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Research Article

The Effect on Gastric Emptying of Telaprevir-Based Triple Therapy for Chronic Hepatitis C Patients

Abstract

Aim: We evaluated food intake in telaprevir-based triple therapy (telaprevir, pegylated-interferon, and ribavirin) and its relation to Gastric Emptying (GE).

Methods: 17 patients received telaprevir combined with pegylated interferon plus ribavirin. The GE study was carried out using the ^{13}C -acetate breath test and GE time was expressed as the peak time of $^{13}\text{CO}_2$ excretion (Tmax).

Results: The average food intake was $1,851 \pm 91$, $1,338 \pm 537$ and $1,453 \pm 537$ kcal at 0, 1, and 2 weeks after the start of treatment, respectively, showing a significant decrease compared to that before treatment ($p < 0.01$ and $p < 0.05$, paired t-test). The averages of Tmax values at 0, 1, and 2 weeks after the start of treatment were 48.4 ± 14.3 min, 56.9 ± 18.4 min and 58.0 ± 19.9 min, respectively. There was a significant difference between baseline and 1 week after the start of treatment ($p < 0.05$, paired t-test). Food intake (kcal) showed a good correlation with the decrease of Tmax values (minutes) (Pearson's correlation test, $r = -0.49$, $p < 0.05$).

Conclusions: Telaprevir-based triple therapy caused reduced food intake and worsened GE.

Abbreviations

GI: Gastro Intestinal; GE: Gastric Emptying; Tmax: Peak Time of $^{13}\text{CO}_2$ excretion; PEG-IFN: Pegylated Interferon; RBV: Ribavirin; HCV: Hepatitis C Virus; TVR: Telaprevir; SVR: Sustained Virological Response; GRS: Gastrointestinal Symptom Rating Scale; SDS: Self-reported Depression Scale

Introduction

Telaprevir-based triple therapy [telaprevir, pegylated-interferon (PEG-IFN), and ribavirin (RBV)] was a standard treatment for patients with hepatitis C virus (HCV) infection. The addition of telaprevir (TVR) to dual therapy with pegylated-interferon and ribavirin improved sustained virological response (SVR) rates in patients with chronic HCV infection [1]. While generally well tolerated by patients in the registration trials, TVR-based triple therapy has significant side effects, including severe rashes that have led to fatalities of patients outside the registration trials [2-4]. Pruritus, gastrointestinal side effects and anemia also occur more frequently in patients on TVR-based triple therapy than in patients on PEG-IFN/RBV dual therapy. In addition, body weight changes are well documented in HCV patients on interferon therapy. These side effects could cause discontinuation of treatment or a decrease of the dose of the drugs. However, the underlying mechanism involved in these changes is poorly understood and rarely reported. In particular, the ideal strategy for the management of gastrointestinal (GI) dysfunction remains uncertain.

The aim of this study was to evaluate changes in gastric emptying (GE), food intake, subsequent symptoms, plasma ghrelin levels, and serum leptin levels in TRV-based triple therapy. Are GE / peptide hormones associated with the food intake of HCV patients?

Methods

Patients

From September 2012 to October 2013, 17 patients who had been diagnosed with chronic hepatitis C received telaprevir combined with pegylated interferon plus ribavirin at Chiba University Hospital. They had no history of previous gastrointestinal surgery and no change of medication affecting gastric motility for at least 4 weeks. None of the patients had general diseases such as renal failure, cardiopulmonary disease, uncontrolled diabetes mellitus, or GI disease. The study was approved by Chiba University Hospital Institutional Review Board and all patients gave informed consent (UMIN000012279). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

Gastric emptying (GE) study

The GE study was carried out using the ^{13}C -acetate breath test (^{13}C -ABT) with a slight modification [5-8]. GE also can be evaluated using the acetaminophen absorption test and by (99m) technetium scintigraphy. However, the acetaminophen absorption test requires repeated blood sample collection and might cause drug-induced liver dysfunction, and scintigraphy requires specialized instrumentation. In contrast, ^{13}C -ABT can be performed at the patient's bedside and the results have been shown to correlate well with those obtained using scintigraphy [9]. Therefore we chose the ^{13}C -ABT to determine the prevalence of delayed GE in patients undergoing triple therapy. ^{13}C -sodium acetate administrated orally with a test meal is ejected from the stomach and absorbed from the digestive tract where it

is metabolized to $^{13}\text{CO}_2$, which is then expired via the lungs. Thus, measurement of $^{13}\text{CO}_2$ in expired breath is an indirect measure of GE. The patients were tested after an overnight 12-hour fast. First, a breath sample was obtained following the ingestion of a liquid test meal (Racol, 200 kcal /200 ml; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) containing 100 mg of ^{13}C -sodium acetate (Sigma-Aldrich Co., LLC, St. Louis, MO, USA). The test meal was consumed in less than 5 minutes and breath samples were collected at 5, 10, 15, 20, 30, 40, 50, 60, 75, and 90 minutes after consuming the test meal. Patients remained in a seated position throughout the examination. All breath samples were analyzed by infrared isotope spectrometry (POCone; Otsuka Electronics Co., LTD., Osaka, Japan). GE time was expressed as the peak time of $^{13}\text{CO}_2$ excretion (Tmax) and the GE rate curve was determined from the pattern of the $^{13}\text{CO}_2$ excretion curve. GE studies were conducted at 0, 7, and 14 days after the start of telaprevir-based triple therapy for chronic hepatitis C.

Evaluation of food intake and body weight

All patients were treated in the hospital and clinical staff recorded the dietary intake and body weight up to two weeks after the initiation of treatment. We calculated the calorific value from the volume of food intake.

Measurement of serum ghrelin and leptin levels

Blood samples were collected from fasting subjects at 0, 7, and 14 days after the start of telaprevir-based triple therapy for chronic hepatitis C. The samples were immediately centrifuged at 1,500 g for 15 min at 4 °C, and HCl was added at a ratio of 1:10 (v/v). The samples were then stored at -80 °C for later analysis. The levels of ghrelin (acylghrelin and desacylghrelin) and leptin in serum were measured at SRL, Inc. (Tokyo, Japan). When ghrelin could not be detected, its level was reported as 0 fmol / mL. Leptin was measured in serum by radioimmune assays.

Evaluation of GI Symptoms

GI symptoms were evaluated by the GSRS (Gastrointestinal Symptom Rating Scale) score of the patient's rating of the overall change in dyspeptic symptoms. Patients completed the GSRS questionnaire at 0, 7, and 14 days after entry [10]. The GSRS is based on 15 questions, with a scale of 1 to 7, assessing the severity of symptoms during the previous week. A higher score indicates more severe symptoms. Combination scores from 15 questions can assess the following five domains: reflux syndrome (heartburn and acid regurgitation), abdominal pain (stomach ache, gastric hunger pains and nausea), indigestion syndrome (gastric borborygmus, gastric bloating, eructation and increased flatus), diarrhea syndrome (diarrhea, loose stools and urgent need to defecate) and constipation syndrome (constipation, hard stools and feeling of incomplete evacuation).

In addition, all patients answered the questionnaires of the Self-reported Depression Scale (SDS) at the same time [11].

Statistical Analysis

All data values are expressed as the mean \pm standard deviation (SD) (Table 1). Commercially available SPSS software was used for

the statistical analysis. Parameters before and during treatment were compared within subjects by paired t- test. The level for significance was $p < 0.05$. The association between body weight, GI symptoms, serum ghrelin levels and GE was established statistically using Pearson's correlation coefficient test or Spearman's correlation coefficient by rank test.

Results

Antiviral treatment

Seventeen patients were treated with telaprevir 1,500 or 2,000 mg per day, ribavirin from 600 to 1,000 mg per day and PEG-IFN. Their doses were reduced, based on the side effects. 11 of 17 patients showed rapid virological responses at 2 weeks after the start of treatment.

Evaluation of food intake and body weight

All patients were treated in the hospital for at least 2 weeks, therefore we could evaluate the volume of food intake and body weight. All consumed each meal completely prior to treatment. The average food intake decreased at 1 and 2 weeks after the start of treatment, with a significant difference compared to that before treatment ($p < 0.05$ and $p < 0.01$, respectively, paired t-test) (Figure 1a). Loss of body weight was observed at 1 and 2 weeks after the start of treatment, with a significant decrease (3.4 % $p < 0.05$ and 3.6 % $p < 0.01$, respectively, paired t-test) (Figure 1b).

Effects of telaprevir-based triple therapy on gastrointestinal symptoms and SDS score in patients with chronic hepatitis C

The change of sub-scales, reflux symptom, abdominal pain, indigestion symptoms, diarrhea symptoms and constipation symptoms and SDS score are shown in Table 2. There was no significant difference in gastrointestinal symptoms and SDS scores between before and after the start of treatment.

Gastric emptying

The Tmax values before treatment and 1 week and 2 weeks after the start of treatment were 48.4 ± 14.3 , 56.9 ± 18.4 and 58.0 ± 19.9 , respectively, indicating that telaprevir based treatment delayed GE (Figure 2). There was a significant difference between baseline and

Table 1: Clinical characteristics of the patients in this study.	
	n=17
Age (years, average \pm SD)	54.1 \pm 8.4
Gender (male/female)	12 / 5
Body Mass Index (kg/m ² , average \pm SD)	24.9 \pm 4.5
HCV Genotype 1b	17
Viral load (Logcopies/ml, average \pm SD)	6.0 \pm 1.8
Alanine aminotransferase (IU/L)	82.7 \pm 59.1
Number of Platelets ($\times 10^3/\mu\text{l}$)	17.6 \pm 3.7
Total Bilirubin (mg/dl)	1.0 \pm 0.4
Liver Cirrhosis (Yes / No)	0 / 17
SD, standard deviation.	

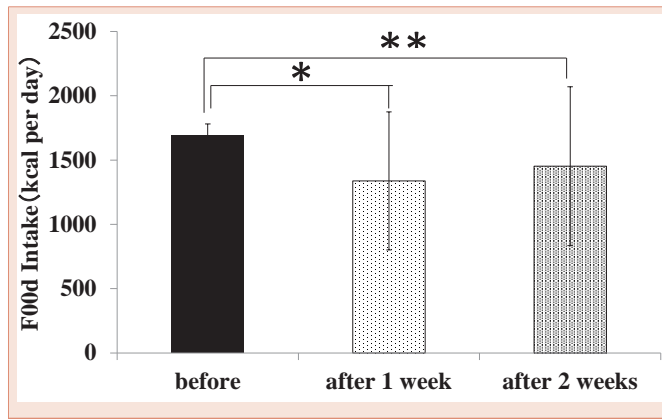


Figure 1a: Changes in food intake during telaprevir-based triple therapy. The average food intake decreased at 1 and 2 weeks after the start of treatment, with a significant difference compared to that before treatment ($p < 0.05$ and $p < 0.01$, respectively, paired t-test).

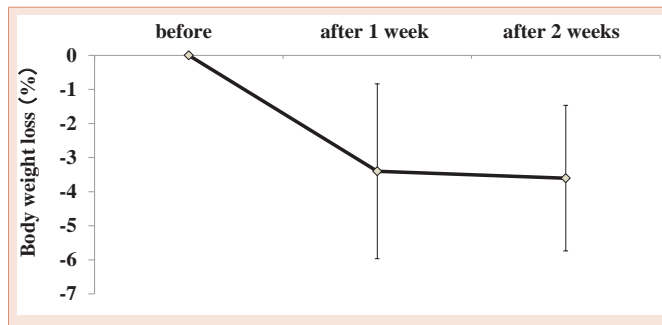


Figure 1b: Body weight loss during telaprevir-based triple therapy. Loss of body weight was observed at 1 and 2 weeks after the start of treatment and showed a significant decrease (3.4% $p < 0.05$ and 3.6% $p < 0.01$, respectively, paired t-test).

1 week after the start of treatment ($p < 0.05$, paired t-test) but no significant difference between baseline and 2 weeks after the start of treatment. Individually, 2 patients showed significant improvement of GE, while 7 patients showed no change. There were no significant associations between body weight and clinical background features such as age, gender, disease duration, GE (Tmax) and ghrelin levels.

The $^{13}\text{CO}_2$ excretion curve showed 2 patterns; a steep shape with an obvious peak and a flattened shape without an obvious peak. These were designated as peak and non-peak patterns, respectively. Before treatment, there were 12 patients with the peak pattern and 4 patients with the non-peak pattern, and 1 week after the start of treatment there were 6 with the peak and 10 with the non-peak pattern

Changes in ghrelin and leptin levels

The acyl-ghrelin and desacyl-ghrelin and leptin levels, before and 1 and 2 weeks after the start of treatment, are shown in Table 3. The levels of acyl-ghrelin and desacyl-ghrelin did not change significantly. In contrast, the leptin level at 2 weeks after the start of treatment was significantly lower than that before treatment ($p < 0.01$, paired t-test).

The relationship between gastric emptying and reduction of food intake

We evaluated the relationship between gastric emptying and reduction of food intake in Figure 3. The amount of food intake (kcal) showed a good correlation with the deterioration of gastric emptying (Pearson's correlation test, $r = -0.49$, $p < 0.05$). Food intake was not correlated with any other factors: age, gender, BMI, dose of drugs, GSRS scores or SDS (data not shown).

Discussion

The addition of TVR to dual therapy with PEG-IFN and RBV has improved SVR rates in patients with chronic HCV infection [1]. Jacobson and colleague reported that 75% of patients with HCV genotype 1 achieved SVR with TVR-based triple therapy [1]. However, TVR-based triple therapy has significant side effects, including GI side effects, although the underlying mechanism involved in these changes is poorly understood and rarely reported [12]. If the side effects cannot be controlled, HCV treatment must be discontinued, which greatly increases the risk of treatment failure. In previous studies, the rate of discontinuation due to adverse effects was 12.7% [13]. In addition, a lower serum albumin level (< 35 g/L) was associated with the occurrence of infection [13].

GE is a major function of the stomach and its disruption is related to various diseases. We previously reported GE dysfunction in patients with Parkinson's disease, and deep brain stimulation of the sub thalamic nucleus improved anti-parkinsonian drug resistant GE dysfunction in such patients [8]. Parkman et al. reported that

Table 2: Changes in GSRS scores and SDS scores during telaprevir-based triple therapy.

GSRS, SDS (average \pm SD)	Before	After 1 week	After 2 weeks	Between Before and After 1 week†	Between Before and After 2 week†
GSRS	1.7 \pm 0.6	1.8 \pm 0.7	1.5 \pm 0.7	n.s.	n.s.
Total	1.7 \pm 0.6	1.8 \pm 0.7	1.5 \pm 0.7	n.s.	n.s.
Reflux symptom	1.7 \pm 0.8	1.8 \pm 0.9	1.6 \pm 0.9	n.s.	n.s.
Abdominal pain	1.7 \pm 0.2	2.0 \pm 0.9	1.6 \pm 0.9	n.s.	n.s.
Indigestion	1.7 \pm 0.6	1.9 \pm 1.0	1.6 \pm 0.8	n.s.	n.s.
Constipation	1.6 \pm 0.7	1.6 \pm 0.7	1.5 \pm 0.8	n.s.	n.s.
Diarrhea	1.6 \pm 0.9	1.7 \pm 0.8	1.5 \pm 0.8	n.s.	n.s.
SDS	38.0 \pm 6.9	39.8 \pm 7.2	40.5 \pm 5.5	n.s.	n.s.

†paired t-test.

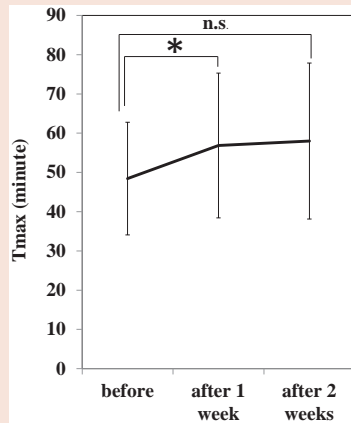


Figure 2: Gastric emptying before and during telaprevir-based triple therapy. There were significant differences between baseline and one week after the start of treatment ($p < 0.05$). However, there was no significant difference between baseline and two weeks after the start of treatment, although gastric emptying was delayed at two weeks after the start of treatment.

Table 3: Changes in acyl ghrelin, desacyl ghrelin, and leptin levels during telaprevir-based triple therapy.

	Before Treatment	After 1 week	After 2 weeks
Acyl ghrelin (fmol/ml, average \pm SD)	7.0 \pm 3.5	8.3 \pm 3.6	7.2 \pm 2.2
Desacyl ghrelin (fmol/ml, average \pm SD)	50.5 \pm 17.6	46.1 \pm 15.9	46.6 \pm 16.8
Leptin (ng/ml, average \pm SD)	7.5 \pm 3.3	7.0 \pm 2.6	5.3 \pm 2.4**

** $p < 0.01$, * $p < 0.05$, paired t-test, compared to the value before treatment; SD, standard deviation.

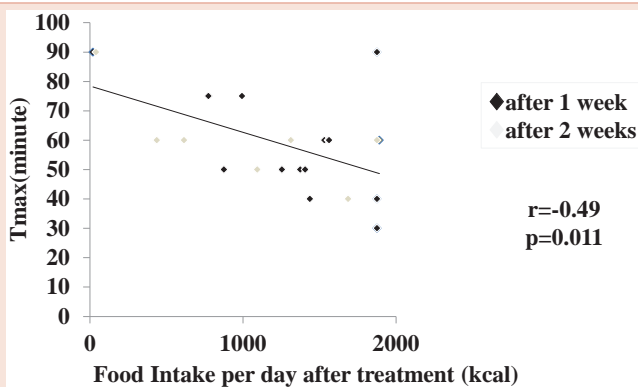


Figure 3: Relationship between reduction of food intake and gastric emptying. The amount of food intake (kcal) showed a good correlation with the deterioration of gastric emptying (Pearson's correlation test, $r = -0.49$, $p < 0.05$).

severely delayed gastric emptying was associated with more severe symptoms, such as vomiting and loss of appetite in patients with idiopathic gastro paresis [14]. In our study, TVR-based triple therapy delayed GE significantly in the first week after the start of treatment. There was no significant difference between baseline and

2 weeks after the start of treatment. On the other hand, food intake and body weight were significantly lower at 1 and 2 weeks after the start of treatment. Although gastric emptying just showed a tendency to be delayed in the second week without significant difference GE, compared to baseline, food intake showed a good correlation with the deterioration of T-max values. We consider the deterioration of to be one of the major causes of reduction of food intake.

Ghrelin is strongly correlated with appetite and GE [15-19]. In a previous study, Watanabe and associates reported the reduction of serum ghrelin concentrations during interferon-alpha therapy in patients with chronic HCV. We also assessed plasma ghrelin levels at the same time points. In this study, the plasma ghrelin levels did not change during TVR-based triple therapy. The differences between our study and theirs might be associated with the different therapies (interferon-alpha vs. TVR-based triple therapy). Leptin, a protein mainly produced predominantly by adipocytes, acts as a negative feedback signal to the normal control of food intake and body weight [20]. In previous studies, serum leptin was found to be an independent risk factor for non-response to antiviral treatment in chronic hepatitis C patients with low viremia [21,22]. In our study, the levels of leptin at 2 weeks after the start of treatment were significantly lower than baseline. There are some reports of changes in leptin levels after interferon therapy [12,23]. Alam and colleagues reported in a review of the literature that the possible mechanisms underlying weight loss or other changes in body composition include suppressed appetite due to induction of TNF by IFN, a decrease in serum leptin levels and, importantly, mitochondrial damage induced by the therapy [12]. Regarding the changes in serum leptin levels, our results are similar to those of previous studies.

In this study, depressive and gastrointestinal symptoms did not change during this period of TVR-based triple therapy but in this period, but we were surprised that loss of body weight was observed without gastrointestinal symptoms. However, some studies have reported that interferon plus ribavirin therapy was associated with a high rate of depression [24]. Although, reduction of food intake was not related to depression in this study, we need careful follow-up to avoid missing the sign of depression.

Our study has some limitations: a small number of patients, and a short period of follow-up. Further studies involving a larger patient cohort are needed.

In conclusion, TVR-based triple therapy for chronic HCV patients caused reduced food intake and body weight, and worsened GE. The deterioration of GE is a major cause of the reduction of food intake. In a previous study, the use of prokinetic agents, antiemetic agents, gastric acid suppressants, narcotic pain medications, and enteral/ parenteral nutrition increased with the increasing severity of delayed gastric emptying [14]. The use of drugs to improve GE could avoid the loss of appetite and body weight, which might result in raising the rate of accomplishing treatment and achieving a sustained virological response.

Conflict of Interest

O.Y. has received grant support from MSD Co., Ltd. and Chugai

Pharmaceutical Co., Ltd. The remaining authors have nothing to declare.

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