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CHANGES IN GLOMERULAR FILTRATION RATE IN LIVER RECIPIENTS AFTER REDUCED EXPOSURE TO CALCINEURIN INHIBITORS WITH CONCOMITANT EVEROLIMUS ADMINISTRATION WITHIN THE FIRST YEAR AFTER IMMUNOSUPPRESSION CONVERSION

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Objective: to compare changes in estimated glomerular filtration rate (eGFR) in liver recipients with initially normal and impaired eGFR within the first year after immunosuppression conversion. **Materials and methods.** Enrolled in the study were 215 recipients of deceased-donor livers from February 2009 to February 2020, who received everolimus with dose reduction or complete withdrawal of calcineurin inhibitors (immunosuppression conversion, ISxC) for varying periods of time. GFR was measured using the MDRD-4 formula immediately before ISxC, then 3, 6, and 12 months after orthotopic liver transplantation (LTx). One month was considered an acceptable temporary deviation from the corresponding point. **Results.** At the time of ISxC, 32 (15%) of 215 recipients had normal renal function. Chronic kidney disease (CKD) increased in 60% of the recipients with normal eGFR by the end of the first year following ISxC; the fall in eGFR was particularly pronounced in older recipients. In the group with a baseline eGFR of 60–89 mL/min/1.73 m^2, eGFR normalized in 62% of cases within 12 months; 28% of cases had no changes in renal function. In the subgroup with a pronounced decrease in eGFR at the time of ISxC, increased eGFR was observed as early as 1 month after ISxC, and the maximum was recorded after 3–6 months. The mean eGFR relative to baseline by month 3 after eGFR were higher for ISxC that was done in the first 2 months after LTx (19.7 ± 15.7 ml/minute/1.73 m^2) than for ISxC done in the long-term period after LTx (10.1 ± 8.7 ml/minute/1.73 m^2, $p < 0.05$). **Conclusion.** Changes in eGFR in liver recipients receiving EVR plus low-dose calcineurin inhibitor (CNI) depend on baseline eGFR and are multidirectional. The use of ISxC in the early post-LTx period led to a more pronounced improvement in eGFR. Maximal changes in eGFR were observed by 3–6 months after ISxC.

Keywords: liver transplantation, immunosuppressive therapy, calcineurin inhibitor nephrotoxicity, everolimus.

Chronic kidney disease (CKD) is a common complication following liver transplantation (LTx). End-stage CKD (eGFR ≤29 mL/min/1.73 m^2 by MDRD formula) occurs in 8% at 1 year and in 18% at 5 years after LTx [1]. The most significant reason for deterioration of renal function in liver recipients is the use of calcineurin inhibitors (CIs) – cyclosporine (CsA) and tacrolimus (TAC) – as the main component of immunosuppressive therapy (IST). Nephrotoxicity of CI is well studied and described in detail [2, 3]. Accordingly, minimizing the exposure (area under the concentration-time curve) to CIs is necessary to slow down CKD progression and preserve kidney function in liver recipients.

A possible way to reduce CI exposure without simultaneously increasing the risk of rejection is to compensate for the IST action by prescribing drugs with a different mechanism of action. One of such drugs is proliferative signal inhibitor, everolimus (EVR). IST efficacy and safety – with respect to progression of CKD in liver recipients – based on EVR combination with simultaneous minimization of TAC exposure has been demonstrated in the CRAD2304 and CRAD2307 clinical trials [4, 5]. In both trials, recipients had relatively high GFR (80 and 90 mL/min/1.73 m^2) at the time of randomization. The effectiveness of GFR restoration after IST conversion (EVR combined with reduced CI dose (ISxC)) in liver recipients with reduced baseline GFR has not been sufficiently studied.

Objective: To compare changes in GFR in liver recipients with normal baseline and impaired GFR within the first year after ISxC.

PATIENTS AND RESEARCH METHODS

We retrospectively analyzed changes in eGFR in 215 recipients who received LTx from a deceased donor between February 2009 and February 2020 and who re-

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ceived one or more EVR doses as part of routine clinical practice. At the time of the analysis, 169 patients were alive and remained patients at the liver transplant center, 27 had died, and 19 had dropped out of hospital care at various times. Of the 169 recipients who were alive at the time of analysis and continued to be seen at the transplant center, EVR was withdrawn in 51 cases, and 118 recipients continued to receive therapy.

Before ISxC, 102 recipients received CIs as the main component of maintenance IST, in 113 cases EVR was administered simultaneously with CIs in the first two weeks after LTx. Cyclosporine (initial dose of 5–6 mg/kg per day) was given to 34 (15.8%) recipients. Target CsA blood concentrations, determined 30 minutes before drug administration (C_0) in the first months after LTx, were 150–250 ng/mL, thereafter 100–150 ng/mL. 181 (84.1%) recipients received TAC (initial daily dose of 0.05–0.075 mg/kg). Target TAC blood concentrations determined 30 minutes before drug administration (C_0): month 1–3, 8–10 ng/mL; thereafter, 6–8 ng/mL.

Mycophenolate mofetil (MMF) drugs were administered to 131 patients, of whom 93 patients received mycophenolic acid; 38 patients received mycophenolate mofetil. MMF drugs were withdrawn in all but one recipient at different times during the postoperative period. No glucocorticoids were administered to 171 recipients in the postoperative period. In 14 recipients, prednisone was discontinued within the first 3–4 months after OLTx. Nineteen recipients were treated at a later stage. Eleven recipients continued to receive low (5 mg/day) doses of prednisolone.

Indications for EVR were: renal failure in 85 recipients (39.5%), presence of hepatocellular carcinoma (HCC) as one of the indications for LTx – in 79 recipients (36.7%). Twenty-three recipients (11%) were prescribed EVR due to renal failure and the presence of HCC prior to LTx; 7 (3%) recipients were prescribed EVR due to HCC progression in the postoperative period. In 4 (2%) cases, EVR was prescribed due to neurological complications while taking CIs. Eight (3.7%) recipients received EVR as part of the CRAD2304 clinical trial [5]. Other indications for EVR were tumors (non-HCC, n = 5), lymphoma (n = 2), and liver transplantation (n = 2).

After ISxC, EVR was administered at 1 to 2 mg per day (0.01 to 0.04 mg/kg) in two doses. The target EVR blood concentration 30 minutes before drug administration (C_0) was 3–5 ng/ml. The CI dose was reduced simultaneously with EVR administration; the target TAC levels in the two-component therapy regimen were 3–5 ng/mL, and the target CsA level was 50–75 ng/mL. In 16 cases, CIs were canceled entirely.

The studied population included 150 men and 65 women aged 53 (50.3; 53.1) years (M (95% CI), with a mean body weight of 76 (74.3; 79) kg. Surgery for end-stage cirrhosis was performed in 199 (92.5%) patients with chronic diffuse liver disease, of which 102 (51.3%) cases were combined with HCC; 12 (5.5%) patients with primary liver tumors without cirrhosis; 4 (1.9%) – for other reasons. Seven recipients underwent combined liver–kidney allotransplantation.

The eGFR was calculated using the MDRD-4 formula immediately before immunosuppression conversion, 3, 6, and 12 months after OLTx [6]. One month was considered an acceptable time deviation from the corresponding point.

Statistical processing of numerical values was performed using the Statistica 7.0 software. Statistical significance of differences between compared parameters was established using Wilcoxon signed-rank test for paired comparisons of dependent variables and Kolmogorov–Smirnov test for comparisons of independent variables. Differences between compared parameters were considered statistically significant if the probability of error was less than 0.05 ($p < 0.05$).

RESULTS

Dependence of change in renal function during the first year of follow-up after IST conversion on baseline eGFR

The majority of recipients at the time of ISxC had eGFR below normal; only 32 (15%) of 215 recipients had normal renal function. Table 2 shows that after ISxC, the proportion of recipients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) gradually decreased, the proportion of recipients with moderate-to-severe renal impairment (eGFR 30 to 44 mL/min/1.73 m^2) remained the same (about 20% of total recipients), whereas the proportion of recipients with mild to moderately mild renal impairment (eGFR 45 to 89 mL/min/1.73 m^2) increased. Despite ISxC, the proportion of recipients with normal eGFR decreased during the first year after LTx.

To identify the effect of baseline renal dysfunction on eGFR dynamics after ISxC, we analyzed the pattern of changes in CKD degree depending on baseline eGFR.

Normal eGFR levels after 12 months of follow-up were preserved only in 40% of liver recipients with normal baseline eGFR (>90 mL/min/1.73 m^2). In the

Table 1

Degree of renal dysfunction at the time of immunosuppression conversion

eGFR range (mL/min/1.73 m^2)	n	eGFR (MDRD4), M (CI)
>90	32	109.2 (103.1; 115.4)
60–89	52	73.0 (70.7; 75.3)
45–59	35	52.6 (51.1; 54.2)
30–44	45	36.6 (35.4; 37.8)
15–29	44	23.2 (21.9; 24.5)
<15	7	10.9 (8.2; 13.7)

rest, eGFR deteriorated, but was not pronounced (eGFR remained more than 60 mL/min/1.73 m^2) in the vast majority of cases (50%) it.

ISxC in the group of patients with a mild decrease in baseline eGFR (60–89 mL/min/1.73 m^2) in 62% of recipients within 12 months led to eGFR normalization. In 28% of these recipients, no change in renal function was observed at follow-up within the first year of ISxC. And only 10% of recipients at 12 months after ISxC had eGFR fall to levels consistent with stage 3 CKD.

In half (45–50%) of the liver recipients who underwent ISxC with moderate renal dysfunction (eGFR correlated with stages 3A and 3B CKD), eGFR remained at the same level during the first 12 months of follow-up. Forty-two percent of recipients with baseline eGFR of 45–59 mL/min/1.73 m^2 and 55% of recipients with baseline eGFR of 30–44 mL/min/1.73 m^2 showed better renal function one year after ISxC, up to complete normalization in 5–17% of recipients.

In the subgroup of recipients who underwent ISxC with baseline severe renal impairment (eGFR 15–29 mL/min/1.73 m^2), as early as one month after ISxC, 70% had increased eGFR, with 12% to levels above 60 mL/min/1.73 m^2; 12 months later, eGFR corresponding to stage 4 CKD, was retained in only 25% of recipients.

In all 7 recipients with baseline eGFR <15 mL/min/1.73 m^2 after ISxC, eGFR increased after 1 month of follow-up, and in 4 of them – to levels >30 mL/min/1.73 m^2. The results of our analysis are shown graphically in Figs. 1 and 2.

The dynamics of median eGFR as a function of baseline eGFR during the first 12 months of follow-up are shown in Figs. 3, 4 and Table 3.

Table 2

Proportion of recipients with different CKD stages depending on eGFR at the time of ISxC in recipients within the first year after LTx

eGFR range (mL/min/1.73 m^2)	ISxC	Month 1	Month 3	Month 6	Month 12
>90	14.9%	14.6%	10.5%	10.1%	8.1%
60–89	24.2%	28.1%	39.0%	42.4%	34.3%
45–59	16.3%	26.5%	27.9%	27.3%	27.3%
30–44	20.9%	21.6%	20.3%	18.7%	23.2%
15–29	20.5%	9.2%	2.3%	1.4%	7.1%
<15	3.3%	0	0	0	0
Number of recipients with known eGFR	215	185	172	139	99

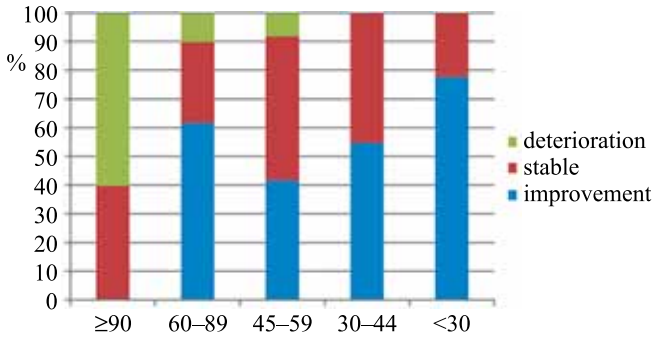

Fig. 1. Changes in renal function 12 months after ISxC

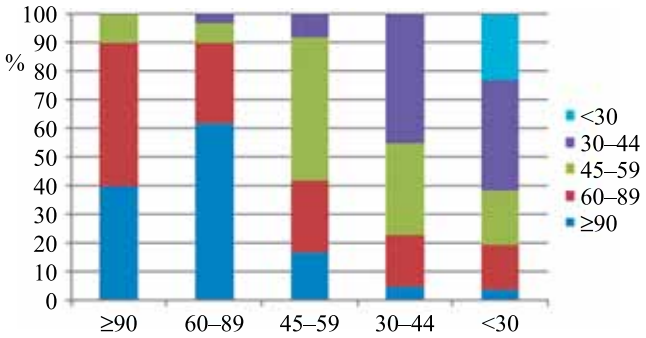

Fig. 2. Changes in eGFR (by CKD stages) 12 months after ISxC

Table 3

Change in median eGFR in the first 12 months of follow-up after ISxC (Me (Q25; Q75), mL/min/1.73 m^2)

Group (by baseline gGFR)	Baseline eGFR	Month 1	Month 3	Month 6	Month 12
>90	103.1 (97.1; 125.5)	89.5 (73.1; 100.4)‡	84.1 (71.6; 94.4)‡	87.0 (70.5; 95.1)‡	82.7 (72.2; 95.5)‡
60–89	73.3 (65.0; 79.2)	71.2 (57.1; 84.2)	64.9 (56.9; 82.0)	68.3 (58.1; 81.5)	69.4 (54.7; 78.6)
<60	34.4 (24.5; 46.3)	46.2 (34.7; 56.9)†	52.2 (41.7; 62.3)†	52.5 (42.5; 64.9)†	48.6 (39.1; 59.7)†

Compared to baseline eGFR: ‡ – $p < 0.01$, † – $p < 0.001$.

Thus, eGFR dynamics depended on the presence and severity of renal failure at the time of ISxC. Analysis of the presented eGFR changes during the first year after ISxC allows us to distinguish three subgroups of recipients. In the subgroup of recipients with normal baseline eGFR, 60% of liver recipients tended to have worsening renal function despite ISxC. In the remaining 40% of recipients, ISxC prevented a decline in eGFR during the one-year follow-up. Overall, in the subgroup, the median eGFR at 12 months after ISxC was 82.7 mL/min/1.73 m^2, a decrease of 19.8% from baseline.

The other subgroup consists of recipients with a mild to moderate decrease in eGFR at the time of ISxC (eGFR 45–89 mL/min/1.73 m^2). During the first year of follow-up, eGFR remained unchanged in 28–50% of recipients in this subgroup. In recipients with a slight initial decrease in eGFR (60–89 mL/min/1.73 m^2), 62% of cases showed eGFR normalization after 12 months. In the subgroup of recipients with a more severe decrease in baseline eGFR (45–59 mL/min/1.73 m^2) one year after ISxC, CKD worsened in only 8% of cases and improved in 42%. On average, eGFR scores in this subgroup of recipients remained stable during the first year after ISxC, with no clear trend toward improvement or deterioration in renal function (Figs. 3 and 4).

Recipients with significantly reduced renal function (eGFR <45 mL/min/1.73 m^2), who formed the third subgroup, showed a clear improvement in renal function after ISxC, with the eGFR increase being more significant the more severe the baseline renal dysfunction. At baseline eGFR 30–49 mL/min/1.73 m^2, 55% of recipients showed improvement in CKD stage after one year of follow-up, with 45% of CKD stage remaining the same. No recipient in the subgroup had a deterioration in CKD stage after 12 months of follow-up.

It should be noted that the increase in eGFR was rapid, reaching the level of statistical significance as early as 1 month after ISxC, and peaked after 3–6 months (Table 3; Fig. 3, 4). The fall in median eGFR by 3 months of follow-up was 13.9% in recipients with baseline eGFR 45–59 mL/min/1.73 m^2, 43.2% in recipients with baseline eGFR 30–44 mL/min/1.73 m^2, and 115% in recipients with baseline eGFR <30 mL/min/1.73 m^2 (!).

Dependence of changes in eGFR on ISxC timing

We compared changes in eGFR in the first 12 months of follow-up after ISxC in recipients with significantly reduced baseline renal function (eGFR <60 mL/min/1.73 m^2) as a function of ISxC timing.

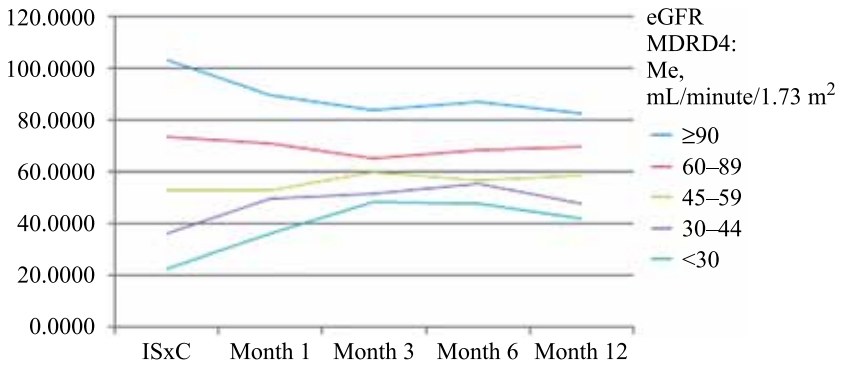

Fig. 3. Changes in median eGFR in the first 12 months of follow-up after ISxC (Me, mL/min/1.73 m^2) depending on baseline eGFR (by CKD stages)

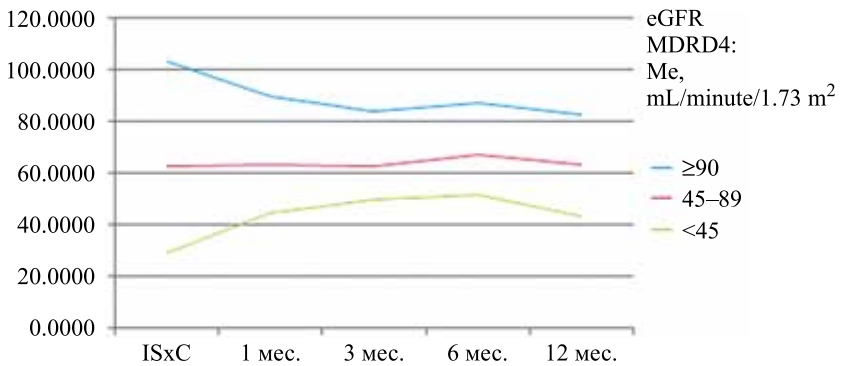

Fig. 4. Changes in median eGFR in the first 12 months of follow-up after ISxC (Me, mL/min/1.73 m^2) depending on baseline eGFR

Most recipients with a significantly reduced baseline eGFR (<60 mL/min/1.73 m^2) underwent ISxC in the first 12 months after LTx. The mean baseline eGFR was lower in this subgroup of recipients than in the subgroup of recipients who underwent ISxC at a later date (Table 4). The mean eGFR when assessed at 1 month, 3 months, 6 months, and 12 months after ISxC between the subgroups of recipients with early and late ISxC were comparable.

However, in the months after ISxC in which the maximum increase in eGFR was observed (months 3 and 6, see Fig. 3), the mean increases in eGFR relative to baseline were higher for early ISxC than for ISxC performed at a later time after LTx (Table 5).

Influence of gender, recipient age, and calcineurin inhibitor on eGFR changes

At the time of ISxC, mean eGFR were comparable in men and women in both the entire recipient population (56.7 ± 30.6 and 49.7 ± 29.0 mL/min/1.73 m^2, respectively) and in the subgroup of recipients with significantly reduced eGFR (34.5 ± 12.6 and 33.7 ± 15.5 mL/min/1.73 m^2). Baseline eGFR were also independent of the CIs variant that the recipients received before ISxC. In the TAC subgroup, eGFR was 55.0 ± 30.3 mL/min/1.73 m^2, and in the CsA subgroup, it was 55.0 ± 30.9 mL/min/1.73 m^2. Comparable results for both baseline eGFR and its dynamics during follow-up after ISxC were also obtained when analyzed based on recipient age. The median age of recipients was 53 years. Table 6 presents the eGFR dynamics as a function of recipient age. Since the eGFR dynamics in recipients with normal baseline eGFR and significantly decreased eGFR were multidirectional, we considered it right to present it separately.

We see that the mean baseline eGFR in younger and older recipients were very similar. After ISxC, eGFR decreased more markedly in older than in younger recipients with baseline eGFR ≥60 mL/min/1.73 m^2. The differences between the subgroups reached statistical

Table 4

Mean eGFR depending on ISxC timing

Months after ISxC	Early conversion (<12 months after OLTx)		Late conversion (>12 months after OLTx)		p
	n	M (SD), mL/min/1.73 m^2	n	M (SD), mL/min/1.73 m^2	
Baseline eGFR	**114**	**34.0 (13.5)**	**17**	**41.4 (11.1)**	**0.03**
Month 1	101	49.0 (19.3)	10	44.7 (12.8)	>0.05
Month 3	87	55.0 (18.1)	13	50.9 (11.2)	>0.05
Month 6	67	54.8 (16.7)	12	52.6 (13.3)	>0.05
Month 12	50	50.3 (17.5)	10	53.7 (20.4)	>0.05

Table 5

Mean increase in eGFR from baseline depending on ISxC timing

Increase by months after ISxC	Early conversion (<2 months after LTx)		Mean conversion (2–12 months after LTx)		Late conversion (>12 months after LTx)		P (between early and late ISxC)
	n	M (SD), mL/min/1.73 m^2	n	M (SD), mL/min/1.73 m^2	n	M (SD), mL/min/1.73 m^2	
By month 1	82	15.9 (20.2)	19	11.9 (10.3)†	10	7.3 (8.0)	>0.1
By month 3	**71**	**22.3 (20.6)**	16	19.7 (15.7)†	**13**	**10.1 (8.7)**	**0.039**
By month 6	**53**	**23.5 (20.0)**	14	13.0 (11.5)†	**12**	**10.4 (8.1)**	**0.03**
By month 12	39	19.0 (18.6)	11	12.1 (18.6)†	10	12.8 (15.0)	>0.1

† – differences between groups are insignificant (P > 0.01).

Table 6

Mean eGFR at the time of ISxC and increase in eGFR from baseline, depending on recipient age

eGFR, M (SD), mL/min/1.73 m^2	Baseline eGFR ≥60 mL/min/1.73 m^2			Baseline eGFR <60 mL/min/1.73 m^2		
	Age		p	Age		p
	≤53 лет	>53 лет		≤53 years	>53 years	
Baseline eGFR	88.7 (23.9)	84.3 (18.4)	>0.1	36.3 (13.6)	33.8 (13.2)	>0.1
Increase by month 1	–1.8 (24.6)	–14.3 (20.6)	>0.05	15.2 (17.7)	13.6 (18.8)	>0.1
Increase by month 3	**–6.0 (22.2)**	**–15.1 (18.7)**	**<0.05**	24.3 (22.5)	16.2 (13.8)	>0.05
Increase by month 6	–6.1 (22.5)	–12.9 (16.6)	>0.05	22.9 (21.6)	16.7 (14.0)	>0.1
Increase by month 12	–12.4 (17.8)	–11.0 (20.9)	>0.1	17.6 (19.1)	15.9 (14.8)	>0.05

significance at month 3 after ISxC. At the same time, the subgroup with baseline eGFR <60 mL/min/1.73 m^2 also showed a trend toward more significant improvement in eGFR in the younger recipient subgroup, but differences between subgroups did not reach statistical significance at all assessment points. Maximum differences between the subgroups of younger and older recipients are also detected at month 3 after ISxC.

DISCUSSION

At the Moscow Liver Transplantation Center, EVR has been used as one of the components of maintenance IST since 2009 as part of the CRAD2304 protocol and since 2010 as part of routine clinical practice. The experience in the use of EVR in liver recipients in our Center is the largest in Russia. Our first publications showed that kidney function in liver recipients who received EVR while minimizing exposure to CIs can be improved [7, 8]. In these works, 10–24 recipients were analyzed. This present paper retrospectively analyzed 215 liver recipients who received EVR as one of the components of maintenance IST. At the time of writing, over 20 recipients have continuously received EVR for more than 5 years (maximum 11 years). However, given the format of the paper, we decided to limit the analysis to changes in GFR in the first year after ISxC.

Direct methods of measuring GFR are difficult to apply in everyday clinical practice. Several formulas have been developed to estimate GFR in CKD patients, such as the Cockcroft–Gault formula [9] and formulas derived from the Modification of Diet in Renal Disease (MDRD) study [6, 10]. The Cockcroft–Gault and MDRD formulas have been shown to be applicable in calculating GFR in a large cohort of liver recipients, with the MDRD formula (including only 4 variables) proving more accurate than the Cockcroft–Gault formula [11].

The most common indications for including EVR in a maintenance IST regimen in liver recipients are impaired renal function and prevention of recurrent HCC (or an attempt to improve the course of recurrent HCC after LTx). Accordingly, a proportion of recipients have normal eGFR at the time of ISxC. As part of routine clinical practice, we have noted that eGFR changes in recipients with normal baseline and impaired renal function after ISxC are multidirectional in nature. Therefore, combining these recipients into one group for analysis results in leveling out eGFR changes. Our analysis not only confirmed this hypothesis but also revealed a number of patterns.

To date, the world has accumulated considerable experience in the use of EVR in liver recipients, and a large number of papers have been published, retrospectively evaluating the results of routine clinical practice. To discuss our results, we have chosen several publications with the least, in our opinion, possibility of systematic errors. One such work is the article by Lee et al. (2020), who analyzed a pool of liver recipients (n = 772) enrolled in clinical trials CRAD2304 and CRAD2307 [12]. The authors report the results of their analysis at 24 months after randomization. Our analysis is limited to 12 months. In addition, Lee et al. combine recipients with baseline eGFR >90 and 60–89 mL/min/1.73 m^2 into one subgroup, treating eGFR >60 mL/min/1.73 m^2 as normal. In our study, eGFR changes in these subgroups differed in the first 12 months after ISxC.

We have shown that recipients with normal baseline renal function have decreased eGFR one year after ISxC, as in the general population of liver recipients receiving standard doses of CIs. Lee et al. reported that of 229 recipients with baseline eGFR ≥60 mL/min/1.73 m^2 receiving EVR against reduced TAC exposure, eGFR ≥60 mL/min/1.73 m^2 was maintained in 189 (82.5%) recipients 24 months after randomization. These results correlate well with ours. At 12 months after ISxC, eGFR ≥60 mL/min/1.73 m^2 was preserved in 90% of our recipients with baseline eGFR corresponding to CKD stages 1/2.

According to Lee et al, eGFR fell in both the group of recipients receiving standard TAC doses and in the group of recipients after ISxC. However, in the subgroup of recipients with normal baseline eGFR and mildly impaired eGFR (≥60 mL/min/1.73 m^2) receiving EVR, the decrease in mean eGFR at month 24 after randomization was less pronounced compared with the same subgroup of recipients receiving standard TAC doses (–12.82 and –17.67 mL/min/1.73 m^2, P = 0.009). The reduction in eGFR in our recipients with normal baseline eGFR at month 12 after ISxC was –20.4 mL/min/1.73 m^2 (Table 3). However, when combined with recipients with baseline eGFR in the 60–89 mL/min/1.73 m^2 range, the difference between medians was –8.6 mL/min/1.73 m^2, which was comparable to the results reported by Lee (–12.82 mL/min/1.73 m^2) [12].

In contrast to Lee et al., who identified and analyzed a subgroup of recipients with GFR ≥60 mL/min/1.73 m^2, we analyzed the subgroups of recipients with eGFR >90 mL/min/1.73 m^2 and 60–89 mL/min/1.73 m^2 separately. We found that after ISxC, the pattern of changes in renal function differed in these subgroups of recipients. In the subgroup of recipients with baseline CKD stage 2, eGFR was essentially unchanged at month 12 after ISxC. We observed similar changes in eGFR in a subgroup of 35 recipients with baseline eGFR of 45–59 mL/min/1.73 m^2 (Figs. 3, 4). In 42% of recipients with baseline CKD stage 3A, there was improved renal function one year after ISxC, up to complete normalization in 17% of recipients. Lee et al. also reported an increase in eGFR to levels >60 mL/min/1.73 m^2 in 25 (51%) of 49 recipients analyzed, who received EVR and whose baseline GFR was consistent with CKD-3A, which correlates well with our results.

We observed the most significant improvement in median eGFR in patients with significantly impaired renal function (CKD-3–5). It was found that the lower the eGFR at the time of ISxC, the higher the increase in median eGFR by month 12 of follow-up. In distinguishing this subgroup, we experienced some difficulty in determining the cutoff threshold (60 or 45 mL/min/1.73 m^2) at which the positive eGFR trend becomes clearly evident (compare Table 3 – cutoff threshold 60 mL/min/1.73 m^2; and Fig. 4 – cutoff threshold 45 mL/min/1.73 m^2). In the subgroup of recipients with baseline eGFR of 45–59 mL/min/1.73 m^2, there was a trend toward increased median eGFR; changes reached the level of statistical significance by month 3 after ISxC (52.7 mL/min/1.73 m^2 and 60.0 mL/min/1.73 m^2, respectively, $p < 0.01$), but after 12 months of follow-up, median eGFR decreased slightly again (58.8 mL/min/1.73 m^2, $p > 0.05$).

We found that sex and nature of CIs had no effect on eGFR changes in our recipient population. Lee et al. included significantly more characteristics (organ from living and deceased donor, cause of LTx, race, presence of diabetes mellitus, donor sex and age) in their analysis. However, as in our case, only two factors had a statistically significant effect on eGFR increase: baseline eGFR and recipient age.

Renal failure develops in liver transplant recipients at different times. According to the TRY study, as early as one month after LTx, the eGFR remained within normal values in only 29.3% of recipients with baseline eGFR >90 mL/min/1.73 m^2 [13]. At longer follow-up, the proportion of such recipients continued to fall, being 14.3% at year 1 and only 10.5% of recipients with normal baseline eGFR at year 5 after LTx.

We showed that ISxC early after LTx resulted in a more pronounced improvement in eGFR. Moreover, the differences in eGFR increase between the subgroups of recipients who underwent ISxC in the first 2 months after LTx and 12 months after LTx were particularly pronounced at months 3–6 after ISxC. Bilbao et al. (2015) also reported that in recipients with impaired renal function who started EVR at a later date (one year after LTx), there was no improvement in GFR, or, having improved at months 3–6, GFR deteriorated again by month 12 after ISxC. When ISxC was performed in the first 12 months after LTx, GFR improvement was greater [14]. We, like the group of researchers from Spain, could not find any differences between particularly early ISxC (first 3 months after LTx) compared to ISxC done at a more distant time (within the next 9 months). Interestingly, the Spanish authors also provide maximal eGFR 3–6 months after ISxC [15]. We have not been able to find a possible explanation for this trend in eGFR after ISxC, but it has been reported by other investigators. In registration clinical trial 2304, differences in GFR between groups were detected very quickly, as early as one month after randomization, with complete distinction between groups achieved by month 4 of therapy. The maximum eGFR in the ISxC group falls within the same time period [5].

FINDINGS

1. Changes in eGFR in liver recipients who receive EVR in combination with reduced CI dose depend on baseline eGFR levels and are multidirectional in nature.
2. 60% of recipients with normal baseline eGFR show worsening CKD by the end of the first year after ISxC; the decline in eGFR is particularly pronounced in older recipients.
3. The median eGFR in the subgroup of recipients with baseline CKD stages 2 and 3A does not change significantly by the end of the first year after ISxC. Deterioration of CKD is observed in no more than 10% of recipients, and improvement in 40–62% of cases.
4. The subgroup of recipients with severely reduced eGFR at the time of ISxC showed rapid (within a month) improvement in renal function at month 12; the increase in median eGFR was the more significant the more severely impaired renal function was at baseline.
5. Performing ISxC early after LTx resulted in a more pronounced improvement in eGFR. Maximum eGFR changes were observed at months 3–6 after ISxC.

The authors declare no conflict of interest.

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