Name of journal: *World Journal of Hepatology*

ESPS Manuscript NO: 8207

Columns: Clinical Trials Study

**Pegylated interferon alfa-2b plus ribavirin for treatment of chronic hepatitis C**

Rao PN *et al.* Treatment of chronic hepatitis C patients

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**Supported by** Virchow Biotech Private Limited, Hyderabad, India

**Author contributions:** All the eleven authors of the manuscript carried out the field research for the study apart from their contribution to the conception and design of the study; Rao PN was also instrumental in writing the paper.

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**Received:** December 19, 2013 **Revised:** April 11, 2014

**Accepted:** May 28, 2014

**Published online:**

**Abstract**

**AIM:** To study the safety and efficacy of pegylated interferon alfa-2b, indigenously developed in India, plus ribavirin in treatment of hepatitis C virus (HCV).

**METHODS:** One-hundred HCV patients were enrolled in an open-label, multicenter trial. Patients were treated with pegylated interferon alfa-2b 1.5 µg/kg per week subcutaneously plus oral ribavirin 800 mg/d for genotypes 2 and 3 patients for 24 wk. On the other hand, the same dose of peginterferon plus weight-based ribavirin (800 mg/d for ≤ 65 kg; 1000 mg/d for > 65-85 kg; 1200 mg/d for > 85-105 kg; 1400 mg/d for > 105 kg body weight) was administered for 48 wk for genotypes 1 and 4 patients. Serological and biochemical response of patients was assessed.

**RESULTS:** Eighty-two patients (35 in genotypes 1 and 4 and 47 in 2 and 3**),** completed the study. In genotype 1, 25.9% of patients achieved rapid virologic response (RVR): while the figures were 74.1% for early virologic response (EVR) and 44.4% for sustained virologic response (SVR). In genotypes 2 and 3, except for one, all patients belonged to genotype 3, and among them, 71.4%, 87.5% and 64.3% achieved RVR, EVR and SVR, respectively. In genotype 4, 58.8%, 88.2% and 52.9% of patients achieved RVR, EVR and SVR, respectively. Majority of patients attained normal levels of alanine aminotransferase (ALT) by 4-12 wk of therapy. Most patients well tolerated the treatment though they exhibited mild-to-moderate adverse events; only two patients discontinued the study medication due to serious adverse events (SAEs). Eleven SAEs were observed in nine patients; however, only four SAEs were related to study medication.

**CONCLUSION:** Peginterferon alfa-2b, developed in India, in combination with ribavirin is a safe and effective drug in the treatment of HCV.

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**Key words:** Hepatitis C virus; Genotype; Peginterferon alfa-2b; Ribavirin; Treatment

**Core tip:** In a multicenter study, the safety and efficacy of pegylated interferon alfa-2b, indigenously developed in India, plus ribavirin was evaluated on 100 hepatitis C virus (HCV) patients with genotypes 1, 2, 3 and 4. Eighty-two patients completed the study. Most patients had mild-to-moderate adverse events except for 9 patients reporting 11 serious adverse events. However, only 4 of them were related to study medication. The percentage of serologic response [rapid virologic response (RVR), early virologic response (EVR) and sustained virologic response (SVR) rates] of patients was similar to those reported in published studies. In conclusion, peginterferon alfa-2b, developed in India, is a safe and cost effective drug in the treatment of Indian patients with HCV infection.

Rao PN, Koshy A, Philip J, Premaletha N, Varghese J, Narayanasamy K, Mohindra S, Pai NV, Agarwal MK, Konar A, Vora HB. Pegylated interferon alfa-2b plus ribavirin for treatment of chronic hepatitis C. *World J Hepatol* 2014; In press

**INTRODUCTION**

According to World Health Organization estimates, over 170 million people–or three percent of the world’s population are infected with chronic hepatitis C virus (HCV)[1]. Each year, about five million people are newly infected, and more than 350000 people, despite availability of treatment, die from HCV-related complications[2]. Hepatitis is an emerging infection in India. There is paucity of large scale prevalence studies on hepatitis C in general population. The reported prevalence rates also vary widely (range 0.09% to 7.89%)[3].However, regardless of its prevalence rates, the burden of HCV infection in India is expected to be high with over 1.2 billion population; as a result, its treatment modalities as well as success rates demand attention.

HCV genotype plays a significant role in therapeutic guidelines since HCV genotypes 1 and 4 are more resistant to treatment as compared to HCV genotypes 2 and 3. Yet, irrespective of genotype, pegylated interferon, in combination with ribavirin, is considered as the gold standard in the treatment of chronic HCV infection[4-7]. Currently, both pegylated interferon alfa-2a and pegylated alfa-2b are available in India. These drugs are exorbitantly priced and are not easily accessible to majority of Indian patients. In view of this, Virchow Biotech developed pegylated interferon alfa-2b from *E. coli* by using recombinant DNA technology, and priced competitively. The aim of the present study is to evaluate the safety and efficacy of the pegylated interferon alfa-2b, manufactured by Virchow Biotech, in chronic hepatitis C patients.

**MATERIALS AND METHODS**

***Patient selection***

Male and female patients, aged between 18-65 (both years inclusive), attending the outpatient department of 12 hospitals, were screened and 100 consecutive patients were enrolled, if they had chronic hepatitis C infection as per the following criteria: presence of HCV RNA and persistent elevation of serum alanine aminotransferase (ALT) levels 1.5 times greater than normal (N < 40 IU/L); compensated liver disease at the time of baseline visit as defined by Child-Pugh class A; hemoglobin ≥ 9 g/dL (females), ≥ 10 g/dL (males); platelet count ≥ 75 × 109/L; neutrophil count ≥ 1.5 × 109/L; thyroid stimulating hormone within normal limits (0.35–5.50 mIU/mL). Only treatment näive patients were included in the study. Patients were excluded, if they had evidence of other liver diseases such as hepatitis A virus, hepatitis B virus, alfa 2 anti-trypsin deficiency, Wilson’s disease, primary biliary cirrhosis, or autoimmune liver disease, hemochromatosis. Other criteria for exclusion were: chronic alcoholic or patients with drug abuse problem or immune suppression associated with organ transplantation; history of hypersensitivity to interferon or its diluents; significant psychiatric disease especially depression; severe cardiovascular disease; patients with co-infection of human immunodeficiency virus infection; pregnant and lactating women. Study procedures were explained to each participant and written informed consent was obtained before enrolment into the study.

***Study design***

This is an open-label, multicenter study and it was conducted, with the approval of Drugs Controller General of India at 12 centers across eight Indian cities, between March 2010 and March 2013. The study, conducted in accordance with principles under 1964 Declaration of Helsinki and later revisions, was initiated after obtaining approval of the study protocol from the institutional ethical committee at respective centers. This trial was registered in Clinical Trial Registry India (CTRI/2011/000028).

***Treatment regimen***

The treatment consisted of administration of peginterferon alfa-2b (manufactured by Virchow Biotech Private Ltd, Hyderabad, India) 1.5 µg/kg per week subcutaneously, in combination with ribavirin 800 mg/d orally, for genotypes 2 and 3 patients for 24 wk. The same dose of peginterferon was administered in combination with weight-based ribavirin (800 mg/d for ≤ 65 kg; 1000 mg/d for > 65-85 kg; 1200 mg/d for > 85-105 kg; 1400 mg/d for > 105 kg body weight) for 48 wk for genotypes 1 and 4 patients.

***Dose modification/discontinuation***

Ribavirin dose was reduced to half if hemoglobin level was < 10 g/dL; treatment was discontinued if hemoglobin level was < 8.5 g/dL. Peginterferon dose was reduced to half in patients with WBC < 1.5 x 109/L or neutrophils < 0.75 x 109/L or platelet count < 50 x 109/L. Peginterferon treatment was discontinued in patients with WBC < 1.0 x 109/L or neutrophils < 0.5 x 109/L or platelet count < 25 x 109/L.

***Assessment of efficacy***

The primary efficacy endpoint was percentage of patients with sustained virologic response (SVR), defined as undetectable serum HCV RNA 24 wk after cessation of therapy. Secondary efficacy endpoints were: rapid virologic response (RVR), defined as undetectable serum HCV RNA at 4 wk; early virologic response (EVR), which is defined as undetectable serum HCV RNA or 2-log10 reduction in HCV RNA from baselineat 12 wk; end of the treatment virologic response (ETVR), which is defined as undetectable serum HCV RNA at 24 wk and at 48 wk1; with normalization of ALT at 12, 24 wk and 48 wk1 and 24 wk after cessation of therapy (1only for patients with genotypes 1 and 4). Data on non-responders, relapse and breakthrough were also collected[4]. Non-responders were defined as those who failed to clear HCV RNA from serum after 24 wk of therapy. Relapse was defined as undetectable HCV RNA at end of the treatment, followed by reappearance of HCV RNA during follow-up. Breakthrough was defined as undetectable HCV RNA during treatment followed by appearance of HCV RNA, despite continued treatment.

Blood samples were obtained for serologic test for quantitative HCV RNA by PCR at baseline and at 4, 12, 24 and 48 wk for genotypes 2 and 3; while for genotypes 1 and 4 at baseline and at 4, 12, 24, 48 and 72 wk. Cobas Taqman HCV test (Roche), using real-time PCR method with a lower detection limit of < 25 IU/ml, was employed for quantification of HCV RNA in serum. Linear array detection kit from Roche was used in HCV genotyping.

***Assessment of safety***

Vitals (respiratory rate, pulse rate, body temperature and blood pressure), hematology (complete blood picture, hemoglobin and platelet count) and ALT levels were measured at each visit. Besides, biochemical parameters (serum lactate dehydrogenase, creatinine, potassium and phosphorus) were measured at specified visits-at screening, week 4, 12, 24 and 48 for genotypes 2 and 3 and for genotypes 1 and 4 at screening, week 4, 12, 24, 48 and 72. Patients were monitored for adverse events (AE) and medication compliance throughout the duration of study. Adverse events were graded as mild, moderate and severe. Treatment was suspended or modified according to severity of adverse event. Dosage of peginterferon alfa-2b or ribavirin, or both, was again increased to the original level when adverse event disappeared. Serious adverse events (SAEs) were documented and communicated to the institutional ethics committee and Drugs Controller General of India.

***Sample size***

Various trials conducted on genotypes 1 and 4 or 2 and 3 patients have reportedaround 40%-80% SVR, which reflects the efficacy of peginterferon alfa-2b in the treatment of hepatitis C virus[6,7]. In our earlier pilot study conducted on 25 patients with HCV infection, 60% SVR was observed. Therefore, considering 60% of efficacy, 95%CI, 80% power and 15% error with 15% dropout rate with two tailed t-test, the calculated sample size was 100 patients.

***Statistical analysis***

Values were expressed as mean (SD). Since an open-label study design was adopted, efficacy assessment basically relied upon descriptive statistics rather than inferential analysis. Intention-to-treat (ITT) analysis was carried out on the population that included all patients who met the eligibility criteria and had received at least one dose of investigational drug during the study period. Besides, per protocol analysis was also carried out which included patients who completed the stipulated study period.

Safety parameters such as vital signs and laboratory findings, including hematology and biochemical parameters, were analyzed by repeated measure analysis of variance. Two-sided p-values were reported and those less than 0.05 were considered statistically significant. All analyses were done using IBM SPSS version 19.0 for Windows.

**RESULTS**

***Patients’ characteristics***

A total of 100 consecutive patients with chronic hepatitis C, who met the inclusion/exclusion criteria, were enrolled into the study. Among them, 27 pertained to genotype 1, 17 with genotype 4, only one with genotype 2 and 55 were of genotype 3. Since there was only one patient with genotype 2, the results, presented on genotypes 2 and 3, basically represent only those of genotype 3. The demographic and baseline characteristics of the 100 enrolled patients are presented in Table 1. At baseline, values of hematogical and biochemical investigations were within normal limits except for liver function tests such as serum ALT, aspartate aminotransferase and alkaline phosphatase. Barring serum ALT levels, other demographic, hematological and biochemical parameters, including HCV RNA levels, were not significantly different between genotypes 1, 3 and 4. The mean ALT levels in genotype 3 patients were significantly higher (*P* < 0.02) than those in genotype 1; but these were similar to those of genotype 4.

Figure 1 shows the flow of patients through the study. Among the 100 patients, 82 completed the study. Eighteen patients could not complete for the following reasons: lost to follow-up (8), withdrawn (6), discontinued due to SAE (2) and therapy discontinued due to non-response by the investigator (2). Treatment compliance was monitored by maintaining a patient dairy. During the study period, the mean daily intake of ribavirin was 14.3 ± 1.84 mg/kg body weight in genotypes 1 and 4 and 12.84 ± 2.29 mg/kg body weight in genotype 3.

***Treatment response***

Overall, 57%, 84%, 72% and 57% of enrolled patients achieved RVR, EVR, ETVR and SVR respectively. Results on virologic response of genotypes 1, 3 and 4, evaluated by ITT and per protocol analysis, are presented in Tables 2 and 3 respectively.

Data on percentage of patients with normalization of ALT at 4, 12, 24 wk of treatment and at the end of treatment (48 wk in genotypes 1, 4 and 24 wk in genotypes 2 and 3) and at 24 wk after cessation of therapy are presented in Table 4. In general, majority of patients, irrespective of their genotype, attained normal levels of ALT by 4 to 12 wk of therapy and the effect was sustained even during follow-up. Mean ALT levels during different study periods are presented in Figure 2.

***Side-effects***

Majority of patients tolerated the scheduled treatment with peginterferon and ribavirin except for known adverse events with these drugs. Adverse events were analyzed for safety of peginterferon alfa-2b and presented in Table 5. Ninety-one patients reported 328 adverse events–95 events by genotype 1 patients, 68 events by genotype 4 patients and 165 events in genotype 3 patients. Administration of peginterferon alfa-2b resulted in common mild-to-moderate adverse events (AEs), which included flu-like symptoms, nausea, loss of appetite etc. None of the patients permanently stopped the study medication due to adverse events, except for two patients. These two patients were discontinued from the study due to serious adverse events (SAEs). Ribavirin was temporarily discontinued due to anemia in ten patients. On the other hand, twenty-four patients required ribavirin dose reduction, four needing peginterferon alfa-2b dose reduction and four requiring both ribavirin and peginterferon alfa-2b dose reduction for management of anemia and thrombocytopenia. Nine patients reported 11 serious adverse events (SAEs); they were relieved with relevant therapy except for one patient who died. Among the 11 SAEs, four were related to the study medication and the remaining seven, including the case of death, were unrelated to it.

**DISCUSSION**

Infection with HCV is one of the most important medical and public health problems worldwide in view of its life-threatening complications such as hepatocellular carcinoma, cirrhosis, or liver failure[8-10]. The goal of therapy in chronic HCV infection, is to achieve SVR and thereby prevent its long-term complications. Despite the promising role of new antiviral therapies[11], to date, use of pegylated-interferon alfa combined with ribavirin continues to be standard care of treatment in HCV infection.

Since genotype constitutes one of the important determinants of the course and outcome of therapy, 24 or 48 wk combination therapy with peginterferon alfa and ribavirin has been recommended for genotypes 2 and 3 and for genotypes 1 and 4 patients, respectively[4-7]. The present open-label, multicentre study, using that standard-of-care therapy, was undertaken to establish that safety and efficacy of peginterferon alfa-2b, manufactured by Virchow Biotech, is comparable to the results of historical controls in the treatment of chronic HCV infection .

One-hundred eligible patients with chronic HCV infection were enrolled and the majority (55%) of them had HCV genotype 3 which is in accordance with the published prevalence studies conducted in India[12-13]. There was only one patient with genotype 2 which is rare among the Indians. Thus the reported combined results of patients with genotypes 2 and 3, in fact, reflect only those of genotype 3. Anticipating 15% attrition, 100 patients were enrolled. However, there was a 18% dropout, and as a result, eighty-two patients completed the specified study period of therapy.

Since the dose and duration of therapy were different, the data on outcome measures were analyzed separately for genotypes 1, 4 and 2 and 3. The SVR (44.4%) observed in the present study for genotype 1, is comparable with those of reported studies[14-16]. In genotypes 2 and 3, 64.3% of patients had achieved SVR which is also in conformity figures results reported by Manns *et al*[17]. The rates of SVR in treatment naïve genotype 2 patients are reported to be 86.5%[18] which is higher than that of genotype 3. Since our patients, except for one, belonged to genotype 3, lower SVR (64.3%) was observed in the present study. In genotype 4, 52.9% patients achieved SVR which is comparable with values from published studies[19-20]. Apart from genotype, baseline viral load has been shown to be one of the determinants of SVR[21]. However, perhaps due to small number of patients covered in the present study, stratified statistical analysis had showed that baseline viral load had no impact on SVR.

In view of the cost factor and incidence of adverse events with use of peginterferon during the long duration of treatment, individualized treatment, based on results of RVR and EVR, has been emphasized. In this respect, presence of RVR is highly predictive of ultimate SVR with a full treatment course of 48 wk in genotype 1 patients[22]. In the current study, all (100%) the genotype 1 patients (*n* = 7), who achieved RVR, also attained SVR; while a study reported SVR rate of 86.8% in patients with RVR[15]. In genotype 4 patients 80% with RVR attained SVR whereas the published study reported 86%[23]. Similarly, among the genotype 3 patients who had RVR, 83.3% attained SVR which is similar (83.7%) to that reported in the literature[24]. This further confirms the utility of RVR in predicting the SVR.

Among the patients who attained EVR, 10 (76.9%) in genotype 1, and 9 (75%) in genotype 4 achieved SVR. In patients with genotypes 2 and 3, the percentage with EVR attaining SVR was 100%. This is in line with the literature[25] which shows that patients with genotype 3 who fail to achieve EVR also fail to achieve SVR. Since the duration of treatment for genotypes 2 and 3 is only 24 wk, it is reported that EVR testing is not cost-effective in these patients[25]. This indicates that utility of RVR is higher than EVR in the prediction of SVR.

Overall, 16 patients had relapse-5 (31.2%) patients in genotype 1, 8 (18.2%) patients in genotypes 2 and 3 and 3 (25%) patients in genotype 4. Among the 100 patients, five patients were non-responders to the study treatment–one (3.7%) patient in genotype 1; two (3.6%) patients in genotypes 2 and 3 and two (11.7%) in genotype 4. In addition four patients had breakthrough during the treatment–two (7.4%) patients in genotype 1; one (1.8%) patient in genotype 3 and one (5.8%) patient in genotype 4.

Biochemical response of peginterferon alfa-2b was assessed by percentage of patients attaining normalization of ALT levels. Overall, majority of patients (51%) had normalization of ALT levels as early as at 4 wk. This denotes that peginterferon is very effective in producing biochemical response in patients with chronic hepatitis C.

The treatment was well tolerated in the majority of patients though with common side-effects usually attributed with interferon or ribavirin. In 32% of patients, temporary dose modifications in peginterferon (4%), ribavirin (24%) or both (4%) and temporary discontinuation of therapy in 10% of patients were required. Though 11 SAEs were observed in nine patients, only 4 were related to study medication and such SAEs were also reported in earlier studies[15,17,26,27].

Limitations of the study are that it is a single arm study and the results on the outcome measures were compared with those of historical controls. Earlier studies on Indian patients with HCV infection were conducted using peginterferon alfa-2b in two studies – one study was carried out on 103 patients but only on genotype 3 patients[25]; the other study, though covered all the four genotypes, had only 16 patients[28]. We are not aware of any study conducted on adequately powered sample of Indian patients with HCV infection following the global guidelines on peginterferon plus ribavirin[4-7,29].

Therefore, despite the limitation of lack of comparator, our results on serological responses such as RVR, EVR, ETVR and SVR provide valuable information on the safety and efficacy of peginterferon alfa-2b, in combination with ribavirin, in the treatment of Indian patients with chronic HCV infection. Currently, peginterferon alfa-2b, developed by Virchow Biotech, is marketed in India and other emerging countries at a very competitive rate. In view of the relatively low incidence of the adverse events and improved virologic and biochemical response, the results of the study show that peginterferon alfa-2b, developed in India, in combination with ribavirin is a safe and cost effective drug in the treatment of chronic hepatitis C.

**COMMENTS**

***Background***

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease in India and accounts for high morbidity and mortality due to its complications. Pegylated interferon, in combination with ribavirin, is the standard treatment recommended for treatment of chronic hepatitis C. One of the reasons could be its cost factor. Besides, studies evaluating the safety and efficacy of these drugs in India are limited. Therefore, an attempt is being to evaluate the efficacy of peginterferon alfa-2b, locally developed in India, in combination with ribavirin.

***Research frontiers***

This prospective study presents the results on the efficacy, in terms of virologic response, of indigenously developed peginterferon alfa-2b plus ribavirin in Indian patients with different genotypes of chronic hepatitis C. In addition, adverse events observed with this combination are also reported.

***Innovations and breakthroughs***

Earlier there have been a few studies on Indian patients with HCV infection using peginterferon alfa-2b. However, these were limited to small number of patients or confined to one genotype.

***Applications***

This study demonstrates that virologic response of peginterferon alfa-2b and ribavirin, when given as per global guidelines in Indian patients with different types of chronic hepatitis C, is similar to that of historical controls.

***Terminology***

Success rate of treatment is assessed based on sustained virologic response (SVR) which is defined as undetectable HCV RNA in blood at 24 wk of cessation of therapy.

***Peer review***

This is a straightforward clinical control study.

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**P-Reviewers:** Ford N, Kanda T, Liu CJ, Shi Z **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1** **Baseline characteristics of patients with genotypes 1, 3 and 4**

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Genotype 1(*n* = 27) | Genotype 3  (*n* = 56)1 | Genotype 4 (*n* = 17) |
| Age (yr)  | 41.9 ± 13.2 | 41.7 ± 10.9 | 46.3 ± 9.3 |
| Weight (Kg) | 60.5 ± 12.0 | 63.3 ± 11.5 | 63.7 ± 10.8 |
| Male number (%)2 | 19 (70.3%) | 11 (19.7%) | 11 (64.7%) |
| Hemoglobin (g/dL)  | 14.1 ± 1.6 | 13.8 ± 1.9 | 14.2 ± 1.2 |
| White blood cell count (109/L)  | 6682 ± 1682 | 7086 ± 1886 | 7201 ± 1886 |
| Neutrophils (%)  | 58.4 ± 8.4 | 56.0 ± 11.8 | 53.3 ± 8.0 |
| Platelet count (103/L)  | 200 ± 80 | 199 ± 78 | 170 ± 50 |
| Alanine Aminotransferase (U/L) | 88.1 ± 41 | 127.7 ± 87.4 | 104.9 ± 61.1 |
| HCV RNA log10 IU/mL | 5.5 ± 1.2 | 5.4 ± 1.1 | 5.5 ± 0.9 |

1Includes one patient with genotype 2; 2 Value in percentage. HCV: Hepatitis C virus.

**Table 2** **Percentage of patients who responded in terms of** rapid virologic response**,** early virologic response**,** end of the treatment virologic response **and** sustained virologic response **in genotypes 1, 3 and 4 by ITT analysis**

|  |  |
| --- | --- |
| **Parameter** | **Genotype** |
| **1****(*n* = 27)** | **31****(*n* = 56)** | **4****(*n* = 17)** |
| RVR | 25.9% | 71.4% | 58.8% |
| EVR | 74.1% | 87.5% | 88.2% |
| ETVR | 59.2% | 78.6% | 70.5% |
| SVR | 44.4% | 64.3% | 52.9% |

1Includes one patient with genotype 2. RVR: Rapid virologic response; EVR: Early virologic response; SVR: Sustained virologic response; ETVR: End of the treatment virologic response.

**Table 3 Percentage of patients who responded in terms of rapid virologic response, early virologic response, end of the treatment virologic response and sustained virologic response in genotypes 1, 3 and 4 by per protocol analysis**

|  |  |
| --- | --- |
| **Parameter** | **Genotype** |
| **1** **% (*n*/N)** | **31****% (*n*/N)** | **4****% (*n*/N)** |
| RVR | 25.9% (7/27) | 74.1% (40/54) | 58.8% (10/17) |
| EVR | 74.1% (20/27) | 100% (49/49) | 88.2% (15/17) |
| ETVR | 84.2% (16/19) | 89.8% (44/49) | 75% (12/16) |
| SVR | 60% (12/20) | 76.6% (36/47) | 60% (9/15) |

1Includes one patient with genotype 2; n: Number of who responded patients; N: Total number of patients studied; RVR: Rapid virologic response; EVR: Early virologic response; SVR: Sustained virologic response; ETVR: End of the treatment virologic response.

**Table 4 Percentage of patients with normalization of alanine aminotransferase levels during different study periods**

|  |  |  |
| --- | --- | --- |
|  Wk |  Genotype  |  |
| 1 (*n* = 27) | 3 (*n* = 56)1 | 4 (*n* = 17) |
| 4 | 16 (59.2%) | 27 (48.2%) | 8 (47.0%) |
| 12 | 17 (62.9%) | 29 (51.7%) | 8 (47.0%) |
| 24 | 17 (62.9%) | 35 (62.5%) | 9 (52.9%) |
| 48 | 17 (62.9%) | 40 (71.4%) | 11 (64.7%) |
| 72 | 17 (62.9%) | - | 12 (70.6%) |

1Includes one patient with genotype 2.

**Table 5** **Number (%) of patients with adverse events**

|  |  |
| --- | --- |
| Adverse event | *n* (%) of patients |
| Genotype 1 (*n* = 27) | Genotype 31 (*n* = 56) |  Genotype 4 (*n* = 17) |
| Injection-site reactions | 9 (33.3%) | 16 (28.6%) | 7 (41.2%) |
| Flu-like symptoms | 24 (88.8%) | 49 (87.5%) | 14 (82.3%) |
| Tiredness | 4 (14.8%) | 5 (8.9%) | 2 (11.7%) |
| Weight loss | 1 (3.7%) | 3 (5.4%) | 1 (5.8%) |
| Chest discomfort | 1 (3.7%) | 2 (3.6%) | 2 (11.7%) |
| Artharlgia | 3 (11.1%) |  0 (0) | 1 (5.8%) |
| Alopecia | 2 (7.4%) | 10 (17.9%) | 3 (17.6%) |
| Anorexia | 2 (7.4%) | 7 (12.5%) | 3 (17.6%) |
| Nausea | 3 (11.1%) | 8 (14.3%) | 3 (17.6%) |
| Vomiting | 2 (7.4%) | 3 (5.4%) | 0 |
| Dyspepsia | 1 (3.7%) | 3 (5.4%) | 2 (11.7%) |
| Gastritis | 1 (3.7%) | 0 (0) | 0 |
| Mucous stool | 1 (3.7%) |  0 (0) | 0 |
| Diahorrea | 1 (3.7%) | 4 (7.1%) | 1 (5.8%) |
| Malena | 1 (3.7%) | 6 (10.7%) | 0 |
| Ascites | 1 (3.7%) | 0 (0) | 0 |
| Thrombocytopenia | 2 (7.4%) | 5 (8.9%) | 1 (5.8%) |
| Anemia | 9 (33.3%) | 13 (23.2%) | 6 (35.3%) |
| Neutropenia | 12 (44.4%) | 15 (26.8%) | 8 (47.0%) |
| Anxiety | 1 (3.7%) | 3 (5.4%) | 1 (5.8%) |
| Depression | 2 (7.4%) | 4 (7.1%) | 3 (17.6%) |
| Insomnia | 1 (3.7%) | 1 (1.8%) | 2 (11.7%) |
| Hypothyroidism | 2 (7.4%) | 2 (3.6%) | 2 (11.7%) |
| Giddiness | 1 (3.7%) | 1 (1.8%) | 2 (11.7%) |
| Dry throat | 1 (3.7%) | 1 (1.8%) |  0 (0) |
| Cough | 2 (7.4%) | 2 (3.6%) | 2 (11.7%) |
| Sinusitis | 1 (3.7%) |  0 (0) |  0 (0) |
| Bleeding gums | 2 (7.4%) | 1 (1.8%) |  0 (0) |
| Palpitation | 1 (3.7%) |  0 (0) |  0 (0) |
| Pruritus |  0 (0) |  0 (0) | 1 (5.8%) |
| Yellow colour sputum |  0 (0) |  0 (0) | 1 (5.8%) |
| Urinary tract infection | 1 (3.7%) | 0 (0) |  0 (0) |
| Death |  0 (0) | 1 (1.8%) |  0 (0) |
| No. of patients reporting AEs | 24 (88.8%) | 49 (87.5%) | 14 (82.3%) |
| Discontinued due to SAEs |  0 (0) | 2 (3.6%) |  0 (0) |
| Temporary discontinuation of Therapy | 4 (14.8%) | 3 (5.4%) | 3 (17.6%) |
| Temporary dose reduction | 11 (40.7) | 16 (29.6%) | 5 (29.4%) |

1Includes one patient with genotype 2

**No. of eligible patients enrolled**

**(*n* = 100)**

**Genotypes 1**

**(*n* = 27)**

**Genotype 4**

**(*n* = 17)**

**No. of patients who completed the study (*n* = 20)**

**No. of patients who completed the study (*n* = 15)**

**Genotype 31**

**(*n* = 56)**

**No. of patients who completed the study (*n* = 47)**

**Figure 1 Disposition of patients.** 1 Includes one patient with genotype 2.



**Figure 2 Mean alanine aminotransferase levels during the study period in patients with different genotypes**. 1 Includes one patient with genotype 2.