ОРИГИНАЛЬНЫЕ ИССЛЕДОВАНИЯ

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РЕЗУЛЬТАТЫ ЛЕЧЕНИЯ ПЕГИЛИРОВАННЫМ ИНТЕРФЕРОНОМ И РИБАВИРИНОМ ПРИ ХРОНИЧЕСКОМ ВИРУСНОМ ГЕПАТИТЕ С

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Резюме. Изучена эффективность комбинированной терапии пегилированным интерфероном и рибавирином при хроническом вирусном гепатите С в Монголии. В исследование были включены 54 HCV-позитивных пациента в возрасте от 21 до 66 лет, соответствующие критериям включения и исключения. Установлено, что 95,7% пациентов были носителями генотип 1b вируса гепатита С. Эффективность комбинированной терапии пегелированным интерфероном и рибавирином у пациентов с хроническим вирусным гепатитом С составила 78%. Некоторые побочные эффекты, такие как головная боль, потеря аппетита, усталость, потеря волос, мышечные слабости, диарея, рвота и лихорадка были статистически значимыми.

Ключевые слова: пегелированный интерферон; рибаверин; вирусный гепатит С; Монголия; эффективность терапии; побочные эффекты.

TREATMENT RESULT OF PEGINTERFERON AND RIBAVIRIN FOR CHRONIC VIRAL HEPATITIS C

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Summary. Aims of the study: treating the chronic HCV infected patients with combination of PEG-IFN and Ribavirin and monitoring the effects in Mongolia was studied. The study included 54 HCV-positive patients aged 21 to 66 years, eligible for inclusion and exclusion. It was found that 95.7% of patients were carriers of the genotype 1b of the hepatitis C virus. The effectiveness of combined therapy with PG and ribavirin in patients with chronic viral hepatitis C was 78%. Some side effects, such as headache, loss of appetite, fatigue, hair loss, muscle weakness, diarrhea, vomiting and fever were statistically significant.

Key words: PEG-IFN; Ribavirin; Viral hepatitis C; Mongolia; The effectiveness of therapy; side effects.

According to WHO, there are about 180 million people who are suffering from Viral Hepatitis C in the world, which covers around 3% of total population. Hepatitis C infection has spread unlikely in different countries of the world.

Interferon alpha-2a has been used for the treatment since 1991. From the interferon types which has been produced by many countries as an injection, IFN secreted by natural cells (lymphoblast) or in the result of molecular biological recombination (a-IFN 2a, a-IFN 2b) has been using in clinical practice for the treatment of viral hepatitis. Treatment effect varies in different countries. In our country, there are studies of treatment effects of Leuferon (Cuba), Reoferon (Russia), Amferon (China), Reildiron (Latvia), and Roferon A (Sweden). According to press review, treatment effect depends on many factors, such as patient age, sex, nationality, duration of disease, and patient's health condition. In some cases, treatment effect can be poor, especially in patients aged above 40, male, overweight, longer duration of the disease, and high accumulation of the iron due to liver cirrhosis. On the other hand, viral genotype and it's high concentration in the blood have direct impact on the treatment effect. It has been considered that the genetic factors of the infected body are very important for clinical process of viral hepatitis C and body tolerance to antiviral drugs.

There are several advantages that it has less side effects during the treatment, and stays longer in the body compared to other IFNs when using PEG-IFN-alpha, which is made by mixing IFN-alpha to polyethylenglicole. There is a guideline that has been followed worldwide as a treatment standard of HCV which includes 180 μg PEG-IFN alpha for a week dose, 1000-1200mg Ribavirin as a daily dose with total treatment duration of 48 week. But the treatment duration and dose can be changed or even stopped regarding the side effects and individual's physiological conditions. The prevalence of HCV infection is 15.6%, the cause of the HCC – 46%, HBV – 35%, and 14% was established as co-infection of HBV and HCV by our researchers in total Mongolian population.

There was limited range of diagnostic and treatment technology, anti HCV drug use and poor treatment effect until 2010. For example; PEG-IFN was first registered in Mongolian drug registration in 2010 while it has been used for the treatment internationally since 2001. Some patients who are financially capable were visiting to other Asian countries for the anti HCV drug and treatment before it's registration in our country. Combined treatment of IFN and Ribavirin had lower effect with higher side effects, longer duration, limited indications with high cost for the single dose. Although combination of PEG-IFN and Ribavirin has not been used at anytime when patients in need due to high cost, quantitative expression of the HCV genotype with monitoring treatment effect of PEG-IFN and Ribavirin has been essential in our country.

Aims of the study: treating the chronic HCV infected patients with combination of PEG-IFN and Ribavirin and monitoring the effects.

Materials and Methods

Our study was conducted based on the Laboratory of MNUMS, Laboratory of Immunology and Micro-Biology in School of Bio medicine and Pharmaceuticals, Hepatologic Center of Severance Hospital, Yonsei University in Korea, Central Research Laboratory of Liver Cirrhosis from 2008 to 2016.

We randomly selected 54 patients who were HCV positive and age of 21-66, monitored by an outpatient clinic of Hepatologic Center and National Center of Infectious Disease of Yonsei University in Korea for 2-8 years. From them, totally 47 patients who were confirmed diagnosis of chronic HCV by clinical examination and lab tests with

detection of HCV-RNA treated with combined therapy of PEG-IFN and Ribavirin followed by 72 weeks of monitoring. Statistical analysis of study results were obtained using Microsoft office Excel 2016 and SPSS 20 programs.

Criteria's for choosing study participants:

1. Anti HCV (+) and HCV-RNA (+)
2. Activation of enzyme ALAT increased two times or more than normal range.
3. No psychological change.
4. Must be able to be treat constantly under monitoring, agreed to be treated.
5. No change in CBC.
6. Not pregnant.

Criteria's to exclude HCV infected patients from IFN therapy:

1. Liver cirrhosis in C category of Child-Pugh classification.
2. Patients with severe depression.
3. Thrombocyte count less than 5000.
4. Autoimmune disease.
5. 3rd or 4th stage of cancer.
6. HIV – AIDS.
7. If patient agrees to stop treatment.

Study results and Discussion

We randomly selected 54 patients who were HCV positive and age of 21-66, monitored by an outpatient clinic of Hepatologic Center and National Center of Infectious Disease of Yonsei University in Korea for 2-8 years. From them, totally 47 patients who were confirmed diagnosis of chronic HCV by clinical examination and lab tests with detection of HCV-RNA treated with combined therapy of PEG-IFN and Ribavirin followed by 72 weeks of monitoring.

From the study participants, 53.2% (n=25) were female, 46.8% (n=22) were male and median age was 45.6±12.6. If we classify participants by age, 14.9% (n=7) in 21-30 years, 25.5% (n=12) in 31-40, 27.6% (n=13) in 41-50, 21.3% (n=10) in 51-60, 10.7% (n=5) was in age above 61.

According to the epidemiological anamnesis, 25.5% (12) were infected with acute HCV, 27.6% (13) were blood transfused, 44.7% (21) were tattooed, 36.1% (17) were underwent for some surgical procedures, 44.7% (21) were attended in dental treatment, 10.6% (5) were with unknown cause of the infection.

Some symptoms such as fatigue for 40 participants (85.1%), signs of dyspepsia which includes flatulence, diarrhea, constipation in 41 participants (87.2%), hemorrhagic signs such as bleeding from nose, gums and blood taste in mouth were in 23 (48.9%), skin rash in 11 (23.4%), arthralgia in 7 (14.9%), itchy skin in 17 (36.1%), migraine in 13 (27.6%), periodic fever in 6 (12.8%), and hepatomegaly observed in 9 (19.1%) patients (table 1).

Table 1

Detection of genotype and HCV-RNA in chronic HCV infected patients

HCV genotype	Percentage (%)
1b	95.7% (45/47)
2a	4.3% (2/47)
HCV RNA genotype	Percentage(%)
Genotype 1b HCV RNA ≤2*10⁶ copies/ml ≥2*10⁶ copies/ml	 37% (17/45) 63% (28/45)
Genotype 2a HCV RNA ≤2*10⁶ copies/ml ≥2*10⁶ copies/ml	 100% (2/2) 0

There fore, main symptoms observed in chronic HCV patients, such as dyspepsia and fatigue are statistically significant ($p<0.001$). There was 87% (47) positive when detecting HCV-RNA in 54 patients followed monitoring, with a diagnosis of chronic HCV.

Genotype detection of HCV

We selected 54 patients who were confirmed diagnosis of chronic HCV with special criteria's, and 7 patients excluded from the study through excluding criteria.

After the molecular biological analysis to determine HCV genotype in the serum of 47 patients with chronic HCV infection, 1b genotype in 95.7% or 45 patients, and 2a genotype was detected in 4.3% or 2 patients.

From the 45 patients detected with 1b genotype, 64.4% were female and 35.6% were male, while patient detected with 2a genotype was Kh/female/47y.o, her ALAT counted as 87 U/L, symptoms such fatigue and dyspepsia started from 2 years with history of undergoing surgery 15 years ago. No signs of hepatomegamy, skin rash and hemorrhage observed. Other patient detected with 2a genotype was G/56 y.o/Male, with ALAT level of 98 U/L, HCV-RNA – 2250000 copies/ml and epidemiological anamnesis not clear (tabl. 2).

Table 2

Clinical Symptoms observed in patients with Anti-HCV (+)

Symptoms	Anti-HCV (+) HCV-RNA (-) (n=7)	Anti-HCV (+) HCV-RNA (+) (n=47)	P
ALAT increase	(3) 38.9±10.4%	(42) 88.9±3.4	<0.001
ALAT normal	(4) 60.3±12.1%	(5) 11.1±4.6%	<0.001
Fatigue	(4) 61.5±11.4	(40) 85.1±3.4%	>0.05
Dyspepsic syndrome	(5) 71.4±11%	(41) 87.2±3.8%	>0.05
Hemorrhagic syndrome	(3) 42.8±8.7%	(23) 48.9±4.9%	<0.05
Skin rash	(1) 14.2±5.5%	(11) 23.4±11.3%	<0.05
Arthralgia	(1) 14.2±5.5%	(7) 14.9±5.6%	<0.05
Itching	(3) 42.8±8.7%	(17) 36.1±3.6%	>0.05
Hepatomegaly	(1) 14.2±5.5%	(9) 19.1±3.6%	<0.05

From 7 patients detected with Anti-HCV positive and HCV-RNA negative, 51.4% or 4 were female with 42.8% or 3 of male while 53.2% or 25 were female with 46.8% or 22 of male from 47 patients who detected as anti-HCV (+) with HCV-RNA (+). Symptoms of fatigue in 85.1%, dyspepsia in 87.2%, hemorrhagic syndrome in 48.9%, skin rash in 23.4%, itching in 36.1%, hepatomegaly in 19.1%, and arthralgia was observed in 14.9% when comparing clinical symptoms in those patients.

Main symptoms, such as hemorrhagic syndrome, skin rash, hepatomegaly, arthralgia and increased ALAT were observed in chronic HCV patients who are in active viral stage with anti-HCV(+), HCV-RNA(+). Some symptoms such as fatigue, dyspepsia and itching are not special for viral activation.

Control study of antiviral treatment

We used 180 μg (0.5 ml) PEG-IFN alpha once a week as subcutaneous injection in umbilical area, 200 mg Ribavirin orally with total dose of 800-1000 mg depending on the body weight for 47 patients who confirmed diagnosis of chronic HCV infection for 48 week. Treatment results were evaluated monthly with peripheral blood count (RBC, WBC, Thrombocyte, Neutrophil, Hemoglobin), Biochemical analysis (ALAT, ASAT, Albumin, Globulin) and Thyroid

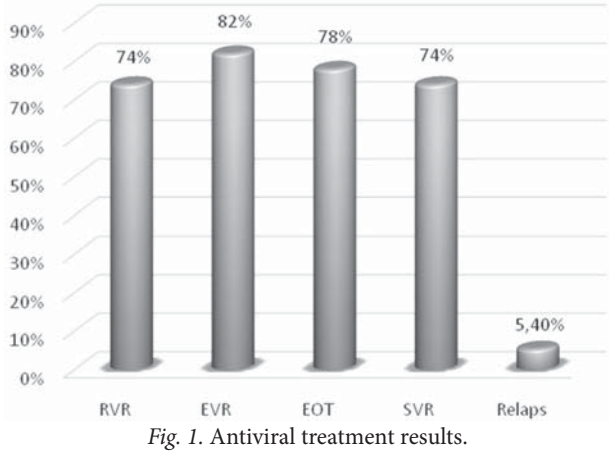

Fig. 1. Antiviral treatment results.

function test during the treatment while monitoring clinical symptoms and side effects. We monitored treatment result as quantitative assessment of HCV-RNA with following methods.

74% or 35 patients were involved in Rapid Viral Response (RVR), 82% (39) were in Early Viral Response (EVR), and 78% (37) were reached to response at the end of the treatment. 8 patients were excluded from the treatment according to the guideline due to not reaching to RVR. Quantitative assessment of HCV-RNA were done 48 weeks after the treatment in patients' blood, which confirmed that it was healed with no virus detected in 78% (35), while 2 patients were started to have an onset with re-detection of virus (fig. 1).

Treatment duration for each patients was unlikely from 16-48 weeks. Patient B /49 /M has excluded from treatment on 16th day due to side effects such as alopecia, weight loss of 15 kg, insomnia, change of the thyroid function test, RBC decrease of 2.8*1012/L, and WBC decrease of 2.21.

The side effects of the treatment were different in every patients with dominantly observed reactions of 10 or more percent of weight loss, headache, loss of appetite, fatigue, alopecia, muscle weakness, diarrhea, vomiting and fever were registered. Most of the patients faced drop of the RBC, WBC and Neutrophil count with depletion of the immune system (tabl. 3).

Table 3

Side effects registered during the treatment

Side effects	Percentage/%/
Fatigue	100%(47/47)
Headache	72.3% (34/47)
Nausea	55.3% (26/47)
Insomnia	31.9% (15/47)
Muscle weakness, pain	34.04% (16/47)
Depression	4.7% (1/47)
Hair loss	78% (37/47)
Fever	36.1% (17/47)
Weight loss	70.2% (33/47)
Diarrhea	29.7% (14/47)
Cause of discontinued treatment (%)	
Due to side effects	11.1% (1/9)
No show of the viral response	88.9% (8/9)

Before the treatment WBC= 6.15±0.42x10^9/ml, Platelet=162.9±26.29x10^9/ml, RBC=4.87±0.13x10^{12}/ml, and HGB counted 149.6±5.6 g/dl, while it changed during the treatment as WBC=4.83±0.42x10^9/ml (p=0.025), Platelet=125.9±25.69x10^9/ml (p=0.458), RBC= 4.19±0.27x10^{12}/ml (p=0.036), and Hemoglobin counted as 126.6±7.48 g/dl(p=0.009) (tabl. 4).

Table 4

Monitoring the treatment of HCV (Complete Blood Count)

	Before Treatment m±SE	During Treatment m±SE	P
White Blood Cells /10^9 /ml/	6.15±0.42	4.83±0.42	0.025
Platelet /10^9 /ml/	162.9±26.29	125.9±25.69	0.458
Red Blood Cell /10^{12} /ml/	4.87±0.13	4.19±0.27	0.036
Hemoglobin /g/dl/	149.6±5.6	126.6±7.48	0.009

According to the table, it suggests that WBC, RBC and Platelet count decrease during PEG-IGN treatment.

Discussion

C viral hepatitis is not only Mongolian, but still one of the world's public health priority attention. Viral hepatitisin Mongolia was registered officially in 1952, and anti-viral treatment started by the researchers and scientists under the direction of Professor Dagvadorj since the mid-1990sat the Department of Infectious Diseases of Medical University. According to the research of Doctor Baatakhuu.O, 15,6% of the total population of Mongolia has infected with hepatitis C virus, 98% of from which occupies 1b infection, and about 380000 people are carriers of hepatitis C virus. And an antibody against HCV was detected in 36% of patients with primary liver cancer.

In our country, we have limited range of C virus diagnosis and treatment technology and drug use in practice, especially we are lack of research described the results of combined therapy of interferon and ribavirin for Hepatitis C virus. PEG-IFN was first registered in Mongolian drug registration in 2010 while it has been used for the treatment internationally since 2001. Due to high cost of treatment against hepatitis C virus, requirement to repeat performing molecular biological analysis and side effects of IFN and ribavirin treatment, the number of patients was limited in our country.

We randomly selected 54 patients who were HCV positive and age of 21-66, monitored by an outpatient clinic of Hepatologic Center and National Center of Infectious Disease of Yonsei University in Korea for 2-8 years. From them, totally 47 patients who were confirmed diagnosis of chronic HCV by clinical examination and lab tests with detection of HCV-RNA treated with combined therapy of PEG-IFN and Ribavirin followed by monitoring the changes of liver function, patient's clinical characteristics, and complete blood counts, biochemical analysis, thyroid changes and genotype reviewed to determine quantitative viral load.

With the help of innovation of direct antiviral drugs (such as bosepryevir and telaprevir which have first introduced for treatment in 2011, simeprevir and sofosbuvir in 2013, Kharvoni and Vikera in 2014) for treatment, chronic HCV has recorded officially as fully curable disease, trying to get rid of the disease for the rest of the world.

Investigators N. Khorolsüren (2002) and O. Baatarkhüü (2006) suggested that an epidemiological anamnesis, such as blood transfusion, surgical procedure and tattooeing were statistically significant in their study while surgical procedure and blood transfusion were significant in our study. Therefore, our study statistically confirmed that dentistry is the main source for transmitting the infection.

According to the clinical study of chronic HCV by O.Baatarkhüü (2006) and N.Khorolsüren (2002), 85% was HCV-RNA positive in HCV RNA detection test from 120 patients who were under control of chronic hepatitis C, while 87% of participants from all participants were HCV positive in our study, which showed similar result.

In our country, HCV genotype 1b, 2a subtypes are detected, and according to the studies done by Ts. Oyunsuren (1996), M. Altankhüü (2003), O. Baatarkhüü (2006), genotype 1b of HCV 1b – 97%, 95% and 98.1% while 2A genotype was 5%, 3%, and 1.9%. Our research survey generally matches with other studies indicating 95.7% of 1b, and 4.3% of 2A genotype. This indicates a dominant genotype is 1b hepatitis C virus in our country.

The side effects of the treatment were different in every patients with dominantly observed reactions of 10 or more percent of weight loss, headache, loss of appetite, fatigue, hair loss, muscle weakness, diarrhea, vomiting and fever were registered. Most of the patients faced drop of the RBC, WBC and Neutrophil count with depletion of the immune system. Before the treatment WBC= 6.3±0.22x109/L, Platelet=162.9±26.29x109/ml, Neutrophil= 3.1±0.2x109/L,RBC was4.7±0.13x1012/L, HGB was decreased as 125.3±5.48g/L (p=0.009) which matches to study of side effects by Mac Nicholas during PEG-IFN and Ribavirin treatment.

Treatment response, genotype, side effects of treatment, duration of treatment, individual features are all factors that affect treatment result. Among the European population on the HCV genotype 1b, antiviral treatment result is 46-54%, while genotype 2a at 75-85%, while it is relatively high among Asians due to IL28B polymorphisms, physical and genetic characteristics of Asians and lack of research. There are many studies that have shown IL 28V genotype are mostly dominated in Asian people.

According to the study by N. Khorolsüren (2002) and B. Bayarmagnai, treatment effects of single interferon for anti-HCV were 27.8% and 41.1%.

We are concluding that our research which resulted in a

relatively higher effect, was related to combined treatment of PEG-IFN and Ribavirin for the first time, not a single Interferon.

74% or 35 patients were involved in Rapid Viral Response (RVR), 82% (39) were in Early Viral Response (EVR), and 78% (37) were fully cured or reached to SVR.

It was the case of controlling the treatment effect of PEG-IFN and ribavirin combination followed by 72 weeks. There fore, according to study conducted by B. Azjargal, treatment effect of PEG-IFN and Ribavirin combination for 16 patients was 85%, which was similar result to our study.

The results of our study were similar to the effectiveness of some of the studies in Asia. According to multicentric study conducted by Taiwanese researcher JH Kao, the effectiveness of combined treatment of PEG-IFN and Ribavirin was 76%, which is similar to our study results.

Thus, the prevalence of HCV infection is the highest with increasing number of infected people year by year, lack of clinical symptoms with slow clinical progress results in getting diagnosed later.

We have conducted this study for providing an information about one of the HCV treatment or combination of PEG-IFN and ribavirin, for not only Mongolian, but also foreign researchers. On the other hand, Mongolian government is working to achieve the elimination of hepatitis C viral infection by the year 2025-2030, based on the registration of effective modern antiviral drugs, such as Harvoni, Ledvir, Hepsinat, Ledifosin Mongolia.

Conclusion

1. The result of combined treatment of PEG-Interferon and Ribavirin for chronic HCV patients was 78%.

2. 95.7% of total patients with chronic HCV demonstrated having 1b genotype in our country.

3. Some side effects such as headache, loss of appetite, fatigue, hair loss, muscle weaknes, diarrhea, vomiting and fever were statistically significant.

Конфликт интересов. *Авторы заявляют об отсутствии конфликта интересов.*

Прозрачность исследования. *Исследование не имело спонсорской поддержки. Исследователи несут полную ответственность за предоставление окончательной версии рукописи в печать.*

Декларация о финансовых и иных взаимодействиях. *Все авторы принимали участие в разработке концепции и дизайна исследования и в написании рукописи. Окончательная версия рукописи была одобрена всеми авторами. Авторы не получали гонорар за исследование.*

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