Iscador Qu for chronic hepatitis C: an exploratory study

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SUMMARY. Five patients with chronic hepatitis C were treated for one year with the herbal immunomodulatory agent Iscador (Weleda, Schwäbisch Gmünd Germany). Two patients showed 6–20 fold decreases in viral load and normalisation of liver inflammation. The treatment was well tolerated; no serious side effects were observed. The quality of life improved on average. Iscador may have potential as a non toxic therapy for chronic hepatitis C treatment.

INTRODUCTION

For several decades a specific viral hepatitis, formerly called non-A non-B hepatitis, was known to exist as a disease entity, but it was not until 1989 that portions of the causative virus were cloned and identified as the hepatitis C virus (HCV). The virus transmission occurs parenterally, like in hepatitis B, mainly by blood transfusions, contaminated needles, sexual contact or during childbirth. Today, we know that 80% of non-A non-B hepatitis comprises HCV, placing this virus third as a cause of hepatitis after hepatitis A and B. The worldwide prevalence of chronic HCV is 170–200 million cases a year, making it a major health problem.[1] Chronic HCV infection is associated with progressive liver disease that may evolve insidiously to cirrhosis, which in turn carries an increased risk of hepatocellular carcinoma. HCV-induced liver cirrhosis is the most common reason for liver transplantation in Europe and the USA.

Spontaneous virus disappearance is very rare in chronic HCV infection. Interferon-A (IFN-A) in combination with Ribavirin has become the standard treatment for HCV patients in the past decade, and is given to prevent aggressive hepatitis, cirrhosis or hepatocellular carcinoma. The working mechanism of IFN-A in HCV consists of the inhibition of virus replication; the addition of Ribavirin increases this effect. Both response rate and duration of response are dependent on the cumulative dose. However, the response rate to this treatment is only 35–50%, relapses after discontinuing the treatment occur frequently, and the therapy has unpleasant side effects (headache, myalgia, arthralgia, flu-like symptoms, fever, and psychiatric disturbances), which often lead to poor compliance or even drop-outs.[2,3]

Recently, Matthes and Fintelman described some HCV patients having achieved complete elimination of HCV after treatment with Viscum album (mistletoe).[4,5] Among the medicines derived from mistletoe, Iscador is the most common, being licensed in the European Union and in several other countries worldwide. Iscador (Weleda AG, Schwäbisch Gmünd, Germany) is the brand name of an aqueous Viscum album, or European mistletoe, extract. Its main biologically active constituents, viscotoxins and lectins, have been characterized pharmacologically.[6] Both components have cytotoxic effects, but in different ways: viscotoxin damages the cell membrane, whereas lectin inhibits ribosomal protein synthesis.[7] Beta-galactoside specific lectins of mistletoe are also responsible for several immunomodulatory mechanisms in animals and in man, including dose-dependent enhancement of phagocytic activity of granulocytes and increases in natural killer- (NK-) and antibody-dependent cytotoxicity.[8] Also elevated secretion of tumour necrosis factor alpha (TNF-A), interleukin-1 and -6 (IL-1; IL-6)[9] and endogenous interferon (IFN) have been reported.[10] This might be the main rationale for Viscum album treatment in HCV. Until now, Iscador has mainly been used as complementary anticancer and immunomodulatory therapy, aiming at a reduction of disease activity and improvement of the

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quality of life.[11] Iscador is well tolerated by healthy subjects as well as by immunocompromised patients with viral disease like HIV.[12] Therefore, Iscador therapy for HCV could be very interesting both from a point of view of efficacy and in terms of convenience. Moreover, the costs of Viscum treatment are substantially lower than IFN therapy.

In the above-mentioned studies by Matthes and Fintelman, the patient groups were heterogeneous with regard to pretreatment, phase of disease and mistletoe therapy. This might have biased their final results. Therefore, in our exploratory study we wanted to investigate whether Iscador Qu treatment in non-IFN pretreated HCV patients:

- reduces the viral load (HCV-RNA) by at least 1 logarithmic grade (i.e. a tenfold reduction)[13]
- reduces liver inflammation (AST and ALT) by at least 50%, or even to normal
- at least does not decrease the quality of life.

PATIENTS AND METHODS

In 1998 and 1999, we studied five patients with chronic-HCV, treating them with Iscador for 12 months with a follow-up of 6 months after the treatment. Four patients had a history of IV drug abuse. All patients had liver disease related complaints such as tiredness, depression, abdominal pain etc. The patients were referred to the Berg en Bosch Medical Centre for internal medicine in Bilthoven, the Netherlands, an institution for outpatient specialist healthcare. About 50% of its patients are referred by the 80 anthroposophical general practitioners of our country, the other half of the patients by regular GPs. We have summarized the inclusion and exclusion criteria in Table 1.

The included patients were instructed to inject themselves subcutaneously. Because Iscador can cause local skin reactions, all patients underwent a pretreatment with incremental doses of Iscador Qu, (derived from mistletoe, harvested from the oak, Quercus) of 0.1 mg, 1 mg, and 5 mg. Then the treatment schedule during 12 months consisted of two ampoules Iscador Qu 5 mg Special subcutaneously three times weekly. The dose was temporarily reduced if this dose was not tolerated. Iscador Qu 5 mg Special ampoules contain 1 ml aqueous extract of 5 mg Viscum album, standardized on the basis of content of lectins (380 ng/ml) and viscotoxines (14 mg/ml). The concentrations have been determined by enzyme-linked lectin assay and high-performance liquid chromatografy.[14] Iscador Qu 5 mg Special was provided by Weleda to the requesting physician.

Initially, patients were evaluated clinically for signs of liver disease; also complete blood count, serum creatinin, albumin, PTT, ALT, AST, LDH, GGT, Alkaline Phosphatase, ANA, HCV-RNA, HCV genotype, HBsAg and HIV were measured. These tests were repeated after 2, 4, 6, 12 and 18 months, except for creatinin, ANA, HBsAg, HIV and HCV genotype. Blood samples for HCV-RNA were sent to the Laboratory of the Utrecht University Medical School to be assessed in a standard way.

Side effects were scored at each evaluation according to the WHO toxicity criteria list.[15] Before and after treatment, the Dutch Rotterdam Symptoms Check List (RSCL) quality of life questionnaire was completed. This measures four variables: physical symptom distress, psychological distress, activity and overall valuation of quality of life.[16] During the investigation, four months after the beginning of the treatment, we decided to add the SF-36 quality of life questionnaire. The SF-36 questionnaire was developed in the USA as one item of the Medical Outcome Study (MOS), a longitudinal study of the self-reported health situation of patients with chronic disease.[17]

RESULTS

During 1998, five patients (two males and three females) with HCV were treated with Iscador. There were no drop-outs. Patients did not report any side effects except temporary skin reactions at the injection site.

Inclusion criteria
age between 16 and 70 years
elevated serum levels of ALT (>1.5 normal), or fluctuating levels during the 6 previous months
positive for anti-HCV and HCV-RNA
informed consent

Exclusion criteria
decompensated liver disease
current alcoholism or drug abuse
serious comorbidity, with a life expectancy less than 2 years or severe psychiatric disorder leading to reduced patient compliance
previous immunosuppressive-, steroid-, or antiviral therapy
serum positivity for hepatitis B surface Antigen (HBsAg), anti human immunodeficiency virus (HIV), or anti nuclear antibodies (ANA)
elevated serum creatinine > 1.5 normal
lowered white cell count (<3.10.9 mmol/l) and / or platelet count (<80.10^9 mmol/l)

Patient	Gender	Age	Medical history	Diagnosis	Liver biopsy	Symptoms
1	m	36	16 years IV drug abuse	1995	HCV	anorexia
2	f	50	10 years IV drug abuse	1997	HCV, chron.act.hep	tiredness, with mild fibrosis, nausea
3	f	37	15 years IV drug abuse	1995	HCV, mild ch.	portal inflammation and periportal fibrosis tiredness, mild abdominal pain
4	m	46	1985, needlestick accident	1995	HCV	tiredness, abdominal pain, depression
5	f	55	probably sexual transmission	1995	HCV	tiredness, abdominal pain

Patient	Genotype	HCV-RNA before treatment (copies/ml)	HCV-RNA 6 months after treatment (copies/ml)
1	4C/4D	5.2×10^3	1.8×10^5
2	3A	2.7×10^5	4.4×10^4
3	2A/2C2	2.8×10^5	3.8×10^5
4	1A	4.3×10^5	1.9×10^5
5	1B	4.4×10^5	1.3×10^4

Demographic and clinical details are summarized in Table 2, and HCV-genotype of the patients and their HCV-RNA values before and after treatment are depicted in Table 3 (some intermediate values are missing because of a communications failure with the laboratory; the available values show no relevant changes). Table 4 shows liver function tests (AST and ALT) before, during and after treatment. Two of our patients (patient 2, genotype 3A and patient 5, genotype 1B) had a 6–20-fold reduction of HCV load (Table 3) 6 months after end of treatment. Also, two of the three patients with pretreatment impairment of liver function showed complete remission (patients 2 & 5) both for AST and ALT; a third (patient 1) had complete remission for AST and partial remission for ALT 6 months after stopping Iscador therapy (Table 4).

In Table 5 changes in quality of life perception (SF-36 and RSCL) during treatment are presented; decrease of distress is expressed by a positive change, increase of distress by a negative change. Changes in the SF-36 questionnaire scores are only available for four patients, because no measurements of patient 4 were performed at the 4 months treatment point. However, three patients clearly had a decrease of distress on balance (patients 1, 2 & 3). Patient 5 showed increased and decreased distress for the different variables. On average, all patients had a distinct decrease of distress according to the RSCL. In a number of variables, both in SF-36 and in RSCL, almost all patients scored a decrease in distress: role function-emotional, bodily pain, vitality, physical symptom distress, and overall valuation of life.

Six months after stopping Iscador treatment only patient 3 reported slight tiredness, the others were well. The three patients with previous permanent jobs were all working and had not had significant absence through illness.

DISCUSSION

In two out of five patients, Iscador treatment for 1 year was associated with 6–20-fold viral load reduction (HCV-RNA) and in complete remission of their elevated AST and ALT.

Although the course of hepatitis C is erratic, these changes are noteworthy for this unknown treatment modality. Moreover, one of these patients had genotype 1B, which is relatively resistant to other treatments. One other patient had an increase of HCV RNA, thus no conclusions can be made about viral reduction. The first aim of hepatitis C treatment is reduction of viral load, but normalization of AST and ALT is correlated with a better prognosis because of reduction in fibrosis and cirrhosis, and reduced development of hepatocellular carcinoma.[18] Therapy modalities which can cause normalization of transaminases may, therefore, be worth investigating.

Conventional IFN therapy for HCV has a negative impact on the quality of life, due to serious toxic side effects.[19] We did not notice any systemic toxicity

Patient	Before treatment	After 6 months treatment	End of treatment	6 months after treatment
1	49/100	9/72	44/98	1/79
2	4/59	28/33	21/33	22/36
3	27/27	19/17	22/21	29/39
4	19/36	18/35	23/58	15/40
5	51/102	30/65	27/58	10/14

SF-36 variables	Patient 1	Patient 2	Patient 3	Patient 4***	Patient 5
physical functioning	+5	0	+5	–	–5
role functioning-physical	–25	0	+25	–	–25
role functioning-emotional	+33	0	+66	–	+34
social functioning	0	0	+75	–	–25
bodily pain	0	+11	+66	–	+11
mental health	+4	+8	+32	–	–24
vitality	+10	+15	+20	–	+10
anxiety	0	+20	0	–	0
depression	+10	0	+40	–	–10
positive well-being	0	+10	+40	–	–5
general health perceptions	0	–5	+5	–	0
RSCL variables	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
physical symptom distress level	+7	+3	+9	+5	+6
psychological distress level	+33	0	+15	–5	+19
activity level	+4	0	+4	0	0
overall valuation of life	+16	+16	+16	+17	0

* Changes can take values between -100 and +100. A negative change indicates an increase in distress, a positive change indicates a decrease of distress.
** SF-36: the first measurement was after 4 month of treatment; the second was after 12 months of treatment. RSCL: the first measurement was at the beginning of treatment, the second was after 12 months of treatment.
*** For this patient there were no measurements available at the 4 month treatment point.

in this exploratory study. Our results suggest that Iscador treatment does not impair the quality of life, but even improves several aspects of it in HCV patients, who generally have liver-disease related complaints for many years. Interferon therapy for hepatitis C has shown to be more effective if it is given in a daily dose or/and if Ribavirin is added. Given the possible working mechanism of Iscador, this might also be relevant for this treatment.

In conclusion, our exploratory study in five patients with HCV treated with Iscador suggests that it may have beneficial effects on viral load, biochemical changes, and quality of life. Further studies on a larger scale are needed to assess the place of this potential new treatment, which is attractive also because of its substantial lower cost than conventional therapies. This could be particularly relevant to the third world, where at this time HCV is a major health-care problem and treatment is almost prohibitively expensive.

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