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ORIGINAL RESEARCH

Long-term safety profile of tolvaptan in autosomal dominant polycystic kidney disease patients: TEMPO Extension Japan Trial

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Satoru Muto[1]
Tadashi Okada[2]
Moriyoshi Yasuda[3]
Hidetsugu Tsubouchi[4]
Koji Nakajima[4]
Shigeo Horie[1,5]

[1]Department of Advanced Informatics for Genetic Disease, Juntendo University Graduate School of Medicine, Tokyo, [2]Department of Clinical Development, [3]Pharmacovigilance Department, [4]Department of Medical Affairs, Otsuka Pharmaceutical Co, Ltd, [5]Department of Urology, Juntendo University Graduate School of Medicine, Tokyo, Japan

Aim: The aim of this trial (ClinicalTrials.gov identifier: NCT01280721) was to investigate the long-term safety profile of tolvaptan in Japanese patients with autosomal dominant polycystic kidney disease (ADPKD).

Methods: This open-label multicenter trial was conducted to examine adverse drug reactions (ADRs) related to tolvaptan up to an additional 3 years in 135 Japanese patients who participated in the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes (TEMPO) 3:4 trial at doses of 60–120 mg/d. Blood samples were collected at baseline; at weeks 1, 2, and 3; at month 3; and every 3 months thereafter.

Results: In total, 134/135 (>99%) patients experienced ADRs. The most frequent ADRs were thirst (77.0%), pollakiuria (57.0%), polyuria (37.8%), and hyperuricemia (14.8%). Any unexpected ADRs were not reported in this trial. Most ADRs occurred early during treatment. Fourteen patients (10.4%) experienced hepatic events, and 8 (5.9%) experienced >3-fold increases above the upper limits of normal in serum alanine aminotransferase or aspartate aminotransferase levels between 3 and 9 months following tolvaptan initiation, which recovered after drug interruption. Of the 8 patients, 7 (5.2%) were previously allocated to the placebo arm in the TEMPO 3:4 trial and 4 (3.0%) discontinued due to the hepatic events. One patient (0.7%) was previously allocated to tolvaptan and experienced similar events in the TEMPO 3:4 trial. None of the hepatic ADRs met Hy's Law laboratory criteria.

Conclusion: ADRs observed in this extension trial were similar to those identified in the TEMPO 3:4 trial and hepatic events were not progressive.

Keywords: autosomal dominant polycystic kidney disease, drug-induced liver injury, liver function test, safety profile, tolvaptan

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disease associated with progressive increase in total kidney volume (TKV), leading to deterioration of kidney function, and almost 50% of patients reach end-stage renal disease.[1–3] Patients with ADPKD maintain a glomerular filtration rate in the normal range for decades. However, continuous cyst growth and proliferation results in loss of kidney function over time, and the estimated glomerular filtration rate (eGFR) only starts to decline after the kidneys are grossly enlarged and little normal renal parenchyma remains.

Early in vivo studies demonstrated that tolvaptan, a potent, highly selective, and orally effective nonpeptide arginine vasopressin V_2 receptor antagonist, reduced kidney cyclic adenosine 3′,5′-monophosphate levels and kinase activity, in addition to slowing disease progression.[4–6] In the pivotal Tolvaptan Efficacy and Safety in Management

Correspondence: Satoru Muto
Department of Advanced Informatics for Genetic Disease, Juntendo University Graduate School of Medicine, Hongo 2-1-1, Bunkyo-ku, Tokyo 113-8421, Japan
Tel +81 3 5802 1227
Fax +81 3 5803 1227
Email s-muto@juntendo.ac.jp

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of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO 3:4) trial (ClinicalTrials.gov identifier: NCT00428948), tolvaptan slowed the annual rate of increase in TKV and slowed the decline in kidney function.[7,8] Tolvaptan was approved for the treatment of ADPKD in Japan (March 2014), Canada (February 2015), the European Union (May 2015), Korea (December 2015), Switzerland (April 2016), and Hong Kong (April 2017).

In the Japanese subset from TEMPO 3:4 (n=118), 3 patients experienced an abnormality in hepatic function classed as serious adverse events (SAEs), and all recovered following drug interruption. Of the 3 patients, 1 met Hy's Law laboratory criteria,[9] defined as 3× the upper limit of normal range (ULN) in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels and 2× the ULN in serum total bilirubin (T-Bil), defined according to Guidance for Industry: Drug-Induced Liver Injury (DILI).[9] The manifestation of hepatocellular injury following long-term tolvaptan treatment in ADPKD revealed the potential for serious irreversible injury; thus, we designed an open-label trial to evaluate the safety profile of tolvaptan in Japanese ADPKD patients following completion of the TEMPO 3:4 trial. In the meantime, the open-label extension trial TEMPO 4:4 (ClinicalTrials.gov identifier: CT01214421, 2010-018401-10) was designed to provide an additional 2 years of data on the long-term safety and efficacy of tolvaptan in subjects who completed TEMPO 3:4, and this was conducted outside of Japan.[10]

Methods

Open-label trial design

This open-label, multicenter, Phase III trial (TEMPO Extension Japan trial) was performed at 30 trial sites in Japan from November 2010 through August 2014. It was conducted in accordance with ethical principles originating from the Declaration of Helsinki and in compliance with good clinical practice guidelines. The protocol was approved by the institutional review board (IRB) at each trial site (Table S1). The first IRB approval was issued by Niigata University (IRB approval number: CH22-010). All patients provided written informed consent. Tolvaptan was administered to Japanese patients who completed the TEMPO 3:4 trial until its approval for the indication of ADPKD in Japan.

This trial consisted of a screening period (5 weeks), a titration period (3 weeks), an additional treatment period, the final evaluation period (1 week), and the follow-up period (8 weeks) (Figure 1). Patients who provided written informed consent underwent the screening evaluation, including vital sign tests, TKV measurements, clinical laboratory tests, electrocardiogram examinations, and kidney function tests.

The inclusion criteria were as follows:

1. Japanese patients who completed the TEMPO 3:4 trial with completed case report forms;
2. Patients who either completed 3 years of repeated administration in the TEMPO 3:4 trial or who discontinued due to pregnancy, and who completed the second follow-up examination in that trial;
3. Patients who had stable adverse events (AEs) or recovered from AEs in the TEMPO 3:4 trial and did not require follow-up examination.

The exclusion criteria were as follows:

1. Patients with eGFR <15 mL/min/1.73 m^2;
2. Patients who received trial drugs other than tolvaptan within 30 days before initiation of tolvaptan use;
3. Female patients who were pregnant, breastfeeding, or suspected to be pregnant, or those who intended to become pregnant during this trial;

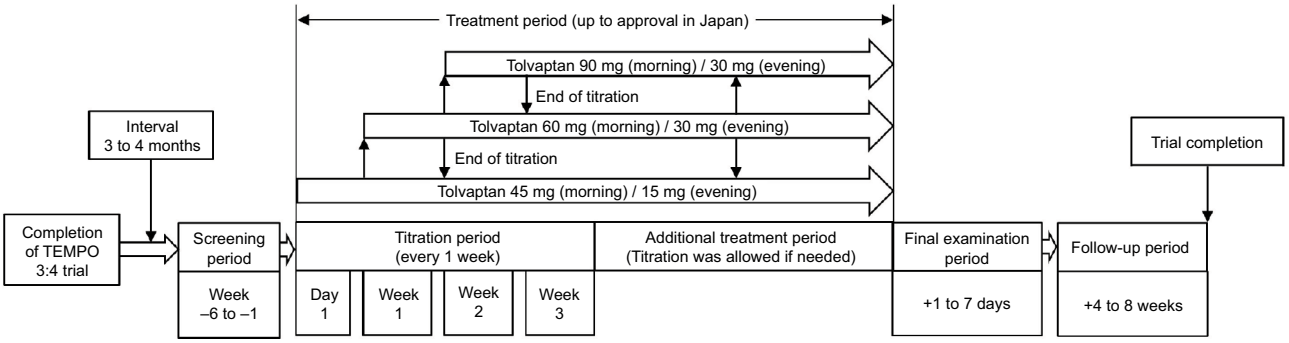

Figure 1 Design of TEMPO Extension Japan Trial.
Notes: This trial involved patients who were previously enrolled in the TEMPO 3:4 trial.[7,8] All participants received tolvaptan. Titration method was according to the previous TEMPO 3:4 trial.
Abbreviation: TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes.

4. Any patient who, in the opinion of the investigator or subinvestigator, should not participate in the trial.

Included patients underwent the baseline evaluation to reconfirm their eligibility immediately before initiation of tolvaptan (baseline data). Tolvaptan was administered to patients in a split-dose regimen in the morning and in the evening during both the titration period and the additional treatment period until tolvaptan was approved for treatment of ADPKD in Japan. Thus, an available maximum amount of time until the approval of tolvaptan was set as the trial period for each patient to obtain longer-term safety data. Three split-dose regimens of oral tolvaptan were tested for patients: a low dose of 60 mg/d (45/15 mg/d), an intermediate dose of 90 mg/d (60/30 mg/d), and a high dose of 120 mg/d (90/30 mg/d). In the 3-week titration period, patients began treatment with the lowest dose of tolvaptan, and doses were titrated to the next highest doses after each 1-week confirmation of a patients' self-reported tolerability. If higher doses were not well tolerated, downtitration was allowed. Thus, the optimal dose of tolvaptan according to tolerability was decided for each patient.

Following the titration period, patients remained on the highest tolerable doses during the additional treatment period. However, uptitration or downtitration was permitted according to patients' tolerability and/or clinician's decision within the 3 defined dosing regimens.

The final evaluation was conducted for patients within 7 days after the final administration of tolvaptan. The follow-up evaluation was conducted within 4–8 weeks after the final administration. If patients discontinued tolvaptan treatment for any reason, the same evaluation as the final one was performed (the discontinuation evaluation). Patients who received at least 1 dose of tolvaptan and had at least 1 observation after initiation of tolvaptan were included in the safety assessment.

Safety assessment

Safety assessment included documentation of adverse drug reactions (ADRs), clinical laboratory tests, vital signs, and electrocardiogram recordings.

Data on ADRs, which depended on physician judgment, were collected throughout the trial. The time points of data collection after initiation of tolvaptan use were as follows. Data on clinical laboratory test results were collected at baseline; at weeks 1, 2, and 3; at month 3; and every 3 months thereafter. Data on vital sign results were collected at baseline at weeks 1, 2, 3, and 4; and each month thereafter. Data on electrocardiogram examinations were collected at baseline, at week 4, at month 12, and every 12 months thereafter. These data were also collected at the final or discontinuation evaluations, as well as at the follow-up evaluation. The discontinuation or interruption criteria for individual patients were as follows:

1. Withdrawal of consent;
2. Deterioration of renal function (eGFR value <15 mL/min/1.73 m^2);
3. Detection of hepatocellular injury (ALT or AST: >3× ULN and T-Bil: >2× ULN);
4. Inability of patient to tolerate the lowest dose regimen (45/15 mg);
5. Patients for whom protocol compliance becomes impossible or for whom the principal investigator or attending subinvestigators judge withdrawal to be necessary for reasons other than those described earlier.

In addition, when any of the biochemical findings listed herein was detected, treatment was suspended promptly (refer to the US Food and Drug Administration [FDA] Guidance for Industry: Drug-induced Liver Injury, 2009).

1. ALT or AST >8× ULN;
2. ALT or AST >5× ULN, which persists for >2 weeks;
3. AST or AST >3× ULN and T-Bil >2× ULN or prothrombin time (international normalized ratio [INR]) > 1.5;
4. ALT or AST level greater than 3 times the ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

ADRs, together with their severities and occurrence time points, were observed after initiation of tolvaptan use. Severity of ADRs was defined as mild when uncomfortable feelings were experienced without difficulty in daily living activity, as moderate when uncomfortable feeling was experienced with limitation or negative influence on daily living activity, and as severe when disability in daily living activity or work occurred. For recurring events in the same patient, the first observation time point was analyzed.

Clinical laboratory tests for measuring serum sodium and potassium levels, as well as serum ALT, AST, and T-Bil levels as biomarkers of hepatic functions, were conducted at each time point.

Statistical analysis

No formal hypothesis testing was performed in the open-label trial. Continuous variables were expressed as a mean value

with SD. Categorical variables were expressed as number and proportion. These data were calculated using SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Demographic characteristics of patients and dose of tolvaptan

In the TEMPO Extension Japan trial, 135 patients were eligible to initiate treatment with tolvaptan and were included in the safety assessment. No patients were excluded from this trial to analyze the safety profile of tolvaptan. Demographic and clinical characteristics of patients at baseline are described in Table 1. During the long-term treatment period, the mean dose of tolvaptan was 91.7±25.7 mg/d, with the majority of patients (47.7%) being able to tolerate the highest dose of 120 mg/d (n=63). Remaining patients were on 90 mg/d (n=27, 20.5%) and 60 mg/d (n=42, 31.8%). The mean duration of tolvaptan administration was 856.3±299.8 days (range: 7–1264 days).

Safety assessment

Patient flow from the TEMPO 3:4 trial to the TEMPO Extension Japan trial is shown in Figure 2. Totally, 12 patients, 7 of tolvaptan and 5 of placebo, did not participate in the extension trial. In total, 22 patients (16.3%) discontinued this trial, 4 (3.0%) due to AEs, 9 (6.7%) due to meeting discontinuation criteria, 3 (2.2%) due to discretion by clinicians, and 6 (4.4%) due to withdrawal of consent. The remaining 113 (83.7%) patients completed the treatment period up to approval. In total, 512 ADRs were reported from 134 patients. Among them, 9 serious ADRs from 4 patients, and 16 severe ADRs from 8 patients were reported. Moreover, 6 patients discontinued tolvaptan use due to ADRs. The most frequent ADR was thirst (77.0%), followed by pollakiuria (57.0%), polyuria (37.8%), hyperuricemia (14.8%), and hepatic events (10.4%), which were all observed at rates of >10% of included patients (Table 2). AEs of cardiac disorder were reported from 13 patients (9.6%) and ADRs were found in 6 patients (4.4%). New dialysis cases were not reported in this study.

ADRs were generally mild in severity and were observed in the first 3 months of treatment (Table 2). Occurrence rates of the first ADRs in patients were 97.8% within 3 months, 0.7% in 3–6 months, 0% in 6–9 months, 0% in 9–12 months, and 0% in 12–30 months (Figure 3). The main ADRs observed after 3 months of treatment were hepatic function abnormality and hyperuricemia.

A total of 9 serious ADRs were found in 4 patients, namely, renal cyst infection (twice in 1 patient), sepsis (n=1), ovarian cancer (n=1), uterine cancer (n=1), dizziness (n=1), renal cyst hemorrhage (n=1), renal cyst rupture (n=1), and renal pain (n=1). All 4 patients were hospitalized due to the events.

Time course profiles of mean serum ALT, AST, and T-Bil are presented in Figure 4. Fourteen patients showed hepatic events. Of those, 8 patients (5.9%) experienced a >3-fold increase above the ULN in serum ALT or AST levels between 3 and 9 months after initiation of tolvaptan use, but 6 of those recovered after interruption of tolvaptan and 2 recovered without interruption (Table 3). Of the 8 patients, 5 discontinued the trial, and 3 completed the trial by continuation of tolvaptan or restarted after interruption. None of the hepatic events met Hy's Law laboratory criteria. Eight patients (5.9%) experienced an increase in blood creatinine levels (7 mild and 1 moderate in severity), which was judged by clinicians as an ADR (Table 2). In 6 of these patients, blood creatinine increased within 15 days after initiation of tolvaptan use. Six patients recovered without dose adjustment and 1 patient with moderate severity recovered following downtitration of tolvaptan dose, while 1 patient discontinued. Time courses of mean serum sodium and potassium levels during treatment are presented in Figure 5. No other deterioration of laboratory tests was observed. No marked abnormalities were observed in vital signs and electrocardiogram recordings. No death was observed.

Table 1 Demographic and clinical characteristics at baseline

Characteristics	n=135
Age, years	42.7±5.9
Sex, n (%)	
Male	77 (57.0)
Female	58 (43.0)
Height, cm	168.3±8.1
Body weight, kg	67.6±13.3
Body mass index	23.7±3.5
TKV, mL	1812±859
htTKV, mL/m	1073±493
eGFR, mL/min/1.73 m^2	61.2±21.7
Serum creatinine, mg/dL	1.11±0.55
Serum cystatin C, mg/L	1.02±0.42
Serum ALT, U/L	19.9±16.9
Serum AST, U/L	22.2±9.7
Total bilirubin, mg/dL	0.60±0.22
Serum sodium, mEq/L	140.1±1.7
Serum potassium, mEq/L	4.09±0.33

Note: Data are expressed as number (%) or mean ± SD.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; htTKV, height-corrected total kidney volume; TKV, total kidney volume.

Discussion

We focused on evaluating the safety profile of tolvaptan in the Japanese subset of ADPKD patients from the TEMPO 3:4

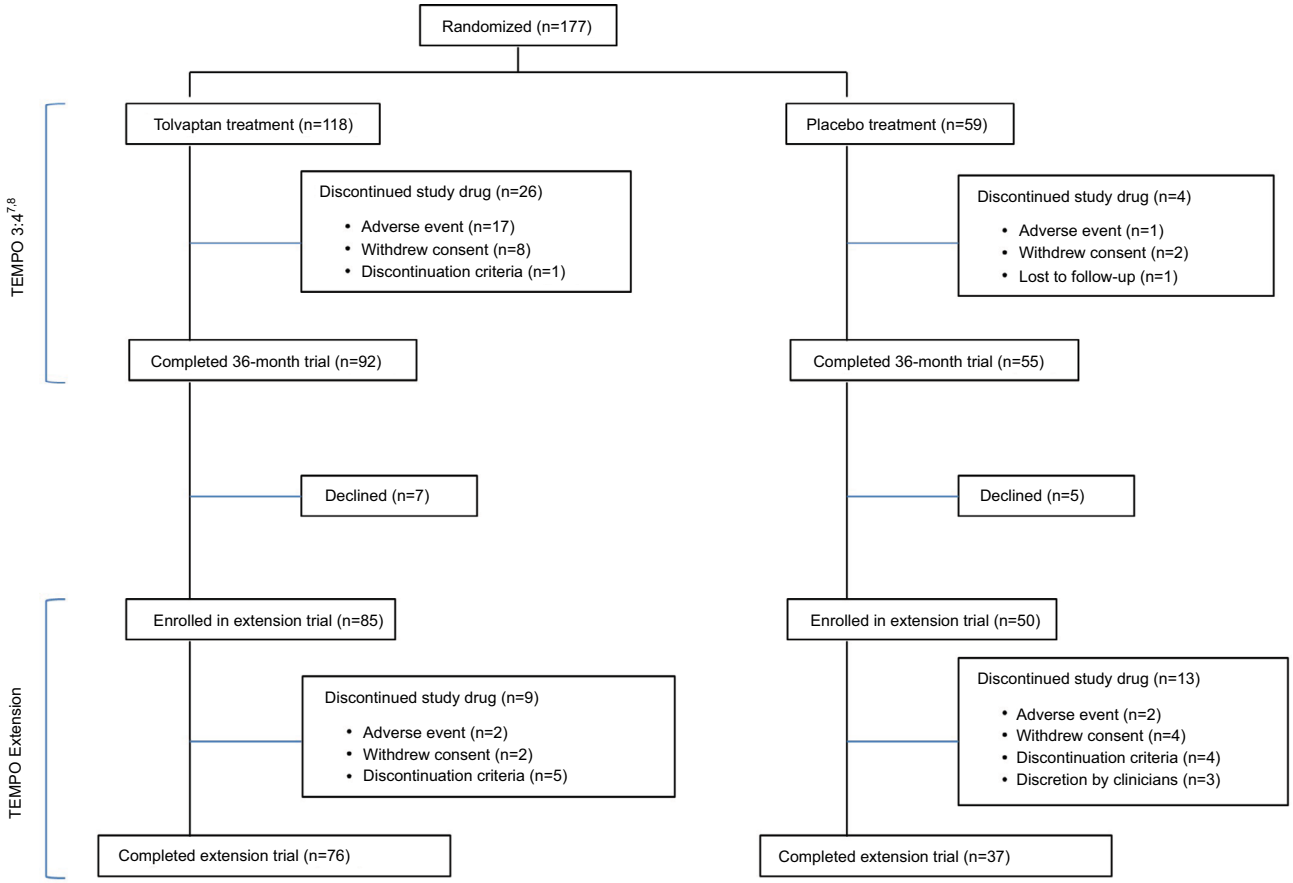

Figure 2 Patient flow chart.
Abbreviation: TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes.

trial through to marketing approval in Japan. ADRs observed in this extension trial were similar to those reported in Japanese patients in the TEMPO 3:4 trial.[8] Most ADRs occurred acutely within 3 months following initiation of tolvaptan use, and the severity of ADRs was generally mild. In the present trial, we stratified the population according to the treatment arm in the pivotal TEMPO 3:4 trial in Japan and calculated withdrawal rates in each group (Figure 6). In the TEMPO 3:4 trial, 4 placebo patients (6.8%) and 26 tolvaptan patients (22.0%) did not complete the trial. Similarly, placebo patients who crossed over onto active treatment discontinued at a similar rate (24.0%), while those who continued on tolvaptan treatment discontinued at a much lower rate (11.8%). Moreover, the percentage of patients reporting a hepatic event was similar across both studies (9.6% in the open-label trial vs 10.2% in the TEMPO 3:4 trial).[8]

ADRs that occurred in ≥10% of patients were thirst, pollakiuria, polyuria, hyperuricemia, and hepatic events. With the exception of the hepatic events, other ADRs were consistent with the pharmacological effect of tolvaptan.[6,12] Serious ADRs observed in this trial included sepsis, renal cyst infection, ovarian cancer, uterine cancer, dizziness, renal cyst hemorrhage, renal cyst rupture, and renal pain. Serious ADRs such as renal cyst infection, renal cyst hemorrhage, renal cyst rupture, and renal pain are common manifestations of ADPKD.

In the TEMPO 3:4 trial, 1 Japanese patient in the tolvaptan arm met Hy's Law laboratory criteria, resulting in discontinuation from the trial.[7] In the present trial, hepatic events were marked ADRs found at a rate of ~10%. Eight patients showed ALT and AST elevations >3-fold the ULN between 3 and 9 months following treatment initiation. One of these patients had received tolvaptan in the TEMPO 3:4 trial. However, this patient initially had high baseline levels of ALT and AST in the present trial. Moreover, this patient eventually discontinued the trial due to renal impairment and not due to a hepatic event; the remaining 7 patients (prior placebo patients in the TEMPO 3:4 trial) had normal hepatic function values at baseline of the extension trial. Of the 7 patients, 4 discontinued the trial due to their hepatic events and the

Table 2 Adverse drug reactions observed in patients treated with tolvaptan and their severity and observed time points

Events	n (%)	Severity			Observed time point after initiation of tolvaptan use, months				
		Mild	Moderate	Severe	≤3	to ≤6	to ≤9	to ≤12	to ≤30
State of general disorders									
Thirst	104 (77.0)	91	12	1	103	–	–	–	1
Hepatic events	14 (10.4)	–	–	–	–	–	–	–	–
Drug-induced liver injury	1 (0.7)	1	–	–	1	–	–	–	–
Abnormal hepatic function	13 (9.6)	12	1	–	4	6	2	–	1
Clinical examination									
Blood creatinine increase	8 (5.9)	7	1	–	6	–	1	–	1
Metabolism and nutritional status									
Decreased appetite	5 (3.7)	3	2	–	4	1	–	–	0
Dehydration	3 (2.2)	3	–	–	3	–	–	–	–
Hyperuricemia	20 (14.8)	20	–	–	9	3	1	–	7
Nervous system disorders									
Headache	10 (7.4)	8	2	–	7	–	1	–	2
Mental disorder	–	–	–	–	–	–	–	–	–
Insomnia	6 (4.4)	2	4	–	4	–	–	–	2
Kidney and urinary tract disorders									
Nocturia	6 (4.4)	2	4	–	5	1	–	–	–
Pollakiuria	77 (57.0)	52	24	1	75	2	–	–	–
Polyuria	51 (37.8)	39	12	–	51	–	–	–	–
Renal impairment	5 (3.7)	5	–	–	2	–	1	–	2
Vascular disorders	–	–	–	–	–	–	–	–	–
Hypertension	6 (4.4)	5	1	–	3	–	1	1	1
Hypotension	4 (3.0)	4	–	–	2	1	–	–	1

Notes: Predictable ADRs, such as liver function abnormality, and those from the aquaretic action of tolvaptan, including kidney function disorders, in addition to vascular events, are listed. As for the ADRs, the time point of the first ADR observed was analyzed. Events were categorized according to the MedDRA. Blank columns denote no ADRs. Data are expressed as the number of patients experiencing the respective ADRs, and the figures in parentheses demonstrate the percentage of those among the total patients who were administered the test drug (n=135).
Abbreviations: ADR, adverse drug reaction; MedDRA, Medical Dictionary for Regulatory Activities.

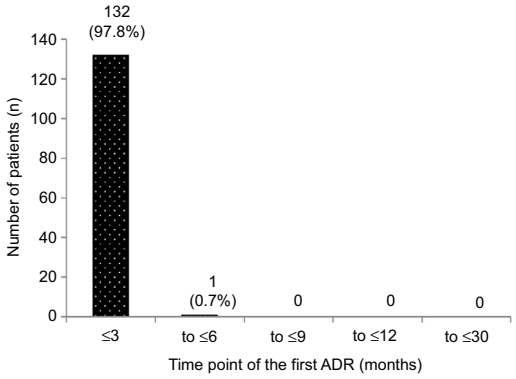

Figure 3 The number of patients experiencing their first ADRs in the course of the trial.
Notes: In the respective patients, the time point of the first ADR observed was noted. Thereafter, the numbers of the patients experiencing first ADR were analyzed every 3 months.
Abbreviation: ADR, adverse drug reaction.

remaining 3 completed the trial either continuing the drug or on treatment following drug interruption (Figure 6). None of the patients met Hy's Law laboratory criteria. Therefore, it is possible that monthly liver enzyme monitoring was sufficient to identify patients early in the hepatocellular injury event, thus preventing those patients from reaching levels consistent with Hy's Law laboratory criteria. All hepatic events observed in this trial were reversible; 2 patients recovered while on treatment (Patients 6 and 7 in Table 3). The 4 patients who discontinued due to hepatic function abnormalities were previously allocated to the placebo arm in the TEMPO 3:4 trial. All liver enzyme elevations occurred from 3 to 14 months following initiation of tolvaptan treatment, which is consistent with the 18-month window of susceptibility identified in the TEMPO 3:4 trial.[8,11] The potential for serious irreversible injury exists; thus, regular monitoring of transaminase levels will be warranted in this patient population to avoid serious deterioration of hepatic function over long-term treatment with tolvaptan. In the TEMPO 3:4 trial and the interim analysis of TEMPO 4:4, the risk of liver failure in ADPKD patients receiving long-term tolvaptan was estimated to be approximately 1:4000.[11] In Japan, tolvaptan was approved for the treatment of ADPKD on the condition that patients should receive monthly hepatic monitoring, a requirement that has been mirrored in other regions where marketing authorization has been granted. The contributing factor to hepatic injury is suggested to be the inhibition of hepatic bile

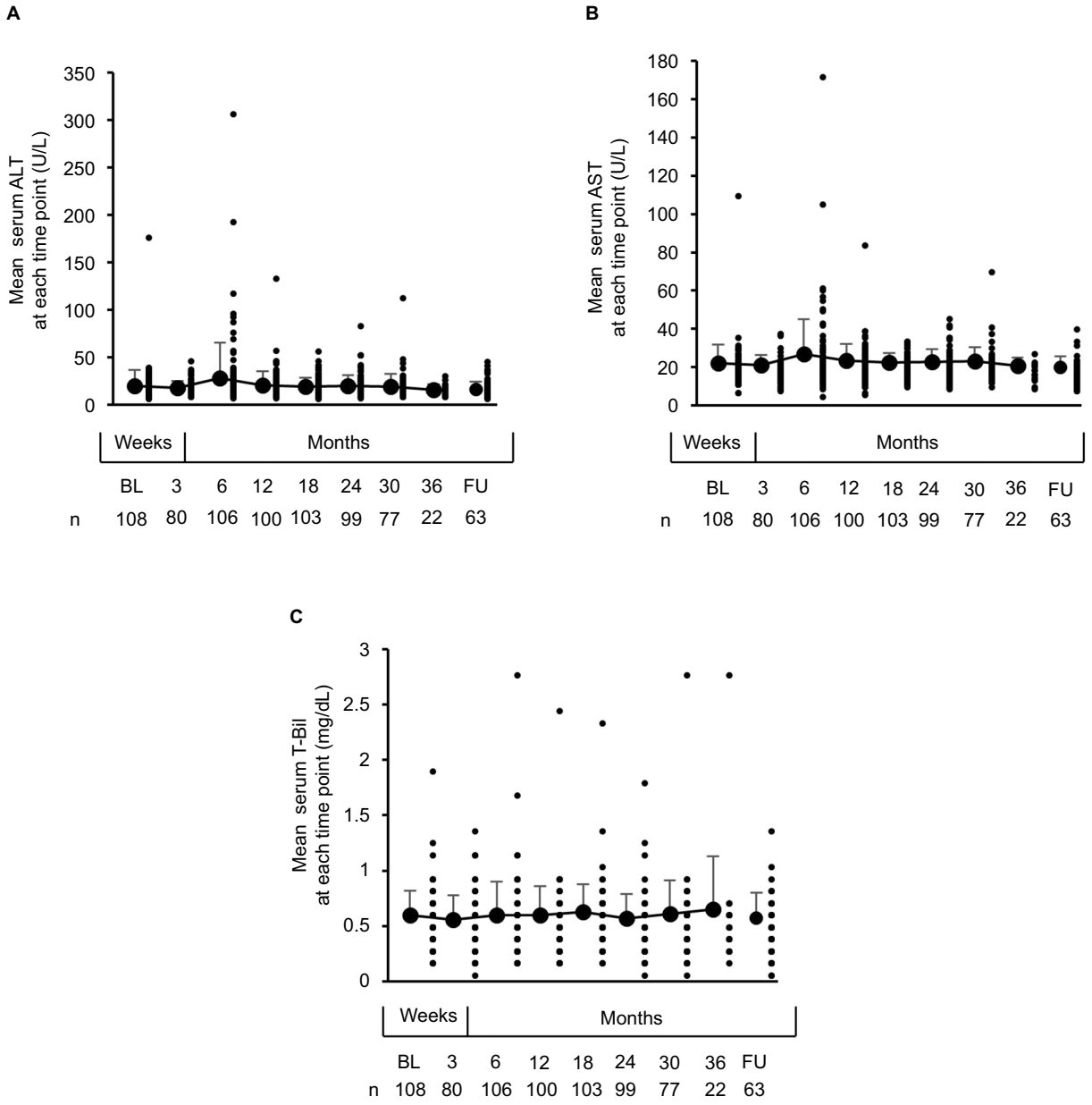

Figure 4 Laboratory test results at each time point.
Notes: (**A**) Serum ALT, (**B**) serum AST, and (**C**) serum T-Bil levels. Data are expressed as mean ± SD. Ranges for normal values are as follows: ALT, 5–45 U/L; AST, 10–40 U/L; T-Bil, 0.2–1.2 mg/dL.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-Bil, total bilirubin; BL, baseline; FU, follow-up; n, number of patients.

acid transporters by tolvaptan and its metabolites.[12] Further investigation of the mechanism of tolvaptan-induced liver injury might contribute to better clinical management.

On the other hand, 8 patients experienced increase in blood creatinine. Although there were similar reports, it is not clear yet whether tolvaptan is the single cause for this.[7,8] However, in this study, the creatinine increase was likely to be transient, and 7 patients continued tolvaptan use, except for 1 discontinuation, resulting in recovery.

Hypernatremia is also a predictable ADR for tolvaptan because of its aquaretic action. According to the postmarketing surveillance for heart failure patients with volume overload,[13] hypernatremia has been observed almost within 1 week after tolvaptan initiation. In this trial, no patient showed hypernatremia as an ADR. One of the reasons could be that water intake was not restricted in this trial, although it was commonly set in other trials to prevent edema. The limitation of this trial in terms of the study design was that it was not a comparative trial; moreover, efficacy analysis of tolvaptan was not performed. In this trial, we effectively conducted the treatment until approval of tolvaptan to obtain information on the long-term safety profile in an open-label manner in patients included in the TEMPO 3:4 trial. In the meantime, the open-label extension trial TEMPO 4:4 was conducted outside of Japan.[10] Of the 1445 patients (n=961

Table 3 Laboratory test results over time in patients showing an increase in serum ALT or AST to >3 times the upper limit of normal

Patient number	Parameter	Baseline	Month																Dose,[a] mg	Allocation in TEMPO 3:4 trial
			3	4	5	6	7	8	9	11	12	17	18	20	24	30	33	35		
1	ALT	176	92	–	–	87	–	177[b]	239	169	133	47	46	79	83	–	–	–	60	Tolvaptan
	AST	107	55	–	–	44	–	132[b]	177	103	83	31	27	52	47	–	–	–		
		–	–	–	–	–	–	–	★	–	–	–	–	–	▲[c]	–	–	–		
2	ALT	18	426	173	300	35	19	–	–	–	–	–	–	–	–	–	–	–	60	Placebo
	AST	21	175	87	147	29	21	–	–	–	–	–	–	–	–	–	–	–		
		–	★	–	–	–	▲	–	–	–	–	–	–	–	–	–	–	–		
3	ALT	17	236	392	221	65	21[b]	70	33	–	–	–	–	–	–	–	–	–	120	Placebo
	AST	19	72	178	72	34	21[b]	45	29	–	–	–	–	–	–	–	–	–	60	
		–	★	–	–	–	☆	★	▲	–	–	–	–	–	–	–	–	–		
4	ALT	20	152	–	86	192	22	15	15	18	17	19	56	20	–	–	–	–	90	Placebo
	AST	20	66	–	59	103	22	16	18	19	18	20	36	19	–	–	–	–	60	
		–	★	–	–	–	–	–	–	–	–	☆	★	▲	–	–	–	–		
5	ALT	20	18	–	–	76	691	241	78	20	26	–	16	–	11	12	10	–	60	Placebo
	AST	25	25	–	-	58	439	179	61	27	30	–	23	–	21	20	20	–		
		–	–	–	–	–	★	–	–	☆	–	–	–	–	–	–	◎	–		
6	ALT	21	24	164	47	24	–	–	23	–	19	–	–	–	14	16	17	–	90	Placebo
	AST	32	32	92	38	31	–	–	28	–	26	–	–	–	24	24	24	–		
		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	◎	–		
7	ALT	17	18	–	–	117	180[b]	121[b]	238	59	59	–	30	–	28	22	19	19	60	Placebo
	AST	17	21	–	–	61	75[b]	56[b]	108	43	39	–	29	–	25	22	23	23		
		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	◎		
8	ALT	18	96	147	522	306	37	18	16	–	–	–	–	–	–	–	–	–	120	Placebo
	AST	25	70	92	261	165	31	26	22	–	–	–	–	–	–	–	–	–		
		–	★	–	–	–	–	–	▲	–	–	–	–	–	–	–	–	–		

Notes: [a]Daily dose of tolvaptan immediately before the day of onset. [b]In-hospital assay. [c]Discontinuation due to decline in renal function. ★, Cessation; ☆, rechallenge; ▲, discontinuation; ◎, completion. Normal range in the TEMPO Extension Japan trial: ALT, 5–45 U/L; AST, 10–40 U/L.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes.

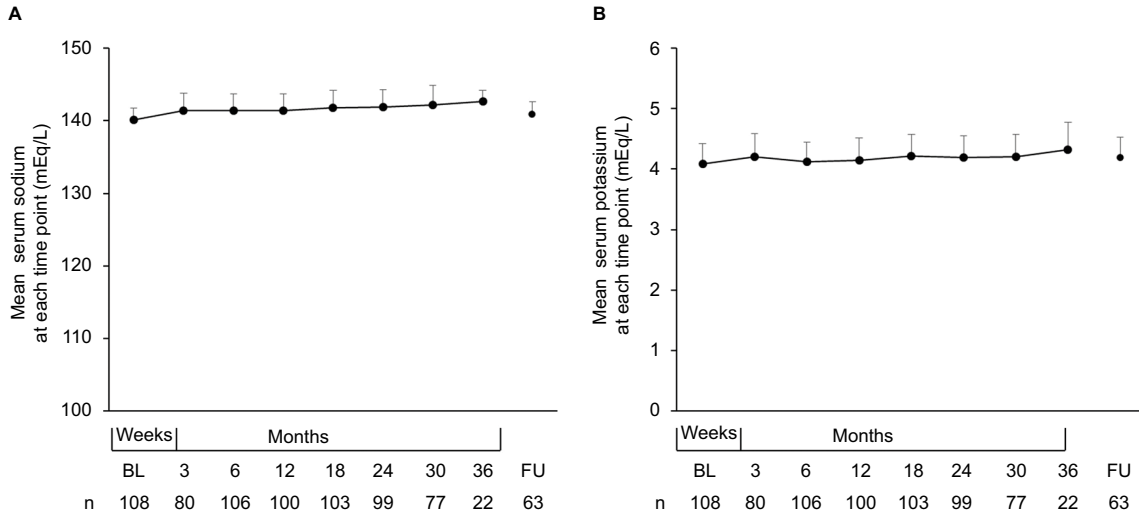

Figure 5 Serum sodium and potassium levels at each time point.
Notes: Serum (**A**) sodium and (**B**) potassium levels. Data are expressed as mean ± SD.
Abbreviations: BL, baseline; FU, follow-up; n, number of patients.

tolvaptan, n=484 placebo) randomized in the TEMPO 3:4 trial, 948 (excluding Japan) completed the trial and 871 of them elected to enroll in TEMPO 4:4 (n=557, early-treatment group, 58.0% of those on prior tolvaptan; n=314, delayed-treatment group, 64.9% of those on prior placebo). In general, the safety profile for tolvaptan in TEMPO 4:4 was similar to that of the tolvaptan arm of TEMPO 3:4. Briefly, most AEs were related to the aquaretic effect of tolvaptan. The incidence of hepatic

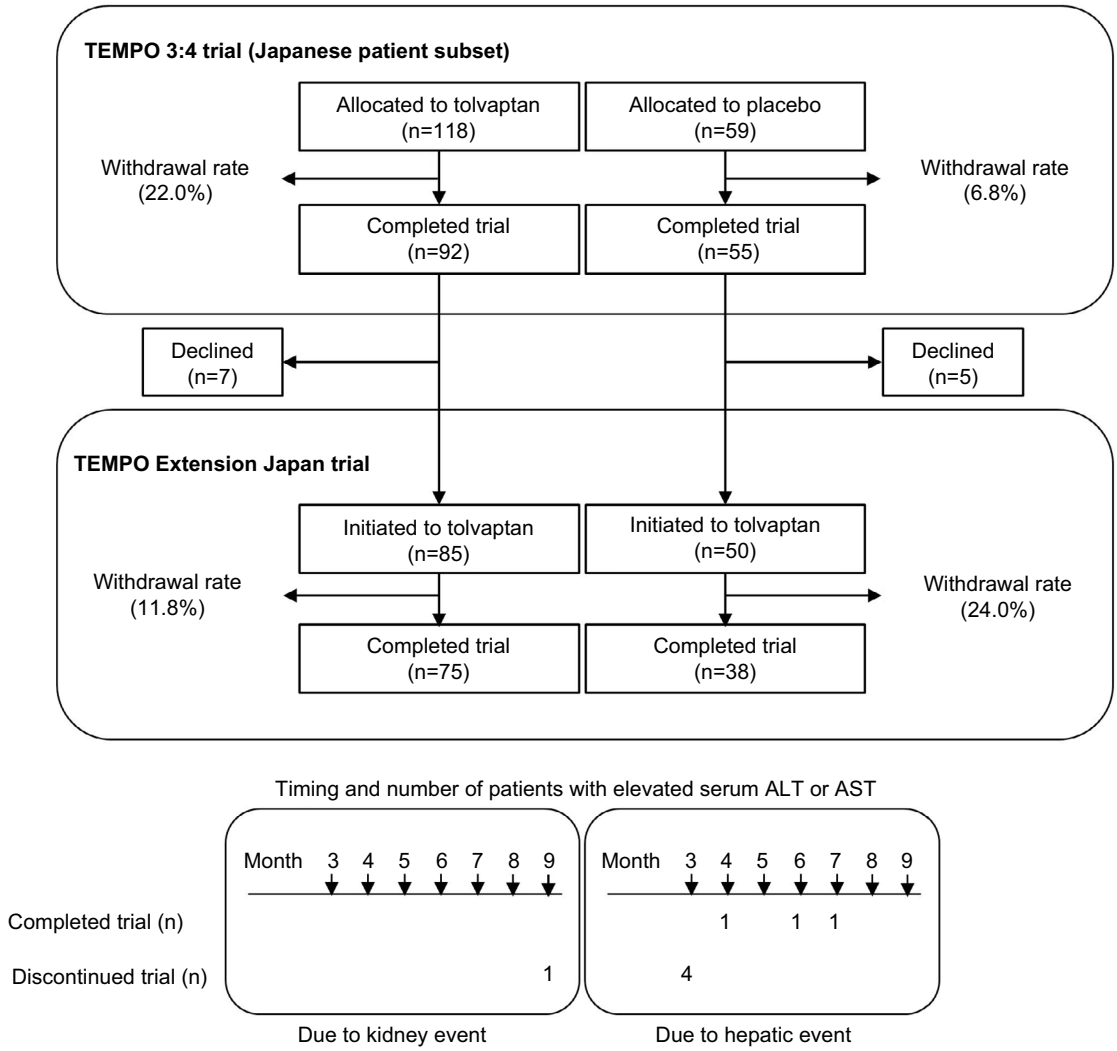

Figure 6 Summary of the TEMPO Extension Japan Trial after the TEMPO 3:4 trial.[7,8]
Abbreviation: TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes.

events in the delayed-treatment patients was similar to that observed in the tolvaptan-treated patients in TEMPO 3:4. One patient in the delayed-treatment group met the criterion for Hy's Law and this has been previously reported.[11]

Conclusion

ADRs observed in this extension trial were similar to those identified in the TEMPO 3:4 trial, and hepatic events were not progressive. During the first 3 years of tolvaptan use, regular monitoring of serum ALT, AST, and T-Bil levels is important to reduce the risk of serious hepatic events. However, further discussion is required regarding the frequency of the monitoring, especially after 3 years of tolvaptan use.

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Sciences, Hiroshima University, Hiroshima), Eiji Ishimura (Osaka City University Graduate School of Medicine, Osaka), Hajime Hasegawa (Saitama Medical Center, Saitama Medical University, Saitama), Hideo Yasuda (Hamamatsu University School of Medicine, Shizuoka), Ichiei Narita (Niigata University Graduate School of Medical and Dental Sciences, Niigata), Kazuhiko Tsuruya (Graduate School of Medical Sciences, Kyushu University, Fukuoka), Kazunari Yoshida (Kitasato University School of Medicine, Tokyo), Keitaro Yokoyama (Jikei University School of Medicine, Tokyo), Kenmei Takaichi (Toranomon Hospital, Tokyo), Kikuo Nutahara (Kyorin University School of Medicine, Tokyo), Koichi Asahi (Fukushima Medical University, Fukushima), Koichi Kamura (National Hospital Organization Chiba-East Hospital, Chiba), Koichi Seta (National Hospital Organization Kyoto Medical Center, Kyoto), Kosaku Nitta (Tokyo Women's Medical University, Tokyo), Kouju Kamata (Kitasato University School of Medicine, Kanagawa), Masayuki Endo (Tokai University School of Medicine, Kanagawa), Michio Kuwahara (Shuuwa General Hospital, Saitama), Mikio Okamura (Ohno Memorial Hospital, Osaka), Naoki Nihei (Chiba University Graduate School of Medicine, Chiba), Sadayoshi Ito (Tohoku University Graduate School of Medicine, Miyagi), Saori Nishio (Hokkaido University Graduate School of Medicine, Hokkaido), Shigeaki Muto (Jichi Medical University, Tochigi), Shinichi Uchida (Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo), Shuichi Tsuruoka (Nippon Medical School, Tokyo), Takeshi Matsubara (Kyoto University Graduate School of Medicine, Kyoto), Taku Miyoshi (Kumamoto University Graduate School of Medical Sciences, Kumamoto), Yoshifumi Ubara (Toranomon Hospital, Tokyo), Yoshitaka Isaka (Osaka University Graduate School of Medicine, Osaka), and Yukio Yuzawa (School of Medicine, Fujita Health University, Aichi).

Author contributions

SM, SH, TO, and MY contributed to implementation of the TEMPO Extension Japan trial and critically revised the manuscript. KN and HT contributed to interpretation of the data and writing of the first draft of the manuscript. Editorial assistance in this study was provided by the Department of Clinical Development and Department of Medical Affairs, Otsuka Pharmaceutical Co, Ltd, Osaka, Japan. The submitted manuscript has been approved by all the authors.

Disclosure

SH has received honoraria for presentations, paid travels, a payment for writing an expert report, and research funding from Otsuka Pharmaceutical; in addition, he has been a medical advisor of the TEMPO Extension Japan trial. SM has received honoraria for presentations, paid travel, and research funding from Otsuka Pharmaceutical. TO, MY, HT, and KN are employees of Otsuka. SM and SH belong to an endowed department sponsored by Otsuka Pharmaceutical Co, Ltd. The authors report no other conflicts of interest in this work.

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Supplementary material

Table S1 Full list of trial sites and IRB approval dates

Trial site number	Trial site and address	Principal investigator	IRB approval date, year/month/day
1	Hokkaido University Hospital, Kita 14, Nishi 5, Kita, Sapporo, Hokkaido 060-8648	Saori Nishio, Sekiya Shibazaki	2010/11/16
2	Teikyo University Hospital, 2-11-1 Kaga, Itabashi, Tokyo 173-8605	Shigeo Horie, Satoru Muto	2010/11/16
3	Nippon Medical School Hospital, 1-1-5 Sendagi, Bunkyo, Tokyo 113-8603	Yasuhiko Iino, Shuichi Tsuruoka	2010/10/28
4	Kyorin University Hospital, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611	Kikuo Nutahara	2010/12/8
5	Kitasato University Hospital, 1-15-1 Kitazato, Minami, Sagamihara, Kanagawa 252-0375	Koju Kamata	2010/11/17
6	Kitasato University Hospital, 1-15-1 Kitazato, Minami, Sagamihara, Kanagawa 252-0375	Kazunari Yoshida	2010/11/17
7	Niigata University Medical and Dental Hospital, 1-754, Asahimachidori, Chuo, Niigata, Niigata 951-8520	Ichiei Narita	2010/10/26
8	Osaka University Hospital, 2-15 Yamadaoka, Suita, Osaka 565-0871	Yoshitaka Isaka	2010/12/13
9	Tohoku University Hospital, 1-1, Seiryo-cho, Aoba-ku, Sendai, Miyagi 980-8574	Sadayoshi Ito	2010/12/6
10	Jichi Medical School Hospital, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498	Eiji Kusano, Shigeaki Muto	2011/2/25
11	Saitama Medical Center, 1981, Kamoda, Kawagoe, Saitama 350-8550	Hajime Hasegawa	2011/2/17
12	Chiba University Hospital, 1-8-1, Inohana, Chuo, Chiba, Chiba 260-8677	Naoki Nihei	2010/11/15
13	Toranomon Hospital, 2-2-2 Toranomon, Minato, Tokyo 105-8470	Kenmei Takaichi	2011/2/25
14	The Jikei University Hospital, 3-19-18 Nishishinbashi, Minato, Tokyo	Tatsuo Hosoya, Keitaro Yokoyama	2011/9/27
15	Tokai University Hospital, 143 Shimokasuya, Isehara, Kanagawa 259-1193	Masayuki Endoh	2010/12/22
16	Toranomon Hospital Kajigaya, 1-3-1 Kajigaya, Takatsu, Kawasaki, Kanagawa 213-8587	Yoshifumi Ubara	2011/1/11
17	Ohno Memorial Hospital, 1-26-10 Minamihorie, Nishi, Osaka, Osaka 550-0015	Mikio Okamura	2011/1/27
18	Hiroshima University Hospital, 1-2-3 Kasumi, Minami, Hiroshima, Hiroshima 734-8551	Akio Matsubara	2011/5/9
19	Fukushima Medical University, Hospital, 1 Hikarigaoka, Fukushima, Fukushima 960-1295	Koichi Asahi	2011/3/2
20	National Hospital Organization, Chiba-East Hospital, 673 Nitona, Chuo, Chiba, Chiba 260-8712	Koichi Kamura	2011/4/26
21	Shuwa General Hospital, 1200, Yaharashinden, Kasukabe Saitama 344-0035	Michio Kuwahara	2011/4/11
22	Tokyo Women's Medical, University Hospital, 8-1 Kawada, Shinjuku, Tokyo 162-8666	Kosaku Nitta	2011/4/27
23	Osaka City University Hospital, 1-5-7 Asahimachi, Abeno, Osaka, Osaka 545-8586	Eiji Ishimura	2011/3/23
24	Kyoto University Hospital, 54, Kawara, Shogoin, Sakyo, Kyoto, Kyoto 606-8507	Atsushi Fukatsu, Noriyuki Iehara, Takeshi Matsubara	2011/9/12
25	Kyushu University Hospital, 3-1-1, Maidashi, Higashi, Fukuoka, Fukuoka 812-8582	Kazuhiko Tsuruya	2011/2/24
26	Hamamatsu University School of Medicine, University Hospital, 1-20-1 Handayama, Higashi, Hamamatsu, Shizuoka 431-3192	Yoshihide Fujigaki, Hideo Yasuda	2011/4/14
27	National Hospital Organization, Kyoto Medical Center, 1-1, Mukaihata, Fukakusa, Fushimi, Kyoto 612-8555	Koichi Seta	2011/5/25
28	Fujita Health University Hospital, 1-98 Dengakugakubo, Kutsukake, Toyoake, Aichi 470-1192	Yukio Yuzawa	2011/4/27
29	Kumamoto University Hospital, 1-1-1 Honjyo, Chuo, Kumamoto, Kumamoto 860-8556	Taku Miyoshi	2011/5/23
30	Tokyo Medical and Dental University Hospital Faculty of Medicine, 1-5-45 Yushima, Bunkyo, Tokyo 113-8519	Sei Sasaki, Shinichi Uchida	2011/7/25

Abbreviation: IRB, institutional review board.

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