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The Effect of Donor Age and Recipient Characteristics on Renal Outcomes in Patients Receiving Prolonged-Release Tacrolimus After Liver Transplantation: Post-Hoc Analyses of the DIAMOND Study

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* **DIAMOND:** ADVAGRAF® studIed in combinAtion with MycOphenolate mofetil aND basiliximab in liver transplantation

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Background: The DIAMOND study of *de novo* liver transplant patients showed that prolonged-release tacrolimus exposure in the acute post-transplant period maintained renal function over 24 weeks of treatment. To assess these findings further, we performed a *post-hoc* analysis in patients according to baseline kidney function, Model for End-stage Liver Disease [MELD] scores, and donor age.

Material/Methods: Patients received prolonged-release tacrolimus (initial-dose, Arm 1: 0.2 mg/kg/day, Arm 2: 0.15–0.175 mg/kg/day, Arm 3: 0.2 mg/kg/day delayed until Day 5), mycophenolate mofetil and 1 steroid bolus. Arms 2 and 3 also received basiliximab. The recommended tacrolimus target trough levels to Day 42 post-transplantation were 5–15 ng/mL in all arms. In this *post-hoc* analysis, change in renal outcome, based on estimated glomerular filtration rate (eGFR), Modified Diet in Renal Disease-4 (MDRD4), values from baseline to Week 24 post-transplantation, were assessed according to baseline patient factors: eGFR (≥60 and <60 mL/min/1.73 m^2), MELD score (<25 and ≥25) and donor age (<50 and ≥50 years).

Results: Baseline characteristics were comparable (Arms 1–3: n=283, n=287, n=274, respectively). Patients with baseline renal function, eGFR ≥60 mL/min/1.73 m^2, experienced a decrease in eGFR in all tacrolimus treatment arms. In patients with lower baseline renal function (eGFR <60 mL/min/1.73 m^2), an advantage for renal function was observed with both the early lower-dose and delayed higher-dose tacrolimus regimens compared with the early introduction of higher-dose tacrolimus. At Week 24, renal function was higher in the early-lower tacrolimus arm with older donors, and the delayed higher-dose tacrolimus arm with younger donors, both compared with early higher-dose tacrolimus.

Conclusions: Pre-transplantation factors, such as renal function and donor age, could guide the choice of prolonged-release tacrolimus regimen following liver transplantation.

MeSH Keywords: Glomerular Filtration Rate • Immunosuppressive Agents • Liver Transplantation • Tacrolimus

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Background

Long-term graft and patient outcomes post-liver transplantation have been associated with factors such as primary disease indication, recipient renal dysfunction, Model for End-stage Liver Disease (MELD) score, donor and recipient age, and diabetes [1–8]. For example, patients with estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 at the time of liver transplantation are reportedly less likely to develop chronic renal failure compared with patients with eGFR <30 mL/min/1.73 m^2 [9]. Furthermore, a MELD score >25 has been reported as an independent risk factor for reduced graft and patient survival in liver transplant recipients [6], while donor age ≥50 has been cited as a significant risk factor for renal dysfunction, graft loss, and patient death [6,10–13].

A decline in renal function in liver transplant recipients is usually observed in the first 3 months after transplantation, often stabilizing by 1-year post-transplantation [14]. About 50% of liver transplant recipients experience renal damage in the immediate post-operative period, for reasons such as viral hepatitis and post-reperfusion syndrome [15–17]. Following the initial post-transplantation period, about 35% of patients develop permanent renal dysfunction or failure over the long term [18].

In the *de novo* liver transplantation patients in the DIAMOND study, immunosuppression therapy with a lower dose of prolonged-release tacrolimus (initial dose: 0.15–0.175 mg/kg/day) initiated immediately post-transplantation, with a subsequent lower tacrolimus exposure over the first 5 days, was associated with significantly better renal function versus a higher first-dose (0.2 mg/kg) prolonged-release tacrolimus-based regimen administered immediately post-transplantation [19]. However, the incidence of biopsy-confirmed acute rejection (BCAR) was significantly greater with both delayed and early initiation of higher-dose, prolonged-release tacrolimus compared with early initiation of lower-dose prolonged-release tacrolimus [19]. This finding raised questions about the widely-accepted practice of trying to preserve kidney function by delaying tacrolimus initiation for several days after transplantation. This practice is supported by results from the ReSpECT trial, in which delayed initiation of lower-dose immediate-release tacrolimus (coupled with daclizumab) supported renal function better than early higher-dose immediate-release tacrolimus (without induction therapy with a monoclonal antibody) [20].

This *post-hoc* analysis aimed to establish whether the results from the main DIAMOND study apply to subgroups of patients, including those with impaired kidney function prior to transplantation, patients deemed to be sicker, as assessed by MELD score, and those who received a liver transplant from an older donor. For the patients receiving each treatment regimen in the DIAMOND study, renal outcomes were assessed based on eGFR Modified Diet in Renal Disease-4 (MDRD4) formula at 24 weeks after transplantation, and analyzed for patient groups stratified by baseline renal function, MELD score, and donor age.

Material and Methods

Study design

The study design and procedures used in the DIAMOND study have been described elsewhere [19]. DIAMOND was a multicenter, 24-week, randomized, open-label, parallel-group, Phase IIIb study, which was conducted in accordance with the Declaration of Helsinki. Patients were randomized 1: 1: 1 to receive prolonged-release tacrolimus (Advagraf®; Astellas Pharma Europe BV, Netherlands) – based regimens for 24 weeks at the following initial doses: 0.2 mg/kg/day on Day 1 post-transplantation (Arm 1; early higher-dose arm), 0.15–0.175 mg/kg/day on Day 1 post-transplantation (Arm 2; early lower-dose arm), or 0.2 mg/kg/day delayed until Day 5 post-transplantation (Arm 3; delayed higher-dose arm). Prolonged-release tacrolimus doses were targeted to recommended whole blood trough level ranges (5–15 ng/mL until Day 42; 5–12 ng/mL from Days 43–168 in the early higher-dose and delayed higher-dose arms, and 4–12 ng/mL in the early lower-dose arm) [19]. All patients received concomitant mycophenolate mofetil (MMF) and a single corticosteroid bolus, and patients in the early lower-dose and delayed higher-dose arms received a dose of basiliximab on Day 0 and Day 4. Maintenance steroids were not used during the study. The primary efficacy variable was eGFR using the MDRD4 at Week 24. Secondary endpoints and adverse events have been described previously [19], and are not reported in this publication.

Post-hoc subgroup analyses

The effect of baseline characteristics on renal function (eGFR; MDRD4) at Week 24 was analyzed in the 3 treatment arms. Patients were stratified by baseline renal function low/normal eGFR (≥60 mL/min/1.73 m^2) and low eGFR (<60 mL/min/1.73 m^2), baseline liver disease severity (MELD score <25 and ≥25, calculated retrospectively), and donor age ≥50 and <50 years.

Statistical analyses

Statistical analyses for the primary and secondary endpoints have been reported previously [19]. Non-inferiority of the difference in renal function for the early lower-dose and delayed higher-dose arms versus the early higher-dose arm at Week 24 was analyzed using the per-protocol set (all randomized

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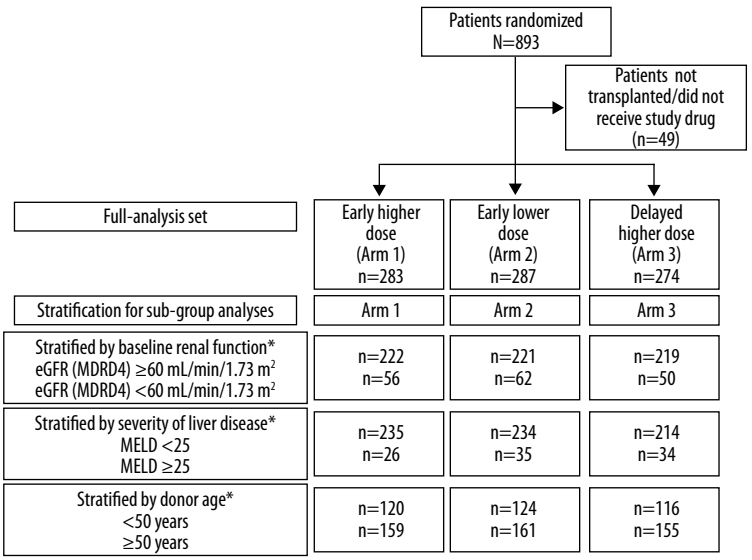

Figure 1. Patient flow through the study stratified by baseline characteristics (FAS). Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day) plus MMF; Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/day) plus MMF and basiliximab; Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day delayed until Day 5) plus MMF and basiliximab; * patients with missing data were omitted from the analyses; eGFR – estimated glomerular filtration rate; FAS – full-analysis set; MDRD4 – Modified Diet in Renal Disease-4; MELD – Model for End-stage Liver Disease; MMF – mycophenolate mofetil.

patients who received ≥1 dose of study drug, were transplanted, and did not have a major protocol violation).

In these post-hoc subgroup analyses, descriptive summary statistics (mean [standard deviation; SD] of renal function assessment [eGFR (MDRD4)] at baseline were obtained for each of the 3 patient subgroups by treatment arm. The same set of covariates (race, hepatitis C, sex) used for the main analyses of the study were also used for the subgroup analyses, where appropriate. The ANCOVA method was used to compare renal function between treatments for each patient subgroup. The analysis was controlled for sex, race (black), hepatitis C virus status, site, and baseline eGFR (used only for MELD score and donor age subgroups). Pairwise comparison of the resulting least squares (LS) means were performed between the treatment arms using Dunnett's test to adjust for multiplicity, as per the primary analysis of the DIAMOND study [19].

Furthermore, to evaluate the potential impact of the interaction between baseline eGFR and MELD score on change in renal function from baseline to Week 24, an ANCOVA analysis including all the covariates indicated above, as well as donor age (<50 and ≥50 years), MELD score (<25 and ≥25), baseline eGFR (<60 and ≥60 mL/min/1.73 m^2), and MELD by baseline eGFR interaction effect was performed. All analyses were performed using the full-analysis set (FAS, all randomized transplanted patients who received ≥1 dose of study drug).

Statistical analyses were carried out using Statistical Analytical System (SAS®, SAS Institute Inc.) Version 9.1.3 or higher. Patients with missing baseline data for stratification factors were omitted from the analyses. Although the initial study design was not powered for these post-hoc subgroup analyses, a *P* value <0.05 was considered significant for all comparisons.

Results

Patients

A total of 857 patients were transplanted and 844 patients were included in the FAS; 283, 287, and 274 patients in the early higher-dose, early lower-dose, and delayed higher-dose arms, respectively (Figure 1). Patient disposition in the DIAMOND study has been reported previously [19]. The proportion of missing data across arms was <5% for each major subgroup, except for MELD score, which was 7.8%, 6.3%, and 9.5% in the early higher-dose, early lower-dose, and delayed higher-dose arms, respectively.

Mean and median tacrolimus dose and exposure over time in the DIAMOND study have been reported previously [19].

For patients included in the subgroup analyses, the primary diagnosis for liver transplantation was hepatocellular carcinoma (29.8%), alcohol-related liver disease (23.9%), hepatitis C virus (15.7%), and other (30.6%). Mean (SD) baseline MELD scores in the early higher-dose, early lower-dose, and delayed higher-dose arms were 14.2 (5.3), 14.6 (4.9), and 14.0 (4.9) respectively for patients with MELD scores < 25, and 31.4 (5.3), 31.4 (4.7), and 29.6 (3.9) respectively for those with MELD scores ≥25. The mean ages of patients at baseline who received organs from donors aged ≥50 years (SD) were 55.6 (8.6), 55.1 (9.4), and 56.1 (8.7) years; patients who received organs from donors aged <50 years at baseline were 52.5 (9.5), 52.4 (9.9),

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Table 1. Baseline renal function (eGFR; MDRD4) according to pre-transplantation stratification factors (FAS).

	Early higher dose (Arm 1)		Early lower dose (Arm 2)		Delayed higher dose (Arm 3)	
	n	Mean (SD) eGFR at baseline, mL/min/1.73 m²	n	Mean (SD) eGFR at baseline, mL/min/1.73 m²	n	Mean (SD) eGFR at baseline, mL/min/1.73 m²
Stratification by baseline renal function						
eGFR ≥60 mL/min/1.73 m²	222	103.9 (31.6)	221	104.6 (31.6)	219	101.2 (26.7)
eGFR <60 mL/min/1.73 m²	56	41.2 (15.7)	62	36.3 (18.2)	50	40.0 (15.7)
Stratification by severity of liver disease						
MELD <25	235	95.9 (37.0)	234	93.3 (37.0)	214	91.4 (31.8)
MELD ≥25	26	63.4 (39.1)	35	65.8 (54.8)	34	77.1 (47.7)
Stratification by donor age						
≥50 years	159	88.4 (38.5)	161	90.9 (39.2)	155	89.3 (35.4)
<50 years	120	95.1 (38.3)	124	87.9 (42.5)	116	90.2 (33.6)

Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day) plus MMF; Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/day) plus MMF and basiliximab; Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day delayed until Day 5) plus MMF and basiliximab; eGFR – estimated glomerular filtration rate; FAS – full-analysis set; MDRD4 – Modified Diet in Renal Disease-4; MELD – Model for End-stage Liver Disease; MMF – mycophenolate mofetil; SD – standard deviation.

and 50.5 (12.0) years in the early higher-dose, early lower-dose, and delayed higher-dose arms, respectively.

Descriptive summary statistics of baseline eGFR (MDRD4) values by treatment arms in the analyses when patients were stratified by pre-transplantation factors (baseline renal function, MELD score, and donor age) are presented in Table 1. Baseline eGFR was numerically lower in the early lower-dose arm versus the early and delayed higher-dose arms in the subgroup defined by eGFR <60 mL/min/1.73 m² (mean 36.3 versus 41.2 and 40.0 mL/min/1.73 m², respectively) and numerically higher in the delayed higher-dose arm versus the early higher- and lower-dose arms in patients with MELD score ≥25 (77.1 versus 63.4 and 65.8 mL/min/1.73 m², respectively).

Baseline eGFR in patients receiving organs from donors aged ≥50 years was generally comparable between arms, while patients who received organs from donors aged <50 years in the early lower-dose arm had lower eGFR (MDRD4) compared with those in the early and delayed higher-dose arms (mean 87.9 versus 95.1 and 90.5 mL/min/1.73 m², respectively).

Kidney function at Week 24

An overview of the significant findings between treatment arms for each baseline factor from the subgroup analyses is shown in Table 2.

Effect of baseline eGFR

The effect of baseline renal function on eGFR (MDRD4) is shown in Figure 2. In patients with a low/normal eGFR at baseline, the mean (SD) decrease in eGFR (MDRD4) from baseline to Week 24 was higher for the early higher-dose arm versus the early lower-dose arm (–38.1 (37.8) versus –29.7 (41.7) mL/min/1.73 m²). Results from the ANCOVA analysis confirmed a significant difference between the early higher- and lower-dose arms (LS mean difference, 7.64 mL/min/1.73 m²; *P*=0.02). However, there was no significant difference in LS mean eGFR (MDRD4) between the delayed and early higher-dose arms (LS mean difference, 2.89 mL/min/1.73 m²; *P*=0.54).

For patients with low eGFR at baseline, mean (SD) improvement in renal function from baseline to Week 24 was 12.1 (33.3) mL/min/1.73 m² in the early lower-dose arm, and 15.1 (30.6) mL/min/1.73 m² in the delayed higher-dose arm; the mean (SD) change in renal function in the early higher-dose arm was –2.2 (29.0) mL/min/1.73 m². Similar results were obtained with the ANCOVA pairwise comparisons. LS mean eGFR (MDRD4) at Week 24 for patients with low eGFR at baseline was significantly higher in the early low-dose arm and the delayed higher dose arm versus the early higher-dose arm (60.5 and 66.5 versus 45.5 mL/min/1.73 m², respectively; *P*=0.04 and *P*=0.004) and comparable between the early low-dose and delayed higher-dose arms (*P*=0.37).

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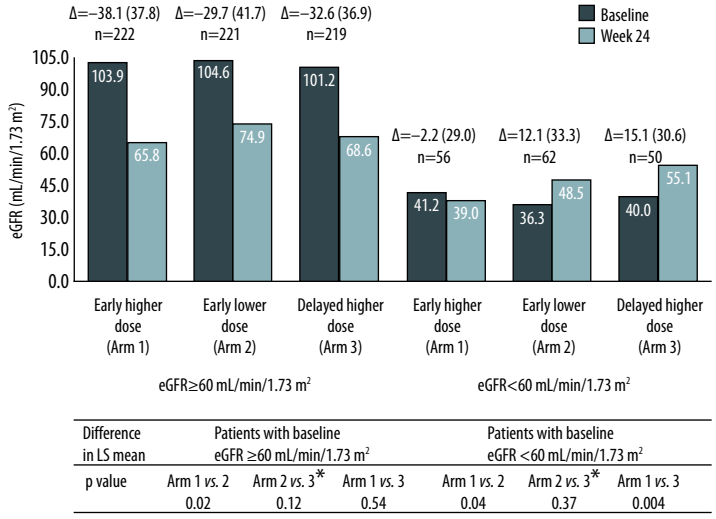
Table 2. Summary of subgroup analyses showing significantly better renal function (eGFR [MDRD4]) at week 24 in patients receiving early lower-dose or delayed higher-dose prolonged-release tacrolimus regimens compared with an early higher-dose tacrolimus regimen.

Baseline characteristic	Early lower dose (Arm 2)	Delayed higher dose (Arm 3)
Stratification by baseline renal function		
eGFR ≥60 mL/min/1.73 m^2	✓	
eGFR <60 mL/min/1.73 m^2	✓	✓
Stratification by severity of liver disease		
MELD <25	✓	
MELD ≥25	✓	✓
Stratification by donor age		
≥50 years	✓	
<50 years		✓

eGFR – estimated glomerular filtration rate; MDRD4 – Modified Diet in Renal Disease-4; MELD – Model for End-stage Liver Disease.



Difference in LS mean	Patients with baseline eGFR ≥60 mL/min/1.73 m^2			Patients with baseline eGFR <60 mL/min/1.73 m^2		
p value	Arm 1 *vs.* 2	Arm 2 *vs.* 3*	Arm 1 *vs.* 3	Arm 1 *vs.* 2	Arm 2 *vs.* 3*	Arm 1 *vs.* 3
	0.02	0.12	0.54	0.04	0.37	0.004

Figure 2. Renal function at Week 24 stratified by eGFR (MDRD4) at baseline (FAS) Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day) plus MMF (n=278); Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/day) plus MMF and basiliximab (n=283); Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day delayed until Day 5) plus MMF and basiliximab (n=269); patients with missing data were omitted from the analyses; Δ denotes unadjusted mean (SD) change from baseline to Week 24 in eGFR (MDRD4); eGFR at Week 24 was compared between arms using ANCOVA, controlling for baseline eGFR, race (black), hepatitis C virus, sex, and site; * *P* values for Arms 1 versus 2 and Arms 1 versus 3 were adjusted according to the Dunnett's procedure; *P* values for Arm 2 versus 3 are unadjusted; ANCOVA – analysis of covariance; eGFR – estimated glomerular filtration rate; FAS – full-analysis set; LS – least squares; MDRD4 – Modified Diet in Renal Disease-4; MMF – mycophenolate mofetil; SD – standard deviation.

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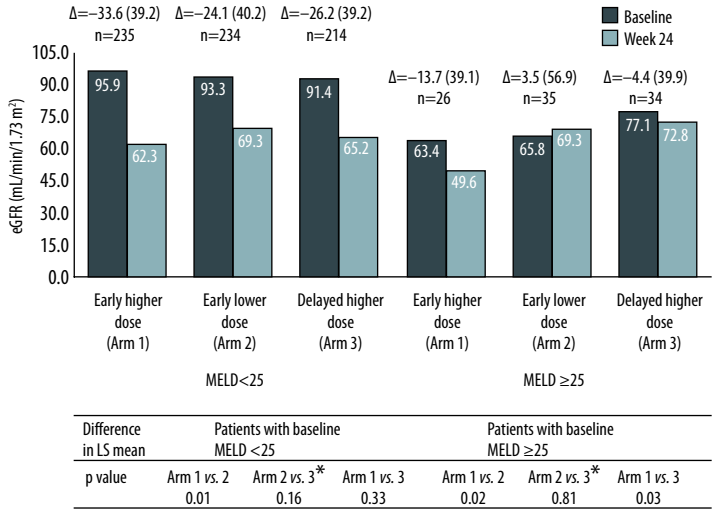

Difference in LS mean	Patients with baseline MELD <25			Patients with baseline MELD ≥25		
p value	Arm 1 *vs.* 2	Arm 2 *vs.* 3*	Arm 1 *vs.* 3	Arm 1 *vs.* 2	Arm 2 *vs.* 3*	Arm 1 *vs.* 3
	0.01	0.16	0.33	0.02	0.81	0.03

Figure 3. Renal function (eGFR; MDRD4) at Week 24 stratified by MELD score at baseline (FAS). Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day) plus MMF (n=261); Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/day) plus MMF and basiliximab (n=269); Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day delayed until Day 5) plus MMF and basiliximab (n=248); patients with missing data were omitted from the analyses; Δ denotes unadjusted mean (SD) change from baseline to Week 24 in eGFR (MDRD4); eGFR at Week 24 was compared between arms using ANCOVA, controlling for baseline eGFR, race (black), hepatitis C virus, sex, and site; * *P* values for Arms 1 versus 2 and Arms 1 versus 3 were adjusted according to the Dunnett's procedure; *P* values for Arm 2 versus 3 are unadjusted; ANCOVA – analysis of covariance; eGFR – estimated glomerular filtration rate; FAS – full-analysis set; LS – least squares; MDRD4 – Modified Diet in Renal Disease-4; MELD – Model for End-stage Liver Disease; MMF – mycophenolate mofetil; SD – standard deviation.

Effect of baseline MELD score

The effect of baseline MELD score on eGFR (MDRD4) is shown in Figure 3. In patients with baseline MELD scores <25, the unadjusted mean (SD) eGFRs (MDRD4) at Week 24 were similar across the 3 arms (62.3, 69.3, and 65.2 mL/min/1.73 m^2, respectively). However, the decrease in eGFR from baseline to Week 24 was less in the early lower-dose and delayed higher-dose arms versus the early higher-dose arm: –24.1 (40.2) and –26.2 (39.2) versus –33.6 (39.2) mL/min/1.73 m^2, respectively. Pairwise comparisons of the LS mean from the ANCOVA model showed that LS mean eGFR (MDRD4) at Week 24 were only significantly higher for the early lower-dose arm versus the early higher-dose arm (75.80 versus 68.04 mL/min/1.73 m^2; LS mean difference, 7.76; *P*=0.01). There was no significant difference in LS mean eGFR between the delayed higher-dose arm and either the early higher-dose arm (71.76 versus 68.04 mL/min/1.73 m^2; LS mean difference, 3.72; *P*=0.33) or the early lower-dose arm (71.76 versus 75.80 mL/min/1.73 m^2; LS mean difference, 4.04; *P*=0.16).

In patients with MELD score ≥25, an increase in renal function from baseline to Week 24, based on unadjusted means, was observed only in the early lower-dose arm: mean (SD), 3.5 (56.9) mL/min/1.73 m^2. However, the pairwise comparisons of the LS mean eGFR from the ANCOVA analysis was significant (*P*<0.05) for both the early lower-dose and delayed higher-dose arms versus the early high-dose arm (87.41 and 85.06 versus 57.12 mL/min/1.73 m^2; *P*=0.02 and *P*=0.03, respectively). No significant results were obtained from the assessment of baseline eGFR by MELD score interaction effect.

Effect of donor age

Data for baseline and Week 24 eGFR (MDRD4) for patients stratified by donor age is shown in Figure 4. For patients who received organs from donors aged <50 years, the mean (SD) decrease in eGFR from baseline to Week 24 was greater for the early higher-dose arm compared with the early lower-dose arm and the delayed higher-dose arm: –36.7 (39.1) versus –21.4 (39.5) and –21.2 (39.7) mL/min/1.73 m^2. Results from the ANCOVA analysis showed that the LS mean eGFR (MDRD4) was significantly higher for the delayed higher-dose arm than the early higher-dose arm (76.7 versus 65.4; *P*=0.01). The difference in LS mean eGFR (MDRD4) was numerically higher in the early low-dose arm compared with the early higher-dose arm (73.5 versus 65.4 mL/min/1.73 m^2; *P*=0.08). There was no significant difference in LS mean eGFR (MDRD4) between the early low-dose and delayed higher-dose arms (LS mean difference, –3.19; *P*=0.42).

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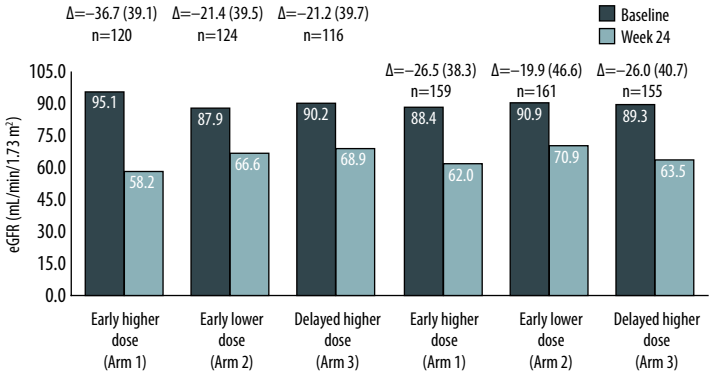

Difference in LS mean	Donors aged <50 years			Donors aged ≥50 years		
p value	Arm 1 *vs.* 2	Arm 2 *vs.* 3*	Arm 1 *vs.* 3	Arm 1 *vs.* 2	Arm 2 *vs.* 3*	Arm 1 *vs.* 3
	0.08	0.42	0.01	0.02	0.04	0.83

Figure 4. Renal function (eGFR; MDRD4) at Week 24 stratified by donor age at baseline (FAS). Arm 1: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day) plus MMF (n=282); Arm 2: prolonged-release tacrolimus (initial dose 0.15–0.175 mg/kg/day) plus MMF and basiliximab (n=287); Arm 3: prolonged-release tacrolimus (initial dose 0.2 mg/kg/day delayed until Day 5) plus MMF and basiliximab (n=273); patients with missing data were omitted from the analyses; Δ denotes unadjusted mean (SD) change from baseline to Week 24 in eGFR (MDRD4); eGFR at Week 24 was compared between arms using ANCOVA, controlling for baseline eGFR, race (black), hepatitis C virus, sex, and site; * *P* values for Arms 1 versus 2 and Arms 1 versus 3 were adjusted according to the Dunnett's procedure; *P* values for Arm 2 versus 3 are unadjusted; ANCOVA – analysis of covariance; eGFR – estimated glomerular filtration rate; FAS – full-analysis set; LS – least squares; MDRD4 – Modified Diet in Renal Disease-4; MELD – Model for End-stage Liver Disease; MMF – mycophenolate mofetil; SD – standard deviation.

In patients with organs from donors aged ≥50 years, the mean (SD) decrease in eGFR (MDRD4) from baseline to Week 24 was greater for the delayed higher-dose arm and early higher-dose arm versus the early lower-dose arm: –26.0 (40.7) and –26.5 (38.3) versus –19.9 (46.6) mL/min/1.73 m^2, respectively. LS mean eGFR (MDRD4) at Week 24 for these patients was significantly higher in the early lower-dose arm compared with the early higher-dose and delayed higher-dose arms (79.5 versus 69.9 and 71.8 mL/min/1.73 m^2, respectively; *P*=0.02 and *P*=0.04) and comparable between the early higher-dose and delayed higher-dose arms (*P*=0.83).

Discussion

In this *post-hoc* analysis, all liver transplant recipients with low/normal renal function at baseline experienced a decrease in eGFR from baseline to Week 24. In patients with low renal function at baseline, an advantage for renal function was reported with both early lower-dose and delayed higher-dose tacrolimus compared with early higher-dose tacrolimus. For patients with MELD ≥25, better renal outcomes were observed in patients receiving the early lower-dose and delayed higher-dose tacrolimus regimens compared with the early higher-dose tacrolimus regimen. In patients with older donors (≥50 years) the patients receiving early lower-dose tacrolimus had better renal function compared with the patients receiving early and delayed higher-dose tacrolimus. The patients with younger donors (<50 years) receiving delayed higher-dose tacrolimus had better renal function compared with those receiving early higher-dose tacrolimus.

The results of the DIAMOND study suggested that delaying tacrolimus initiation for several days after transplantation preserved kidney function compared with higher-dose prolonged-release tacrolimus-based regimen initiated immediately post-transplantation. Furthermore, early lower-dose prolonged-release tacrolimus was also associated with a lower incidence of BCAR versus higher-dose prolonged-release tacrolimus delayed until Day 5 post-transplant [19]. In our analysis, patients receiving early lower-dose or delayed higher-dose prolonged-release tacrolimus, who had low baseline eGFR (<60 mL/min/1.73 m^2), experienced an improvement in renal function over 24 weeks of treatment. Among patients in both baseline kidney function groups (eGFR <60 or ≥60 mL/min/1.73 m^2), compared with early higher-dose tacrolimus, a renal function advantage was reported with both early lower-dose tacrolimus and delayed higher-dose tacrolimus regimens. In patients with a low baseline eGFR, early lower-dose tacrolimus significantly improved renal function versus early higher-dose tacrolimus.

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A similar outcome was seen in a study by Giannelli et al., using creatinine clearance to estimate renal function, which showed a significant renal function benefit at 2 years post-transplantation with prolonged-release tacrolimus in patients with renal dysfunction (creatinine clearance <60 mL/min) compared to those with creatinine clearance ≥60 mL/min at baseline [21]. However, patients with eGFR <30 mL/min/1.73 m^2 at the time of liver transplantation were reportedly more likely to develop chronic renal failure compared with patients with eGFR ≥60 mL/min/1.73 m^2 in the same period (P<0.001) [9]. Furthermore, eGFR <30 mL/min/1.73 m^2 at 3 months post-transplantation has been associated with the development of stage 4–5 chronic kidney disease 5 years post-transplantation (P<0.03) [14].

As well as facilitating organ allocation for the transplant waiting list [22], MELD scores can be used to predict long-term outcomes following transplantation [23,24]. Sharma et al. demonstrated that patients with a pre-transplantation MELD score <20 had a significantly lower cumulative incidence of chronic renal failure post-transplantation compared with those with a MELD score ≥20 (P=0.03) [9]. Additionally, a MELD score >25 was found to be an independent risk factor for reduced graft and patient survival in a European Liver Transplant Registry study [6], supporting the stratification of MELD score selected in our study.

We found that patients with a MELD score ≥25 receiving early lower-dose tacrolimus, experienced a mean increase in eGFR (MDRD4) of 3.5 mL/min/1.73 m^2 over the treatment period. ANCOVA analysis of adjusted data confirmed that there was a significant improvement with early low-dose tacrolimus when compared with early higher-dose tacrolimus in patients with a MELD score ≥25. By contrast, patients with a MELD score ≥25 in the early higher-dose arm experienced a significant decrease in eGFR (MDRD4) compared with both the early lower-dose and delayed higher-dose tacrolimus regimens.

Patients with a MELD score <25 experienced a decrease in renal function in all tacrolimus groups; mean decrease in eGFR (MDRD4) was higher in patients receiving early higher-dose tacrolimus versus other tacrolimus groups. While we recognize that the standard deviations were high for the ANCOVA data, the results support the use of an initial lower dose of prolonged-release tacrolimus (and subsequent lower exposure) for maintaining renal function over time.

Donor age ≥50 has been reported as a significant risk factor for renal dysfunction, graft loss, and patient death in liver transplantation patients, supporting age 50 years as a cut-off in our study [6,10–13]. In patients who received organs from donors aged ≥50 years, lower dose, tacrolimus administered immediately post-transplantation provided a significant renal function advantage versus the other tacrolimus regimens. In patients who received organs from donors aged <50 years, renal function was significantly higher with delayed higher-dose tacrolimus than early higher-dose tacrolimus.

As well as the previously described limitations of the DIAMOND study [19], the main limitation of this study was the *post-hoc* design such that it was not powered for these analyses. In addition to the limitations associated with open-label studies, the DIAMOND study was of short duration. In this sub-analysis, there may be some overlap in the different stratification groups, for example, patients with MELD score <25 could also have had good renal function at baseline. Another limitation is the higher number of patients in the eGFR ≥60 versus <60 mL/min/1.73 m^2 group and in the MELD ≥25 versus <25 group, which may have affected the statistical analyses.

Conclusions

This *post-hoc* analysis in *de novo* liver transplantation patients suggests that the extent of early or delayed tacrolimus exposure post-transplantation may be important for preserving renal function depending upon pre-transplantation factors. In patients with poor kidney function or more severe liver disease, delaying initiation of prolonged-release tacrolimus did not provide better renal function over immediate administration of a lower tacrolimus dose. These findings suggest that pre-transplantation factors could guide the choice of prolonged-release tacrolimus regimen following liver transplantation.

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