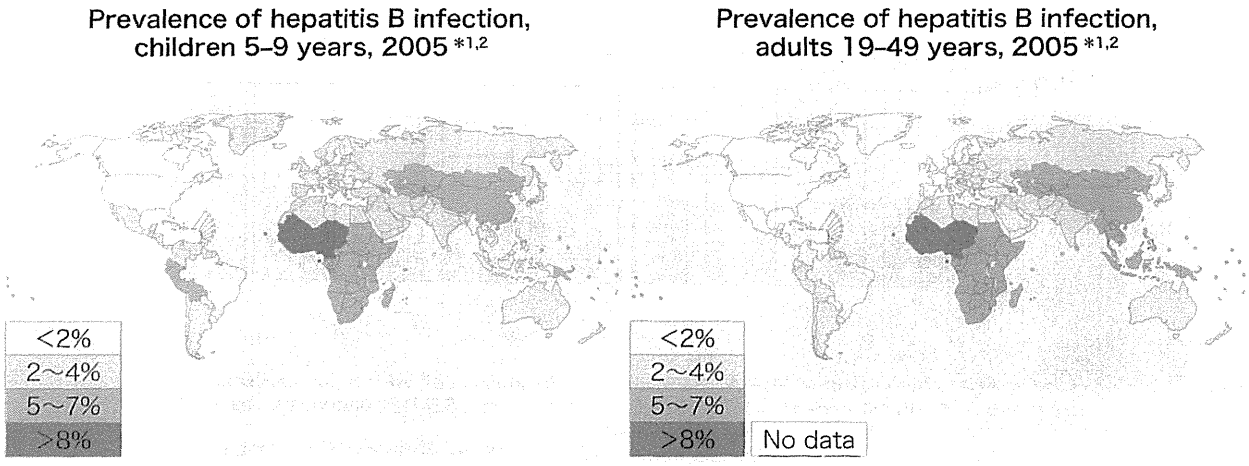

HBV exposed cases: 2 billion
Persistently HBV infected cases: > 240 million

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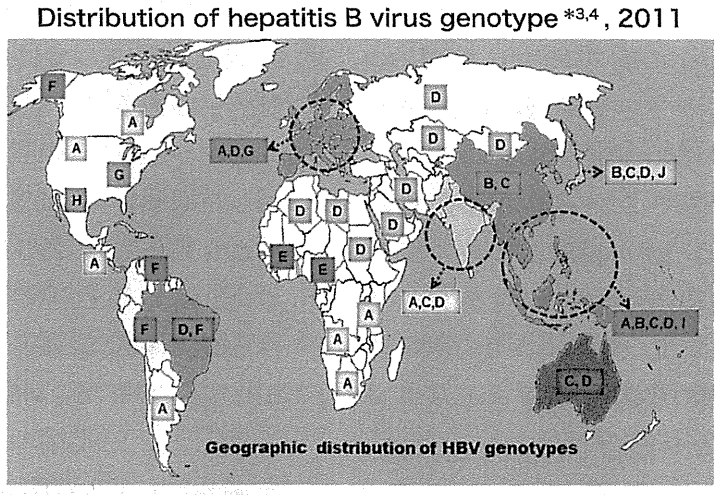

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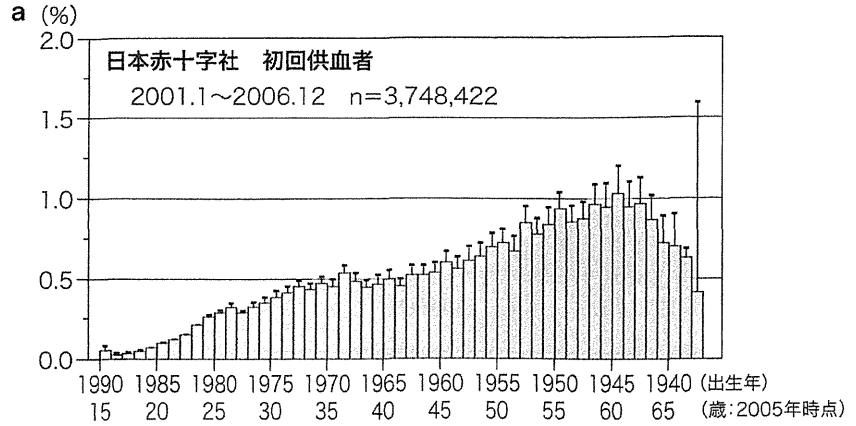
図3　世界のHBV感染状況とHBV genotypeの分布

比較すると，2001～2006年と比べて，2007～2011年ではやや低い値となることがわかる．2001年から6年の間に初めて献血を行った集団よりも2007年から6年の間に初めて献血を行った集団のHBs抗原陽性率が低下した理由は，この期間に肝炎ウイルス検査を受ける機会が増えたことから，感染が判明した者は献血には来ないこと，あるいは献血時の問診が強化し感染リスクの高い者が指導を受け献血しなかったことなどが考えられる．いずれにしても感染を知らないまま社会に潜在するHBVキャリアが減少した可能性を示している．

なお，疫学的視点からみると，HBV母子感染防止事業が開始された1986年以後に出生した集団においても，HBs抗原陽性率が0にはならず，0.08～0.1％の値を依然として保っていることに注視すべきである．HBV



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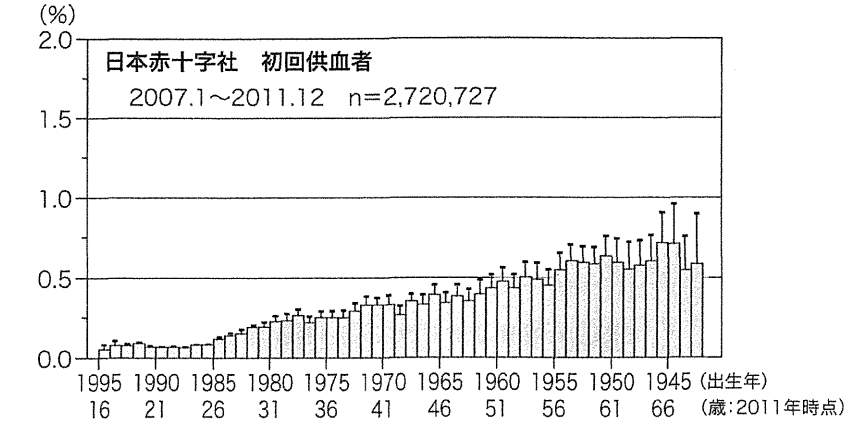

田中純子：平成26年度厚生労働科学研究費補助金　肝炎等克服政策研究事業. 急性感染も含めた肝炎ウイルス感染状況・長期経過と治療導入対策に関する研究班 報告書2015より引用

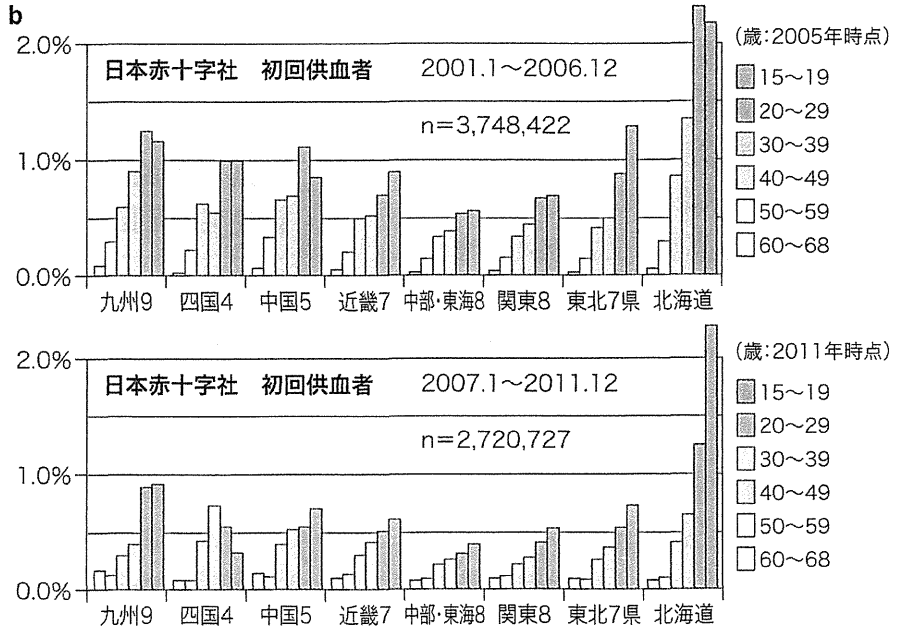

図4　初回供血者集団における年齢階級別，地域別にみたHBs抗原陽性率
a：年齢階級別にみたHBs抗原陽性率，b：地域別にみたHBs抗原陽性率

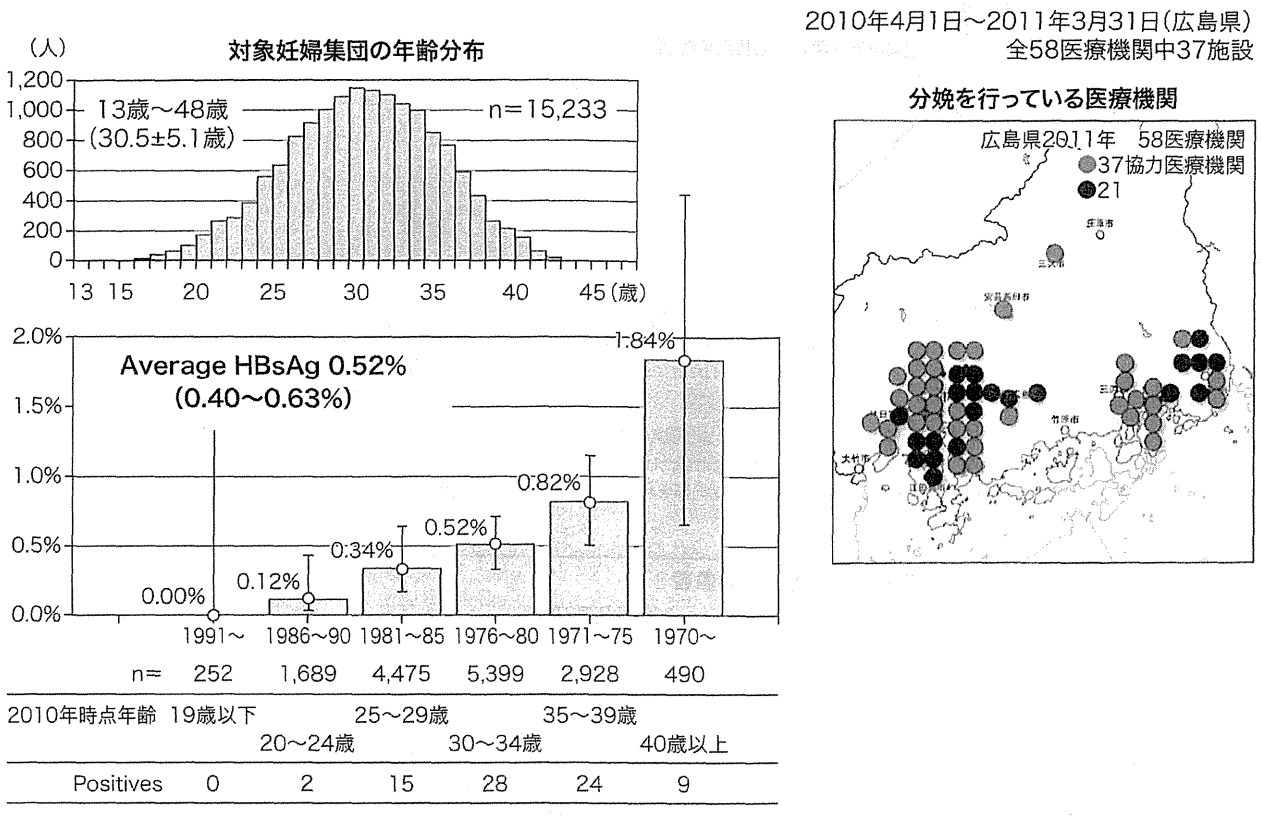

図5　妊婦集団におけるHBs抗原陽性率

母子感染が抑えられている一方，水平感染によるHBV感染が依然として存在している可能性も考えられる．

全国を8つの地域に分割して年齢階級別に算出したHBs抗原陽性率をみると，2001～2006年の初回献血者集団では，団塊の世代および肝癌好発年齢である50～60歳代の陽性率がいずれの地域でも高く，北海道・東北地域および西日本地域が特に高い傾向がみられる．一方，2007～2011年の初回献血者集団では，北海道地域を除く地域でHBs抗原陽性率が低下した．

上記の成績から考えると，自身が感染を知らないまま社会に潜在するHBVキャリアの数は，2005年時点と比較して2011年時点には減少したことが推定される．これは，前述したように1990年代後半から2000年代にかけて，節目検診や無料検査の実施などによりさまざまな肝炎ウイルス検査の機会(診療，手術時における肝炎ウイルス検査など)が増加したこと，行政・医師会などによる啓発活動の普及により肝炎ウイルス感染の知識が浸透したことが理由の1つであると考えられる．

4　妊婦集団における出生年別にみたHBs抗原陽性率

広島県域の産婦人科を有し分娩を行っている58医療機関のうち，41施設の協力を得て行った妊婦を対象とした全数調査の成績[6]を図5に示す．2010年4月から翌年3月末までに41施設で分娩をした全妊婦15,233人(平均年齢：30.5±5.1歳)のHBs抗原陽性率である．前年の同県の出生総数は25,596人であり，対象者は約60％に相当する．

全体のHBs抗原陽性率は0.52％(95％信頼区間：0.40～0.63％)であるが，HBV母子感

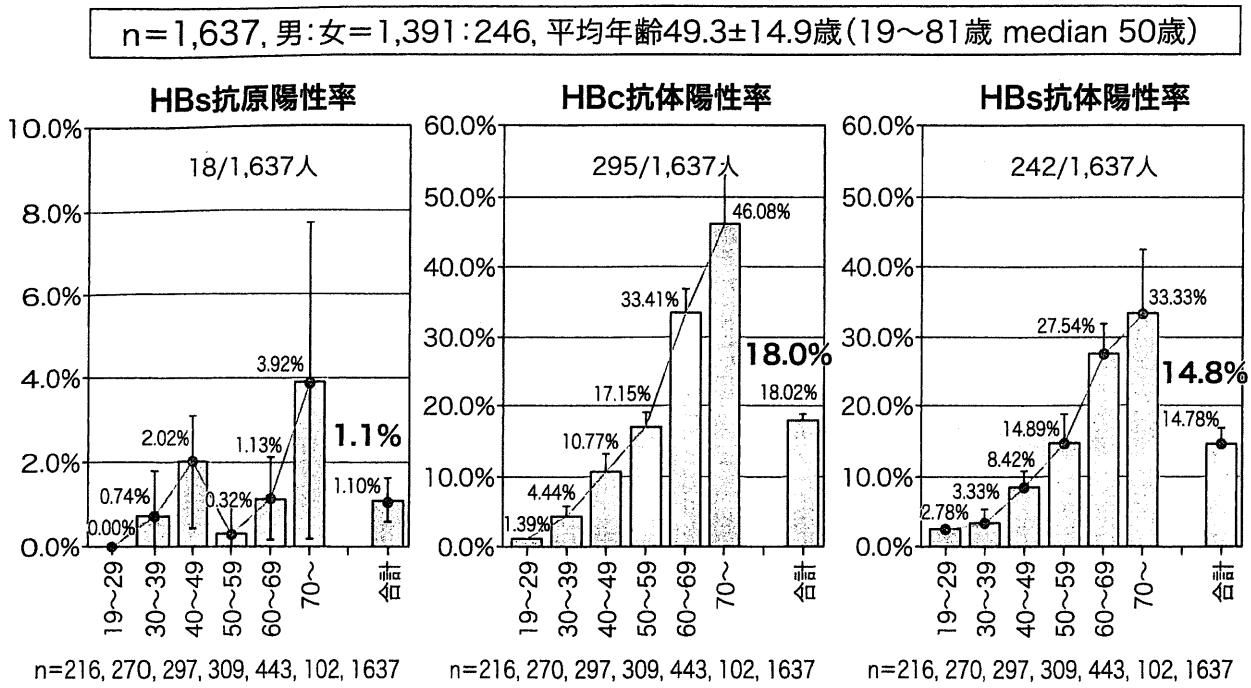

図6　職業集団における感染状況－2011～2013年(広島県)

染防止事業が開始された1986年以降に出生した年齢集団ではHBs抗原陽性例はわずか2例，陽性率は0.0～0.12％と極めて低い値を示した．引き続き，対策が行われれば次世代には母子感染によるHBV感染は消滅し，母子感染由来のHBVキャリアはいなくなることが期待できる．

5　職域集団における出生年別にみたHBV感染状況

職域集団では，住民健診と比較すると肝炎ウイルス検査がすすんでいないと考えられている．職域集団におけるHBV感染状況を把握する目的で，定期健康診断時に併せて肝炎ウイルス検査を勧奨する出前検査をパイロットで行った成績を図6に示す．運輸業およびサービス業に従事する1,637人を対象とした結果，HBVキャリア率は1.1％(95％ CI：0.59～1.60％)，年齢階級別に相違は認められなかった．HBs抗体の陽性率は14.8％(95％ CI：13.1～16.5％)，HBc抗体の陽性率は18.0％(95％ CI：16.2～19.9％)であり，いずれも年齢階級が高い集団で高い値を示していた．特に，60歳代・70歳代のHBc抗体陽性率は33～46％，HBs抗体陽性率は28～33％と高い値を示し，同集団でのHBV感染既往の可能性があるのは対象全体の19.5％(95％ CI:17.4～21.6％)にのぼるものと推定された．

さらに，厚生労働省肝炎疫学研究班[7]で報告された日本赤十字社中央血液研究所のデータでは，平成22年4月から24年3月までの初回供血者1,079,341人(男性619,582人，女性459,759人)のHBc抗体陽性率は前項で述べた団塊の世代である1941～1945年出生集団が最大値を示しており(男性約23％，女性約18％)，出生年が若くなるとともに低い値となっていた．したがって，HBV再活性化の可能性のあるHBV感染既往者は，高年齢層になるに従いその割合が多くなり，また，これまで検査の機会がなく自身が感染を知らな

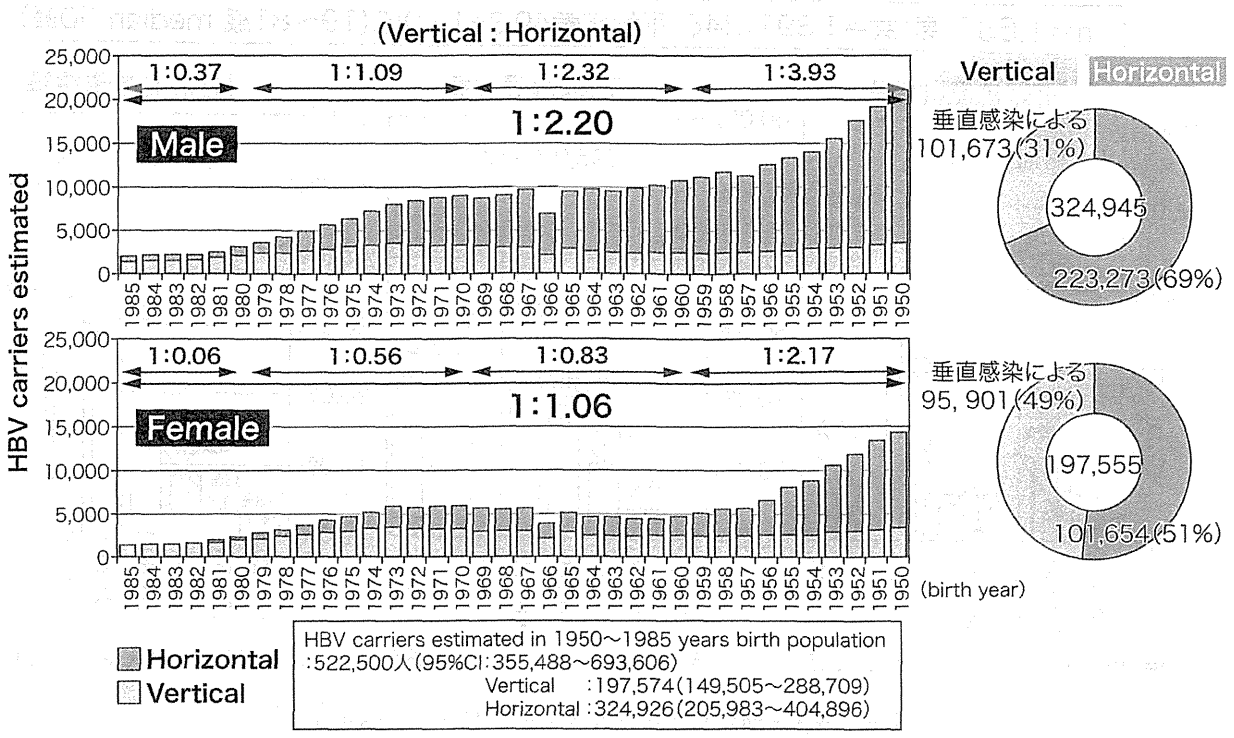

図7　1950～1985年に出生した児の垂直感染と水平感染別HBVキャリア数の推計(文献8より引用)

い場合があることから，高齢者に対する免疫抑制・化学療法治療前のHBc抗体検査はガイドラインに従い十分慎重に行うことが重要である．

6 1950～1985年出生集団におけるB型肝炎ウイルス感染者数の感染経路別人数の推計

出生した児の母親の年齢分布は人口動態統計に記されていることから，HBV母子感染防止事業開始前(1950～1985年)に出生した児のうち，母子感染によるHBVキャリアと水平感染によるHBVキャリアの割合の推定を試みたものを紹介する(図7)．前述した出生年別の大規模集団の疫学資料，年齢別HBe抗原陽性率の文献，人口動態資料などを基に一定の仮定を設定して算出したものである．

当該出生年(1950～1985年出生)のHBVキャリア数は522,500人(95% CI：355,488～693,606人)であり，そのうち母子感染由来は38%，197,574人(95% CI：149,505人～288,709人)，水平感染由来は62%，324,926人(205,983人～404,896人)と推定されている．男女別にみると，HBVキャリアのうち男性では母子感染由来と水平感染由来が1：2.20であるのに対し，女性では1：1.06とほぼ同数と推定されている．1950年時点の水平感染の経路は多岐にわたり，衛生・医療環境の整備や感染に対する知識は現在と比較すると充分とはいえず，さらに生活の場での感染リスクも多く存在していたと推察される．

1970年以後には，特に水平感染由来のHBVキャリア数の減少が認められ，1985年出生集団では，母子感染由来のHBVキャリアがほぼ9割を占めるまでになっている．HBV母子感染防止事業が開始された1986年以後の動向が興味深い．

7 おわりに

わが国では1986年より実施されたHBV母子感染予防対策事業以降に出生した集団のHBVキャリア率は低く，引き続きHBV母子感染予防対策が適切に講じられた場合，わが国の垂直感染によるHBVキャリアの発生は次世代でほぼ消滅すると推測される．一方，乳幼児期の同世代・異世代からの水平感染率およびHBVキャリア化率については疫学的検討が残されていること，さらに成人におけるHBV genotype Aを含む新規感染例が確認されていることから，HBV感染を防止するワクチンの若年齢集団や一般集団およびハイリスク集団への導入が必要と考えられる．

一方，人口減少と生産年齢人口割合の減少に伴い，アジア諸国をターゲットとしたグローバル化が拡大する可能性が検討されているなか，アジア諸国と比較するとわが国のHBVキャリア率は低く，また，若・中年層においてHBs抗体保有率が極めて低いことからも，HBワクチンを含めた十分なHBV感染予防対策が必要となる時期がきているといえる．

また，HBV再活性化の可能性のあるHBV感染既往者は高年齢層になるに従いその割合が高いことが示されており，免疫抑制・化学療法関連治療前の検査はガイドラインに従い十分慎重に行うことが重要である．

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The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Survey of survival among patients with hepatitis C virus-related hepatocellular carcinoma treated with peretinoin, an acyclic retinoid, after the completion of a randomized, placebo-controlled trial

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Abstract

Background This study examined the effects of peretinoin, an acyclic retinoid, on the survival of patients with hepatitis C virus-related hepatocellular carcinoma (HCC) who had completed curative therapy and participated in a randomized, placebo-controlled trial.

Methods This study was an investigator-initiated retrospective cohort study. Subjects were all patients who were administered the investigational drug (peretinoin 600 mg/day, peretinoin 300 mg/day, or placebo) in the randomized trial. Survivals between the groups were compared using the log-rank test, and hazard ratios were estimated by Cox regression.

Results Survey data were collected from all patients ($n = 392$) who participated in the randomized trial, all of whom were then divided into the peretinoin 600 mg/day ($n = 132$), peretinoin 300 mg/day ($n = 131$), and placebo ($n = 129$) groups. At the median follow-up of 4.9 years, 5-year cumulative survival rates for patients in the 600 mg/day, 300 mg/day, and placebo groups were 73.9, 56.8, and 64.3 %, respectively. Comparison of overall survival among patients classified as Child-Pugh A revealed that

UMIN clinical trial registration number: UMIN000006728.

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survival of the 600 mg/day group ($n = 105$) was significantly longer than that of the placebo group ($n = 108$) (hazard ratio 0.575, 95 % CI 0.341–0.967; $P = 0.0347$).
Conclusions Administration of 600 mg/day peretinoin to patients with hepatitis C virus-related HCC who have completed curative therapy may improve survival for those classified as Child-Pugh A, for whom liver function is relatively stable.

Keywords Hepatocellular carcinoma · Hepatitis C virus · Multicentric carcinogenesis · Overall survival · Peretinoin

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world, affecting 740,000 people annually [1]. The incidence of HCC has been rising due to an increase in hepatitis C virus (HCV) infections [2–4]. HCC comprises 94 % of all primary liver cancers in Japan; one prominent cause is infection by HCV [4]. Hepatitis C virus-related HCC (HCV-HCC) comprises 75 % of all HCC cases, while HCC due to hepatitis B virus infection (HBV-HCC) comprises 10–15 % [5].

Early diagnosis and curative treatment for HCC, such as hepatectomy or radiofrequency ablation (RFA, a localized therapy), has become more prevalent in recent years. However, high recurrence rates and unfavorable prognoses remain even after curative treatment for HCV-HCC. Cumulative recurrence rates of HCV-HCC are high, with reported rates of 24, 76, and 92 % at 1, 3, and 5 years, respectively, after treatment for the initial onset of liver cancer [6]. Characteristics of HCC recurrence include metastases within the liver, and many patients experience multicentric cancer onset due to underlying liver conditions (e.g., cirrhosis) related to viral liver disease. As underlying liver disease can provide optimal sites for oncogenesis, suppression of multicentric cancer onset is particularly important for improving HCC prognosis, even after curative treatment. Hepatitis virus-related HCC is often treated effectively by antiviral therapies such as interferon [7–9]. However, strategies to control recurrence following cured HCC have not yet been established [10–12].

One method used to control cured HCC recurrence employs a retinoid-based chemoprevention strategy [13]. Peretinoin [(2*E*,4*E*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,4,6,10,14-pentaenoic acid] is a retinoid with a vitamin A-like structure discovered by Muto et al. (1980) [14], and currently is one of the potential drugs anticipated to suppress HCC recurrence [15–17].

According to a randomized trial [18], administration of 600 mg/day peretinoin suppressed HCV-HCC recurrence following curative therapy. In Japan, 75 % of patients with HCC test positive for HCV, and compared to other causes of HCC, HCV has the highest risk of recurrence. Thus, the randomized trial aimed to examine the suppressive effects of peretinoin on recurrence among a population with a homogeneously high risk for recurrence, and thus focused on patients who tested positive for HCV following curative therapy. The trial was a multicenter, parallel-group, double-blind, randomized, placebo-controlled trial. Patients who tested positive for HCV (negative for HBV) and underwent liver resection or RFA to treat initial onset or initial recurrence, and who were classified as Child-Pugh A or B, were assigned to one of the following three groups: peretinoin 600 or 300 mg/day, or placebo. The investigational drug was administered orally once a day, for no longer than 2 years. Of the 401 patients registered in the randomized trial between March 2005 and July 2007, 268 were administered the investigational drugs (peretinoin 600 mg/day, $n = 134$; peretinoin 300 mg/day, $n = 134$; placebo, $n = 133$). Our analysis revealed no superiority of the treatment groups (peretinoin 600 and 300 mg/day) over the placebo group with respect to the primary endpoint of recurrence-free survival ($P = 0.434$). However, the highest 3-year cumulative recurrence-free survival rate (43.7 %) was found in the group administered 600 mg/day peretinoin. The peretinoin 600 mg/day group also showed a significantly lower recurrence rate after 2 years relative to that of the placebo group (hazard ratio 0.27; 95 % CI

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0.07–0.96). Sub-group analysis revealed that within the peretinoin 600 mg/day group, the recurrence risk also decreased significantly among those classified as Child-Pugh A (hazard ratio to the placebo group, 0.60; 95 % CI 0.41–0.89) and those with tumor size under 2 cm (hazard ratio to the placebo group, 0.41; 95 % CI 0.23–0.73). Notably, the follow-up duration for the randomized trial was short (median, 2.5 years), and we did not evaluate overall survival among groups.

This study was conducted as an investigator-initiated research, independently of the randomized trial to evaluate the effects of peretinoin on the overall survival up to 6 years of follow-up.

Methods

Study design

This study was a retrospective cohort study which assessed survival outcomes of all participating patients to the randomized trial from the time the trial ended through December 31, 2011. The randomized trial was conducted in accordance with Good Clinical Practice guidelines.

Setting and participants

The principal investigator obtained permission to conduct the study from the ethics committee of Shimonoseki Kohsei Hospital. Approval for data provision was obtained in accordance with the respective institution's regulations. The study was conducted in compliance with the Declaration of Helsinki, as well as the "Ethical Guidelines for Epidemiological Research" set in Japan by the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour, and Welfare.

Of the 41 medical institutions where the randomized trial was conducted, we targeted all the institutions that provided written consent to participate in this cohort study and used a data collection form to collect data in the medical records. The collected data included the dates of any deaths up through December 31, 2011 and the last recorded date of survival (in cases where observation was not possible). Data collection forms were collected between January 1, 2012 and December 31, 2012. Data collection forms were mailed from the data center to the medical institutions providing the data. At the medical institutions providing the data, either the physician in charge of the study or the person delegated by this physician provided answers to the questions according to existing resources (medical records, etc.). Anonymized data collection forms were then sent back to the data center.

The primary endpoint was overall survival, defined by the time period beginning on the date of patient registration for the randomized trial until death from all causes or the final date when survival was confirmed. Patients for whom survival was last confirmed before December 2011 were treated as "lost to follow-up."

At the medical institutions providing the data, if a delegate of the physician in charge of the study completed the data collection form, the physician validated the data such that data reliability was guaranteed. The data center conducted an independent and careful review of the collected data according to the data management plan, and then created and maintained the database.

Statistical analysis

In accordance with the principle of the intention-to-treat analysis, this study analyzed data from all patients who had been administered the investigational drug in the randomized trial. Cumulative survival rates in each treatment group were calculated by the Kaplan–Meier method with the dates of each patient registration for the randomized trial as the starting point. The log-rank test was used to compare the 600 mg/day peretinoin and placebo groups, and the 300 mg/day peretinoin and placebo groups. We also calculated hazard ratios and 95 % confidence intervals (CIs) using the Cox proportional hazards model. Two-tailed statistical significance was set at $P < 0.05$, and P values were not adjusted for multiplicity. All data from December 31, 2011 onwards were treated as censored.

In sub-group analyses, the same survival time analysis method used to evaluate primary endpoints was employed on the classification factors which were set in advance. Classification factors included Child-Pugh classification (A, B), tumor size (<2 cm, ≥2 cm), curative treatment procedure (local ablation, resection), sex (male, female), and age when consent was provided (<65 years, 65–74 years, ≥75 years). All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA). This study is registered in the UMIN Clinical Trials Registry (UMIN000006728).

Results

Patients

Survey data were collected from all 392 patients (600 mg/day, $n = 132$; 300 mg/day, $n = 131$; placebo, $n = 129$) (Fig. 1). Patient demographic factors are summarized in Table 1. Sex, age, treatment approach, Child-Pugh classification, and primary tumor size were well balanced among the three treatment groups. Number of deaths in the

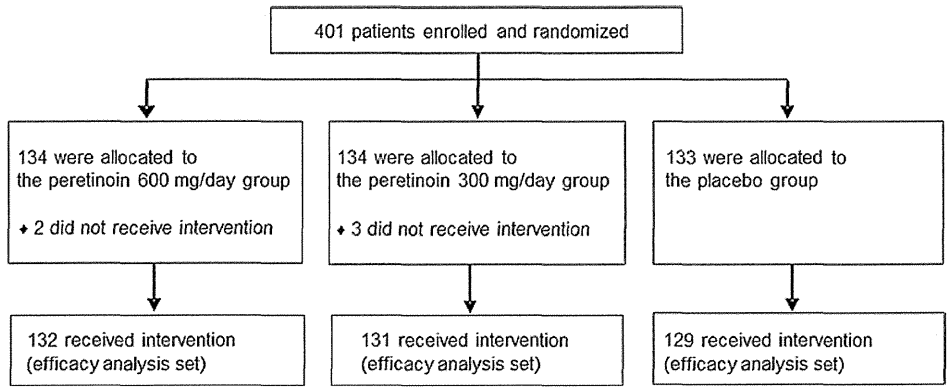

Fig. 1 Flow diagram of patient selection. For the randomized trial, a total of 401 individuals were registered and assigned randomized treatments (peretinoin 600 mg/day, $n = 134$; peretinoin 300 mg/day, $n = 134$; placebo, $n = 133$). Of these, those who were ultimately not administered the investigational drug (2 in the 600 mg/day group, 3 in the 300 mg/day group, and 2 in the placebo group) were excluded, and data from the remaining patients were analyzed (peretinoin 600 mg/day, $n = 132$; peretinoin 300 mg/day, $n = 131$; placebo, $n = 129$)

Table 1 Patient demographics

	Peretinoin		Placebo ($n = 129$)	P value (χ^2)
	600 mg/day ($n = 132$)	300 mg/day ($n = 131$)		
Sex				
Male	85 (64.4 %)	76 (58.0 %)	89 (69.0 %)	0.1806
Female	47 (35.6 %)	55 (42.0 %)	40 (31.0 %)	
Age (years)[a]				
<65	38 (28.8 %)	42 (32.1 %)	41 (31.8 %)	0.7331
65–74	69 (52.3 %)	62 (47.3 %)	57 (44.2 %)	
≥75	25 (18.9 %)	27 (20.6 %)	31 (24.0 %)	
Curative treatment				
Local ablation	85 (64.4 %)	84 (64.1 %)	85 (65.9 %)	0.9497
Resection	47 (35.6 %)	47 (35.9 %)	44 (34.1 %)	
Child-Pugh				
A	105 (79.5 %)	107 (81.7 %)	108 (83.7 %)	0.6842
B	27 (20.5 %)	24 (18.3 %)	21 (16.3 %)	
Tumor size				
<2 cm	58 (43.9 %)	58 (44.3 %)	59 (45.7 %)	0.9531
≥2 cm	74 (56.1 %)	73 (55.7 %)	70 (54.3 %)	

[a] Age at the time of registration in the randomized trial

600 mg/day group, the 300 mg/day group, and the placebo group were 36, 55, and 47, respectively. In the 600 mg/day group, the 300 mg/day group, and the placebo group, 19, 15, and 15 patients, respectively, were "lost to follow-up."

The median follow-up duration was 1,782 days (4.9 years), with a maximum of 2,364 days (6.5 years). Median and maximum follow-up durations for each of the groups were as follows: 1,815 days (5.0 years) and 2,364 days (6.5 years) for the 600 mg/day group, 1,681 days (4.6 years) and 2,320 days (6.4 years) for the 300 mg/day group, and 1,768 days (4.8 years) and 2,336 days (6.4 years) for the placebo group.

Overall survival

Table 2 shows cumulative survival rates determined using the Kaplan–Meier method. The 2-year survival rates in the 600 mg/day, 300 mg/day, and placebo groups were 93.1, 88.5, and 93.0 %, respectively. The 5-year survival rates in the 600 mg/day, 300 mg/day, and placebo groups were

Table 2 Patients with follow-up and survival rates

Group	*n*	Censored[a]	Event[c]	Survival rate	
				2 years	5 years
600 mg/day	132	96 (19[b])	36	93.1 %	73.9 %
300 mg/day	131	76 (15[b])	55	88.5 %	56.8 %
Placebo	129	82 (15[b])	47	93.0 %	64.3 %

Median follow-up time: 4.9 years

[a] Data from after 12/31/2011 were considered censored cases

[b] If the last date on which survival was confirmed was before December of 2011, then the patient was considered lost to follow-up

[c] Death due to any cause was considered an event

73.9, 56.8, and 64.3 %, respectively, with the maximum cumulative survival rate observed in the 600 mg/day group. Median survival time in the 300 mg/day and placebo groups were 2,102 days (5.8 years) and 2,165 days (5.9 years), respectively; this parameter could not be calculated for the 600 mg/day group due to good prognosis. Figure 2 shows the Kaplan–Meier curves for the 600 mg/day and placebo groups. With regard to overall survival, no significant difference was observed between the 600 mg/day and placebo groups (hazard ratio 0.726; 95 % CI 0.470–1.122; $P = 0.1475$ by the log-rank test). Similarly, no significant difference in overall survival was observed between the 300 mg/day and placebo groups (hazard ratio 1.253; 95 % CI 0.849–1.850; $P = 0.2547$ by the log-rank test).

Sub-group analysis (600 mg/day vs. placebo group)

Results from the sub-group analysis of survival time, which compared the 600 mg/day and placebo groups, are shown in Fig. 3. Factors from the sub-group analysis that were significant at the $P < 0.05$ level by the log-rank test included the Child-Pugh A classification (hazard ratio 0.575; 95 % CI 0.341–0.967; $P = 0.0347$ by the log-rank test) and primary tumor size under 2 cm (hazard ratio 0.447; 95 % CI 0.218–0.919; $P = 0.0245$ by the log-rank test). Kaplan–Meier curves by Child-Pugh A classification for the 600 mg/day and placebo groups (600 mg/day, $n = 105$; placebo, $n = 108$) are shown in Fig. 4.

Discussion

Early diagnosis and curative treatment for HCC has become widespread, but following completion of curative treatment for HCV-HCC, recurrence rates remain high and prognosis is poor. The 5-year cumulative survival rate in this cohort study was higher in the 600 mg/day peretinoin group than in the placebo group. Particularly for patients with the Child-Pugh A classification, the 600 mg group had significantly longer survival compared to the placebo group. We believe that this finding will contribute to future attempts for developing measures to prevent HCC recurrence.

The guidelines for clinical studies of HCC [19] recommend that only patients with the Child-Pugh A classification be incorporated into clinical studies, because death due to cirrhosis among patients classified as Child-Pugh B or Child-Pugh C could mask treatment effects. In this study, roughly 80 % of our patients were classified as Child-Pugh A, and thus our results relating to this group may be generalizable. In addition, the results of this study, expressed in patients with tumor size of under 2 cm, are consistent with the report of Nakashima et al. [20] that suggests the incidence of multicentric recurrence is high amongst

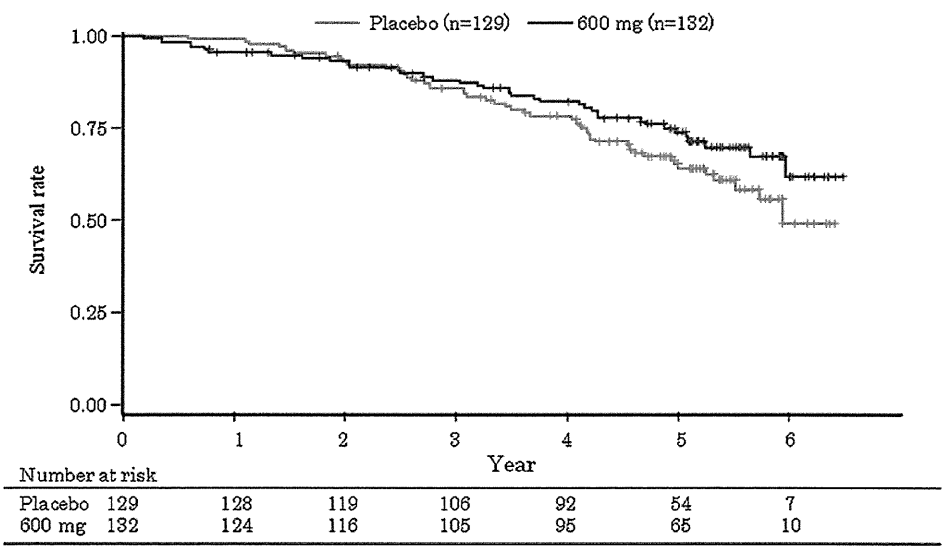

Fig. 2 Kaplan–Meier plot of overall survival: peretinoin 600 mg/day vs placebo. Hazard ratio 0.726; 95 % CI 0.470–1.122; $P = 0.1475$ by log-rank test

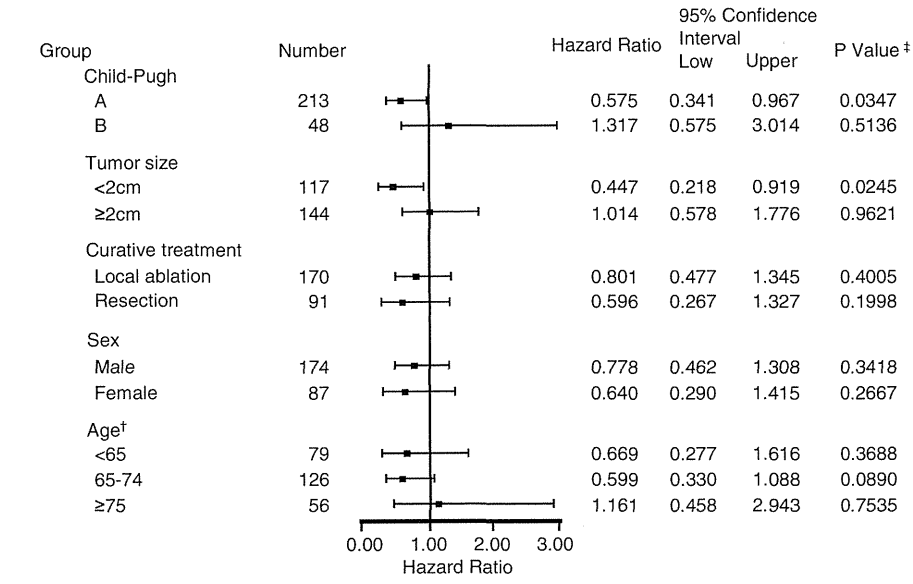

Fig. 3 Sub-group analysis: peretinoin 600 mg/day vs. placebo. †Age at the time of registration to the randomized trial. ‡Log-rank test

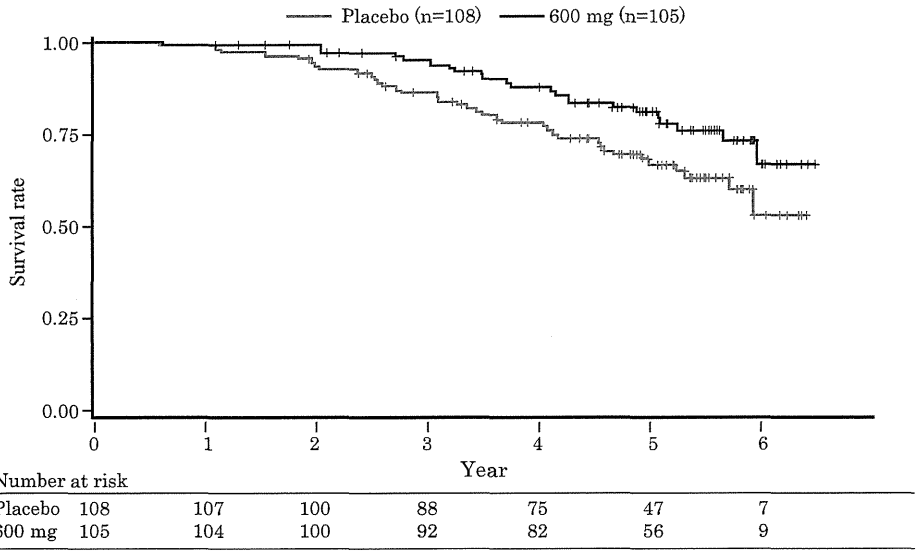

Fig. 4 Kaplan–Meier plot of overall survival in Child-Pugh A: peretinoin 600 mg/day vs. placebo. Hazard ratio 0.575; 95 % CI 0.341–0.967; log-rank test, $P = 0.0347$

patients with tumor size of under 2 cm, and peretinoin is particularly effective at suppressing multicentric recurrence in such cases.

From the results of this study and the randomized trial, we speculate that peretinoin improves patient survival time by suppressing HCC recurrence. Among those classified as Child-Pugh A, the hazard ratio of recurrence-free survival for peretinoin and placebo in the randomized trial was 0.60 (95 % CI 0.41–0.89) [18], and the hazard ratio of overall survival for peretinoin 600 mg/day and placebo was 0.575 (95 % CI 0.341–0.967). The similar hazard ratios could be explained by the following reasons. First, the investigational drug was administered for 2 years maximum in the randomized trial, and the median follow-up duration of this cohort study was nearly 5 years. Peretinoin is particularly well-known for its capacity to suppress multicentric recurrence, so given that a certain duration of time is required for a pre-cancerous lesion to develop into cancer, we surmise that peretinoin may have continued to work effectively in suppressing recurrence even after completion of peretinoin treatment. A follow-up survey [21] of the randomized trial conducted by Muto et al. [16] found that after administering this drug for 1 year, continued effects were noted for at least 150 weeks (roughly 3 years) following treatment completion. In addition, peretinoin has been found to suppress platelet-derived growth factor C

[22, 23], and thus it may be continuously suppressing recurrence by inhibiting the progression of hepatic fibrosis.

The limitation of this study was that the randomized trial was designed to evaluate recurrence-free survival in peretinoin-treated patients, and thus the number of patients may have been insufficient for evaluating the primary endpoint of this cohort study, i.e., overall survival. However, being able to collect and evaluate data from all patients who were administered the investigational drug in the randomized trial improved the statistical accuracy of our analysis.

Despite the limitation, the important point of this study is that by focusing on survival versus death, which is an index with no room for subjectivity, we were able to determine that among those classified as Child-Pugh A, the 600 mg/day group had a significantly longer overall survival compared to the placebo group. Notably, independent of this cohort study, a phase III trial is currently underway to examine the effects of peretinoin on controlling HCC recurrence among those classified as Child-Pugh A who have completed curative treatment for HCV-HCC. In conclusion, administration of 600 mg/day peretinoin to patients who have completed curative treatment for HCV-HCC is anticipated to improve survival of patients with relatively stable liver function, such as those classified as Child-Pugh A. Our finding provides novel insights into the understanding of 5-year survival after treatment with investigational drug in patients with HCV-HCC.

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Conflict of interest Okita has received lecture fees from Kowa. Izumi has received lecture fees from MSD, Chugai Pharmaceutical, Daiichi Sankyo, and Bayer Yakuhin. Masafumi Ikeda has received research funding from Kowa. Kokudo has received research funding from Dainippon Sumitomo Pharma, Bayer Yakuhin, Merk Serono, Bristol-Myers Squibb, Chugai Pharmaceutical, Taiho Pharmaceutical, and Yakult Pharmaceutical. Ueshima has received lecture fees from Bayer Yakuhin, MSD, Ajinomoto Pharmaceuticals, Eisai, Dainippon Sumitomo Pharma, Eidia, Takeda Pharmaceutical, Janssen Pharmaceutical, Daiichi Sankyo, and Boehringer Ingelheim Japan. Kudo has received lecture fees from Bayer Yakuhin and Eisai. Okusaka has received research funding from Kowa. Ohashi received executive salaries from Statcom, lecture fees from Chugai Pharmaceutical and Shionogi, manuscript fee from DNP Media Create, and research funding from Kowa Pharmaceutical, Astellas Pharma, Takeda Pharmaceutical, and Kyowa Hakko Kirin. Kumada holds a patent on SRL, and has received lecture fees from MSD, Bristol-Myers Squibb, Mitsubishi Tanabe Pharma, Dainippon Sumitomo Pharma, Toray Industries, and Ajinomoto Pharmaceuticals. The other authors declare that they have no conflict of interest.

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Original Article

Therapeutic effects of short- and intermediate-term tolvaptan administration for refractory ascites in patients with advanced liver cirrhosis

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Aim: Tolvaptan, an oral arginine vasopressin V2 receptor antagonist, became available for hepatic ascites. We evaluated the therapeutic efficacy and safety of tolvaptan administration to treat refractory ascites.

Methods: Data were collected from 15 hospitalized patients with cirrhosis (hepatitis C, 10; alcoholism, five) after adding tolvaptan (3.75–11.25 mg/day) to conventional diuretics. Bodyweights and serum sodium and creatinine concentrations were measured. Tolvaptan was continued for 4 weeks or longer for a median follow-up period of 42 days (range, 28–56).

Results: In the first week (introduction phase), tolvaptan significantly reduced median weight (66.6, 65.9 and 63.1 kg on days 0, 1 and 7, respectively; $P < 0.004$). The numbers of good responders (≥3 kg reduction in 4 days), responders (<3 kg weight reduction) and non-responders (no weight reduction) were seven (46.7%), six (40.0%) and two of the 15 (13.3%), respectively. The two non-responders had concomitant chylous pleural effusion or spontaneous bacterial peritonitis. All patients continued tolvaptan for 2 weeks or longer and six (40%, three good responders and three responders) were treated for a median of 42 days without additional intervention. During this intermediate-term administration of tolvaptan, the median weight reduction was statistically significant (65.4, 61.9 and 56.9 kg on days 0, 7 and 42, respectively; $P < 0.030$) and there was no serum sodium imbalance or renal dysfunction; but two of these six developed hepatic coma.

Conclusion: Tolvaptan safely alleviated fluid retention caused by hepatic cirrhosis. Intermediate-term administration of tolvaptan apparently helped maintain weight reduction achieved during the introduction phase.

Key words: liver cirrhosis, refractory hepatic ascites, tolvaptan

INTRODUCTION

ASCITES IS THE most frequent manifestation of cirrhosis.[1] Diuretics, including spironolactone, aldosterone antagonists and the loop diuretic furosemide, have been developed to control fluid retention.[2] In actual practice, many cirrhosis patients complain of abdominal distension, leg edema and dyspnea due to fluid retention. Conventional diuretics are not always effective to alleviate these symptoms. Alternative therapies, including large-volume paracentesis with i.v. albumin infusion or cell-free and concentrated ascites reinfusion therapy (CART), are applicable[3,4] in such cases, but in spite of their use, refractory ascites occurs, and its optimal management remains unresolved.

Tolvaptan, a novel oral arginine vasopressin V2 receptor antagonist, which has been indicated for heart failure, recently became available for use in hepatic edema.[5–7] By inhibiting reabsorption in the renal collecting tubules, tolvaptan increases electrolyte-free urine excretion, without, therefore, increasing electrolyte excretion. This mechanism seems to help reduce the occurrence of diuretic-induced renal failure, which is

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well known as the most frequent complication of furosemide use.[8]

According to previous reports, short-term tolvaptan add-on therapy was effective for the treatment of hepatic edema and ascites-related clinical symptoms without worsening the electrolyte balance.[6,7] Here, we report an evaluation of the clinical courses of 15 cirrhosis patients after initiating tolvaptan therapy, which illustrates the efficacy of short- and intermediate-term administration.

METHODS

ENROLLED IN THIS study were 15 cirrhosis patients with ascites who had been receiving combinations of loop diuretics, thiazide or anti-aldosterone agents. Tolvaptan 3.75 mg/day (7.5 mg/day in one patient) was initiated with mean doses of concomitant diuretics as follows: furosemide 44 mg/day ($n = 15$), trichlormethiazide 1.67 mg/day ($n = 3$), spironolactone 43.2 mg/day ($n = 11$) and/or eplerenone 50 mg/day ($n = 1$).

Patients were recruited between September 2013 and January 2014 and were required to be hospitalized for approximately 1 week. Clinical characteristics of patients are presented in Table 1. The 15 patients (11 men and four women) had a median age of 70 years (range, 56–79). The etiology of cirrhosis was hepatitis C for 10 patients and alcoholism for five; six patients were Child–Pugh classification B and nine were C. The median bodyweight was 66.6 kg (range, 45.1–78.5).

Table 1 Demographic and baseline characteristics of patients

Characteristics	Values (range or percentage)
Age (years)	70 (56–79)
Sex	
Male	11 (73.3%)
Female	4 (26.7%)
Bodyweight (kg)	66.6 (45.1–78.5)
Liver disease	
Hepatitis C	10 (66.7%)
Alcohol	5 (33.3%)
Child–Pugh classification A/B/C	0/6/9
Serum albumin (g/dL)	2.6 (1.8–3.7)
Total bilirubin (mg/dL)	1.5 (0.8–4.5)
PT (%)	61.3 (13.8–83.4)
Platelet (10^4 counts/μL)	10.8 (2.3–23.6)
Serum creatinine (mg/dL)	1.23 (0.63–1.80)
Complications*	
Hepatocellular carcinoma	10/15 (66.7%)
Esophageal varix	12/15 (80%)
Splenomegaly	11/15 (73.3%)

Data presented as median or *n* (%) patients.
*Present or past complications.
PT, prothrombin time.

Day 0 was defined as the first day of tolvaptan administration. Subsequently, the bodyweight, which can be an objective marker to assess improvement of hepatic edema during short-term diuretic therapy,[9] was measured every morning and cumulative urine volumes were collected daily. Blood was collected to determinate sodium and creatinine concentrations on days 0 (before and ~6 hours after tolvaptan administration), 1, 3, 6 and 7. According to these results, the dose of tolvaptan was gradually increased to 11.25 mg/day.[10] The daily dose of tolvaptan was increased from 3.75 mg to 7.5 mg in seven (46.7%) and to 11.25 mg in one (6.7%), respectively.

Patients who had a weight reduction of more than 3 kg in 4 days were defined as "good responders"; those whose weight decreased to a lesser extent were defined as "responders" and those with no weight loss were defined as "non-responders".

After the introduction of tolvaptan, all 15 patients continued on the same dose, and bodyweight and serum sodium and creatinine concentrations were evaluated. Patients categorized as group 1 were observed without additional interventions for ascites for a median follow-up period of 42 days (range, 28–56), and were defined as those for whom intermediate-term tolvaptan administration was efficacious. Patients who required additional measures to manage their ascites during the intermediate-term tolvaptan administration period were categorized as group 2. Groups 1 and 2 were compared to extract factors associated with the efficacy of intermediate-term tolvaptan administration.

Differences between each measured value (bodyweight, serum sodium and serum creatinine concentration) before and after the implementation of tolvaptan were analyzed by the Wilcoxon signed-ranks tests. To compare group 1 with group 2, continuous data were analyzed using the Mann–Whitney *U*-test. Categorical data were analyzed using the χ^2-test. Statistical significance was assigned to differences having two-sided *P*-values of less than 0.05.

RESULTS

Early effect of tolvaptan

THE CHANGE IN bodyweight from baseline was measured for 7 days (the introduction phase) after

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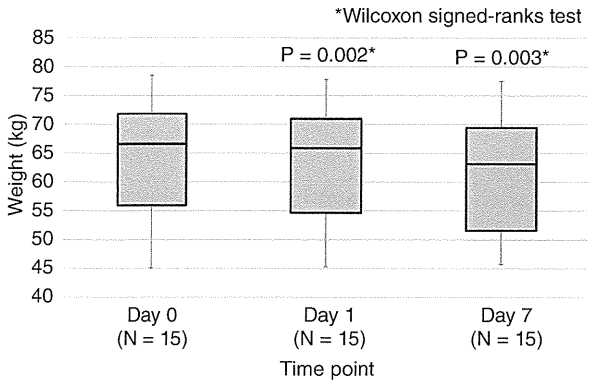

Figure 1 Box and whisker plots of bodyweight (kg) in the first week (introduction phase) of tolvaptan administration. Median weights: 66.6 (range, 45.1–78.5; $n = 15$), 65.9 (range, 45.3–77.8 kg; $n = 15$) and 63.1 kg (range, 45.7–77.5 kg; $n = 15$) on days 0, 1 and 7, respectively. Wilcoxon signed-ranks tests.

initial tolvaptan administration. The median weights were 66.6 (range, 45.1–78.5; $n = 15$), 65.9 (range, 45.3–77.8; $n = 15$) and 63.1 kg (range, 45.7–77.5; $n = 15$) on days 0, 1 and 7, respectively. The differences between days 0 and 1 and days 0 and 7 were statistically significant ($P = 0.002$ and 0.003, respectively) (Fig. 1). The urine volume increased from the baseline on day 0 of a median of 1400 mL/day (range, 532–2700; $n = 12$) to its highest level on day 2 of 2050 mL/day (range, 871–3300; $n = 14$); it then decreased gradually until day 7 to 1322 mL/day (range, 800–2300; $n = 12$) (Fig. 2). Serum sodium concentration did not change significantly (Fig. 3), with the median sodium concentration remaining fairly stable while the range widened slightly, as follows: day 0, 139.5 mEq/L (range, 131–145; $n = 14$); day 1, 139 mEq/L (range, 132–146; $n = 15$); and day 7, 139.5 mEq/L (range, 129–144; $n = 12$). The serum creatinine concentration also did not change significantly (Fig. 4): median values were 1.23 mg/dL (range, 0.63–1.8; $n = 14$) on day 0; 1.29 mg/dL (range, 0.71–1.66; $n = 15$) on day 1; and 1.29 mg/dL (range, 0.70–1.51; $n = 11$) on day 7. The number of good responders was seven (46.7%), responders six (40.0%) and non-responders two of the 15 patients (13.3%).

Case reports for one representative good responder and the two non-responders

Case 1

A77-year-old man with ascites due to hepatitis C cirrhosis added tolvaptan 3.75 mg/day to furosemide 40 mg/day (Fig. 5). The Child–Pugh classification was B. Change in weight from day 0 (60.1 kg) to day 4 (57.0 kg) was –3.1 kg. After day 4, the change in weight was not significant. There was no sodium imbalance or renal dysfunction due to tolvaptan. This patient, with a weight reduction of more than 3 kg in 4 days, was categorized as a good responder.

Clinical characteristics of the two non-responders included: (i) concomitant chylous pleural effusion; and (ii) ascites with spontaneous bacterial peritonitis (SBP) (Table 2).

Case 2

A69-year-old man complained of dyspnea due to ascites and right pleural effusion secondary to hepatitis C cir-

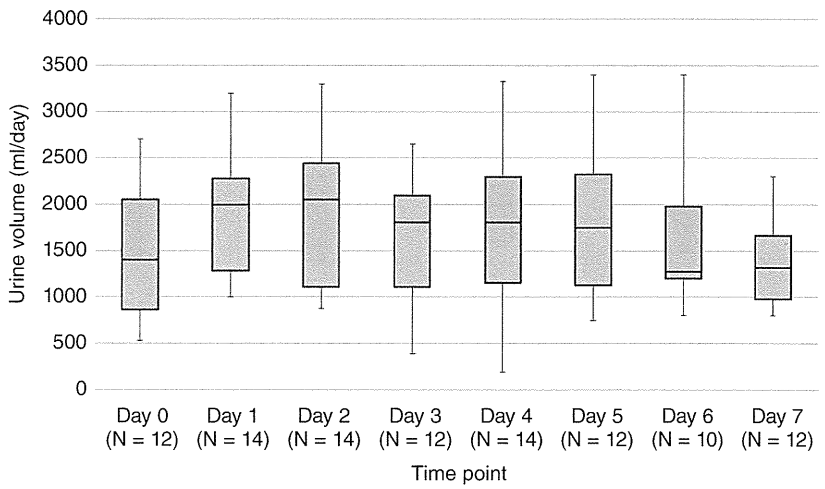

Figure 2 Box and whisker plots of daily urine volumes (mL/day) in the introduction phase of tolvaptan administration. Median urine volume was highest on day 2 (2050 mL/day) and then decreased gradually.

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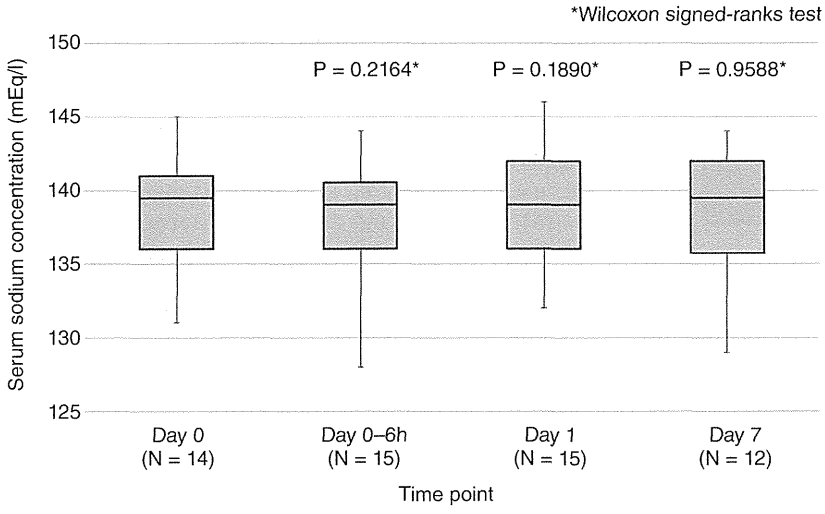

Figure 3 Box and whisker plots of serum sodium concentration (mEq/L) in the introduction phase of tolvaptan administration. Serum sodium concentrations at days 0–6 h were 139 mEq/L (range, 128–144 mEq/L). There was no significant difference between sodium concentration at day 0 and at days 0–6 h (6 h after administration of tolvaptan), 1 and 7 ($P = 0.2164$, 0.1890 and 0.9588, respectively). Wilcoxon signed-ranks tests.

rhosis (Fig. 6). The Child–Pugh classification was C. After thoracentesis to alleviate dyspnea, tolvaptan 3.75 mg/day was added to his conventional diuretics regimen of furosemide 20 mg/day and spironolactone 25 mg/day. However, neither weight nor dyspnea improved. Therefore, the dose of tolvaptan was increased to 7.5 mg/day on day 3. However, the weight increased from baseline, and thoracentesis revealed a triglyceride concentration of 114–201 mg/dL.

Case 3

A64-year-old woman with Child–Pugh score B and ascites due to hepatitis C cirrhosis added tolvaptan 3.75 mg/day to furosemide 60 mg/day, spironolactone 25 mg/day and trichlormethiazide 1 mg/day. The change in weight from day 0 (45.1 kg) to day 6 (48.2 kg) was +3.1 kg, and tolvaptan was increased to 7.5 mg/day on day 6. However, the increased tolvaptan was not effective, and paracentesis revealed a high concentration of polymorphonuclear leukocytes (415 cells/μL); SBP was diagnosed.

Intermediate-term (≥4 weeks) administration of tolvaptan

All 15 patients continued tolvaptan after the introduction period of 1 week; six patients (40%, three good

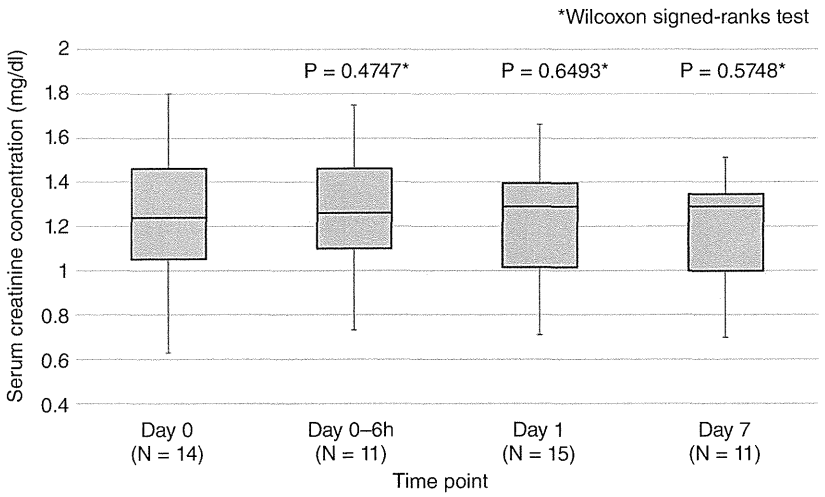

Figure 4 Box and whisker plots of serum creatinine concentration (mg/dL) in the introduction phase of tolvaptan administration. There were no significant differences when comparing day 0 with days 0–6 h (6 h after administration of tolvaptan), 1 and 7 ($P = 0.4747$, 0.6493 and 0.5748, respectively). Wilcoxon signed-ranks tests.

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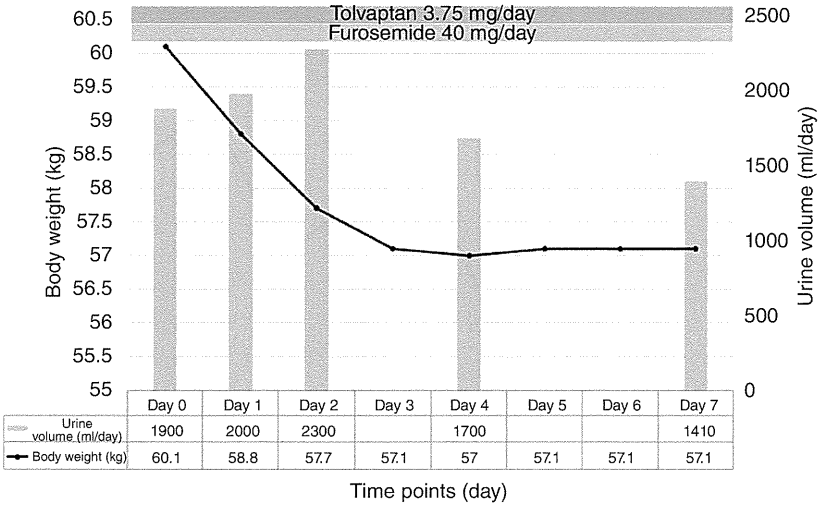

Figure 5 Clinical course of a good responder (case 1). A 77-year-old man having ascites due to hepatitis C cirrhosis added tolvaptan 3.75 mg/day to furosemide 40 mg/day. Child–Pugh classification B. Change in weight from day 0 (60.1 kg) on day 4 (57.0 kg) was −3.1 kg.

responders and three responders) were observed for a median of 42 days (range, 28–56) without additional interventions for ascites (group 1).

Of the other nine patients (60%, four good responders, three responders and two non-responders), four (two good responders and two responders) needed additional therapies for ascites within 4 weeks, either i.v. albumin or furosemide infusion ($n = 2$) or paracentesis ($n = 2$); three (two good responders and one responder) ended up categorized as forgetting to take the tolvaptan ($n = 1$), a failure of observation ($n = 1$) and heavy alcohol drinking ($n = 1$); and two (two non-responders) depended on paracentesis or thoracentesis despite tolvaptan use. After excluding one good responder (for forgetting to take tolvaptan) and the two non-responders, a total of six patients (three good responders and three responders) were categorized as group 2.

Evaluation of group 1 data following intermediate-term administration of tolvaptan revealed statistically significant differences in median weight between days 0 and 7 and days 0 and 42 ($P = 0.028$ and 0.028, respectively) (Fig. 7). However, the median weights on days 7 and 42 were not different ($P = 0.345$). Changes in serum sodium and creatinine concentrations between days 0 and 42 were not statistically significant ($P = 0.893$ and 0.225, respectively). The median sodium concentrations were 140 (range, 132–141; $n = 6$) and 139 mEq/L (range, 135–144; $n = 6$) on days 0 and 42, respectively. The median creatinine concentrations were 1.25 (range, 0.8–1.8; $n = 6$) and 1.29 mg/dL (range, 0.76–1.67; $n = 6$) on days 0 and 42, respectively.

Comparing groups 1 and 2 revealed no significant differences in demographic and clinical characteristics (Table 3). Patients' age, sex, weight at baseline, cirrhosis etiology, extent of liver damage, present or past history of hepatocellular carcinoma and esophageal varix were not relevant to the efficacy of intermediate-term tolvaptan use.

During the intermediate-term administration of tolvaptan, one patient was able to quit tolvaptan

Table 2 Clinical characteristics of non-responders (Case 2 and 3)

Case	Age/sex	Child–Pugh classification	Characteristics	Conventional diuretics
2	69 years/male	C	TG in pleural effusion, 114–201 mg/dL	Furosemide 20 mg/day, spironolactone 25 mg/day
3	64 years/female	B	SBP: polymorphonuclear leukocytes in ascites, 415 cells/μL	Furosemide 60 mg/day, spironolactone 25 mg/day, trichlormethiazide 1 mg/day

SBP, spontaneous bacterial peritonitis; TG, triglyceride.

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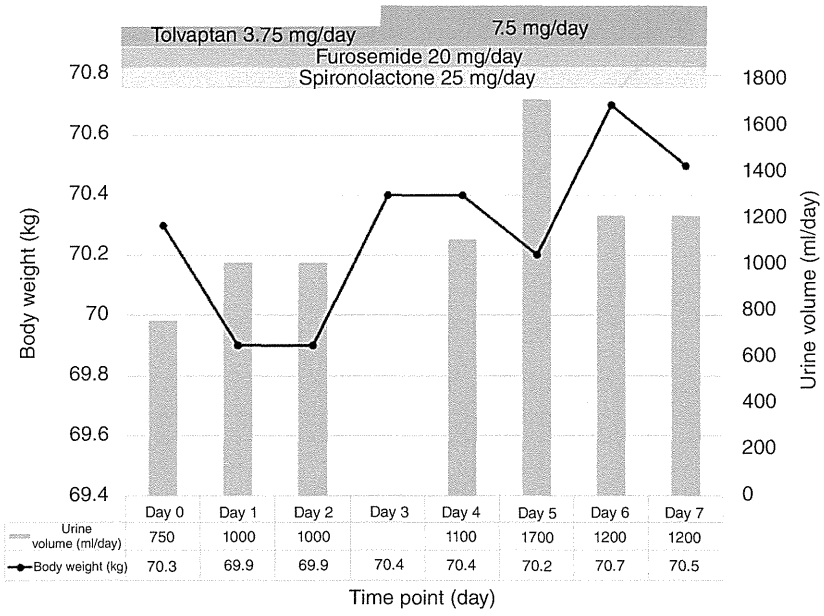

Figure 6 Clinical course of a non-responder (case 2). A 69-year-old man with dyspnea due to ascites and right pleural effusion caused by hepatitis C cirrhosis. Child–Pugh classification C. Tolvaptan 3.75 mg/day added to furosemide 20 mg/day and spironolactone 25 mg/day. Symptoms did not improve. Dose of tolvaptan increased to 7.5 mg/day on day 3; however, weight was increased from baseline.

because his ascites stabilized after treatment of portal thrombosis with danaparoid. Three patients needed additional therapy, as follows: CART ($n = 2$), i.v. albumin infusion ($n = 1$); and two patients developed hepatic coma.

DISCUSSION

DURING THE TOLVAPTAN introduction phase (first week of administration), the reduction in median weight from baseline was significant. Sodium imbalance or worsening of renal function, which are serious adverse effects of conventional diuretics, did not occur. On the other hand, two of the 15 cases were non-responders (Table 2). Case 2 developed chylous pleural effusion. It has been hypothesized that chylous ascites may be secondary to the rupture of lymph vessels due to the portal hypertensive state.[11] Although we were not able to perform paracentesis due to the small amount present, this thoracentesis result must reflect a

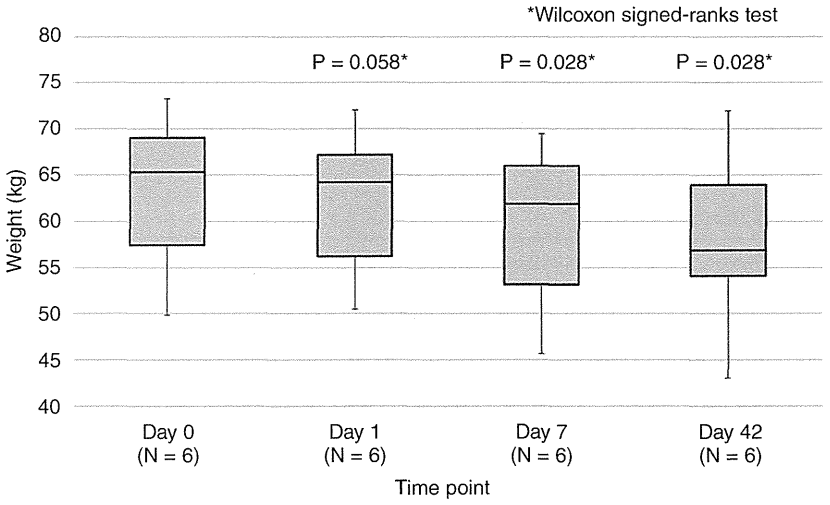

Figure 7 Intermediate-term administration of tolvaptan. Box and whisker plots of bodyweight (kg). Median weight was 65.4 (range, 49.9–73.3 kg; $n = 6$), 64.2 (range, 50.5–72.1 kg; $n = 6$), 61.9 (range, 45.7–69.5 kg; $n = 6$) and 56.9 kg (range, 43.1–72.0 kg; $n = 6$) on days 0, 1, 7 and 42, respectively. Differences between days 0 and 7 and days 0 and 42 were statistically significant ($P = 0.028$ and 0.028, respectively), but that between days 7 and 42 was not ($P = 0.345$). Wilcoxon signed-ranks tests.

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