Biomarkers of Inflammation and eGFR in an Ongoing Phase 1B Study of an Anti-CD40L Antibody Tegoprubart, For The Prevention of Rejection In Kidney Transplant

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Background

More than 40,000 people receive a kidney transplant annually in the United States. Twenty-five years ago the calcineurin inhibitor (CNI) tacrolimus in conjunction with standard polypharmacy regimens was shown to reduce cellular and antibody mediated rejection making kidney transplantation a realistic option for patients with end stage renal disease (ESRD). Although tacrolimus has had a dramatic impact on 1 year survival rates for kidney transplant (1 year graft survival > 90%), long-term survival rates (> 3 years) have not changed, and treatment is associated with serious side effects like nephrotoxicity, diabetes, and CNS symptoms. Alternative immunosuppression drug is highly desirable to eliminate these negative effects, improve graft function, and maintain low rate of rejection.

CD40L is a costimulatory type II transmembrane receptor for CD40. Binding of CD40L on T helper cells to CD40 on antigen-presenting cells induces multiple downstream immune and inflammatory responses. These include B and T cell clonal expansion; antibody production, class-switching, and maturation; and pro-inflammatory cytokine and chemokine production. Tegoprubart (AT-1501) is a humanized IgG1, kappa monoclonal antibody that blocks CD40L (CD154, gp39) binding to CD40.

Pre-clinical studies over the last 30 years have shown that costimulatory inhibition is an effective strategy for the prevention of transplant rejection in nonhuman primates. Inhibition of CD40L is proved to be more effective at preventing transplant rejection than tacrolimus and other costimulatory signaling pathways.

Tegoprubart has been shown effective in the prevention of cellular and antibody mediated rejection in nonhuman primates and is currently being studied in kidney transplant recipients to determine the possibility of replacing tacrolimus as the core component of immunosuppressive therapy for kidney transplantation.

Methods

This is a phase 1B safety study of tegoprubart in the prevention of transplant rejection for adults undergoing a de novo kidney transplant procedure (from deceased or living donor) at five transplant centers in Canada, Australia, and the United Kingdom.

Inclusion/Exclusion

To be eligible, this must be their first transplant, they must be seropositive for EBV, free of donor specific antigens, have low panel reactive antibodies, and the organ cannot be from an extended criteria donor or have a prolonged cold ischemia time.

Treatment Schedule (Figure 1)

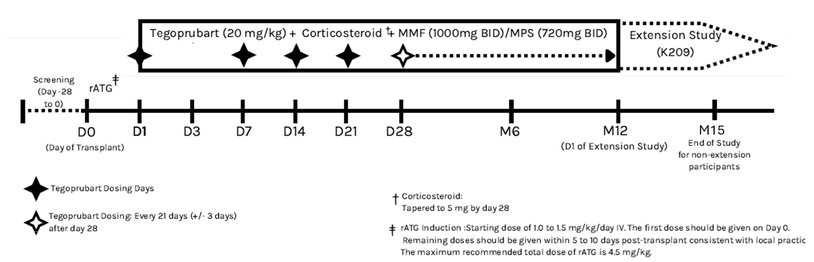
Participants one through eleven received 6 mg of rabbit anti-thymocyte globulin (rATG) and participants twelve and thirteen received 4.5 mg of ATG starting on day of transplant through the first 10 days after transplant. Participants receive corticosteroids starting on day of transplant tapering to a 5 mg dose by day 28 post transplant. Participants receive 1000 or 720 mg BID mycophenolate mofetil or mycophenolate sodium respectively starting on day of transplant. Participants receive 20 mg/kg of tegoprubart via IV infusion weekly until day 28 followed by infusions every 21 days.

Participants will remain on study for a year, after which time they will have the option of continuing tegoprubart in an extension study. The primary endpoint is safety. Other endpoints include characterizing the pharmacokinetic profile of tegoprubart, the incidence of biopsy proven rejection (BPAR), changes in estimated glomerular filtration rate (eGFR) and exploratory biomarkers including donor derived cell free DNA.

A retrospective protein biomarker study was conducted on a subset of plasma and urine samples using a custom Somascan immune panel containing aptamers targeting 100 proteins associated with pro-inflammatory activity based on Gene Ontology terms from the Gene Ontology Database (https://geneontology.org/).

Results

Figure 1: Trial Schematic



Demographics & Disposition

Age/ Gender	Ethnicity	Donor	Underlying Disease	Donor Age	HLA Mismatch	Status
60/F	White	Living	Polycystic Kidney Disease	40	5	Discontinued study on day 217 due to patient decision
77/F	White	Deceased	Diabetes	42	5	Enrolled in K209 (long term extension)
62/M	White	Living	Cystic Disease	55	4	Discontinued study on day 54 due to Polyomavirus viremia
68/M	White	Living	Diabetes	57	4	Enrolled in K209 (long term extension)
23/F	Asian	Living	Glomerulonephritis	49	2	Enrolled in K209 (long term extension)
44/M	White	Deceased	Polycystic Kidney Disease	42	4	Discontinued study on day 176 due to rejection
65/M	White	Living	Diabetes	64	2	
57/F	White	Living	Diabetes	45	6	
35/M	Other	Living	Glomerulonephritis	59	5	
56/F	White	Living	Cystic Disease	54	4	
59/M	White	Living	Diabetes	63	6	
38/M	Asian	Deceased	FSGS	32	5	
68/M	Other	Deceased	Diabetes	38	5	

* Enrollment cut off for Demographics and Disposition is April 3rd 2024.

Treatment Emergent Adverse Events*

System Organ	Preferred Term	N (%)
Gastrointestinal	Diarrhea	5 (38%)
	Constipation	5 (38%)
	Nausea	4 (31%)
	Vomiting	3 (23%)
Infections	Polyomavirus (BK) viremia	5 (38%)
	Cytomegalovirus viremia	2 (15%)
	Upper respiratory tract infection	2 (15%)
	Urinary tract infection	2 (15%)
Procedural Complication	Transplant surgery complications	3 (23%)
	Procedural pain	3 (23%)
Blood and Lymphatic System	Leukopenia	4 (31%)
	Neutropenia	4 (31%)
Cardiac	Tachycardia	4 (31%)
General	Peripheral edema	2 (15%)
	Pyrexia	2 (15%)
Metabolism	Hypophosphatemia	3 (23%)
	Hypoglycemia	2 (15%)
Musculoskeletal and Connective Tissue	Pain	4 (31%)
Skin and Subcutaneous tissue	Alopecia	2 (15%)
Vascular	Hypertension	2 (15%)
	Hypotension	3 (23%)

* Occurring in 2 or more study subjects as of April 3rd 2024. Of all the reported TEAEs, 8 events experienced by 3 subjects are reported as serious. These SAEs include neutropenia, acute kidney injury, T-cell rejection, Polyomavirus viremia, anterior abdominal wall collection, URI rhinovirus and hyperkalemia

Figure 2: Mean eGFR

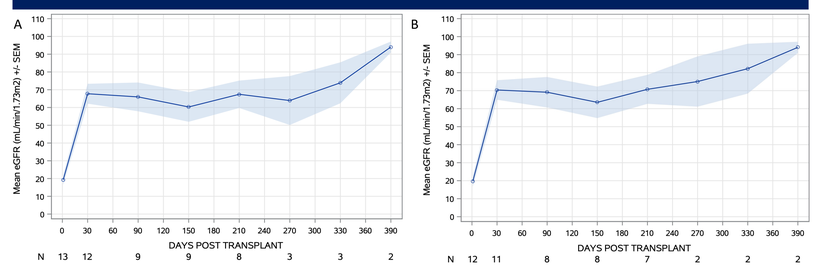


Figure 2: Estimated glomerular filtration rate (eGFR) as of March 20, 2024, calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) creatinine equation. N is the number of participants at that time contributing data to mean eGFR calculation. (A) eGFR of all 13 participants. (B) eGFR of 12 participants. Excludes 1 participant who experienced acute tubular necrosis on day 0 prior to the first infusion of tegoprubart.

Figure 3: Protein Biomarkers of Cellular Mediated Rejection

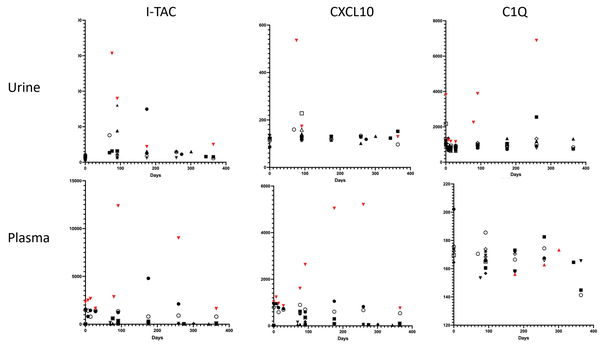


Figure 3: Levels of pro-inflammatory biomarkers (I-TAC, CXCL-10, C1Q) in urine and plasma that increased in a participant at time of cellular mediated rejection. Patient 6 experienced a cellular mediated rejection on day 78 with a decline in eGFR and histology suggesting a Banff1B rejection per central pathology reading. Plasma and urine samples for all participants were analyzed on a custom Somascan pro-inflammatory panel. Several pro-inflammatory proteins showed increased expression around the time of rejection.

Conclusions

- Preliminary data suggest that tegoprubart is safe and well tolerated in patients undergoing de novo kidney transplantation.
- Aggregate mean eGFR is greater than or equal to 60 mL/min/1.73m^2 starting thirty days post transplant.
- 1 patient experienced a T cell mediated rejection (Banff score 1b) on day 78 based on local pathology. Several pro-inflammatory biomarkers showed increased expression in plasma or urine around the time of rejection.
- 1 patient experienced acute tubular necrosis on day 0 (prior to administration of study drug) which impacted their kidney function. This patient continues to be in the study.
- There have been 5 cases of Polyomavirus viremia and 2 cases of cytomegaloviremia. Viral titers have been well managed with transient reductions in immunosuppressive medications or anti-virals as per standard of care.
- There have been no cases of hyperglycemia, new onset diabetes, or tremor.
- These preliminary data suggest that tegoprubart may provide an alternative to CNIs in the prevention of kidney transplant rejection. Furthers studies are required.