A pilot study of add-on oral hypoglycemic agents in treatment-naïve genotype-1 chronic hepatitis C patients receiving peginterferon alfa-2b plus ribavirin

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KEYWORDS
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Background/Purpose: Insulin resistance (IR) affects sustained virological response (SVR) to peginterferon alfa plus ribavirin (PR) in patients with chronic hepatitis C (CHC). Whether add-on oral hypoglycemic agents (OHAs) to PR improve SVR remains unclear; therefore, we conducted a prospective, randomized pilot trial on 23 consecutive patients with genotype 1 CHC and IR in Taiwan.

Methods: Patients were randomized to receive acarbose (Arm A; n = 7) or metformin (Arm B; n = 6) or pioglitazone (Arm C; n = 5) in addition to peginterferon alfa-2b (1.5 μg/kg/week)
**Introduction**

Hepatitis C virus (HCV) infection is the leading cause of liver diseases and liver transplantation worldwide. Peginterferon alfa plus ribavirin (PR) is the standard choice of treatment for HCV infection in many parts of the world, but it is only effective in a certain proportion of chronic hepatitis C (CHC) patients. Because HCV may hijack host glucose or lipid metabolism to complete its life cycle, interventions on host metabolism may inhibit HCV replication by affecting its replication complex. Therefore, modifying metabolic factors becomes a reasonable measure for the comprehensive management of HCV infection.

Among the various metabolic factors, insulin resistance (IR) is known to aggravate hepatic steatosis, drive liver fibrosis progression, increase the risk of hepatocellular carcinoma, and is associated with hepatitis C viral load and poor virologic response of interferon (IFN) in CHC patients. Because oral hypoglycemic agents (OHAs) could improve IR, several studies have examined the effects of improving IR on the virologic response of IFN by combining OHA with IFN-based therapy for white patients with CHC genotype 1 and IR. Although Taiwanese patients have a better response to IFN-based therapy than white patients, whether an add-on OHA to PR benefits Taiwanese CHC patients remains unknown.

To this end, we conducted a prospective, randomized pilot trial on 23 consecutive patients with genotype 1 CHC infection and IR, and examined the impact of add-on OHA to PR on the virologic responses of these patients.

**Patients and methods**

**HCV group**

Eligible patients were those who were 20 years of age or older, chronically infected with HCV genotype 1, and naive to IFN treatment and other experimental antiviral or immunosuppressive therapy. All patients had antibodies to HCV and a quantifiable serum HCV RNA for more than 6 months, abnormal serum alanine aminotransferase (ALT) levels, and a homeostasis model assessment of IR (HOMA-IR) index ≥ 2 (Table 1). Liver biopsy was not considered mandatory for study inclusion. The enrollment for this study started in May 2009, and the trial ended in December 2011. Exclusion criteria were a neutrophil count <1500/μm³, a platelet count <90,000/μm³, a hemoglobin level <12 g/dL for women and <13 g/dL for men, positive for hepatitis B surface antigen or human immunodeficiency virus antibody, alcohol intake >20 g/day, a known history or serological evidence of autoimmune liver disease, inheritable disorders such as hemochromatosis or Wilson’s disease, diabetes mellitus or under OHA therapy, liver cirrhosis, renal insufficiency, malignancy, and the presence of drug abuse, chronic disease, psychiatric disease, or pregnancy and lactation.

**Study design**

This was a prospective, multicentered, randomized, open-label controlled trial (registered in ClinicalTrials.gov; No. NCT01025765). The study was conducted in three academic centers. All sites received approval from their respective ethics committees. Each patient provided written informed consent for participation. Patients were randomly assigned in a 1:1:1:1 ratio to receive acarbose 50 mg/day for the 1st month and 50 mg/meal from Week 5 to 12 (Arm A; n = 6), metformin 500 mg for the 1st month and 500 mg three times daily from Week 5 to 12 (Arm B; n = 6), pioglitazone 15 mg/day for the 1st month and 30 mg from Week 5 to 12 (Arm C; n = 6), or under observation for the 1st 3 months (Arm D; n = 5) and received peginterferon alfa-2b (PEG-Intron; Schering-Plough Inc., Kenilworth, NJ, USA) at a dose of 1.5 μg/kg of body weight weekly plus oral ribavirin (Rebetol; Schering-Plough Inc.) at a dose of 1000 mg (for those with body weight <75 kg) or 1200 mg (for those with a body weight ≥ 75 kg) daily from Week 5 to 52 (Fig. 1). Participants were assessed on an outpatient basis at Weeks 5, 9, 13, 17, 29, 41, and 53 during treatment and followed every 12 weeks for 24 weeks after discontinuation of treatment to confirm sustained virological response (SVR). Treatment was discontinued in patients who did not achieve an early virological response (EVR) at Week 17 or were HCV RNA positive at Week 29.
Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of each study site.

Data collection and laboratory analyses

Data on sex, age, body mass index (BMI), serum fasting blood glucose, triglyceride (TG), total cholesterol (CHO), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and ALT levels were collected. BMI was calculated as weight in kilograms divided by height in square meters. Blood samples were collected in the morning after 12-hour fasting and were measured by standard laboratory techniques. Serum fasting blood glucose, TG, CHO, LDL, HDL, and ALT levels were measured using an autoanalyzer (Hitachi 7250, Special; Hitachi, Tokyo, Japan). An upper limit of normal serum ALT levels was set at 30 U/L for men and 19 U/L for women. Serum insulin was measured using an immunometric assay (IMMULITE; Diagnostic Products Co., Los Angeles, CA, USA). HBsAg, anti-HCV, and antihuman immunodeficiency virus were assayed using commercial kits (Abbott Laboratories, Chicago, IL, USA).

The IR index was determined using HOMA-IR model [$\left(\frac{\text{fasting insulin (mU/L)}}{\text{fasting glucose (mg/dL)}}\right) \times 0.05551/22.5$] as previously described. Serum HCV RNA was measured using a standardized automated qualitative reverse transcription polymerase chain reaction assay (COBAS TaqMan HCV Test v2.0). The detection limit was 25 IU/mL. HCV genotyping was performed with the use of a hybridization technique (INNO-LiPA HCV; Innogenetics, N.V., Zwijnaarde, Belgium).

Efficacy assessments

The primary end point was SVR. The secondary end points were viral clearance (HCV RNA < 25 IU/mL) at Weeks 17, 29, and 53. Rapid virologic response (RVR) was defined if an undetectable serum HCV RNA level at Week 9 was achieved. EVR was defined as an undetectable serum HCV RNA level or at least a two-log decrease of the baseline HCV RNA level at Week 17. Complete EVR (cEVR) was defined as undetectable serum HCV RNA at Week 17 of therapy, and partial EVR (pEVR) as at least a two-log reduction of serum HCV RNA from baseline to Week 17 of therapy. Virologic responder was defined as those having RVR or EVR. SVR was defined as an undetectable serum HCV RNA level (<25 IU/mL) at 24 weeks after treatment.

| Table 1 Baseline characteristics of chronic hepatitis C patients receiving OHA plus Peg-IFN/RBV therapy. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case no. | Age | Sex | HOMA-IR | Treatment | Body weight (kg) | ALT (U/L) | HCV RNA (log10 IU/mL) | PLT (K/L) | Tbil AC-sugar Insulin CHO TG RVR EVR EOTR SVR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 51.2 | M | 4.4 | Pioglitazone 64 | 137 | 5.65 | 311 | 0.46 | 90 | 20.0 | 200 | 215 0 1 0 0 |
| 7 | 31.5 | F | 2.3 | Pioglitazone 43 | 53 | 5.65 | 156 | 0.49 | 90 | 10.5 | 143 | 45 0 1 1 1 |
| 14 | 51.5 | M | 2.0 | Pioglitazone 66.2 | 48 | 6.40 | 206 | 0.95 | 98 | 8.3 | 188 | 74 0 pEVR 1 0 |
| 15 | 44.3 | M | 2.1 | Pioglitazone 65 | 76 | 6.20 | 137 | 1.03 | 92 | 9.3 | 247 | 118 1 1 1 1 |
| 17 | 55.9 | F | 3.4 | Pioglitazone 54 | 110 | 5.01 | 106 | 1.58 | 108 | 12.6 | 215 | 133 1 1 1 1 |
| 19 | 66.5 | F | 2.7 | Pioglitazone 56 | 19 | 4.56 | 143 | 0.78 | 109 | 10.0 | 174 | 187 1 1 1 1 |
| 2 | 72.6 | F | 3.7 | Metformin 74 | 117 | 4.33 | 178 | 1.30 | 104 | 14.6 | 130 | 76 1 1 1 1 |
| 10 | 54.4 | M | 4.9 | Metformin 65.2 | 120 | 6.34 | 137 | 0.67 | 90 | 17.6 | 120 | 70 0 0 0 0 |
| 12 | 61.9 | F | 4.0 | Metformin 67 | 96 | 6.24 | 187 | 0.57 | 92 | 17.6 | 173 | 156 1 1 1 1 |
| 20 | 61.9 | F | 2.1 | Metformin 59 | 97 | 6.13 | 219 | 0.79 | 92 | 9.3 | 193 | 86 1 1 1 1 |
| 14 | 51.5 | M | 2.0 | Metformin 72 | 75 | 6.25 | 155 | 1.02 | 126 | 12.8 | 167 | 334 1 1 1 1 |
| 18 | 67.8 | M | 3.5 | Metformin 71 | 57 | 6.97 | 114 | 0.81 | 112 | 12.7 | 107 | 205 0 1 1 1 |
| 5 | 56.6 | F | 3.4 | Acarbose 54.5 | 123 | 5.77 | 221 | 0.38 | 88 | 15.8 | 179 | 111 1 1 1 1 |
| 6 | 36.8 | F | 4.3 | Acarbose 62.8 | 198 | 4.51 | 238 | 0.53 | 89 | 19.5 | 174 | 109 1 1 1 1 |
| 8 | 56.4 | F | 5.0 | Acarbose 75.7 | 67 | 6.57 | 130 | 0.58 | 95 | 21.2 | 175 | 61 1 pEVR 1 1 |
| 11 | 36.9 | M | 5.1 | Acarbose 76.4 | 92 | 7.74 | 252 | 0.84 | 109 | 19.1 | 189 | 108 0 1 0 0 |
| 13 | 58.0 | F | 3.8 | Acarbose 54 | 97 | 4.66 | 143 | 0.58 | 105 | 14.5 | 166 | 65 1 1 1 0 |
| 3 | 43.1 | M | 2.1 | Acarbose 80.4 | 227 | 6.27 | 211 | 0.73 | 80 | 10.5 | 146 | 90 1 1 1 1 |
| 9 | 54.2 | M | 3.7 | Control 73.5 | 71 | 6.95 | 139 | 0.61 | 99 | 15.1 | 176 | 63 1 1 1 1 |
| 4 | 41.1 | M | 3.1 | Control 75.7 | 112 | 5.57 | 241 | 0.42 | 92 | 13.6 | 133 | 41 1 1 1 1 |
| 21 | 64.2 | F | 2.7 | Control 49 | 97 | 5.92 | 265 | 1.22 | 150 | 7.2 | 207 | 90 0 1 1 0 |
| 22 | 62.7 | F | 6.3 | Control 89 | 97 | 6.95 | 132 | 0.59 | 103 | 24.6 | 178 | 161 0 pEVR 1 0 |
| 23 | 46.7 | M | 3.9 | Control 83 | 31 | 7.09 | 183 | 0.95 | 115 | 13.7 | 179 | 73 0 1 1 1 |

Homeostasis model assessment of insulin resistance (HOMA-IR) = $\left(\frac{\text{fasting insulin (mU/L)}}{\text{fasting glucose (mg/dL)}}\right) \times 0.05551/22.5$. For virologic response (SVR, EVR, EOTR, and RVR), Yes = 1 and No = 0.

AC = ante cibum; ALT = alanine aminotransferase; CHO = total cholesterol; EOTR = end-of-treatment response; EVR = early virologic response; HCV = hepatitis C virus; OHA = oral hypoglycemic agents; Peg-IFN = pegylated interferon; pEVR = partial early virologic response; PLT = platelet count; RBV = ribavirin; RVR = rapid virologic response; SVR = sustained virologic response; Tbil = bile total bilirubin; TG = triglyceride.
weeks after the discontinuation of treatment. Virological breakthrough was defined as a detectable HCV RNA level during treatment in patients who had undetectable HCV RNA at Week 29. Virological relapse was defined as a detectable HCV RNA level during follow up in patients who had undetectable HCV RNA at Week 53.

Safety assessments

Adverse events were recorded and assessed on an outpatient basis by clinical examinations and laboratory tests at Weeks 5, 9, 13, 17, 29, 41, 53, and 77. Stepwise reductions of PR were permitted in managing clinically significant adverse events, or laboratory abnormalities recorded.

Statistical analysis

Patients who dropped out of the trial were classified as not having a virologic response, and the analyses included all randomized patients for whom outcome data were available. Categorical data were presented as percentages, whereas continuous data were presented as mean with standard deviations. Log transformation was performed for variables with a significant deviation from normal distribution. Differences in baseline characteristics among the arms were assessed using Chi-square test with Yates’s correction for discrete variables. We compared the virological response of patients in each arm with the ones receiving PR (Arm D) at Weeks 9, 17, and 77. Linear regression and multivariate analyses using logistic regression were performed to examine the associations of add-on OHA, SVR, and various clinical factors. All analyses were performed using Stata statistical software (version 8.0; Stata Corp., College Station, TX, USA). All tests were two sided and \( p < 0.05 \) was considered statistically significant.

Results

Baseline characteristics of patients among different treatments

A total of 23 patients were consecutively recruited and randomly assigned into four different treatment groups and received at least one dose of medication; two patients were excluded from per protocol analysis (PPA) because of not receiving complete treatment and follow up after enrollment [one patient in the acarbose group (Arm A, Case 11) discontinued treatment at Week 28 because of hyperthyroidism, and the other patient in the metformin group (Arm B, Case 10) discontinued treatment at Week 13 because of vertigo after a peginterferon alfa injection]. The four treatment groups were comparable in terms of age, sex, and other variables measured on entry into the trial (Table 1).

Virological responses among different treatment groups

In the intent-to-treat analysis, SVR was observed in 66.7% (4/6), 83.3% (5/6), 66.7% (4/6), and 60% (3/5) in Arms A, B, C, and D, respectively. In the PPA, SVR was 80.0% (4/5) in Arm A, 100% (5/5) in Arm B, 66.7% (4/6) in Arm C, and 60% (3/5) in Arm D. Patients with SVR had lower IR than those without. Females receiving add-on OHA [90% (9/10)] had a higher SVR than males [50% (4/8)].

RVR was 100% (5/5) in Arm A, 60% (3/5) in Arm B, 50% (3/6) in Arm C, and 40% (2/5) in Arm D. Add-on OHA to PR increased the RVR [Arms A + B + C vs. D: 11/18 (61%) vs. 2/5 (40%)].

All patients attained EVR, and one patient in Arm A, one in Arm C, and one in Arm D had pEVR. Add-on OHA to PR did not change the cEVR [15/18 (83%) vs. 4/5 (80%)].
Virological breakthrough was slightly lower in patients receiving add-on OHA [11.1% (2/18) vs. 40% (2/5)]. Among the four patients with virological breakthrough, one in Arm A was male, and the other three were female (Table 1).

### Safety

The most common adverse events were anemia, fever, gastrointestinal upsets, headache, skin rash, itching, and cough, which were similar to reports from previous trials of IFN-based therapy. Three patients experienced hyperthyroidism during therapy (Cases 6, 7, and 11) and one discontinued medication (Case 11). Two patients experienced vertigo (Cases 10 and 13) and one discontinued treatment (Case 10). Among patients who received pioglitazone in Arm C, one had pancreatitis (Case 14) and another one had pancytopenia (Case 3). One patient who received acarbose in Arm A experienced hyperglycemia and hyperlipidemia during the therapy (Case 5). All these patients recovered after supportive treatment and reductions in the doses of peginterferon alfa-2b or ribavirin administered. No significant side effects were observed during the period when patients received add-on OHA.

### Discussion

IR is known to affect SVR of CHC patients. Several proof-of-concept trials with different pharmacological interventions aiming at reducing IR in CHC patients have shown the improvement of hepatitis treatment outcomes, but the optimal modality, treatment schedule, and the applicability to different ethnicity and HCV genotypes remain unclear. In this pilot study, we examined the virological effects of different OHAs (pioglitazone, metformin, and acarbose) on CHC patients with HOMA-IR ≥ 2, and found that add-on OHAs to PR may improve RVR and SVR in these difficult-to-treat Asian patients. Our results echo previous reports and indicate that short-term OHAs might be beneficial to the virological response of CHC patients.

In this study, two patients discontinued treatment because of adverse events and withdrew from the study, but none of these adverse events were attributed to OHAs. One patient in the metformin group (Arm B, Case 10) discontinued her treatment at Week 13 because of vertigo after peginterferon injection, and the other one in the acarbose group (Arm A, Case 11) withdrew at Week 28 because of hyperthyroidism. The remaining patients who received add-on OHAs completed treatment and follow up, and none of them had significant side effects during the period of add-on OHA therapy. Therefore, a combination of OHAs and PR is safe to CHC patients. In addition, previous reports demonstrated a better virological response in female CHC patients receiving add-on OHA therapy. We also observed a trend of increasing SVR in female patients receiving add-on OHA to PR, although the difference did not reach a statistical significance, which could be attributable, at least in part, to a type 2 error in small sample size.

This study had a few limitations. First, the sample size is relatively small, hence it is not powerful enough to detect significant improvements of virologic response in patients receiving add-on OHA therapy. However, the trends shown in this study were comparable with reports from other groups. Therefore, our results might imply that this proof-of-concept approach could work in Asian CHC patients. To detect significant differences between groups, a larger study including at least 140 patients in each study arm is needed in the future. Second, because most patients attained EVR in this study and patients receiving add-on OHA had a higher RVR than PR controls, it seemingly implies that OHAs might affect patients’ viral kinetics in the beginning. Further studies to examine detailed impacts of OHAs on viral kinetics are needed. Of note, an 8-week use instead of a 48-week use of OHA in this study not only decreases additional adverse effects and cost, but also highlights that the first 8 weeks of OHA therapy might be the key to improving IR in CHC patients. Future studies are needed to examine the efficacy of OHA with different combinations, time series, and dosage. Third, IL28B polymorphism is an important and well-known therapeutic predictor for CHC patients receiving IFN-based therapy. Because the association of IL28B polymorphism and HCV was identified in 2009, which is after the implementation of this study, IL28B polymorphism was not included in this study. However, according to our previous data, most Taiwanese CHC patients have the favorable IL28B genotype contributing to better responses to IFN-based therapy (i.e., rs8099917 TT genotype). Therefore, knowing the distribution of IL28B genotypes in our patients might not significantly change our major conclusions. However, future studies examining the effects of IL28B genotypes on the therapeutic efficacy of adding OHA in CHC patients are still needed. Finally, because of the high therapeutic efficacy of direct acting antiviral (DAA)-based therapy, the value of insulin sensitizer would be limited in the era of DAA-based therapy. However, as most Asian countries cannot afford the price of DAA-based therapy, insulin sensitizer might be a good alternative for CHC patients in low-income areas. By contrast, considering the IR-prone feature of HCV and increased stroke and cardiovascular disease (CVD) risks in CHC patients, adding insulin sensitizer may not only benefit CHC patients who have increased IR before IFN-based therapy, but also potentially decrease stroke and CVD risks in most CHC patients. However, future studies examining the effects of insulin sensitizer on stroke and CVD risks of CHC patients receiving IFN-based therapy are awaited.

In summary, our preliminary data show the promising results of add-on OHAs to PR for the treatment of Asian CHC patients. Considering the lower cost, better safety, and greater accessibility of OHAs, further larger proof-of-concept studies are anticipated.

### Author contributions

C.-S.H. planned and conducted this study, and was responsible for data analysis and the interpretation of data, in addition to writing this paper; S.-J.H., H.H.L., T.-C.T., and C.-C.W. helped in the enrollment of patients; D.-S.C. helped in the critical revision of the manuscript for important intellectual content; and J.-H.K. supervised this
study, obtained funding, planned this project, interpreted results, and wrote this paper along with C.-S.H.

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