Comparative Study Concerning the Efficacy of Peg-IFN alpha-2a versus Peg-IFN alpha-2b on the Early Virological Response (EVR) in Patients with Chronic Viral C Hepatitis

Ioan Sporea[1], Mirela Danilă[1], Roxana Şirli[1], Alina Popescu[1], Ariana Laza[1], Luminița Bădițoiu[2]

1) Department of Gastroenterology. 2) Department of Epidemiology, University of Medicine and Pharmacy Timişoara

Abstract

Background. Pegylated interferons (Peg-IFNs) represent, in association with Ribavirin, the first line of treatment in chronic C viral hepatitis. **The aim** of our paper was to compare the efficacy of Peg-IFN alpha 2a (Pegasys) and Peg-IFN alpha 2b (PegIntron) in a group of patients from the Department of Gastroenterology in Timişoara. **Material and method**. 116 patients with chronic C viral hepatitis were treated. The patients were randomized in chronological order (1:1), so that 58 patients were treated with Peg-IFN alpha 2a 180 μg/kg/week + Ribavirin (group 1) and 58 were treated with Peg-IFN alpha 2b 1.5 μg/kg/week + Ribavirin (group 2). Ribavirin was administered in the recommended doses, according to weight. The mean age was: group 1 – 49.3 years, group 2 – 50.9 years (p=0.37). Group 1 consisted of 37 women and 21 men and group 2 of 44 women 14 men (p=0.22). In group 1, 48 patients were nad've (N1), 7 were relapsers after previous treatment (RL1) and 3 non-responders to previous treatment (NR1). In group 2, 33 patients were nad've (N2), 18 relapsers (RL2) and 7 non-responders (NR2). After 12 weeks of treatment we evaluated the early virological response (EVR), defined as a drop in the viral load with 2 logs compared to the baseline viremia. **Results.** The following EVR rates were found: in group 1 – 82.2% (48/58); in group 2 – 67.2% (39/58) (p=0.08). There were also no significant statistical differences between the response rates in the subgroups: nad've patients [89.6% vs. 75.2%, p = 0.61], relapsers [57.1% vs. 66.6%, p = 0.67] and non responders [33.3% vs. 28.6%, p = 1]. **Conclusion.** Our head to head comparative study showed that there are no statistically significant differences in the EVR between the patients treated with Peg-IFN alpha 2a and Peg-IFN alpha 2b.

J Gastrointestin Liver Dis
June 2006 Vol.15 No.2, 125-130
Address for correspondence: Prof.Ioan Sporea
Dept.Gastroenterology
University of Medicine and Pharmacy
Str.Ion Bulbuca no.156
Timişoara, Romania
E-mail: isporea@excite.com

Key words

Peg-IFN alpha 2a - Peg-IFN alpha 2b - early viral response - chronic viral C hepatitis - therapy

Rezumat

Premize. Prima linie în tratamentul hepatitei cronice HCV o constituie asocierea unui Interferon pegylat (Peginterferon alfa 2a – Pegasys, sau Peginterferon alfa 2b -PegIntron) cu Ribavirina. Se consideră că ambele produse au eficiență similară. **Scopul** studiului nostru a fost compararea eficacității celor două produse administrate unui grup de pacienți aflați în evidența Clinicii de Gastroenterologie din Timişoara. **Material şi metodă**. Au fost incluşi în studiu 116 pacienți cu hepatită cronică HCV. Pacienții fost randomizați 1:1, astfel încât 58 de pacienți au fost tratați cu Peginterferon alfa 2a 180 μg/kg/săpt + Ribavirină (grupul 1) şi 58 cu Peginterferon alfa 2b 1,5 μg/kg/săpt. + Ribavirină (grupul 2). Ribavirina a fost administrată în dozele recomandate în funcție de greutate. Vârsta medie a fost 49,3 ani în subgrupul 1şi 50,9 ani în subgrupul 2 (p=0,37 NS). Grupul 1 a fost constituit din 37 femei şi 21 de bărbați, iar grupul 2 din 44 femei şi 14 bărbați (p=0,22 NS). In grupul 1, 48 de pacienți erau naivi (subgrup N1), 7 erau relapseri la terapie anterioară (subgrup RL1) şi 3 erau non-responderi la terapie anterioară (subgroup NR1). In grupul 2, 33 de pacienți erau nad'vi (subgrup N2), 18 erau relapseri (subgrup RL2) ți 7 erau non-responderi (subgrup NR2). După 12 săptămâni de tratament am evaluat la toți pacienții răspunsul virusologic precoce (EVR), definit ca o scădere a viremiei cu 2 logi (de cel puțin 100 de ori) față de viremia inițială. **Rezultate.** Ratele EVR au fost: în grupul 1 82,2% (48/58); în grupul 2 67,2% (39/58). Nu am găsit diferențe semnificative statistic între cele două grupuri în ceea ce priveşte EVR (p=0,08 NS). Diferențele dintre cele două produse rămân nesemnificative din punct de vedere statistic şi în ceea ce priveşte subgrupurile de pacienți naivi [89,6% vs. 75,2%, p = 0,61], relapseri [57,1% vs. 66,6%, p = 0,67] şi non-responderi [33,3% vs. 28,6%, p = 1]. **Concluzie.** Studiul nostru comparativ cap-la-cap a

demonstrat că nu există diferențe semnificative statistic în ceea ce privește răspunsul virusologic precoce la pacienții tratați cu Peginterferon alfa 2a comparativ cu cei tratați cu Peginterferon alfa 2b.

Introduction

For more than 10 years, interferon (IFN) has been the standard treatment for chronic C viral hepatitis. Subsequent changes of therapy aimed to increase the response rate. Both the association of Ribavirin to the treatment with standard IFN, as well as pegylation of IFN increased the response rate with 10 - 20%.

Two pegylated IFNs are currently in use: Peg-IFN alpha 2a (40KD) and Peg-IFN alpha 2b (12KD) (1). Peg-IFN alpha 2a (40KD) is a covalent conjugate of recombinant alpha 2a interferon with a single branched molecule of polyethylene glycol (PEG). After s.c. injection the absorption is prolonged, so that the maximum serum concentration occurs 72-96 hours post-dose (2). Because of the size of the PEG molecule, the distribution volume available for this type of Peg-IFN is limited, so that the dose of Peg-IFN alpha-2a (Pegasys) is the same, no matter the weight of the patient (180 µg /week).

Peg-IFN alpha-2b (12KD) has a distribution volume four times larger than Peg-IFN alpha–2a (40 l vs. 10 l), a mean half-life two times shorter (40 vs. 80 hours) and a maximum serum concentration at 15-44 hours (3). Therefore, Peg-IFN alpha-2b (PegIntron) is administered according to the weight of the patient. The recommended dose is 1.5 µg/kg/week (4-6).

For both types of Peg-IFN the standard therapy regimen includes Ribavirin. The recommended dose of Ribavirin is 800-1200 mg/day (according to the patient's weight). The reduction of Ribavirin dose, especially in the first 12-24 weeks of treatment, diminishes the rate of sustained virological response (SVR) (5, 7, 8). The predictors of the viral response are: genotype 2 and 3, absence of advanced fibrosis, low viral load, female gender, lower weight (old predictors of response), lack of steatosis, compliance, early response, Ribavirin dose, ethnicity (9).

Because there are two types of Peg-IFN on the market, it was considered important to perform comparative studies on their efficacy in association with Ribavirin. The study IDEAL (**I**ndividualized **D**osing **E**fficacy vs. flat dosing to **A**ssess optima**l** pegy**l**ated interferon therapy) performed in the United States (accepted by the FDA) is a head-to-head comparative trial with three arms, comparing the efficacy of two dosages of Peg-IFN alpha-2b plus Ribavirin and Peg-IFN alpha-2a plus Ribavirin (3). The first end-point of this study is to compare the efficacy of Peg-IFN alpha-2b 1µg/kg/week plus Ribavirin to that of Peg-IFN alpha-2b 1.5µg/kg/week plus Ribavirin. The second end-point is to compare the efficacy of Peg-IFN alpha-2b 1.5µg/kg/week plus Ribavirin to that of Peg-IFN alpha-2a 180µg/week plus Ribavirin. The investigators are going to enroll in this multicentric American study 2,880 nad've patients with genotype 1 chronic viral C hepatitis.

Because of the high costs of combined therapy with Peg-IFNs and Ribavirin, of their frequent side-effects and of the rather unsatisfactory results (SVR for genotype 1 is 42-52%) (10), new early predictors of the response were searched for. Analyses of data from two pivotal trials showed that the early virological response (EVR) at 12 weeks was a strong predictor of a subsequent SVR (0% and 3% negative predictive value) (10-12).

The aim of this study was to compare in a randomized trial the EVR to Peg-IFN apha-2a plus Ribavirin vs. Peg-IFN alpha-2b plus Ribavirin in patients with chronic C viral hepatitis.

Material and method

We performed a prospective, head-to-head, randomized 1:1 trial, between October 2003 and June 2005. The inclusion criteria were the presence of chronic C viral hepatitis (proven by liver biopsy performed maximum 6 months before the treatment) and the quantification of the viral load (by PCR) before treatment and after 12 weeks of treatment. The patients were randomized in chronological order to be treated with either one of the two products.

The EVR was defined as a drop in the viral load of =2 log 10 after 12 weeks of treatment.

According to the Romanian legislation and to the Guidelines of the National Health Insurance Company, only patients with chronic viral C hepatitis having a necroinflammatory score of = 6 may do receive therapy with Peg-IFN, no matter the fibrosis score, or patients with a fibrosis score 3 no matter the necroinflammatory activity.

We compared the two groups of patients (treated with Peg-IFN alpha 2a and Peg-IFN alpha 2b, respectively) regarding age, gender and severity of the morphopathological lesions. These were assessed by means of Knodell score (maximum necroinflammatory score of 18 and fibrosis score ranging from 0 to 4).

In both groups, if EVR was not obtained after 12 weeks, treatment was discontinued. The patients who presented a decrease in the viral load of more than 2 log after 12 weeks of treatment, but were not aviremic, were treated for another 12 weeks. Only the patients aviremic after 24 weeks of treatment (<50 UI/ml or 23 UI/ml) continued the treatment up to 48 weeks.

Since we included in our study both nad've patients and patients who previously received antiviral therapy (non-responders and relapsers), we also compared the EVR in the subgroups of nad've, non-responder and relapser patients treated either with Peg-IFN alpha 2a or with Peg-IFN alpha 2b.

For statistical analysis we used the SPSS (EPI INFO 2002) program. The percentages were compared using the chi^2 test and the Fisher exact test. The variable distribution was assessed by the Kolmogorov-Smirnov test. To compare the means we used the unpaired *t* test. In order to compare the fibrosis and Knodell scores we used nonparametric tests

(Wilcoxon). To study the correlation between the response to treatment and different variables Pearson's correlation coefficient (for numeric variables), the Spearman correlation coefficient (for rank-type variables) and Kendall correlation coefficient (for ordinal variables) were used.

Results

The two groups of patients matched with regard to age, gender, initial viral load and necroinflammatory score (Table I). We found statistically significant differences between the two groups only regarding the fibrosis score.

In the group treated with Peg-IFN alpha 2a, 48 out of 58 patients were nad've (subgroup N1), 7 were relapsers (subgroup RL1) and 3 were non-responders (subgroup NR1). In the group treated with Peg-IFN alpha 2b, 33 out of 58 patients were nad've (subgroup N2), 18 were relapsers (subgroup RL2) and 7 were non-responders (subgroup NR2).

The subgroups of nad've patients, relapsers and non-responders matched with regard to mean age, gender, initial viral load, necroinflammatory score and fibrosis score (Table I).

We did not find significant statistical differences in the EVR between the subgroups of nad've patients treated either with Pegasys or PegIntron, nor in the non-responder patients or relapsers (Table II). As expected, the best results were obtained in nad've patients (89.6 vs. 75.2%), followed by relapsers (57.1 vs. 66.6%) and the worst results in non-responders (33.3 vs. 28.6%).

In the responders, there were no statistically significant differences between the two groups regarding age, level of aminotransferases, total Knodell score and fibrosis score (Table III). No significant differences between the two groups were found in the non-responders (Table IV).

EVR did not correlate with either age, gender or fibrosis score in the two groups of patients (Table V).

The power calculated for our study was 39.3%, probably due to the small number of patients.

Discussion

This study performed in 116 patients aimed to assess if there was a statistically significant difference between the response rate to the treatment with Peg-IFN alpha 2a plus Ribavirin versus Peg-IFN alpha 2b plus Ribavirin in patients with chronic C hepatitis. We tried to compare in a 1:1 randomized, head-to-head study the efficacy of the two drugs, based on the EVR. This is only the first step of the study, which will be extended by comparing the sustained virological response (SVR) The standard combined therapy in chronic viral C hepatitis with Peg-IFN and Ribavirin has been introduced in Romania since October 2003. At least one year is needed in order to have a large enough group of patients who finished the treatment for at least 6 months in order to compare the SVR after combined therapy with

Table I Comparative data of the subgroups

Variable	Group 1 - Peg-IFN alpha 2a				Group 2 - Peg-IFN alpha 2b				p		
	Total	Nad've (N1)	Relapsers (RL1)	Non responders (NR1)	Total	Nad've (N2)	Relapsers (RL2)	Non responders (NR2)	Total	Nad've	Relapsers	Non responders
Number	58	48	7	3	58	33	18	7	-	-	-	-
Age (years) Mean ± SD	49.38± 10.1	49.35 ± 9.9	51.57 ± 10.59	46.6 ± 13.8	50.94 ± 8.76	49.06 ± 8.9	53.72 ± 8.35	52.7 ± 8.44	0.37	0.89	0.59	0.26
Gender: females/males	37/21	33/15	3/4	1/2	44/14	26/7	14/4	4/3	0.22	0.44	0.15	1
Initial viral load (MIU/mL) Mean ± SD	1.20± 0.43	1.10± 0.92	2.14 ± 3.26	0.66± 0.57	1.38± 1.85	1.40± 1.98	1.56± 1.94	0.88± 0.86	0.92	0.36	0.58	0.99
Total Knodell score Mean ± SD	10.0 ± 2.4	9.83 ± 2.46	11.57 ± 1.7	9 ± 1.72	10.7 ± 2.8	10.18 ± 2.6	11.22 ± 3.11	11.57 ± 2.76	0.22	0.54	0.78	0.20
Fibrosis score Mean ± SD	1.1 ± 0.98	1.02 ± 0.97	1.85 ± 0.89	0.66 ± 0.57	1.6 ± 1.4	1.45± 1.4	1.72 ± 1.22	2 ± 1.29	**0.02**	0.36	0.79	1

Table II The EVR in the two groups of patients

Patients		No.patients	Responders	Non-responders	P
Total	1- Peg-IFN alpha 2a	58 (100%)	48 (82.75%)	10 (17.25%)	0.08 (chi^2 2.9)
	2- Peg-IFN alpha 2b	58 (100%)	39 (67.24%)	19 (32.76%)	OR = 2.33 (0.97<OR<5.60)
					RR = 1.23 (0.99<RR<1.52)
					0.61
Nad've	N1-Peg-IFN alpha 2a	48 (100%)	43 (89.6%)	5 (10.4%)	OR=2.75 (0.81<OR<9.33)
	N2- Peg-IFN alpha 2b	33 (100%)	25 (75.2%)	8 (24.8%)	RR=1.18 (0.95<RR<1.46)
					(Fisher exact test)
Relapsers	RL1- Peg-IFN alpha 2a	7 (100%)	4 (57.14%)	3 (42.8%)	0.67
	RL2- Peg-IFN alpha 2b	18 (100%)	12 (66.6%)	8 (33.3%)	OR = 0.66 (0.11<OR<3.99)
					RR = 0.85 (0.41<RR<1.76)
					(Fisher exact test)
Non-res-	NR1- Peg-IFN alpha 2a	3 (100%)	1 (33.3%)	2 (66.6%)	1
ponders	NR2- Peg-IFN alpha 2b	7 (100%)	2 (28.6%)	5 (71.4%)	OR = 1.25 (0.06<OR<22.89)
					RR = 1.16 (0.16<RR<1.25)
					(Fisher exact test)

Table III Variables analyzed in responders from both groups

Variable	Subgroup 1 Peg-IFN alpha 2a		Subgroup 2 Peg-IFN alpha 2b		p
	Mean	SD	Mean	SD	
Age	48.9	10.2	50.6	9.1	0.52
Initial GOT	81.2	51.9	82.7	50.5	0.88
GOT after 12 weeks	32.4	13.7	30.7	18.1	0.18
Initial GPT	81.7	48.4	80.2	50.3	0.88
GPT after 12 weeks	31.7	14.4	29.6	16.7	0.51
Total Knodell score	10.0	2.5	10.2	2.7	0.65
Fibrosis score	1.1	1.0	1.5	1.4	0.18

Table IV Variables analyzed in non-responders from both groups

Variable	Subgroup 1 Peg-IFN alpha 2a		Subgroup 2 Peg-IFN alpha 2b		p
	Mean	SD	Mean	SD	
Age	51.4	10.3	51.5	8.2	0.97
Initial GOT	76.0	45.1	80.2	43.5	0.81
GOT after 12 weeks	61.6	45.5	51.5	44.5	0.56
Initial GPT	88.4	51.8	87.5	52.3	0.96
GPT after 12 weeks	46.6	22.9	46.7	32.1	0.62
Total Knodell score	10.0	2.0	11.5	2.7	0.10
Fibrosis score	1.2	0.98	1.8	1.2	0.12

Table V Correlations between the response rate and various variables in the two groups

Group	Variable	p
Peg-IFN alpha 2a	Age	0.54
	Gender	0.60
	Fibrosis score	0.38
Peg-IFN alpha 2b	Age	0.72
	Gender	0.92
	Fibrosis score	0.16

Ribavirin and one of the two types of Peg-IFN. Until the results of such a study will be available, these preliminary results may be important.

Regarding the pharmacokinetics of IFN, after injecting Peg-IFN alpha 2b, the serum concentration slowly decreases, being almost 0 after 168 hours (7 days). When Peg-IFN alpha 2a is administered, the serum concentration after 168 hours is about 20 mg/ml (13). Peg-IFN alpha 2b has a half time of about 40 hours (14), and its serum concentration decreases under the detection limit before the end of the period between injections (7 days) (4). Some studies on the viral kinetics showed a closed relation between the plasma level of Peg-IFN and the rebound level of HCV RNA (14, 15). It was even suggested to administer Peg-IFN alpha 2b twice a week in order to improve the viral dynamics (15, 16). Considering all these facts, if Peg-IFN alpha 2b is administered in the doses recommended by the present guides (1.5 µg/kg/week), there is a risk that at the end of the interval of 7 days between injections, the serum concentration decreases so much as to enable the virus to replicate, an important factor in the formation of quasispecies and the development of resistance (17). In contrast, Peg-IFN alpha 2a has a half-time longer than 80 hours, so that the suppression of viral replication for the whole interval between doses (7 days) is maintained (17).

The viral kinetics under therapy is a good therapeutic guide. The 2 log decrease of the viral load after 12 weeks of therapy is already used as a criteria for continuing the therapy in all available guidelines of therapy in chronic C viral hepatitis. Other strategies using the viral dynamics are evaluated. Berg et al proposed that the patients in whom after 12 weeks of combined therapy the viral load decreased by more than 2 log, but are not aviremic, the therapy should be continued up to 72 weeks instead of 48 weeks, thus obtaining a higher rate of SVR (18). Another strategy would be to determine the viral load after 4 weeks of therapy so that the patients who do not have a rapid virological response by week 4 should have a treatment longer than 48 weeks (19).

Apart from the Peg-IFN molecule size and pharmacokinetics, an important factor that influences the response

rate is maintaining a minimum dose of Ribavirin of more than 10.8 mg/kg/day, especially in the first three months of therapy (20).

Data from recent multicentric randomized controlled trials (RCTs) on Peg-IFN alpha 2a and Peg-IFN alpha 2b have unequivocally demonstrated that, when administered in combination with Ribavirin, these agents achieved SVR rates significantly higher than those previously obtained by treatment with standard interferon alpha 2a or alpha 2b with or without Ribavirin (5,21,22). Also, a RCT of Peg-IFN alpha 2b plus Ribavirin in patients with chronic hepatitis C previously treated demonstrated that a SVR was only obtained in those who were partial responders to previous IFN monotherapy or combination therapy (23). In contrast, a RCT of Peg-IFN alpha 2a and Ribavirin in chronic hepatitis C patients showed that a SVR can be achieved in those who failed prior antiviral therapy (24).

In our study, we evaluated EVR in both nad've patients and patients that already received antiviral therapy (standard interferon alone or standard interferon plus Ribavirin) and had been non-responders or relapsers. A limit of our study could be the relatively small number of patients included.

Conclusion

Our head-to-head randomized study showed that there were no statistically significant differences in the EVR between patients with chronic hepatitis C treated with Peg-IFN alpha 2a or Peg-IFN alpha 2b plus Ribavirin. The differences remained statistically non-significant in the subgroups of nad've patients, in relapsers and in non responders.

Conflicts of Interest

This study was not financed by any of the pharmaceutical companies producing the Peg-IFNs.

References

1. Ferenci P. Peg-IFN alpha–2a (40KD) (Pegasys) for the treatment of patients with chronic hepatitis C. Int J Clin Pract 2003;57:610-615
2. Roche, UK. Pegasys solution for injection: summary of product characteristics, 2002
3. McHutchison JG, Dev A, Patel K. A comparative landmark trials for the current treatment of hepatitis C and the need for a head-to-head comparison. Hepatology 2004;1:5-12
4. Glue P, Fang JW, Rouzier-Panis R et al. Pegylated interferon alfa-2b: pharmacokinetics, pharmacodynamics, safety and preliminary efficacy data. Hepatitis C Intervention Therapy Group. Clin Pharmacol Ther 2000;68:556-567
5. Manns MP, McHuchison JG, Gordon SC et al. Peg-IFN alpha – 2 b plus Ribavirin for initial treatment of chronic hepatitis C: a randomized trial. Lancet 2001;358:958-965
6. Zeuzem S. Comparative analyses of the impact of body weight, mass and surface area with individualized weight adjusted Peg-IFN alfa-2b and flat doses interferon alfa-2b therapies. Meeting: Innovations in HCV science, clinical and patient management initiatives. Viena 8-10.09.2002;28-30
7. Zeuzem S, Neumann A. New advances in the treatment of chronic hepatitis C. Editor Alberti A, Yamanouchi Europe BV, Leiderdorp 2001
8. Shiffman M. Enhancing sustained virological response: adherence early during therapy. Symposium: Effective side effect management in anti-HCV therapy. New Orleans 2004, Education in Gastroenterology: 6-11
9. McHutchison JG. State of the science: Today's treatment for hepatitis C. Symposium: Effective side effect management in anti-HCV therapy. New Orleans 2004, Education in Gastroenterology: 2-5
10. Keefe EB. Hepatitis C: Science and treatment 2005. In: Difficult Clinical Issues in Gastroenterology: Practical Advice and Its scientific Basis. 2005 AGA Spring Postgraduate Course Syllabus: 63-70
11. Hadziyannis SJ, Sette H Jr, Morgan TR et al. Peg-IFN alfa-2a and Ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and Ribavirin dose. Ann Intern Med 2004;140:346-355
12. Davis GL, Wong JB, McHutchison JG et al. Early virological response to treatment with Peg-IFN alfa-2b plus Ribavirin in patients with chronic hepatitis C. Hepatology 2003; 3: 645-652
13. Vitat P, Foster G, Pockros PJ et al. Optimizing clinical outcomes in difficult to treat patients with chronic hepatitis C. Gastroenterology and Endoscopy News, Special Report 2005:1-7
14. Buti M, Sanchez-Avila F, Lurie Y et al. Viral kinetics in genotype 1 chronic hepatitis C patients during therapy with 2 different doses of Peg-IFN alpha 1b plus Ribavirin. Hepatology 2002; 35:930-936
15. Formann E, Jessner W, Bennett L, Ferenci P. Twice-weekly administration of Peg-IFN alpha 2b improves viral kinetics in patients with chronic hepatitis C genotype 1. J Viral Hepat 2003; 10:271-276
16. Jessner W, Stauber R, Hackl F et al. Early viral kinetics on treatment with pegylated interferon alpha 2b in chronic hepatitis C virus genotype 1 infection. J Viral Hepat 2003; 10:37-42
17. Ferenci P. Predicting the therapeutic response in patients with chronic hepatitis C: the role of viral kinetic studies. J Antimicrob Chemother.2004;53:15-18
18. Berg T, von Wagner M, Hinrichsen H et al. Reduction of the relative relapse rate by prolongation of the duration of the therapy with Peg-IFN alpha 2a plus Ribavirin in patients with genotype 1 infection up to 72 weeks. Hepatology 2004;40(10 suppl 1):66A. Abstract 169
19. Sanchez-Tapias JM, Diago M, Escarin P et al. Longer treatment duration with Peg-IFN alpha-2a (40KD) (Pegasys) and Ribavirin (Copegus) in nad've patients with chronic hepatitis C and detectable HCV RNA by week 4 of therapy: final results of the randomized, multicenter TERAVIC-4 study. Hepatology 2004;40(10 suppl 1):61 A. Abstract 126
20. Aspinall RJ, Pockros PJ. The management of side-effects during therapy for hepatitis C. Aliment Pharmacol Ther 2004; 20: 917-929

21. Fried MW, Shiffman ML, Reddy KR et al. Peg-IFN alpha 2a plus Ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975-982
22. Pockros PJ, Carithers R, Desmond P et al. Pegasys International Study Group. Efficacy and safety of two-dose regiments of PegIntron alpha 2a compared with interferon alpha 2 a in chronic hepatitis C: a multicenter, randomized controlled trial. Am J Gastroenterol 2004;99:1298-1305
23. Iacobson IM, Ahmed F, Russo MW et al. Pegylated interferon alpha 2b plus Ribavirin in patients with chronic hepatitis C: a trial in nonresponders to interferon monotherapy and in combination therapy relapsers (final results) [abstract]. Gastroenterology 2003; 124 (suppl 1); A 540
24. Shiffman ML, Di Bisceglie AM, Lindsay KL et al. Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial Group. Peg-IFN alpha 2a and Ribavirin in patients with chronic hepatitis C who have failed prior treatment. Gastroenterology 2004;126:1015-1023