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Intravenous liposomal amphotericin B versus voriconazole for chronic pulmonary aspergillosis: a multicenter trial in Japan

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Chronic pulmonary aspergillosis (CPA) is slowly progressive inflammatory pulmonary syndrome due to infection of *Aspergillus* spp. We conducted a randomized, multicenter, open-label trial comparing intravenous liposomal amphotericin B (L-AMB) of 2.5-5.0 mg/kg once daily with intravenous voriconazole (VRCZ) of 6 mg/kg twice on Day 1 followed by 4 mg/kg twice daily. Treatment effectiveness was defined by clinical, and radiological improvement at both 2 weeks after the initial administration and at the end of therapy. The total of 166 patients were recruited and 83 patients for each drug group were assigned. Total of 51 and 59 cases of L-AMB and VRCZ, respectively were assessed as per-protocol populations. The difference in efficacy rates between L-AMB and VRCZ was not significant, either after 2 weeks [49.0% vs. 59.3%; the absolute difference, 10.3% with a 95% confidence interval (CI), -8.4 to 29.00, P=0.279] or at the end of therapy (52.9% vs. 67.8%; the absolute difference, 14.9% with a 95% CI, -3.4 to 33.2, P=0.111). In the safety evaluation, no statistical difference of occurrence rates in both L-AMB and VRCZ group (54.2% vs. 59.0%, P=0.531). L-AMB was as effective as VRCZ with no significant difference of adverse effects in the treatment of CPA. (UMIN Clinical Trials Registry number, UMIN000002236.)

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Key words: chronic pulmonary aspergillosis, liposomal amphotericin B, voriconazole

Introduction

Chronic forms of pulmonary aspergillosis (CPA) are characterized as a slowly progressive inflammatory pulmonary syndrome due to *Aspergillus* spp. [1, 2]. Recently, both Infectious Diseases Society of America and European Respiratory Society issued guidelines namely Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America and Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management, respectively [3, 4]. Although recommendations for treatment for CPA are described in both guidelines, utility of intravenous antifungals are not stated much.

We previously conducted national multicenter trial for comparing intravenous micafungin (MCFG) and voriconazole (VRCZ) for induction therapy of CPA patients in Japan and proved that both are effective with less adverse effects in MCFG arm [5]. Although oral antifungals are main stream of treatment of CPA, there is a need for accumulation of

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evidence of intravenous antifungals. We conducted second national multicenter trial comparing intravenous liposomal amphotericin B (L-AMB) versus VRCZ. Only limited data is available for efficacy of amphotericin B and L-AMB for CPA [6]. A retrospective patient case-note review of 48 CPA patients (23 females, 25 males) revealed 30 of 46 (65%) patients experienced a clinical response to L-AMB. The dose and duration of L-AMB given ranged between 2.47 to 5 (mean 3.03) mg/kg daily and 1 to 36 (mean 16.9) days, respectively [7]. Since there are no large-scale and comparing trials of L-AMB for patients with CPA, this study will be important for establishing new induction treatment option in CPA patients who require immediate treatment.

Methods

Patients

From July 1, 2009, to June 30, 2011, we enrolled patients with CPA at 59 Japanese hospitals in this study, which was approved by the ethics committee at each hospital. Every patient provided written informed consent. Sumitomo Dainippon Pharma Co., Ltd. (Tokyo, Japan) supported the study with a grant; Sumitomo Dainippon Pharma Co., Ltd. was not involved in the design of study, the enrollment of patients, the collection, analysis, and interpretation of the data or preparation of the manuscript. All authors vouch for the completeness and accuracy of the data presented.

Patients were eligible for enrollment if they were at least 20 years old and had been given a diagnosis of CPA. Proposed enrollment criteria for prospective clinical studies of CPA by Denning with minor modifications were used for this trial [6]. Patients with CPA had to fulfill the following conditions: (1) the existence of at least one of the symptoms in the complex consisting of fever, weight loss, sputum, cough, hemoptysis, fatigue, and shortness of breath; (2) new infiltrates, cavity formation, or expansion of pre-existing cavities with or without peri-cavitary infiltrates and adjacent pleural thickening in last six months.; (3) at least one positive result of serologic tests including the Platelia *Aspergillus* test (Fujirebio, Tokyo, Japan) for detecting *Aspergillus* galactomannan antigen by enzyme-linked immunosorbent assay (cut-off value, 1.0), and/or the *Aspergillus* immunodiffusion system (Microgen Bioproducts, Ltd., Camberley, United Kingdom) for anti-*Aspergillus* antibody detection, any positive evidence of the existence of *Aspergillus* spp. by molecular diagnosis, culture, or pathological findings; (4) positive findings of at least one of the inflammation markers such as white blood cell (WBC) counts, value of C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR); (5) lack of improvement of symptoms or signs after at least 3 days administration of broad-spectrum antibiotics such as carbapenems, wide-broad cephems and penicillins, and quinolones. The following patients were excluded from the study: (1) patients who received amphotericin B (AMPH-B), L-AMB or VRCZ within a month at the time of enrollment, (2) patients received other antifungal drugs such as itraconazole, flucytosine, miconazole, fluconazole, nystatin or MCFG and have already started to being improved or with unknown medical course, (3) patients who are diagnosed as other than CPA, (4) patients who fulfilled the contraindication of AMPH-B, L-AMB and VRCZ, (5) patients with liver, kidney or heart failure which fulfilled the Grade II level defined in the Common Toxicity Criteria grading system of the National Cancer Institute [8], (6) pregnant or breast feeding patients, and patients who are willing to have baby, and (7) patients whom are considered to be excluded by the attending physicians with various reasons.

Procedures

The patients were allocated to either the L-AMB or VRCZ treatment group. The randomization of the minimization method was performed at a centralized web site by attending physicians after obtaining the informed consent from each patient. Random numbers were generated by the computer. Stratification factors of severity and past history of treatment of CPA including aspergilloma were used. Severity was defined as mild, moderate and severe. The factors that were used for determining severity were (1) serum albumin value (less than 2.5 g/dl), (2) SpO_2 less than 90% or PaO_2 less than 60 Torr, (3) impaired oral administration of drugs, (4) expansion of newer infiltration shadow on chest X-ray film that was more than half of the lung field, (5) the existence of severe complications such as malignancies, cerebral vascular disorders, hepatic diseases, kidney diseases or heart failure, and (6) administration of corticosteroids. Mild severity was defined as the patient possessing none of the above factors. Moderate severity was defined as the patient possessing only one of the factors listed above. Severe severity was defined as the patient possessing at least two of the factors listed above. The randomization schedule was generated by a computer to ensure balanced treatment allocation. Briefly, when the difference of number of allocated patients between the L-AMB and VRCZ groups was less than two, the patients were completely randomized. Hence, when the difference was more than three, the patients were allocated to the smaller number therapy group at 90% probability or the

bigger number therapy group at 10% probability.

VRCZ was given intravenously at 6 mg/kg every 12 h for 24 h, and then 4 mg/kg every 12 h. L-AMB was given at 2.5 mg/kg/day with duration of infusion was more than 2 hours. Dose of L-AMB was accepted to be decreased or increased up to 5.0 mg/kg per day due to patient's condition by the decision of the attending physician. Patients received treatment for at least 2 weeks with a maximum duration of 4 weeks. Following preparations and treatments were allowed for expected infusion reaction of L-AMB. Hydration with saline or water for preventing renal dysfunction, use of acetaminophen for fever during infusion, antiemetic for nausea and vomit, potassium supplementation and heparin for thrombophlebitis.

Patients were followed up until 4 weeks after the first administration. Clinical assessments were made daily during treatment. Clinical laboratory tests were run once every week. Radiological and mycological investigations were performed at 2 weeks and at the end of treatment with a maximum 4 weeks. Concurrent treatment with antibiotics was prohibited in this study.

The primary efficacy end point was response to treatment, which was classified as 'success' or 'failure' at the end of administration (at least 2 weeks of administration with a maximum duration of 4 weeks). Each case was carefully reviewed by the investigators. All clinical response criteria were defined as follows.

Clinical and radiological factors were assessed as primary factors. (1) Clinical factors were clinical symptoms and signs such as hemosputum, cough, dyspnea and fever which were recorded individually by attending physicians and assessed by a data-review committee. Clinical improvement was defined by reduction or disappearing of these symptoms or signs. (2) Radiological factors with CT were also evaluated individually by three pulmonologists. Briefly, improvement was defined only if there was apparent improvement in the newly appeared lesions on radiological images; no transitional changes in lesions, were not considered improvements.

A 'success' with respect to clinical response at the end of the treatment was defined as follows: improvement in at least one of the two factors without deterioration in the other factor. A 'failure' was defined as a clinical response that did not match with the 'success' definition.

The secondary efficacy end point was response to treatment, which was classified as 'success' or 'failure' at the end of 2 weeks administration. All two factors were used as in the primary endpoint and the criterion of "success" was not changed.

Laboratory and mycological factors were also assessed as secondary factors, however, these two factors were not applied for efficacy of treatment. (1) Laboratory data such as CRP level, WBC counts, and ESR were independently assessed by a data-review committee. Laboratory data improvement was defined by reduction levels of these inflammatory markers. The transition of titer of anti-*Aspergillus* antibody was not evaluated. (2) Mycological factors were determined by culture or histopathological tests using clinical samples such as sputum, bronchoalveolar lavage fluid, and percutaneous aspiration biopsy samples. Mycological improvement was defined by disappearing of *Aspergillus* from clinical samples. The data-review process was not blinded to the treatment assignment on the evaluation of the outcomes or side effects.

Adverse events were recorded from randomization until the last day of treatment. These events were classified according to the Common Toxicity Criteria grading system of the National Cancer Institute [8]. The expected number of recruited patients was 75 patients for each treatment group and this open-labelled, randomized trial was registered in UMIN Clinical Trials Registry (UMIN number, 000002236.)

Statistical analysis

The primary objective was to show the superiority of either one of the two drugs in the per-protocol population. The efficacy rate of VRCZ for CPA patients was 54.3% from the previous trial [5]. On the basis, by assuming a difference in the efficacy of 20% with the power of 0.80 and probability of significance of 5.0%, a total sample size of 150 patients (75 assigned L-AMB and 75 assigned VRCZ) was calculated as necessary. However, the prevalence of CPA was very low and the budget was limited to extend the study period, we were obliged to terminate this clinical trial before reaching to the required data size

The intention-to-treat population was defined as patients who underwent randomization. The per-protocol population was defined as patients who were confirmed to have a baseline diagnosis of CPA, the availability of an investigator's assessment of overall treatment at the end of therapy, and no prohibited medication. The population included in the safety analysis consisted of all patients who received their initial study drug. The investigator's assessments of overall treatment success at the end of therapy and at the end of the first 2 weeks were analyzed by chi-square tests for categorical variables, and by Mann-Whitney test for ordinal or continuous variable. Descriptive statistics for continuous variables were expressed as medians and 95% confidence intervals. A P-value of <0.05 was considered statistically significant.

Results

Enrollment and baseline characteristics of the patients

A total of 166 patients were recruited by 59 centers in Japan during study period. A total of 83 and 83 patients were assigned to the L-AMB and VRCZ group, respectively; these patients comprised the intention-to-treat population. Trial profile was presented in Figure 1. All 166 patients were included for safety analysis. The demographic characteristics and underlying conditions of the patients in the intention-to-treat population are summarized in Table 1. The L-AMB and VRCZ groups were well matched and no significant difference was observed except the frequency of underlying disease of chronic obstructive pulmonary diseases.

A total of 56 patients (32 and 24 cases for L-AMB and VRCZ group, respectively) were excluded from the intention-to-treat population (Figure 1). Among them, 31 cases in both groups were excluded due to lack of radiological assessment with CT at the primary and secondary endpoint so that the efficacy evaluation was not carried. Eleven cases in both groups were excluded since they did not fulfill inclusion criteria.

Base-line characteristics of the infection and the serological findings

Characteristics of the patients with CPA such as symptoms, signs including body temperature, respiration rate and SpO_2, and inflammation markers including WBC, CRP and ESR in the per-protocol populations are summarized in Table 2. The results of the serum tests prior to the administration of study drugs are listed in Table 3. Positivity of β-D-glucan and Platelia *Aspergillus* antigen test were both low with 27% and 37%. There were no significant differences in the clinical characteristics including symptoms, laboratory findings and the serological test result between the L-AMB and VRCZ groups.

The results of the culture test of respiratory specimens are shown in Table 4. The overall positive rate of culture tests for *Aspergillus* at the initial workup, counting only once for duplicate positive results, were at 55.5 (61/110)% including *A. fumigatus* 28.1 % (31/110), followed by *A. niger* 19.1 % (21/110) and *A. flavus* 8.2 % (9/110).

Table 1. Characteristics of the patients in the intention-to-treat population

characteristic	overall (n=166)	liposomal ampotericin B (n=83)	voriconazole (n=83)	P
Age - yr				
Median	72.0	72.0	71.0	M-W
95% (2.5% - 97.5%)	43.0 - 87.0	49.3 - 91.4	41.7 - 87.0	0.213
Sex - no. (%)				
Male	131 (78.9)	62 (74.7)	69 (83.1)	χ^2
Female	35 (21.1)	21 (25.3)	14 (16.9)	0.183
Height - cm				
Median	162	161.7	162.0	M-W
95% (2.5% - 97.5%)	141.0 - 174.7	136.6 - 173.3	142.6 - 178.2	0.338
Weight - kg				
Median	46.0	45.5	47.0	M-W
95% (2.5% - 97.5%)	28.9 - 72.2	28.9 - 66.1	29.3 - 77.3	0.078
Underlying condition - no. (%)				
n	282	145	137	χ^2
Old pulmonary tuberculosis	56 (19.9)	26 (17.9)	30 (21.9)	0.404
Nontuberculous mycobacterial infection	27 (9.6)	15 (10.3)	12 (8.8)	0.651
Chronic obstructive pulmonary disease	40 (14.2)	13 (9.0)	27 (19.7)	0.010
Diabetes	22 (7.8)	12 (8.3)	10 (7.3)	0.760
Lung cancer	16 (5.7)	9 (6.2)	7 (5.1)	0.691
Interstitial pneumonia	10 (3.5)	7 (4.8)	3 (2.2)	0.231
Bronchiectasis	9 (3.2)	4 (2.8)	5 (3.6)	0.744
Others	102 (36.2)	59 (40.7)	43 (31.4)	

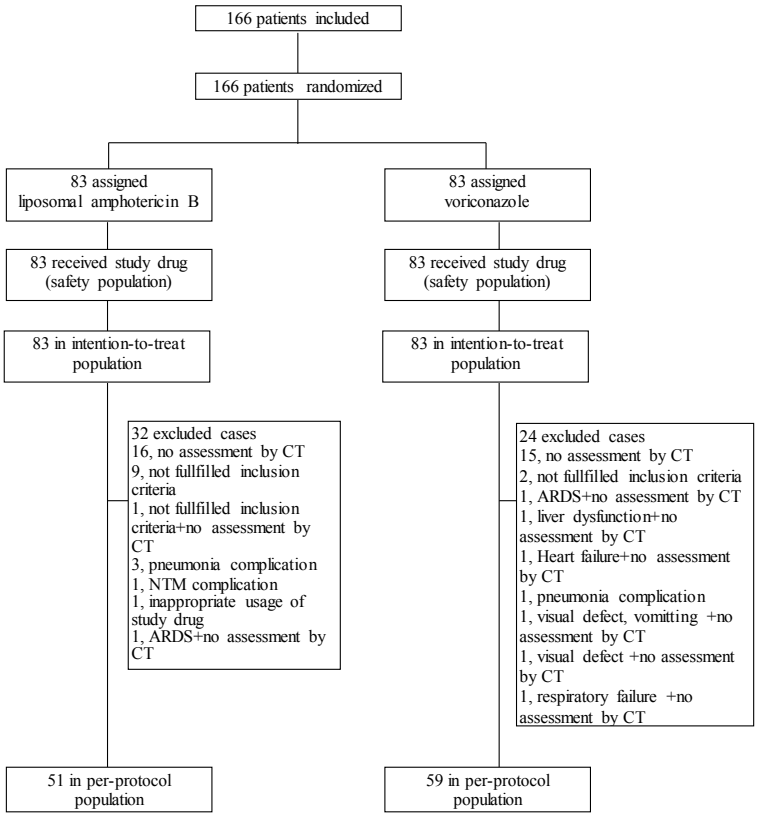

Figure 1: Trial profile. Total of 166 cases were recruited and 110 case were analyzed as a per-protocol population. CT, computed tomography; ARDS, acute respiratory distress syndrome; NTM, non-tuberculosis mycobacterium

Response

The median (2.5~97.5% range) duration of administration was 21 (9.9~30) days for the L-AMB group and 28 (6.9~43.4) days for the VRCZ group with no statistical difference. The median dose of L-AMB was 113 mg/day (range, 74 – 300 mg/day, average, 2.5 mg/kg/day/patient) and that for VRCZ was 326 mg/ day (range, 158 – 615 mg/day, average 6.8 mg/ kg/day/patient).

The outcome at end of treatment in the per-protocol populations was not significantly different between the L-AMB and VRCZ group (Table 5). There was no significant difference in the response rates among all factors except mycological and inflammatory factors between the L-AMB and VRCZ groups (Table 6). Although there was no difference for these four factors at the first two weeks, VRCZ showed statistically better response rate in the inflammatory and mycological factors at the end of treatment compared to L-AMB. Since the median treatment duration of VRCZ was 7 days more than that of L-AMB, VRCZ may indicate better response rate in some factors. The outcome, however, did not show any statistical difference for these two drugs.

Safety

Table 7 shows the treatment-related adverse events and reasons for discontinuation from the study in patients who received at least one dose of study drug. No significant difference of overall adverse effects occurrence was observed in both the L-AMB (54.2%) and the VRCZ (59.0%) groups (P=0.531). Serious adverse effects were observed in four cases in the VRCZ group, which include possible drug-induced pneumonia, hemoptysis, hyponatremia and ventricular tachycardia. The drug-induced pneumonia case needed discontinuation of VRCZ. VRCZ was continued in other three cases and all recovered during the course.

Hepatic and visual events were occurred in VRCZ group specifically. Various visual events including photophobia, xanthopsia, abnormal vision, defective color vision, vision blurred, and visual disturbance occurred only in the VRCZ group and all visual events were transient and resolved without intervention. On the other hand, renal events and hypokalemia were specific in L-AMB group. There were statistically difference in these four adverse events.

Table 2. Clinical characteristics and laboratory findings of the patients in the per-protocol population

characteristic	overall (n=110)	liposomal amphotericin B (n=51)	voriconazole (n=59)	P
Body temperature (℃)				
Number of cases evaluated	109	51	58	
Median	36.9	36.9	36.9	0.490
95% (2.5% - 97.5%)	36.0 -38.4	36.1 -38.4	35.9 - 38.4	
Respiration rate (/ min)				
Number of cases evaluated	98	46	52	
Median	18.0	18.0	18.0	0.715
95% (2.5% - 97.5%)	12.0 - 28.4	12.0 - 25.4	12.0 - 36.8	
Symptoms (%)				
Number of cases evaluated	110	51	59	
Cough	78 (70.9)	39 (76.5)	39 (66.1)	
Sputum	70 (63.6)	32 (62.7)	38 (64.4)	
Hemosputum	32 (29.1)	10 (19.6)	22 (37.3)	
SpO_2 (%)				
Number of cases evaluated	110	51	59	
Median	97.0	97.0	97.0	0.536
95% (2.5% - 97.5%)	93.0 - 99.0	92.8 - 99.0	94.0 - 100.0	
WBC (/mm^3)				
Number of cases evaluated	109	51	58	
Median	7270	7270	7270	0.841
95% (2.5% - 97.5%)	3345 - 17350	3455 - 16773	2929 - 17945	
CRP (mg/dl)				
Number of cases evaluated	110	51	59	
Median	3.21	3.17	3.25	0.947
95% (2.5% - 97.5%)	0.08 - 17.6	0.17 - 15.7	0.07 - 17.9	
ESR (mm/hr)				
Number of cases evaluated	42	22	20	
Median	81.0	84.5	57.0	0.212
95% (2.5% - 97.5%)	21.9 - 144.7	18.8 - 141.4	25.0 - 148.0	

M-W test

Table 3. Serological findings of the patients in the per-protocol population

characteristic	overall (n=110)	liposomal amphotericin B (n=51)	voriconazole (n=59)	P
β-D-glucan / WAKO (pg/ml)				
Number of cases tested	43	18	25	χ^2
Positive (> 11pg/m)	16 (37.2 %)	6 (33.3 %)	10 (40.0 %)	0.656
Median	6.0	7.0	6.0	M-W
95% (2.5% - 97.5%)	1.0 - 212.6	3.0 - 235.0	1.0 - 188.5	0.921
β-D-glucan / Fungitec G test (pg/ml)				
Number of cases tested	29	11	18	Fisher
Positive (> 20pg/ml)	8 (27.6 %)	3 (27.3 %)	5 (27.8 %)	0.659 (1.00)
Median	10.0	11.0	9.0	M-W
95% (2.5% - 97.5%)	4.2 - 153.9	7.0 - 37.0	4.0 -162.0	0.417
Platelia *Aspergillus* test				
Number of cases tested	79	36	43	
Median	0.40	0.40	0.40	M-W
95% (2.5% - 97.5%)	0.00 - 22.4	0.04 - 35.8	0.00 - 17.8	0.473
Platelia *Aspergillus* test (%) cut off: 1.0				
Number of cases tested	79	36	43	χ^2
Positive	22 (27.8 %)	10 (27.8 %)	12 (27.9 %)	0.990
Aspergillus immunodiffusion system (%)				
Number of cases tested	66	31	35	χ^2
Positive	55 (83.3 %)	27 (87.1 %)	28 (80.0 %)	0.440

Table 4. Mycological findigs of the patients in the per-protocol population

	overall (n=110)	liposomal amphotericin B (n=51)	voriconazole (n=59)
CULTURE			
A. fumigatus			
Sputum	16	9	7
BALF	13	5	8
Biopsy	2	1	1
A. niger			
Sputum	9	4	5
BALF	3	1	2
Biopsy	8	4	4
tracheal aspirate	1	0	1
A. flavus			
Sputum	2	1	1
BALF	2	1	1
Biopsy	4	3	1
tracheal aspirate	1	1	0

n: number of cases of which culture tests were performed any of respiratory specimens

Table 5. Treatment success in the per-protocol population

	liposomal amphotericin B (n=51)	voriconazole (n=59)	Difference in proportion (95% CI)	P
At the end of treatment (primary endpoint)				
Number treated successfully (%)	27 (52.9)	40 (67.8)	14.9 % (-3.4 to 33.2)	0.111
At the first two weeks (secondary endpoint)				
Number treated successfully (%)	25 (49.0)	35 (59.3)	10.3 % (- 8.4 to 29.0)	0.279

two-sided 95% confidence intervals

Table 6. Response rate of clinical, laboratory findings, radiological, and mycological factors at the end of the treatment and two weeks after initial administration in the per-protocol populations

	at the end of treatment					at the first two weeks				
	n	liposomal amphotericin B	n	voriconazole	P	n	liposomal amphotericin B	n	voriconazole	P
Clinical	51	32 (62.7)	59	42 (71.2)	0.334	51	29 (56.9)	59	38 (64.4)	0.351
Inflammatory tests	51	19 (37.3)	58	35 (60.3)	0.046*	48	20 (41.7)	56	35 (62.5)	0.111
Radiological tests	51	15 (29.4)	59	24 (40.7)	0.248	51	12 (23.5)	59	17 (28.8)	0.787
Mycological tests	50	13 (26.0)	58	28 (48.3)	0.021*	47	12 (25.5)	55	24 (43.6)	0.086

M-W test

Table 7. Treatment-related adverse events and reasons for discontinution from study in patients who received at least one dose of study drug

liposomal amphotericin B (n=83)		voriconazole (n=83)		P
Serious	0 (0.0 %)	Serious	4 (4.8 %)	
		Drug-induced pneumonia (suspected)	1 (1.2 %)	
		Hemoptysis	1 (1.2 %)	
		Hyponatremia	1 (1.2 %)	
		Ventricular tachycardia	1 (1.2 %)	
Treatment discontinuation	0 (0.0 %)	Treatment discontinuation	1 (1.2 %)	
		Drug-induced pneumonia (suspected)	1 (1.2 %)	
Overall	52	Overall	69	
n	45 (54.2 %)	n	49 (59.0 %)	0.531
Hepatic events	1 (1.2 %)	Hepatic events	22 (26.5 %)	<0.0001
Visual events	0 (0.0 %)	Visual events	30 (36.1 %)	<0.0001
Renal events	14 (16.9 %)	Renal events	0 (0.0 %)	<0.0001
Central nervous system disorder	0 (0.0 %)	Central nervous system disorder	1 (1.2 %)	---
Hypokalemia	29 (34.9 %)	Hypokalemia	1 (1.2 %)	<0.0001
Hyperkalaemia	2 (2.4 %)	Hyponatremia	2 (2.4 %)	
Fever & Headache	1 (1.2 %)	Fever	1 (1.2 %)	
Phlebitis	1 (1.2 %)	Drug-induced pneumonia (suspected)	1 (1.2 %)	
Aspiration pneumonitis	1 (1.2 %)	Thrombocytopenia	1 (1.2 %)	
Gastric distress	1 (1.2 %)	Dry mouth	1 (1.2 %)	
Anorexia	1 (1.2 %)	Anorexia	1 (1.2 %)	
Appendicitis	1 (1.2 %)	Constipation	1 (1.2 %)	
		Stomatitis	1 (1.2 %)	
		Hemoptysis	1 (1.2 %)	
		Cheilitis angularis	1 (1.2 %)	
		Vomiting	1 (1.2 %)	
		Heart failure	1 (1.2 %)	
		Hypertension	1 (1.2 %)	
		Ventricular tachycardia	1 (1.2 %)	

Discussion

We previously indicated the efficacy of MCFG and VRCZ for CPA patients [5]. The difference in efficacy rates between MCFG and VRCZ was not significant, either after 2 weeks [68.0% vs. 58.7%; the absolute difference, 9.3% with a 95% confidence interval (CI), -9.97 to 28.58, P=0.344] or at the end of therapy (60.0% vs. 53.2%; the absolute difference, 6.8% with a 95% CI, -12.92 to 26.54, P=0.499). In the safety evaluation, fewer adverse events occurred in the MCFG than VRCZ group (26.4% vs. 61.1%, P=0.0004). MCFG was as effective as VRCZ and significantly safer than as an initial treatment of CPA.

In the current study, we compared intravenous L-AMB and VRCZ for CPA patients. Since there was no large-scale controlled trail for both drugs was existed, this trial is worth for adding new evidence for treatment options for CPA patients. We changed the efficacy assessment criteria from previous trial. All of four factors including clinical, radiological, serological and mycological factors were taken into consideration for efficacy assessment in previous study. In current study, we applied only two factors such as clinical and radiological factors, since mycological and serological factors are revealed to not to reflect the accurate efficacy of tested drugs in such short period of treatment (maximum 4 weeks) in this chronic infection after previous study [5]. However, the transitional changes in first two weeks in simple X-ray films are considered difficult and CT scanning was completely required for radiological assessment before the treatment, 2 weeks after the treatment and end of treatment. Unfortunately, CT scanning was not conducted in 31 cases in this study and they were excluded from efficacy assessment and this result indicated radiological efficacy assessment in such short period seems difficult.

We speculated that L-AMB will indicate better efficacy compared to VRCZ due to its strong fungicidal activity. The result, however, indicated that there was no statistically difference, either after 2 weeks [L-AMB, 49.0% vs. VRCZ, 59.3%; the absolute difference, 10.3% with a 95% confidence interval (CI), -8.4 to 29.00, P=0.279] or at the end of therapy (L-AMB, 52.9% vs. 67.8%; the absolute difference, 14.9% with a 95% CI, -3.4 to 33.2, P=0.111).

Comparison of efficacy rate of VRCZ in both current (2 weeks, 59.3% and end of treatment, 67.8%) and previous study (2 weeks, 58.7 % and end of treatment, 53.2%) indicated almost similar rate except end of treatment data of current study. Although efficacy rate of first two weeks are quite similar, the difference of that of end of treatment seems to be generated by the difference of definition of treatment success. As we described previously, the first study comparing VRCZ and MCFG applied stricter definition consisted of four factors such as clinical, radiological, serological and mycological data [5], compared to that of current study assessed by only clinical and radiological factors for end of treatment assessment. These data indicated that there is a consistency of VRCZ efficacy in both studies. On the other hand, though there was no statistical difference for the duration of administration of L-AMB and VRCZ, average seven days more administration of VRCZ compared to L-AMB might influence to the better result in inflammatory and mycological tests at the end of treatment.

Our results indicated no significant overall adverse effects occurrence in the L-AMB and VRCZ. As we speculated, typical adverse effects for both drugs are specific each other. Liver dysfunction and visual disturbance were almost specific for VRCZ. Occurrence rate of liver dysfunction was 26.5% in current study and comparable to 35.2% in previous study [5]. On the other hand, kidney dysfunction and hypokalemia were more specific to L-AMB.

Surprisingly, serious adverse effects were seen only in VRCZ group (4 cases) and only one case with possible drug-induced pneumonia requires discontinuation. There was another case with ventricular tachycardia and trough level was 22.46 ug/ml and recovered at the end of treatment. Although high concentration of VRCZ, the occurrence of ventricular tachycardia is reported not to be related to its concentration [9]. Since hydration with saline or water for preventing renal dysfunction, use of acetaminophen for fever during infusion, antiemetic for nausea and vomit, potassium supplementation and heparin for thrombophlebitis are allowed in L-AMB group, these preparations and treatments were well effective during L-AMB usage.

In conclusion, this large-scale prospective clinical trial comparing intravenous L-AMB and VRCZ for patients with CPA indicated that both drugs showed good therapeutic effects without unacceptable adverse effects. Consideration of liver and kidney function of CPA patients is a guide to select the appropriate drug due to their contrasting adverse effects occurrence in liver and kidney.

Conflict of interests

All authors declared conflict of interests in this study. All authors received either of honorarium, research grants and consultation fee from both from Sumitomo Dainippon Pharma Co., Ltd. (Tokyo, Japan) and Pfizer Japan, Inc. (Tokyo, Japan).

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