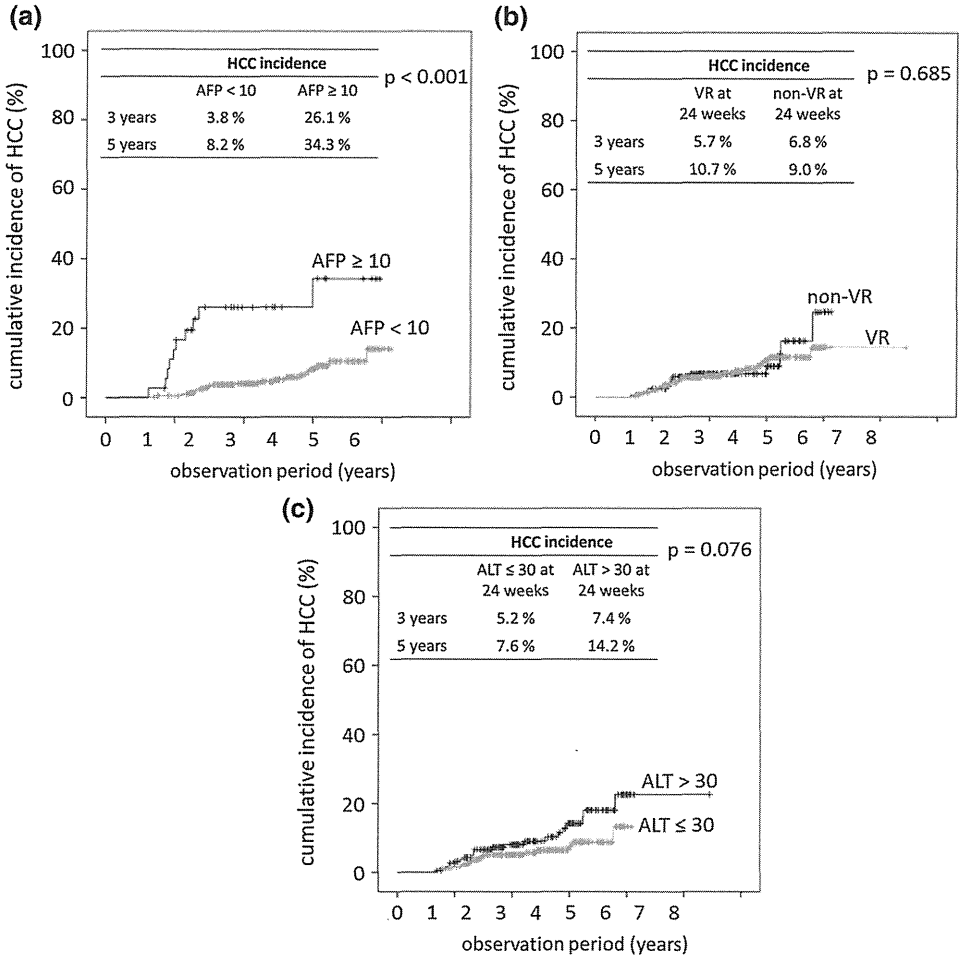

Fig. 3 Cumulative HCC incidence among patients with HBV infection according to factors at 24 weeks after ETV treatment initiation (log-rank test). Virological response (*VR*) is defined as HBV DNA of less than 2.6 log copies per milliliter. **a** Cumulative HCC incidence according to AFP levels at 24 weeks (*back line* AFP level of 10 ng/mL or greater at 24 weeks, *gray line* AFP level below 10 ng/mL at 24 weeks). **b** Cumulative HCC incidence according to virological response at 24 weeks (*black line* no VR at 24 weeks, *gray line* VR at 24 weeks). **c** Cumulative HCC incidence according to biochemical response at 24 weeks [*black line* alanine aminotransferase (*ALT*) level above 30 IU/L at 24 weeks, *gray line* ALT level of 30 IU/L or lower at 24 weeks]

course. However, low levels of serum HBV DNA achieved by ETV treatment do not always indicate low intracellular HBV cccDNA levels [21, 22]. Therefore, it is possible that an insufficient decrease of intracellular HBV DNA levels cannot bring the apparent HCC suppression in noncirrhotic liver with low malignant potential. A longer observation period is required to clarify the suppressive effect on HCC incidence among noncirrhotic patients. The relationship between HBV cccDNA levels in the liver and HCC incidence should also be examined.

In this study, in the analysis of the relationship between on-treatment factors and HCC incidence, only higher AFP levels (10 ng/mL or higher) at 24 weeks after the initiation of ETV treatment were found to be associated with HCC incidence. This is the first study to investigate the significance of AFP levels as a representative marker for the potential of HCC development among patients with chronic HBV infection undergoing ETV treatment. Originally, AFP was known as a tumor-associated antigen in HCC and as a target for immunotherapy. AFP has been used in the surveillance of HCC and in the evaluation of treatment response in HCC patients. The use of AFP as a marker to identify HCC among patients with HBV infection has previously been shown in patients with a natural course of the disease [23]. In recent reports that have focused on AFP levels for HCC diagnosis in patients undergoing ETV treatment, elevated AFP levels at 6 months before or at the time of HCC incidence were shown to be useful in detecting existing HCC [24, 25]; that is, elevated AFP levels implied the existence of cancer cells. However, the present study clarified that a high AFP level at 24 weeks did not suggest the existence of cancer cells, but indicates a potential for HCC incidence before the initiation of carcinogenesis. A possible reason is as follows. The AFP levels among patients who developed HCC decreased from 24 to 48 weeks after the initiation of ETV treatment and increased again from 24 weeks before HCC incidence to the time of HCC incidence. Furthermore, it took a considerably long time before HCC incidence, on average 32.6 months of the observation period (Fig. S1). With regard to the relationship between serum AFP levels and HCC incidence among HCV-infected patients, AFP levels at 24 weeks after the end of IFN treatment have been associated with HCC [26, 27]. AFP levels after the

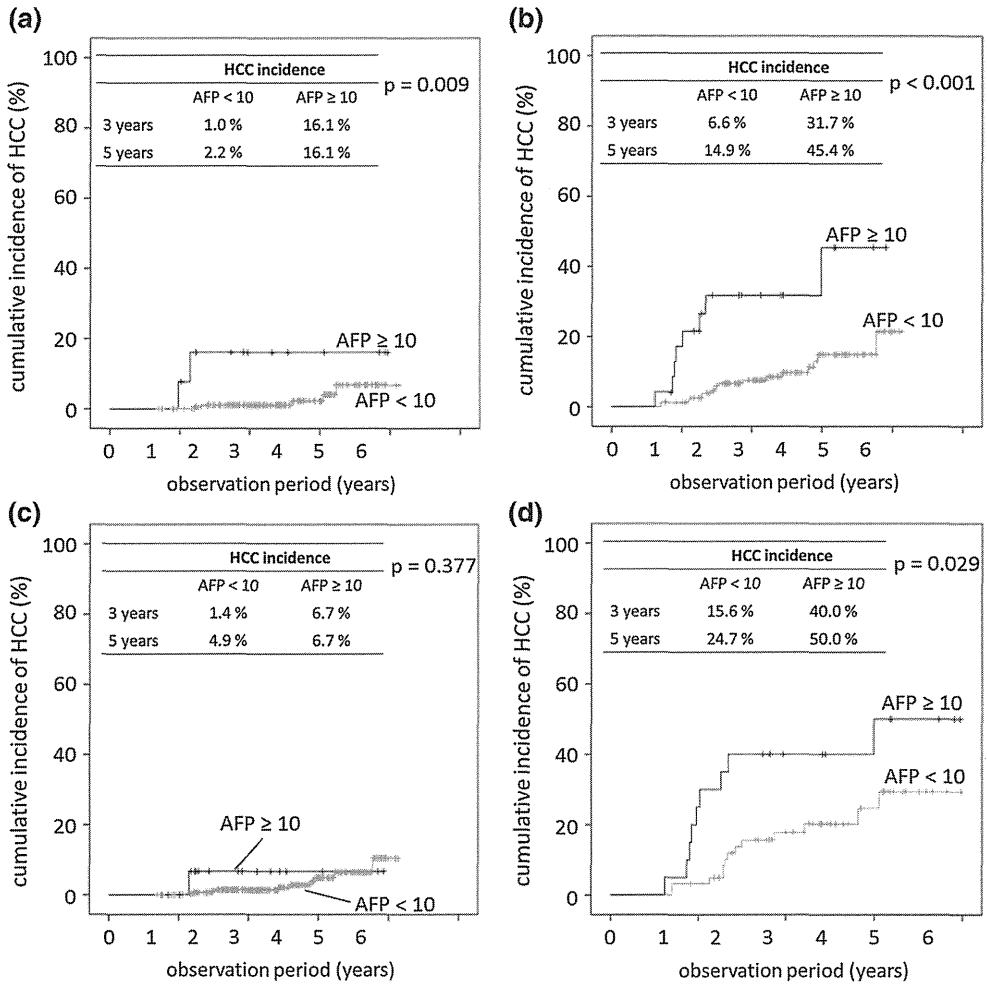

Fig. 4 Cumulative HCC incidence among patients with HBV infection according to AFP levels at 24 weeks after ETV treatment initiation, stratified with baseline factors (log-rank test). **a** Patients younger than 55 years. **b** Patients 55 years or older. **c** Patients without cirrhosis. **d** Patients with cirrhosis. *Black line* AFP level of 10 ng/mL or higher at 24 weeks, *gray line* AFP level below 10 ng/mL at 24 weeks

initiation of treatment of both HBV infection and HCV infection appear to have important implications for HCC incidence.

What the AFP levels at 24 weeks actually represent in patients undergoing ETV treatment is uncertain. The AFP level is a surrogate marker that appears to predict a disease condition from various pathological factors including inflammation, fibrosis, and liver regeneration, which involve carcinogenesis. Moreover, a previous study reported that the activation of natural killer cells by dendritic cells was inhibited when they were co-cultured with AFP; this result suggests an association between HCC development and the maintenance of high AFP levels [28]. Therefore, AFP is thought to be an important biomarker that can reflect various aspects of liver disease.

American Association for the Study of Liver Disease practice guidelines for the management of HBV have defined the goal of NA treatment as to decrease serum HBV DNA levels to undetectable levels to suppress HCC development. In this study, the HBV DNA levels and ALT levels were rapidly lowered in most patients. However, this study shows that the virological and biochemical treatment responses had no association with HCC development, whereas advanced age, liver cirrhosis, and a higher AFP level at 24 weeks after the initiation of ETV treatment were independent risk factors that were significantly associated with HCC development. It is considered that decreasing serum HBV DNA levels to undetectable levels is the necessary, but not sufficient condition to suppress HCC development. In fact, the HCC incidence rate even in patients undergoing ETV treatment who achieved virological response at 24 weeks with the three factors of age of 55 years or older, liver cirrhosis, and AFP level of 10 ng/mL or higher increased to as high as approximately 60 % at 5 years (Fig. S2). Accordingly, the undetectable HBV DNA level in patients with chronic HBV infection undergoing ETV treatment is in itself of little consequence and does not mean a riskless environment.

The limitation of this study is that analysis including other HCC-related factors, such as hepatitis B surface antigen levels, precore and core promotor mutations, and family history of HCC or alcohol consumption, was not

performed. Especially, further investigation is needed to clarify the relationship between the change in hepatitis B surface antigen levels during treatment and HCC incidence in patients with HBV infection.

In conclusion, in the consecutive surveillance for HCC after the initiation of ETV treatment, monitoring the change in AFP levels at 24 weeks is essential, especially among patients of advanced age or with cirrhosis.

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The real impact of telaprevir dosage on the antiviral and side effects of telaprevir, pegylated interferon and ribavirin therapy for chronic hepatitis C patients with HCV genotype 1

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SUMMARY. Triple therapy with telaprevir, pegylated interferon and ribavirin has been reported to improve antiviral efficacy but have potentially severe adverse effects in patients with chronic hepatitis C. To avoid the severe effects of telaprevir, lowering the dose has been suggested. However, impact of dosage changes on antiviral and adverse effects remains unclear. One hundred and sixty-six Japanese patients with HCV genotype 1 were treated with triple therapy. The drug exposure of each medication was calculated by averaging the dose actually taken. The overall SVR rate was 82%. The telaprevir discontinuation rate was 26%. The factors associated with discontinuation were an older age (≥65 y.o.) and a higher average dose during treatment. The telaprevir discontinuation rates were 42%, 25% and 14% in patients at ≥35, 25–35 and <25 mg/kg/day of telaprevir and 58% in older patients at ≥35 mg/kg/day of TVR. The factors associated with SVR were treatment-naïve, relapse to previous treatment, higher average telaprevir dose during treatment and completion of treatment. The SVR rate was higher, at 91%, in patients at 25–35 mg/kg/day of telaprevir than the 71% and 78% observed in those at <25 and ≥35 mg/kg/day of drug. In Japanese patients, a mean telaprevir dose of 25–35 mg/kg/day during treatment can augment its efficacy in triple therapy for patients with HCV genotype 1.

Keywords: chronic hepatitis C, discontinuation rate, drug adherence, older patients, telaprevir with pegylated interferon and ribavirin.

INTRODUCTION

Antiviral therapy for patients with chronic hepatitis C virus (HCV) genotype 1 infection has changed from interferon (IFN) monotherapy to dual therapy with pegylated interferon (Peg-IFN) and ribavirin (RBV) and even triple therapy with protease inhibitor (PI), Peg-IFN and RBV [1]. Although clinical trials of triple therapy with telaprevir (TVR), which is a first-generation PI, Peg-IFN and RBV have reported that the addition of TVR leads to a substantial improvement in sustained virologic response (SVR) [2–9], adverse effects caused by TVR, such as the rapid progression of anaemia, severe rash and renal dysfunction, have also been reported [2,3,8–11]. Patients with a high risk of hepatocellular carcinoma (HCC), such as older patients and patients with advanced liver fibrosis, should be treated with antiviral therapy as early as possible to eliminate HCV.

A 2250 mg/day fixed-dose regimen was selected for TVR worldwide [12,13], although the safety was inferior in Japan compared with Europe and the United States

Abbreviations: c-EVR, complete early virologic response; CH-C, chronic hepatitis C; EOT, end of treatment; ETR, end of treatment response; Hb, haemoglobin; HCV, hepatitis C virus; IFN, interferon; Peg-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; RVR, rapid virologic response; SMV, simeprevir; SVR, sustained virologic response; TVR, telaprevir; WBC, white blood cell.

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(discontinuation rate of all drugs, 17% *vs* 7–10%; discontinuation of only TVR, 19% *vs* 7–12%) in a phase-3 study of triple therapy with TVR, Peg-IFN and RBV [5–9]. In particular, severe adverse events such as rash and anaemia were more frequent in Japan compared with Europe and the United States (rash, 12% *vs* <1%; anaemia, 11% *vs* 2%). Higher adverse events with triple therapy in Japanese patients may result from an excessive dose of TVR due to reduced body weight compared with Westerners. An initial dose reduction of TVR was therefore recommended in Japanese patients, especially for older patients, and we have reported similar SVR rates among two groups with the introduction of TVR at 1500 and 2250 mg [14]. However, the real impact of low-dose TVR on antiviral efficacy and adverse effects remains unknown. The optimum dosage of TVR should be examined for older patients in Japan because Japanese patients infected with HCV tend to be 10–20 years older than those in the United States and European countries.

In this study, we examined the antiviral efficacy and adverse effects with a focus on TVR dosage in Japanese patients with HCV genotype 1 treated with TVR, Peg-IFN and RBV.

PATIENTS AND METHODS

Patients

The current study was a retrospective, multicentre study conducted by Osaka University Hospital and other institutions participating in the Osaka Liver Forum. A total of 202 patients with chronic hepatitis C (CH-C) treated with TVR, Peg-IFN and RBV combination therapy between December 2011 and December 2012 were enrolled in this study.

Eligible patients were those who were 20 years of age and older, had chronic HCV genotype 1b infection with a viral load of more than 10^5 IU/mL and did not have co-infection with hepatitis B virus (HBV) or anti-human immunodeficiency virus (HIV). The patients were excluded if they had decompensated cirrhosis, HCC or other forms of liver disease (alcohol liver disease, autoimmune hepatitis), a history of splenectomy or partial spleen embolization (PSE), chronic renal failure, depression or immunodeficiency. Patients using erythropoietin were also excluded. After enrolment, 42 patients (co-infection with HBV, $n = 3$; co-infection with HIV, $n = 2$; splenectomy, $n = 5$; PSE, $n = 2$) were excluded, and a total of 166 CH-C patients were assessed. This study was conducted according to the ethics guidelines of the 1975 Declaration of Helsinki amended in 2002 and approved by the ethics commission of Osaka University Hospital and independent or institutional review boards of all study centres. All patients provided written informed consent before participating in the study.

Study design

All patients received TVR (TELAVIC; Mitsubishi Tanabe Pharma, Osaka, Japan) with Peg-IFN alfa-2b (PEGINTRON; MSD, Tokyo, Japan) and RBV (REBETOL; MSD). TVR was administered orally at a dose of 500 or 750 mg every 8 h after food. Peg-IFN alfa-2b was administered subcutaneously once a week at a dose of 60–150 μg/kg based on body weight (body weight 35–45 kg, 60 μg; 46–60 kg, 80 μg; 61–75 kg, 100 μg; 76–90 kg, 120 μg; 91–120 kg, 150 μg). RBV was administered orally twice a day at a total dose of 600–1000 mg/day based on body weight (body weight <60 kg, 600 mg; 60–80 kg, 800 mg; >80 kg, 1000 mg), according to a standard treatment protocol for Japanese patients. In principle, the patients were treated with TVR, Peg-IFN and RBV for 12 weeks, followed by Peg-IFN and RBV for 12 weeks. If a patient had detectable HCV RNA at 12 weeks or any time during weeks 13 through 20, that patient was not permitted to complete the remainder of the assigned duration of therapy.

Dose modification

Dose modification followed, as a rule, the manufacturer's drug information in Japan. The initial dose of RBV was reduced by 200 mg per day in case of the Hb level <13 g/dL at baseline. The dose of Peg-IFN alfa-2b was reduced to 50% of the assigned dose if the white blood cell (WBC) count declined to $<1500/mm^3$, the neutrophil count to $<750/mm^3$ or the platelet count to $<8 \times 10^4/mm^3$. RBV was also reduced from 1000 to 600 mg or 800 to 600 mg or 600 to 400 mg if the Hb level decreased to <12 g/dL and was reduced by an additional 200 mg per day when the Hb level was <10 g/dL. The dose of RBV was also reduced by 200 mg per day if the Hb level dropped by more than 1 g/dL within a week, and this level was <13 g/dL. TVR, Peg-IFN alfa-2b and RBV were withdrawn or interrupted if the WBC count declined to $<1000/mm^3$, the neutrophil count to $<500/mm^3$ or the platelet count to $<5 \times 10^4/mm^3$ or the Hb level decreased to <8.5 g/dL. TVR was reduced according to adverse events related to TVR by the physician's decision. The use of erythropoietin was not allowed for increasing the Hb level. In case of drug interruption of TVR or Peg-IFN and RBV, resumption of treatment was allowed if the peripheral blood findings or adverse events were reversed.

Histological evaluation

Pretreatment liver biopsies were conducted within 6 months of the start of combination therapy. Histopathological interpretation of the specimens was performed by experienced liver pathologists who had no clinical, biochemical or virologic information of the patients. The

histological appearance, activity and fibrosis were evaluated according to the METAVIR histological score [15].

Virologic assessment and definition of viral response

The serum HCV RNA level was quantified with the COBAS Taqman HCV test, version 2.0 (detection range 1.2–7.8 log IU/mL; Roche Diagnostics, Branchburg, NJ, USA) and was assessed before treatment, every 4 weeks during treatment and 24 weeks after therapy. A rapid virologic response (RVR) was defined as undetectable serum HCV RNA at week 4, a complete early virologic response (c-EVR) as undetectable serum HCV RNA at week 12 and an EOT response (ETR) as undetectable serum HCV RNA at the end of treatment (EOT). SVR was defined as an undetectable serum HCV RNA level at 24 weeks after EOT. Relapse was defined as an undetectable serum HCV RNA level at EOT but a detectable amount after EOT. Nonresponse was defined as a detectable HCV RNA level during therapy. Breakthrough was defined as quantifiable HCV RNA after undetectable HCV RNA during therapy.

Safety assessment

Chemical and haematologic assessments and safety assessment were performed every week during the start to first 12 weeks of treatment and every 4 weeks from week 12–24 of treatment. At each visit, data on adverse events were collected, and physical examinations were performed if clinically indicated.

Assessment of drug exposure

The amounts of TVR, Peg-IFN alfa-2b and RBV actually taken by each patient during treatment were evaluated by reviewing the medical records. The mean doses of each drug were calculated individually as averages based on body weight at baseline: TVR was expressed as mg/kg/day, Peg-IFN alfa-2b was expressed as μg/kg/week, and RBV was expressed as mg/kg/day.

Statistical analysis

Baseline continuous variables were expressed as the means ± standard deviation or median and categorical variables as frequencies. The virologic response was evaluated in an intention-to-treat (ITT) set. Differences between the two groups were assessed by a chi-square test or a Mann–Whitney *U*-test in univariate analyses. The factors selected as significant by the univariate analysis were evaluated by multivariate logistic regression analyses. The cumulative discontinuation of the drug was assessed by the Kaplan–Meier method and the log-rank test. A *P*-value <0.05 was considered significant. The statistical analysis was conducted using SPSS, version 19.0J (IBM, Armonk, NY, USA).

RESULTS

Progress of patients treated with TVR, Peg-IFN a-2b and RBV

The baseline characteristics of the patients are summarized in Table 1. There were 59 treatment-naïve patients and 73 and 29 relapsers and nonresponders to previous Peg-IFN with RBV treatment. Of the 166 patients, 119 completed the 12 weeks of TVR and 24 weeks of Peg-IFN and RBV, 42 discontinued TVR, and 22 discontinued Peg-IFN and RBV. Among the patients who discontinued TVR or Peg-IFN and RBV, 17 discontinued all drugs before treatment week 12.

Virologic response

Five patients (four patients discontinued TVR, one patient discontinued all drugs) were lost during follow-up and were excluded for the analysis of SVR. The RVR, cEVR, ETR and SVR rates were 82% (122/149), 96% (154/160), 93% (150/162) and 82% (132/161). The SVR rate was 85% (101/119) among the patients who completed the entire treatment schedule, 70% (26/37) among those who discontinued TVR, 57% (12/21) among those who discontinued Peg-IFN and RBV and 44% (7/16) among those who discontinued all drugs before treatment week 12.

Table 1 Baseline characteristics of patients

Factor	
Number	166
Age (y.o.)	60.3 ± 8.8
Gender: male/female	85/81
Past history of IFN*: naïve/relapse/nonresponse	59/73/29
HCV RNA (median, log IU/mL)	6.7
Liver histology†, ‡:	
Activity: A0/1/2/3	1/63/25/0
Fibrosis: F0/1/2/3/4	7/41/20/17/4
White blood cell (/μL)	4808 ± 1306
Haemoglobin (g/dL)	14.2 ± 1.4
Platelets ($\times 10^4$/μL)	16.4 ± 5.1
ALT (IU/L)	57 ± 55
IL28B SNP(rs8099917)§: TT/TG/GG	56/19/1
TVR dose at stat (mg/kg/day): 2250 mg/1500 mg	31.6 ± 7.9, 83/83
Peg-IFN dose at start (μg/kg/week)	1.48 ± 0.16
RBV dose at start (mg/kg/day)	11.3 ± 1.7

*Five patients missing.
†METAVIR.
‡77 patients missing.
§90 patients missing.

Discontinuation of treatment by adverse events

The discontinuance rate of all drugs was 11% (18/166), and the discontinuance rate of TVR was 26% (43/166). The discontinuance rates and the reasons for all drugs and TVR according to age are shown in Table 2. The discontinuance rate of TVR was significantly higher in patients ≥65 y.o. than that in those <65 y.o. ($P = 0.015$).

Factors associated with TVR discontinuance

The factors associated with TVR discontinuance were assessed among demographic, haematological, biochemical and virologic factors and drug adherence by a univariate analysis (Table 3A). Next, the factors selected as significant by the univariate analysis were evaluated by a multivariate analysis (Table 3B), and older age (≥65 y.o.) and higher TVR dose during treatment (≥35 mg/kg/day) were extracted as the factors associated with the discontinuance of TVR. Figure 1 shows the cumulative discontinuance of TVR according to age and TVR dose. The cumulative discontinuance rates were significantly higher in patients at ≥35 mg/kg/day of TVR than in those at <25 mg/kg/day of TVR among the patients <65 y.o. (Fig. 1a) and ≥65 y.o. (Fig. 1b). The cumulative discontinuance rate of TVR was highest in patients ≥65 y.o. at ≥35 mg/kg/day of TVR (58%). Among this group, 25% of the patients discontinued TVR during treatment week 1.

Factors associated with SVR

In a per protocol (PP) analysis including the patients who completed the entire treatment schedule, the SVR rate was very high in the patients at ≥25 mg/kg/day of TVR (25–35 mg/kg/day of TVR, 93%; ≥35 mg/kg/day of TVR, 95%) compared with 67% in those at <25 mg/kg/day (Fig. 2a). However, in an ITT analysis including the patients who discontinued any drugs as well as those who completed the entire treatment schedule, the SVR rate was higher at 91% in the patients at 25–35 mg/kg/day of TVR compared with 78% in those at ≥35 mg/kg/day and 71% in those at <25 mg/kg/day (Fig. 2b). According to previous IFN treatment response and TVR dose, the highest SVR rates (ITT analysis) were obtained at a dose of 25–35 mg/kg/day of TVR among naïve patients and prior relapsers; the SVR rate at ≥35 mg/kg/day of TVR was not less than that at 25–35 mg/kg/day among the nonresponders (80% *vs* 73%) (Fig. 2c).

The factors associated with SVR were assessed among demographic, haematological, biochemical and virologic factors, drug adherence and treatment discontinuance by a univariate analysis (Table 4A). Next, the factors selected as significant by the univariate analysis were evaluated by a multivariate analysis (Table 4B). The favourable factors associated with SVR were treatment-naïve, relapse to previous treatment, TVR dose during treatment (25–35 mg/kg/day) and completion of treatment.

DISCUSSION

Baseline factors such as the virologic response to previous IFN therapy, the degree of liver fibrosis progression and genetic polymorphism near the IL28B gene have been reported to be associated with SVR in triple therapy with TVR, Peg-IFN and RBV [7,16,17]. The setting of an optimum dosage of TVR that can increase the antiviral effect and decrease adverse effects is necessary because such baseline factors do not change. Regarding the TVR dosage, a phase 1b, placebo-controlled, double-blinded study conducted in Europe indicated that HCV RNA reduction was greatest at 750 mg of TVR every 8 h than at 450 mg of TVR every 8 h or 1250 mg of TVR every 12 h; as a result,

Table 2 Adverse events leading to drug discontinuation

	All drug discontinuation		TVR discontinuation	
Factor	Age <65 y.o.	Age ≥65 y.o.	Age <65 y.o.	Age ≥65 y.o.
Rash	4	4	7	8
Anaemia	2	1	8	5
Gastrointestinal disorder	1	1	3	5
Fatigue	1	1	2	1
Hyperbilirubinaemia		1		2
Thrombopenia	1		1	
Renal dysfunction			1	
Unknown		1		
Discontinuance rate	8% (9/110)	16%* (9/56)	20% (22/110)	38%† (21/56)

*$P = 0.12$, Age <65 y.o. Age ≥65 y.o.
†$P = 0.015$, Age <65 y.o. Age ≥65 y.o.

Table 3 Factors associated with TVR discontinuation

A. Univariate analysis

Factor	No (n = 123)	Yes (n = 43)	P-value
Age (y.o)	59.1 ± 9.2	63.9 ± 5.9	0.002
Gender: male/female	67/56	18/25	0.15
Past history of IFN: naïve/relapse/nonresponse	44/52/24	15/21/5	0.48
HCV RNA (median, log IU/mL)	6.65	6.7	0.48
Liver histology: Activity: A0-1/2-3	45/21	19/4	0.28
Fibrosis: F0-2/3-4	49/17	19/4	0.57
White blood cell (/μL)	4928 ± 1357	4469 ± 1093	0.07
Haemoglobin (g/dL)	14.2 ± 1.4	14.0 ± 1.2	0.10
Platelets ($\times 10^4$/μL)	16.5 ± 5.3	16.2 ± 4.6	0.91
ALT (IU/L)	54 ± 38	64 ± 86	0.94
TVR dose (mg/kg/day): <25/25–35/35≤	42/59/22	7/20/16	0.013
Peg-IFN dose (μg/kg/week): <1.2/1.2–1.5/1.5≤	26/61/36	7/14/21	0.049
RBV dose (mg/kg/day): <6/6–10/10≤	35/59/29	12/21/9	0.96

B. Multivariate analysis

Factor	Category	Odds ratio	95% CI	P-value
Age	0: <65 y.o			
	1: ≥65 y.o.	2.266	1.062–4.835	0.034
TVR dose	0: <25 mg/kg/day			
	1: 25–35 mg/kg/day	2.062	0.778–5.469	0.146
	2: ≥35 mg/kg/day	3.877	1.323–11.362	0.014
Peg-IFN dose	0: <1.2 μg/kg/week			
	1: 1.2–1.5 μg/kg/week	0.792	0.275–2.279	0.666
	2: ≥1.5 μg/kg/week	1.701	0.598–4.839	0.319

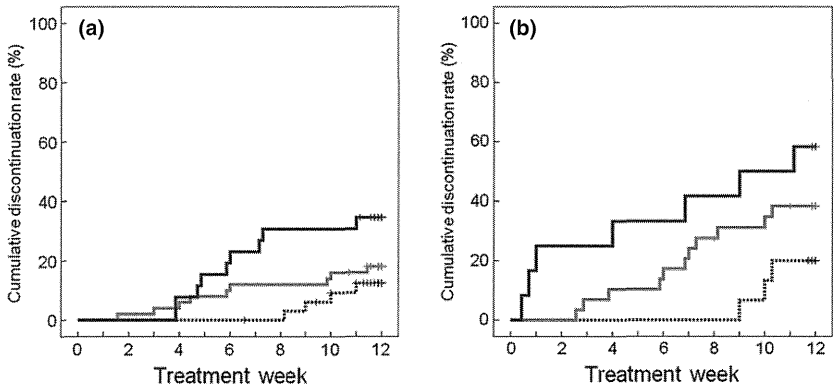

Fig. 1 The cumulative discontinuance rate of TVR according to the mean TVR dose. (**a**) age <65 y.o. (**b**) age ≥65 y.o. Dashed line, mean TVR dose <25 mg/kg/day. Grey line, mean TVR dose of 25–35 mg/kg/day. Black line, mean TVR dose ≥35 mg/kg/day. P = 0.025, mean TVR dose ≥35 mg/kg/day *vs* mean TVR dose <25 mg/kg/day among patients <65 y.o. P = 0.023, mean TVR dose ≥35 mg/kg/day *vs* mean TVR dose <25 mg/kg/day among patients ≥65 y.o.

the regimen of 750 mg of TVR every 8 h (total 2250 mg/day) was selected [12]. However, HCV RNA was reduced similarly with TVR at 500 or 750 mg every 8 h in a phase 1, open-label, two-arm study of TVR with Peg-IFN alfa-2b and RBV conducted in Japan using 20 patients with CH-C [13]. Recently, in Japanese CH-C patients limited with IL28B rs8099917 TT or relapse to previous IFN therapy, a similar antiviral effect was reported at 750 mg TVR every 8 or 12 h with Peg-IFN alfa-2b and RBV [18]. Furthermore, in a prospective study, we have reported that similar antiviral efficacies and fewer treatment-related adverse effects were obtained with initial TVR at 500 mg every

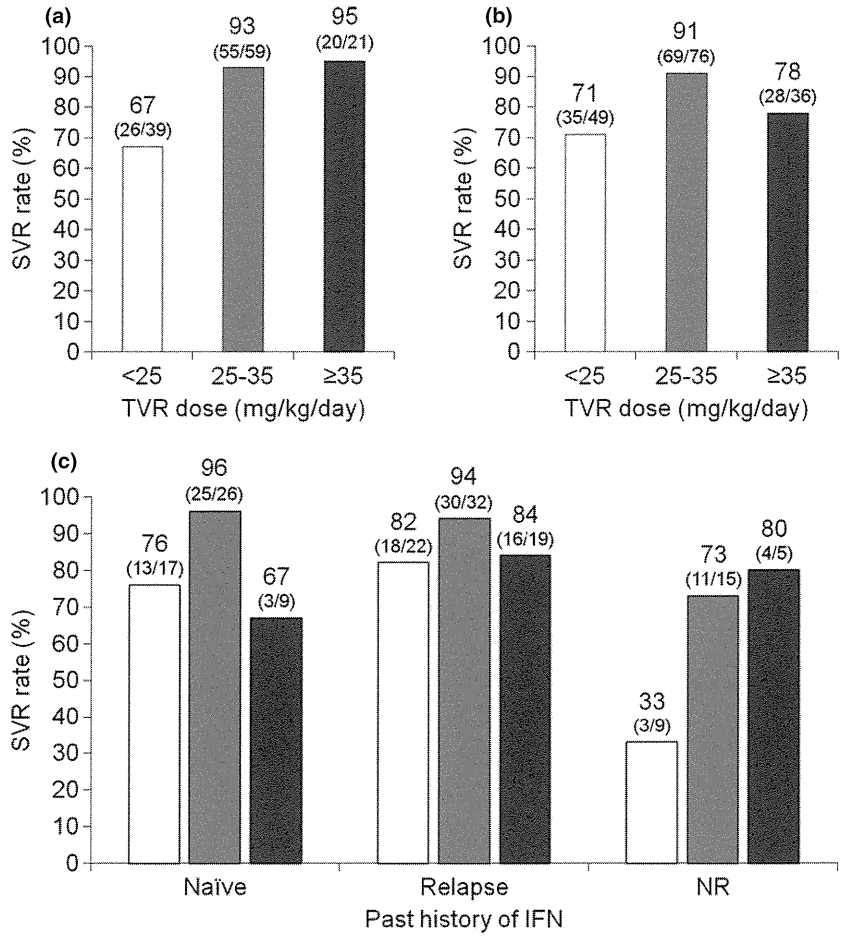

Fig. 2 The SVR rate according to the mean TVR dose. (**a**) Per protocol analysis. (**b**) Intention-to-treat analysis. (**c**) According to past history of IFN in intention-to-treat analysis. White bar, mean TVR dose <25 mg/kg/day. Grey bar, mean TVR dose of 25–35 mg/kg/day. Black bar, mean TVR dose ≥35 mg/kg/day.

8 h compared with initial 750 mg every 8 h with Peg-IFN alfa-2b and RBV. However, these reports have not shown how the dosage of TVR increases or decreases the antiviral effect and adverse effects in patients treated with TVR, Peg-IFN and RBV [14]. The usual dose for individuals originally differed on the basis of body weight, with an initial TVR dosage ranging from 22.5 to 45 mg/kg/day at 2250 mg/day and 15 to 30 mg/kg/day at 1500 mg/day among patients weighing 50–100 kg. In the present study, we examined the antiviral effect and prevalence of side effects with a focus on a weight-based TVR dosage.

The SVR rate was significantly higher, at 85%, in patients who completed the entire treatment schedule of all three drugs than the 70% found for those who discontinued TVR. Because the discontinuance rate of TVR was high at 25%, avoiding the discontinuance of TVR and completing treatment have the potential to increase the SVR rate. As a result of a multivariate analysis for TVR discontinuation, the factors of age and TVR dose were found to be significantly associated. Although it has been reported that there is no difference in the TVR discontinuance rate between patients <60 y.o. and those ≥60 y.o. [17], the TVR discontinuance rates in this study were significantly higher with advanced age (<60 y.o., 14%, 8/56; 60–64 y.o., 26%, 14/54; ≥65 y.o., 38%, 21/56, $P = 0.02$). Because the haematopoietic capacity and renal function are generally low in older patients, TVR tolerability can be poor. Moreover, the discontinuance of TVR occurred dose dependently, regardless of age. Remarkably, 58% of the patients ≥65 y.o. at ≥35 mg/kg/day of TVR discontinued TVR treatment. Therefore, older patients should be treated with caution to prevent the administration of a higher dose of TVR (≥35 mg/kg/day) to avoid its discontinuation. In contrast, even in the patients ≥65 y.o., none discontinued TVR before treatment week 8 if given <25 mg/kg/day.

The SVR reflects the result that increases according to the antiviral effect of the drug and is countered by the discontinuation of the drug. To examine the real impact of TVR dosage on antiviral effect, a PP analysis among the patients who completed the entire treatment schedule was

Table 4 The factors associated with SVR

A. Univariate analysis

Factor	SVR (n = 132)	Non-SVR (n = 29)	P-value
Age (y.o)	60.0 ± 9.1	61.3 ± 7.0	0.90
Gender: male/female	72/60	10/19	0.05
Past history of IFN: naïve/relapse/nonresponse	46/64/18	9/9/11	0.01
HCV RNA (median, log IU/mL)	6.7	6.5	0.35
Liver histology: Activity: A0-1/2-3	53/17	9/7	0.12
Fibrosis: F0-2/3-4	55/15	10/6	0.18
White blood cell (/μL)	4869 ± 1409	4467 ± 725	0.15
Haemoglobin (g/dL)	14.2 ± 1.4	13.9 ± 1.3	0.30
Platelets ($\times 10^4$/μL)	16.8 ± 5.1	14.5 ± 4.9	0.01
ALT (IU/L)	54 ± 57	73 ± 44	0.002
IL28B SNP(rs8099917): TT/non-TT	45/14	10/6	0.27
TVR dose (mg/kg/day): <25/25–35/35≤	35/69/28	14/7/8	0.02
Peg-IFN dose (μg/kg/week): <1.2/1.2–1.5/1.5≤	25/63/44	7/9/12	0.32
RBV dose (mg/kg/day): <6/6–10/10≤	40/62/30	5/15/8	0.40
TVR discontinuation: no/yes	105/27	18/11	0.045
PEG/RBV discontinuation: no/yes	120/12	20/9	0.001
RVR: yes/no	105/15	16/12	<0.001

B. Multivariate analysis

Factor	Category	Odds ratio	95% CI	P-value
Past history of IFN	0: Naïve			
	1: Relapse	1.183	0.320–4.371	0.801
	2: NR	0.185	0.048–0.702	0.013
Platelets	By 1 × 10^4 /μL	1.087	0.962–1.228	0.180
ALT	By 1 IU/L	0.995	0.988–1.002	0.133
TVR dose	0: <25 mg/kg/day			
	1: 25–35 mg/kg/day	4.537	1.348–15.266	0.015
	2: ≥35 mg/kg/day	2.602	0.651–10.398	0.176
TVR discontinuation	0: no			
	1: yes	0.563	0.148–2.143	0.399
PEG/RBV discontinuation	0: no			
	1: yes	0.154	0.034–0.703	0.016
RVR	0: RVR			
	1: Non-RVR	0.442	0.129–1.514	0.194

performed. In the PP analysis, TVR was dose dependently correlated with SVR, and the SVR rate was higher in patients at ≥25 mg/kg/day of TVR than that in those at <25 mg/kg/day. In addition, TVR was also dose dependently correlated with the discontinuance of TVR, and the discontinuance rate of TVR was lower in patients at <25 mg/kg/day of TVR and higher in patients at ≥35 mg/kg/day. As a result, according to an ITT analysis, among the patients at <25 mg/kg/day of TVR, the discontinuance rate of TVR decreased, but the SVR rate also decreased due to a poor antiviral effect; among the patients at ≥35 mg/kg/day of TVR, the SVR rate decreased because the discontinuance rate of TVR increased. Finally, based on the ITT analysis, the highest SVR rate was obtained in the patients at 25–35 mg/kg/day of TVR. Therefore, a TVR dose of 25–35 mg/kg/day can be optimal. As for the results of the multivariate analysis for SVR in the ITT analysis for all patients including those who discontinued any drugs as well as those who completed the entire treatment schedule, the factors of treatment-naïve, relapse to previous treatment, TVR dose during treatment and completion of treatment were found to be the significant factors. Regarding the response to previous treatment and TVR dose during treatment, similar results that the highest SVR rate was obtained in patients at 25–35 mg/kg/day of TVR in the ITT analysis were obtained in the naïve patients and relapsers. However, because the patient group with nonresponse to previous Peg-IFN and RBV was too small to

examine the relationship between the SVR rate and TVR dose, there was no significant difference between the SVR rate and TVR dose. However, the SVR rate among patients with nonresponse to previous Peg-IFN and RBV was insufficient in triple therapy with simeprevir (SMV), a second-generation PI, Peg-IFN and RBV; the SVR rates were calculated to be 51.7% (46/89) from a phase-2 study of triple therapy with SMV, Peg-IFN and RBV [19]. Moreover, because SMV is one tablet (100 mg of 150 mg), dose adjustment is impossible. In contrast, TVR doses are adaptable, and higher doses of TVR might have the potential to increase SVR in nonresponse patients. Further analysis using a larger cohort is needed to clarify the optimal dose of TVR in patients with nonresponse.

In conclusion, in Japanese patients, the administration of 25–35 mg/kg/day of TVR can result in the highest SVR rate in TVR, Peg-IFN and RBV triple therapy. Although it is important to avoid adverse effects by reducing TVR dosage and to complete treatment, when TVR is reduced, special attention is needed not to reduce it to <25 mg/kg/day. These data have important implications for clinicians treating Japanese patients – whether similar dosing changes are appropriate for light weight elderly patients from other countries remains to be determined.

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CONFLICT OF INTEREST

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Anaplastic lymphoma kinase-negative anaplastic large cell lymphoma with colon involvement

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CASE PRESENTION

A 65-year-old man was referred to the authors' hospital for examination of a painful hard mass in the left buttock. Magnetic resonance imaging revealed a mass in the left ilium, and ^{18}F-fluoro-2-deoxy-glucose positron emission tomography/computed tomography revealed uptake in the left ilium and ascending colon. Colonoscopy revealed a reddish ulcerative lesion with protrusions in the ascending colon (Figure 1A). Endoscopy with dual-focus narrow-band imaging revealed dilated, tortuous microvessels and avascular areas in the protrusions (Figure 1B). Histopathological examination of biopsy specimens revealed infiltration of large lymphoid cells with immunohistological characteristics similar to those of the iliac tumour (Figure 2A). Immunohistochemical staining was positive for CD30 (Figure 2B) and negative for anaplastic lymphoma kinase (ALK). Based on these findings, the patient was diagnosed with ALK-negative anaplastic large cell lymphoma (ALCL) with colon involvement. He received six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy and achieved complete remission.

DISCUSSION

ALCL is a CD30-positive T cell neoplasm; systemic-type ALCL represents 2% to 3% of all non-Hodgkin lymphomas and 12% to 14% of T cell non-Hodgkin lymphomas (1,2). The WHO classification system divides ALCLs into ALK-positive and ALK-negative groups. Systemic ALK-negative ALCL patients have a worse prognosis than ALK-positive ALCL patients, with five-year survival rates of 49% and 70%, respectively (1). ALK-negative ALCL involves both lymph nodes and extranodal sites (20% of cases) (2). The most frequent extranodal involvement sites are the skin, lungs, liver and gastrointestinal tract, whereas colon involvement is extremely rare (1,2). To our knowledge, only two previous case reports presented endoscopic findings of ALCL with colon involvement; one case showed multiple elevated lesions with ulceration at the apex, and the other showed ulcerated stricture (3,4). If ulcerative colonic lesions are observed on colonoscopy, colon involvement of ALCL should be considered as a rare differential diagnosis.

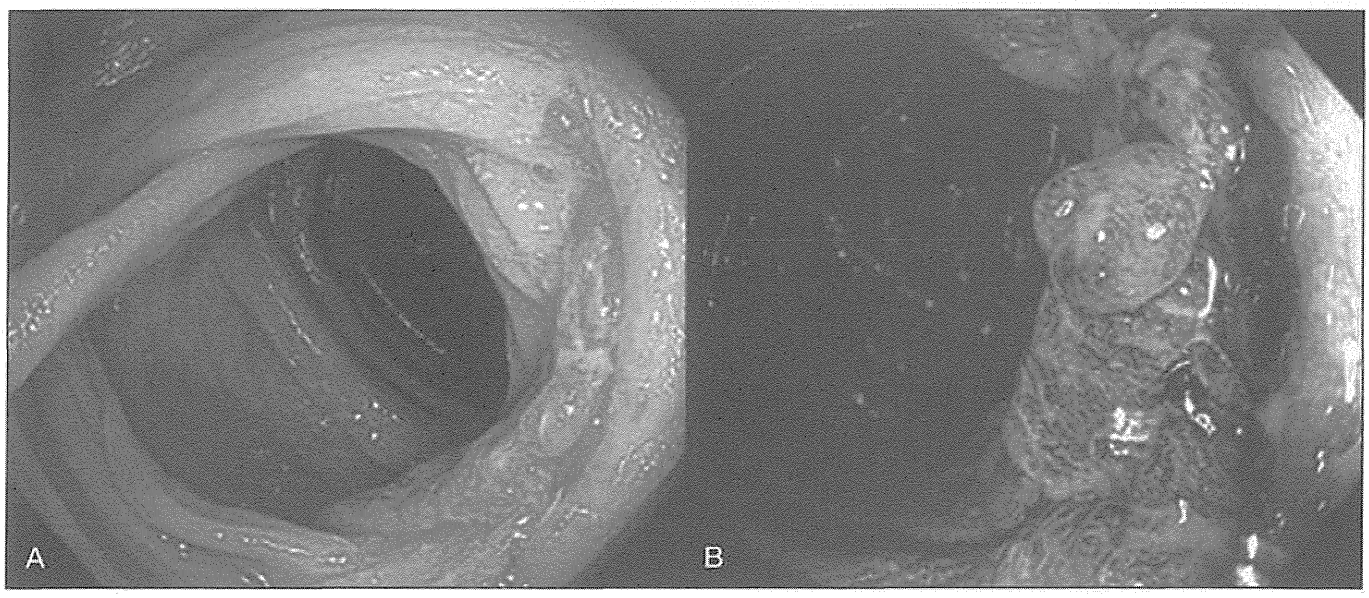

Figure 1) A *Endoscopic image of the ascending colon showing a reddish ulcerative lesion with protrusions.* B *Endoscopy with dual-focus narrow-band imaging revealing dilated, tortuous microvessels and avascular areas in the protrusions*

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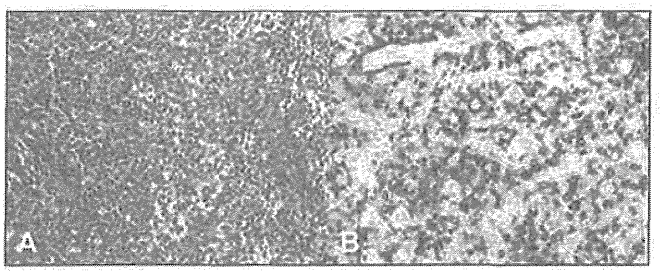

Figure 2) A *Photomicrograph of the biopsy specimen from the ascending colonic lesion shows infiltration of large lymphoid cells (hematoxylin and eosin stain, original magnification ×20).* B *Immunohistochemical staining showing large lymphoid cells strongly positive for CD30*

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Original Article

Burnout of Long-term Care Facility Employees: Relationship with Employees' Expressed Emotion Toward Patients☆

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SUMMARY

Background: This study determined factors related to the burnout of long-term care facility employees, including employees' expressed emotion (EE) toward patients.
Methods: A survey of 411 long-term care facility employees was conducted. Employee burnout was evaluated using the Maslach Burnout Inventory (MBI). EE levels were evaluated using the Nurse Attitude Scale (NAS).
Results: The percentage of high scorers on the MBI's three subscales of emotional exhaustion, depersonalization, and low personal accomplishment were as follows: emotional exhaustion, 197 people (51.6%); depersonalization, 122 people (31.4%); and low personal accomplishment, 301 people (83.8%). Results of multiple logistic regression analysis using presence of a high score on the MBI subscales as dependent variables confirmed significant relevant factors. For emotional exhaustion, this was criticism [odds ratio (OR): 1.74, $p = 0.046$], for depersonalization, male (OR: 1.99, $p = 0.021$), younger than 40 years (OR: 1.84, $p = 0.038$), and hostility (OR: 2.99, $p < 0.001$).
Conclusion: Results indicate that employees' EE of criticism and hostility toward patients is related to burnout.

1. Introduction

According to the World Health Organization, in 2010 there were 35.6 million people with dementia in the world and that number is estimated to reach 115.4 million people by 2050.[1] In 2013, the prevalence of dementia in the elderly, aged ≥ 65 years, in Japan was estimated to be 15%, with an estimated 4.62 million people, and the prevalence of mild cognitive impairment was calculated to be 4 million people.[2] Therefore, dealing with dementia is an urgent issue.

The long-term care (LTC) facility (*Roken*) is a new facility for the elderly, established in 1986 as a transitional facility between hospital and home. The number of elderly patients with dementia in *Roken* is rising, and an improvement in dementia care quality is needed.[3] However, at *Roken*, the turnover of nursing staff is high, securing staff is difficult, and chronic staff shortages are serious problems.[4] Prior to this, there have been various reports on factors related to employee burnout in providing the elderly LTC, although it is easy to become exhausted with elderly dementia patients.[5] This is due to the fact that within dementia, there is a high rate of behavioral and psychological symptoms of dementia (BPSD), and this places a heavy burden on employees.[6] In addition, employees' burden and poor interpersonal relationships between elderly dementia patients and employees exacerbate BPSD.[6]

The best index for evaluating relationships between patients and employees is expressed emotion (EE).[7,8] Katsuki et al[9,10] developed the Nurse Attitude Scale (NAS) to evaluate nurses' EE and studied the factors influencing nurses' EE.[11] However, there are

☆ Conflicts of interest: All contributing authors declare that they have no conflicts of interest.

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no studies investigating EE and related factors of *Roken* staff. Therefore, this study elucidated the factors related to the burnout of LTC facility employees, including the employees' EE.

2. Materials and Methods

2.1. Participants

The participants are nurses and caregivers employed at *Roken*. We distributed 30 surveys to each of the 49 *Roken* staff belonging to the Nagasaki Association of Geriatric Health Services Facilities (a total of 1470 surveys), and received responses from 411 people (response rate, 28.0%). The survey period was from October 2008 to December 2008. The survey was conducted anonymously, and respondents were asked to post the survey directly after sealing the questionnaire in an envelope. This study received approval from the Nagasaki University Graduate School of Biomedical Sciences Department of Health Ethics Committee (approval number: 08092576).

2.2. Questionnaire

The questionnaire items included the Maslach Burnout Inventory (MBI),[12] NAS,[9] and the participants' basic attributes.

MBI is a scale developed by Maslach et al[12] to measure burnout, and consists of 22 items evaluated on a 7-point Likert-type scale ranging from never (0 points) to every day (6 points). The scale is composed of three subscales: emotional exhaustion (9 items), depersonalization (5 items), and personal accomplishment (8 items). High burnout is defined as an emotional exhaustion score of 27 points or higher, depersonalization score of 10 points or higher, and personal accomplishment score of 33 points or lower.[12] The reliability and validity of the Japanese version of MBI have been proven in several references.[10,13,14]

NAS evaluates staff EE and it has a 30-item version[9] and a 12-item version.[10] It was created by Katsuki et al[9,10] by revising the phrasing of the Japanese version[15] of the Family Attitude Scale,[16] a questionnaire for evaluating families' EE. The 30-item version used in this study has a total score of 120 points rated on a 5-point scale (very much applies: 4 points; to does not apply at all: 0 points), and is composed of three subscales: positive remarks (10 items), criticism (12 items), and hostility (8 items).[11] The NAS obtained high reliability and validity in a study of psychiatric nurses.[9–11] When determining the total scores of NAS, the 10 items for positive remarks were reverse calculated. Thus, a high total score on the NAS indicates a high EE of the participants. For the NAS responses, we used the same method of Katsuki et al,[11] asking participants to recall one difficult patient from the past 2 months and then respond.

For basic attributes, we inquired about sex, age, job, work department, night shifts, years of service at current workplace, and length of time dealing with the recalled patient.

2.3. Statistical analyses

For comparison between the two groups, we used a Mann-Whitney test, and for comparison between three or more groups we used a Kruskal–Wallis test. In order to study the magnitude of the independent effects on each factor of the MBI, we performed multiple logistic regression analysis (forced entry method) with the presence of a high score on the MBI subscales as dependent variables. We used SPSS (version 17; SPSS Inc., Chicago, IL, USA) statistical software and a statistical significance level of 5%.

3. Results

3.1. Sociodemographic characteristics

Of the 411 participants, 107 were male (26.0%), 303 were female (73.7%), and one person did not respond (0.2%). In age, 115 people were in their 20s (28%), 114 people were in their 40s (27.7%), and 110 people were in their 30s (26.8%), which were the most common ages respectively, and the average age was 37.5 years [N = 410, standard deviation (SD) = 10.8]. For jobs, 112 people (27.3%) were nurses, 291 people (70.8%) were caregivers, nine people were other (2.2%), and one person did not respond (0.2%). For work departments (location), 384 people (93.4%) were responsible for patients living in facilities, 24 people were responsible for home-care patients' outpatient rehabilitation services, and five people were other (1.3%). With regards to night shifts, 343 people (83.5%) worked night shifts, 61 people (14.8%) did not, five people were other (1.5%), and one person did not respond (0.3%). Average years of clinical experience was 10.1 years (SD = 8.3), and average years of service at current workplace was 5.8 years (SD = 4.6). Ninety (21.9%) people had a dementia specialty ward established in their workplace, 315 people did not have one established (76.6%), and six people did not respond (1.5%).

3.2. Factors related to burnout and mental health

The percentages of high scorers for each scale were as follows: emotional exhaustion, 197 people (51.6%); depersonalization, 122 people (31.4%); low personal accomplishment, 301 people (83.8%). Cronbach α coefficients for emotional exhaustion, depersonalization, and personal accomplishment were 0.85, 0.76, and 0.79, respectively. The mean score on the NAS was 44.28 (N = 371, SD = 18.27). The mean scores on the NAS subscales were positive remarks, 21.9 (N = 389, SD = 6.19, median 22); criticism, 14.86 (N = 397, SD = 9.25, median 14); and hostility, 11.53 (N = 397, SD = 11.53, median 11). Cronbach α coefficients for positive remarks, criticism, and hostility were 0.81, 0.91, and 0.81, respectively. Table 1 shows the relationship between the MBI subscales and basic characteristics. For emotional exhaustion, a significant difference was seen with the presence of night shifts. For depersonalization, a significant difference was seen with sex, age, and the presence of night shifts. For personal accomplishment, significant differences were seen with the presence of night shifts, years of clinical experience, and the number of years of service at current workplace.

Table 2 shows the results of multiple logistic regression analysis (forced entry method) performed with scores on the MBI subscales. The NAS subscales were divided into two groups based on the median and analyzed. Significantly correlated factors were: for emotional exhaustion, the NAS subscale of criticism; for depersonalization, male, younger than 40 years, and the NAS subscale of hostility.

4. Discussion

According to Juthberg et al,[17] the percentage of high burnout among nurses working at Sweden's elderly tenant facilities for emotional exhaustion was (N = 131) 22.1%, depersonalization (N = 141) 9.2%, and low personal accomplishment (N = 136) 14.7%. By contrast, results of Asai et al's[13] survey targeting 697 Japanese clinical oncologists found the percentage of high burnout to be 23% for emotional exhaustion, 10% for depersonalization, and 65% for personal accomplishment. In addition, in Umeno-Nakano et al's[14] survey targeting 704 Japanese psychiatrists, the percentage of high burnout for emotional exhaustion was 21%, depersonalization

Table 1
Bivariate association of basic attributes with Maslach Burnout Inventory subscales in long-term care facilities.

	Emotional exhaustion[a]			Depersonalization[a]			Personal accomplishment[a]		
	n	Mean (SD)	*p*	*n*	Mean (SD)	*p*	*n*	Mean (SD)	*p*
Sex									
Male	101	27.3 (10.9)	0.950	103	8.8 (7.0)	0.011*	99	22.5 (9.6)	0.070
Female	280	27.3 (10.7)		284	6.8 (5.9)		259	24.4 (9.1)	
Age (y)									
20–29	110	28.0 (10.4)	0.576	112	9.1 (6.7)	0.001**	103	24.4 (9.5)	0.434
30–39	103	28.0 (10.0)		104	7.4 (6.1)		96	24.3 (8.2)	
40–49	106	27.0 (11.4)		108	6.8 (6.1)		101	23.9 (9.6)	
50–59	60	25.8 (11.4)		60	4.9 (5.3)		55	22.0 (10.0)	
Job									
Nurse	103	27.1 (11.0)	0.715	104	7.0 (6.3)	0.474	96	24.8 (9.2)	0.370
Care giver	270	27.7 (10.5)		275	7.5 (6.3)		254	23.7 (9.3)	
Work department									
Outpatient	19	27.2 (12.3)	0.964	20	5.2 (4.9)	0.124	16	19.0 (9.7)	0.050
Inpatient	357	27.2 (10.6)		362	7.4 (6.4)		337	24.1 (9.2)	
Night shift									
Yes	320	27.8 (10.7)	0.042*	326	7.6 (6.3)	0.002**	302	24.4 (9.0)	0.044*
No	57	24.5 (10.5)		57	4.8 (4.5)		53	21.6 (10.6)	
Y of clinical experience									
< 3	45	26.1 (10.7)	0.475	47	7.3 (6.4)	0.186	44	23.6 (8.6)	0.017*
3–< 6	86	26.3 (10.9)		87	6.7 (5.3)		80	26.2 (9.5)	
6–< 10	97	28.5 (10.1)		98	8.8 (7.4)		88	21.8 (9.2)	
≥ 10	148	27.4 (11.2)		150	6.7 (6.0)		141	23.7 (9.0)	
Y of service at current workplace									
< 3	106	27.2 (10.5)	0.423	108	7.1 (6.0)	0.829	99	24.0 (8.4)	0.037*
3–< 6	111	26.3 (11.2)		113	7.6 (6.7)		105	25.5 (9.5)	
6–< 10	80	27.7 (9.7)		82	7.7 (6.3)		79	22.0 (9.5)	
≥ 10	79	28.8 (11.3)		79	6.9 (6.2)		70	22.5 (8.7)	
Dementia ward									
Yes	84	26.8 (11.1)	0.486	86	6.9 (5.8)	0.639	82	22.6 (9.7)	0.251
No	295	27.6 (10.6)		299	7.4 (6.4)		274	24.3 (9.2)	

S.D. = standard deviation.
* $p < 0.05$.
** $p < 0.01$.
[a] Mann–Whitney test, Kruskal–Wallis test.

Table 2
Factors related to Maslach Burnout Inventory subscales.

Independent variable	Emotional exhaustion[a]			Depersonalization[a]			Personal accomplishment[a]		
	OR	(95% CI)	*p*	OR	(95% CI)	*p*	OR	(95% CI)	*p*
Sex									
Male/female	0.89	(0.53–1.52)	0.677	1.99	(1.11-3.58)	0.021*	1.27	(0.57–2.83)	0.561
Age (y)									
–39/40+	1.30	(0.79–2.14)	0.312	1.84	(1.03-3.27)	0.038*	1.07	(0.53–2.17)	0.855
Job									
Nurse/care giver	1.14	(0.63–2.06)	0.668	1.72	(0.88-3.38)	0.112	0.53	(0.24–1.18)	0.122
Work department									
Outpatient/inpatient	1.73	(0.49–6.07)	0.391	1.10	(0.24-5.07)	0.908	1.55	(0.17–13.95)	0.694
Night shift									
Yes/no	1.96	(0.91–4.22)	0.085	2.17	(0.83-5.69)	0.115	0.89	(0.30–2.63)	0.837
Y of clinical experience									
6 ± 5	1.08	(0.57–2.07)	0.810	1.63	(0.79-3.35)	0.185	1.35	(0.56–3.26)	0.506
Y of service at current workplace									
6 ± 5	1.22	(0.66–2.25)	0.523	0.69	(0.35-1.35)	0.277	1.48	(0.64–3.43)	0.362
Dementia ward									
Yes/no	0.81	(0.47–1.39)	0.444	0.83	(0.45–1.53)	0.548	1.60	(0.70–3.68)	0.266
NAS									
Positive remarks									
>22/≤22	0.82	(0.50–1.35)	0.437	0.91	(0.52–1.60)	0.751	1.70	(0.84–3.45)	0.141
Criticism									
>14/≤14	1.74	(1.01–3.00)	0.046*	1.67	(0.91–3.05)	0.095	1.07	(0.50–2.31)	0.856
Hostility									
>11/≤11	1.04	(0.61–1.77)	0.874	2.99	(1.65–5.42)	<0.001**	0.71	(0.33–1.50)	0.363

CI = confidence interval; NAS = Nurse Attitude Scale; OR = odds ratio.
* $p < 0.05$.
** $p < 0.01$.
[a] Logistic regression analysis (forced entry method).

12.2%, and low personal accomplishment 72%. In comparison with these previous studies, which used the same cut-off scores as this study, the participants of this study indicated a high level of burnout.

About 70% of the participants of this study were caregivers, and we can therefore assume that they are working without adequate education on dementia and BPSD, or skills for coping with stress. In addition, a chronic staffing shortage is the norm in the healthcare field. These are speculated to be contributing factors to high burnout.

According to Katsuki et al,[9,11] the mean NAS score of 189 nurses working at a psychiatric hospital was 42.6 (SD = 13.5),[9] and the mean NAS score of 281 nurses working at a different psychiatric hospital was 47.6 (SD = 19.0).[11] By contrast, Fujita et al[15] found that the mean NAS scores of 41 families with schizophrenic children was 39.9 (SD = 20.4). The average NAS scores in this study were 44.3 (SD = 18.3), and were close to Katsuki et al's[9,11] data from nurses working at psychiatric hospitals.

Results from this study's multiple logistic regression analysis showed that significantly correlated factors were: for emotional exhaustion, the NAS subscale of criticism; for depersonalization, male, younger than 40 years, and the NAS subscale of hostility. Thus, employees' negative EE toward patients were significantly related to burnout.

The NAS questions items on criticism include "I wish he would leave me alone," "I feel very frustrated with him," and "I wish he were not here." Question items on hostility include "I shout at him," "I lose my temper with him," and "I argue with him," and are considered to be states expressing anger toward the patient through actual behavior. A critical comment on the Camberwell Family Interview[7] is defined as a critical feeling toward the behavior of the patient, and hostility is defined as negative feelings toward the patient as an individual in general. It is difficult to say that they match exactly with the NAS's criticism and hostility; however, it is certain that the NAS captures aspects that are close to EE. There have been studies targeting families of dementia patients that investigated the relationship between EE and care burden and abuse.[18–21] There was also a study on the care burden of dementia patients that targeted care-facility employees[22]; however, there are no studies as of yet investigating the EE of care facility employees. Therefore, we believe there is great significance to this study, which has elucidated the factors related to burnout and mental health of LTC employees, including the employees' EE.

In our study, other factors significantly related to depersonalization were male and aged younger than 40 years. These can be regarded as major problems in LTC facilities for the elderly in Japan. Firstly, for men, the following may influence depersonalization: tendency to be strongly affected by higher career consciousness, and lack of preparation for an adequate labor environment such as an increase in pay level appropriate to their career and ability. Secondly, for younger employees, the following may influence depersonalization: poor human experience and/or care experience, poor coping strategies for BPSD, and/or overall stress.[23]

In a review of 17 studies, Moyle et al[24] concluded that behavior skill training programs that equip LTC staff with education on mental illness in the elderly and skills for coping with disruptive behavior are effective. Since adequate specialized education is thought to be lacking among LTC caregivers, this type of program is believed to be effective.

Numerous studies have investigated the effectiveness of training for LTC employees. Compared with routine care, person-centered care and care mapping was found to be effective in reducing patient agitation[25] and also contributed to alleviating staff burnout.[26]

In any case, the needs of dementia patients are complex, and since they change over time, new care approaches will continually be necessary. Additionally, as support by one person is challenging, support by interdisciplinary teams and overall maintenance of the care environment is needed.

Lastly, we would like to discuss this study's limitations and future issues. The NAS used in this study included question items regarding negative emotions toward patients, to which professional staff find it difficult to respond frankly to. Therefore, in consideration of ease of response, we did not collect basic data about the "recalled" patients in this study. Despite such considerations, the return rate for our study was low, and there seems to be limitations in terms of the universality of the results. We will investigate this issue in the future; however, the low return rate might have been influenced by the high burnout rate of employees. In order to discuss the basis for the relationship between staff burnout and BPSD in the inhabitants of LTC facilities, it is necessary to have data including the number of patients with dementia and the prevalence of BPSD, as well as to conduct studies of staff-patient dyads. We intend to address these issues in the future.

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Regular Article

Barriers to mental health care in Japan: Results from the World Mental Health Japan Survey

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Aims: The reasons for accessing and maintaining access to mental health services in Japan may be different to those in other countries. Using the World Health Organization World Mental Health Japan survey data, this study investigated the prevalence of sociodemographic correlates of barriers for the use of, reasons for delayed access to, and reasons for dropping out from mental health care in a Japanese community-based sample.

Methods: An interview survey was conducted with a random sample of residents living in 11 communities across Japan during the years 2002–2006. Data from 4130 participants were analyzed.

Results: The most frequently reported reason for not seeking mental health care was a low perceived need (63.9%). The most common reason for delaying access to help was the wish to handle the problem on one's own (68.8%), while the most common reason for dropping out of care was also a low perceived need (54.2%). Being a woman and of younger age were key sociodemographic barriers to the use of mental health services.

Conclusions: Low perceived need was a major reason for not seeking, delay in using, and dropout from mental health services in Japan. In addition, low perceived need and structural barriers were more frequently reported than attitudinal barriers, with the exception of a desire to handle the problem on one's own. These findings suggest that improving therapist–patient communication and quality of mental health care, as well as mental health literacy education in the community, might improve access to care in Japan.

Key words: barriers to mental health care, epidemiologic study, mental health service use, sociodemographic correlates, stigma.

ALTHOUGH MENTAL DISORDERS are common,[1] many people with mental illness remain untreated,[2] which may result in poor outcomes. Extended periods of untreated illness[3] and ceasing treatment early[4,5] are particularly associated with worse outcomes in people with mental illness. In addition to poor health outcomes, untreated mental conditions are also associated with societal economic loss.[6]

There are three types of reasons for not seeking professional help, as reported previously[7]: (i) low perceived need (e.g. not feeling a need for help); (ii) structural barriers (e.g. unavailable or inaccessible treatments, personnel or transportation or the presence of other inconveniences); and (iii) attitudinal barriers (e.g. perceived stigma, low perceived efficacy of treatments, or the desire to handle the problem on one's own) (Table S1). Of these, the attitudinal bar-

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