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<th>26–28 September 2013</th>
<th>Frankfurt Messe Congress Centre, Frankfurt, Germany</th>
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### HCV: TREATMENT AND LATE-STAGE CLINICAL TRIALS (PHASE IIB, PHASE III AND PHASE IV)  
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**P17** Responses to peginterferon alfa-2a vs alfa-2b plus ribavirin in a Mexican population with chronic hepatitis C  
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The primary aim of this study was to investigate the impact of added FLU to SOC on viral relapse in genotype 3 patients. No studies were performed regarding the impact of FLU on viral relapse in genotype 3 patients.

In conclusion, combination of fluvastatin and SOC significantly reduced viral relapse in chronic hepatitis C genotype 1 but not genotype 3 patients.
The standard therapy is pegylated interferon and ribavirin combination therapy for eradication of hepatitis C virus, the efficacy is depends on genotype. HCV genotype 1 is less effective than other genotype, triple therapy including protease inhibitor is developed. But the sustained viral response (SVR) of genotype 1 is higher than reported data. So, we report the effectiveness of current standard therapy for chronic hepatitis C in South Korea through single center experience.

**Background/Aims**

The standard therapy is pegylated interferon and ribavirin combination therapy for eradication of hepatitis C virus, the efficacy is depends on genotype. HCV genotype 1 is less effective than other genotype, triple therapy including protease inhibitor is developed. But the sustained viral response (SVR) of genotype 1 is higher than reported data. So, we report the effectiveness of current standard therapy for chronic hepatitis C in South Korea through single center experience.

**Methods**

We reviewed the medical records of patients who were diagnosed chronic hepatitis and treated by pegylated interferon and ribavirin combination therapy. The patients were diagnosed chronic hepatitis C between 2006 and 2012 at Yeouido St. Mary’s hospital. Before the treatment, HCV RNA level, serum ALT, liver biopsy were done for baseline characteristics. The treatment regimen was pegylated interferon α-2b or α-2a and ribavirin, the early virologic response (EVR), the end of treatment virologic response (ETR), the SVR and relapse were evaluated the efficacy of treatment. Three patients with genotype 3a were foreigner, so we exclude them from our study.

**Results**

In genotype 1b, the patients completed treatment were 66.7%, the ETR, EVR and SVR rates were 96.2%, 85.7% and 85.2%. In genotype 2a or 2c, the patients completed treatment were 84.8%, the ETR, EVR and SVR rates were 100%, 100% and 98.6%. Relapse occurred 80% of overall, 15.4% in 1b and 3% in 2a or 2c.

**Conclusions**

In genotype 1b, the efficacy of eradication is poor than genotype non 1. But the virologic response is effective in any group of chronic hepatitis C infection by pegylated interferon and ribavirin combination therapy. So, we think that more aggressive treatment is needed in any genotype of chronic hepatitis C.
The prevalence of these polymorphisms differs among ethnic groups [Figure 1]; however, there is a paucity of information about South American populations.

The aim of this study was to determine the prevalence of these SNPs in the healthy population of different ethnic groups residing in Argentina.

SUMMARY OF RESULTS

Figure 2. World-wide frequency of C and T alleles (related to response and non-response to HCV antiviral treatment, respectively) of SNP rs12979860 (IL28B). East and south-west Asia exhibit the highest frequency of the IL28B-“favoured” (C) allele, whereas in Africa the lowest frequency is observed (Thomas et al., Nature 2009; 461: 798-801).

Figure 3. Prevalence of mtDNA haplogroups among Argentines, Bolivians, Peruvians and Paraguayans. Native American maternal ancestry (A, B, C and D haplogroups) was found in 42.7% of Argentines, 94.6% of Bolivians, 94% of Peruvians and 98% of Paraguayans (p<0.0001).

* p<0.001 when comparing Argentines with the remaining groups.

Table 1. T-Plate Deficiency Variables. Modified from Thompson et al., Electrometabolomics 2010; 139: 1181-1189.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ARGENTINES</th>
<th>BOLIVIANS</th>
<th>PERUVIANS</th>
<th>PARAGUAYANS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homzygosity (A/A)</td>
<td>10.6%</td>
<td>1.5%</td>
<td>2.8%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Heterozygosity (A/C)</td>
<td>9.7%</td>
<td>2.2%</td>
<td>10%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Wild-type (C/C)</td>
<td>79.7%</td>
<td>94.1%</td>
<td>87.3%</td>
<td>86.5%</td>
</tr>
</tbody>
</table>

**p<0.001, * p<0.01 when comparing Argentines with the remaining groups.

Figure 4. Prevalence of Y-SNPs haplogroups among Argentines, Bolivians, Peruvians and Paraguayans. Native American paternal ancestry (E1b1b) was found in 1% of Argentines, 71.1% of Bolivians (p<0.0001), 40% of Peruvians and 27.7% of Paraguayans (p<0.001).

* p<0.001, * p<0.01 when comparing Argentines with the remaining groups.

Figure 5. Prevalence of SNP rs12979860C>T (IL28B gene) genotype among Argentines, Bolivians, Peruvians and Paraguayans. CC genotype -related to higher risk of ribavirin-induced-hemolytic anemia was observed in 84.5% of Argentines vs. 90.9% of Bolivians (p<0.0001), 95.7% of Peruvians (p<0.01) and 93.2% of Paraguayans (p<0.01).

**p<0.001, * p<0.01 when comparing Argentines with the remaining groups.

Figure 6. Prevalence of SNP rs1273545C>A (ITPA gene) genotype among Argentines, Bolivians, Peruvians and Paraguayans. CC genotype -related to higher risk of ribavirin-induced-hemolytic anemia was observed in 840 of Argentines vs. 94.6% of Bolivians (p<0.0001), 95.7% of Peruvians (p<0.01) and 92.5% of Paraguayans (p<0.01).

**p<0.001, * p<0.01 when comparing Argentines with the remaining groups.

Table 2. Prediction of risk of ribavirin-induced-hemolytic anemia among Argentines, Bolivians, Peruvians and Paraguayans.

<table>
<thead>
<tr>
<th>ITPA A/C SNP</th>
<th>Argentines</th>
<th>Bolivians</th>
<th>Peruvians</th>
<th>Paraguayans</th>
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<tbody>
<tr>
<td>Wild-type (C/C)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Heterozygosity (A/C)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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</tr>
<tr>
<td>Homzygosity (A/A)</td>
<td>0%</td>
<td>0%</td>
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<td>0%</td>
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</table>

**p<0.001, * p<0.01 when comparing Argentines with the remaining groups.

CONCLUSIONS

This is the first systematic study of polymorphisms related to antiviral response in HCV infection and ethnicity characterization in the South American population.

There is a significant bias in the distribution of predictive polymorphisms of response to HCV treatment according to the population ancestry.

This study highlights the importance of the previous characterization of these variants to evaluate the risk-benefit of antiviral treatment according to the patient ancestry, particularly in a multiethnic and admixed population.
The Health Protection Agency (HPA) estimated that approximately 203,000 hepatitis C (HCV) antibody positive individuals aged 15-59 were living in England in 2005; 150,000 of whom were chronically infected [1]. Antiviral treatments are available that will successfully clear the virus in the majority of patients. Those who are treated and achieve a sustained virological response (SVR) experience long-term disease remission and liver-related mortality rates comparable to the general population, and are generally considered ‘cured’ [2]. However, service provision in England, despite well disseminated guidelines on the management and treatment of HCV [3], is variable with low rates of onward referral and treatment [4].

In England, the detection of anti-HCV antibodies is the primary diagnostic test for HCV which, if positive, should be routinely followed up by testing for the presence of HCV-RNA, usually by PCR. For those who undergo treatment, response is monitored through repeat PCR testing. PCR testing is usually undertaken at the outset of treatment, at 12 and 24 weeks (for individuals on a 48 week regimen) to establish whether an individual is responding to therapy and likely to achieve a SVR, and again at the end of treatment [3]. Each individual on treatment should therefore have a minimum of three PCR test results within one year of the treatment start date, and be genotyped.

Current trends in surveillance in England are not suitable to estimate treatment rates. There is no national surveillance system in place through which it is possible to monitor access to, and success of treatment, without which the implementation of national HCV strategies cannot be evaluated. The aim of this study was to utilise routine laboratory testing data to identify individuals undergoing patterns of repeat HCV-RNA testing suggestive of referral, treatment and response over time.

RESULTS

Estimating treatment:
- 267,887 HCV-RNA test results were performed among 100,640 individuals, of whom 78.9% (79,360) tested positive for viral RNA indicating an active infection.
- Approximately one in three (29.8% (16,538) of these individuals had a repeat pattern of HCV-RNA testing suggestive of treatment-monitoring.
- Annual numbers of individuals treated increased significantly (p<0.001) between 2002 and 2009 (p<0.001), but declined by 2010.
- Treatment rates were highest in the population of patients treated in 2007 and 2009 compared to 2006 and 2008 (p<0.001). The proportion of individuals treated was strongly associated with ethnicity, genotype and age group (p<0.001) (Table 1).

Treatment outcome:
- Overall 10,468 (63.3%) of those treated achieved a sustained virological response (SVR), including 55.3% and 67.1% of those with a genotype-1 and non-1 virus, respectively.
- The adjusted odds of a treatment response was significantly higher among females, those of Asian or Asian British, and those with a non-genotype-1 infection.
- Individuals achieving a SVR were significantly younger than those without evidence of response to treatment (Wilcoxon p<0.001, median 38 vs. 42).

Validation:
- Validation against the Trent clinical database demonstrated that the algorithm was 95% sensitive and 93% specific in detecting treatment, and 100% sensitive and 93% specific for detecting treatment outcome (Figure 2).
- Using surveillance data to determine treatment rates for patients with chronic hepatitis C virus infection

DISCUSSION

Here we examined over 250,000 PCR test results, among 100,809 individuals, of whom approximately four in five had an active infection, with only one in five having received antiviral therapy between 2002 and 2011.

The number of individuals being treated in the catchment of the sentinel laboratories annually, increased rapidly from under 500 in 2002 to well over 3000 by 2008, but a more modest increase to 2297 in 2009, and again at the end of treatment [3]. Each individual on treatment should therefore have a minimum of three PCR test results within one year of the treatment start date, and be genotyped.

Comparison with the Trent HCV cohort data demonstrated that the algorithm based on testing patterns was both highly sensitive and specific at both identifying individuals on treatment, as well as treatment outcome.

CONCLUSIONS

HCV is curable for the majority of individuals, but it is essential that opportunities for treatment exists, and can be monitored. Our findings suggest low, but improving rates of onward referral, treatment, and as a result, low overall rates of sustained virological clearance.

Laboratory testing activity, collected through a sentinel laboratory surveillance programme has enabled the first country-wide analysis of treatment and response among HCV infected individuals, producing trends comparable to those estimated from drug prescribing data [6]. Our approach provides a sensitive, robust, and sustainable method by which service provision across England can be monitored.

ACKNOWLEDGEMENTS

We thank all the staff in the testing laboratories, including the IT, medical and scientific staff who supported this study on an on-going basis. The sentinel surveillance of the hepatitis testing study was funded by the English Department of Health (study reference AIDB 2:3) until September 2009.
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ABSTRACT

An open-label drug interaction study was performed in healthy subjects to characterize serum pharmacokinetic (PK) parameters of pegylated interferon-alpha (PEG-IFNα) and ribavirin before and after treatment with miravirsen. On Days 1 and 36, 5 subjects were administered ribavirin (BID, orally) and PEG-IFNα (SID, subcutaneously (s.c.), once weekly). The serum PK for ribavirin and PEG-IFNα were followed after the first and second doses of these compounds and the serum exposure at each occasion compared. The study showed that four weeks of dosing with miravirsen (5 doses over 29 days) had no clinically significant effect on exposure (expressed as AUC values) of the subsequently administered PEG-IFNα or ribavirin.

Conclusion: Co-administration of miravirsen and PEG-IFNα and ribavirin was safe and well tolerated in this study. There were no meaningful drug interactions between miravirsen and PEG-IFNα or ribavirin upon co-administration in healthy subjects.

Pharmacokinetics, cont.

Serum PK parameters of ribavirin showed little variation between subjects or before and after miravirsen treatment. A smaller increase was noted in the AUC0-168h values on Day 37, as compared to Day 1 values, and a paired ANOVA analysis (two-tailed) showed that the AUC0-168h values on Day 37 were higher than the Day 1 values (p=0.035). An increase in AUC0-168h with repeat ribavirin dosing in this study was expected since substantial accumulation of ribavirin has been shown upon multiple dosing in standard treatment regimens for HCV infection. The increase in ribavirin AUC in this study was small compared to the published changes. Hence, the changes noted in this study were likely to be of little clinical significance.

The PEG-IFNα serum concentrations varied substantially (along with the PK parameters) between the subjects, as revealed by the high RSD values for the PK parameters (Table 19). Thus, within the context of the high inter-individual variations in serum concentrations, the exposure (AUC values) of PEG-IFNα was not affected by miravirsen treatment.

RESULTS

In this study five subjects were administered PEG-IFNα + ribavirin on Day 1. Subjects then received 5 weekly s.c. doses of miravirsen (5 mg/kg, s.c., once weekly). The serum PK for ribavirin and PEG-IFNα were followed after the first and second doses of these compounds and the serum exposure at each occasion compared.

Background

A combination of PEG-IFN and ribavirin has been used as standard of care treatment against chronic Hepatitis C virus infection and is still used today in combination with a direct acting antiviral protease inhibitor such as telaprevir. Other combinations are also possible.

Miravirsen sodium (miravirsen) is a β-D-2′-O-Methyl Nucleic Acid (LNA)-modified phosphorothioate anti-sense oligonucleotide that is complementary to the liver-specific microRNA-122 (miR-122), a host factor required by HCV for efficient accumulation. Prior clinical and non-clinical studies have demonstrated miravirsen activity against all HCV genotypes (GT) and long-lasting suppression of HCV viremia without evidence of viral resistance. Miravirsen is not metabolized by CYP450 enzymes suggesting it has a low propensity for drug-drug interactions.

Safety

Miravirsen was well tolerated in the study.

Headache, flu-like symptoms, and upper respiratory tract infection were the most commonly reported Treatment Emergent Adverse Events (TEAEs). Flu-like symptoms are commonly reported with administration of PEG-IFNs

Four (40) TEAEs were considered by the clinical investigator as possibly related to study treatment. These events were mild to moderate in character and were considered by the clinical investigator to be of no clinical concern. No serious adverse events (SAEs) were reported. No TEAE prompted discontinuation of any subject from the study.

Pharmacokinetics

This study was designed to characterize serum PK parameters of PEG-IFNα + ribavirin in healthy subjects before and after treatment with miravirsen. Blood samples for the quantification of ribavirin and PEG-IFNα were collected from all subjects on Days 1 and 37 at the following time points: pre-dose (0 hour) and 2, 6, 8, 10, 12, 24, 48, 96, and 168 hours post-dose.

Ribavirin in healthy subjects: The mean concentrations (± standard deviation (SD)) of the five subjects were plotted against the dosing on Days 1 and 37.

CONCLUSIONS

- Co-administration of miravirsen and PEG-IFNα and ribavirin was safe and well tolerated.
- No serious adverse events were reported and no treatment emergent adverse events prompted discontinuation of any subject.
- No evidence of clinically significant prothrombotic or anticoagulant effect in the study.
- There were no meaningful drug interactions between miravirsen and PEG-IFNα or ribavirin upon co-administration in healthy subjects.

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MIRAVIRSEN DOES NOT INTERACT WITH TELAPRE Virgin

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1Santaris Pharma A/S, Hørsholm Denmark and 4San Diego, CA, USA, 2Spaulding Clinical Research, West Bend, WI, USA and 3University of Puerto Rico, FDI, San Juan, USA

ABSTRACT

An open-label drug interaction study was performed in healthy subjects to assess the effect of miravirsen on telaprevir plasma PK. Five subjects received telaprevir every day during a week (Days 1 to 7). The subjects subsequently received 5 single doses (SDs) of miravirsen (7 mg/kg, on Days 8, 15, 22, 29 and 36). In the period from Day 30 to Day 36, the subjects once more received telaprevir daily. Telaprevir was administered as a single dose on Days 1 and 30, whereas it was administered TID Days 2 to 7 and Days 31 to 36.

The plasma pharmacokinetics (PK) for telaprevir were followed on Days 1, 7, 30 and 36 and those for miravirsen on Days 15 and 36. The plasma PK of telaprevir before and after miravirsen treatment were compared, as well as those after a single- and multiple dosing with telaprevir. The effect of telaprevir on miravirsen plasma PK was also studied.

Study design:

Week | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7
--- | --- | --- | --- | --- | --- | --- | ---
YRD | TID | TID | TID | TID | TID | TID | TID

The study showed that repeated dosing with miravirsen (5 doses over 29 days) had no effect on exposure (expressed as AUC values) of the subsequently administered telaprevir, Day 36 versus Day 7 (A). Neither had repeated dosing with telaprevir during one week any effect on subsequently administered miravirsen, Day 36 versus Day 15.

Background

Hepatitis C virus (HCV) is the major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma and is the leading indication for liver transplantation. Treatment for HCV infection depends on several factors, including HCV genotype and viral load. There are six major genotypes of HCV. The current antiviral standard of care treatment for chronic HCV genotype 1 infection is a combination of a direct acting antiviral protease inhibitor, e.g. telaprevir, with pegylated interferon alpha (PEG-IFNα) plus ribavirin. This triple therapy regimen is highly active (sustained viral response after 24 weeks of about 75%) but is often poorly tolerated because of the PEG-IFNα + ribavirin. Consequently, there continues to be a pressing need for highly active therapeutic regimens without PEG-IFNα + ribavirin.

Miravirsen sodium (miravirsen) is an LNA-modified phosphorothioate antisense oligonucleotide inhibitor of the liver-expressed microRNA-122 (miR-122). miR-122 is a critical host factor for the HCV infection. By binding to and sequestering miR-122, miravirsen effectively exposes the virus to nucleolytic degradation and innate immune response. Thus, miravirsen reduces HCV RNA levels indirectly rather than by directly targeting the virus. Miravirsen has activity against all HCV genotypes, since the miR-122 target sites are conserved across all HCV genotypes and subtypes. Since miravirsen is metabolized by cellular nucleases and not by the CYP450 system, it has a low propensity for drug-drug interactions.

RESULTS

Safety

Co-administered miravirsen and telaprevir was safe and well tolerated by the healthy male subjects in the study. A single treatment emergent adverse event (TEAE) of headache was reported 20 days after miravirsen administration that was considered mild in severity and unlikely related to study drug. No deaths, SAEs or TEAEs leading to study drug discontinuation were reported during the study. No treatment-related trends were observed in AEs, clinical laboratory results, vital sign measurements, 12-lead ECG results or physical examination findings.

Pharmacokinetics

**Mean Plasma Concentrations of Telaprevir** - Plasma samples were collected at different times, pre-dose and then 2, 4, 6, 8, 12 and 24 hours post-dose on:

- Day 1 - after a single 750 mg dose of telaprevir administered alone
- Day 7 - after 5 days of multiple 750 mg doses of telaprevir administered TID
- Day 30 - after a single 750 mg dose of telaprevir administered alone after 4.0 mg/kg doses of miravirsen
- Day 36 - after a single 750 mg dose of telaprevir administered alone after 5 days of multiple 750 mg doses of telaprevir administered TID together with a single 7.0 mg/kg dose of miravirsen

After TID dosing (on Day 7), there was a marked accumulation of telaprevir, as compared to on Day 1 – mean Cmax increased 2.2-fold and the mean AUC0-18h increased 3.4-fold. Likewise, on Day 36, after 5 days of multiple TID doses (750 mg) of telaprevir, the mean Cmax increased 1.9-fold and the mean AUC0-18h increased 3.0-fold as compared to on Day 30.

**Effect of miravirsen on the PK of telaprevir:**

The most important comparison for assessing drug interaction was to compare the effect of miravirsen on the steady-state systemic exposure of telaprevir on Day 7 (after multiple doses of telaprevir administered alone) versus Day 36 (multiple doses of telaprevir administered in the presence of miravirsen). No statistical significant differences were observed, indicating that systemic exposure of telaprevir was not affected when co-administered with miravirsen (based on the geometric mean values, see below).

**Mean Plasma Concentrations of Miravirsen** – Plasma samples were collected at different times, pre-dose and then 2, 4, 6, 10 and 24 hours post-dose on:

- Day 15 - after a single 7.0 mg/kg of miravirsen administered alone
- Day 36 - after 5 days of multiple 750 mg doses of telaprevir administered TID

**Pharmacokinetics of miravirsen (mean ± SD):**

After repeated dosing (on Day 36), the Cmax and the AUC0-18h values were similar, as compared to the situation on Day 15. This is in agreement with earlier observations that miravirsen is not accumulated in the blood.

**Effect of telaprevir on the PK of miravirsen:**

The effect of telaprevir on the single dose PK of miravirsen was assessed by comparing miravirsen PK parameters obtained on Day 15 (miravirsen administered alone) with those on Day 36 (miravirsen administered in the presence of telaprevir). There was no statistically significant difference in AUC value on Day 15 versus on Day 36 (based on the geometric mean values, see below).

CONCLUSIONS

- Co-administered miravirsen and telaprevir was safe and well tolerated in the study.
- No treatment-related trends were observe in AEs, clinical lab. measurements, 12-lead ECG results or physical examination findings.
- Co-administration of telaprevir with miravirsen did not significantly affect systemic exposure of telaprevir.
- Co-administration of miravirsen with telaprevir did not effect the AUC of miravirsen.
- Miravirsen does not interact with telaprevir.
INTRODUCTION

HCV infection although the virus is known since 1989 still remains clinical and therapeutic problem. According to World Health Organization it affects about 150 million people worldwide and 3-4 million new cases appears every year.

The disease can range in severity from a mild illness to chronic serious lifelong condition leading to liver cirrhosis or hepatocellular carcinoma development.

There are external and host factors that can increase the risk of progression of liver disease. Host risk factors include older age at time of infection, male gender, coinfection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), comorbid conditions such as immunosuppression, insulin resistance, non-alcoholic steatohepatitis, hemochromatosis, and schistosomiasis and the degree of inflammation and fibrosis present on the liver biopsy. Fibrosis implies possible progression to cirrhosis but the rate of progression varies widely. Histopathological examination of liver sample is widely recognized method of assessing tissue changes in chronic liver diseases. Successful treatment of chronic hepatitis C may change the course of the disease and can result in reversal of liver fibrosis.

Matrix metalloproteinases enzymes involved in connective tissue turnover and tissue inhibitors of matrix metalloproteinase regulating their activity participate in changing the dynamic balance between fibrogenesis and fibrolysis.

LITERATURE SHOWS THAT PROTEINS INVOLVED IN METABOLISM OF CONNECTIVE TISSUE AS TISSUE INHIBITOR OF METALLOPROTEINASES 1 (TIMP-1) AND METALLOPROTEINASE 2 (MMP-2) AMONG OTHERS, ARE DETECTED IN CIRCULATION AND MAY BE USEFUL AS SERUM MARKERS OF FIBROSIS DURING CHRONIC HCV INFECTION.

In cases where there are contraindications to liver biopsy or to evaluate and monitor disease progression there is a place for non-invasive diagnostic methods.

PURPOSE OF THE STUDY

Aim of the study was to assess the impact of therapy with pegylated interferon alpha and ribavirin on plasma TIMP-1/MMP-2 ratio depending on the sustained virological response (SVR) achieved and its usefulness in monitoring the effects of antiviral treatment in patients with chronic hepatitis C.

METHODS

Study group included 54 chronic hepatitis C (CHC) patients (25 females, 29 males), aged from 21 to 57 years (mean 37 years), infected with HCV genotype 1. Liver biopsy Metavir results were: grading 2 in 52 (96.3%), grading 3 in 2 (3.7%) patients and staging 2 in 51 (94.4%), staging 3 in 3 (5.6%) patients. Treatment with pegylated IFN alpha and ribavirin according to guidelines was conducted for 48 weeks. Plasma TIMP-1 and MMP-2 concentrations were determined by enzyme immunoassay method using ready kit Human TIMP-1 Instant ELISA and Human/Mouse/Rat MMP-2 (total) Immunoassay twice:

1. at the beginning of therapy (Examination I)
2. 6 months after treatment (Examination II).

TIMP-1/MMP-2 ratio was calculated for each probe. Results were analyzed according to SVR achievement at 6 months after completion of therapy. Statistical analysis was done using Shapiro-Wilk, Wilcoxon and Mann-Whitney test.

SUMMARY OF RESULTS

In the group of 26 (48%) patients with SVR the TIMP-1/MMP-2 ratio decreased significantly after treatment (p < 0.001). Fig. 1.

In 28 (52%) patients who did not achieve SVR, the TIMP-1/MMP-2 ratio obtained after treatment was significantly higher than the values at the beginning of therapy (p < 0.05). Fig. 2.

Comparative analysis of results in groups of patients according to SVR revealed that there were no statistically significant differences in plasma TIMP-1/MMP-2 ratio at the beginning of therapy (Fig. 3) but 6 months after cessation of treatment TIMP-1/MMP-2 ratio was significantly lower in patients with a virologic response after treatment compared with no SVR group (p < 0.001). (Fig. 4)

CONCLUSION

The study results showed that the balance between concentration of tissue inhibitor of metalloproteinases 1 and matrix metalloproteinase 2 in plasma may be useful in assessing effects of antiviral treatment and predicting fibrosis in patients with chronic hepatitis C treated with antiviral therapy. It appeared that the predictive value was the ratio TIMP-1 to MMP-2, which decreased in patients with SVR. However, in patients without sustained viral response the ratio increased, suggesting a predominance of processes inhibition of the fibrosynthetic activity of metalloproteinases and progress of liver fibrosis.

REFERENCES


INTRODUCTION

HCV infection although the virus is known since 1989 still remains clinical and therapeutic problem. According to World Health Organization it affects about 150 million people worldwide and 3-4 million new cases appears every year.

The disease can range in severity from a mild illness to chronic serious lifelong condition leading to liver cirrhosis or hepatocellular carcinoma development.

There are external and host factors that can increase the risk of progression of liver disease. Host risk factors include older age at time of infection, male gender, coinfection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), comorbid conditions such as immunosuppression, insulin resistance, non-alcoholic steatohepatitis, hemochromatosis, and schistosomiasis and the degree of inflammation and fibrosis present on the liver biopsy. Fibrosis implies possible progression to cirrhosis but the rate of progression varies widely. Histopathological examination of liver sample is widely recognized method of assessing tissue changes in chronic liver diseases. Successful treatment of chronic hepatitis C may change the course of the disease and can result in reversal of liver fibrosis.

Matrix metalloproteinases enzymes involved in connective tissue turnover and tissue inhibitors of matrix metalloproteinase regulating their activity participate in changing the dynamic balance between fibrogenesis and fibrolysis.

LITERATURE SHOWS THAT PROTEINS INVOLVED IN METABOLISM OF CONNECTIVE TISSUE AS TISSUE INHIBITOR OF METALLOPROTEINASES 1 (TIMP-1) AND METALLOPROTEINASE 2 (MMP-2) AMONG OTHERS, ARE DETECTED IN CIRCULATION AND MAY BE USEFUL AS SERUM MARKERS OF FIBROSIS DURING CHRONIC HCV INFECTION.

In cases where there are contraindications to liver biopsy or to evaluate and monitor disease progression there is a place for non-invasive diagnostic methods.

PURPOSE OF THE STUDY

Aim of the study was to assess the impact of therapy with pegylated interferon alpha and ribavirin on plasma TIMP-1/MMP-2 ratio depending on the sustained virological response (SVR) achieved and its usefulness in monitoring the effects of antiviral treatment in patients with chronic hepatitis C.

METHODS

Study group included 54 chronic hepatitis C (CHC) patients (25 females, 29 males), aged from 21 to 57 years (mean 37 years), infected with HCV genotype 1. Liver biopsy Metavir results were: grading 2 in 52 (96.3%), grading 3 in 2 (3.7%) patients and staging 2 in 51 (94.4%), staging 3 in 3 (5.6%) patients. Treatment with pegylated IFN alpha and ribavirin according to guidelines was conducted for 48 weeks. Plasma TIMP-1 and MMP-2 concentrations were determined by enzyme immunoassay method using ready kit Human TIMP-1 Instant ELISA and Human/Mouse/Rat MMP-2 (total) Immunoassay twice:

1. at the beginning of therapy (Examination I)
2. 6 months after treatment (Examination II).

TIMP-1/MMP-2 ratio was calculated for each probe. Results were analyzed according to SVR achievement at 6 months after completion of therapy. Statistical analysis was done using Shapiro-Wilk, Wilcoxon and Mann-Whitney test.

SUMMARY OF RESULTS

In the group of 26 (48%) patients with SVR the TIMP-1/MMP-2 ratio decreased significantly after treatment (p < 0.001). Fig. 1.

In 28 (52%) patients who did not achieve SVR, the TIMP-1/MMP-2 ratio obtained after treatment was significantly higher than the values at the beginning of therapy (p < 0.05). Fig. 2.

Comparative analysis of results in groups of patients according to SVR revealed that there were no statistically significant differences in plasma TIMP-1/MMP-2 ratio at the beginning of therapy (Fig. 3) but 6 months after cessation of treatment TIMP-1/MMP-2 ratio was significantly lower in patients with a virologic response after treatment compared with no SVR group (p < 0.001). (Fig. 4)

CONCLUSION

The study results showed that the balance between concentration of tissue inhibitor of metalloproteinases 1 and matrix metalloproteinase 2 in plasma may be useful in assessing effects of antiviral treatment and predicting fibrosis in patients with chronic hepatitis C treated with antiviral therapy. It appeared that the predictive value was the ratio TIMP-1 to MMP-2, which decreased in patients with SVR. However, in patients without sustained viral response the ratio increased, suggesting a predominance of processes inhibition of the fibrosynthetic activity of metalloproteinases and progress of liver fibrosis.

REFERENCES


Background

- More than 170 million patients infected with chronic Hepatitis C.
- New antiviral treatments are increasingly evaluated and approved.
- The management of Hepatitis C is complex (Fig. 1).
- Complexity is a factor which drastically increases the costs of the patients management.
- Efficient and reliable data management software to collect data and enable clinicians to stratify patients for personalized treatment and monitoring is required to improve the management of HCV patients.
- We developed HepatiC, a centralized patient management registry used to optimally define patients' profiles.

Methods

- HepatiC has been built through a collaboration with the "Asociación Española para el Estudio del Hígado" (AEEH - http://aeeh.es) and the "Centro de Investigación Biomédica en Red en el Área temática de Enfermedades Hepáticas y Digestivas" (CIBERehd - https://www.ciberehd.org).
- Multisite and secured web application which handles data coming from any hospital or laboratory in order to stratify patients at a regional, national or international level.
- Ability to record clinical information overtime, including demographics, baseline visit, follow-up visits, side effects, pre/post-transplant information (Fig. 2).
- Tracking of the use of any new Direct Antiviral Agents (DAA).
- Combined with a powerful data visualization and mining application: VisibleChek.

Results

- HepatiC publically announced during the XXXVIII annual congress of the Spanish Association of Liver Disease (AEEH) in Madrid, Spain.
- The beta evaluation started in June 2013 and permitted to collect more than 230 patients aged from 33 to 74 (median age 57 years) coming from 4 hospitals in Spain (Fig. 3).
- 500 patients expected to be collected in 2013 and up to 1500 during 2014.
- After 2 months of use (beta evaluation), the HepatiC database could be summarized as shown in Fig. 4 and Fig. 5.

Conclusions

What can HepatiC do?
- Used as a support of epidemiological studies
- Monitor patient outcomes
- Reporting to regional, national or international institutions (prevention, treatment monitoring, clinical outcomes...)
- Used as a support of publications
- Assist physicians to make best practice decisions to ensure better patient outcomes
  - optimal drug choices
  - optimal use of healthcare money (Fig. 7)
- Allow physicians to compare their patients to
  - Local database
  - Published databases
  - Guidelines and to
  - Large treated patient datasets
- Provide Physician Educational patient cases which are in-line with HCV treatment and monitoring guidelines.
- Published databases
- Guided by the EASL guidelines
- Effective and efficient data management software to collect and manage data and enable physicians to stratify patients for personalized treatment and monitoring.

Table 1: Median duration for a full patient file capturing process.

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HEMATOLOGICAL ADVERSE EVENTS AS PREDICTORS OF RESPONSE TO PEGYLATED INTERFERON AND RIBAVIRIN TREATMENT IN PATIENTS WITH CHRONIC HEPATITIS C GENOTYPE 4

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Background and aim:
Chronic hepatitis C (CHC) is a major health problem in Egypt with an estimated prevalence up to 22% of general population. Treatment strategy of this disease is challenged by many factors, particularly cost/benefit and factors influencing response to therapy. Pegylated interferon and ribavirin combination is still the standard of care in patients with CHC. Hematological adverse events are frequent during this kind of treatment and may necessitate dose reduction. These events may have an impact on the sustained virological response (SVR) in these patients. The aim of this work is to assess the role of hematological adverse events in prediction of response to this treatment in patients with CHC.

Patients and Methods:
The study included patients with CHC genotype 4, eligible for treatment according to national protocol. All patients received pegylated interferon α-2a 160 µg weekly (Reiferon Retard, Rhein Minapharm, Egypt) in combination with ribavirin 1200 mg/day. Early responders, who achieved complete viral clearance or decreased viral load by two log compared to pretreatment level, after 12 weeks completed a course for a total of 48 weeks. Regular monitoring for hematological adverse events was performed at 2 weeks interval. Anemia was considered when hemoglobin level was below 10 g/dL, neutropenia was considered when neutrophils were less than 800/mm³ while thrombocytopenia was considered when platelets were below 80/mm³. Patients with anemia were treated by erythropoietin 4000 units subcutaneously once weekly till the end of the course. Dose reduction of ribavirin was considered when anemia could not be controlled with erythropoietin treatment. Patients with neutropenia and thrombocytopenia were treated by dose adjustment of pegylated interferon with or without growth factors. The sustained virological response (SVR) rates in patients with different hematological adverse events were compared to those in patients without these events.

Results:
This work included 436 patients with CHC (342 males and 94 females). The overall SVR rate in our series was 58.26% (254 patients). 113 from the total number of patients (25.9%) developed anemia during treatment and 76 of them (67.26%) could achieve SVR and this rate was significantly higher than the SVR rate in patients who did not develop anemia (178 patients, 55.11%, p=0.024) (figure 1). Neutropenia was reported in 61 patients (14%) while thrombocytopenia occurred in 56 patients (12.8%) from the total number of patients. The SVR rate in patients who developed neutropenia (34 patients, 55.74%) was statistically indifferent from the SVR rate in patients without neutropenia (220 patients, 58.87%) (p=0.667) (figure 2). There was no significant difference between the SVR rates in patients with thrombocytopenia (32 patients, 57.14%) and patients without thrombocytopenia (222 patients, 58.42%) (p=0.865) (figure 3).

Conclusion:
Occurrence of anemia is a predictor of response to treatment with pegylated interferon and ribavirin combination in patients with chronic hepatitis C genotype 4. Occurrence of neutropenia or thrombocytopenia has no impact on the response to this treatment in these patients.
INTRODUCTION

Hepatitis C virus (HCV) is the major causative agent of non-A, non-B post-transfusion parenterally-acquired hepatitis worldwide. The standard treatment for chronic hepatitis C is pegylated interferon-α and ribavirin. Success in treatment depends on both viral and host factors. High treatment costs, adverse drug effects and poor viral clearance are existing challenges. Several studies have shown that response to antiviral therapy links to single nucleotide polymorphisms (SNP) in the interleukin (IL) 28B gene. Since it is very important to know both the genotype and genetic variations of the HCV in Uruguayan patients chronically infected with HCV, as a first approach to a personalized therapy.

RESULTS

Viral Genotype

From serum of 27 HCV-infected patients, we performed a nested amplification of the viral 5’NCR from cDNA obtained by RT with random hexamers. Three isolates did not render any amplification product. The amplified products (250bp) were purified and submitted for sequencing. The sequences were used to perform phylogenetic studies (Fig. 1) which showed that genotype 1 is the predominant one among our isolates (20). The remainder belong to genotype 3, subtype a (4 isolates).

Mutations within 5’NCR

By sequence analysis of the amplified 5’NCR (a region that covers 250bp of the IRES - Internal Ribosome Entry Site) mutations were found in all isolates (Fig. 2), some of which have already been reported elsewhere.

Host IL28B Genotype

Three polymorphisms near the IL28B gene were analyzed in 15 healthy individuals and 25 chronically HCV-infected patients. The frequencies of the three SNPs in the healthy population are similar among each other (60% harbour the favourable genotype –homozygous for the favourable allele) (Fig. 3). This frequency changes and seems to be more variable within the infected population (22-40% harbour the favourable genotype) (Fig. 4). Due to limited patients’ clinical data it was not possible to assess the association between the SNPs and response to therapy (Table 3).

CONCLUSIONS & PERSPECTIVES

The predominant viral genotype circulating in Uruguay is genotype 1, however we have also described some isolates belonging to genotype 3. By sequence analysis of 250bp of the 5’NCR (region with IRES activity) we were able to determine the presence of various mutations, two of them found in all isolates. The frequencies of the host’s genotypes seem to be similar to those reported for the Caucasian population, European-desendant (favourable genotypes in 60-70% of the healthy population). This frequency tends to change in the population infected with HCV, being about 22-40% depending on the SNP studied. A better understanding of patients’ clinical data as well as an increase in the number of enrolled patients is necessary to establish correlations of statistical significance between the evaluated factors. We also seek to perform translational efficiency studies to assess the significance of the mutations described.

REFERENCES


ACKNOWLEDGEMENTS
RESPONSES TO PEGINTERFERON ALFA-2A VS ALFA-2B PLUS RIBAVIRIN IN A MEXICAN POPULATION WITH CHRONIC HEPATITIS C

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PURPOSE:
The objective of this study was to conduct a “real-life” comparison of peginterferon alfa-2a vs alfa-2b plus ribavirin in a Mexican population with CHC genotype 1.

METHOD:
We conducted a retrospective cohort study at a single infectious disease center in Mexico City. We included patients if they had received treatment with peginterferon alfa-2a or peginterferon alfa-2b plus ribavirin. We assessed the age, sex, body mass index, APRI score, ALT and AST levels, bilirubin, albumin, hemoglobin, platelets, leukocytes, and the HCV RNA viral load before the first peginterferon dose and at weeks 4, 12, 24, 48 and 6 months posttreatment.

RESULTS:
Eighty-seven patients met the inclusion criteria; SVR occurred in 33 (37%), 11 (29%) with peginterferon alfa-2a and 22 (44%) with peginterferon alfa-2b (P = 0.17). Seventeen patients (19.5%) relapsed, seven (18%) with peginterferon alfa-2a and 10 (20%) with peginterferon alfa-2b (P = 0.76); 27 (31%) patients were nonresponders (P = 0.09). We had the same rates of anemia, thrombocytopenia and leukopenia.

CONCLUSION:
In conclusion both interferons can be used to treat HCV infections in the Mexican population with similar virological response rates and the same frequency of adverse events.