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Interleukin-2 receptor antibody induction with early low dose tacrolimus preserves post-liver transplant renal function in at risk individuals



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ABSTRACT

Background: Renal dysfunction post liver transplantation (LT) is common. We report our real-world experience of IL2Ra induction with immediate exposure to reduced dose tacrolimus used for patients with chronic kidney disease (CKD) and evolving acute kidney injury (AKI).

Method: A single-centre retrospective analysis of elective adult LT from 1/1/17 to 31/12/17. The primary outcome measure was increase in CKD stage at month 6 post-LT, and secondary outcome was early biopsy proven acute rejection (BPAR).

Results: 161 patients were included: 17 planned-IL2Ra for CKD; 38 unplanned-IL2Ra for AKI; and 106 standard immunosuppression. IL2Ra group had lower trough tacrolimus levels till month 3 post-LT. Patients receiving IL2Ra did not have an increased risk of increase in CKD class at month 6 (aOR 0.95, 95% CI 0.34–2.75, $P = 0.92$), or of early BPAR (aOR 0.53, 95% CI 0.19–1.32, $P = 0.19$).

Conclusion: IL2Ra induction with immediate exposure to reduced dose tacrolimus can be given to patients with CKD or early evolving AKI post-LT, with no greater attrition of renal function at 6 months or an increased risk of early BPAR when compared to standard IS. Longer-term outcome data is required, however this regimen can be considered for high risk LT recipients with CKD and AKI.

Abbreviations: AKI, acute kidney injury; AST, aspartate aminotransferase; BPAR, biopsy-proven acute rejection; CKD, chronic kidney disease; CNl, calcineurin inhibitor; DCD, donor cardiac death; EAD, early allograft dysfunction; eGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; IL2Ra, interleukin 2 receptor antibodies; INR, international normalized ratio; IS, immunosuppression; ITU, intensive therapy unit; LT, liver transplantation; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil; NAFLD, non-alcoholic fatty liver disease; PNF, primary non-function; RRT, renal replacement therapy; UKELD, United Kingdom model for end-stage liver disease; uPCR, urinary protein creatinine ratio

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Introduction

Advances in immunosuppression (IS) and surgical techniques in liver transplantation (LT) have contributed to significant improvements in graft and patient survival post-LT over time [1]. Longer-term outcomes reflecting morbidity and quality of life are now a major focus of the transplant community. Chronic kidney disease (CKD) is a common complication following LT, and is associated with significant morbidity and mortality [2,3]. The development of post-LT acute kidney injury (AKI) and CKD are often multi-factorial [4], and AKI is associated with progression to CKD with inferior short and long-term patient outcomes [5,6].

As immunosuppressive drugs can be nephrotoxic, various IS regimens have been trialled to reduce the risk of AKI and CKD, mainly through minimising calcineurin inhibitor (CNI) exposure [4,7]. These include induction with interleukin 2 receptor antibodies (IL2Ra) to allow delayed introduction of CNI, usually in combination with mycophenolate mofetil (MMF) [8,9]. It is challenging to interpret these historic studies in the current day as practice has shifted to using target trough levels of tacrolimus of 6–10 mcg/L, from >10 mcg/L reported in these studies, due to renal toxicity associated with higher doses [10]. Furthermore, it is not possible to delineate the respective contributions of adjunctive IS with IL2Ra or MMF, from the lower exposure to tacrolimus prevalent in post-transplant care to improved renal function in these studies. The IS protocol in our centre differs from previously published regimens, with IL2Ra induction used in conjunction with immediate exposure to reduced dose tacrolimus, without routine MMF.

The aim of our study was to report the real-world short- and medium-term outcomes from a high volume single centre using a modified IL2Ra induction regimen for patients with pre-existing CKD and those who develop AKI immediately post-LT.

Patients and methods

This is a single-centre retrospective analysis of adult patients undergoing LT. Sequential patients who underwent LT at our institution from 1/1/17 to 31/12/17 were included. We excluded patients with acute liver failure, multi-organ transplantation, and patients on individualised IS for non-renal reasons. This was performed as an audit in accordance with the ethical standards laid down in the Declaration of Helsinki 2000 and the Declaration of Istanbul 2008.

Clinical data including demographics, aetiology of liver disease (grouped into: alcohol-related; autoimmune liver disease [autoimmune hepatitis, sclerosing cholangitis, primary biliary cholangitis]; cryptogenic; genetic; non-alcoholic fatty liver disease [NAFLD]; polycystic liver disease; vascular disorders; viral hepatitis), prognostic scores (United Kingdom model for end-stage liver disease [UKELD], model for end-stage liver disease [MELD]), assessment for underlying CKD, peri-operative management, surgical techniques, post-LT biochemistry and biopsy results, were collected retrospectively from clinical notes and electronic patient records.

Outcome measures

The primary outcome measures was an increase in CKD stage at 6 months post-LT from time of LT. A secondary outcome was the development of biopsy-proven acute rejection (BPAR).

Definitions

Estimated glomerular filtration rate (eGFR) and creatinine were used as indicators of renal function. Chronic kidney disease was

defined and classified according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [11]. Acute kidney injury (AKI) was defined and classified according to the Risk of renal dysfunction; Injury to the kidney; Failure of kidney function; Loss of kidney function and End-Stage kidney disease (RIFLE) criteria [12]. Routine analysis of urinary protein creatinine ratio (uPCR) is not performed post-LT so CKD stages 0 and 1 were combined. Bloods taken immediately prior to LT were used as baseline for renal function to calculate changes in renal function post-LT. Early allograft dysfunction (EAD) was defined by the presence of one or more of the following: bilirubin ≥ 171 $\mu\text{mol/L}$ on day 7; international normalised ratio (INR) ≥ 1.6 on day 7; and aspartate aminotransferase (AST) >2000 IU/L within the first 7 days [13]. A diagnosis of BPAR was in accordance with Banff classification [14]. BPAR episodes requiring supplemental immunosuppressive therapy were documented, as were episodes of presumed acute rejection treated with supplemental immunosuppressive therapy without a biopsy.

IS protocol

Standard IS. An initial dose of tacrolimus (2 mg twice a day Prograf, or 5 mg once a day Advagraf) was administered 12 to 24 h post-LT and daily thereafter. A target trough tacrolimus level was 5–10 mcg/L. Patients received 16mg intravenous methylprednisolone and were converted to 20 mg oral prednisolone once eating and drinking. Dose reduction of prednisolone was typically commenced on day 14 post-LT.

IL2Ra induction. For patients with IL2Ra induction (Basiliximab) the initial dose of tacrolimus was reduced (1 mg twice a day Prograf, or 2 mg once a day Advagraf) and was administered 12 to 24 h post-LT and daily thereafter. A target trough tacrolimus level was 2–5 mcg/L. Induction therapy with the IL2Ra, was given at 20 mg/day on day 1 and 4 post-LT.

Planned-IL2Ra induction. Patients with existing pre-LT CKD (defined by eGFR and CKD stage at time of assessment as per the KDIGO guidelines [11]) were selected for planned-IL2Ra at the time of listing for LT by a multi-disciplinary assessment team.

Unplanned-IL2Ra induction. Patients who developed AKI within 24 h post-LT (defined by a decrease in eGFR by 50% or a urine output of less than 0.5 ml/kg/h as per RIFLE criteria [12]) were considered for unplanned-IL2Ra induction by attending Transplant Hepatologist and Intensivist.

MMF was added to the IS regimen at the clinician's discretion following an episode of acute rejection or in patients with renal impairment.

Statistical analysis

Comparisons were made between standard IS and IL2Ra induction cohorts; standard IS and planned-IL2Ra cohorts; and standard IS and unplanned-IL2Ra cohorts. Continuous variables were analysed for normality using the D'Agostino and Pearson test. Normally distributed data were analysed using unpaired t tests with results reported as mean (standard deviation [SD]). Non-normally distributed data were analysed using Mann-Whitney U tests with results reported as median (interquartile range [IQR]). Categorical variables were analysed by Fisher's exact tests with results reported as number (percentage). Multiple logistic regression was performed to ascertain if IL2Ra, planned-IL2Ra and unplanned-IL2Ra affected our primary or secondary outcomes. We used complete case analysis, excluding individuals with missing data. Variables with a P value of <0.2 or of

particular interest were included in each model and backwards elimination was performed. An r^2 threshold with other variables within the model was set at <0.5 to reduce co-linearity. Results were recorded as odds ratios (OR) with 95% confidence intervals (95% CI) and P values. The Hosmer-Lemeshow test was used for goodness of fit. Correction for multiple comparisons was performed using the Benjamini-Hochberg procedure with a false discovery rate set at 0.10. Statistics were performed using Prism V8.4.2 (GraphPad).

Results

Characteristics

A total of 161 patients were included in the analysis. The majority of the patients were male (62.7%), median age at transplant was 55.8 years (interquartile range [IQR], 49.2–61.7). The most common aetiologies of liver disease were autoimmune liver disease (53, 33.1% [30 sclerosing cholangitis, 15 primary biliary cholangitis, 8 autoimmune hepatitis]), alcohol related liver disease (39, 24.2%), NAFLD (27, 16.8%) and chronic viral hepatitis (22, 13.7%). 32 (19.9%) were transplanted for hepatocellular carcinoma (HCC). 20 patients (12%) were re-do liver transplants. 44 (27.3%) had a pre-LT diagnosis of diabetes. At assessment for transplant 13 (8.1%) had CKD stage 3a, 8 (5%) patients had CKD stage 3b, 3 (1.9%) patients CKD stage 4.

The majority of the organs were from donor after brain death (70.8%), the remainder were donor cardiac death (DCD). BPAR was identified in 37 (23.0%) of all patients. MMF was added to the immunosuppression regimen at discharge in 35 (21.7%) of patients.

Survival

There was 1 case of primary non-function (0.6%). There were 3 deaths (1.9%) during follow up. There was no association between IS regimen and death ($P = 0.33$).

Immunosuppression regimen

Univariate analysis of clinical, demographic and laboratory values of patients who received IL2Ra (planned or unplanned) compared with patients receiving standard IS is shown in Table 1. Patients who received IL2Ra had significantly more renal dysfunction at assessment (creatinine 81 $\mu\text{mol/L}$ [69–118] v 64 $\mu\text{mol/L}$ [55–75], $P < 0.001^*$) and immediately prior to transplant (creatinine 94 $\mu\text{mol/L}$ [72–118] v 67 $\mu\text{mol/L}$ [54–80], $P < 0.001^*$). This was associated with the IL2Ra group having significantly higher prognostic scores for mortality from chronic liver disease as defined by UKELD (56 [52–59] v 53 [49–56], $P = 0.004^*$) and MELD (16 [11–19] v 11 [8–16], $P < 0.001^*$). Patients who received IL2Ra were significantly more likely to have a diagnosis of NAFLD and ascites pre-LT.

We further interrogated the 17 patients who received planned-IL2Ra for underlying CKD and compared them to the standard IS group. Whilst there was no significant difference in UKELD scores (53 [50–60] v 53 [49–56], $P = 0.45$), the planned-IL2Ra cohort had significant higher MELD scores (16 [13–21] v 11 [8–16], $P = 0.008^*$). Creatinine levels at assessment (128 $\mu\text{mol/L}$ [110–139] v 64 $\mu\text{mol/L}$ [55–75], $P < 0.001^*$) and at time of transplant (112 $\mu\text{mol/L}$ [87–155] v 67 $\mu\text{mol/L}$ [54–80], $P < 0.001^*$) were significantly higher in the planned-IL2Ra cohort. There was no difference in age, sex, aetiology of liver disease, prevalence of diabetes or pre-LT ascites compared to the standard IS group. Patients undergoing re-do LT were more likely to be in the planned-IL2Ra group (35.3% v 12.3%, $P = 0.03^*$).

Of those scheduled to have standard IS, 38 patients (26.4%) switched to unplanned-IL2Ra induction due to AKI. On univariate analysis of this unplanned-IL2Ra cohort to those who received standard IS, again the unplanned-IL2Ra cohort had significantly higher prognostic scores for mortality from chronic liver disease with higher UKELD (57 [52–59] v 53 [49–56], $P = 0.002^*$) and MELD scores (16 [11–19] v 11 [8–16], $P = 0.006^*$). The unplanned-IL2Ra cohort also had significantly higher creatinine levels at assessment (76 $\mu\text{mol/L}$ [65–88] v 64 [55–75], $P < 0.001^*$) and at time of transplant (78 $\mu\text{mol/L}$ [66–107] v 67 $\mu\text{mol/L}$ [54–80], $P < 0.001^*$). There was no difference in age, sex or prevalence of diabetes. Patients in the unplanned-IL2Ra cohort were significantly more likely to have NAFLD ($P < 0.001^*$), significantly less likely to have autoimmune liver disease ($P = 0.001^*$), and significantly more likely to have pre-LT ascites ($P = 0.008^*$) and diuretic use ($P = 0.004^*$).

Fig. 1 shows post-LT trough tacrolimus levels in patients who received IL2Ra induction compared to those who received standard IS. With the exception of day 2,3, those who received IL2Ra induction had significantly lower trough tacrolimus levels till month 6: day 2,3 (2.6 ng/ml [1.6–4.0] v 1.8 ng/ml [1.1–3.9], $P = 0.25$); day 5 (3.3 ng/ml [2.6–5.6] v 2.0 ng/ml [0.9–3.0], $P < 0.001^*$); day 7 (4.9 ng/ml [3.6–7.5] v 2.3 ng/ml [1.5–3.4], $P < 0.001^*$); day 10 (5.8 ng/ml [4.3–7.6] v 3.4 ng/ml [2.6–4.9], $P < 0.001$); day 14 (5.6 ng/ml [3.8–7.7] v 4.4 ng/ml [3.5–6.0], $P = 0.02^*$); month 1 (6.8 ng/ml [5.0–8.6] v 4.9 ng/ml [3.8–7.3], $P < 0.001^*$); and month 3 (7.4 ng/ml [5.5–9.3] v 6.0 ng/ml [4.9–7.6], $P = 0.007^*$). There was no difference in tacrolimus trough levels at month 6 (6.1 ng/ml [4.6–8.1] v 5.9 ng/ml [3.8–8.3], $P = 0.29$).

MMF was added to the IS regimen in 21.7% of all patients, with no difference in its use between the IS groups.

Acute kidney injury and renal replacement therapy

Of the total cohort 36 patients (22.4%) required renal replacement therapy (RRT) immediately post-LT. Those that required RRT had a higher pre-LT UKELD ($P = 0.01^*$) and MELD scores ($P = 0.02^*$), higher creatinine levels at assessment (81 $\mu\text{mol/L}$ [65–113] v 66 $\mu\text{mol/L}$ [56–76], $P < 0.001^*$) and at time of LT (97 $\mu\text{mol/L}$ [72–125] v 69 $\mu\text{mol/L}$ [56–84], $P < 0.001^*$) than the non-RRT group. Patients requiring RRT had a higher peak AST ($P = 0.003^*$) and were more likely to have received a DCD donor graft ($P < 0.001^*$). There was a significant difference in RRT requirement between the IS regimens (Table 2), with patients receiving IL2Ra, both for CKD and AKI, more likely to need RRT (4.7% standard IS, 47.1% planned-IL2Ra, 57.9% unplanned-IL2Ra, $P < 0.001$). No patients who required RRT immediately post-LT required long-term RRT.

Early biopsy-proven acute rejection

37 patients (23%) had evidence of early BPAR, and 32 (20%) received pulsed methylprednisolone as treatment for early BPAR. BPAR by IS regimen is outlined in Table 2. On univariate analysis shown in Supplementary Table 1, patients with underlying autoimmune liver disease were more likely to develop BPAR ($P < 0.001^*$), and patients with pre-LT diabetes less likely to develop early BPAR ($P = 0.003^*$). Patient age was not associated with BPAR. IL2Ra regimens were associated with lower rates of early BPAR than standard IS on univariate analysis (12.7% v 28.3%, $P = 0.03^*$).

A multiple logistic regression model was utilised to determine if the IL2Ra regimens utilised in this study were independently associated with early BPAR (Table 3). We adjusted for age, autoimmune liver disease and pre-LT diabetes, and identified no significant effect of IL2Ra on the likelihood of early BPAR in all patients receiving IL2Ra, and in the subgroups of planned- and unplanned-IL2Ra.

Table 1

Baseline and transplant characteristics of IL2Ra (planned and unplanned) and standard IS cohorts. Continuous variables expressed as median (IQR), categorical variables are represented as number (percentage). * indicates statistical significance following correction for false discovery.

Variable	n	IL2Ra	n	Standard IS	P value
Age (years)	55	56.2 (49.8–62.0)	106	55.6 (40.6–61.7)	0.39
Male sex	55	33 (60%)	106	68 (64.2%)	0.61
Aetiology of liver disease					
Alcohol	55	15 (27.3%)	106	24 (22.6%)	0.56
NAFLD	55	18 (32.7%)	106	9 (8.5%)	<.001*
Viral hepatitis	55	4 (7.3%)	106	18 (17%)	0.10
Autoimmune liver disease	55	11 (20%)	106	42 (39.6%)	0.01*
HCC	55	8 (14.6%)	106	24 (22.6%)	0.30
Re-do LT	55	7 (12.7%)	106	13 (12.3%)	>0.99
UKELD	55	56 (52–59)	106	53 (49–56)	0.004*
MELD	55	16 (11–19)	106	11 (8–16)	<0.001*
Pre-LT diabetes	55	21 (38.2%)	106	23 (21.7%)	0.04
Pre-LT ascites	55	40 (72.7%)	106	51 (48.1%)	0.004*
Pre-LT diuretic use	55	33 (60%)	106	46 (43.4%)	0.05
Creatinine at assessment (umol/L)	55	81 (69–118)	106	64 (55–75)	<0.001*
Creatinine at LT (umol/L)	55	94 (72–118)	106	67 (54–80)	<0.001*
RRT pre-LT	55	1 (1.8%)	106	3 (2.8%)	>0.99
ITU pre-LT	55	1 (1.8%)	106	3 (2.8%)	>0.99
DCD organ	55	21 (38.2%)	106	26 (24.5%)	0.10
Caval replacement	55	14 (25.5%)	106	26 (24.5%)	>0.99
Estimated blood loss (ml)	40	4800 (3000–7900)	78	4000 (2650–6000)	0.10

Abbreviations: IL2Ra, interleukin 2 receptor antibodies; IS, immunosuppression; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; LT, liver transplant; UKELD, UK score for patients with end-stage liver disease; MELD, model for end-stage liver disease; uPCR, urinary protein creatinine ratio; RRT, renal replacement therapy; ITU, intensive therapy unit; DCD, donor cardiac death.

Early allograft function

There were 43 cases (26.7%) of EAD in the cohort (8 [5%] bilirubin ≥ 171 umol/L day 7; 2 [1.2%] INR ≥ 1.6 day 7; 36 [22.5%] AST >2000 IU/L within the first 7 days). There was 1 case

of primary non-function. The median peak AST within 7 days of transplant was 1076 IU/L (561–1844). There was no difference in peak AST between those who received standard IS and IL2Ra ($P = 0.15$), and no difference in rate of EAD between IS groups (22.6% v 34.6%, $P = 0.13$).

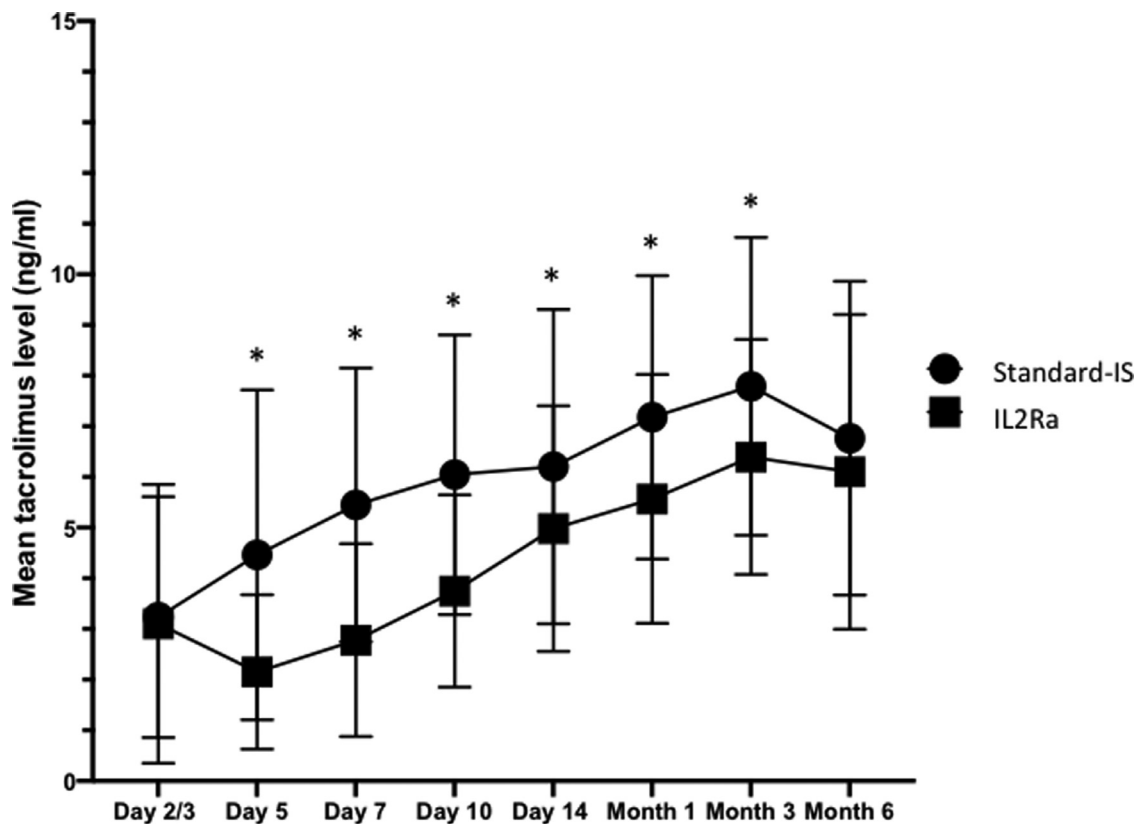


Fig. 1. Trough tacrolimus levels post-LT. Comparison between patients receiving standard IS (circle) and IL2Ra (square). * indicates statistical significance. Abbreviations: LT, liver transplant; IS, immunosuppression; IL2Ra, interleukin 2 receptor antibodies.

Table 2

Post-transplant characteristics of standard IS cohorts, planned-IL2Ra and unplanned-IL2Ra. Continuous variables expressed as median (IQR), categorical variables are represented as number (percentage). * indicates statistical significance for planned-IL2Ra v standard IS, ** indicates statistical significance for unplanned-IL2Ra v standard IS, both following correction for false discovery.

Variable	n	Standard IS	n	Planned-IL2Ra	P value	n	Unplanned-IL2Ra	P value
Peak AST (IU/L)	106	1063 (588–1525)	17	913 (422–2643)	0.97	38	1225 (592–3729)	0.07
EAD	106	24 (22.6%)	17	6 (35.3%)	0.36	38	13 (34.2%)	0.20
PNF	106	1 (0.9%)	17	0 (0%)	>0.99	38	0 (0%)	>0.99
Post-LT RRT	106	5 (4.7%)	17	8 (47.1%)	<0.001*	38	22 (57.9%)	<0.001**
MMF post-LT	106	22 (20.8%)	17	7 (41.2%)	0.12	38	6 (15.8%)	0.64
BPAR	106	30 (28.3%)	17	2 (11.8%)	0.23	38	5 (13.2%)	0.08
Increase in CKD class at month 3	100	60 (60.0%)	15	5 (33.3%)	0.09	33	19 (57.6%)	0.84
Change in creatinine from LT to month 3 (umol/L)	100	+25.0 (+9.8 to +39.8)	15	-2.0 (-27.0 to -17.0)	0.003*	33	+18.0 (-5.5 to +42.0)	0.30
Increase in CKD class at month 6	95	61 (64.2%)	13	6 (46.2%)	0.23	28	20 (71.4%)	0.65
Change in creatinine from LT to month 6 (umol/L)	95	+27.0 (+13.0 to +41.0)	13	+16.0 (-13.0 to +29.0)	0.36	28	+27.0 (+7.0 to +47.8)	0.99

Abbreviations: IL2Ra, interleukin 2 receptor antibodies; IS, immunosuppression; LT, liver transplant; RRT, renal replacement therapy; AST, aspartate aminotransferase; EAD, early allograft dysfunction; PNF, primary non-function; MMF, mycophenolate mofetil; BPAR, biopsy-proven acute rejection; CKD, chronic kidney disease.

Post transplant renal function

The post-LT serum creatinine levels for each cohort are shown in Fig. 2 which demonstrates that patients receiving IL2Ra induction had significantly higher creatinine levels at all points of study follow up compared to the standard IS group.

Post-LT renal function by IS regimen is outlined in Table 2. At month 3 post-LT 87/148 patients (58.8%) had an increase of at least one CKD stage from immediately pre-LT, and 26/148 (17.6%) had CKD stage 3b or 4. The standard IS group had a significantly greater increase in creatinine in this time period compared to the planned-IL2Ra cohort. At month 6 post-LT 90/136 patients (66.2%) had an increase of at least one CKD stage from immediately pre-LT, and 26/136 (19.1%) had CKD stage 3b or 4. No significant association was demonstrated for the development of increasing at least one CKD stage from pre-LT (Supplementary Table 5).

Multiple logistic regression models were utilised to determine if IL2Ra was independently associated with preservation of CKD class at month 6 post-LT (Table 4, Supplementary Tables 6–8). When adjusted for age, MMF post-LT and pre-LT diabetes, IL2Ra, planned- and unplanned-IL2Ra, were not associated with an increase in CKD class at month 6 post-LT.

Discussion

Induction therapy with IL2Ra has been described in LT to allow the delayed introduction of CNI, and patient associated outcomes are excellent [15]. The protocols reported involve the use of IL2Ra (daclizumab or basiliximab) in combination MMF immediately post-LT, with the introduction of CNI after 5 days [8,9]. Daclizumab has been withdrawn from the market for commercial reasons, and basiliximab is the IL2Ra now used in solid organ transplantation. In this study of real-world data, we outline an alternative regimen utilising basiliximab in combination with lower dose CNI (tacrolimus) immediately post-LT without the need for additional MMF. Our protocol has been successfully employed in patients with CKD and planned minimisation of early tacrolimus (planned-IL2Ra), and in patients with early

evolving AKI (unplanned-IL2Ra). Both these subgroups would be expected to have increased risk of developing post-LT renal impairment and higher rates of RRT immediately post-LT that are associated with deleterious effects on long-term renal function [6]. Despite this, there was no additional attrition of renal function in the medium-term compared to the standard IS group, and importantly there was no difference in BPAR or early allograft loss.

Renal function early post-LT, specifically AKI, is a major determinant of long-term outcome in terms of the development of CKD and mortality [5,6]. In addition, the development of CKD post-LT is associated with morbidity and mortality [2]. CNI is associated with renal dysfunction post-LT and various strategies have been employed to attempt to minimise this effect and exposure to CNI [4,7]. The relevance from these trials to current clinical practice is limited, as patients with CKD [8] and those who developed AKI post-LT [9] were excluded from participation in trials. These groups undoubtedly represent the highest risk who need to be targeted, and the role of IS modification is less well recognised. The findings from our study have potential implications for patient management, as our data includes 17 patients with CKD and planned-IL2Ra, and 38 patients with significant AKI post-LT and unplanned-IL2Ra. In addition, our data indicate that additional non-CKD based risk factors may be needed to be considered when instituting immunosuppression post-LT.

CNI nephrotoxicity and early exposure to higher levels of tacrolimus are important factors in renal outcomes [4]. The early clinical studies involving IL2Ra induction employed a target trough tacrolimus level above 10 mcg/L early post-transplant [8,9], which would be deemed a supranormal dose in most current practice in LT. From a recent systematic review and meta-analysis we know that lower target tacrolimus level of 6–10 mcg/L has no influence on rejection and is associated with improved long-term renal outcomes compared to higher levels [10]. A major limitation of the early data using IL2Ra induction is that the control group does not reflect current standard of care, making it difficult to assess the relevance of these findings to current clinical practice. In our study the standard IS group had trough tacrolimus levels of 5–8 mcg/L early post-LT, whilst the IL2Ra induction had a level of 3–6 mcg/L. The aim of our protocol is to utilise IL2Ra induction to enable lower tacrolimus exposure early post-LT compared to the standard IS group, which we have demonstrated. We found no significant difference in trough levels of tacrolimus at month 6 post-LT, demonstrating that IL2Ra induction can be used as a ‘bridge’ in the early post-LT phase.

The development of CKD is common post-LT [2] and an increase in CKD stage by month 3 was seen in the majority of our transplant recipients, and was maintained to month 6 post-LT. A previous randomised controlled clinical trial demonstrated better preservation of eGFR at 1 year in patients who received IL2Ra induction and delayed tacrolimus compared to standard

Table 3

Adjusted odds ratios for the risk of developing BPAR in each of the IL2Ra groups.

Variable	aOR (95% CI)	P value
IL2Ra	0.53 (0.19–1.32)	0.19
Planned-IL2Ra	0.36 (0.05–1.47)	0.20
Unplanned-IL2Ra	0.65 (0.20–1.89)	0.45

Abbreviations: BPAR, biopsy-proven acute rejection; IL2Ra, interleukin 2 receptor antibodies.

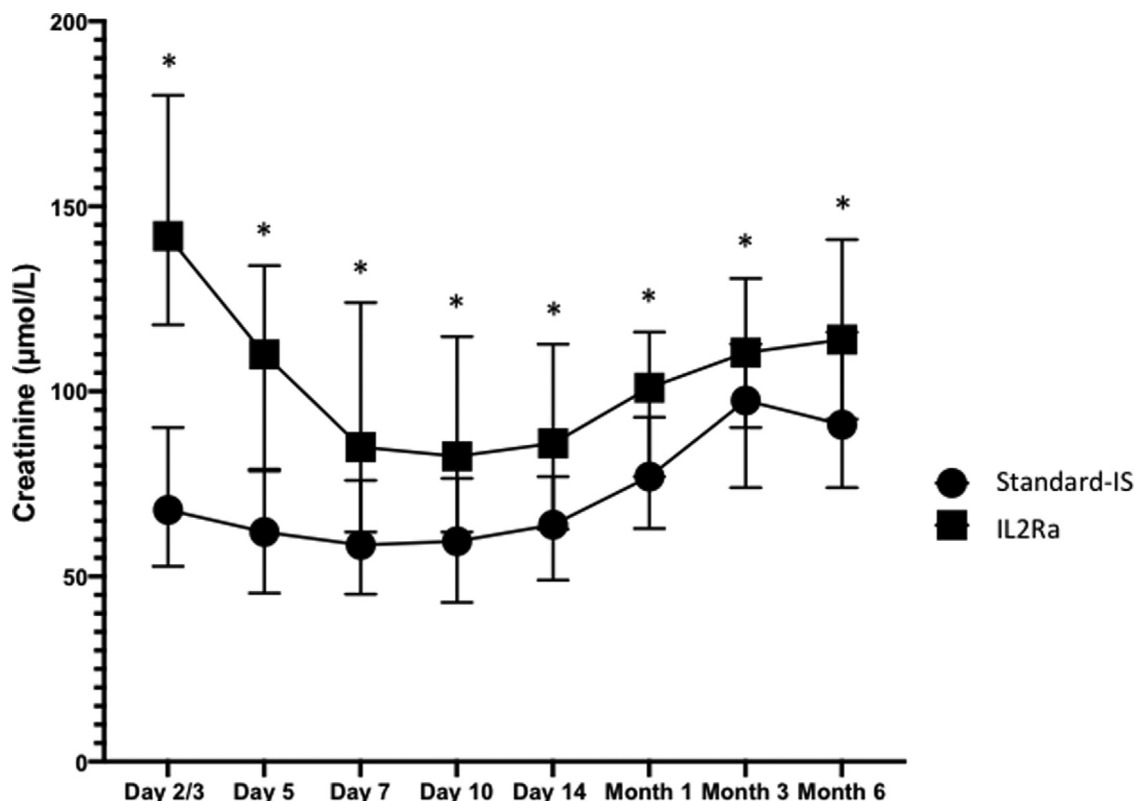


Fig. 2. Serum creatinine levels post-LT. Comparisons between patients receiving standard IS (circle) and IL2Ra (square). * indicates statistical significance. Abbreviations: LT, liver transplant; IS, immunosuppression; IL2Ra, interleukin 2 receptor antibodies.

tacrolimus [8], which is supported by systematic review and meta-analysis data [15]. Despite being an at risk cohort, we observed a smaller increase in creatinine in our IL2Ra cohort at 3 months compared to the standard IS group and a comparable increase in creatinine and CKD stage between the IS regimens at 6 months. This was despite the higher levels of existing CKD and severe AKI in the patients receiving IL2Ra induction which would be expected to be associated with a greater risk of developing progressive renal impairment [5,6]. Our data suggests that using IL2Ra-induction with immediate exposure to lower dose of tacrolimus in high-risk groups, is not associated with significantly more progressive CKD when compared to a lower-risk group receiving standard IS.

The historical trials utilising IL2Ra induction involved the addition of MMF immediately post transplant. Our protocol does not incorporate MMF routinely, only in individual cases for immunological reasons or if lower dose of tacrolimus is required, and from our data MMF use was similar across IS groups. A concern with using lower dose tacrolimus without the addition of MMF would be the increased rates of BPAR, however no increased rate of BPAR was seen in our IL2Ra regimen.

The AKI which develops post-LT is multifactorial and difficult to predict.⁴ Risk factors associated with AKI include recipient characteristics such as undiagnosed renal disease, graft related factors, hepatic ischaemic reperfusion injury (IRI) and IS [6,16–19]. It is notable in

this cohort that patients with presumably greater IRI developed more impaired renal function post-LT. Patients with multiple risk factors for AKI, including existing CKD and significant IRI, require close monitoring of renal function post-LT. It is probable that they represent a group who may benefit from an early switch from planned standard IS to unplanned-IL2Ra with lower dose CNI [18]. Furthermore, our data indicate that other risk factors including NAFLD, pre-LT ascites and use of DCD grafts may need to be considered in any individualised approach to early post-LT immunosuppression, aimed at preventing long-term renal dysfunction.

There are a number of limitations inherent to our study. This is a single centre retrospective analysis which was not powered to identify certain differences between the subgroups. Patients were not randomised to IS protocols and decisions were at the discretion of the attending clinicians, which has a potential for selection bias. However our main aim was describe a real-world experience and demonstrate if this regimen can be utilised safely in the short and medium-term. Although long-term follow up data on renal function are not available, it is accepted that renal function within the first year post-LT can predict long-term outcomes of CKD [16]. It would be reasonable to predict that the renal function observed at 6 months in our cohort would be sustained.

Conclusions

In conclusion, we have demonstrated that a clinically tractable regimen of IL2Ra induction with basiliximab in conjunction with immediate exposure to reduced dose tacrolimus can be used both in patients with CKD and those with evolving AKI post-LT. We demonstrate that this IS regimen is safe and effective in the early post-LT setting and minimises renal attrition in at risk groups. Although longer-term data on these patients are needed, as is validation in an independent cohort, this is an appropriate regimen to consider for more widespread use, particularly in patients with CKD and at high risk of AKI.

Table 4
Adjusted odds ratios for increase in CKD class at 6 months post-LT in each IL2Ra group.

Variable	aOR (95% CI)	P value
IL2Ra	0.95 (0.34-2.75)	0.92
Planned-IL2Ra	0.70 (0.14-3.39)	0.65
Unplanned-IL2Ra	1.22 (0.32-5.25)	0.77

Abbreviations: CKD, chronic kidney disease; LT, liver transplant; IL2Ra, interleukin 2 receptor antibodies.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.liver.2021.100028](https://doi.org/10.1016/j.liver.2021.100028).

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