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Supplement 1

Safety and tolerability of the combination therapy with pegylated interferon alfa-2a (Pegasys®) and ribavirin (Copegus®) in patients with chronic hepatitis C in Poland – interim analysis of data from EAP program

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Summary

Open-label, multicenter extended availability program with peginterferon alfa-2a used in combination with ribavirin in patients with CHC in Poland was analysed. Finally, 572 patients were enrolled. The interim analysis of safety and tolerability was performed in 190 patients whose data were available after 72 weeks of observation. Mean hemoglobin level was 14.8 g/dl and decreased to week 24, then remain stable until the end of therapy and returned to the baseline value. Lekocytes level in week 2 decreased, reach a plateau in week 8 and return to baseline values at end observation. Similar phenomenon was observed with neutrophils. Platelet count during the treatment fell gradually in week 8 and remained stable. Reported adverse events requiring PEGASYS® or COPEGUS® dose reduction were also analyzed. The most frequent adverse effect leading to the reduction of peginterferon alfa-2a dose was

neutropenia (81/185), followed by thrombocytopenia (23/185) (12.4%). Anemia was the most frequent reason of ribavirin dose reduction. It was noted in 16 patients out of 18, who had the doses reduced because of adverse effects. Only in 5 patients, the dose was reduced because of depression or anxiety. Combined therapy was generally well-tolerated, preliminary analysis data confirms similar tolerability profile to that observed in phase III clinical trials.

Key words: chronic hepatitis C • combination therapy with pegylated interferon alfa-2a and ribavirin • safety and tolerability

INTRODUCTION

I Monotherapy with pegylated interferon alfa-2a PEGASYS®

The safety and tolerability of pegylated interferon alfa-2a (PEGASYS®) in monotherapy was assessed in phase 2 and 3 studies with almost 1580 patients included. The analysis included 995 patients who had received at least one dose of pegylated interferon alfa-2a and 584 patients treated with standard interferon alfa-2a. The data concerning safety were based on the treatment period (up to 48 weeks) and an observation period of at least 8 weeks after completion of the therapy, whereas adverse effects were analyzed to week 72. Approximately 30% of patients have been diagnosed as hepatic cirrhosis or advanced fibrosis. The reported adverse effects were typical of interferon therapy, and their incidence was comparable in the groups treated with pegylated interferon alfa-2a and standard interferon given 3 × a week therapy. No differences were observed in the frequency of reported serious adverse events (SAE). The most frequently reported adverse effects were flu-like symptoms (analogous to those observed due to enhanced production of endogenous interferon in response to viral infections). Other adverse effects included hair loss, psychical disturbances (irritability, dysphoria, mood disturbances). The adverse effects were usually mild or moderate in intensity.

The necessity of dose modification because of adverse effects was also similar.

In the study by Zeuzem et al. [1] the safety of pegylated interferon alfa-2a and standard interferon alfa-2a in monotherapy was compared. The necessity of treatment discontinuation because of adverse effects was noted in 7% of patients treated with pegylated interferon alfa-2a and 10% of those receiving interferon alfa-2a, while the necessity of dose modification was comparable in both groups (19 and 18%).

II Safety and tolerability of combined therapy with ribavirin

The rate of the treatment discontinuations due to adverse events was lower in the group of patients treated with pegylated interferon alfa-2a (5.8% in monotherapy and 7.1% in combination with ribavirin) as compared with standard interferon plus ribavirin (9.7%) and higher with respect to treatment discontinuations because of laboratory abnormalities (0.9%, 2.6% and 0.9%, respectively) [2].

Hadziyannis et al. [3] presented the rates of discontinued 24- and 48-week therapies with pegylated interferon alfa-2a – PEGASYS® and ribavirin combination. It was necessary to discontinue treatment in 5% and 4% of patients on the 24-week treatment schedule and in 16% and 15% in the group treated for 48 weeks (the patients received 800 and 1000/1200 mg daily doses of ribavirin, respectively) due to adverse events or laboratory abnormalities. Reduction or omissions of ⩾1 doses of pegylated interferon alfa-2a was necessary in 30% and 26% in the group treated for 24 weeks (on 800 and 1000/1200 mg daily doses, respectively) and in 33% and 36% for the patients treated for 48-weeks (on 800 and 1000/1200 mg, respectively). The incidence of serious adverse events (SAE) associated with the therapy was 3% and 7% (for 24-week treatment), and 9% and 10% (for 48-week treatment) [3].

Changes of neutrophil counts both during monotherapy and combined therapy were comparable, and the observed decrease slightly more pronounced than in case of combined therapy with standard interferon given 3 × a week plus ribavirin. Neutropenia <750, >500 cells/ml (toxicity level 3) was observed in 22%, and < 500 cells/ml (grade 4) in 4.7% of patients.

Changes of platelet counts during monotherapy and combined therapy were comparable, and the observed decrease slightly more pronounced than in case of combined therapy with interferon 3 × a week plus ribavirin. Thrombocytopenia <50.000 cells/ml (toxicity level 3) was noted in 4.9% of patients [4].

Lower incidence of fever, myalgia, chills and depression was observed in the group treated with pegylated interferon alfa-2a in comparison with interferon administered 3 times a week [2]. Reduced ribavirin dose (800 mg/d versus 1000/1200 mg/d) was associated with a lower incidence of SAE, less frequent necessity of dosage modifications and less frequent severe decreases of hemoglobin level.

Manns and al. [5] compared efficacy and safety of peginterferon alfa-2b with ribavirin and interferon alfa-2b with ribavirin at 514 and 505 patients, respectively. They found that overall discontinuation rate was similar (14 vs. 13%). Dose decreasing was necessary at 42% and 34% of patients. Higher rate of neutropenia (18% vs. 8%), fever, nausea and injection- site reaction was observed in group treated with peginterferon alfa-2b. Injection- site reaction may be serious (see case report by Gallelli). [6]

Lindsay and al. [7] performed randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C, concluded that no new adverse events were reported, and the majority of adverse events and changes in laboratory values were mild or moderate.

Table 1. Mean hemoglobin levels (g/dl).

Weeks	0	2	4	8	16	24	32	40	48	72
Mean ±standard deviation	14.8±1.4	14.0±1.5	13.2±1.5	12.9±1.5	12.6±1.4	12.5±1.4	12.6±1.3	12.5±1.4	12.6±1.4	14.7±1.6
95% confidence interval	(14.6–15.0)	(13.8–14.2)	(13.0–13.4)	(12.6–13.1)	(12.4–12.8)	(12.2–12.7)	(12.4–12.8)	(12.3–12.7)	(12.4–12.9)	(14.4–14.9)

Table 2. Mean leukocyte counts ($\times 10^9$/l).

Weeks	0	2	4	8	16	24	32	40	48	72
Mean ±standard deviation	6.1±1.4	4.3±1.5	3.7±1.2	3.4±1.2	3.3±1.0	3.3±1.5	3.2±1.0	3.1±1.1	3.1±1.1	5.8±1.6
95% confidence interval	(5.9–6.3)	(4.0–4.5)	(3.5–3.8)	(3.2–3.6)	(3.1–3.4)	(3.0–3.5)	(3.1–3.4)	(2.9–3.2)	(3.0–3.3)	(5.6–6.0)

Tolerability of pegylated interferon alfa-2a (PEGASYS®) in patients with liver cirrhosis

The adverse events in patients assigned to pegylated interferon alfa-2a at either dose were typical of those seen with standard IFN. Adverse effects necessitating dose reduction were more frequent in the group receiving 180 μg PEGASYS® than in the group receiving 90 μg dose of the drug, but the same as for patients receiving standard IFN therapy. The proportions of patients who had to discontinue the therapy were similar in all groups; no patient discontinued due to neutropenia, and only two patients receiving the higher dose of pegylated interferon alfa-2a were discontinued due to thrombocytopenia [8].

Tolerability of pegylated interferon alfa-2a (PEGASYS®) in patients with renal failure

In a small open-label PK study the frequency of reported adverse effects increased with the severity of renal insufficiency. In the group of patients with creatinine clearance >100 ml/min, adverse effects were reported in 50% of cases, and in the group with creatinine clearance <40 ml/min – in 100% [9].

III Open-label, multicenter extended availability program (EAP) with peginterferon-2a (40KD) (PEGASYS®) used in combination with ribavirin (COPEGUS®) in patients with chronic hepatitis C in Poland

Safety and tolerability – study phase summary

To the study 572 patients in total were enrolled according to the Roche protocol BV 16209 in 14 centers in the whole country. Detailed inclusion criteria are given by Juszczyk et al. [10].

The following interim analysis was performed in 190 patients.

The patients were monitored according to the approved study protocol.

The study visits were scheduled for weeks 0, 2, 4, 8, 16, 24, 32, 40, 48 during treatment and follow-up visits for weeks 8 and 24 after the completion of treatment. The monitored safety parameters included blood cell count, biochemical parameters of liver, kidney and thyroid function.

The results of safety parameters assessment after 72 weeks of observation and are currently available in 148 of 163 patients. This group accounts for 78–85% of patients enrolled in the study and it seems that analysis at this stage may be useful for the needs of study monitoring.

Table 1 presents the changes of mean hemoglobin levels during the therapy.

The analysis includes 163 subjects whose complete data are available. At the baseline, before the treatment, mean hemoglobin level was 14.8 g/dl. In week 2 from the start of the therapy, mean hemoglobin value was 14.0 g/dl and decreased to week 24 of treatment when it reached the level of 12.5 g/dl. That level remained more or less stable until the completion of the therapy in week 48. These values differed from the baseline with statistical significance ($p<0.001$).

In week 72 of observation, mean hemoglobin levels returned to the baseline value of 14.7 g/dl.

Table 2 presents the changes of mean leukocyte counts during the therapy.

The analysis includes 162 subjects whose data were available. The mean baseline leukocyte count at the beginning of treatment was 6.1 ($\times 10^9$/l). In week 2 of the therapy it decreased to 4.3 ($\times 10^9$/l), reaching in week 8 value of 3.4 ($\times 10^9$/l) slowly decreased until to 3.1 ($\times 10^9$/l) in week 48. The difference from the baseline was statistically significant ($p<0.001$) Control tests in week 72 of observation confirmed return of leukocyte count to baseline values at the level of 5.8 ($\times 10^9$/l).

A similar phenomenon (Table 3) was observed with respect to neutrophils.

Table 3. Mean neutrophil counts ($\times 10^9$/l).

Weeks	0	2	4	8	16	24	32	40	48	72
Mean ±standard deviation	3.2±1.0	1.9±0.9	1.6±0.8	1.5±0.7	1.6±0.6	1.7±1.4	1.7±0.8	1.6±0.8	1.7±0.9	3.3±1.2
95% confidence interval	(3.0–3.4)	(1.7–2.0)	(1.5–1.7)	(1.4–1.6)	(1.5–1.7)	(1.5–2.0)	(1.6–1.8)	(1.5–1.7)	(1.5–1.8)	(3.1–3.5)

Table 4. Mean platelet counts ($\times 10^9$/l).

Weeks	0	2	4	8	16	24	32	40	48	72
Mean ±standard deviation	198.7 ±53.9	160.3 ±48.5	149.5 ±46.3	137.3 ±45.5	138.3 ±50.3	143.3 ±48.0	138.7 ±46.2	134.5 ±43.2	137.1 ±45.8	198.1 ±54.7
95% confidence interval	(190.2 –207.1)	(152.7 –168.0)	(142.2 –156.7)	(130.2 –144.5)	(130.4 –146.2)	(135.8 –150.9)	(131.5 –146.0)	(127.7 –141.3)	(129.9 –144.3)	(189.5 –206.7)

Table 5. Reported adverse events leading to reduction of drug doses.

Adverse effect type	Dose reduction PEGASYS®	Dose reduction COPEGUS®
Neutropenia	81	1
Thrombocytopenia	23	0
Anemia	1	16
Elevated AIAT activity	3	0
Headache	6	0
Asthenia	7	0
Depression/anxiety	3/2	0
Hair loss	1	0
Others	18	1
Total	**145**	**18**

Table 6. Reported serious adverse events (SAE).

Adverse effect type	Number of cases
Diarrhoea	1
Hypertension – aggravation	1
Syncope	1
Fever	1
Subarachnoid hemorrhage	1
Hypothyroidism	1
Renal carcinoma	1
Acute gastroenteritis	1
Tonsillitis	1
Open left tibia fracture	1
Thyroiditis	1
Thyroid adenoma	1
Thumb injury	1
Depression	1
Pregnancy of patient's wife (healthy offspring)	1
Total	**15**

To the analysis were included 148 patients. The baseline value was 3.2 ($\times 10^9$/l). In week 2, the neutrophil count decreased to 1.9 ($\times 10^9$/l) reaching a plateau of values ranging from 1.5 a 1.7 ($\times 10^9$/l) by week 4. These differences were also statistically significant in comparison with the baseline ($p<0.001$). After the completion of treatment, in week 72, the mean neutrophil count was 3.3 ($\times 10^9$/l).

Table 4 analyzes mean platelet counts in 158 patients.

At the beginning of the treatment, the mean value was 198.7×10^9/l. During the treatment, the platelet counts fell gradually to the level of 137.3×10^9/l in week 8 and remained at that level until the end of the therapy in week 48. The difference from the baseline was statistically significant ($p<0.001$). After the completion of treatment, mean platelet counts normalized, reaching the value of 198.1×10^9/l.

The reported adverse events requiring PEGASYS® or COPEGUS® dose reduction were also analyzed. Five patients were excluded from the analysis, because the dates of completion of their treatment were unknown. Thus, the analysis included 185 subjects.

It was necessary to reduce (temporarily or permanently) the dose of interferon in 145 cases (what means that a dose reduction could take place more than once in a single patient case), in 18 cases the reduction of ribavirin was required. The most frequent adverse effect leading to the reduction of peginterferon alfa-2a dose was neutropenia (81/185) (43.8%), followed by thrombocytopenia (23/185) (12.4%). Anemia was the most frequent reason of ribavirin dose reduction. It was noted in 16 patients out of 18, who had the doses reduced because of adverse effects. Only in 5 patients, the dose was reduced because of depression or anxiety. The data are presented in Table 5.

In the analyzed group of 190 patients, the total number of reported SAE was 15. None of the SAE occurred more frequently than in one case. The list of such adverse events is presented in Table 6.

CONCLUSIONS

- combined therapy with PEGASYS® 180 ug/week/COPEGUS® 800 mg/day administered for 48 weeks was generally well-tolerated,

- the therapy requires frequent monitoring of blood parameters, especially leukocyte and thrombocyte counts. In case of early detection of abnormalities, dose reduction is sufficient,

- preliminary analysis of EAP – Pegasys program data confirms similar tolerability profile to that observed in phase III clinical trials,

- considerably lower depression rates (as compared with standard therapy) are interesting,

- only 9/190 (4.7%) did not complete the therapy (including 3.2% withdrawn because of side effects). According to literature data, discontinuation rates reach 10–16.1%.

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