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# Interferon-Based Antiviral Treatment of Chronic Hepatitis C in Combination with Metformin in Patients with HCV-1 Genotype and Insulin Resistance

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## ABSTRACT

***Aim:*** *To investigate whether adding metformin, a potent agent reducing insulin resistance (IR), improves treatment efficacy of chronic hepatitis C (genotype 1) naïve patients.*

***Methods:*** *133 patients were analyzed: 70 patients with IR and 63 patients without it. 28 of 70 patients with IR received metformin. Metformin was added to conventional Peg-IFNα-2b/ribavirin therapy, or 3-6 months before the starting of antiviral treatment and continue throughout the course of therapy. Patients in the second (control) group with IR did not receive metformin (n=42). Patients receiving and not receiving metformin did not differ significantly by gender, the average of viral load and the degree of liver fibrosis (measured with using FibroScan®502).*

***Results:*** *Among the patients with HCV-1 without IR, SVR rate was 46% (n=29/63), and in patients with HCV-1 with IR (not receiving metformin), SVR was achieved in 42% of patients (n=18/42), p=0,33. In patients with HCV-1 and IR, receiving metformin, the SVR rate was 64% (n=18/28), p=0,001.*

***Conclusion:*** *Correction of IR with using of metformin has led to an increase of SVR in HCV-1 patients by 1.5 times. Significant reduction of glucose levels in patients with IR receiving metformin, wasn't noted. Thus, metformin is safe for use in patients with chronic hepatitis C and IR as a medication reducing IR.*

## Keywords

Insulin resistance, Chronic hepatitis C, Metformin.

## Introduction

The efficacy of the antiviral therapy in patients with HCV genotype 1 infection rarely exceeds 40%.The main pre-treatment predictors of a sustained virological response (SVR) are: host genotype (in particular the CC genotype at the locus rs12979860 of the IL28B gene), viral genotype and pre-treatment viral load [1,2].

Other baseline factors providing a sustained response are: the right doses of Peginterferon (1.5 mcg/kg/week) and RBV (>10.6 mg/kg/day), female gender, age less than 40 years, body weight (≤ 75 kg), elevated ALT (three-fold higher than upper limit of normal), the absence of bridging fibrosis or cirrhosis and the absence of insulin resistance (IR) [1-3]. Insulin resistance is the basic pathogenetic part of the metabolic syndrome. Obesity which is observed worldwide increases the number of patients with metabolic syndrome and hepatitis C. Also, it is assumed that HCV infection contributes to insulin resistance. [4]. IR caused by HCV together with insulin resistance as a result of metabolic syndrome, can accelerate the progression of disorders of carbohydrate metabolism leading to diabetes type II. Insulin resistance in hepatitis C, regardless of the pathogenesis leads to the development of steatohepatitis, promotes the progression of hepatic fibrosis, cirrhosis [5], and also reduces SVR rate during antiviral therapy for chronic hepatitis C [6].

The most discussed drug, which can reduce IR, and may increase the SVR rate in patients with chronic hepatitis C- is metformin [7]. Better insulin sensitivity may increase the response to antiviral treatment. The results of several clinical trials that have used insulin sensitizers (metformin and PPAR-γagonists) have proved

the efficacy of these drugs in patients with HCV [8].

Since November 2009 we have conducted a prospective study aimed to estimate the frequency of the SVR in 133 Russian patients with chronic hepatitis C (HCV-1), receiving standard therapy (PegIFNα-2b+ribavirin) in combination with metformin (in IR patients only).

We studied IR using the method of "Homeostatic model» (Homeostasis Model Assessment). HOMA-index (HOMA-IR) is calculated based on the indices of insulin and glucose in one portion of serum: HOMA-IR = fasting insulin level (MkME/mL) x fasting glucose (mmol/L)/22.5. The criterion for the presence of IR value was decided to be HOMA-IR ≥ 2. All patients were assigned to the standard combination therapy PegIFN-α-2b (1.5 mcg/kg/week) and ribavirin (15 mg/kg/day). 28 of 70 patients with chronic hepatitis C (HCV-1) and IR were given metformin (20 mg/kg/day). Liver fibrosis was measured with FibroScan®502 (Table 1).

| | HOMA-IR <2 | HOMA-IR≥2 | p |
|---|---|---|---|
| Patients (numbers) | 63 | 70 | |
| Men, n (%) | 29 (46%) | 37 (53%) | 0,51 |
| Women, n (%) | 34 (54%) | 33 (47%) | |
| Viral load, ME/ml | 5,792 ± 0,894log | 5,587 ± 0,842log | 0,57 |
| ALT, U/l | 54,4 ± 4,55 | 58,32 ± 9,68 | 0,7 |
| AST, U/l | 36,49 ± 2,37 | 41,37 ± 4,33 | 0,33 |
| Glucose, mmol/l | 5,15 ± 0,089 | 5,35 ± 0,096 | 0,39 |
| Insulin, mkME/ml | 4,745 ± 0,38 | 14,9 ± 2,48 | 0,00012 |
| HOMA-IR | 1,15 ± 0,06 | 3,143 ± 0,27 | 0,05 |
| Weight, kg | 69,57 ± 2,07 | 74,72 ± 2,2 | 0,09 |
| Liver fibrosis (kPa): | 7,8 ± 0,49 | 7,22 ± 0,39 | 0,35 |
| Liver fibrosis ≥ 9,5 kPa (F3, F3-4, F4)by METAVIR score, n (%) | 12 (19%) | 10 (14%) | 0,22 |

**Table 1:** Clinical and laboratory characteristics of patients with chronic hepatitis C (HCV-1), considering the presence of insulin resistance.

## Results

133 patients were tested: 63 patients without IR and 70 patients with IR. 28 of 70 patients with IR received metformin. Metformin was prescribed at the start of antiviral treatment, or 3-6 months before the start of treatment and continued throughout the whole course of therapy. Patients in the second (control) group with IR did not receive metformin (n=42) (Table 2).

| | Therapy regimen | n=133 |
|---|---|---|
| HOMA-IR<2 | PegIFN-α-2b 1,5 mkg/kg/week + ribavirin 15 mg/kg/day | n=63 |
| HOMA-IR≥2 | PegIFN-α-2b 1,5 mkg/kg/week + ribavirin 15 mg/kg/day | n=42 |
| | PegIFN-α-2b 1,5 mkg/kg/week + ribavirin 15 mg/kg/day + Metformin 20 mg/kg/day | n=28 |

**Table 2:** The distribution of patients with chronic hepatitis C(HCV-1).

In patients in both groups receiving and not receiving metformin did not differ significantly in viral load , the degree of liver fibrosis (measured with FibroScan®502) and gender.

Among the patients with HCV-1 without IR,SVR rate was 46% (n=29/63), and in patients with HCV-1 with IR (not receiving metformin), SVR was achieved in 42% of patients(n=18/42), p=0,33 (Figure 1).

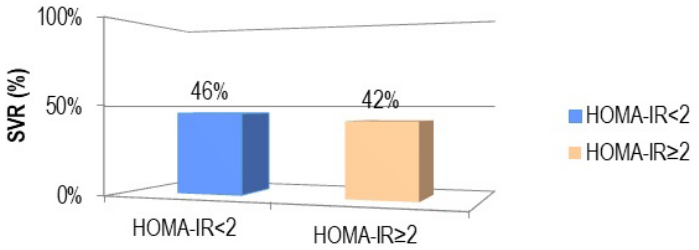


**Figure 1:** Efficacy of antiviral treatment in chronic hepatitis C (HCV-1) patients with HOMA-IR<2 and HOMA-IR≥2 (without metformin).

In patients with HCV-1 and IR, receiving metformin, the SVR rate was 64% (n=18/28), p=0,001 (Figure 2).

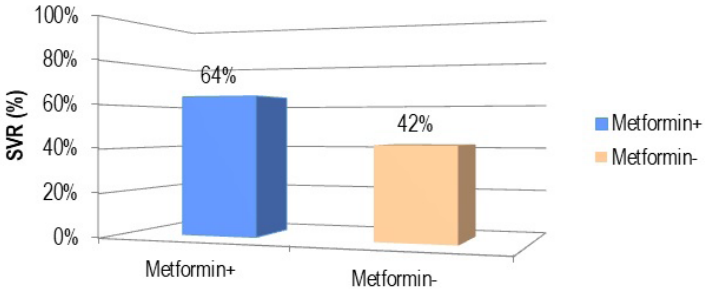


**Figure 2:** Efficacy of antiviral treatment in chronic hepatitis C (HCV-1) patients with HOMA-IR≥2 (with and without metformin).

Thus, correction of IR by using of metformin has led to an increase in its efficacy by 1.5 times.

Significant reduction of glucose levels in patients with IR receiving metformin was not revealed. Thus, metformin is not only effective but also safe for patients with chronic hepatitis C as a drug reducing IR (Table 3).

| AE | Before initiation of metformin | End of treatment | p |
|---|---|---|---|
| Reduced glucose, mmol/l | 5,28 ± 0,15 | 4,95 ± 0,18 | 0,181 |
| Reduction of body weight, kg | 72,17 ± 3,52 | 69,1 ± 3,35 | 0,516 |
| Diarrhea (once) | 14% (n=4/28) | | |
| Diarrhea (3 times a day) | 3% (n=1/28) | | |

**Table 3:** Adverse events of metformin therapy in patients with chronic hepatitis C (HCV-1) with IR (n = 28).

## Discussion

In patients with chronic hepatitis C (genotype 1) and insulin resistance, the adding of metformin 20 mg/kg/day as a third component of antiviral therapy based on PegIFNα-2b+ribavirin significantly improves the efficacy of therapy, as compared

with PegIFNα-2b+ribavirin without adding of metformin. It is important, that significant reduction of glucose levels was not observed. Among the patients with HCV-1 without IR, SVR rate was 46%, and in patients with HCV-1 with IR (not receiving metformin), SVR was achieved in 42% of patients.In patients with HCV-1 and IR, receiving metformin, the SVR rate was 64%. HCV can induce IR directly by stimulating SOCS3 and PPA2, and both of these molecules have proved to inhibit interferon-α signaling. The published data also have showed the possible association of HCV core and NS5A protein with IR. Improvement of insulin sensitivity may increase the response to antiviral treatment [8]. Thus, IR – an important prognostic factor reducing the efficacy of the antiviral therapy in patients with chronic hepatitis C. Using metformin to normalize HOMA-IR in patients with HCV, treated with Peg-IFNα-2b+ribavirin increases the efficacy of therapy which is particularly important for patients with genotype 1 HCV.

## Conclusions

Adding for patients with chronic hepatitis C and IR as a drug reducing IR. metformin 20 mg/kg/day as a third component of a standard dual therapy (PegIFNα-2b + ribavirin) for treatment-naive patients with chronic hepatitis C (genotype 1) and insulin resistance improves its efficiency by 1.5 times (SVR 42% vs 64%). Metformin is safe and efficient.


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