Etanercept Treatment to Enable Successful Hepatitis C Virus Clearance in a Patient with Rheumatoid Arthritis

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rthralgias and the presence of serum rheumatoid factor are common in patients infected with hepatitis C virus (HCV). True rheumatoid arthritis is rarer, but it can limit the ability to cure HCV infection with interferon due to exacerbation of rheumatic disease. In this case study, we report the successful clearance of HCV by using etanercept (Enbrel, Immunex) in combination with pegylated interferon- α (pegIFN- α) and ribavirin in a patient with rheumatoid arthritis who had previously stopped therapy prematurely due to worsening of joint symptoms.

Case Report

A 53-year-old male with genotype 3 HCV infection presented to our clinic in 2007 with a history that was significant for the premature cessation of pegIFN- α and ribavirin therapy secondary to profound arthropathy and joint swelling in 2003. His liver biopsy from 2003 had revealed stage 1 fibrosis (on a 0–4 scale). To confirm the benign course of his HCV infection, he underwent a repeat liver biopsy in 2007. This liver biopsy revealed grade 2 inflammation and stage 2–3 fibrosis. The significant progression was likely due to coexisting α 1-antitrypsin deficiency, which was discovered on the 2007 biopsy. Because the patient's HCV infection had progressed and because he was infected with an HCV genotype that is associated with high response rates

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to treatment, we wished to reinitiate HCV treatment. As treatment regimens remain interferon-based, we requested a rheumatology evaluation for consideration of empiric therapy of his rheumatoid arthritis.

At the time of this evaluation, the patient was having minimal joint symptoms. His rheumatoid arthritis diagnosis was confirmed by the presence of antibodies to cyclic citrullinated protein (anti-CCP). Additionally, radiographs of his hands and feet revealed erosions that provided further confirmation of significant disease. While a less potent antirheumatoid therapy may have been indicated for sole treatment of his rheumatoid arthritis, he was initiated on subcutaneous etanercept at a dose of 50 mg weekly in anticipation of starting HCV re-treatment. Three months later, his HCV treatment began with pegIFN- α at a dose of 180 mcg per week plus ribavirin at a dose of 400 mg twice daily.

During HCV treatment, the patient had one flare of joint symptoms that was successfully relieved with a 6-day course of prednisone. No further exacerbations occurred, and he completed the 24 weeks of HCV treatment. Etanercept was discontinued 5 days after his last pegIFN- α injection, at which time he also stopped taking ribavirin. Unfortunately, upon cessation of etanercept, he developed a significant flare of his rheumatoid arthritis that required reinitiation of etanercept as well as another course of prednisone. This event is suggestive of premature cessation of etanercept. Fortunately, the rheumatoid arthritis flare was treated successfully, and laboratory evaluation 24 weeks after the completion of pegIFN- α plus ribavirin therapy indicated sustained HCV clearance.

Discussion

Joint complaints are common in patients with HCV infection. Additionally, treatment with interferon can lead to nonspecific arthralgias and myalgias, which usually do not warrant treatment interruption. However, the patient described in this case report had underlying rheumatoid arthritis, as evidenced by positive anti-CCP testing and joint erosions on radiographs. This condition clearly complicated his ability to tolerate interferon.

The development or unmasking of autoimmune disease in patients treated with interferon has been frequently described and includes cases of autoimmune thyroiditis, sarcoidosis, polyarthropathies, and exacerbation of psoriasis.¹ A baseline assessment including history, physical examination, and laboratory studies, if indicated, is important to determine underlying autoimmune disease in patients who are being considered for interferon-based therapies.

Etanercept is a tumor necrosis factor– α (TNF- α) antagonist that is frequently used to treat rheumatoid arthritis that is refractory to other agents. It has been found to be safe for use in patients with HCV infection, as it does not cause significant hepatotoxicity and/or immune effects that could lead to unchecked viral replication and worsening of liver disease.² More than 60 reports exist in the literature confirming the safety of etanercept when used to treat autoimmune conditions in patients with chronic HCV infection, and no increases in alanine aminotransferase level or worsening of liver histopathology have been noted.³

The patient described in this report was empirically treated with etanercept prior to reinitiating treatment for HCV infection. He did have a mild rheumatoid arthritis flare during treatment that was easily managed; however, he experienced a significant flare after cessation of etanercept. This flare could have potentially been avoided by continuing etanercept for a few additional weeks after completion of interferon therapy. His rheumatoid arthritis remained well controlled for 9 months after the end of his HCV treatment, and plans are currently underway to taper him off of etanercept. The appropriate duration of concurrent rheumatoid arthritis treatment during and after HCV treatment is unknown, and further research will be necessary to answer this question.

To our knowledge, this case is the first report of etanercept being used to enable the completion of HCV therapy with pegIFN- α in a patient with rheumatoid arthritis. Recently, a similar approach involving the use of etanercept to enable interferon therapy and HCV viral clearance was reported in a patient with psoriasis.⁴

Furthermore, preliminary reports indicate that etanercept may be useful as an adjunctive agent in the

treatment of HCV infection. A phase II trial of etanercept in addition to standard pegIFN- α and ribavirin therapy resulted in more negative viral loads at 24 weeks in the group that received etanercept compared to the group that received placebo (63% vs 32%; P=.04).5 Patients in the etanercept group also had higher rates of negative viral loads at 48 weeks, although this difference was not statistically significant (53% vs 42%; P=.17). Differences in sustained virologic response (SVR) rates were not statistically significant, but rates were higher in the etanercept group (42% vs 32%). The group that received etanercept also reported fewer adverse events. These results are limited by this study's small sample sizes and the fact that etanercept was used for only 24 weeks (when interferon treatment continued for 48 weeks), so further research is required prior to recommending this combination therapy in routine practice.

Production of TNF- α is upregulated in patients with chronic HCV infection.⁶⁻⁸ Potential mechanisms by which etanercept may lead to improved virologic response include direct antiviral activity or "boosting" of the effect of pegIFN- α and ribavirin. TNF- α has also been shown to impair the proliferation of CD4 cells and inhibit the production of type 1 T-helper cells after antigen stimulation.⁹⁻¹¹ Inhibiting TNF- α may restore the function of CD4 cells, which may explain the improved rates of viral eradication in patients who received etanercept in addition to pegIFN- α and ribavirin.⁵

Additionally, patients with rheumatoid arthritis who are treated with etanercept demonstrate reduced levels of interleukin-15 and interferon- γ inducible protein (IP)-10.¹² Interestingly, IP-10 has associations with virologic response in patients with chronic HCV infection. Low plasma IP-10 levels were independent predictors of rapid virologic response and SVR in patients who were treated for HCV infection with pegIFN- α and ribavirin therapy.^{13,14} This association provides an additional mechanism by which etanercept may improve viral response rates in patients undergoing treatment for chronic HCV infection.

In conclusion, this report describes a potential solution to a treatment dilemma within the field of HCV treatment. It also nicely illustrates how etanercept may be used safely in conjunction with pegIFN- α and ribavirin for treatment of HCV infection. The mechanisms by which etanercept may aid in viral clearance include direct viral suppression, restoration of CD4 activity, and/or reduction in IP-10 level. Now that direct-acting antiviral medications have been approved by the US Food and Drug Administration for use in combination with pegIFN- α and ribavirin to treat HCV genotype 1 infection, etanercept likely does not have a role as adjunctive therapy for HCV infection alone. However, etanercept still has a

role in the treatment of certain rheumatologic diseases during HCV therapy. While etanercept is generally well tolerated, potential toxicities include serious infections, increased malignancy risk, cytopenias, and neurologic side effects.

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Review Hepatitis C Virus Treatment Complicated by Rheumatoid Arthritis

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Hepatitis C virus (HCV) infection poses a significant disease burden, affecting an estimated 170 million people worldwide.¹ In the United States alone, 3.2 million

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individuals are chronically infected.² Untreated, chronic HCV infection can lead to progressive hepatic fibrosis, cirrhosis, end-stage liver disease, and hepatocellular carcinoma.¹ In addition, HCV infection remains the leading indication for liver transplantation in the United States. Effective HCV therapy and viral eradication are essential to decrease the morbidity, mortality, and economic burden associated with this condition.

Chronic HCV infection is associated with a number of extrahepatic manifestations, of which rheumatologic complaints are the most common. In a large, prospective study of 1,614 HCV-infected patients, arthralgias were the most common complaint, with a reported prevalence of 23%.³ A symmetric, inflammatory polyarthritis primarily involving small joints, which resembles rheumatoid arthritis (RA), has been described in association with HCV infection.⁴ Rheumatoid factor may be present in up to 50–85% of these patients; however, unlike RA, no erosive joint changes are noted. The presence of true RA coexisting with HCV infection is far less common. In the United States, the estimated prevalence of coexisting HCV infection and RA is 0.02% (approximately 55,000 people).⁵

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Treating HCV infection in the setting of chronic inflammatory conditions such as RA poses unique challenges. All current HCV treatment regimens involve the use of interferon α (IFN- α).⁶ IFN- α may be poorly tolerated in patients with chronic inflammatory conditions due to the drug's ability to induce or aggravate underlying autoimmune diseases.^{7,8} Indeed, IFN- α therapy has been associated with de novo development of RA and unmasking of subclinical disease.^{7,9} Conversely, treatment of chronic inflammatory conditions, including RA, can be difficult in the setting of chronic HCV infection, as many traditional therapies may aggravate hepatitis or increase viremia.¹⁰

Tumor necrosis factor– α (TNF- α), a proinflammatory cytokine, plays a pivotal role in the pathogenesis of RA.¹¹TNF- α and TNF- α receptor levels are increased in the synovial membranes and joints of patients with RA. If unregulated, this inflammatory cascade results in the destruction of bone and cartilage. Etanercept (Enbrel, Immunex) is a dimeric fusion protein of the human p75 TNF- α receptor linked to the Fc portion of human immunoglobulin G1. Etanercept binds to and inactivates TNF- α , thereby neutralizing its proinflammatory effects. Anti–TNF- α agents, such as etanercept, are now widely used for the treatment of several chronic inflammatory conditions, including RA, although these drugs are generally reserved for patients who have failed other treatment options.¹²

Patients infected with HCV are also known to have increased serum levels and hepatocellular expression of TNF- α and TNF- α receptors. 13,14 TNF- α has been implicated in the pathophysiology of HCVrelated liver injury through augmented hepatocyte apoptosis and progression of hepatic fibrosis.^{15,16} The role of TNF- α in HCV-mediated liver injury was assessed in a phase II, randomized, double-blind, placebo-controlled trial that evaluated etanercept as an adjuvant to IFN and ribavirin therapy.¹⁷ In this small study of treatment-naïve patients with chronic HCV infection, addition of etanercept to the treatment regimen resulted in an increase in the number of patients achieving HCV RNA undetectability after 24 weeks of treatment (63% vs 32%; P=.04). However, this study's small sample size may have limited its ability to confirm an improvement in sustained virologic response (SVR) rates, thereby preventing the study's authors from establishing a clear clinical benefit for adjuvant etanercept in the treatment of HCV infection. Interestingly, patients who received etanercept reported fewer adverse events compared to patients who received IFN and ribavirin alone.¹⁷ Furthermore, a recent systematic review confirmed the safety of anti–TNF- α agents in patients with chronic HCV infection.18

Jazwinski and colleagues describe the prophylactic use of etanercept to enable IFN therapy and successful attainment of SVR in a patient with concomitant HCV infection and RA.¹⁹ The patient was previously intolerant to IFN therapy due to profound arthropathy and joint swelling, which resulted in premature cessation of IFN- α and ribavirin treatment. A follow-up liver biopsy 4 years after the failed IFN- α therapy revealed significant progression of liver fibrosis, although this progression was felt to be largely secondary to coexisting α 1-antitrypsin deficiency. Although the patient had no clear indication for anti–TNF- α therapy, empiric therapy with etanercept was initiated in an attempt to enable completion of HCV treatment with successful viral clearance. This case is the first report of empiric therapy with a TNF- α antagonist in a patient with minimally active RA prior to initiation of HCV treatment.

Concomitant IFN- α and anti–TNF- α therapy has previously been described in a patient with simultaneous RA and HCV infection.²⁰ In that case, etanercept was initiated prior to HCV treatment in a patient with an active RA flare. Similar to the case presented by Jazwinski and colleagues, the patient was maintained on etanercept throughout the course of HCV therapy and experienced no further rheumatoid flares.¹⁹ Prophylactic use of etanercept is further supported by a case report that described a strategy similar to that employed by Jazwinski and coauthors, in which use of etanercept facilitated successful completion of HCV therapy and viral clearance in a patient with concurrent HCV infection and psoriasis.^{19,21}

Currently, there are no guidelines regarding the management of patients with HCV infection and concurrent RA. Although such a treatment dilemma is relatively uncommon, Jazwinski and colleagues propose a safe and effective way to treat patients with RA who would not otherwise be able to tolerate IFN- α -based HCV treatment.¹⁹ This approach may also benefit other patients with coexisting autoimmune diseases that limit their ability to tolerate HCV therapy.

The appropriate duration of prophylactic anti-TNF- α therapy remains unclear. Withdrawal of etanercept in the current case 5 days after the last pegylated IFN- α injection resulted in a significant flare of RA that necessitated reinitiation of etanercept and a course of corticosteroid treatment. In a similar case involving the use of prophylactic etanercept to enable IFN- α treatment in a patient with psoriasis and HCV infection, etanercept was continued for 14 months after completion of HCV treatment, which facilitated continued improvement of the patient's psoriasis.²¹

At present, all HCV treatment regimens are IFN- α -based. Recent efforts to improve rates of SVR have focused on oral direct-acting antiviral agents. Indeed, boceprevir (Victrelis, Merck) and telaprevir (Incivek, Vertex), 2 HCV serine protease inhibitors,

have recently been shown to significantly improve SVR rates in patients with HCV genotype 1 infection.^{22,23} Like other protease inhibitors, boceprevir and telaprevir must be administered with peginterferon and ribavirin in order to prevent emergence of viral resistance. As treatment options for chronic HCV infection continue to evolve, the use of IFN- α -based strategies may no longer be necessary. Until that time, however, coexisting autoimmune disease will continue to pose a therapeutic challenge in patients with chronic HCV infection.

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