Bacterial Infection as an Adverse Effect of Telaprevir-based Triple Therapy for Chronic Hepatitis C Infection

Akira Kawano¹, Eiichi Ogawa², Norihiro Furusyo², Makoto Nakamuta³, Eiji Kajiwara⁴, Kazufumi Dohmen⁵, Hideyuki Nomura⁵, Kazuhiro Takahashi⁶, Takeaki Satoh⁶, Koichi Azuma⁸, Yuichi Tanabe¹⁰, Shinji Shimoda¹¹, Kazuhiro Kotoh¹² and Jun Hayashi²; for The Kyushu University Liver Disease Study (KULDS) Group

Abstract

Objective There is little information regarding the incidence of bacterial infections as an adverse effect of telaprevir (TVR)-based triple therapy. This study was performed in order to evaluate the baseline and on-treatment predictors of bacterial infections in patients treated with TVR-based triple therapy.

Methods This multicenter study evaluated 430 patients with chronic hepatitis C who received 12 weeks of TVR in combination with 24 weeks of pegylated interferon α2b plus ribavirin. The occurrence of a bacterial infection during anti-viral treatment was defined as the onset of local or systemic inflammation as a result of pathogenic bacteria.

Results Bacterial infections occurred in 21 of the 430 (4.9%) patients during TVR-based triple therapy. Among these subjects, 71.4% (15 of 21) experienced bacterial infections during the initial eight weeks of treatment. Urinary tract infections were the most frequent infection, observed in 2.8% of cases (12 of 430). The rate of urinary tract infection among women (11 of 215, 5.1%) was significantly higher than that observed among men (1 of 215, 0.5%) (p<0.0001). According to a multivariable logistic regression analysis, the only significant independent predictor was the pretreatment serum albumin level (p=0.0008). Of the 21 patients who experienced bacterial infections, only one (4.8%) had to discontinue the treatment; however, the others were able to continue anti-viral treatment in combination with antibiotic treatment.

Conclusion Clinicians should be concerned regarding the incidence of bacterial infections among patients treated with TVR-based triple therapy, especially those with a low serum albumin level.

Key words: hepatitis C virus, telaprevir, adverse effect, bacterial infection

(DOI: 10.2169/internalmedicine.54.3457)

Introduction

Chronic hepatitis C virus (HCV) infection may result in serious health problems, including decompensated liver cirrhosis and hepatocellular carcinoma (1, 2). The goal of treatment for chronic hepatitis C is to achieve a sustained virological response (SVR), defined as undetectable HCV RNA in the serum 24 weeks after the end of treatment. SVR has been reported to be associated with a reduced incidence of hepatocellular carcinoma and hepatic decompensation as well as prolonged survival (2-4). In Japan, the majority of
patients are infected with HCV genotype 1. Treatment with a combination of pegylated interferon α (PegIFNα) plus ribavirin (RBV) for 48 weeks has been the first-line therapy for HCV for the past decade. However, the rate of a SVR is only approximately 50% among patients infected with HCV genotype 1 (5-8).

Telaprevir (TVR), a first-generation HCV non-structural 3/4A (NS3/4A) protease inhibitor, has been approved for the treatment of chronic hepatitis C genotype infection in Japan since 2011 (9). The SVR rate improved to over 70% for HCV genotype 1 patients following the introduction of TVR-based triple therapy, combined with PegIFNα and RBV (10-13). Notably, the SVR rate rises to over 80% among prior relapsers (14-17). However, many adverse effects have been reported during TVR-based triple therapy, including severe anemia and drug-induced skin disorders (13, 17, 18). Malaise, anorexia, increased serum creatinine and depression have also been reported (19). Nevertheless, there remain little data regarding the occurrence of bacterial infections during TVR-based triple therapy in clinical practice.

For this reason, we conducted a multicenter study to investigate the characteristics and baseline and on-treatment predictors of the incidence of bacterial infections in chronic hepatitis C patients treated with TVR-based triple therapy.

**Materials and Methods**

**Patients**

The current study evaluated 430 patients (age range: 22-75 years) for whom data were available at the end of treatment. The study population included 165 patients (38.4%) who were treatment-naïve, 165 (38.4%) with a history of prior relapse, 81 (18.8%) with a prior partial/null response and 19 (4.4%) with an unknown response. The exclusion criteria were as follows: (1) positivity for antibodies to human immunodeficiency virus or hepatitis B surface antigens; (2) clinical or biochemical evidence of hepatic decompensation (ascites, bleeding varices or encephalopathy); (3) other causes of liver disease (autoimmune hepatitis or primary biliary cirrhosis); (4) excessive active alcohol consumption (a daily intake of more than 40 g of ethanol) or drug abuse; (5) suspected hepatocellular carcinoma or active cancer at entry; (6) treatment with anti-viral or immunosuppressive agents prior to enrollment; (7) very poorly controlled heart disease, pulmonary disorders, diabetes or thyroid disease; (8) current or a history of depression, a history of suicide attempts; or (9) pregnancy in progress or planned during the study period for either partner. The study protocol was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the Ethics Committee of each participating hospital. Informed consent was obtained from all patients prior to enrollment.

**Clinical and laboratory assessments**

The clinical parameters were measured according to standard laboratory techniques at a commercial laboratory (SRL Laboratory, Tokyo, Japan). The body mass index was calculated as the patient’s weight in kilograms/height in square meters. The estimated glomerular filtration rate was calculated based on the Modification of Diet in Renal Disease formula.

**Assessment of liver fibrosis**

Liver biopsies were performed in 248 (57.7%) of the studied patients by experienced hepatologists. All anti-viral treatments were initiated within one month after the liver biopsy. The minimum length of the liver biopsy specimen was 15 mm, and at least 10 complete portal tracts were required for inclusion. For each specimen, the stage of fibrosis and grade of activity were established according to the METAVIR score (20).

**Determination of HCV markers**

Clinical follow-up of HCV viremia was conducted using real-time polymerase chain reaction (COBAS TaqMan HCV test v2.0, Roche Diagnostics, Tokyo, Japan), with a detectability level of ≥15 IU/mL and a linear dynamic range of 1.2-7.8 log IU/mL. The HCV RNA level was measured at baseline, regularly during treatment, at early discontinuation and at each follow-up visit after the end of treatment. The HCV genotype was determined according to a sequence analysis of the 5’non-structural region of the HCV genome followed by a phylogenetic analysis (21).

**Anti-viral treatment**

All patients received combination treatment consisting of TVR (Telavic, Mitsubishi Tanabe Pharma, Osaka, Japan), PegIFNα2b (Peg-Intron, MSD, Tokyo, Japan) and RBV (Rebetol, MSD) for 12 weeks, followed by an additional 12 weeks of PegIFNα2b and RBV alone. TVR was administered at a dose of 750 mg three times a day at an eight-hour interval after each meal. If marked anorexia, elevation of serum creatinine or severe anemia developed, the TVR dose was reduced. PegIFNα2b was injected subcutaneously once weekly at a dose of 1.5 μg/kg. RBV was given orally at a daily dose of 600-1,000 mg based on body weight (600 mg for patients weighing <60 kg, 800 mg for those weighing 60-80 kg and 1,000 mg for those weighing >80 kg).

**Diagnosis of bacterial infection**

The occurrence of bacterial infection during anti-viral treatment was defined as the onset of local or systemic inflammation as a result of pathogenic bacteria. Laboratory examinations and medical diagnostic imaging were performed in cases involving clinical symptoms, such as fever, during treatment. Antibiotics were administered after identifying the foci of infection. The decision to discontinue the TVR-based triple therapy due to bacterial infection was...
made primarily based on the discretion of the physicians at each hospital.

**Statistical analysis**

The statistical analyses were conducted using the SPSS statistics 19.0 software program (IBM SPSS, Chicago, USA). Continuous data are expressed as the median with the interquartile range, and categorical variables are reported as frequencies and percentages. Univariate analyses were performed with bacterial infection as the outcome. In order to identify independent factors predicting bacterial infection, variables with a p value of <0.05 in the univariate tests were used as candidate factors for the multivariable logistic regression analysis. The results are expressed as the odds ratio (OR) and 95% confidence interval (CI). A p value of less than 0.05 was considered to be statistically significant in all analyses.

**Results**

**Patient characteristics and incidence of bacterial infection**

The characteristics of the 430 studied patients are shown in Table 1. Bacterial infections occurred during the treatment period in 21 of the 430 (4.9%) patients. The bacterial infections observed in this study are listed in Table 2. Urinary tract infections were the most frequent bacterial infections, observed in 2.8% of the patients (12 of 430). Other bacterial infections observed during the treatment period were bacterial pneumonia (n=3), acute bacterial prostatitis (n=1), cellulitis (n=1), cholecystitis (n=1), infectious enterocolitis (n=1), liver abscesses (n=1) and otitis media (n=1). The rate of urinary tract infections among women (11 of 215, 5.1%) was significantly higher than that observed among men (1 of 215, 0.5%) (p<0.0001).

The percentage of patients experiencing on-treatment bacterial infections is shown in Figure. Bacterial infections occurred throughout the treatment period, although the onset of bacterial infections was most frequently observed from week 0 to 4, and 71.4% (15 of 21) of the patients who developed bacterial infections did so during the initial eight weeks of treatment.

**Pretreatment and on-treatment factors associated with the incidence of bacterial infections**

The univariate analysis extracted a low serum albumin level (p=0.001) and estimated glomerular filtration rate (p=0.033) as being significantly associated with the occurrence of bacterial infection (Table 3). In multivariable logistic regression analysis of possible pretreatment and on-treatment predictors of the incidence of bacterial infection, a signifi-

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients n=430</th>
<th>Male n=215</th>
<th>Female n=215</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>215 (50.0)</td>
<td>94 (43.8)</td>
<td>121 (56.4)</td>
<td>0.123</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61.0 (12.0)</td>
<td>61.5 (11.7)</td>
<td>60.7 (12.6)</td>
<td>0.739</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.3 (4.2)</td>
<td>23.5 (4.1)</td>
<td>23.1 (4.2)</td>
<td>0.255</td>
</tr>
<tr>
<td>Baseline HCV RNA level (log IU/mL)</td>
<td>6.5 (0.9)</td>
<td>6.5 (0.9)</td>
<td>6.5 (0.9)</td>
<td>0.552</td>
</tr>
<tr>
<td>White blood cell count (&gt;10⁹/L)</td>
<td>4.710 (2.100)</td>
<td>4.650 (2.000)</td>
<td>4.760 (2.150)</td>
<td>0.638</td>
</tr>
<tr>
<td>Neutrophil count (&gt;10⁶/L)</td>
<td>2,340 (1,273)</td>
<td>2,320 (1,270)</td>
<td>2,360 (1,280)</td>
<td>0.463</td>
</tr>
<tr>
<td>Hemoglobin level (g/L)</td>
<td>139 [20]</td>
<td>139 [20]</td>
<td>139 [20]</td>
<td>0.744</td>
</tr>
<tr>
<td>Platelet count (&gt;10⁶/L)</td>
<td>158 [72]</td>
<td>158 [72]</td>
<td>158 [72]</td>
<td>0.954</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>40 [6.0]</td>
<td>40 [6.0]</td>
<td>40 [6.0]</td>
<td>0.987</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>47 [40.8]</td>
<td>48 [41.2]</td>
<td>46 [40.4]</td>
<td>0.615</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>51 [55.8]</td>
<td>51 [55.8]</td>
<td>51 [55.8]</td>
<td>0.999</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (mL/min/1.73m²)</td>
<td>79.6 [20.3]</td>
<td>79.6 [20.3]</td>
<td>79.6 [20.3]</td>
<td>0.528</td>
</tr>
<tr>
<td>Categorical variables are reported as frequencies and percentages.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pretreatment factors</th>
<th>All n=430</th>
<th>Male n=215</th>
<th>Female n=215</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>67 (15.6)</td>
<td>33 (15.5)</td>
<td>34 (15.9)</td>
<td>0.816</td>
</tr>
<tr>
<td>History of splenectomy or partial splenic embolization, n (%)</td>
<td>26 (6.0)</td>
<td>13 (6.0)</td>
<td>13 (6.0)</td>
<td>0.882</td>
</tr>
<tr>
<td>Liver histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage, F0-2/F3-4, n</td>
<td>165/83</td>
<td>78/57</td>
<td>87/26</td>
<td>0.033</td>
</tr>
<tr>
<td>Grade, A0-1/A2-3, n</td>
<td>93/155</td>
<td>45/60</td>
<td>48/95</td>
<td>0.0001</td>
</tr>
<tr>
<td>Not determined, n</td>
<td>182</td>
<td>97</td>
<td>85</td>
<td>0.0001</td>
</tr>
<tr>
<td>On-treatment neutrophil count &lt;800 (&gt;10⁶/L), n (%)</td>
<td>69 (16.0)</td>
<td>36 (16.8)</td>
<td>33 (15.0)</td>
<td>0.769</td>
</tr>
<tr>
<td>Oral administration of corticosteroid, n (%)</td>
<td>120 (27.9)</td>
<td>60 (27.6)</td>
<td>60 (27.1)</td>
<td>0.883</td>
</tr>
<tr>
<td>Discontinuation of treatment, n (%)</td>
<td>53 (12.3)</td>
<td>26 (12.1)</td>
<td>27 (12.8)</td>
<td>0.846</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as median [interquartile range].

Categorical variables are reported as frequencies and percentages.

* p value draws a comparison between Male and Female patients.
The incidence of adverse effects of TVR-based triple therapy. The incidence of studies regarding the occurrence of bacterial infection as an ing PegIFN receiving TVR-based triple therapy than among those receiv- nal disorders, occur at a higher rate among the patients re-
verse effects, including hematological, skin and gastrointesti-
bilirubin and creatinine (12, 13, 15, 17-19, 22). Major ad-
rhea), general fatigue and elevated serum levels of uric acid, 
rashes), gastrointestinal disorders (nausea, anorexia and diar-
neutropenia), drug-induced skin disorders (pruritus and 
disorders (anemia, thrombocytopenia, leukocytopenia and 
incidence of bacterial infection is considered to be a rare ad-
verse effect. Arase et al. (23) reported that, in their study, 
only 2 of 612 (0.3%) Japanese patients who received 
PegIFNα2b and RBV alone developed bacterial infections 
(pneumonia), while Kuboki et al. (24) reported that none of 
99 Japanese patients receiving PegIFNα2a and RBV alone 
developed bacterial infections. Therefore, it is necessary to 
investigate the characteristics of bacterial infections as ad-
verse effects of TVR-based triple therapy.

According to the results of the present study, bacterial in-
fecions occurred during the treatment period in 21 of the 
430 (4.9%) patients. The reason for the higher than expected 
rate of bacterial infections is likely because this study in-
cluded both patients with and without premature discontinu-
ation. Urinary tract infections occurred in 2.8% (12 of 430 
patients) and constituted the most frequent bacterial infec-
sion. In addition, the rate of urinary tract infection was sig-
ificantly higher among women (11 of 215, 5.1%) than 
among men (1 of 215, 0.5%) (p<0.0001). A multivariable 
logistic regression analysis of pretreatment and on-treatment 
predictors of bacterial infections found a low serum albumin 
level to be the only independent predictor. It is thought that 
the low serum albumin levels seen in chronic hepatitis pa-
tients are associated with advanced liver fibrosis; however, 
in the present study, we found no such associations, as there 
were no significant differences in the platelet count or liver 
histology between the patients with bacterial infections and 
those without. Moreover, no significant differences were 
noted in the white blood cell count, neutrophil count, on-
treatment neutrophil count or frequency of a past history of

<table>
<thead>
<tr>
<th>Table 3. Pretreatment and On-Treatment Factors Associated with the Occurrence of Bacterial Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Features</strong></td>
</tr>
<tr>
<td>Sex (male to female)</td>
</tr>
<tr>
<td>Age (per 1 yr)</td>
</tr>
<tr>
<td>Body mass index (per l kg/m²)</td>
</tr>
<tr>
<td>Baseline HCV RNA (per 1 log IU/mL)</td>
</tr>
<tr>
<td>White blood cell count (per 1×10⁶/L)</td>
</tr>
<tr>
<td>Neutrophil count (per 1×10⁶/L)</td>
</tr>
<tr>
<td>Hemoglobin level (per 1g/L)</td>
</tr>
<tr>
<td>Platelet count (per 1×10⁹/L)</td>
</tr>
<tr>
<td>Serum albumin (per 1g/L)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (per 1 U/L)</td>
</tr>
<tr>
<td>Alanine aminotransferase (per 1 U/L)</td>
</tr>
<tr>
<td>γ-glutamyl-transpeptidase (per 1 U/L)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (mL/min/1.73m²)</td>
</tr>
<tr>
<td>History of splenectomy or partial splenic embolization</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Fibrosis stage (F3-4 to F0-2)</td>
</tr>
<tr>
<td>On treatment neutrophil count &lt;800 (×10⁶/L)</td>
</tr>
<tr>
<td>Oral administration of corticosteroid</td>
</tr>
</tbody>
</table>

HCV: hepatitis C virus

Discussion

This multicenter study was carried out in order to evalu-
ate the baseline and on-treatment predictors of bacterial in-
fecion in patients treated with TVR-based triple therapy. 
The availability of protease inhibitors has improved the treat-
ment outcomes of chronic hepatitis C by achieving higher 
rates of SVR. However, adverse events are experi-
enced by almost all patients. The most frequently reported 
adverse effects associated with TVR include hematological 
disorders (anemia, thrombocytopenia, leukocytopenia and 
neutropenia), drug-induced skin disorders (pruritus and 
rashes), gastrointestinal disorders (nausea, anorexia and diar-
rhea), general fatigue and elevated serum levels of uric acid, 
bilirubin and creatinine (12, 13, 15, 17-19, 22). Major ad-
verse effects, including hematological, skin and gastrointesti-
nal disorders, occur at a higher rate among the patients re-
ceiving TVR-based triple therapy than among those receiv-
ing PegIFNα2a and RBV alone (12, 13, 15). There are few 
udies regarding the occurrence of bacterial infection as an 
adverse effect of TVR-based triple therapy. The incidence of 
bacterial infections, such as cellulitis, pneumonia, bronchitis 
and sepsis, was recently reported to be less than 1% of pa-
tients treated with TVR-based triple therapy in some stud-
ies (12, 15). Among patients with chronic hepatitis C infec-
tion receiving treatment with PegIFNα and RBV alone, the 
icidence of bacterial infection is considered to be a rare ad-
verse effect. Arase et al. (23) reported that, in their study, 
only 2 of 612 (0.3%) Japanese patients who received 
PegIFNα2b and RBV alone developed bacterial infections 
(pneumonia), while Kuboki et al. (24) reported that none of 
99 Japanese patients receiving PegIFNα2a and RBV alone 
developed bacterial infections. Therefore, it is necessary to 
investigate the characteristics of bacterial infections as ad-
verse effects of TVR-based triple therapy.

Of the 21 patients, one (4.8%) had to discontinue the treat-
dment due to liver abscess formation. The other 20 pa-
tients were able to continue the anti-viral treatment in com-
bination with antibiotic treatment. The rate of discontinu-
amtion among the patients with bacterial infections was lower 
than that observed in those without bacterial infection (52 of 
409, 12.7%), although the difference was not significant (p= 
0.494).

Premature discontinuation of treatment due to bac-
terial infection

The most significant independent predictor was the serum albumin (OR, 
0.160; 95% CI, 0.055-0.469; p=0.0008).

According to the results of the present study, bacterial in-
fecions occurred during the treatment period in 21 of the 
430 (4.9%) patients. The reason for the higher than expected 
rate of bacterial infections is likely because this study in-
cluded both patients with and without premature discontinu-
tation. Urinary tract infections occurred in 2.8% (12 of 430 
patients) and constituted the most frequent bacterial infec-
tion. In addition, the rate of urinary tract infection was sig-
ificantly higher among women (11 of 215, 5.1%) than 
among men (1 of 215, 0.5%) (p<0.0001). A multivariable 
logistic regression analysis of pretreatment and on-treatment 
predictors of bacterial infections found a low serum albumin 
level to be the only independent predictor. It is thought that 
the low serum albumin levels seen in chronic hepatitis pa-
tients are associated with advanced liver fibrosis; however, 
in the present study, we found no such associations, as there 
were no significant differences in the platelet count or liver 
histology between the patients with bacterial infections and 
those without. Moreover, no significant differences were 
noted in the white blood cell count, neutrophil count, on-
treatment neutrophil count or frequency of a past history of
splenectomy/partial splenic embolization or the oral administration of corticosteroids between the groups. Because a low serum albumin level was identified to be the only predictor, it is very difficult to predict the incidence of bacterial infections during TVR-based triple therapy. Further studies are thus required to clarify the association between a low serum albumin level and the onset of bacterial infections during TVR-based triple therapy.

In this study, we showed that bacterial infections occurred throughout the treatment period, although 71.4% (15 of 21) of the patients who developed bacterial infections did so during the initial eight weeks of treatment. This result is useful for predicting the occurrence of bacterial infections. Furthermore, there were no significant differences in the rates of SVR or premature discontinuation between the patients with bacterial infections and those without in this study. Therefore, obtaining an early diagnosis of bacterial infections may help to reduce the risk of premature discontinuation and increase the rate of successful completion of treatment, thus optimizing the outcomes of HCV treatment.

The study has a number of limitations. First, we studied only Japanese patients infected with HCV. As is characteristic of Japanese chronic hepatitis C patients, the age of our patients was much higher than that seen in other ethnic groups (12, 15). Hence, our results may not be generalizable to patients in other ethnic groups. Second, our patients received only 24 weeks of therapy in total, which is not the same as that observed for the standard response-guided therapy used in other facilities, although it is the approved regimen of the Japanese Ministry of Health, Labour and Welfare. Third, our patients were under favorable baseline conditions and had no severe baseline comorbidities, such as cardiac, pulmonary, renal or hematological diseases. Hence, the ability to draw conclusions regarding infections associated with TVR-based triple therapy may be limited. Nevertheless, our findings provide significant information as this is the first study of bacterial infections as an adverse effect of TVR-based regimens. Because bacterial infections are adverse effects associated with TVR, a first-generation HCV protease inhibitor, clinicians should be cautious of this adverse effect when prescribing a second-generation HCV protease inhibitor.

In conclusion, clinicians should be concerned for the potential for bacterial infections in patients receiving TVR-based triple therapy, especially those with a low serum albumin level. Proper management and careful monitoring of symptoms of bacterial infection are needed in such cases, particularly during the first eight weeks of treatment.

The authors state that they have no Conflict of Interest (COI).

References

20. The French METAVIR Cooperative Study Group. Intraobserver

© 2015 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html