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CASE REPORT

Induction of clinical remission with adalimumab–methotrexate combination therapy in a patient with rheumatoid arthritis and concomitant hepatitis C virus infection

Osamu Noguchi · Yukio Gibo

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Abstract The patient described here is a 49-year-old woman who had hepatitis C virus (HCV) infection and rheumatoid arthritis (RA). Her RA had been successfully managed with methotrexate for about 10 years. After a sustained virological response was achieved with interferon therapy, treatment with adalimumab was instituted. This resulted in a rapid and sustained remission that lasted for more than a year, without HCV reactivation. The results in this case suggest that a sequential strategy, with initial HCV clearance followed by the targeting of remission with biologics, may be a favorable option in patients with RA and concomitant HCV infection.

Keywords Rheumatoid arthritis · Hepatitis C virus infection · Clinical remission · Adalimumab

Introduction

Interferons (IFNs) are known to be involved in the pathogenesis of certain autoimmune conditions, and in patients with rheumatoid arthritis (RA) treated with IFN-α for viral infections this treatment can exacerbate the RA [1–3]. Accordingly, the treatment of hepatitis C with IFNs in patients affected by RA may pose a relevant clinical challenge to both rheumatologists and hepatologists, considering the potential risk of increasing such adverse events. The advent of biologic agents targeted at specific cytokines, including tumor necrosis factor α (TNF-α), has allowed rheumatologists to pharmacologically manage RA more strictly, while the introduction of pegylated IFN-α combined with ribavirin has provided hepatologists with better control of chronic hepatitis C virus (HCV) infection.

An RA patient affected with chronic hepatitis C was initially treated with methotrexate (MTX) and salazosulfapyridine (SASP) for 10 years prior to receiving antiviral therapy. After the antiviral therapy–an IFN-α and ribavirin combination–a sustained virological response (SVR) was achieved, and then an RA flare was treated with adalimumab in combination with MTX, which led to clinical remission while maintaining the SVR. We report herein the case of an RA patient with HCV infection that was successfully controlled with sequential treatment with antiviral and anti-TNF-α agents. We report the details of this case in order to provide further clues about treating patients with concurrent RA and HCV infection.

Case report

A 39-year-old female with RA of about 4 years' duration visited our clinic in July 1997. At that time, she had arthritic symptoms and X-ray examination of her hand revealed joint-space narrowing and bone erosion; she had a daily activity functional status of class 2. Asymptomatic HCV infection had been found in 1993, with seropositivity for anti-HCV antibodies, and the diagnosis was subsequently confirmed in February 1999 with results showing 180 kIU/mL of HCV-ribonucleic acid (RNA) (polymerase chain reaction). It was speculated that the HCV infection episode had occurred when she had undergone a blood

O. Noguchi (✉)
Department of Rheumatology, Gennoki Clinic, 2680-1 Nishiharuchika, Ina, Nagano 399-4431, Japan
e-mail: gennoki@inacatv.ne.jp

Y. Gibo
Gibo Gastroenterology and Internal Medicine Clinic, Chikuma Building 2F, 237 Yoshikawamurai-cho, Matsumoto, Nagano 399-0032, Japan

transfusion during oophorectomy for endometriosis in 1988.

After the initiation of MTX treatment in July 1997, the RA activity had rapidly decreased and low disease activity was maintained thereafter for 9 years and 10 months until the introduction of antiviral therapy to eradicate HCV (Fig. 1a). The careful initiation of MTX along with laboratory monitoring led to her hepatitis staying mild, with both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) being within a normal range of <30 IU/L until the dose was increased to 15 mg/week. The increase in MTX dose to 15 mg/week, which was the standard dose in the European Union and the United States, was associated with only mild and transient increases in liver AST and ALT (45 and 48 IU/L, respectively). At 3 months after the dose increase, HCV-RNA was detected at a level of 180 kIU/mL, yet there were no further elevations of AST and ALT. In order to improve the patient's hepatic function while maintaining the RA activity at a low level, the dose of MTX was reduced to 12.5 mg/week, with concomitant administration of SASP. Consequently, her RA remained in a state of low disease activity as assessed

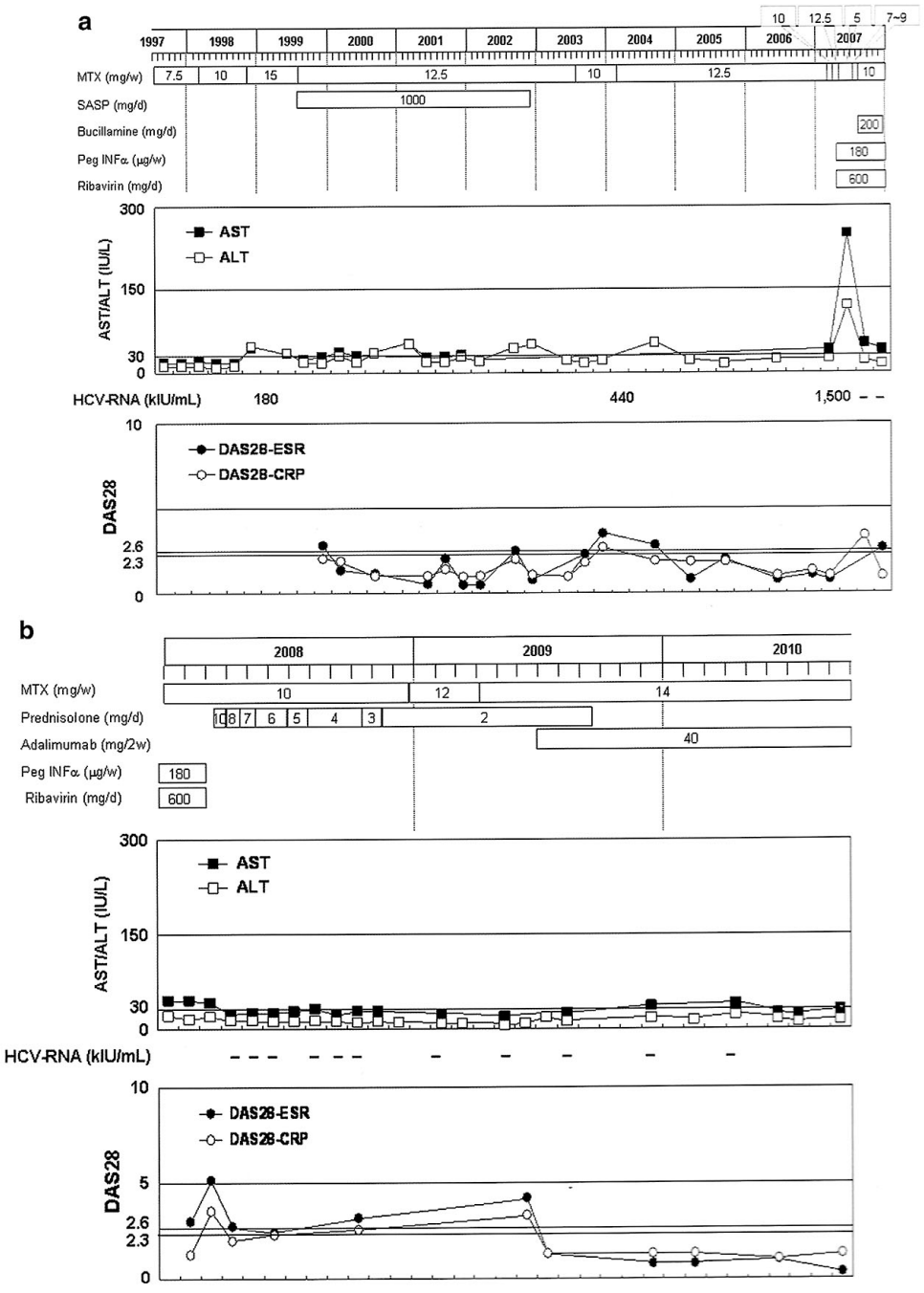

Fig. 1 **a** Clinical course of the patient between June 1997 and December 2007. **b** Clinical course of the patient between January 2008 and September 2010. The "*dash*" symbol denotes an undetectable level of hepatitis C virus RNA (*HCV-RNA*). *MTX* methotrexate, *SASP* salazosulfapyridine, *INFα* interferon alfa, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *DAS28* disease activity score in 28 joints, *DAS28-ESR* DAS28 using erythrocyte sedimentation rate, *DAS28-CRP* DAS28 using C-reactive protein

by the disease activity score in 28 joints (DAS28), without deterioration of liver function and with only transient increases in AST and ALT (Fig. 1a).

Although no liver biopsy was performed the present patient was strongly suspected to have moderately advanced chronic hepatitis with fibrosis, based on her 16-year history as an HCV carrier with a decline in the platelet count over time ($23.24 \times 10^4/\mu L$ in 1998; $18.23 \times 10^4/\mu L$ in 2000; $17.90 \times 10^4/\mu L$ in 2002) [4], as well as a nearly constant AST/ALT ratio of >1.0 [5, 6]. In March 2004, 1 month after the HCV-RNA level had increased to 440 kIU/mL, we judged that the benefits of an attempt at HCV eradication outweighed the potential risks, and made a decision to refer the patient to a hepatologist. However, due to her coexisting RA, the introduction of IFN therapy was refused by the first specialist she visited, at a general hospital in the community. The patient was rejected again by another hospital because of the potential risk of interstitial pneumonia. At the third medical institution she visited, she finally met a doctor who accepted to undertake antiviral therapy. Two weeks after combination therapy with Pegasys® (Chugai, Tokyo, Japan) (peginterferon alfa-2a 180 μg once weekly) and Copegus® (Chugai, Tokyo, Japan) (ribavirin 600 mg/day) was initiated, on 2 April, 2007, both the AST and ALT rose, to 249 and 119 IU/L, respectively (Fig. 1a). At the time of initiation of the combination therapy the HCV-RNA value had further increased to 1,500 kIU/mL. Meanwhile, the MTX dose was reduced to 5 mg/week because her white blood cell and platelet counts (/μL) had decreased from 4,500 and 20.6×10^4 to 1,800 and 6.8×10^4, respectively. Then RA flares prompted a dose increase of MTX to 10 mg/week, and subsequently bucillamine (200 mg/day) was added to her treatment. In March 2008, prednisolone (10 mg/day) was instituted to suppress inflammation (Fig. 1b).

However, because moderate rheumatoid disease activity had persisted, Humira® (Abbott Japan, Tokyo, Japan) adalimumab, a fully human anti-TNF-α monoclonal antibody treatment (40 mg every 2 weeks) was commenced, on June 29, 2009. Within 1 month after the initiation of adalimumab, the disease activity with swollen and tender joints was significantly attenuated, leading to the complete withdrawal of prednisolone (Fig. 1b). The efficacy of adalimumab was evident as represented by the patient's disease meeting the clinical remission criteria of both the DAS28-erythrocyte sedimentation rate (ESR) and the DAS28-C-reactive protein (CRP), of <2.6 and <2.3, respectively (Fig. 2) [7]. HCV-RNA became negative 1 week after the elevations in AST and ALT observed post-IFN therapy and remained negative thereafter. Further, since the initiation of the adalimumab therapy, her hepatitis has been in a quiescent state and to date HCV-RNA has not become positive (Fig. 1b).

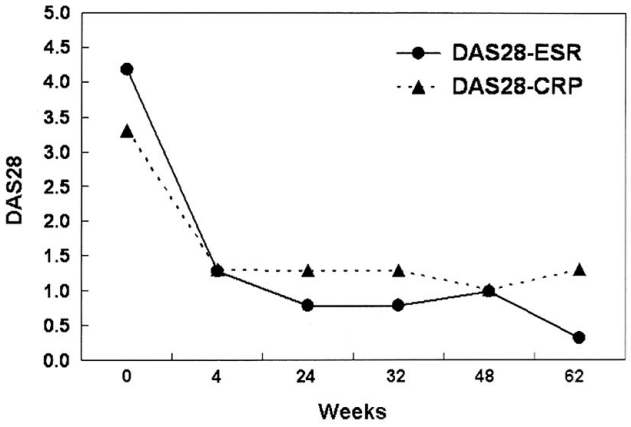

Fig. 2 Patient's disease activity status as measured by DAS28-ESR and DAS28-CRP following commencement of adalimumab treatment. *DAS28* disease activity score in 28 joints, *DAS28-ESR* DAS28 using erythrocyte sedimentation rate, *DAS28-CRP* DAS28 using C-reactive protein

The patient returned to work as a hair stylist and resumed a normal active life with daily activities such as snow shoveling in winter without any difficulties. The option of self-injection that comes with adalimumab was favorable to the patient for continuing her work; in particular, eliminating the need to visit the clinic solely for the purpose of injection, because she lives far from the clinic.

Discussion

In Japan, the prevalence of RA is reported to be about 0.6 million [8], while the prevalence rate of HCV carriers is estimated to be 0.7% [9]. Because the prevalence of HCV infection increases with age, this comorbidity can be considered to exist in at least 4,200 RA patients in Japan. Management of the state of coexisting RA and HCV infection is often considered as a therapeutic challenge by specialists in both rheumatology and hepatology. In the natural course of hepatitis C, although it shows considerable variation between individuals, HCV infection is a major cause of chronic liver disease, which may advance to cirrhosis within the first 20 years and then to hepatocellular carcinoma [10, 11]. In the present patient, after almost 20 years of HCV carriage, the antiviral treatment we have described could have been regarded as a last-minute attempt to prevent progression of the liver condition.

Despite the idea that hepatotropic viral infection precludes treatment with biologic agents in patients with RA [12], the present patient with RA was successfully treated with adalimumab, a TNF-α inhibitor, after viral clearance; from the standpoint that even HCV-infected RA patients have a right to receive the benefits of viral clearance. Since the occurrence, or the worsening of autoimmune diseases,

including RA, in patients receiving IFN-α therapy has been reported in several case studies [1–3], this therapy is known to involve some risks. Although the treatment of HCV-infected patients with MTX does not necessarily lead to deleterious effects on hepatic function, as reported by Nissen et al. [13], the possibility of viral hepatitis worsening in RA patients cannot be ruled out, according to the Japan College of Rheumatology 2011 guidelines on the use of MTX for RA in Japan [14]. Therefore, before initiating MTX therapy in RA patients, consideration should be given to consulting with a doctor who specializes in gastroenterological medicine, and then carefully weighing the risks versus benefits.

In general, it could hardly be said that there is no risk or a negligible risk of the reactivation of HCV infection with MTX therapy. In the present patient, the good control of RA activity with MTX resulted in no marked elevations of hepatic aminotransferases. There were only transient increases in AST and ALT levels after the dose increase to 15 mg/week and during the treatment at 12.5 mg/week. However, it is not known whether the mild elevations of liver enzymes were due to MTX or whether they were associated with the HCV infection. It should be noted that the HCV-RNA had increased from 180 to 440 and then to 1,500 kIU/mL during the last 10 years of the patient's MTX treatment. It was also not possible to determine whether this was due to the effects of the MTX therapy or the natural course of the disease. It is considered good timing that the IFN–ribavirin combination therapy was initiated when the HCV-RNA value happened to be increased to 1,500 kIU/mL.

Although no liver biopsy was performed and no sustained elevations of AST and ALT were observed in the present case, the patient was clinically diagnosed as having moderately advanced chronic hepatitis C, taking into consideration the long duration of HCV infection, the AST/ALT ratio, and the platelet counts. Therefore, antiviral therapy was considered, which agreed with the standard practice in Japan according to the 2011 guidelines for the treatment of chronic hepatitis C [15].

Although a phase 2 study demonstrated that the use of a TNF inhibitor as adjuvant to IFN and ribavirin in patients with chronic HCV infection improved the virological response and decreased adverse events [16], it is also possible that the use may worsen chronic hepatitis infections, leading to the development of fulminant hepatitis [17, 18]. Rheumatologists tend to be hesitant to treat HCV-infected RA patients with potent anti-rheumatic drugs such as TNF-α inhibitors because of the risk of favoring viral replication, while hepatologists may be reluctant to give IFN therapy to these patients because of the risk of worsening RA. Consequently, HCV-infected RA patients are often undertreated, with clinical, social, and psychological consequences.

The observed clinical course in the present patient provides one solution to the problem of how these conditions can be managed. Although therapeutic approaches with the use of anti-TNF therapy alone or in combination with IFN-α therapy were reported in the past [19–21], a sequential strategy with initial hepatitis C viral clearance with pegylated IFN-α and ribavirin, followed by RA treatment with a potent anti-rheumatic agent such as anti-TNF-α seems to be an alternative therapeutic option, because the risk of life-threatening fulminant hepatitis would override the risk of RA progression. Therefore, it is strongly recommended to strictly monitor clinical and virological activities in close cooperation between rheumatologists and hepatologists. That is, the top priority needs to be placed on viral clearance, and rheumatologists should therefore try to provide a favorable environment for the hepatologists to treat their patients. Once viral clearance is achieved, disease control with disease-modifying anti-rheumatic drugs will follow, aiming at clinical remission to achieve optimum therapeutic outcomes in RA. It has been reported that serious de-novo hepatitis developed after treatment with biologics or chemotherapy in hepatitis B virus carriers [22], and so the similar occurrence of de-novo hepatitis after an inactive HCV carrier state cannot be excluded; thus, further research is required. Yet the risk of HCV reactivation is considered to be extremely low [23, 24], a factor which would support the proposed treatment strategy as a practical option from the patient's perspective.

In the present patient, the combined antiviral therapy (IFN-α and ribavirin) rapidly reduced the HCV-RNA viral load to an undetectable level, thereby achieving an SVR, but the reduction in the MTX dose and possibly the antiviral therapy, in part, resulted in RA flares. The introduction of adalimumab therapy in conjunction with her previous regimen of MTX produced a significant clinical and serological improvement of the persistent RA symptoms for 2 years without the reactivation of HCV, and thus returned the patient to an active life; these features support the use of a TNF-α inhibitor after viral clearance in RA patients with an inadequate response to traditional treatments.

Conflict of interest None.

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