The promise of tolerance in living-donor kidney transplant (LDKT): A retrospective, real-world assessment of the safety and efficacy of LDKT with FCR001 investigational cell therapy compared with standard of care (SOC)

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BACKGROUND

- Long-term outcomes after kidney transplants have been limited by adverse impacts of current immunosuppressive drugs, including the risk of kidney toxicity, dyslipidemia, hypertension, diabetes, infection, and malignancy.[1,2] There is a 65.5% 10-year graft survival rate among living-donor kidney transplant (LDKT) recipients[3]
- Donor-specific transplant tolerance established by facilitated allogeneic hematopoietic stem cell transplant has the potential to establish durable chimerism, eliminating the need for long-term immunosuppression (IS) in human leukocyte antigen (HLA)-mismatched LDKT recipients[4]
  - FCR001 is an investigational, cryopreserved allogeneic cell therapy designed to induce tolerance by establishing chimerism in LDKT recipients
  - FCR001, derived from mobilized peripheral blood mononuclear cells from the same donor as the allograft, contains hematopoietic progenitor cells, facilitating cells, and αβ T cells
  - An uncontrolled Phase 2 study showed FCR001 induced tolerance in 70% of FCR001 recipients (FCR-R)[5]

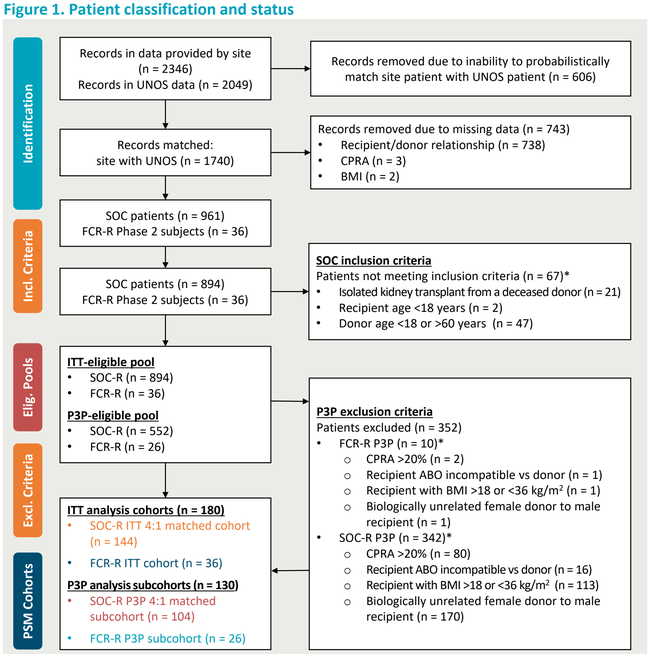
OBJECTIVE

- The objective of this single-center, retrospective, observational study was to compare the effect on LDKT outcomes of FCR001-treated patients from the Phase 2 study vs propensity score matched contemporaneous patients treated with standard of care (SOC) IS

METHODS

- Electronic medical record (EMR) data from FCR-R participants in the Phase 2 study[5,6] were compared with EMR data from a cohort of 4:1 propensity score-matched LDKT recipients who received SOC IS consisting of tacrolimus, mycophenolate, and antibody induction with or without long-term corticosteroids (**Figure 1, Table 1**)
  - The FCR-R intent to treat (ITT) population encompassed 36 of 37 FCR-R, including patients who failed to achieve durable chimerism; the excluded patient was treated at a different study site
  - The SOC recipients (SOC-R) ITT cohort (n = 144, age ≥18 years, HLA 0–6 mismatch, panel reactive antibody ≤20%, body mass index 18–36 kg/m^2), identified from EMR data, received their transplant at the same institution where the Phase 2 trial was conducted and were managed according to an SOC post-transplant IS regimen that included tacrolimus, mycophenolate, and antibody induction with or without long-term corticosteroids
  - A predefined subset analysis (per Phase 3 protocol [P3P] population, n = 26 FCR-R, n = 104 SOC-R) involved patients eligible for the FREEDOM-1 Phase 3 trial (NCT03995901)
- The primary endpoint was a composite of death, graft failure, or biopsy-proven rejection within 5 years after transplant
- Predefined secondary endpoints included kidney function (defined as estimated glomerular filtration rate [eGFR] by Modification of Diet in Renal Disease 4 [MDRD4]) and the incidence of adverse events including infection, malignancy, hospitalization, and cardiovascular complications identified using electronic medical record data and international classification of diseases (ICD)-9/10 and systemized nomenclature of medicine (SNOMED) codes
- Study limitations are the retrospective nature of the analysis

Figure 1. Patient classification and status



*Individual categories may not be added up to total as participants could fail to meet more than one inclusion criterion.
BMI, body mass index; CPRA, Calculated panel reactive antibody; Elig., eligibility; Excl., exclusion; FCR-R, FCR001 recipients; Incl., inclusion; ITT, intent to treat; site, Northwestern; P3P, per Phase III protocol; PSM, propensity score matched; SOC, standard of care; SOC-R, standard of care recipients; UNOS, United Network for Organ Sharing Procurement and Translation Network.

Table 1. Post-PSM baseline demographic and clinical characteristics

ITT population	FCR-R, n = 36[1] n (%)	SOC-R, n = 144[1] n (%)	Standardized mean difference
Age at kidney transplant, years			
18–20	1 (2.8)	5 (3.5)	0.0
21–25	3 (8.3)	9 (6.2)	0.1
26–30	3 (8.3)	18 (12.5)	-0.1
31–35	3 (8.3)	15 (10.4)	-0.1
36–40	5 (13.9)	17 (11.8)	0.1
41–45	7 (19.4)	12 (8.3)	0.3
46–50	5 (13.9)	14 (9.7)	0.1
51–55	5 (13.9)	19 (13.2)	0.0
56–60	1 (2.8)	13 (9.0)	-0.4
61–65	3 (8.3)	18 (12.5)	-0.1
66–70	0	3 (2.1)	NA
71–75	0	0	NA
75–80	0	1 (0.7)	NA
Gender, male	30 (83.3)	108 (75.0)	0.2
Race			
White	27 (75.0)	105 (72.9)	0.0
Nonwhite[2]	9 (25.0)	39 (27.1)	0.0
BMI at baseline, kg/m^2			
≥18 to <25 (normal)	19 (52.8)	59 (41.0)	0.2
25 to <30 (overweight)	10 (27.8)	52 (36.1)	-0.2
≥30 (obese)	7 (19.4)	33 (22.9)	-0.1
Primary cause of ESRD[3]			
Diabetes	3 (8.3)	12 (8.3)	0.0
Hypertensive nephrosclerosis	3 (8.3)	13 (9.0)	0.0
Other diagnoses[4]	28 (77.8)	113 (78.5)	0.0
Related donor/recipient	20 (55.6)	81 (56.2)	0.0
ABO compatible	35 (97.2)	143 (99.3)	-0.1
HLA mismatches			
0–3	14 (38.9)	60 (41.7)	-0.1
4–6	19 (52.8)	75 (52.1)	0.0
Missing	3 (8.3)	9 (6.2)	0.1

NA is presented for the standardized difference for categories where cell counts were 0 and therefore not calculable.
[1]Denominator for percentages is the column total unless otherwise specified; [2]Propensity score matching used two categories for race (white vs nonwhite); [3]Percentages may not add to 100%, because participants can have multiple causes of ESRD/comorbidities; [4]Glomerular diseases, tubular and interstitial diseases, congenital/familial/metabolic diseases, renovascular/vascular diseases, neoplasms.
BMI, body mass index; ESRD, end-stage renal disease; FCR-R, FCR001 recipient; HLA, human leukocyte antigen; ITT, intent to treat; NA, not applicable; PSM, propensity score matched; SOC-R, standard of care recipient.

RESULTS

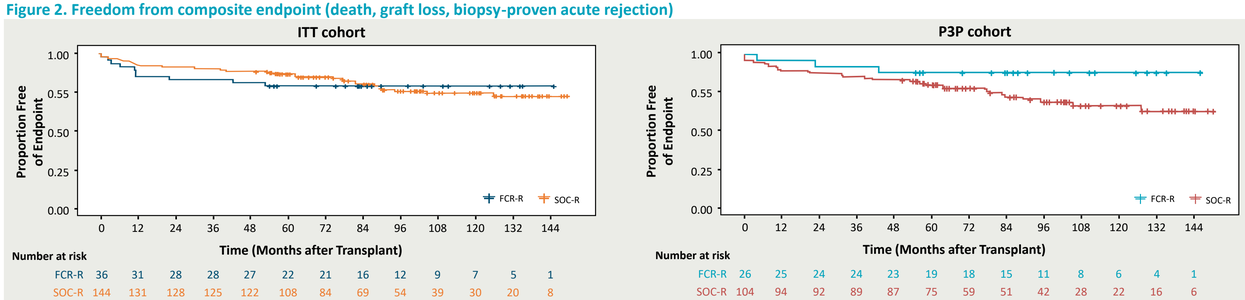
ITT

- **Primary outcome:** There was no significant difference (P = 0.9) in the incidence of the composite endpoint between FCR-R and SOC-R patients who remained on SOC IS (**Figure 2, left**)
- **Kidney function:** At 60 months, eGFR was significantly higher in the FCR-R ITT arm vs the SOC-R arm (P = 0.02; **Figure 3, left)**
- **Adverse events:** Fewer FCR-R patients experienced new-onset type 2 diabetes mellitus (T2DM) or dyslipidemia compared to SOC-R patients (**Figure 4, left**)

P3P

- **Primary outcome:** There was no significant difference (P = 0.09) in composite endpoint for FCR-R compared to SOC-R at 24 months. 88.5% of SOC-R and 92.3% of FCR-R were free from biopsy proven acute rejection (BPAR), death, or graft loss **(Figure 2, right)**. No FCR-R had BPAR after IS withdrawal
- **Kidney function:** Although kidney function increased over time in the FCR-R P3P group, there was no significant difference in eGFR vs the SOC-R P3P group ($P \geq 0.14$) at any timepoint analyzed **(Figure 3, right)**
- **Adverse events:** More than 20% of the SOC-R P3P patients had new onset T2DM or dyslipidemia, but there were no new onset events of either condition in the FCR-treated P3P patients **(Figure 4, right)**

Figure 2. Freedom from composite endpoint (death, graft loss, biopsy-proven acute rejection)

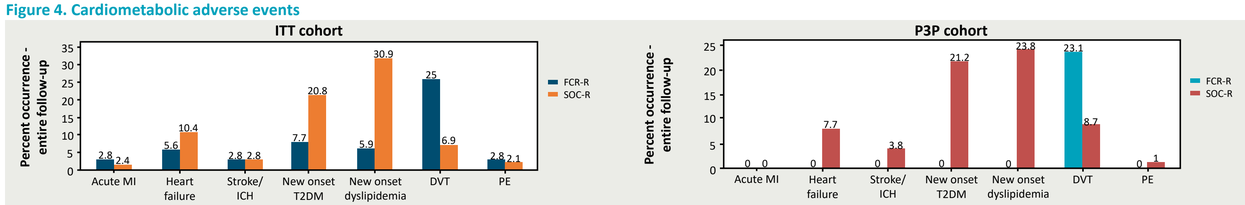


Kaplan-Meier survival analysis was performed with log-rank tests to identify statistically significant differences in each outcome between FCR-R and SOC-R.
FCR-R, FCR001 recipients; ITT, intent to treat; P3P, per Phase III protocol; SOC-R, standard of care recipients.

Figure 3. Kidney function

Kidney function was analyzed between FCR-R and SOC-R for both the ITT and P3P cohorts.
eGFR, estimated glomerular filtration rate; FCR-R, FCR001 recipients; ITT, intent to treat; P3P, per Phase III protocol; SOC-R, standard of care recipients.

Figure 4. Cardiometabolic adverse events



DVT, deep vein thrombosis; FCR-R, FCR001 recipients; ICH, intracerebral hemorrhage; ITT, intent to treat; MI, myocardial ischemia; P3P, per Phase III protocol; PE, pulmonary embolism; SOC-R, standard of care recipients; T2DM, type 2 diabetes mellitus.

CONCLUSIONS

- Tolerance induction with FCR001 allowed successful cessation of IS in the majority of patients without increasing the risk of death, graft loss, or BPAR
  - FCR001 treatment led to improvement/preservation in eGFR over time, whereas SOC was associated with a progressive decline in kidney function
- Key IS-related complications appeared to be less frequent in FCR-R compared to SOC-R who remained on IS

References

1) Farouk S, Rein JL. *Adv Chronic Kidney Dis.* 2020;27(1):56–66; 2) Hariharan S, et al. *N Engl J Med.* 2021. 385(8):729–743; 3) USRDS 2021 annual report. https://adr.usrds.org/2021/end-stage-renal-disease/7-transplantation; 4) Leventhal JR, Ildstad ST. *Hum Immunol.* 2018. 79(5):272–276; 5) Leventhal J, et al. *American Transplant Congress.* 2021. 21(suppl 3): Abstract 685; 6) Leventhal JR, et al. *Transplantation.* 2015. 99(2):288–298.

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