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Review

Allogeneic Hematopoietic Cell Therapies to Induce Tolerance in Kidney Transplantation

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Abstract

This review summarizes the latest results from the interventional clinical trials for inducing clinical tolerance in the recipients of human leukocyte antigen (HLA)-matched or mismatched living donor kidney transplants via allogeneic hematopoietic stem cell (HSC)-based therapies. The protocols utilized by the three medical centers in the United States differ in degree of HLA-matching, relatedness or unrelatedness, donor cell composition of the hematopoietic stem cells transplant (HSCT), timing for infusion and conditioning regimens. Tolerant recipients from the clinical trials benefited from better long-term outcome, improved quality of life and reduction in lifetime healthcare expenses compared with standard-of-care recipients on conventional immunosuppression. Durable chimerism induced by concomitant HSCT is indispensable to achieve immunologic tolerance to kidney transplantation and to protect against recurrence of the original renal disease in HLA-mismatched related and unrelated kidney transplant recipients.

Keywords

Tolerance; hematopoietic stem cells; facilitating cells; chimerism; kidney transplantation

1. Introduction

Kidney transplantation is a life-saving procedure. Results are significantly superior to dialysis [1]. However, there is still room for improvement due to the complications and accelerated mortality caused by the immunosuppressive agents required to prevent rejection [2]. Three medical centers in the United States have performed combined hematopoietic stem cell and living donor kidney transplantation to achieve tolerance to renal allografts. Here, we update the progress from the interventional clinical tolerance studies of living donor kidney transplantation conducted by the three centers.

2. Massachusetts General Hospital (MGH) Protocol

In 1998, the group at Massachusetts General Hospital (MGH) initiated a clinical trial of living related HLA-matched combined kidney/nonmyeloablative bone marrow transplantation (CKBMT) to achieve remission of myeloma and to induce tolerance for renal allografts [3]. The initial preparative regimen (NCT00854139) for the first 10 patients with end-stage renal disease (ESRD) secondary to multiple myeloma (MM) consisted of pre-transplant high-dose cyclophosphamide (60 mg/kg on days -5 and -4), peri-transplant equine anti-thymocyte globulin (ATG) (15-20 mg/kg on days -1, +1, +3 and +5) and pre-transplant thymic irradiation (TI) (700 cGy on day -1). On day 0, the recipients underwent kidney transplantation, followed by infusion of un-manipulated donor bone marrow cells (>2 $x10^8$/kg) obtained from HLA-matched siblings. Cyclosporine A (CyA) was given at a dose of 5 mg/kg *i.v.* on day -1 and subsequently postoperatively orally at 3 to 12 mg/kg per day. CyA was tapered rapidly in patients without graft versus host disease (GVHD) and discontinued. Following CyA withdrawal, donor leukocyte infusions (DLI) (1 $x10^7$/kg $CD3^+$ T cells) were performed to enhance graft-versus-myeloma effect in the patients without GVHD and the patients who develop progressive MM. All 10 recipients achieved mixed chimerism. Five of 10 recipients are alive. Despite loss of chimerism three months post-transplantation, two recipients were in sustained complete remission of myeloma from 8 to 20 years post-transplant and three recipients remained off immunosuppression (IS) with normal or near-normal renal function [3]. Two recipients who were off IS returned to immunosuppressive therapy because of chronic GVHD. Two recipients developed acute GVHD and five developed chronic GVHD (three were after the first transplant and two were after the second stem cell transplant from the original donor for progressive MM).

Two additional ESRD patients with hematologic disorders (one with MM and one with systemic amyloidosis and myelodysplastic syndrome) received HLA-matched CKBMT after the conditioning was revised to a total body irradiation (TBI)-based regimen (NCT02158052), in which the pre-transplant high-dose cyclophosphamide was replaced by two doses of 200 cGy TBI on day -1 and the post-transplant CyA was replaced by tacrolimus [4, 5]. These two recipients achieved durable full donor chimerism (one after re-transplant due to hematopoietic graft rejection) and were currently off IS (Table 1).

Table 1 Comparison of tolerance induction protocols in US

Center	**MGH**			**Stanford**		**Northwestern**	
HLA Matching	Matched related	Mismatched/haplo-identical related	Mismatched/haplo-identical related	Mismatched/haplo-identical related	Matched related	Mismatched related and unrelated	Matched related
Underlying disease	Hematological malignancies/disorder	Hematological disorder	Nonmalignant	Nonmalignant	Nonmalignant	Nonmalignant	Nonmalignant
HSCT	Whole bone marrow cells			Selected $CD34^+$ cells with add-back $CD3^+$ T cells		FCRx	$CD34^+$ cells
No. patients transplant	12	5	13	28	29	37*	19
ClinicalTrials.gov Identifier	NCT00854139 NCT02158052	NCT02158042	NCT02314403	NCT03292445 NCT01165762	NCT00319657	NCT00497926	NCT00619528
Lead follow-up (year)	19	5	14	7	12	9	8.5
Chimerism	Transient mixed / Full	Full	Transient mixed	Immunosuppression-dependent chimerism	Durable mixed	Transient mixed / Full	Transient mixed
No. patients taken off IS	7	2	8	8	24	27	5
No. patients continuously off IS (% of transplant)	5 (42%)	2 (40%)	5 (38%)	0 (0%)	21 (72%)	27 (73%)	4 (21%)
No. patients to resume IS	2	0	3	8	1	0	0
No. with GVHD	7	0	0	0	0	2	0
No. with AKI	0	0	9	2	0	0	0
Kidney graft loss	0	0	3	0	2	2	0
No. of Death	5	1	0	0	3	1	1

* one was performed at Duke University

This protocol has recently been extended to haplo-identical CKBMT for patients with chronic kidney disease and blood disorders using post-transplant cyclophosphamide for conditioning and GVHD-prophylaxis [5]. In this ongoing pilot clinical trial (NCT01758042), the conditioning regimen initially consisted of pre-transplant low-dose cyclophosphamide (14.5 mg/kg on days -6 and -5), rabbit ATG (1.5 mg/kg on days -4 to -2), and 200 cGy of TBI at day -1. Post-transplant high-dose cyclophosphamide (50 mg/kg on days +3 and +4) was administered followed by tacrolimus and mycophenolate mofetil (MMF) starting on day +5. After the first patient, the conditioning regimen was revised for the next two patients to substitute ATG for five doses of fludarabine (24 mg/m^2 at day -6 to -2), followed by hemodialysis. After the third patient, the fludarabine dose was reduced from five to three doses (24 mg/m^2 at day -4 to -2) due to a death related to fludarabine neurotoxicity. Five haplo-identical CKBMT have performed and two of the subjects are off IS [5] (Table 1).

The MGH group has reported the results of HLA-mismatched living related haplo-identical CKBMT in 13 recipients with ESRD not associated with hematologic malignancies [4, 6-10]. The conditioning regimen has been under continuous revision and evolution. The initial conditioning for the first 3 recipients consisted of pre-transplant high-dose cyclophosphamide (60 mg/kg on days -5 and -4), local TI (700 cGy) and CyA (5mg/kg) i.v. on day -1, peri-transplant humanized anti-CD2 mAb (MEDI507, 0.1 to 0.6 mg/kg/dose) on days -2, -1, 0 and +1. On day 0, kidney transplantation was performed, followed by infusion of un-manipulated donor iliac crest bone marrow cells (2-3 ×10^8/kg). Oral CyA (8-12 mg/kg/day) was administered postoperatively and then tapered slowly after 6 months and completely discontinued by 9-14 months. After the third recipient developed donor specific antibodies and lost his renal allograft, the conditioning was modified for the fourth and fifth recipients with the addition of pre-transplant rituximab (375 mg/m2/dose) on days -7 and -2, and prednisone (2 mg/kg/dose), starting on day 0 and tapering to withdrawal on day +10. The regimen was further revised for the sixth to tenth recipients by adding post-transplant rituximab on days +5 and +12, plus a prolonged course of prednisone until day 20, and substituting CyA for tacrolimus. Tacrolimus was slowly tapered and completely discontinued at 8-9 months. To eliminate transient acute kidney injury (AKI) observed in all but the first of these initial 10 recipients, the regimen was further revised for the eleventh and twelfth recipients by replacing the pre-transplant high-dose cyclophosphamide with low dose TBI (150 cGy x 2) on days -6 and -5 [7]. In the thirteenth recipient, the conditioning was further modified (NCT02314403), in which peri-transplant humanized anti-CD2 mAb was substituted for Belatacept (10 mg/kg on days 0, +3, +10, +17, +24, +38, +52), ATG (on days -2, -1, 0), and prednisone (2 mg/kg/dose) was administrated for a shorter course (starting on day +4 and tapering to withdrawal on day +20). AKI did not occur in the last three recipients. Transient mixed chimerism (up to 3 weeks) was induced in all except one (the twelfth subject) of 13 recipients. In 12 recipients with transient mixed chimerism, IS was successfully discontinued in 8 recipients for more than 3 years. Five subjects remained off IS with normal kidney function with follow-up time of more than 14.5 years. IS was resumed in three recipients after 5, 7 and 8 years because of either recurrence of the original renal disease (membranoproliferative glomerulonephritis type I), or development of chronic rejection [9]. Before complete tapering off IS, one of 12 recipients with transient mixed chimerism had recurrence of the original renal disease (IgA nephropathy) [7], and three recipients had graft loss due to acute rejection or calcineurin inhibitor induced thrombotic microangiopathy (Table 1).

3. Stanford Protocol

Since 2000, the group at Stanford University School of Medicine has performed 29 HLA-matched and 28 HLA-mismatched/haploidentical (6 cases in the first cohort between 2000 and 2003) combined hematopoietic stem cells and kidney transplants in living-related donors. The HSCT infusion consisted of $CD34^+$-selected mobilized cells with a defined add-back dose of $CD3^+$ T cells [11-14]. The post-transplant conditioning regimen was comprised of total lymphoid irradiation (TLI) (80-120 cGy/day, 10 daily doses starting on day +1) and ATG (1.5 mg/kg/day, 5 daily doses starting on day 0). Following the last dose of TLI, $CD34^+$ enriched (HLA-matched: 4.3 to 17.5 $x10^6$/kg; HLA-mismatched/haploidentical: 3.1 to 11.1 $x10^6$/kg for the first cohort, 8 to 22 $x10^6$/kg for the current cohort) granulocyte-colony stimulating factor (G-CSF) mobilized peripheral blood mononuclear cell (PBMC) were infused with a fixed number (matched:1-10x 10^6/kg; mismatched/haplo-identical: <0.1 x 10^6 for the first cohort, 3 to 100 $x10^6$/kg for the current cohort) of $CD3^+$ T cells. For HLA-matched donor-recipient pairs, the maintenance immunosuppression was prednisone (10 days from day 0), MMF (1 month from day +11) and CyA (6-12 months from day 0). For HLA-mismatched/haploidentical living related donor-recipient pairs, maintenance IS included prednisone (30 days from day 0), tacrolimus (12-15 months from day 0) and MMF (9-12 months from day 0).

Mixed chimerism was induced in 28 of 29 HLA-matched related recipients. Among these 28 recipients, twenty-four recipients who demonstrated stable chimerism for at least 6-9 months were withdrawn from IS without evidence of GVHD or rejection with up to 12 years follow-up [15]. One of 14 recipients who lost chimerism in the 2nd year developed mild rejection at 3 years off IS. There were two graft losses due to recurrence of the original renal disease. There were two deaths associated with pulmonary embolism and coronary artery disease in two recipients with normal kidney graft function, and one death because of stroke after graft loss due to a flare from systemic lupus (Table 1).

Of six HLA-mismatched/haploidentical related recipients in the first cohort, only 2 recipients achieved transient mixed chimerism and met the criteria for IS withdrawal. However, these two recipients developed Banff I rejection 3.5 and 5.5 months after tapering off IS and therefore IS was instituted. Of twenty-two HLA-mismatched/haploidentical recipients in the current cohort with an escalating dose of infused $CD34^+$ and $CD3^+$ T cells to promote establishment of stable mixed chimerism, nine of 18 patients who had persistent chimerism for at least 12 months were withdrawn from MMF at 9 to 12 months and were maintained on tacrolimus monotherapy. Unfortunately, six of these nine recipients lost chimerism and mild rejection episodes occurred in three recipients. All 6 recipients resumed tacrolimus therapy with or without MMF. The other 3 chimeric recipients were continued on tacrolimus monotherapy. To date, none of the mismatched subjects have been successfully completely withdrawn from IS drugs [12] (Table 1). The investigators refer to this as “immunosuppression dependent chimerism”. It is apparent from the Stanford studies that transient chimerism does not prevent recurrence of underlying autoimmune renal disease, which is an exclusion criteria for the phase 3 clinical trials.

4. Northwestern Protocol

In 2009, Northwestern University implemented a Phase II trial (FDA, investigational device exemption # 13947, ClinicalTrials.gov identifier # NCT00497926) to induce tolerance and establish

robust donor macrochimerism in HLA-mismatched and related or unrelated recipients of combined hematopoietic stem cell and living donor kidney transplantation. The approach utilized a mobilized allogenic cell therapy based on $CD8^{+}TCR^{-}$ facilitating cell (FC)-based HSCT (termed FCRx) [16-20]. The human FC population is composed of two equally divided phenotypic subpopulations: $CD56^{bright}$ and $CD56^{dim/negative}$ FC. The $CD56^{dim/negative}$ FC subpopulation enhanced early engraftment of HSC, whereas $CD56^{bright}$ FC prime HSC migration and enhance HSC clonogenicity, which significantly contribute to long-term chimerism [21]. The nonmyeloablative conditioning regimen consisted of fludarabine (30 mg/m^2 on days -5, -4 and -3), cyclophosphamide (50 mg/kg day -3 and +3) and 200 cGy TBI (day -1), followed by the living donor kidney transplant on day 0. A PBMC product mobilized by G-CSF with or without Plerixafor was apheresed from the donor at least 2 weeks before the kidney transplant. The product was processed to remove GVHD-producing cells but retain $CD34^{+}$ cells, hematopoietic progenitor cells and tolerogenic FC. The final cell product of FCRx was cryopreserved until the infusion at the bedside. After release criteria for the product were satisfied, it was administered to the recipient on day +1. Patients are discharged on post-operation day +2 and managed as outpatients. Tacrolimus and MMF immunosuppression were continued at therapeutic levels until 6 months after transplant. If renal function and protocol biopsy were normal, and stable chimerism was established, IS was weaned beginning at month 6 and completely discontinued at 1 year.

As September of 2018, 37 subjects have been transplanted (one was performed at Duke University). Subjects have ranged from 18 to 65 years of age. 20 subjects are related (HLA Matching: 6/6 two patients, 5/6 three patients, 4/6 four patients, 3/6 five patients, 2/6 four patients, 1/6 two patients) and 17 subjects unrelated to their donors (HLA Matching: 0/6 three patients, 1/6 ten patients, 2/6 four patients). Two of 37 recipients failed to establish donor chimerism. Both subjects had panel reactive antibody (PRA) levels >20%, indicating sensitization. Transient mixed chimerism developed in 8 recipients and high levels of donor chimerism developed in 27 recipients, with the majority showing full (>95%) donor whole blood/T cell chimerism. The failure to establish chimerism and transient mixed chimerism were associated with suboptimal cell dosing, intercurrent infection and high PRA titers. All twenty-seven recipients with durable chimerism were successfully withdrawn from IS (time off IS from 11 - 99 months) [20]. They retained chimerism after removal of IS and remained rejection-free after the IS withdrawal. They also maintained immunocompetence during post transplant [19]. Two of 8 recipients with transient chimerism had graft loss related to infection and 6 were maintained on low dose of IS monotherapy with stable renal function. The ability to establish durable chimerism was not influenced by degree of HLA mismatch or relatedness. No durable chimeric subjects have had to resume immunosuppression after it was discontinued and none has lost chimerism.

There have been two cases of GVHD. Both occurred in HLA mismatched unrelated transplants from multiparous female donors and had high donor chimerism levels (87% and 93%, respectively) at the first month after the transplantation. The first subject with mild acute skin/GI GVHD occurred during conversion from CNI inhibitors to sirolimus and was promptly diagnosed and was treated with corticosteroids. This patient developed grade 1-2 ocular/musculoskeletal chronic GVHD. He has been weaned from IS for 37 months and is clinically stable. The second had treatment-resistant GI GVHD with associated severe tissue-invasive cytomegalovirus colitis. He presented late following development of symptoms and expired at 11 months post-transplant

from sepsis. A second death was unrelated to the study protocol and occurred in a heavy smoker who developed advanced stage lung cancer 4.5 years post-transplant and >3 years off IS (Table 1).

The protocol has been modified to improve safety and enhance efficacy. Subjects are required to promptly seek treatment for any symptoms at a specialized transplant center rather than a local community hospital. Exclusion criteria were added to avoid sensitized subjects with a pre-transplantation PRA >20% and exclude female to male donor/recipient living unrelated pairs from enrollment in an effort to minimize the risk of developing GVHD [18].

A second regulatory-cell-based study at Northwestern University investigated the safety and efficacy of tolerance induction by infusion of donor $CD34^+$-selected HSC in HLA-matched living related kidney transplantation (NCT00619528) [22, 23]. IS consisted of two doses of alemtuzumab (0.3 mg/kg, on days 0 and +4) with maintenance tacrolimus and MMF twice daily. At 3 months, tacrolimus was replaced by sirolimus. MMF was discontinued between 12 and 18 months and sirolimus was withdrawn between 18 and 24 months if protocol renal biopsy was normal. The first HSC infusion was given on day +5 and consisted of $CD34^+$ cells (0.3-1.0 x 10^6cells/kg) purified from donor iliac crest marrow cells. The second, third, and fourth HSC infusions were given at months +3, +6, and +9 and consisted of $CD34^+$ cells (>0.7 x 10^6cells/kg) purified from G-CSF mobilized PBMC. As September of 2018, twenty subjects have been enrolled and 5 subjects have been removed from the study due to recurrence of original renal disease, noncompliance, or development of a positive B cell cross-match. Five of the remaining 15 subjects have been off IS and had normal renal biopsy at 5 years post transplantation [24]. There was one death unrelated to the study protocol in the five tolerant subjects (Table 1).

5. Conclusions

In conclusion, four allogeneic cell-based approaches aimed to reduce or eliminate IS in kidney transplant recipients have demonstrated the safety and feasibility of such an approach. This is motivated by the fact that quality of life and life expectancy are reduced in standard of care kidney transplant recipients compared to the tolerant kidney transplant recipients [20, 25-27]. It is likely that tolerant kidney transplant recipients could envision “one transplant for life” instead of potentially multiple kidney transplants as occurs for standard of care. The most robust and broadly applicable tolerance approach is one that achieves durable chimerism in up to unrelated and unmatched donor/recipient pairs. The difference in donor cell composition of HSCT, timing for infusion and conditioning regimens might contribute to the differential efficacies of the protocols utilized by the three medical centers.

Abbreviations List

AKI, acute kidney injury; ATG, anti-thymocyte globulin; CKBMT, combined kidney/nonmyeloablative bone marrow transplantation; CyA, Cyclosporine A; DLI, donor leukocyte infusions; DSA, donor-specific antibody; ESRD, end-stage renal disease; FC, facilitating cell; FCRx, CD8+TCR− facilitating cell (FC)-based HSCT approach; GVHD, graft versus host disease; G-CSF, granulocyte-colony stimulating factor; HLA, human leukocyte antigen; HSC, hematopoietic stem cell; HSCT, hematopoietic stem cells transplantation; IS, immunosuppression; MGH, Massachusetts General Hospital; MM, multiple myeloma; MMF, mycophenolate mofetil; PBMC,

peripheral blood mononuclear cell; PRA, panel reactive antibody; TBI, total body irradiation; TI, thymic irradiation; TLI, total lymphoid irradiation

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Author Contributions

YW and STI wrote and revised the manuscript. AYC and JRL provided advice and comments on writing and reviewing the manuscript. All authors read and approved the manuscript.

Competing Interests

Joseph R. Leventhal, MD, PhD, Ownership interest, TRACT Therapeutics Inc. Suzanne T. Ildstad, MD, is the Chief Scientific Officer and Founding Scientist of Regenerex, LLC, a biotechnology company that was formed to develop and commercialize a bone marrow product to treat numerous diseases.

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