab (40 mg every other week) for 5, 3 and 8 months, respectively. Laboratory results, which were negative for hepatitis A, B and C viruses, did not show any significant changes in liver function during therapy. Treatment with anti-TNF-α agents has been reported in 3 patients with rheumatoid arthritis and primary biliary cirrhosis – two autoimmune diseases that are frequently linked [6–8]. Serology for hepatitis was negative in all patients. One patient was initially treated with infliximab (3 mg/kg, 5 infusions) followed by etanercept (50 mg) weekly for 30 months because of poor articular clinical response [6]. Moreover, this patient showed an amelioration of liver function tests during etanercept treatment, which was not seen with the previous infliximab therapy. Concomitant improvement in liver function and treatment efficacy for rheumatoid arthritis was also reported in another 2 cases by Ogata et al. [8] and Kubo et al. [9], who were treated with etanercept for 12 and 19 months, respectively. In a small case series, 3 cirrhotic patients suffering from inflammatory bowel disease were safely treated with infliximab [10]. One patient had cryptogenic cirrhosis and 2 patients had primary sclerosing cholangitis, but data on hepatitis B and C infection were not given.

The role of an anti-TNF-α agent in the absence of high-risk liver disease as a ‘pure’ hepatocarcinogen seems to be negligible. To the best of our knowledge, only a few cases have been reported [10–14] of HCC arising in patients treated with anti-TNF-α agents (infliximab, etanercept, adalimumab) for inflammatory bowel disease. Notably, in all reported cases, the patients did not have any established chronic liver disease, and all but 1 patient had a medical history of prolonged treatment with azathioprine, which is likely to have played an important role in the development of HCC in these patients [11]. Quite surprisingly, the 2 cases reported by Kumar and Le [12] had a prolonged survival after withdrawal of the anti-TNF-α agent therapy.

In a case reported by Collazo et al. [15], a patient who had undergone liver transplant due to HCV, liver cirrhosis and HCC was treated with etanercept for recalcitrant generalized psoriasis, achieving clearance of psoriasis without any adverse effects. Finally, in the large case series reported by Navarro et al. [16], 2 out of 20 psoriatic patients affected by HCV and treated with anti-TNF-α agents developed HCC. Both patients received etanercept, but just 1 patient suffered from liver alcoholic cirrhosis.

In sum, considering the 9 patients with liver cirrhosis treated with anti-TNF-α agents whom we were able to find in the literature, just 1 (reported by Navarro et al. [16]) developed HCC. On the other hand, out of all 61 psoriatic patients affected by HCV reported in online supplementary e-table 1, only 2 patients presented HCC – 1 with liver cirrhosis and 1 without. Quite surprisingly, the proportion of HCC among HCV patients in our experience is much higher. Patient 1 had a long-lasting history of HCV infection (40 years) and more than 10 years of liver cirrhosis. In addition, he had a past history of heavy alcohol consumption. In this regard, the combined deleterious effects of HCV infection and alcohol in the progression from end-stage liver disease to HCC are substantially more than additive and are well recognized [17]. Whether etanercept contributed to hepatocarcinogenesis in our patients is not known. The basic science underlying the hypothesis that TNF-α plays a role in the induction of liver fibrosis during chronic viral infection is sound and is well established in both human and murine models [18]. On this basis, it has been speculated that the anti-TNF-α treatment may even have a therapeutic role by means of inhibiting inflammation, scar accumulation, fibrosis, and cirrhosis. On the other hand, one should not discard the hypothesis that TNF-α blockade may directly or indirectly lead to early progression of dormant HCC. Chew et al. [19] found that HCC patient survival was positively associated with the higher expression of a group of inflammatory genes within the tumors. More specifically, they showed that TNF-α was highly enriched in leukocytes isolated from livers of HCC patients with better prognosis. Therefore, the potential interac-

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tions between anti-TNF-α treatment and local immune responses in cirrhotic HCV+ patients at high risk of developing HCC warrant further investigations.

Anti-TNF-α therapy deserves strong consideration as second-line treatment in HCV+ psoriatic patients. This topic is possibly underestimated in the literature. However, it may represent an emerging issue which we need to face. The annual incidence of HCC once cirrhosis is established is 2–6% per year [20] and, in particular, 5.0–5.4% for patients with HCV-related severe fibrosis or cirrhosis [21]. Independent risk factors for HCC in patients with HCV-related chronic hepatitis were found to be higher α-fetoprotein values, older age, male gender, and HBV coinfec-
tion or concomitant alcohol consumption [22].

Overall, 2 out of 4 HCV+ psoriatic patients treated with anti-TNF-α drugs here-in described developed HCC. Notably, both psoriatic patients affected with advanced liver disease and receiving anti-TNF-α treatment developed HCC – the first after 21 months of treatment and the second after 75 months. Therefore, assuming a 5% yearly rate of HCC development from liver cirrhosis (according to the literature), it could be hypothesized that both our HCV+ patients affected by advanced liver disease and treated with anti-TNF-α drugs may have developed HCC due to the concomitance of these conditions rather than by chance.

Appropriate patient counseling and selection, as well as clinical follow-up, are necessary to maximize safety. Psoriatic patients with latent tuberculosis infection treated with anti-TNF-α agents adhere to a standardized follow-up schedule [23]. Likewise, for HCV+ psoriatic patients we would like to introduce some recommendations.

First of all, the severity of the underlying liver disease needs to be thoroughly assessed. We stress the importance of a strict collaboration with the hepatologist, who should provide a clinical, biochemical and serological evaluation. Moreover, the hepatologist should decide whether a baseline biopsy or a noninvasive evaluation of the fibrosis stage is needed. There is no clear indication on the frequency of transaminase monitoring during treatment; however, testing every month during the first 3 months, and every 3 months thereafter, could be recommended. Functional liver evaluation should be performed every 3 months in patients with underlying high-risk liver disease and every 6 months for the others. In the former patients, HCC screening by US examination has to be performed every 6 months, and measuring α-fetoprotein levels (even if no longer recommended) might be useful if evaluated in association with US [24].

Conclusion

Here we have presented 2 cases of HCV+ psoriatic patients with advanced liver disease who developed HCC during treatment with etanercept. Whether anti-TNF-α therapy needs to be considered an additional risk factor for HCC occurrence may not be proven on the basis of the available data. Thus, further cumulative clinical investigations and data from observational registries are necessary to elucidate any links between anti-TNF-α agents and HCC in patients with advanced liver disease. We suggest that particular attention be paid to this subgroup of patients with strict clinical, biochemical and imaging follow-up and that treatment decisions be considered on a case-by-case basis, balancing the severity of psoriasis and PsA, as well as additional cofactors impacting on the progression of liver disease.

Statement of Ethics

Patients were treated according to the Declaration of Helsinki and to good clinical practice.

Disclosure Statement

The authors have no conflicts of interest to declare.

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