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 $^{13}$CO$_2$ excretion ($T_{max}$).

Results: The average food intake was 1,851 ± 91, 1,338 ± 537 and 1,453 ± 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 $T_{max}$ 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 $T_{max}$ values (minutes) (Pearson’s correlation test, $r = -0.49$, $p < 0.05$).

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

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?
is metabolized to $^{13}$CO$_2$, which is then expired via the lungs. Thus, measurement of $^{13}$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 13C-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 $^{13}$CO$_2$ excretion (Tmax) and the GE rate curve was determined from the pattern of the $^{13}$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 be calculated to evaluate the severity of symptoms. The GSRS can also evaluate the sub-scales, reflux symptom, abdominal pain, indigestion symptoms, diarrhea symptoms and constipation symptoms.

**Statistical Analysis**

All data values are expressed as the mean ± 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. |
|-----------------|-----------------|
| Age (years, average ± SD) | 54.1±8.4 |
| Gender (male/female) | 12 / 5 |
| Body Mass Index (kg/m², average ± SD) | 24.9±4.5 |
| HCV Genotype 1b | 17 |
| Viral load (Logcopies/ml, average ± SD) | 6.0±1.8 |
| Alanine aminotransferase (IU/L) | 82.7±59.1 |
| Number of Platelets (×10^3/μl) | 17.6±3.7 |
| Total Bilirubin (mg/dl) | 1.0±0.4 |
| Liver Cirrhosis (Yes / No) | 0 / 17 |
| SD, standard deviation. | |
The $^{13}$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>
<thead>
<tr>
<th>GSRS, SDS (average ± SD)</th>
<th>Before</th>
<th>After 1 week</th>
<th>After 2 weeks</th>
<th>Between Before and After 1 week†</th>
<th>Between Before and After 2 week†</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSRS</td>
<td>1.7 ± 0.6</td>
<td>1.8 ± 0.7</td>
<td>1.5 ± 0.7</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total</td>
<td>1.7 ± 0.6</td>
<td>1.8 ± 0.7</td>
<td>1.5 ± 0.7</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Reflux symptom</td>
<td>1.7 ± 0.8</td>
<td>1.8 ± 0.9</td>
<td>1.6 ± 0.9</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.7 ± 0.2</td>
<td>2.0 ± 0.9</td>
<td>1.6 ± 0.9</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Indigestion</td>
<td>1.7 ± 0.6</td>
<td>1.9 ± 1.0</td>
<td>1.6 ± 0.8</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.6 ± 0.7</td>
<td>1.6 ± 0.7</td>
<td>1.5 ± 0.8</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.6 ± 0.9</td>
<td>1.7 ± 0.8</td>
<td>1.5 ± 0.8</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>SDS</td>
<td>38.0 ± 6.9</td>
<td>39.8 ± 7.2</td>
<td>40.5 ± 5.5</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

†paired t-test.
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

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

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After 1 week</th>
<th>After 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyl ghrelin (fmol/ml, average ± SD)</td>
<td>7.0 ± 3.5</td>
<td>8.3 ± 3.6</td>
<td>7.2 ± 2.2</td>
</tr>
<tr>
<td>Desacyl ghrelin (fmol/ml, average ± SD)</td>
<td>50.5 ± 17.6</td>
<td>46.1 ± 15.9</td>
<td>46.6 ± 16.8</td>
</tr>
<tr>
<td>Leptin (ng/ml, average ± SD)</td>
<td>7.5 ± 3.3</td>
<td>7.0 ± 2.6</td>
<td>5.3 ± 2.4**</td>
</tr>
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</table>

**p <0.01, *p < 0.05, paired t-test, compared to the value before treatment; SD, standard deviation.**
Pharmaceutical Co., Ltd. The remaining authors have nothing to declare.

References


