

# Interferon and ribavirin with or without amantadine for interferon non-responders with chronic hepatitis C

## A randomised, controlled pilot study

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## Summary

**Background/aims:** Treatment options for interferon-non-responders (INF-NR) with chronic hepatitis C are limited. Our aim was to compare efficacy and tolerability of an interferon-alfa-2a (INF), ribavirin (RIBA) and amantadine (AMA) combination with those of an INF and RIBA combination.

**Methods:** 30 patients with biopsy proven chronic hepatitis C were randomised to INF-RIBA-AMA or INF-RIBA, stratified according to genotype (1/4 versus 2/3) and presence or absence of cirrhosis. They were treated with INF 6 million units subcutaneously daily for the first four weeks, RIBA ( $\geq 75$  kg 1200 mg,  $< 75$  kg 1000 mg) with or without AMA 200 mg daily. If serum hepatitis C RNA was undetectable after 28 days, therapy was continued for a total of 48 weeks and INF was reduced to 6 million units thrice weekly (tiw). After

stopping therapy all patients were followed up for six months.

**Results:** The end of treatment response was 25% (4/16) after INF-RIBA-AMA and 29% (4/14) after INF-RIBA, and a sustained virologic response (SVR) was observed in 19% (3/16) in the triple therapy group compared to 14% (2/14) in the double therapy group, with a similar safety and tolerability profile.

**Conclusion:** Although similarly tolerated triple combination with INF, RIBA and AMA does not seem to offer relevant efficacy advantages over double combination with INF and RIBA in INF non-responders with chronic hepatitis C.

**Key words:** hepatitis C; drug therapy; amantadine; human study, triple therapy

## Introduction

Hepatitis C virus (HCV) infection follows a chronic course in the majority of subjects and leads in a significant proportion of patients within decades to liver cirrhosis and hepatocellular carcinoma [1–3]. HCV-associated liver disease is a leading cause of liver-related morbidity and mortality and of liver transplantation for end-stage liver disease in Western countries. While pharmacotherapy of chronic hepatitis C has evolved rapidly in recent years [4–10], even the best available treatment regimens combining pegylated interferons with ribavirin (RIBA) fail to clear the virus in 40–50% of patients [8–10]. Several therapeutic options have been investigated for patients with chronic hepatitis C not responding to previous in-

### Abbreviations used in this paper:

ALT alanine aminotransferase

AMA amantadine

AST Aspartate aminotransferase

HBV hepatitis B virus

HCV hepatitis C virus

copies cps

INF Interferon-alfa

INF-NR Interferon Non responder

n.s. non significant

RIBA ribavirin

SVR sustained virologic response

tiw thrice weekly

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terferon-alfa monotherapy, but no established treatment strategy exists for these patients. The retreatment of interferon (INF) non-responders with INF and RIBA was examined in several trials and was the subject of three meta-analyses [11–13]. Sustained virologic response (SVR) rates after re-treatment with INF (3x3–6 MIU/week s.c.) and RIBA (1000–1200 mg) varied widely from 0–21%, but in most studies the rates ranged from 12–15% [14]. Thus, additional therapeutic options are warranted.

In recent years beneficial effects of amantadine (AMA) monotherapy in hepatitis C virus infection have been reported in some [15, 16], but not all [17] clinical pilot studies. Two recent meta-analyses on the combination of INF-alfa with AMA yielded divergent results. One demonstrated a benefit for INF naïve patients [18], whereas in the second study, no such benefit could be observed [19].

In INF monotherapy non-responders double

therapy with INF-alfa and AMA was not effective [20–23].

Triple therapy with INF-alfa, RIBA and AMA however was significantly more efficient (48% SVR) than INF-alfa and RIBA (5% SVR) in INF monotherapy non-responders [24]. This was confirmed in a second randomised controlled trial [25]. In an open label pilot study however, the efficacy of triple therapy in INF monotherapy non-responders was associated with a low SVR of 0% [26].

The aim of the present study was, therefore, to investigate in a randomised, controlled trial the efficacy and safety/tolerability of INF-alfa, 6 MIU daily for four weeks followed by 6 MIU thrice weekly (tiw), RIBA and AMA compared to combination therapy of INF and RIBA in patients with chronic hepatitis C, non-responsive to a previous INF monotherapy.

## Patients and methods

### Patients

Patients of both genders, aged 18–65 years, with chronic hepatitis C who had previously failed to respond to INF-alfa-2a or -2b given in a dose of 3–6 million units three times weekly for at least 12 weeks were eligible to participate in the study. The entry criteria included: 1) elevated alanine aminotransferase (ALT) within 12 months of entry on at least two occasions, 2) positive HCV RNA test in serum by RT-PCR (Amplicor® HCV Monitor™ version 2.0, Roche Diagnostics, Basel, Switzerland) within 2 months of entry, and 3) a liver biopsy within 5 years before entry consistent with chronic hepatitis C.

Patients with one of the following were excluded from the study: any other cause of liver disease including hepatitis B virus (HBV) – coinfection (HBsAg pos.) and alcohol intake (>20 g/day in females and >40 g/day in males); a history of or actual decompensation of liver disease (ascites, variceal bleeding or encephalopathy); cirrhosis ≥8 Child-Pugh points; other clinically relevant disorders including cardiovascular, pulmonary, renal, metabolic, haematological, rheumatologic, neurological and psychiatric diseases, autoimmune disorders, HIV infection, immunosuppression within 12 months of entry, organ transplantation, malignant neoplastic disease within two years of study entry, illicit drug use within one year of study entry or psychosocial instability, pregnancy or lactation, refusal to practice effective contraception during treatment and follow-up or treatment with any investigational drug within six months of study entry.

Patients with one of the following laboratory abnormalities were also excluded: leucocytes <2000/ul, neutrophils <1000/ul, platelets <50000/ul, serum creatinine >1.5 times upper limit of normal, elevated thyroid stimulating hormone, alpha-fetoprotein above normal limits and/or focal lesion on ultrasound performed within one month of study entry.

### Study design

This is a randomised controlled pilot study on behalf of the Swiss Association of the Study of the Liver in 11 centres (see acknowledgments). Recruitment started in August 1999 and ended in June 2001. The study was approved by the local Ethic Committees of all participating centres and conducted in accordance with the declaration

of Helsinki and the guidelines on good clinical practice of the Swiss regulatory authorities (Interkantonale Kontrollstelle für Heilmittel, Berne, Switzerland). All patients gave written informed consent before enrolment.

Patients were randomised with a ratio of 1:1 to receive INF-alfa-2a, RIBA and AMA or INF-alfa-2a and RIBA. Randomisation was carried out in blocks of ten using random numbers stratified according to the presence/absence of cirrhosis and genotype ¼ or ¾, respectively. Cirrhosis was either defined by histology or on clinical grounds. INF-alfa-2a (Roferon® A), RIBA and AMA sulphate (PK Merz®) were provided by Roche Pharma (Schweiz) AG, Reinach, Switzerland. Treatment consisted of INF-alfa-2a 6 MIU sc daily for 4 weeks, followed by 6 MIU sc tiw for an additional 44 weeks, RIBA (<75 kg: 1000, ≥75 kg: 1200 mg) with or without AMA sulphate (100 mg po twice daily). Treatment was stopped, if after 4 weeks HCV RNA in serum remained detectable by RT-PCR (Amplicor® HCV Monitor™ version 2.0, Roche Diagnostics, Switzerland; detection limit: 1000 copies/ml). Patients were followed for 24 weeks after stopping therapy.

Patients were evaluated on an outpatient basis for safety/tolerability and efficacy at the end of treatment weeks 1, 2, 3, 4, 8 and subsequently every 4 weeks until week 48 as well as 12 and 24 weeks after stopping treatment.

Haematological tests (haemoglobin, leucocytes, neutrophils and platelet count) as well as biochemical tests (ALT, aspartate aminotransferase (AST), alkaline-phosphatase, gamma-glutamyltransferase, creatinine, albumin and prothrombin time) were performed by local laboratories. HCV RNA was determined by RT-PCR (Amplicor® HCV Monitor™ version 2.0, Roche Diagnostics, Switzerland; detection limit: 1000 copies (cps)/ml) in serum collected at baseline, at treatment weeks 4 and 48, and at follow-up week 24. The HCV genotype was determined using a reverse hybridisation assay (Inno-Lipa® HCV II, Innogenetics, Ghent, Belgium).

### Data analysis and statistics

Data were analysed for 1) sustained virologic response, ie HCV RNA in serum below detection limit (1000 cps/ml) at the end of follow-up week 24 and 2) ini-

tial and end of treatment virologic responses, ie HCV RNA below detection limit at end of treatment week 4 and 48, respectively, virologic breakthrough and relapse, ie reappearance of HCV RNA during therapy and follow-up, respectively, and for the corresponding biochemical efficacy measures, ie normalisation of ALT, at the respective time points. Safety and tolerability as reflected by clinical and laboratory adverse events and quality of life were described.

Efficacy analysis is based on the intention-to-treat populations, who were randomly assigned to treatment and received at least one dose of therapy. Missing data were treated by a worst case method, eg missing HCV RNA determinations during/after therapy were taken to have remained above detection limit.

All statistical analyses were performed using the SPSS 11.5.0 (2002) Statistical software package (SPSS Inc., Chicago, Illinois, USA).

## Results

### Baseline characteristics

Thirty-two patients were recruited for the pilot phase of whom two (one in the triple, one in the combination therapy group) withdrew written consent after baseline evaluation but before starting treatment. Thirty patients started the pilot phase. Figure 1 depicts the overall trial profile of this intention-to-treat population. Baseline variables (table 1) were similar in both groups, except genotype 1/4 infection and cirrhosis tended to be

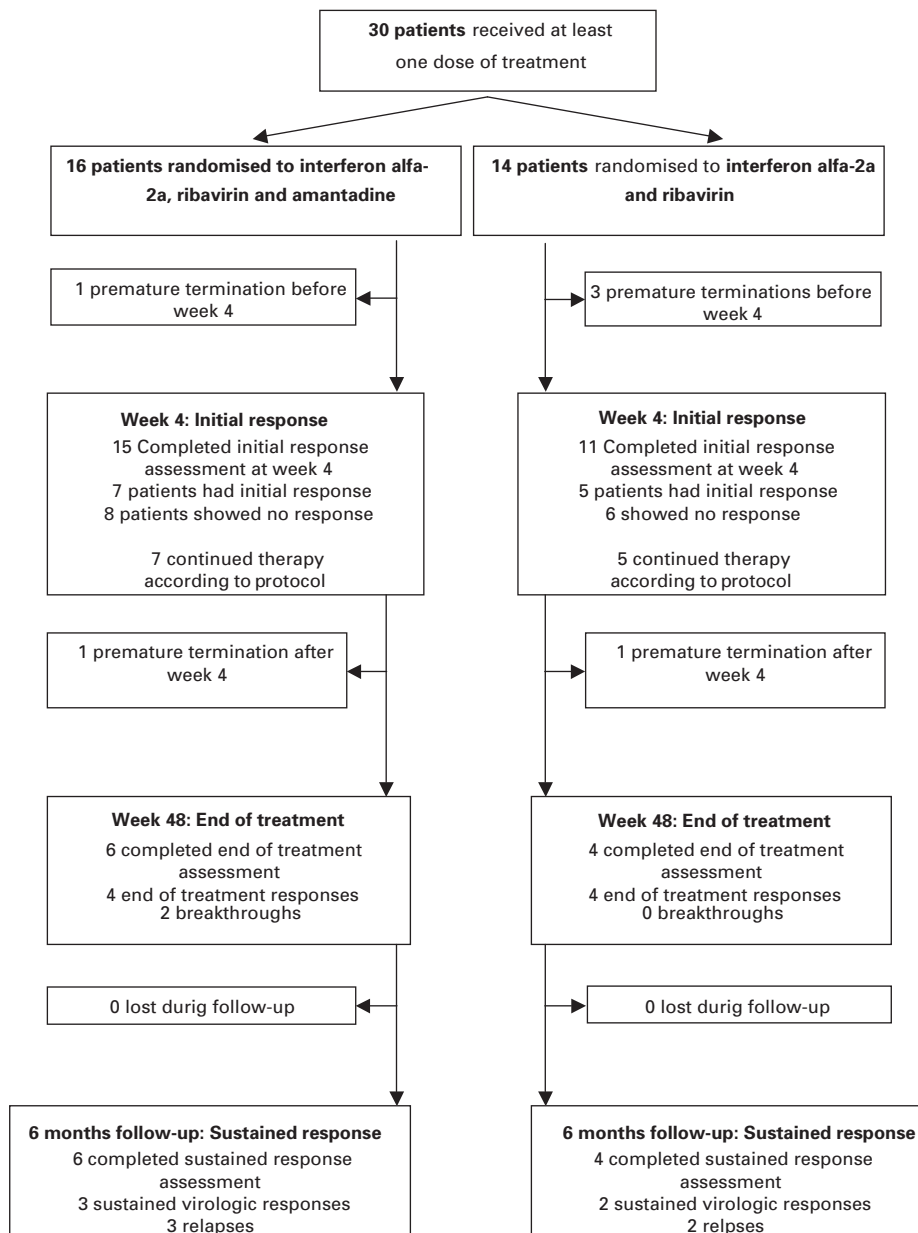
slightly more prevalent in the double and triple therapy group, respectively.

### Efficacy

#### *Virologic response*

Sustained virologic response tended to be slightly higher in the triple therapy (19%- 3/16) compared to the double therapy group (14%- 2/14). Moreover, initial virologic response (week 4)

**Figure 1**  
Overall trial profile of the intention-to-treat population.



**Table 1**

Baseline characteristics.

	IFN/RIBA/AMA (16 patients)	IFN/RIBA (14 patients)
Male n [%]	13 [81]	12 [86]
Body Mass Index Median, [range]	25 [20-33]	26 [21-40]
Age (yrs) Median, [range]	47 [28-65]	45 [23-59]
ALT* [U/l] Median, [range]	77[48-567]	89 [53-397]
Viraemia [106 copies/ml] Median, [range]	4.3 [0.16-25]	2.0 [0.12-26.2]
>2x106 copies/ml n [%]	56 [9]	50 [7]
Genotype Distribution		
1 + 4 n [%]	9 [56]	11[79]
2 + 3 n [%]	7 [44]	3 [21]
Cirrhosis n [%]	3 [19]	1 [7]

**Table 2**

Number of adverse events.

	Total	INF/RIBA/AMA	IFN/RIBA
Any adverse event	40	32	8
Flu-like symptoms	11	10	1
Nervous systema	14	10	4
Gastrointestinal tract	7	4	3
Bloodb	-	-	-
Skin	4	4	-
Cardiovascular system	1	1	-
Endocrine system	-	-	-
Respiratory system	-	-	-
Urinary tract	2	2	-
Other	1	1	-

a: including headache, dizziness, irritability, mood changes and major depression

b: mostly leucopenia, neutropenia and/or thrombocytopenia

tended to be higher in the triple therapy (44%-7/16 *vs* 36%- 5/14) whereas end of treatment response (week 48) were comparable in both groups (25%- 4/16 *vs* 29%- 4/14). Virologic relapse was similar between the two groups whereas viral breakthrough was slightly albeit not significantly higher in the triple therapy group.

### Safety and tolerability

A total of 40 adverse events were recorded and occurred more frequently in the triple therapy group (32) compared to the double therapy group [8]. Adverse events were mostly mild, attributable to INF-alfa and were of similar pattern and frequency in both treatment groups (table 2). Of all adverse events 40% were judged by the responsible investigators to be definitely related to the study medication; 44% of the adverse event in the triple therapy group and 25% the double therapy group, respectively.

Eleven adverse events, occurring in five (17 %) patients, were classified as serious by the investigators: eight in three (19%) patients of the triple therapy group and three in two (14%) patients of the double therapy group, respectively. Eight of these eleven serious adverse events (seven in the triple therapy group and one in the double therapy group) were classified by the investigators as definitely or probably related to the study treatment. Adverse events led to a total of seven episodes of dose reductions (two in the triple therapy, and five in the double therapy group).

Six patients (two in the triple and four in the double therapy group) terminated therapy prematurely: four of the premature terminations (two in the triple therapy, two in the double therapy group) were for adverse events and two in the double therapy group because of the patient's wish.

## Discussion

Pharmacotherapy of chronic hepatitis C has evolved rapidly in recent years [4-9], but even with the best currently available treatment regimens combining pegylated interferons with RIBA only

50-60% of patients definitively clear the virus [8, 9]. This non-responder percentage was even higher in the area of INF monotherapy. Therefore an increasing number of non-responders patients

**Table 3**

Summary of the most important findings from the studies published as full papers investigating the effect of triple therapy in interferon monotherapy non-responders and the current study.

Author	Study design	Treatment	Patients n	Prev treatment	Genotype I (%)	advanced fibrosis cirrhosis (%)	SVR <sup>6</sup> %
Brillanti (27)	RCT	INF-RIBA-AMA1	10	INF for 6 months	40	50	30
		INF-RIBA	10		40	40	0
Brillanti (24)	RCT	INF (3MIU)-RIBA-AMA2	40	3 × 3 or 3 × 6 MIU INF for	58	25	48
		INF – RIBA	20	at least 4 months	55	25	5
Adinolfi (25)	RCT	INF (3 × 3)-RIBA3	44	3 × 3 or 3 × 6 MIU INF for at	70	25	2
		INF-RIBA	46	for months	71	26	4
		INF (3 MIU)-RIBA-AMA	24		72	33	25
Berg (26)	open label	INF-RIBA-AMA4	14	INF for at least 6 months	93	64	0
Current study	RCT	INF-RIBA	14	INF for at least 3 months	79	7	14
		INF-RIBA-AMA5	16	56	19	19	

1: INF-alfa-2b 5 MIU every other day, RIBA: <75 kg = 800 mg, ≥75 kg = 1000 mg, Amantadine hydrochloride 2×100 mg

2: INF-alfa-n3 3 MIU every other day, RIBA: <75 kg = 800 mg, ≥75 kg = 1000 mg, Amantadine 100 mg

3: INF-alfa-2b 3 MIU daily for the first 4 weeks, then 3 MIU tiw for a total of 12 month, RIBA: 1000 mg, Amantadine hydrochloride 2×100 mg

4: INF-alfa-2a 9 MIU daily for 7 days, 9 MIU every other day for 5 weeks, 6 MIU tiw for 6 weeks, 36 weeks, RIBA: <75kg = 1000 mg, ≥75 kg = 1200 mg, Amantadine sulphate 2x100 mg

5: INF-alfa-2a 6 MIU daily for 4 weeks, then 3x6 MIU for 44 weeks, RIBA: <75 kg = 1000 mg, ≥75 kg = 1200 mg, Amantadine sulphate 2×100 mg

6: SVR: Sustained virological response, ie HCV-RNA not detectable in serum 6 months after completing therapy, except in reference 25, where SVR was determined after 12 months

are in need of an effective antiviral treatment. Re-treatment with a double therapy combining INF and RIBA or AMA showed only limited therapeutic efficacy in INF monotherapy non-responders [11, 12, 20–23].

Preliminary studies with triple therapy in INF monotherapy non-responders yielded very conflicting results with sustained virologic response ranging from 0 to 48% [24–27].

In the present study we observed a trend towards a higher sustained virologic response rate in the triple therapy group with 19% compared to 14% in the combination therapy group. However, due to the small patient number, it is difficult to draw firm conclusions from our study. In a recent meta-analysis, evaluating the effect of AMA for the treatment of chronic hepatitis C, eight randomised controlled trials were identified which compared triple therapy with AMA to combination therapy [19]. Although there was no significant effect of AMA on end of treatment response, a significant effect on sustained virological response was found, with a mean difference of 8%. The sustained virological response in the triple therapy group was 22.9% and 14.9% in the double therapy group, almost identical to our results.

However only four of the eight randomised controlled trials have been published as full papers so far [24, 25, 28, 29] and only two studies were specifically designed for INF monotherapy non-responders [24, 25]. In addition two pilot studies [26, 27] investigating the effect of triple compared to double therapy in INF monotherapy non-responders have been published as full papers. These

are summarised in table 3. In the three studies, reporting a significant benefit of triple compared to double therapy, the SVR in the double therapy group was extremely low, whereas it was surprisingly high for the triple therapy group in the two studies by Brillanti. In our study the SVR in the double therapy group was similar to the average SVR reported in recent reviews [14]. Whether efficacy differences between the aforementioned studies might be explained by differing patient populations, different study designs and or different formulations of AMA (hydrochloride versus sulphate), remains unclear.

The intense INF-alfa induction dosing was relatively well-tolerated. Nevertheless 72% of the patients in the triple therapy group and 42% in the double therapy group experienced side effects during the first four weeks. Most of the side effects were however mild and during the induction phase, only one patient in the triple therapy group and three in the double therapy group stopped treatment. Luckily, today patients with chronic hepatitis C, including non-responders can be treated with pegylated interferon in combination with RIBA, which necessitates only one injection per week and might offer some slightly better chance of cure.

In conclusion, addition of AMA to INF-alfa-2a and RIBA may increase efficacy marginally, at best in INF non-responder patients with chronic hepatitis C. While well-tolerated, the routine clinical use of triple therapy seems not justified in INF-alfa non-responder patients with chronic hepatitis C.



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