ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2023.105.4.228
Annals of Surgical Treatment and Research

Evaluation of the efficacy and safety of conversion from the tacrolimus capsule to tablet in stable liver transplant recipients with maintenance therapy: a 24-week, open-label, single-center, phase IV exploratory clinical study

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Purpose: The tablet form of tacrolimus is more convenient for drug ingestion than the capsule form. We examined the efficacy and safety of tacrolimus tablets and a satisfaction survey after formula conversion in liver transplant (LT) recipients.
Methods: This study was an open-label, prospective clinical trial for tacrolimus formula 1:1 conversion from capsule to tablet in 41 adult LT recipients with tacrolimus maintenance therapy of more than 1 month. The primary endpoint was incidence of biopsy-proven acute rejection (BPAR) within 24 weeks. Surveys 1 week before and 4 weeks after formula conversion were conducted for total daily dose of medication, number, scale of discomfort and satisfaction.
Results: The overall incidence of BPAR was 0% and there was no graft loss or patient death. The incidence of adverse effects was 34.1% (n = 14) after formula conversion. The most common severe adverse effect was abnormal liver function test (n = 5): biliary complications (n = 4) and alcoholic recidivism (n = 1). Total daily dose and number of tacrolimus doses were significantly lower after formula conversion ($P < 0.05$) without changes in trough level. According to survey analysis, there was no significant difference in discomfort and satisfaction scales from capsule to tablet conversion ($P < 0.05$).
Conclusion: The present study suggests that the new tablet formula can be a useful treatment option to maintain a consistent level of tacrolimus with a lower total daily dose and number in adult LT recipients.
[Ann Surg Treat Res 2023;105(4):228-236]

Key Words: Efficacy, Immunosuppression therapy, Liver transplantation, Tacrolimus

INTRODUCTION

Liver transplantation (LT) is the only means of sustaining life for patients with acute liver failure or end-stage disease. Despite improvements in LT outcomes, recipients must take immunosuppressants for the rest of their lives to keep their grafts functioning [1-3]. Tacrolimus, a calcineurin inhibitor (CNI), has shown a remarkable positive impact on LT outcomes [4]. Due to the nature of the immunosuppressants that must be taken for life, the improvement of medication compliance remains a task to be solved [5]. In contrast, CNI is known to cause several side effects such as metabolic disorders (diabetes, high blood pressure, hypercholesterolemia), nephrotoxicity, and neurotoxicity [1,3].

Received May 26, 2023, **Revised** July 19, 2023, **Accepted** August 17, 2023

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The tacrolimus tablet (0.25-, 0.5-, 1-, or 2-mg formula; Chong Kun Dang Pharmaceutical Corporation) developed for user convenience is considered bioequivalent to the capsule form according to the Korean Ministry of Food and Drug Administration rulings. However, no clinical studies regarding the efficacy and safety of tablet formulation usage have been conducted in LT patients receiving tacrolimus as well as evaluation of compliance.

Therefore, we compared the efficacy and safety of the tablet formulation after conversion from the capsule form of tacrolimus in patients who had undergone LT. In addition, we evaluated a survey of convenience after conversion.

METHODS

Ethics statement

Written informed consent was obtained from all patients following the approval from the Institutional Review Board of Seoul National University College of Medicine (H-1703-058-838), and the study was conducted in accordance with the guidelines for Good Clinical Practice, applicable local regulations, and the Declaration of Helsinki.

Study design

This study was an open-label, prospective, single-center, clinical trial in adult recipients of a first LT from living or deceased donor with stable liver function.

Inclusion criteria were the patients (aged 19–70 years) at least 1 month after LT with tacrolimus maintenance therapy. Exclusion criteria were patients with multiorgan or any other previous organ transplant; a liver graft donated after cardiac death; leukopenia (<2,500/mm^3) and/or serum creatinine of >2.0 mg/dL prior to enrollment abnormal liver function (total bilirubin, AST, or ALT, >1.5 times the upper limit of normal ranges) at the time of screening; biopsy-proven acute rejection (BPAR) within the last month; proven or suspected malignancy after transplantation; HCV RNA-positive or taking or planning to take HCV therapeutics; use of any other investigation drug within 4 weeks before screening (visit 0); evidence of severe or systemic infection; history of severe allergy or hypersensitivity that requires acute (within the last 4 weeks) or chronic treatment to a drug used in this clinical trial or a drug having a similar chemical structure (tacrolimus, etc.); women who were pregnant or lactating; women of childbearing potential who were unwilling to use an effective form of contraception for the duration of the study; people who could not communicate because of psychological problems within the last 6 months; and unable to participate in clinical trials due to the judgment of the investigator.

Immunosuppression

Before the screening period, the patients received immediate-release tacrolimus capsules. After enrollment, the patients received the same dose of tacrolimus tablets. Dosage was decided according to maintaining a tacrolimus trough level of 3–8 ng/mL throughout the study period. Methylprednisolone was tapered

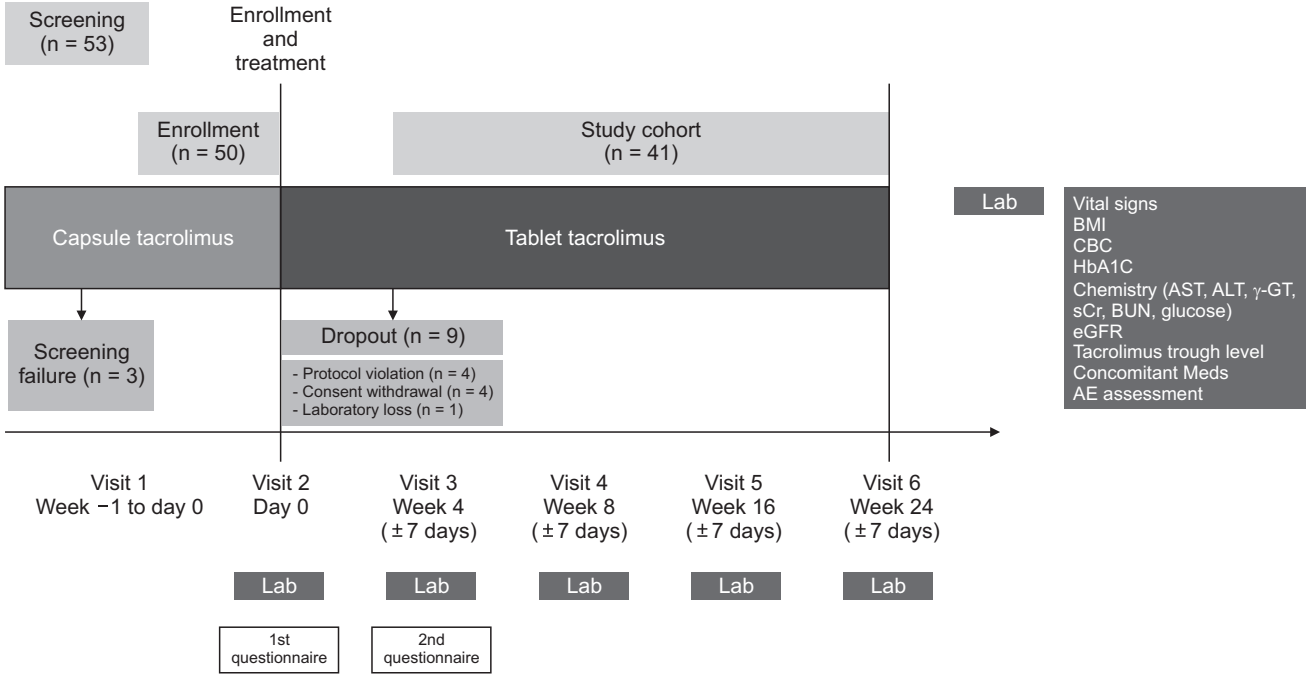


Fig. 1. Study design. Lab, laboratory results; BMI, body mass index; CBC, complete blood count; HbA1C, hemoglobin A1C; sCr, serum creatinine; Meds, medications; eGFR, estimated glomerular filtration rate; AE, adverse effect.

to a maintenance oral dose (≥5 mg/day) and discontinued within 6 months after LT. Mycophenolate mofetil or everolimus was used as combination dual immunosuppressant to reduce the adverse effect of tacrolimus.

Assessment

Study visits took place within 1 week before enrollment (screening period, visit 1); on day 0 (visit 2); and then 4, 8, 16, and 24 weeks after enrollment (visits 3, 4, 5, and 6, respectively) (Fig. 1). At each visit, body weight, vital signs including blood pressure, a complete physical examination and laboratory values concerning the liver, kidney, and hemoglobin A1C (HbA1C) as well as tacrolimus trough concentration were taken. Any problems between visits were documented. Renal function was measured by serum creatinine level and estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease formula [6,7]. Data were recorded, entered into an electronic database, and reevaluated by external monitors. Study monitoring and database analyses were performed, and all adverse events (AEs) and serious adverse events (SAEs) were documented.

The satisfaction questionnaire (Supplementary Fig. 1) for tacrolimus formula conversion was conducted at day 0 (visit 2), and the questionnaire at 4 weeks of tablet conversion (visit 3). As survey items, dosage, number, and degree of discomfort (a scale of point 1 [no discomfort] to 5 [very discomfort]), reason for discomfort and satisfaction (a scale of point 1 [very discomfort] to 5 [very comfort]), were conducted.

Endpoints

The primary efficacy endpoint was the incidence of BPAR and the secondary endpoints were the incidence of graft failure and patient death by 24 weeks after enrollment. Biopsy specimens were graded according to Banff criteria [8].

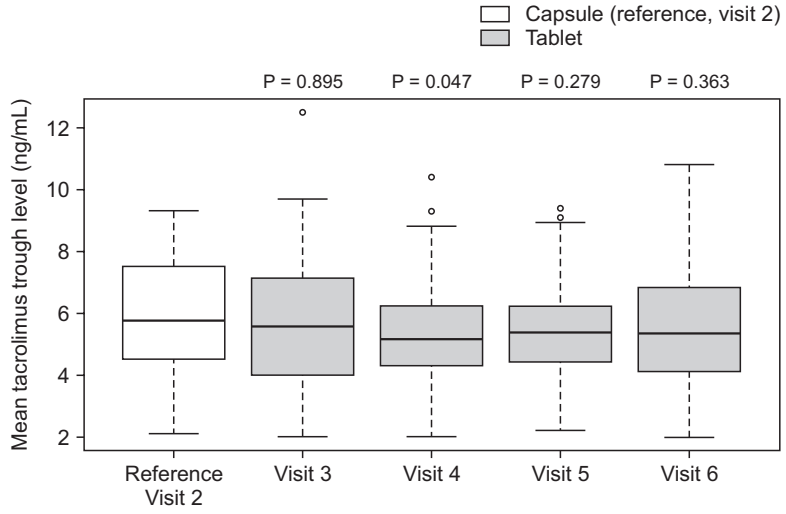
Statistical analysis

Categorical variables were analyzed using the chi-square test or Fisher exact test with IBM SPSS Statistics ver. 27.0 (IBM Corp.). Continuous variables were analyzed using the Mann-Whitney U-test and expressed as mean ± standard deviation. In this study, the P-values of <0.05 were considered significant. Combination drugs taken prior to administration of clinical

Table 1. Demographic and baseline characteristics

Characteristic	Visit 2	Visit 6
No. of patients	41	41
Male sex	34 (82.9)	NC
Age (yr)	55.7 ± 8.7	NC
ABO incompatibility	6 (14.6)	NC
Diagnosis		
Hepatitis B	28 (68.3)	NC
Alcoholic liver disease	7 (17.1)	NC
Others	6 (14.6)	NC
Coexistence of HCC	20 (48.8)	NC
Medical MELD score	16.6 ± 9.0	NC
Deceased donor	11 (26.8)	NC
Liver graft type (%), right/left/whole	29/1/11 (70.7/2.4/26.8)	NC
Posttransplantation (yr)	7.5 ± 7.3	NC
Body mass index (kg/m^2)	24.8 ± 2.9	25.2 ± 3.1
Diabetes	20 (48.8)	20 (48.8)
Hypertension	16 (39.0)	16 (39.0)

Values are presented as number only, number (%), or mean ± standard deviation (range).
HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NC, no change.



n=41	Reference: capsule	Visit 3	Visit 4	Visit 5	Visit 6
Tacrolimus trough level (ng/mL)	5.69 ± 1.91	5.66 ± 2.27, P = 0.895	5.24 ± 1.94, P = 0.047	5.40 ± 1.83, P = 0.279	5.45 ± 1.94, P = 0.363
Tacrolimus TDD (mg/day)	4.40 ± 3.24	4.16 ± 3.03, P = 0.031	4.06 ± 2.93, P = 0.042	4.01 ± 2.87, P = 0.044	

Fig. 2. Mean trough levels and total daily dose (TDD) of tacrolimus.

trial drugs are coded using the latest version of WHO-ART (World Health Organization Adverse Reaction Terminology), and the number of cases is calculated by body institution, and the percentage is presented.

RESULTS

Among 53 patients screened from January 2017 to December 2021, 41 eligible individuals were enrolled in conversion study from tacrolimus capsules to tablets. At the time of enrollment, male sex was 82.9% (n = 34) and the mean age was 55.7 ± 8.7 years. ABO incompatibility case was 14.6% (n = 6) (Table 1). There were no significant changes between visits 2 and 6 regarding body mass index, the incidence of diabetes, and the incidence of hypertension ($P < 0.05$).

Efficacy

The overall incidence of BPAR was 0% before the time of enrollment and no newly observed BPAR in the study period. No graft loss or patient death was reported.

Changes of mean blood through level of tacrolimus

The mean blood trough levels of tacrolimus at each time point are shown in Fig. 2. The trough level at visit 2 (capsule, 5.69 ± 1.91 ng/mL) was statistically higher than those at visit 4 (5.24 ± 1.94 ng/mL) ($P = 0.047$).

Total daily dose (TDD) of tacrolimus at visit 2 (capsule, 4.40 ± 3.24 mg/day) was higher than those after tablet conversion; at visit 3 (4.16 ± 3.03 mg/day, 94.5%), visit 4 (4.06 ± 2.93 mg/day, 92.3%), and visit 5 (4.01 ± 2.87 mg/day, 91.1%) ($P < 0.05$).

Safety

Adverse events and serious adverse events

The incidence of AE after tablet conversion was 34.1% (n = 14). The most frequent AE was abnormal liver function test (LFT) (n = 5), followed by upper respiratory symptoms (n = 4), gastrointestinal problems (n = 3), urogenital problems (n = 2), hematologic events (n = 2), subacute thyroiditis (n = 1), and skin scaling (n = 1).

All SAEs were abnormal LFTs (Table 2). However, there was no BPAR nor change of immunosuppressant to resolve SAEs. Four cases of biliary complications (case numbers 21, 37, 39, and 49) were resolved after biliary intervention or medical treatment. The other one (case number 49) was alcoholic recidivism showing fatty changes in imaging studies without evidence of BPAR.

Changes of serum liver function tests

The ALT level at visit 2 was not significantly different after tablet conversion ($P < 0.05$). However, other LFTs

Table 2. Severe adverse events (SAE)

Case No.	SAE	Cause	POD at event	Event visit after enrollment (wk)	TBil (mg/dL)	AST (IU/L)	ALT (IU/L)	γ-GT (IU/L)	Treatment	Relationship with IS	IS	Result
21	Biliary complication	Stricture	822	24	1.0	12	13	61	Percutaneous drainage	Not related	No change	Recovered
37	Biliary complication	Stricture	479	24	0.7	78	92	1,069	Endoscopic retrograde biliary drainage	Not related	No change	Recovered
39	Biliary complication	Leakage from external drainage tube	126	8	1.4	15	13	65	Tube removal	Not related	No change	Recovered
47	Biliary complication	Stricture	193	24	3.8	110	192	338	Conservative management	Unlikely	No change	Recovered
49	Acute hepatitis	Alcohol recidivism	101	8	2.2	666	1,011	148	Steroid treatment after liver biopsy confirmation	Unlikely	No change	Recovered

POD, postoperative day; TBil, total bilirubin; IS, immunosuppressant.

were significantly different at some time points after tablet conversion (Fig. 3). The AST level at visit 2 (capsule, 19.51 ± 5.75 IU/L) was significantly lower than those at visit 3 (21.07 ± 7.30 IU/L) and visit 5 (23.49 ± 15.04 IU/L) ($P < 0.05$). The one (case number 49, Table 2) showing high AST and ALT levels at visit 4 was related to acute hepatitis due to alcohol recidivism. Total bilirubin at visit 2 (capsule, 0.81 ± 0.31 mg/mL) was significantly lower than those at visit 3 (0.89 ± 0.33 mg/mL) and visit 6 (1.00 ± 0.58 mg/mL) ($P < 0.05$). The γ-GT level at visit 2 (capsule, 38.29 ± 61.83 IU/L) was significantly lower than those at visit 5 (53.59 ± 98.47 IU/L) ($P = 0.046$). Those high levels of total bilirubin (case number 47) and γ-GT levels were related to biliary complications (case number 37) (Table 2).

Changes in renal function and hemoglobin A1C examination

The eGFR at visit 2 (capsule, 78.70 ± 17.27 mL/min/1.73 m^2) was significantly higher than those at visit 6 (76.07 ± 18.36 mL/min/1.73 m^2) ($P = 0.043$) (Fig. 4). Serum creatinine (capsule, 0.98 ± 0.20 mg/dL) was significantly lower than those visit 6 (1.02 ± 0.25 mg/dL) ($P = 0.020$).

However, HbA1C at visit 2 (capsule, 5.71% ± 0.99%) was not significantly different after tablet conversion ($P > 0.05$). One patient (case number 28) showed not well-controlled type 2 diabetes with insulin in a short period of time on an outpatient basis.

Satisfaction questionnaire for tacrolimus formula conversion

TDDs at visits 2 and 3 were significantly different ($P = 0.031$) but the difference was minimal and the trough level at visit 2 and 3 was not different ($P = 0.895$). Total number of tacrolimus doses were significantly decreased at visit 3 compared to visit 2 (3.61 ± 1.67 *vs.* 5.02 ± 3.16, $P < 0.01$) (Table 3). This change was related to the 2-mg tablet formula which is a new invention.

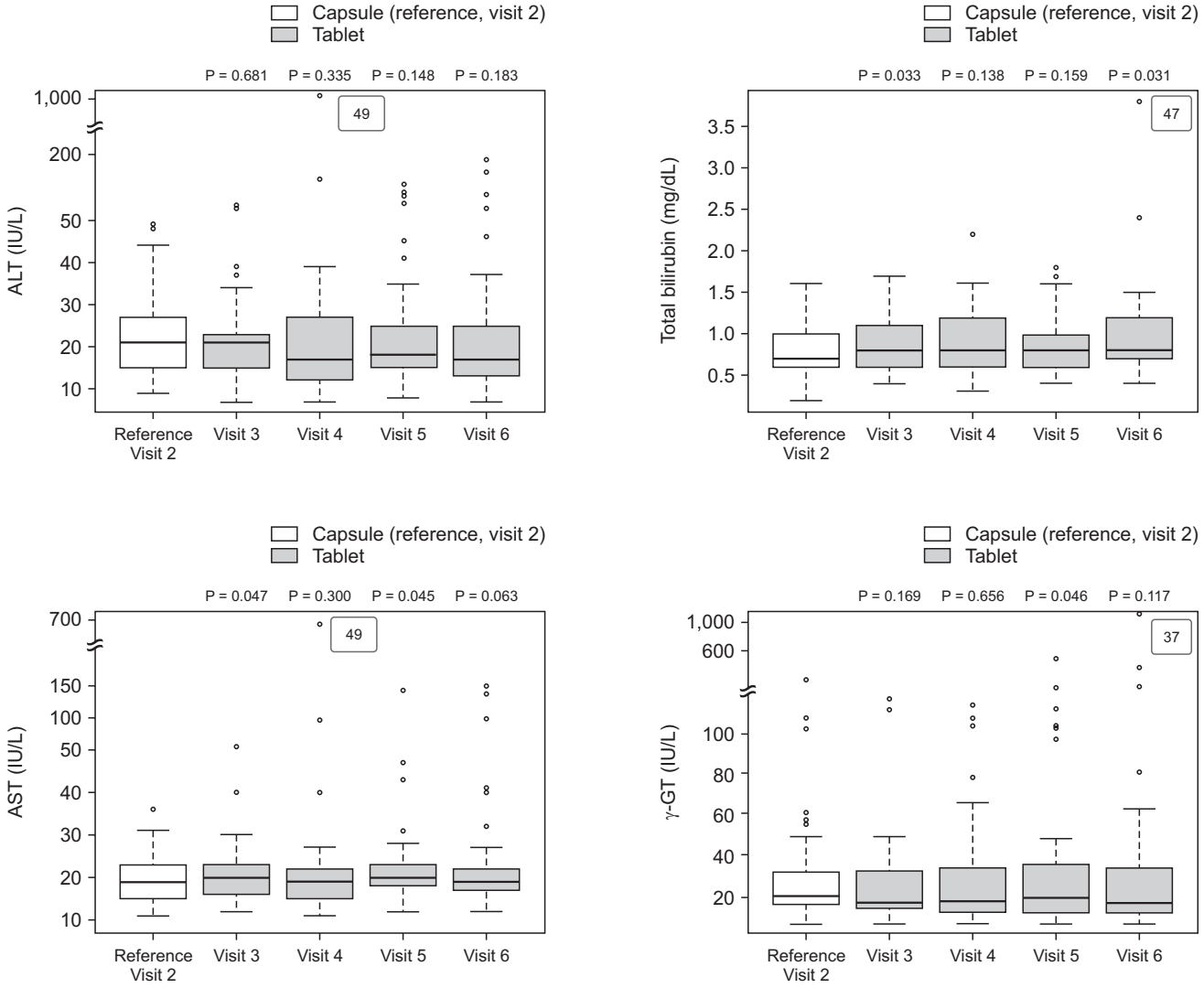


Fig. 3. Laboratory findings of liver function test. Numbers in the boxes means the patient numbers.

Discomfort scales at visit 2 *vs.* visit 3 showed a decreasing trend but were not significant (2.51 ± 1.38 *vs.* 2.37 ± 1.14, P = 0.577) (Fig. 5). The most common cause of discomfort was keeping medication time (Table 3).

Satisfaction scales at visit 2 *vs.* visit 3 showed an increasing trend but were not significant (3.80 ± 0.95 *vs.* 4.12 ± 0.81, P = 0.068). The most common reason for improvement of any convenience after the drug formula change from capsule to tablet was improvement of swallowing difficulty (n = 5) followed by reduction drug amount (n = 4), smaller size of tablet (n = 1), and easier carriage (n = 1). In contrast, the causes of discomfort after the drug formula change from capsule to tablet were difficulties in carriage (n = 2), swallowing difficulty (n = 1), and development of adverse event (n = 1).

DISCUSSION

Part 1. Efficacy and safety

In this prospective study, stable adult LT recipients were safely converted from tacrolimus capsule to tablet (1:1) without development of BPAR or patient deaths. Tacrolimus trough level was significantly lower after tablet conversion at week 8 (visit 4, P = 0.047), but this was not related to graft function or loss. Moreover, the total number of tacrolimus doses was decreased on the same TDD; and trough level was related to the benefit of the 2-mg tablet formula, which was a new invention. According to a previous paper, the geometric mean rati for Cmax (maximum whole-blood tacrolimus concentration) and AUClast (area under the whole-lood tacrolimus concentration-time cirve from 0 hour to the last quantifiable concentration) between the tablet and capsule formulations was close to unity with their 0% confidence intervals falling entirely within the conventional bioequivalence range of 0.80–1.25 [9]. There were

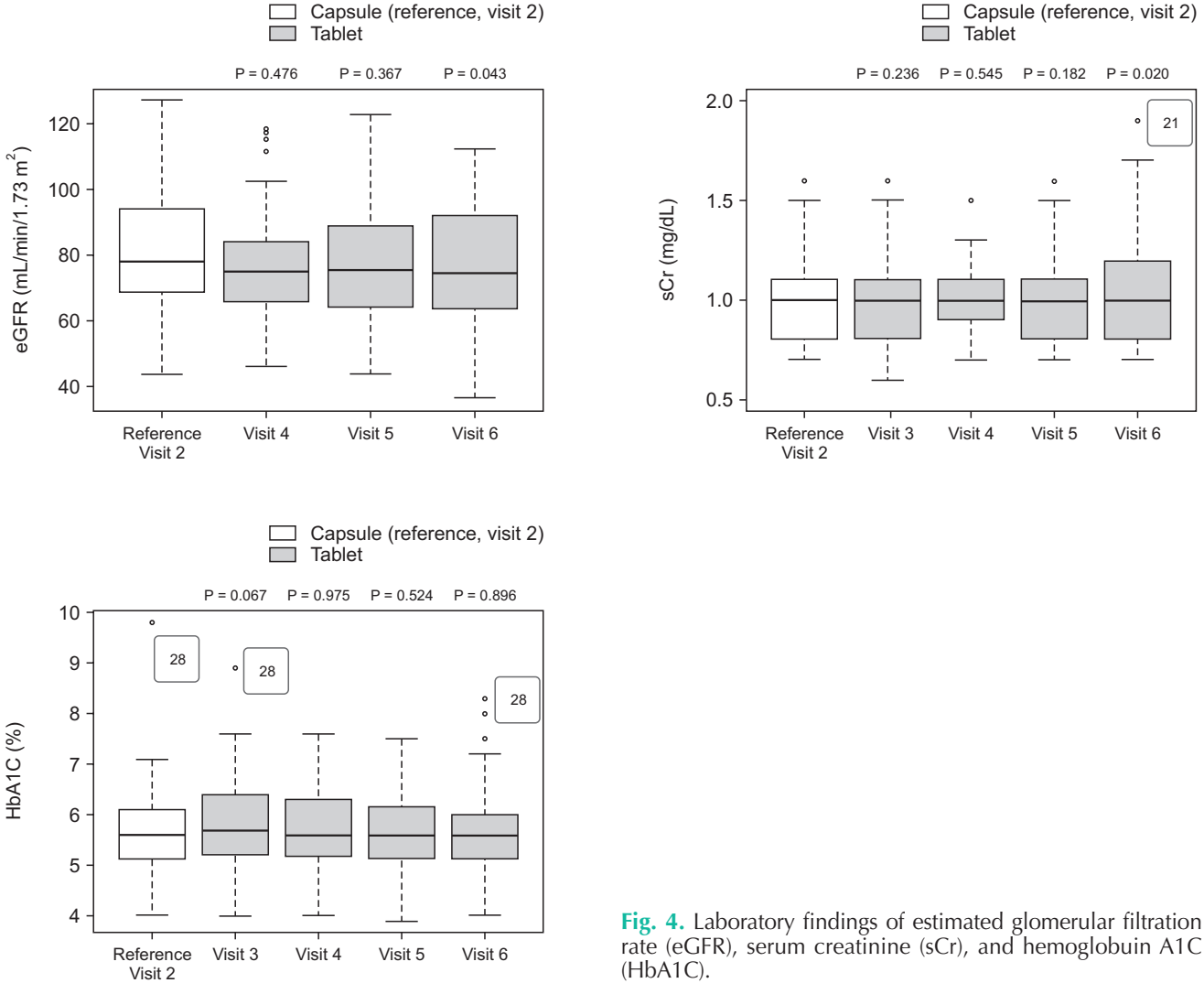
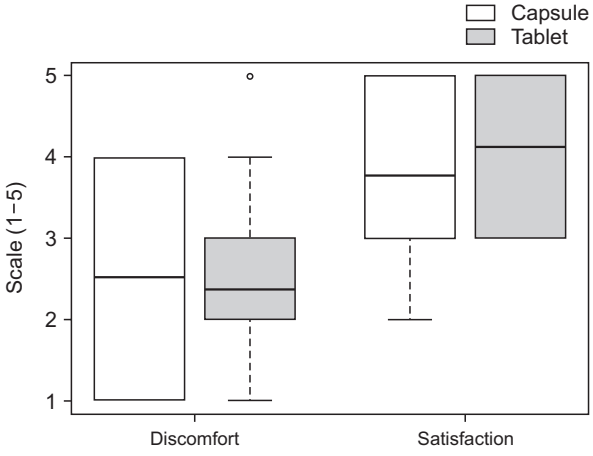


Fig. 4. Laboratory findings of estimated glomerular filtration rate (eGFR), serum creatinine (sCr), and hemoglobuin A1C (HbA1C).

Table 3. Satisfaction questionnaire before and after tacrolimus formula conversion from capsule to tablet (n = 41)

Questionnaire items	Visit 2[a]	Visit 3[b]	P-value
TDD of tacrolimus (mg/day)	4.40 ± 3.24	4.16 ± 3.03	0.031
No. of tacrolimus	5.02 ± 3.16	3.61 ± 1.67	<0.010
Tacrolimus trough level (ng/mL)	5.69 ± 1.91	5.66 ± 2.27	0.895
Discomfort, scale 1–5	2.51 ± 1.38	2.37 ± 1.13	0.577
Reason of discomfort			
Medication time	15	7	
Amount of drug	1	0	
Size of drug	1	1	
Swallowing	0	1	
Carriage	2	1	
Satisfaction, scale 1–5	3.80 ± 0.95	4.12 ± 0.81	0.068
Improvement after conversion from capsule to tablet, scale 1–5	Reference	3.29 ± 0.84	

Values are presented as mean ± standard deviation or number only.
TDD, total daily dose.
[a]Day 0, at the time of enrollment; [b]4 weeks after enrollment.



	Discomfort (scale 1–5)	Satisfaction (scale 1–5)
Capsule	2.51 ± 1.38	3.80 ± 0.95
Tablet	2.37 ± 1.13	4.12 ± 0.81
P value	0.577	0.068

Note: the higher the number, the stronger the scale

Fig. 5. Discomfort and satisfaction survey results.

14 patients who had been less than 6 months after LT; and after transplantation, we were tapering the tacrolimus to a target trough level of 5. Therefore, there was no difference in trough level, but it is thought to have decreased in TDD. The tendency for the trough level to decrease in visits 4 visit 5, to which the TDD capacity change in visit 3 was reflected, coincides with the tendency to decrease in TDD and seems to support the rationale.

There were significant differences in AST, total bilirubin, and γ-GT levels at certain time points after tacrolimus formula conversion. However, ALT levels which are mostly rapidly changed and related to graft inflammation were not significantly changed. The other LFTs changes as SAEs were related to alcohol recidivism (n = 1) and biliary complications (n = 4). Because 20 patients (48.8%) of this cohort were less than 1 year after LT, biliary complication was the most common cause of LFT abnormality.

The most common long-term adverse effect of tacrolimus is a decreased renal function and metabolic syndrome. There was no patient report or observation of AEs in cardiovascular issues, as well as incidence of hypertension being not changed during the study period. The incidence of diabetes and HbA1C were not changed. AEs occurred in 14 patients, but 2 events were thought to be related to tacrolimus conversion: 1 heartburn and 1 serum creatinine elevation. Heartburn was improved only with follow-up observation without special treatment, and the serum creatinine elevation also increased from 1.25 (visit 2) to 1.55 (visit 3) but improved to 1.02 (visit 4) after reducing the tacrolimus dose. Although eGFR was significantly lower at 24 weeks, but it was within normal range, we should consider the time gap between visits 2 and 6.

This study focused on the short-term results of the tablet form within 24 weeks. Therefore, further research is needed on the long-term effects of tablets in terms of *de novo* cancers, recurrence of viral hepatitis or hepatocellular carcinoma, and other known AEs as well as economic burdens.

Part 2. Satisfaction questionnaire

In general, patients may find it more difficult to swallow capsules than tablets because of the floating properties of capsules. In contrast, tablets are generally heavier than water and can minimize discomfort in the mouth when swallowed. Therefore, tablet formulations may theoretically help alleviate patient discomfort, increase medication compliance, and

improve quality of life. In addition, the tablets undergo a more efficient and scalable manufacturing process than those used in capsule manufacturing and are considered as preferred drug administration formulations for commercial production of higher unit volumes.

In the survey of satisfaction questionnaire, we expect improvement in swallowing difficulty and carriage. In visit 2, discomfort due to difficulty in swallowing seems to have been checked as there was no comparison target before the tablet switch, so no one felt discomfort. At visit 3, 5 patients noted improvement in swallowing difficulty in the questionnaire regarding improvement points. Thus, it is thought to be an improvement in swallowing difficulty after switching to the tablet. However, half of the study cohort (51.2%) was a long-term follow-up stable recipient (>1 year after LT). Therefore, their amount of TDD including tacrolimus was not large enough to be a meaningful result for conversions.

In this study, comparing capsules to tablets, discomfort decreased after conversion, and satisfaction increased, although it was not statistically significant. Nevertheless, the most common reason for improvement after formula conversion was swallowing difficulty, as expected. On the other hand, this formula is a 2-mg tablet, which can be theoretically more convenient for the initial period requiring a higher trough level. Therefore, a further large-scale study regarding immediate post-transplant recipients who inevitably require a much greater number of drugs will show more promising results regarding satisfaction scales. In addition, this study cohort number was small from a single center, though this is a prospective study. Therefore, further study requires the validation of a larger cohort in long-term follow-up.

In conclusion, the incidence of BPAR and graft survival as well as other AEs related to tacrolimus tablet 24 weeks after conversion from capsule to tablet of tacrolimus by 1:1 dosing were not inferior to those of THE capsule period. In addition, it showed a decreasing trend in discomfort scales and an increasing trend in satisfaction scales after tablet conversion, especially regarding drug swallowing. In terms of medication compliance, the tacrolimus tablet formula can be thought to have higher satisfaction without increasing the risk of BPAR with the smaller number of drugs using the new 2-mg tablet. This requires validation of a larger cohort in long-term follow-up.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1 can be found via https://doi.org/10.4174/astr.2023.105.4.228.

ACKNOWLEDGEMENTS

Fund/Grant Support

This study was sponsored by Chong Kun Dang Pharmaceutical Corporation.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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