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International, Multicenter, Randomized, Controlled Study Comparing Dynamically Individualized Versus Standard Treatment in Patients with Chronic Hepatitis C *, **

Stefan Zeuzem[1], Jean-Michel Pawlotsky[2], Esther Lukasiewicz[3], Michael von Wagner[1], Ioannis Goulis[4], Yoav Lurie[5], Elia Gianfranco[6], Jan-Maarten Vrolijk[7], Juan I. Esteban[8], Christophe Hezode[2], Martin Lagging[9], Francesco Negro[10], Alexandre Soulier[2], Elke Verheij-Hart[7], Bettina Hansen[7], Ronen Tal[3], Carlo Ferrari[6], Solko W. Schalm[7], Avidan U. Neumann[3]

[1] Saarland University Hospital, Homburg/Saar, Germany
[2] Hôspital Henri Mondor, Université Paris XII, Créteil, France
[3] Bar-Ilan University, Ramat-Gan, Israel
[4] Aristotle University of Thessaloniki, Thessaloniki, Greece
[5] Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel
[6] Azienda Ospedaliera di Parma, Parma, Italy
[7] University Hospital Rotterdam Dijkzigt, Rotterdam, The Netherlands
[8] Hospital General Vall d'Hebron, Barcelona, Spain
[9] University of Gothenburg, Gothenburg, Sweden
[10] Hospital University of Geneva, Geneva, Switzerland

Background and Aims: **The aim of this study was to increase virologic response rates by individualized treatment according to the early virologic response.**

Methods: **Serum HCV-RNA was frequently quantified in patients with chronic hepatitis C (n=270) treated with peginterferon alfa-2a (180 µg/week) and ribavirin (1000-1200 mg/day). After 6 weeks patients were classified as rapid (RVR), slow (SPR), flat (FPR), or null responders (NUR) and randomized within each viral kinetic class to continue therapy either with an individualized or standard regimen. Individualized therapy comprised peginterferon monotherapy (48 weeks) or shorter combination therapy (24 weeks) for RVR, triple therapy with histamine (1 mg/day) (48 weeks) or prolonged combination therapy (72 weeks) for SPR, triple therapy for FPR, and high-dose peginterferon (360 µg/week) plus ribavirin for NUR patients.**

Results: **Patients were categorized as RVR (n=171), SPR (n=65), FPR (n=10), or NUR (n=22). Overall end-of-treatment and sustained virologic response rates were 77 and 60% in the individualized and 77 and 66% in the standard treatment arm, respectively. Histamine in addition to peginterferon and ribavirin and highdose peginterferon plus ribavirin did not improve virologic response rates in patients with FPR and NUR, respectively.**

Conclusions: **An improvement in virologic efficacy was not achieved with the available individualized treatment options.**

Keywords: **Hepatitis C virus; Pegylated interferon; Ribavirin; Histamine; HCV-RNA quantification; Viral kinetics**

Introduction

Combination therapy with peginterferon alfa and ribavirin for 48 weeks achieves sustained virologic response rates of 54-63% in patients with chronic hepatitis C[(1-3)]. However, it must be anticipated that current therapy recommendations lead to under-treatment in some and over-treatment in other individuals. Current guidelines only recommend a different treatment duration for

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Correspondence:
Klinik für Innere Medizin II, Universitätsklinikum des Saarlandes, 66421 Homburg/Saar, Germany.

Tel: *+49 6841 16 23201*
Fax: *+49 6841 16 23267*

E-mail: *Zeuzem@uniklinik-saarland.de*

patients infected with HCV-1 and those infected with HCV-2/3 (48 and 24 weeks, respectively). Furthermore, early discontinuation of antiviral therapy is suggested for HCV-1 infected patients who cannot achieve a 2 log decline of serum HCV-RNA within the initial 12 weeks of treatment[4, 5].

In the present study we compare a dynamically individualized treatment schedule according to the early virologic response versus a standard of care combination therapy with peginterferon alfa-2a plus ribavirin for 48 weeks. The primary aim of this study was to increase the sustained virologic response rate by optimizing dose and treatment duration of available drugs.

Patients and Methods

Inclusion and Exclusion Criteria

Previously untreated patients with compensated liver disease and the following characteristics were eligible: positive test for anti-HCV antibody, HCV-RNA >1000 IU/mL (Cobas Amplicor HCV Monitor v2.0, Roche Diagnostics, Branchburg, NJ), two serum alanine aminotransferase values above the upper limit of normal within 6 months of treatment initiation, and a pretreatment (within previous 12 months) liver biopsy consistent with a diagnosis of chronic hepatitis C. Major exclusion criteria were identical to previous studies[2,3]. Because of the possibility of allocation to histamine dihydrochloride therapy within the study, patients using H1- or H2-receptor antagonists, antihypertensive agents, anticoagulants, antidepressants with the exception of SSRIs during antiviral therapy were also not enrolled.

Study Design

This phase III, open-label, randomized, multicenter trial was conducted by the DITTO-HCV study group between February 2001 and November 2003. The study was approved by ethics committees at each center and all patients provided written informed consent. The study was designed by the members of the steering committee (C.F., A.U.N., J.-M. P., S.W.S., S.Z.), data were collected by the investigators and data analysis was again performed by the members of the steering committee of DITTO-HCV study group.

Patients were initially treated for 6 weeks with 180 µg peginterferon alfa-2a once weekly (Pegasys, Hoffmann-LaRoche, Basel, Switzerland) and 1000-1200 mg ribavirin daily (Copegus, Hoffmann-LaRoche). HCV-RNA was quantified on days 0, 1, 4, 7, 8, 15, 22, and 29. Patients were classified according to their viral kinetic pattern and randomized within each viral kinetic class to either an individualized treatment regimen or to a control group (Fig. 1). Investigators and patients remained blinded for the HCV-RNA results until randomization. Patients randomized to the control group continued therapy with peginterferon alfa-2a (180 µg) and ribavirin (1000-1200 mg) for further 42 weeks.

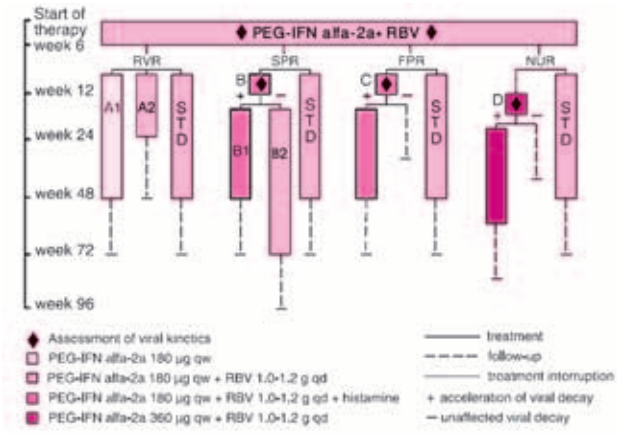

Fig 1. Treatment allocation of patients with chronic hepatitis C according to initial virologic response pattern.

Mathematical Modeling and Viral Kinetic Classes

The individualized treatment strategy is based on results from modeling viral dynamics[6, 7]. Typically, a biphasic pattern of viral decay can be observed. Rapid viral response (RVR) was defined as a total log drop of HCV-RNA during the first 4 weeks 2 and a second-phase decline 0.09/day. Slow partial response (SPR) was defined as no RVR but a second phase decline 0.09/day and (i) a log drop of HCV-RNA during the first 4 weeks 1 or (ii) a log drop of HCV-RNA during the first 4 weeks 0.6 and a first-phase decline of 0.5 log. Flat partial response (FPR) was defined as no RVR or SPR but a first-phase decline of 0.5 log, whereas null response (NUR) was defined as no RVR or SPR and a first-phase decline £0.5 log. Initial viral kinetic characteristics and the first- and second-phase decline were assessed by different methods (full biphasic viral kinetics fit; piecewise linear fit; simplified rule using baseline, day 4 and 29; bootstrap method). The worst response class was chosen as final classification in each patient.

Individual Treatment Regimens

Patients with an RVR were randomized to group A1, A2, or control group (STD) (1:1:2). Patients in group A1 received peginterferon alone for additional

42 weeks and patients in group A2 peginterferon plus ribavirin for additional 18 weeks. Patients with SPR were randomized to group B or control group (1:1). The patients in group B received histamine dihydrochloride (1 mg s.c. daily) in addition to peginterferon and ribavirin for 8 weeks. During this period the viral kinetic response was reassessed (HCV-RNA quantification at days 43, 50, 57, 71, 85). Patients with an accelerated viral decline (slope 0.09/day) remained on triple therapy for additional 34 weeks (B1). The remaining patients in group B stopped histamine and continued peginterferon plus ribavirin for additional 58 weeks (B2). Patients with FPR were randomized to group C or control group (1:1). Patients in group C received histamine dihydrochloride (1 mg s.c. daily) in addition to peginterferon and ribavirin for 8 weeks. As for patients in group B the viral kinetic response was reassessed. Patients with an accelerated viral decline (slope 0.09/day) continued on triple therapy for additional 34 weeks, while those in group C who showed no virologic response to histamine, discontinued all trial medication. Patients with NUR were randomized to group D or control group (1:1). Considering interferon resistance to 180 µg peginterferon alfa-2a plus ribavirin, patients in group D first discontinued antiviral therapy for 6 weeks. Subsequently, patients were restarted on 360 µg peginterferon alfa-2a qw plus ribavirin. For 6 weeks the HCV-RNA levels were monitored (day 0, 1, 4, 7, 8, 15, 22, 29). Antiviral therapy was continued for additional 42 weeks in patients who showed a viral decline with a slope <0.09/day, all other patients stopped treatment.

At the end of treatment, all patients in the individualized treatment regimens as well as in the control group were followed for an additional 24 week untreated period.

Dose Modification and Discontinuation

Treatment was discontinued at the discretion of the investigator in two patients because HCV-RNA was detectable at week 24.

Patients in arm B2 stopped therapy in case of viral break-through before week 48. Patients in group C and D treated for 8 weeks without a viral decline (slope <0.09/day) were considered non-responders and also discontinued therapy. Adverse events and laboratory values were assessed at baseline, at weeks 1, 2, 4, 6, 8, 10, 12, and then every 6 weeks for the rest of the study period. Patients who discontinued their assigned treatment were encouraged to remain in the study for assessments in the 24-week follow-up period. The protocol permitted dose modifications for patients who had clinically significant adverse events or important abnormalities in laboratory values. In patients treated with 180 µg peginterferon alfa-2a a 25, 50, or 75% reduction, in patients treated with 360 µg a 50, 62.5, or 75% reduction was scheduled. Ribavirin was reduced by 50% and for histamine the administration time was doubled from 10 to 20 min. If toxicity continued, the histamine dose was reduced by 20% at the extended injection time. On resolution of the event or abnormality, only doses for peginterferon and ribavirin could be restored to their original levels.

Study End Points and Objectives

The primary end point was sustained virologic response, the secondary endpoint virologic end-of-treatment response (HCV-RNA <50 IU/mL; Cobas Amplicor™ HCV v2.0). The main objective of the study was to test for a statistically significant difference between the efficacy endpoint rates of individualized and standard treatment. Secondary objectives of the study were (i) to find the distribution of patients within the different viral kinetic response categories, (ii) to assess viral kinetics in patients treated with peginterferon alfa-2a, ribavirin with or without histamine, and (iii) to test for statistically significant differences between the sustained virologic response rates of the dynamically individualized treatment and the control arm for viral kinetic response categories separately.

Statistical Analysis

Within each viral kinetic response category patients were randomized according to Pocock's minimization method to balance the distribution of HCV genotype and center between the treatment arms[8]. A power of 80% and a two-sided significance level of 0.05 were used in the calculation to detect an improvement from 43 to 68% in the sustained virologic response rate of the individualized treatment over standard therapy for the total study population. Due to the exploratory nature of the present study, we did not expect to prove the non-inferiority of the individualized arm of patients with RVR (A1, A2) in comparison with the control group. To detect an increase in the sustained virologic response rate from 5% (for NUR and FPR) or 10% (for SPR) in the control group (STD) to 50% in the individualized treatment groups (D, C, B1, and B2, respectively), the number of evaluable patients required was 38 for the NUR and FPR groups and 50 for the SPR group. Because the fraction of patients in these groups was expected

to be 55% of the study population, a total of 240 evaluable patients was anticipated. Efficacy analysis was based on an intention-to-treat population. All patients who received at least one dose of study medication were included in the safety analysis. Fisher's exact, c^2, Student's t, and Wilcoxon tests were applied as appropriate. All tests were two-tailed for a significance level of 0.05. The baseline variables sex, age, BMI, weight, fibrosis, HCV-RNA (>800,000 versus £800,000 IU/mL), normalized ALT (£median versus > median), and HCV genotype (HCV-2/3 versus HCV-1, HCV-2/3 versus HCV-4/5) were analyzed for association with sustained virologic response.

Statistical analyses were done using SPSS for Windows, release 12, Chicago, IL.

Results

Characteristics of the Patients

Two-hundred-seventy-three patients with chronic hepatitis C were enrolled, 270 patients completed the initial 6 weeks of combination treatment and were randomized (Fig. 2). Baseline host and virus-related variables were similar in the standard and the individualized treatment groups (Table 1).

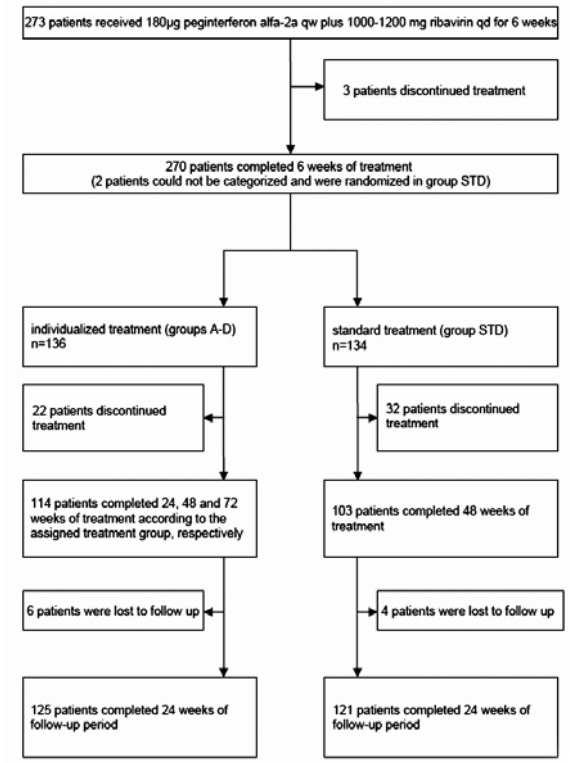

Fig 2. Flow of participants through the study. Patients who withdrew prematurely from treatment, were encouraged to return for follow-up. For this reason, the number of patients who completed follow-up is higher than the number of patients who completed treatment.

Initial Viral Kinetics and Response Categories

Patients were categorized as RVR (n=171), SPR (n=65), FPR (n=10), or NUR (n=22). More than 90% of patients infected with HCV-2/3 were rapid responders compared with 51% of patients infected with HCV-1 (Table 1).

Efficacy

Treatment individualization could not improve virologic efficacy compared with standard combination therapy. The overall end-of-treatment and sustained virologic response rates were 77 and 60% in the individualized and 77 and 66% (P= n.s.) in the standard treatment arm, respectively. Sustained virologic response rates in the individualized and the standard arm according to HCV genotype are shown in Table 2. From univariate analysis, baseline characteristics associated with sustained virologic response in all patients of the control arm were HCV-2/3 (P=0.002), baseline HCV-RNA £800,000 IU/mL (P=0.12), and age (P=0.14).

Rapid Virologic Responders (RVR)

Although sustained virologic response rates among patients with HCV-1 infection seemed lower in groups A1 and A2 (67% and 65%, respectively) than in STD (83%), the difference did not reach statistical significance, possibly because of a lack of power. When stratifying by baseline HCV-RNA among HCV-1 infected patients, differences in sustained virologic response rates between group A1 and STD and between A2 and STD achieved statistical significance in patients with a baseline HCV-RNA > 800,000 IU/mL, but not in patients with baseline HCV-RNA £800,000 IU/mL. Patients in group A1 with a high baseline HCV-RNA (n=15) had a lower sustained virologic rate compared with patients in the respective STD group (n=25) with high baseline HCV-RNA (53 versus 83%, P=0.04). Similarly, patients in group A2 with a high baseline HCV-RNA (n=12) had a lower sustained virologic rate than patients in the respective STD group with high baseline HCV-RNA (50 versus 83%, P=0.05)

Slow Partial Responders (SPR)

In patients randomized to the individualized treatment arm, histamine was added and the virologic response reassessed within an additional 6-week

Table 1. Demographic, biochemical, molecular, and histological profile of patients with chronic hepatitis C at baseline

	All patients (n=268)[a]	A1 (n=44)	A2 (n=43)	SDT (n=84)	B1 (n=9)	B2 (n=24)	STD (n=32)	C (n=5)	STD (n=5)	D (n=11)	STD (n=11)
Demography											
No. (M/F)	179/89	31/13	33/10	55/29	4/5	17/7	21/11	5/0	2/3	6/5	5/6
Caucasian	256(95%)	40(91%)	42(98%)	79(94%)	9(100%)	24(100%)	32(100%)	5(100%)	4(80%)	10(91%)	11(100%)
Body weight (kg)[b]											
	74.3 ¡13.4	72.2 ¡13.3	74.7 ¡12.7	74.2 ¡11.8	72.5 ¡9.9	74.3 ¡14.2	74.6 ¡16.7	86.0 ¡9.3	67.2 ¡9.9	79.0+14.6	71.2 ¡10.4
Mean age (years)[b]	41.6 ¡10.2	42.2 ¡9.9	39.1 ¡10.2	40.4 ¡9.8	47.0 ¡4.9	43.7 ¡10.0	41.4 ¡10.7	45.8 ¡10.7	41.2 ¡14.3	42.6 ¡11.9	44.6 ¡11.2
Biochemistry											
ALT(X ULN)[c]	2.1[0.8-58.8]	1.8[0.8-58.8]	2.5[0.9-6.5]	2.3[0.8-22.7]	1.9[1.1-4.9]	2.0[0.9-5.9]	1.8[1.0-8.1]	1.8[1.1-4.6]	2.6[1.0-5.1]	2.2[0.9-10.7]	2.6[1.1-32.2]
Molecular Parameters											
HCV-1	177(66%)	21(48%)	23(54%)	47(56%)	9(100%)	22(92%)	30(94%)	4(80%)	4(80%)	9(82%)	8(73%)
HCV-2	23(9%)	6(14%)	4(9%)	12(14%)	0	1(4%)	0	0	0	0	0
HCV-3	54(20%)	12(27%)	15(35%)	23(28%)	0	1(4%)	2(6%)	0	0	0	1(9%)
HCV-4.5	14(5%)	5(11%)	1(2%)	2(2%)	0	0	0	1(20%)	1(20%)	2(18%)	2(18%)
Baseline	1.8[0.002-27]	1.9[0.002-9]	1.9[0.02-27]	1.1[0.002- 16]	3.5[0.5-13]	2.0[0.2-14]	2.9[0.03-16]	6.1[0.1-13]	2.0[0.2-5]	2.0[0.09-11]	1.2[0.1-13]
HCV-RNA (106 IU/mL)[c] Ishak scorec,[d]											
A (interface hepatitis)	2.0[0-3]	2.0[0-3]	1.0[0-3]	1.0[0-3]	2.0[0-2]	1.5[0-3]	2.0[0-3]	3.0[0-3]	1.0[1-2]	2.0[0-3]	2.0[2-3]
B (confluent necrosis)	0.0[0-0]	0.0[0-0]	0.0[0-0]	0.0[0-0]	0.0[0-0]	0.0[0-0]	0.0[0-0]	0.0[0-0]	0.0[0-0]	0.0[0-0]	0.0[0-0]
C (focal inflammation)	2.0[0-3]	2.0[1-3]	2.0[0-3]	2.0[0-3]	2.0[1-3]	2.0[1-3]	2.0[1-2]	2.0[1-3]	2.0[1-3]	2.0[1-3]	2.0[1-3]
D (portal inflammation)	2.0[0-3]	1.0[1-3]	2.0[0-3]	1.0[0-3]	2.0[0-2]	1.5[1-3]	2.0[2-3]	1.5[1-3]	1.0[1-3]	2.0[1-3]	2.0[1-3]
A-D (total inflammation)	5.0[0-9]	5.0[2-8]	5.0[0-8]	5.0[0-9]	6.0[1-7]	4.5[2-9]	5.0[1-8]	6.5[1-8]	5.0[3-7]	6.5[4-9]	7.0[4-8]
F (fibrosis)	2.0[0-6]	2.0[0-6]	2.0[0-5]	2.0[0-6]	2.0[0-5]	2.0[0-6]	3.0[0-6]	2.5[0-6]	2.0[1-5]	3.0[1-5]	2.5[2-6]
Number of patients with fibrosis stage 5 or 6 [d]	35	6	3	7	1	4	8	1	1	2	2

a- Two patients could not be classified to a viral kinetic pattern: one male patient infected with HCV-1 had a viral load of 800 IU/mL at day 0 and HCV-RNA immediately become undetectable, the other patient (female; infected with HCV-4) had strong oscillations during the first month.
b- mean ¡ standard deviation; A1, A2 B1, B2, C, D see Fig 1, SDT refers to standard combination treatment.
c- median[range].
d- data from the central pathologist (n=230).

kinetic study period. Nine of 33 patients showed an accelerated virologic response and continued triple therapy for a total treatment duration of 48 weeks (B1). In contrast, 24 of 33 patients showed no effect of histamine on the viral decline. In these patients histamine was discontinued and patients treated with peginterferon alfa-2a plus ribavirin for a total of 72 weeks (B2). Ten of 13 patients who were HCV-RNA negative at week 24 of therapy and only 2 of 11 patients who remained HCV-RNA positive at week 24 achieved a sustained virologic response in arm B2 (Table 2).

Flat Partial and Null Responders (FPR and NUR)

One out of five patients randomized into arm C showed an accelerated viral decline after addition of histamine and continued triple therapy for a total of 48 weeks. This patient and no patient in the standard group achieved a sustained virologic response. Only one of the 11 patients in arm D showed an acceleration of viral decline, continued high-dose peginterferon for 48 weeks, and achieved a sustained virologic response. Two of the 11 patients with an initial null-response who were randomized to continue standard combination therapy for 48 weeks achieved a sustained virologic response (Table 2).

Safety

Adverse events were typical of those previously reported for combination therapy with (pegylated) interferon and ribavirin[1-3]. In Table 3 adverse events of special interest are summarized. Nineteen serious adverse events were reported, including

Table 2. End-of-treatment (ETR) and sustained virologic response rates (SVR) according to HCV genotype and initial virologic response

		All patients		Rapid responders(RVR)			Slow responders(SPR)			Flat responders (FPR)		Null responder (NUR)	
		Individual	STD*	A1	A2	STD	B1	B2	STD	C	STD	D	STD
All genotypes	ETR	1041/136 (77%)	103/134 (77%)	41/44 (93%)	39/43 (91%)	77/84 (92%)	4/9 (44%)	18/24 (75%)	21/32 (66%)	1/5 (20%)	1/5 (20%)	1/11 (9%)	3/11 (27%)
	SVR	81/136 (60%)	89/134 (66%)	33/44 (75%)	34/43 (79%)	71/84 (85%)	0/9(0%) -	12/24 (50%)	15/32 (47%)	1/5 (20%)	0/5(0%) -	1/11 (9%)	2/11 (18%)z
HCV-1	ETR	62/88 (71%)	65/90 (72%)	19/21 (91%)	20/23 (87%)	42/47 (89%)	4/9 (44%)	17/22 (77%)	19/30 (63%)	1/4 (25%)	1/4 (20%)	1/9 (11%)	2/8 (25%)
	SVR	42/88 (48%)	54/90 (60%)	14/21 (67%)	15/23 (65%)	39/47 (83%)	0/9(0%) -	11/22 (50%)	13/30 (43%)	1/4 (25%)	0/4(0%) -	1/9 (11%)	1/8 (13%)
HCV-2,3	ETR	37/39 (95%)	35/38 (92%)	18/18 (100%)	18/19 (95%)	33/35 (94%)	- -	1/2 (50%)	2/2 (100%)	- -	- -	- -	0/1(0%) -
	SVR	35/39 (90%)	33/38 (87%)	16/18 (89%)	18/19 (95%)	31/35 (89%)	- -	1/2 (50%)	2/2 (100%)	- -	- -	- -	0/1(0%) -
HCV-4,5	ETR	5/9 (56%)	3/6 (50%)	4/5 (80%)	1/1 (100%)	2/2 (100%)	- -	- -	- -	0/1(0%) -	0/1(0%) -	0/2(0%) -	1/2 (50%)
	SVR	4/9 (44%)	2/6 (33%)	3/5 (60%)	1/1 (100%)	1/2 (50%)	- -	- -	- -	0/1(0%) -	0/1(0%) -	0/2(0%) -	1/2 (50%)

Two patients could not be classified to a viral kinetic pattern and were rendomized to the control group (STD). Therefore, the total STD group comprises 134 patients, while the sum of STD patients categorized according to the initial viral decay (RVR, SPR, FPR, NUR) adds up only to 132 patients.

Table 3. Adverse events of special interest according to treatment group

	All patients (n=270)	A1 (n=44)	A2 (n=43)	B1 (n=9)	B2 (n=24)	C (n=5)	D (n=11)	STD (n=134)
Discontinuation	54	4	4	4	7	0	3	32
Dose modification								
Due to adverse event	96	13	9	9	8	0	6	51
Due to laboratory abnormality	52	1	4	11	8	0	0	28
Neutropenia	82(30%)	13(30%)	11(26%)	4(44%)	4(17%)	0	4(36%)	46(34%)
Anemia	60(22%)	7(16%)	7(16%)	7(78%)	7(29%)	0	1(9%)	31(23%)
Flushinga	11(4%)	3(7%)	0	0	0	0	1(9%)	7(5%)
Thrombocytopenia	15(6%)	0	0	7(78%)	5(21%)	3(60%)	0	0
Fatigue	15(6%)	1(2%)	0	0	7(29%)	0	0	7(5%)
Headachea	14(5%)	0	0	8(89%)	4(17%)	2(40%)	0	0
Urticaria	10(4%)	0	0	2(22%)	3(3%)	1(20%)	0	4(3%)
Depression	9(3%)	0	0	2(22%)	1(4%)	0	1(9%)	5(4%)
Dyspnea	7(3%)	0	1(2%)	2(22%)	1(4%)	0	0	3(2%)
Tachycardiaa	6(2%)	0	0	3(33%)	1(4%)	2(40%)	0	0
Asthenia	6(2%)	1(2%)	1(2%)	0	1(4%)	1(20%)	0	2(1%)

Adverse events of special interest were defined as serious adverse events and as all non-serious adverse events uncommon for pegylated interferon or ribavirin, adverse events leading to dose modification, and certain laboratory abnormalities (anemia, neutrocytopenia, thrombocytopenia).

febrile neutropenia, appendicitis, ileus, oral lichen planus, gastroenteritis, renal colic, pharyngitis, cerebral infarction, anxiety, loss of consciousness, malignant melanoma, generalized urticaria, pregnancy of partner, chronic fungal infection and renal failure, violent behavior, chorioretinitis, hemolytic anemia, and self-limiting episode of blurred vision.

Three patients discontinued combination therapy within the initial 6 weeks of treatment: two patients because of an adverse event (urticaria and depression) and one patient due to personal reasons. Peginterferon alfa-2a and ribavirin were dose-reduced in 34 and 31 patients, respectively, with no significant differences between the individualized and standard arms. Thirty-eight patients received histamine which was generally well tolerated. Typical side effects associated with histamine treatment were flushing, headache, and tachycardia (Table 3). Peginterferon alfa-2a (360 µg/week) plus ribavirin was given to 11 patients in group D for at least 6 weeks. The one patient who continued beyond this time point tolerated the high dose well for the complete 48-week treatment course.

Discussion

The present study represents the largest cohort of patients with chronic hepatitis C in whom the initial viral kinetics were prospectively assessed. From previous smaller trials with standard interferon-alfa plus ribavirin treatment[7,9], we anticipated in the original study protocol that a rapid, slow partial, flat partial, or null response may be observed in approximately 35, 20, 40, and 5% of patients, respectively. All patients in the present study were treated with pegylated interferon alfa-2a and ribavirin. To our surprise, a rapid or slow initial response was observed in 63 and 24% of patients, respectively. Less than 5% of patients showed a flat response and less than 10% were initial null-responders. Therefore, the number of patients in treatment groups C and D became substantially smaller than originally anticipated.

The overall sustained virologic response rate within the control group was 66% and therefore, higher than in previous studies by Fried et al.[2] (56%) and Hadziyannis et al.[3] (63%) using the same treatment regimen. These excellent sustained virologic response rates may in part be related to highly motivated and adherent patients enrolled in the present study as well as to experienced hepatology services in the participating centers.

Discontinuation of ribavirin after 6 weeks and continuation with peginterferon monotherapy for 42 weeks compromised sustained virologic response rates in HCV-1 infected patients and particularly in those with a baseline viral load >800,000 IU/mL. It may be possible to stop ribavirin early in rapid virologic responders infected with HCV-1 and a low baseline viral load and in rapid virologic responders infected with HCV-2/3 without affecting sustained virologic response rates. It must be kept in mind that previous studies did not support this concept of early discontinuation of ribavirin; however, these studies were not restricted to rapid virologic responders[10].

The results in treatment arm A2 confirm previous studies that in patients infected with HCV-2/3 combination therapy with pegylated interferon-alfa plus ribavirin for 24 weeks is sufficient without compromising sustained virologic response rates[3, 11]. The sustained virologic response rate in HCV-1 infected patients with an initial rapid virologic response who were treated only for 24 weeks was substantial (65%) but was lower than in those patients treated for 48 weeks (83%). This difference was significant in patients with baseline HCV-RNA >800,000 IU/mL but not in patients with lower baseline viral load. Therefore, a prospective trial should be initiated to investigate the possibility to reduce the treatment duration from 48 to 24 weeks exclusively in rapid virologic responders infected with HCV-1.

Histamine blocks the production and release of reactive oxygen metabolites, thereby protecting natural killer cells and T cells, facilitating their activation by cytokines such as interferon-alfa and leading to improved natural killer and CTL cell antiviral activity [12,13]. In the present study, a histamine dose of 1 mg/day was chosen for two reasons: H2-histamine receptors reach saturation when histamine is given at this dose [14,15] and the combination of interferon-alfa plus histamine in patients with chronic hepatitis C showed no difference in virologic efficacy when given either once or twice daily[16].

Viral kinetics were assessed in a 6-week period of triple therapy with pegylated interferon alfa-2a, ribavirin, and histamin. Acceleration of viral decline was observed in 10/38 patients; however, only one patient achieved a sustained virologic response. The majority of patients with a slow virologic response (24/33) in the individualized treatment arm showed no histamine-induced acceleration of viral decline and were therefore, treated with peginterferon and ribavirin for a total of 72 weeks. Half of the patients achieved a sustained virologic response further supporting the concept that prolongation of treatment beyond 48 weeks may in particular be

advantageous in patients with an impaired initial viral decline [17-19].

In conclusion, individualization of antiviral therapy is feasible not only according to baseline parameters [3,11] but also according to the early virologic response. With more antiviral drugs becoming available, it can be anticipated that treatment individualization according to the early virologic response will gain further importance. Treatment individualization could not only improve virologic response rates but also optimize treatment-related quality-of-life and the socio-economical burden of therapy. However, with the individualized treatment options available in the present study, no overall improvement in virologic efficacy was achieved.

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