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Cyclosporine A for the treatment of autoimmune disorders in HCV infected patients

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Abstract

Due to the relatively high prevalence of both HCV infection and autoimmune disorders (AD), it is not rare to encounter patients with AD also carrying HCV. Considering that the use in HCV infected individuals of corticosteroids or immunosuppressant drugs, that are indeed needed to treat AD, is considered a risk for worsening the clinical outcome of HCV infection, rheumatologist have often refrained from using these drugs in AD when HCV-RNA is also present. Cyclosporine (CsA) is an immunosuppressive agent used to treat a wide range of autoimmune disorders but there is in literature a large body of evidence suggesting that CsA also exerts an inhibitory effect on HCV replication at standard therapeutic dose. The anti-HCV effect of CsA has been demonstrated both in vitro and in vivo. Therefore, these evidences have opened new ways to improve the therapy and the prognosis in patients with HCV-related liver diseases including transplanted ones. Recent reports, although limited in number, also suggest the safety of CsA, in the treatment of patients with AD and concomitant HCV infection. Good results have also been obtained in the treatment in rheumatoid arthritis patients even in association with anti-TNF agents.

Keywords: HCV infection; Cyclosporine A; Immunosuppressant; Autoimmune disorders; Anti-TNF

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1. Introduction

It has been calculated that the prevalence of hepatitis C virus (HCV) infection is about 3% in western countries and that there are areas in south Italy where the prevalence rises up to 20% of the population. It is also known that, all together, autoimmune disorders (AD) have a prevalence of about 10% in western population, it is therefore not rare to encounter in daily clinical practice patients with AD also carrying HCV. The treatment of AD, especially in systemic severe forms, includes the usage of immunosuppressant agents and/or glucocorticoids that have the potential effect of worsening the outcome of HCV infection. For this reason rheumatologist have often refrained from using immunosuppressants in AD when HCV-RNA is also present. Cyclosporine A (CsA) is an immunosuppressive agent used to treat a wide range of autoimmune disorders but there are sufficient evidences suggesting that CsA also exerts antiviral effects being able to inhibit HCV viral replication in vitro. This ability has also been confirmed in vivo, in liver transplanted patients and in patients affected by chronic active hepatitis (CAH). Nevertheless, very little is known about the efficacy and safety of CsA in patients with autoimmune disorders and concomitant chronic HCV infection. For the present paper, we have reviewed the current literature focusing our attention on the in vitro and in vivo evidences of anti-HCV action of CsA and on the antiviral mechanism of action of CsA. We have also reported personal and others experiences with CsA in the treatment of autoimmune disorders in the presence of chronic HCV infection.

2. CsA in the treatment of liver transplanted patients and in chronic active hepatitis

Cirrhosis caused by chronic hepatitis is responsible for approximately one-half of all liver transplantation procedures [1]. Recurrence of HCV infection occurs in up to 90% of cases following liver transplantation [2]. The increased viral replication, the frequent development of histological features characteristic of chronic hepatitis and the increased incidence of HCV-related disease progression in transplant patients was attributed to the effect of immunosuppressive therapy [3–5].

Nevertheless, some clinical trials, in HCV+ liver transplanted patients [6], have suggested that the outcome could be improved when CsA is included in the therapeutic regimen.

The effectiveness of CsA in de novo liver transplant patients was investigated in the LIS2T trial [6]. This was the first multicenter, open-label, randomised study comparing the efficacy and safety of CsA microemulsion (ME) versus tacrolimus. The study randomised 495 patients to receive either CsA-ME ($n=250$) or TAC ($n=245$), in combination with steroids, with/without azathioprine, for 6 months. No differences were found in the two groups about the incidence of biopsy-proven acute rejection at 3 months and at 6 months but death or graft loss was more frequent in those receiving tacrolimus (15% vs. 6%, $P<0.05$). A further analysis performed on 129 patients from one center showed that at 3 years post-transplantation, in HCV+ patients CsA treatment resulted in better survival (90% vs. 78%; $p<0.05$), lower viral titres (1.05 vs. 3.2; $p<0.05$) and markedly improved hepatic biochemical tests [6]. These results demonstrated that CsA treatment results in decreased frequency of both death and graft loss in HCV+ patients.

Casanovas Taltavull also studied 14 HCV+ liver transplant patients treated with IFN-α+ribavirin and immunosuppressed with CsA or TAC monotherapy. The results showed that a sustained virological response was achieved in 6 patients while the others were non-responders. Interestingly, all the responders were receiving CsA treatment, while 6 out of 8 non-responders were on TAC therapy [7].

In another study, Kugelmas et al. [8] showed that liver transplanted patients treated with CsA have earlier HCV clearance (from 12 weeks to 7 months) in comparison to those treated with TAC (from 3 to 18 months). Ghobrial et al. [9] have also shown that CsA treatment was associated with a longer time interval to re-transplantation in liver transplant patients with recurrence of hepatitis C disease (mean interval: 787±805 days for CsA patients and 142±34 days for TAC; $p=0.09$).

Histological progression of chronic HCV-associated hepatitis to fibrosis is a critical step in disease progression that often leads to cirrhosis and decompensation. Berenguer et al. evaluated the histological