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RESEARCH REPORT

Clinical Study Report –MV25600
An International, Multi-Center Study Evaluating the
Correlation of IL28B Genotypes with Chronic Hepatitis C
Disease Characteristics and Patient Demographics(GEN-C)

Date of Report October 2014

Study Sponsor(s) Hoffmann-La Roche Ltd.

Study Dates: First Patient/Subject Entered: 30.08.2011
Data cut-off / LPLV: 10.10.2013
Date of early termination: -

Trial Phase: Non-interventional Study

Indication: Chronic Hepatitis C

Name of Principal Investigator: **Affiliation:**
No Principal Investigator appointed -

Sponsor's Signatory:

George Bakalos, 22.09. 2014

Personnel Responsible for Clinical and Statistical Analyses:

IML	Fernando Tatsch 25.3.2010 to 16.08.2013
IMM	Antonietta Caputo 01.07.2013 to 30.09.2013
IML	George Bakalos since 01.10.2013
Project Statistician	Diethelm Messinger

GCP Compliance:

This study was conducted in accordance with the principles of GCP

SYNOPSIS OF RESEARCH REPORT (PROTOCOL MV25600)

COMPANY: F.Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: Not applicable NAME OF ACTIVE SUBSTANCE(S): Not applicable	(FOR NATIONAL AUTHORITY USE ONLY)
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TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Final Clinical Study Report – MV25600 An International, Multi-Center Study Evaluating the Correlation of IL28B Genotypes with Chronic Hepatitis C Disease Characteristics and Patient Demographics(GEN-C) / Report No. Not applicable, Report Date October 2014
INVESTIGATORS / CENTERS AND COUNTRIES	Argentina (2), Belgium (20), Chile (2), Egypt (7), Estonia (5), France (16), Germany (16), Greece (10), Italy (49), Kuwait (1), Latvia (1), Lebanon (7), Lithuania (8), Macedonia (2), Mexico (5), Oman (1), Pakistan (8), Peru (2), Portugal (9), Qatar (1), Romania (8), Serbia (2), Slovakia (6), Sweden (3), Switzerland (2), Syria (1), Taiwan (6), Turkey (17), United Arab Emirates (2) and Venezuela (5).
PUBLICATION (REFERENCE)	A. Mangia, V. de Lédinghen, J. Keiss, J. Valantinas, J. Brahm, N. Rasmann, D. Messinger, F. Tatsch, on behalf of the gen-C Study Group. CORRELATION OF IL28B POLYMORPHISM WITH DEGREE OF FIBROSIS: ANALYSIS OF TREATMENT-NAIVE AND TREATMENT- EXPERIENCED CAUCASIAN PATIENTS INFECTED WITH HCV GENOTYPE 1 IN THE GEN-C STUDY. Journal of Hepatology 2013. 58: S229–S407 (EASL 2013) A. Mangia, V. De Ledinghen, F. Bailly, J. Brahm, J. Keiss, J. Valantinas, N. Rasmann, G. Riachi, D. Messinger, A. Caputo, G.R. Foster, on behalf of the Gen-C Study Group. rs12979860 IL28B GENOTYPE IS ASSOCIATED WITH ADVANCED FIBROSIS IN HCV GENOTYPE 1-INFECTED EUROPEAN PATIENTS WITH CHRONIC HEPATITIS C: RESULTS FROM THE INTERNATIONAL GEN-C STUDY. Journal of Hepatology 2014. 60: S361–S522 (EASL 2014)
PERIOD OF TRIAL	From August 30, 2011 (first patient in) to October 10, 2013 (last patient out)
CLINICAL PHASE	Non-interventional Study
OBJECTIVES	<u>Primary Objective</u> Correlation of Interleukin 28B (IL28B) genotypes rs12979860 (CC vs. TC vs. TT) and rs8099917 (TT vs. GT vs. GG) with liver fibrosis related to CHC <u>Secondary Objectives</u> <ul style="list-style-type: none"> • Correlation of IL28B genotypes (rs12979860 and

	<p>rs8099917) with liver inflammation related to CHC</p> <ul style="list-style-type: none"> • Correlation of IL28B genotypes (rs12979860 and rs8099917) with demographics in patients with CHC • Distribution of IL28B genotypes (rs12979860 and rs8099917) in patients with CHC in different HCV genotypes and in different countries • Correlation between the two IL28B genotypes (rs12979860 and rs8099917) in patients with CHC • Distribution of inosine triphosphatase (ITPA) genotypes rs1127354 (AA vs. CA vs. CC) and rs7270101 (CC vs. AC vs. AA) in patients with CHC in different HCV genotypes and in different countries • In treatment-experienced patients, retrospective analysis of <ul style="list-style-type: none"> ○ Correlation between IL28B genotypes (rs12979860 and rs8099917) and previous treatment outcome ○ Correlation between ITPA genotypes (rs1127354 and rs7270101) and Hb decline during prior treatment
STUDY DESIGN	Prospective, international, multicenter cohort study in CHC patients.
NUMBER OF SUBJECTS	4,766 patients were enrolled, including treatment-naïve and treatment-experienced patients
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	<p>Treatment-naïve and treatment-experienced male and female patients with CHC, including patients with HCV HIV co-infection, in the care of specialized outpatient clinics were eligible for this study.</p> <p><u>Inclusion Criteria</u></p> <p>To be eligible for this trial, patients had to have the following documented:</p> <ul style="list-style-type: none"> • Adult (according to local legislation) male or female patients • Chronic hepatitis C (CHC) • Patients naïve to CHC treatment or patients who received prior IFN based therapy for CHC for whom data on treatment received (type of therapy, dose, duration) and treatment outcome (i.e. RVR, cEVR, pEVR, EoT, SVR, relapse, breakthrough, non-response) of prior therapy were available. In addition information on fibrosis stage prior to the previous treatment course was required. • Written informed consent. <p><u>Exclusion Criteria</u></p> <ul style="list-style-type: none"> • Co-infection with hepatitis B • History or other evidence of decompensated liver disease • History of major organ transplantation with an existing functional graft (including liver transplantation) • End stage renal disease.
TRIAL DRUG / STROKE (BATCH) No.	Not applicable

DOSE / ROUTE / REGIMEN / DURATION	Not applicable
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REFERENCE DRUG / STROKE (BATCH) No.	Not applicable
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DOSE / ROUTE / REGIMEN / DURATION	Not applicable
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CRITERIA FOR EVALUATION

SAFETY AND EFFICACY:

Variables for the Primary Objective:

To investigate the association of IL28B genotypes with liver fibrosis related to CHC:

- Cirrhosis Status (Cirrhosis or transition to cirrhosis, No Cirrhosis) based on biopsy and non-invasive assessments
- Liver fibrosis stage based on biopsy using the following 5 categories (Cirrhotic, Transition to cirrhosis, Advanced fibrosis-non-cirrhotic, Mild/minimal fibrosis, No fibrosis)
- Liver fibrosis stage based on biopsy using METAVIR
- FibroScan value
- IL28B genotypes rs12979860 (CC vs. TC vs. TT)
- IL28B genotypes rs8099917 (TT vs. GT vs. GG)

Variables for the Secondary Objectives:

To investigate the association of IL28B genotypes with liver inflammation related to CHC:

- Liver inflammation stage using METAVIR
- Gender (Male, Female)
- Self-reported ethnic origin (Caucasian/White, Black, and Asian/Oriental)
- Body weight
- BMI
- HCV RNA genotype (G1, G2, G3, G4)
- HCV RNA level
- Alanine aminotransferase (ALT) ratio
- Aspartate aminotransferase (AST) ratio
- Platelet count
- HCV RNA genotype (G1, G2, G3, G4)
- Geographic region of study site (Asia, Europe, Middle East, Latin America)
- Country of study site
- ITPA genotypes rs1127354 (AA vs. CA vs. CC)
- ITPA rs7270101 (CC vs. AC vs. AA)
- Virological response to previous treatment within the first 12 weeks (RVR, cEVR, pEVR, noRVR/EVR)
- End of treatment response (HCV undetectable, HCV detectable)
- Overall virological response (SVR, Relapse, Breakthrough, Non-responder)
- Hemoglobin < 10 g/dL or drop of > 3 g/dL from baseline at any time during prior treatment (Yes, No)
- Use of erythropoietin at any time during prior treatment (Yes, No)

PHARMACODYNAMICS: Not applicable

PHARMACOKINETICS: Not applicable

The core analysis population was defined to include all patients who fulfilled the following criteria: (1) Written informed consent at study entry and no rejection of consent at study completion, (2) Adult (according to local legislation) male or female patients, (3) Data for the primary variables (IL28B genotype rs12979860 and rs8099917) available, (4) CHC, (5) No co-infection with hepatitis B, (6) No history or other evidence of decompensated liver disease, (7) No history of major organ transplantation with an existing functional graft (including liver transplantation), (8) No end-stage renal disease, (9) Sufficient information available of whether the patient is treatment-experienced or treatment-naïve.

All study variables were summarized using descriptive or exploratory statistical methods stratified by treatment-naïve and treatment-experienced patients of the core analysis population. As specified in the study protocol, no pooled analysis across both strata was planned, because relevant differences in the distribution of IL28B genotypes between treatment-naïve and treatment-experienced patients were expected.

The Cochran-Armitage Trend test was used to investigate the association between IL28B genotypes with the cirrhosis status (cirrhosis or transition to cirrhosis, no cirrhosis) based on biopsy and non-invasive assessments, i.e. the question of whether the incidence of 'cirrhosis/transition to cirrhosis' was increasing or decreasing with an increasing number of T alleles (i.e. for rs12979860: CC to CT to TT; rs8099917: GG to GT to TT). The association between IL28B and the two ordinal 5-level liver fibrosis stage variables based on biopsy staging were investigated using the Jonckheere-Terpstra Trend test. The same test was applied for the association between FibroScan values and IL28B.

The same methods (Cochran-Armitage Trend test and Jonckheere-Terpstra Trend test) were also used to investigate various secondary objectives (i.e. the association between IL28B and continuous, ordinal or binary secondary variables). For the association between IL28B and nominal variables (e.g. ethnic origin, HCV RNA genotype, or country) the Pearson chi-square test was used.

Univariate and multivariate logistic regression (ULR, MLR) analyses with various patient characteristics as explanatory variables were used to investigate their impact on the following dependent variables in the core analysis population.

In treatment-naïve and treatment-experienced patients, respectively:

- Cirrhosis status (cirrhosis or transition to cirrhosis vs. no cirrhosis)

In treatment-experienced patients only:

- SVR (yes vs. no)
- RVR/cEVR (yes vs. no)
- Hb decline to <10 g/dL or drop of >3 g/dL at any

time during prior therapy (yes vs. no).

Where appropriate, the analyses were also stratified by HCV RNA genotype (Genotype 1, 2, 3, 4, other, total). In addition the primary objective 'association between IL28 genotype and the incidence of cirrhosis or transition to cirrhosis' was also investigated by HCV RNA genotype and pretreatment status for the following subgroups:

- Region (Asia, Europe, Latin America, Middle East)
 - Ethnic Origin (Asian, Caucasian)
 - European Caucasian patient.
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METHODOLOGY

MV25600 was a prospective, international, multicenter study in treatment-naïve or treatment-experienced patients with CHC for whom a liver fibrosis evaluation prior to previous treatment and the outcome of this therapy was available.

Patients attended the participating study center for a screening visit where they received all relevant information about the study including the informed consent form (ICF).

There was only one study visit in this trial. Patients deciding to participate in the study by providing written informed consent, had a blood sample drawn for IL28B and ITPA assessments.

Treatment was NOT part of this study.

Available data from the medical records and a patient interview on medical history and disease characteristics (which are routinely performed in accordance with current guidelines and local standard of care) were documented in the electronic Case Report Form (eCRF).

In patients who did receive a treatment course in the past, relevant data concerning treatment outcome of this prior treatment course were documented in the eCRF.

Safety assessments included the documentation of serious adverse events caused by a protocol-mandated intervention during the study visit.

RESULTS

Of the 4766 patients enrolled by 233 centers across 30 countries (mostly in Europe, followed by Middle East, Asia and Latin America) 4616 were eligible for the core analysis population. There were no major differences in age, gender and ethnic origin as well as height, body weight and BMI between patients of different IL28B rs12979860 genotypes (CC vs. TC vs. TT) and different IL28B rs8099917 genotypes (TT vs. GT vs. GG).

The numbers of treatment-naïve and treatment-experienced patients in the core analysis population were 2916 (63%) and 1700 (37%), respectively. Treatment-experienced patients in comparison to treatment-naïve patients were slightly older, the proportion of Asians was higher, time since HCV infection was longer, probable mode of infection was more often transfusions and less often injectable drug use, and the proportions of patients with G1, with cirrhosis or transition to cirrhosis as well as elevated ALT values were slightly higher in the former than the latter patients.

Prevalence of IL28B genotypes - geographical regions, countries, ethnicities

Over the various geographical regions IL28B rs12979860 TC and IL28B rs8099917 TT were prevailing, with the exception of Asia where CC was the most common genotype for IL28B rs12979860 and Latin America where TG was the most common genotype for IL28B rs8099917.

Regarding the distribution of genotypes across ethnic groups, in both treatment-naïve and treatment-experienced patients, relatively more Asians and Caucasians had genotype IL28B rs12979860 CC than Blacks, whereas relatively more Asians and Blacks had genotype rs8099917 TT than Caucasians.

As expected from the distribution by regions, distribution of IL28B rs12979860 genotypes across countries was not homogenous. Higher proportions of IL28B rs12979860 CC patients were noted in Taiwan, Latvia and Syria than in other countries, whereas TT was more common

in Venezuela than in other countries. In most countries IL28B rs8099917 TT was most common and GG least common.

A slightly lower proportion of subjects with genotype IL28B rs12979860 CC observed in treatment-experienced as compared with treatment-naïve patients (28.8% vs 35.5%) is likely to be due to a selection process, as cured patients (with a relatively high proportion of the 'good' C alleles) may have less need to see their doctor than others that have not been cured (having less often the good alleles).

Patient demographics and other characteristics and IL28B genotypes

These analyses were done in order to investigate whether any imbalances in patient characteristics were likely to have an impact on the study results. There were no major differences between the IL28B genotype subgroups regarding previous and concurrent diseases or alcohol consumption, smoking and drug use.

Considering treatment-naïve and treatment-experienced patients together, there was no clear trend for an association of gender, body weight or BMI and the IL28B genotypes.

HCV RNA level and IL28B genotypes

In the two largest HCV RNA genotype groups G1 and G3 there were trends for the HCV RNA level to decrease from IL28B rs12979860 CC over TC to TT and from IL28B rs8099917 TT over TG to GG. Hypothetically, patients with the rs12979860 C and IL28B rs8099917 T alleles, respectively, may have a lower activity of endogenous IFN α , allowing a higher rate of HCV replication whilst, simultaneously, being more susceptible to exogenous IFN α .

Liver enzymes, platelets and association with IL28B genotypes

In most HCV RNA genotype groups, regardless of patients' pretreatment status, there was a statistically significant association between ALT and the IL28B rs12979860 genotype (ALT falling from CC to TT) as well as the rs8099917 genotype (ALT falling from TT to TG). This is in good agreement with a stronger reaction of the host vs. the virus. Similar trends were also seen for AST. In some HCV RNA genotype groups there was a trend towards IL28B rs12979860 CC and IL28B rs8099917 TT patients to have lower platelet numbers than other patients.

HCV RNA genotypes and IL28B genotype

In treatment-naïve and treatment-experienced patients alike, G1 was the most common HCV RNA genotype, followed by G3, G2 and G4. Apart from the finding that CC was the most common IL28B rs12979860 genotype in treatment-experienced G2 patients, TC was the most common IL28B rs12979860 genotype and TT the most common IL28B rs8099917 genotype in treatment-naïve and treatment-experienced patients. There was a common pattern across treatment-naïve and treatment-experienced patients in that IL28B rs12979860 CC and rs8099917 TT were less common and IL28B rs12979860 TT and rs8099917 GG more common in G1 than in G2-4 patients. These correlations between HCV RNA genotypes and IL28B genotypes are certainly a result of the regional distribution patterns of two – per se independent - characteristics.

Correlation between IL28B rs12979860 and IL28B rs8099917 genotypes

When the IL28B subgroups were juxtaposed it was found that most patients who had IL28B rs12979860 CC had IL28B rs8099917 TT, most who had TC had TG and most who had TT had either TG or GG.

IL28B genotype and cirrhosis or transition to cirrhosis, liver fibrosis and liver inflammation

The primary objective of the trial was to investigate the association of IL28B rs12979860 and rs8099917 genotypes with the liver fibrosis stage of the patients. In treatment-naïve G1 patients a clear trend was seen towards an increasing prevalence of cirrhosis or transition to cirrhosis from IL28B rs12979860 CC patients over TC to TT patients and from IL28B rs8099917 TT patients over TG to GG patients. This, however, was not confirmed in naïve patients of other HCV RNA genotype groups or in the treatment-experienced patients. In the latter, though, a trend towards higher numbers of patients with cirrhosis or transition to cirrhosis was observed in G4 patients with the IL28B rs8099917 TG genotype as compared with the TT subgroup.

The finding, that in the relatively large group of treatment-experienced G1 patients there was no association between the IL28B genotypes and the prevalence of cirrhosis or transition to cirrhosis, may be explained by a selection bias. In the present group of

treatment-experienced patients subjects with SVR were less frequent than would be expected in an unselected sample. As SVR is obtained more frequently in patients with the favorable genotypes IL28B rs12979860 CC and IL28B rs8099917 TT than in others, a 'negative patient selection (recruitment) factor SVR' would prove more important in patients with these genotypes than in others. Patients with SVR are generally likely to have fewer negative predictive factors for response (including cirrhosis) than pretreated patients with no SVR. Hence, by losing a relevant proportion of SVR patients (with few negative predictors) to recruitment, a bias may have been introduced leading to a population of treatment-experienced patients that has, in comparison with an unselected population of patients or of treatment-naïve patients, more negative predictors for response in general and of cirrhosis in particular. This selection effect would be expected to be greater in treatment-experienced patients with the favorable genotypes IL28B rs12979860 CC and IL28B rs8099917 TT than in treatment-experienced patients with unfavorable genotypes. This may explain why the association between cirrhosis and genotypes seen in treatment-naïve G1 patients could not be confirmed in treatment-experienced G1 patients.

Biopsically assessed stages of liver fibrosis did not show a clear association with the IL28B genotype. However, the low proportion of patients with liver biopsy data overall and for each HCV RNA genotype should be considered. Moreover, different staging systems for fibrosis were used in daily practice (e.g. METAVIR or ISHAK) and thus may have prevented sample sizes to be reached that were necessary to detect an association.

Also, in none of the analyses an association between the inflammation grade of the liver and the IL28B genotype was found, which might also be due to the variety of grading systems used and the resulting low patient numbers.

Multiple logistic regression (MLR) analysis was used to identify independent risk factors for an increased probability of cirrhosis or transition to cirrhosis, and to investigate, whether the IL28B genotype remains a predictive factor after inclusion of other predictors into the MLR models. In the treatment-naïve patients, old age category, higher BMI, Asian region vs. European region, Middle East region vs. European region, HCV RNA genotype G1 vs G2, higher AST and lower number of platelets, but not IL28B, were predictive for cirrhosis or transition to cirrhosis. Additional factors found in treatment-experienced patients were longer duration of HCV infection and lower ALT.

An association between cirrhosis or transition to cirrhosis and the IL28B rs12979860 genotype was only found in the MLR analyses of treatment-naïve G1 patients where patients with TT or TC were more likely than those with CC to have cirrhosis or transition to cirrhosis. This confirms the association seen in the univariate analysis and shows that the IL28B rs12979860 genotype remains an independent predictor of cirrhosis or transition to cirrhosis in treatment-naïve G1 patients after adjusting for other well-known predictors, like higher age or lower platelet count. The IL28B rs8099917 genotype was not identified as an independent factor over and above the IL28B rs12979860 genotype, which is not surprising due to the strong association between the two genotypes.

The statistical significant association observed between the IL28B genotype and the prevalence of fibrosis cirrhosis/transition to cirrhosis in treatment-naïve G1 patients was also found in treatment-naïve G1 Caucasians, whereas there was no significant association in treatment-naïve G1 Asians. Other origins (Black, Native American/American Indian) were not analyzed due to low sample sizes). When the analysis was repeated by geographical region (instead of ethnic origin), a significant association between the IL28B genotype and the prevalence of cirrhosis/transition to cirrhosis was found in treatment-naïve G1 patients from Europe, but not in treatment-naïve patients from Asia, Latin America and Middle East, respectively. This was most likely due to the much lower sample sizes in these regions as compared with that in Europe.

When the analysis was restricted to European Caucasians the aforementioned trends for an increasing prevalence of cirrhosis/transition to cirrhosis with the presence of the IL28B rs12979860 T allele were seen again in treatment-naïve G1 and treatment-experienced G4 patients. The same applies to the prevalence of cirrhosis or transition to cirrhosis and the IL28B rs8099917 G allele.

Despite the aforementioned results for cirrhosis or transition to cirrhosis fibrosis indices APRI and FIB-4 tended to be higher in IL28B rs12979860 CC and IL28B rs8099917 TT patients than in patients with other genotypes.

Prior treatment and response in treatment-experienced patients

Regarding the prior antiviral treatment of treatment-experienced patients it was noted that the vast majority had been treated with the combination of a pegylated interferon with ribavirin, while non-pegylated interferon mono- or combination therapy had been used in a low proportion of the patients only. In the G1 group IL28B rs12979860 TT patients and IL28B rs8099917 GG patients tended to have been treated less often for 48 weeks than patients of the other subgroups. In PEG-IFN alfa-2a patients in particular, a 48-week regimen was completed more often in IL28B rs12979860 CC patients and in IL28B rs8099917 TT patients than in others. This is in agreement with the expectation, that patients with the aforementioned genotypes show better treatment responses and thus are less likely to have their treatment prematurely discontinued for insufficient response on treatment.

As to the response to previous antiviral treatment percentages of G1 patients with RVR, cEVR, HCV RNA undetectable at EOT and SVR were all clearly higher in the IL28B rs12979860 CC subgroup than in the TC and TT subgroups. In other HCV RNA genotype groups, too, RVR and SVR had been more common in the IL28B rs12979860 CC subgroup than in others.

Also, RVR, cEVR, HCV RNA undetectable at EOT and SVR in the G1 group were more common in IL28B rs8099917 TT patients than in TG and GG patients. The proportion of patients with SVR was 3 to 4 times higher in the former than the latter patients. Across all HCV RNA genotype groups higher proportions of subjects with RVR and SVR in IL28B rs8099917 TT than TG patients were noted.

In the multiple logistic regression analysis IL28B rs12979860 CC was identified as a positive predictive factor for SVR as well as for RVR/cEVR. Other positive predictive factors for SVR were no cirrhosis, lower BMI, Asia (vs. Europe), genotypes G2, G3, G4 (vs. G1) and lower HCV RNA concentration. Positive predictive factors for achieving RVR/cEVR in addition to IL28B rs12979860 CC were Asia (vs. Europe), genotypes G2, G3 (vs. G1), lower HCV RNA concentration and lower AST.

These findings are in agreement with the notion that the IL28B genotype is, in addition to other well-known predictors, an independent factor for virological response. However, as far as the absolute response rates are concerned, it should be considered that the limitations of this study (selection bias) did not allow an unbiased estimation of RVR, cEVR, or SVR.

Prevalence of ITPA genotypes

ITPA rs1127354 CC was most common in all regions, CA was more common in Asia than elsewhere. ITPA rs7270101 AA was most common in all regions and more frequent in Asia than elsewhere. ITPA rs1127354 AA and ITPA rs7270101 CC were very rare.

ITPA rs1127354 CC was also most common in all countries, the proportion of patients with CA was higher in some countries than in others. Likewise, ITPA rs7270101 AA was prevailing in all countries and the proportion of patients with AC was higher in some countries than in others.

ITPA rs1127354 CC and ITPA rs7270101 AA were predominant in all IL28B rs12979860 and IL28B rs8099917 genotype subgroups.

By far, most patients had the combination of ITPA rs1127354 CC with ITPA rs7270101 AA.

ITPA genotype, hemoglobin and use of erythropoietin during prior therapy

In the multiple regression analysis a hemoglobin decline to <10 g/dl or drop of >3 g/dl at any time during prior therapy in treatment-experienced patients was associated with ITPA rs7270101 AA vs. CC and AC vs. CC, ITPA rs1127354 CC vs. CA, higher age, female vs. male gender, lower BMI, Asia vs. Europe, Latin America vs. Europe and erythropoietin use vs. no use at any time during prior therapy. Erythropoietin had been used more often in G1 patients with ITPA rs1127354 CC than in those with CA. This supports previous findings indicating that the ITPA genotype is a predictor for anemic events in patients treated with PEG-IFN plus ribavirin.

PHARMACODYNAMIC RESULTS

Not applicable

PHARMACOKINETIC RESULTS

Not applicable

SAFETY RESULTS

No serious adverse events were reported.

CONCLUSIONS

In treatment-naïve G1 patients, but not in the total of treatment-naïve patients or in treatment-experienced patients, increasing proportions of subjects with cirrhosis or transition to cirrhosis were seen from IL28B rs12979860 CC over TC to TT patients and from IL28B rs8099917 TT over TG to GG patients. This was also shown in G1 patients living in Europe, in patients being of European origin and in G1 European Caucasians. A further trend was noted towards a higher proportion of G4 patients with cirrhosis or transition to cirrhosis with IL28B rs8099917 TG as compared with TT.

The multiple logistic regression analysis showed the IL28B rs12979860 genotype to be an independent predictor of cirrhosis or transition to cirrhosis in treatment-naïve G1 Caucasian patients after adjustment for other prognostic factors. However, the association seems less pronounced compared with other well-known prognostic factors (e.g. age or platelets).

Whether this is also true for none-Caucasian patients (e.g. Asians or Blacks) remains unclear as sample sizes in these subpopulations were relatively small. In treatment-experienced patients with genotypes IL28B rs12979860 CC and IL28B rs8099917 TT proportions of subjects with RVR and SVR were higher than in patients with other IL28B genotypes. The data support previous findings that both IL28B rs12979860 and IL28B rs8099917 are predictors of increased virological response. Also other known factors for response such as no cirrhosis, lower body weight or HCV RNA genotype were confirmed.

ITPA rs1127354 CC and ITPA rs7270101 AA were identified as factors for a hemoglobin value of <10 g/dL, a drop in hemoglobin by >3g/dL or both during previous therapy. The use of erythropoietin was more common in patients with ITPA rs1127354 CC than in patients with ITPA rs1127354 CA.