

## CASE REPORT

# TREATMENT OF CHRONIC HEPATITIS C IN NON-RESPONSIVE PATIENTS WITH PEGYLATED INTERFERON ASSOCIATED WITH RIBAVIRIN AND THALIDOMIDE: REPORT OF SIX CASES OF TOTAL REMISSION

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### SUMMARY

Hepatitis C virus (HCV) infection is an important public health issue worldwide. It is estimated that over 170 million people are infected with the virus. The present study reports six cases in which patients did not respond to combination therapy with pegylated interferon and ribavirin. However, after the addition of thalidomide to the therapy, the patients presented negative RNA PCR. The use of thalidomide combined with pegylated interferon and ribavirin for the treatment of hepatitis C is described here for the first time in the related literature.

**KEYWORDS:** Hepatitis C; Thalidomide.

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### INTRODUCTION

The World Health Organization has estimated that there are 170 million people infected with Hepatitis C (HCV), which means that this infection is currently one of the most important public health issues worldwide<sup>40</sup>. In 2001, there were around 1.4 million deaths caused by chronic liver diseases, among which 796,000 were caused by cirrhosis and 616,000 were caused by primary liver cancer (hepatocarcinoma). Twenty percent (280,000) of the total number of deaths were probably due to HCV infection<sup>21</sup>.

HCV infection is the primary cause of death in patients with chronic liver diseases worldwide<sup>2,17,21,40</sup>. Combination therapy with pegylated interferon (IFNp) and ribavirin is currently the only available treatment for HCV approved by the Food and Drug Administration (FDA). This therapy is given for 24 weeks for genotypes 2 and 3, and for 48 weeks for genotype 1. Patients with genotype 1 undergoing IFNp-alfa-2b and ribavirin combination therapy achieve a sustained viral response (SVR) rate of 42%. Patients with genotypes 2 and 3 achieve an SVR rate of 82%<sup>46</sup>. SVR rates in patients undergoing IFN-alfa-2a and ribavirin combination therapy are 46% and 76%, respectively<sup>27,33,46</sup>.

The success rate of the treatment is not yet optimal and, considering the potential complications related to the long-term chronicity of HCV infection, it is imperative that we explore other treatment options. Thalidomide has several properties as a sedative-hypnotic,

immunomodulatory, anti-inflammatory and antiangiogenic drug. Initially, it was indicated for nausea and caused human teratogenicity in pregnant women. Currently, it has been indicated for the treatment of cutaneous manifestations of erythema nodosum leprosum and has been investigationaly used in combination with anticancer drugs to treat several types of carcinoma<sup>11,30,31,36,49,53,63,70,83</sup>. There exists no published evidence that it has ever been tested in patients with chronic hepatitis C.

### CASE REPORT

A male patient with chronic HCV infection, aged 44 years, with positive HCV antibodies identified in November 1996, and with unknown exposure to HCV, sought the medical center for clinical assessment on October 12, 1999. His liver function test showed alanine aminotransferase (ALT) 86 U/L, aspartate aminotransferase (AST) 178 U/L, and initial viremia was determined by HCV RNA of 340,463 U/mL (genotype 1a). Liver biopsy showed structural lesion (level 3) and steatosis.

In May 2001, the patient began therapy for HCV infection with weekly injections of IFN 3,000,000 U and ribavirin, for a total of 12 months. At the end of this treatment, HCV RNA was 1,309,317 U/mL, with ALT 151 U/L and AST U/L 272, which defined a non-responsive case. The patient was then referred to our service for reevaluation. As of October 2002, 1.5 µg/kg of IFNp alfa-2b once a week and 500 mg

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of ribavirin b.i.d. were administered to the patient for a total of 12 weeks. In January 2003, the viral load test showed HCV RNA of 2,126,000 U/mL and the patient complained of multiple ulcers, pain and had difficulty to eat. No response to local therapy or anesthetics and other medications was observed. In addition to IFN and ribavirin, a dose of 100 mg of thalidomide was prescribed b.i.d. for 30 days to treat the patient's mouth ulcers. At the follow-up appointment, one month later, the patient presented remission of the symptoms, and reported that the ulcers had disappeared in one week. His liver function test showed a decrease in AST (32 U/L) and ALT (40 U/L). Thalidomide administration was maintained for 30 days. In May 2003, the HCV RNA viral load was undetectable and in August 2003, the qualitative polymerase chain reaction (PCR) was negative, as well as in October, at the end of the treatment.

After this case, five other patients who presented no decrease in HCV viral load after 12 weeks of weekly treatment with 1.5 µg/kg of IFNp alfa-2b and 500 mg of ribavirin b.i.d. were treated with the same dose of thalidomide for 30 days. Four patients presented negative HCV PCR and one patient, who weighed 130 kg, had a decrease in HCV viral load of 1 log at the follow-up appointment 30 days after thalidomide use. Five patients presented sustained virologic response (SVR) at 48 weeks and 72 weeks.

## DISCUSSION

Various therapeutic approaches have been reported for the treatment of hepatitis C in patients with no response to previous treatment combining IFN (conventional or pegylated) and ribavirin. Among these are the combination of IFN alpha + ribavirin + amantadine<sup>5,22,74,75,84</sup>, IFN alpha + phlebotomy<sup>24,26,56,68</sup>, IFN alpha + prednisolone<sup>32,73</sup>, IFN alpha + cimetidine, IFN alpha + N-acetylcysteine<sup>42,54</sup>, IFN alpha and vitamin E<sup>43,45,57,67</sup>. In addition to these, other adjuvant therapies include Levorin, glycyrrhizine<sup>10,28,39,41,52,55</sup>, ursodeoxycholic acid<sup>12,14,23,59,60</sup>, Maxamine<sup>7</sup>, pentoxifylline, Isoprinosine<sup>61,80,87</sup>, colchicine<sup>5,25,64,65</sup>, histamine<sup>34</sup>, IL-10<sup>1,18,44</sup>, IL-12<sup>29,35,76,85,86</sup>, IL-2<sup>8,13,37,66,72</sup>, IFN gamma<sup>9,16,69</sup>, granulocyte colony-stimulating factor (G-CSF)<sup>47,78,81</sup>, granulocyte-macrophage colony-stimulating factor (GM-CSF)<sup>48,58,77</sup>, and thymosin alpha 1<sup>3,4,38,51,62</sup>. None of these approaches has proved more effective than IFNp and ribavirin combination therapy. The present study described the action of thalidomide and IFNp + ribavirin combination therapy. The use of thalidomide against various pathologies is well known<sup>11,30,31,36,49,53,63,70,82,83</sup>. However, no studies have reported its use in HCV treatment. Various hypotheses can be formulated with regard to the efficacy of thalidomide, for instance, as an immunomodulatory, anti-inflammatory agent which inhibits TNF-alpha<sup>50</sup>, or even the effects of thalidomide on lymphocytes, increasing interferon gamma secretion<sup>79</sup>. Nevertheless, various questions remain. It is still unknown whether thalidomide has any effect on viral replication; whether it acts on the modulation of cytokines which act on the inflammatory process of liver diseases caused by HCV; and whether it is necessary to combine thalidomide with pegylated interferon and ribavirin. Other questions to consider are the appropriate dose of thalidomide; the duration of treatment; and the time to initiate treatment. Only a randomized clinical trial can provide us with the answers. We have already begun a pilot trial which will soon allow us to present more consistent data.

## RESUMO

### Tratamento de hepatite C crônica em pacientes não respondedores, com a associação interferon peguilado, ribavirina e talidomida. Relato de seis casos

A infecção pelo vírus da Hepatite C (HCV) representa um importante problema de saúde pública no mundo, estima-se que mais de 170 milhões de pessoas estejam infectadas. Relatamos o encontro de 6 pacientes não respondedores à associação de Interferon Peguilado e Ribavirina que negativamente seu PCR-RNA após a associação com talidomida. Trata-se do primeiro relato desta associação no tratamento da hepatite C encontrado na literatura.

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