

## Comparison of metformin and pioglitazone in achieving sustained virological response in chronic hepatitis C patients with insulin resistance: A quasi-experimental study

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### Abstract

**Objective:** To compare metformin and pioglitazone with standard interferon and ribavirin in achieving sustained virological response in chronic hepatitis C patients.

**Methods:** This quasi-experimental, comparative, interventional study was conducted at Mayo Hospital, Lahore, Pakistan, from January 2015 to March 2016, and comprised chronic hepatitis C patients who had insulin resistance. The patients were divided evenly in three groups. Group A had patients treated with interferon 3 million units, three times in a week and ribavirin 400mg three times in a day. In addition to interferon and ribavirin, group B was treated with metformin, and group C received pioglitazone. Polymerase chain reaction was done at the completion of 24 and 48 weeks to assess the end treatment and sustained virological response, respectively. SPSS 20 was used for data analysis.

**Results:** Of the 138 patients, there were 46(33.3%) in each group. The mean age of the patients in group A was 36.83±9.65 years, in group B was 37.72±10.00 years and in group C it was 38.07±8.85 years. Overall, there were 70(50.72%) males and 68(49.28%) females. At the end of 24 weeks, polymerase chain reaction exhibited that in group A, the score was <100 in 28(60.9%) and >100 in 18(39.1%) patients. In group-B, it was <100 in 39(84.8%) and >100 in 7(15.2%) patients. In group-C, it was <100 in 31(67.4%) and >100 in 15(32.6%) patients. The sustained virological response was considerably higher in group B (p=0.003)

**Conclusion:** Sustained virological response with standard therapy with metformin gave high-end response as compared to other groups.

**Keywords:** Hepatitis C, Interferon, Insulin resistance, Metformin, Pioglitazone. (JPMA 67: 1848; 2017)

### Introduction

A major proportion of the liver diseases across the world has been reported to be caused by hepatitis C virus (HCV).<sup>1</sup> According to an estimate, 170 million people in the world have been infected with HCV.<sup>2</sup> Local data suggests an overall prevalence of HCV to be 4.8%.<sup>3</sup> Conventional interferon (INF) along with ribavirin (RBV) therapy remained an effective therapy in HCV with genotype 2 and 3 naive patients in this region.<sup>4</sup> Significant sustained virological response (SVR) rates were observed in patients taking conventional INF alfa-2a and ribavirin therapy.<sup>5</sup> Among the patients who are chronically infected with HCV, the prevalence of type 2 diabetes mellitus (T2DM) and insulin resistance (IR) is higher in comparison to general population. Adverse outcomes of chronic hepatitis (CHC) patients are observed with both the IR and T2DM.<sup>6</sup> IR is an important factor leading to various complications having

association with HCV. Recent studies show that patients having both HCV and IR can develop fibrosis, steatosis, hepatocellular carcinoma (HCC) and resistance to antiviral treatment. HCV regulates the cellular gene expressions by interfering with insulin signalling pathway.<sup>7</sup> Peg interferon alfa-2a and ribavirin combination with metformin therapy showed improved SVR in CHC patients. The SVR rate of group taking treatment with metformin in addition to the standard therapy was significantly greater than that of the control group (59.2% vs 38.8%, p=0.042). Also, homeostatic model assessment-insulin resistance (HOMA-IR) index of the patients on metformin was subsequently lower than in the control group.<sup>8</sup> Pioglitazone also reduces the hepatitis C virus ribonucleic acid (HCV-RNA) titer in serum independently of standard peg interferon alfa-2a/ribavirin treatment.<sup>9</sup> On the contrary, there was no statistically marked difference among efficacy of both groups, and the reduction from baseline till week 12 of standard peginterferonalpha-2a along with ribavirin in mean log<sub>10</sub> HCV-RNA titer was 23.5, 61.71 and 23.7 6 1.623IU/mL in case of pioglitazone and the standard therapy, respectively. Moreover, the final SVR rate was 26% in the

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pioglitazone and standard therapy as compared to 38.4% among patients on standard care groups alone.<sup>10</sup> Despite a few available studies, data regarding the role of metformin and pioglitazone in improving SVR in patients of CHC is scanty and presently these drugs are not the part of management plan for hepatitis C. There is a need to plan a well-designed study to determine impact of these drugs on SVR. The current study was planned to compare metformin and pioglitazone with standard interferon and ribavirin in achieving SVR.

### Patients and Methods

This quasi-experimental, comparative, interventional study was conducted at the Department of Medicine of Mayo Hospital, Lahore, Pakistan, from January 2015 to March 2016, and comprised CHC patients who had IR. Ethical approval was obtained from the institutional review board. Non-probability convenient sampling was used. The sample size was calculated using 95% power of test, 5% level of significance and by taking expected percentage of SVR at 26% in pioglitazone + standard care<sup>10</sup> and 59.2% in metformin + standard care,<sup>8</sup> respectively. Initial workup including complete blood count, liver function tests, ultrasound abdomen, fasting blood glucose and HCV RNA by polymerase chain reaction (PCR) was carried out. Informed consent was taken from every patient. Patients aged 18-65 years with HCV genotype 3 and insulin resistance calculated by HOMA-IR  $\geq 2.5$  were included. Patients having diagnosed with any malignancy and renal dysfunction on clinical examination and investigation, patient with any stigmata of decompensated liver disease, pregnant and lactating women on history were excluded.

The participants were equally divided into three groups. Group A included patients treated with interferon 3 million units, three times in a week and ribavirin 400mg three times in a day. Group B had patients treated with metformin 850mg twice daily in addition to interferon and ribavirin as of group A. Group C patients were treated with pioglitazone 15mg twice daily in addition to interferon and ribavirin. Patients were enrolled from the outpatient department. Real-time PCR for HCV was done and HOMA-IR score was calculated. The therapy was continued for 24 weeks. PCR for HCV RNA was done at the completion of the therapy to assess the end treatment response after 24 weeks of treatment completion to assess SVR. Moreover, creatinine, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT) and bilirubin levels were performed on receiving and then after three months of the treatment. Patients with haemoglobin  $<8\text{g/dl}$ , total lymphocyte count (TLC)  $<500\text{mm}^3$  and platelet count  $<2500/\text{mcl}$  during the treatment were excluded. All this information was recorded through a pre-designed proforma. Primary outcome measure was the achievement of SVR. Data was calculated using SPSS 20. Continuous data was expressed as mean  $\pm$  standard deviation (SD). Frequency and percentages were calculated for gender and repeated measures analysis of variance (ANOVA) was applied for the outcome which was SVR amongst each group.  $P \leq 0.05$  was considered statistically significant. Chi-square test was used to compare the outcome among the groups.

### Results

Of the 138 patients, there were 46(33.3%) in each group.

**Table-1:** Fasting BSL, Random blood sugar, fasting insulin, HOMA-IR score before treatment.

		Mean	S.D.	Minimum	Maximum	p-value
Fasting BSL (Baseline)	Group-A	6.24	0.86	5.1	9.5	0.202
	Group-B	5.98	0.94	4.7	9.5	
	Group-C	6.28	0.82	4.7	9.5	
	Total	6.17	0.88	4.7	9.5	
Random blood sugar (Baseline)	Group-A	8.34	0.90	6.7	9.9	0.592
	Group-B	8.56	0.94	6.7	10.1	
	Group-C	8.51	1.28	3.4	10.7	
	Total	8.47	1.05	3.4	10.7	
Fasting insulin (Baseline)	Group-A	13.97	2.70	10	20	0.160
	Group-B	14.67	2.63	10	22	
	Group-C	13.57	3.02	9	22	
	Total	14.07	2.80	9	22	
HOMA-IR score (Baseline)	Group-A	3.84	0.80	3	6	0.785
	Group-B	3.79	0.62	3	5	
	Group-C	3.73	0.79	3	6	
	Total	3.79	0.74	3	6	

BSL: Blood sugar level. HOMA-IR: Homeostatic model assessment-insulin resistance. SD: Standard deviation.

**Table-2:** Comparison of PCR- Quantitative at baseline and 24th week.

Study Groups		Mean	S.E.M	p-value
Group-A	PCR (baseline)	20381918.17	17866292.240	<0.001
	PCR 24th week	23319.15	21081.884	
Group-B	PCR (baseline)	4939288.07	2092379.040	<0.001
	PCR 24th week	3959.48	2846.531	
Group-C	PCR (baseline)	17276095.72	11417722.609	<0.001
	PCR 24th week	2593.63	2010.934	

PCR: Polymerase chain reaction

SEM: Standard error of the mean.

The mean age of patients in group-A was 36.83±9.64 years, in group-B was 37.72±10.00 years and in group-C was 38.07±8.85 years. Overall, 70(50.72%) participants were males and 68(49.28%) were females. The mean white blood cell (WBC) count, haemoglobin, prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalised ratio (INR) at baseline of patients amongst groups were statistically not different ( $p>0.05$ ).

The overall mean fasting blood sugar (FBS) level was 6.17±0.88, random blood sugar level was 8.47±1.05, fasting insulin was 14.07±2.80 and HOMA-IR was 3.79±0.74, with difference between the groups being statistically insignificant ( $p=0.202, 0.592, 0.160$  and  $0.785$ , respectively) (Table-1).

After conducting final PCR at 24th week, it was found that in group A the score was normal (<100) in 28(60.9%) patients and above normal in 18(39.1%) patients. In group B, the score was normal (<100) in 39(84.8%) patients and above normal in 7(15.2%) patients. In group C, the score was normal (<100) in 31(67.4%) patients and above normal in 15(32.6%) patients. The final PCR score was considerably higher in group B compared to A and C ( $p=0.003$ ) (Table-2).

## Discussion

HCV infection is one of the leading causes of both the acute and chronic hepatitis, and can lead to the development of cirrhosis and further HCC. According to an estimate, about 150 to 200 million people are exposed to HCV worldwide, and out of them about 85% are chronically infected.<sup>11</sup> As HCV has significant impact on the life quality and the current therapies have remained successful in achieving the sustained response.<sup>12</sup> HCV with spectrum of severity of liver diseases lead to cirrhosis.<sup>13</sup> IR precedes T2DM in CHC patients. However, IR may occur in the absence of HCV. Many studies show the link between HCV and IR.<sup>14</sup> Moreover, 40-54% of patients having HCV genotype 1, after getting treatment with pegylated interferon (PEG-IFN) plus ribavirin at

recommended doses for duration of 48 weeks achieved the SVR.<sup>15</sup> Some studies also showed that the achievement of SVR may decline with IR. Deltenre P et al.<sup>16</sup> confirmed that SVR was less in patients with IR than in patients without IR by the HOMA-IR (mean difference: -19.6%, 95% confidence interval (CI): -29.9% to -9.4%,  $p<0.001$ ).<sup>16</sup> Researchers have proved that as the insulin sensitivity improves, the response to treatment improves too. Therefore, the different combinations are being tried to find the optimum match for satisfactory response to traditional therapy and improvement in patient's health. Some insulin-sensitisers like pioglitazone has been tried earlier but results were inconsistent. Overbeck K.<sup>17</sup> conducted a trial on first 5 patients and found that none of the patients displayed the satisfactory virological response even after 12 weeks from the start of the treatment, and even the IR improved in three of them. So, the study was terminated. Another study showed that addition of metformin to peginterferon along with ribavirin was not only safe but also improved the insulin sensitivity.<sup>18</sup> Due to these controversial results, we considered it important to compare metformin and pioglitazone when added to standard interferon along with ribavirin therapy for its impact in improving SVR, CHC patients with IR. In the current study, the mean age of patients in group-A was 36.83±9.64 years, in group-B was 37.72±10.00 years and in group-C was 38.07±8.85 years. Overall, there were 70(50.72%) males and 68(49.28%) females in our study. The mean body mass index (BMI) of patients in group-A was 22.81±3.24, in group-B was 23.73±3.52 and in group-C was 22.79±3.16. There were 84(60.87%) patients with normal weight, 38(27.54%) were overweight, 11(7.97%) were underweight and 5(3.62%) were obese.

Jian-Wu Yu.et al. conducted a study in which 98 patients having genotype 1 and CHC along with IR were divided equally into the treatment group and the control group randomly. Patients in the control group were treated with peginterferon alfa-2a and ribavirin, and patients in the treatment group were given metformin along with peginterferon alfa-2a and ribavirin. The mean age of patients in the treatment group was 42±6 years and in the control group was 40±7 years. The mean BMI of patients in the treatment group was 28.2±2.8 and in the control group was 28.0±2.9.<sup>8</sup> It was also found that at week 24, there were 31 patients, out of which 6 patients were in the control group and 25 patients were in the treatment group, with a HOMA-IR index of <2. 24.<sup>8</sup>

In this study, the mean haemoglobin (baseline) of patients in group-A was 13.48±2.28, in group-B was 13.85±1.80 and in group-C was 13.49±1.96. The mean

WBC (baseline) of patients in group-A was  $9.90 \pm 12.90$ , in group-B was  $7.20 \pm 2.27$  and in group-C was  $8.04 \pm 3.03$ . The mean PT (baseline) of patients in group-A was  $13.11 \pm 0.31$ , in group-B was  $13.15 \pm 0.42$  and in group-C was  $14.13 \pm 4.15$ . The mean fasting blood sugar level (BSL) (baseline) of patients in group-A was  $6.24 \pm 0.86$ , in group-B was  $5.98 \pm 0.94$  and in group-C was  $6.28 \pm 0.82$ . The mean thyroid-stimulating hormone (TSH) (baseline) of patients in group-A was  $2.21 \pm 1.24$ , in group-B was  $2.40 \pm 1.23$  and in group-C was  $2.53 \pm 1.37$ . The mean APTT (baseline) of patients in group-A was  $32.28 \pm 3.38$ , in group-B was  $32.83 \pm 1.49$  and in group-C was  $32.20 \pm 4.71$ . It was also found after conducting PCR that in group A, the score was normal ( $<100$ ) in 28(60.9%) patients and above normal in 18(39.1%) patients. In group B, the score was normal ( $<100$ ) in 39(84.8%) patients and above normal in 7(15.2%) patients. In group C, the score was normal ( $<100$ ) in 31(67.4%) patients and above normal in 15(32.6%) patients. The final PCR score was considerably higher in group B compared to A and C ( $p=0.003$ ). Khattab M et al.<sup>19</sup> conducted a randomised-controlled study so the safety and efficacy of pioglitazone in improvement of insulin sensitivity and SVR could be evaluated in patients with CHC, genotype 4 receiving standard therapy. Ninety-seven patients with CHC and IR [homeostasis model assessment (HOMA $>2$ )] were divided into the two arms randomly; (arm A;  $n=48$ ) took pioglitazone 30mg/day in combination with peginterferon alpha-2a along with RBV for 48 weeks, and (arm B;  $n=49$ ) were given standard of care Peg-IFN- $\alpha$  along with RBV for 48 weeks). In the baseline data of both groups, there were no significant statistical differences similar to our study. The calculated percentages of rapid virological response (RVR) and SVR were significantly higher in those patients who were on triple therapy in comparison to the patients with standard treatment (27.08 vs. 6.1%;  $p=0.006$  and 60.4 vs. 38.7%;  $p=0.04$ , respectively). Patients in arm A showed a greater decrease in the HOMA index than the patients in arm B ( $-1.8 \pm 0.3$ ,  $-2.1 \pm 0.3$  vs.  $-1.1 \pm 0.6$ ,  $-1.3 \pm 0.7$ ) at week 24 and at the end of follow-up ( $p=0.001$  at both time points). Triple therapy was tolerated by patients. The conclusion was that the combination of Peg-IFN- $\alpha$ -2b and ribavirin and pioglitazone increased both RVR and SVR and also decrease the IR, compared with patients given Peg-IFN plus ribavirin without an adverse event.<sup>19</sup> Another study<sup>18</sup> was conducted with hypothesis that SVR could be improved when metformin is added to the standard therapy in patients having CHC and genotype 1 with IR. In this study 125 patients were taken out of which 123 were randomly assigned to the treatment group. Out of them, in females (54), addition of metformin to peginterferon alfa-2a plus ribavirin showed that the SVR rate was double

in 58% patients in arm A in comparison to arm B (29%). The viral decline was greater during the first 12 weeks in females who were taking metformin than placebo (mean [standard deviation (SD)]  $-4.88$  (1.18) versus  $-4.0$  (1.44);  $p=0.02$ ). On the other hand, no reduction in virus was seen in male patients.<sup>18</sup> It was also found that that decrease in HOMA index in patients who were receiving metformin was considerable in comparison to the patients on placebo. In arm A, the HOMA index decreased from 4.3 (2.2) to 2.6 (1.7) and in arm B from 4.6 (2.7) to 3.8 (2.1) ( $p=0.001$ ).<sup>8</sup> All these studies, similar to our results, support that combination of pioglitazone and/or metformin to standard HCV therapy significantly decreases IR and increases SVR. However, it is important to assure different schedules, doses and requirement of respective patients to achieve desirable results. Further researches are thus essentially needed to describe more in-depth aspects related to it.

## Conclusion

Improvement in SVR with standard therapy in combination with metformin patients having CHC infection with insulin resistance gave high-end response as compared to other groups.

**Disclaimer:** This manuscript was part of a thesis of Master's degree in Medicine.

**Conflict of Interest:** None.

**Source of Funding:** None.

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