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Versatility of Therapeutic Uses of Costimulation Blockade in Kidney Transplantation

Supported by an educational grant from Bristol Myers Squibb

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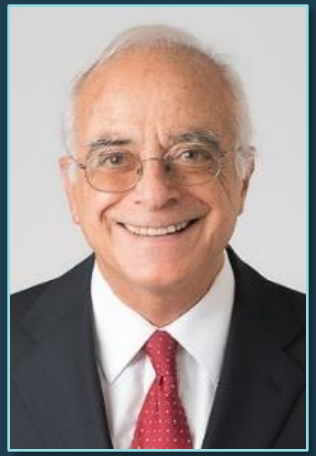

Flavio G. Vincenti, MD

Transplant Nephrologist
UCSF Medical Center
Professor of Clinical Medicine
University of California San Francisco
San Francisco, CA

Disclosures

Faculty

Flavio G. Vincenti, MD reports the following financial relationships:

- *Advisory Board*—Alexion Pharmaceuticals, Inc. and eGenesis
- *Consultant*—Bristol Myers Squibb Company; Eledon Pharmaceuticals, Inc.; Mallinckrodt Pharmaceuticals; Merck & Co., Inc.; and Veloxis Pharmaceuticals, Inc.
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Planner

Annie Doyle, RN, BSN, CCTN reports the following financial relationships:

- Ms. Doyle reports no financial relationships to disclose

Christian P. Larson, MD, Dphil reports the following financial relationships:

- *Advisory Board*—Bristol Myers Squibb Company

Payaswini Vasanth, MBBS, MD reports the following financial relationships:

- Ms. Doyle reports no financial relationships to disclose

Disclosures were obtained from the peer reviewer and CME Outfitters staff—no disclosures to report

- Jeffrey Helfand, DO (peer reviewer)
- Albert Eubanks, Jr., RN (planning committee)
- John Jones, PharmD (planning committee)
- Evan Luberger (planning committee)
- Scott J. Hershman, MD, FACEHP, CHCP
- Sandra Caballero, PharmD (planning committee)
- Sharon Tordoff (planning committee)

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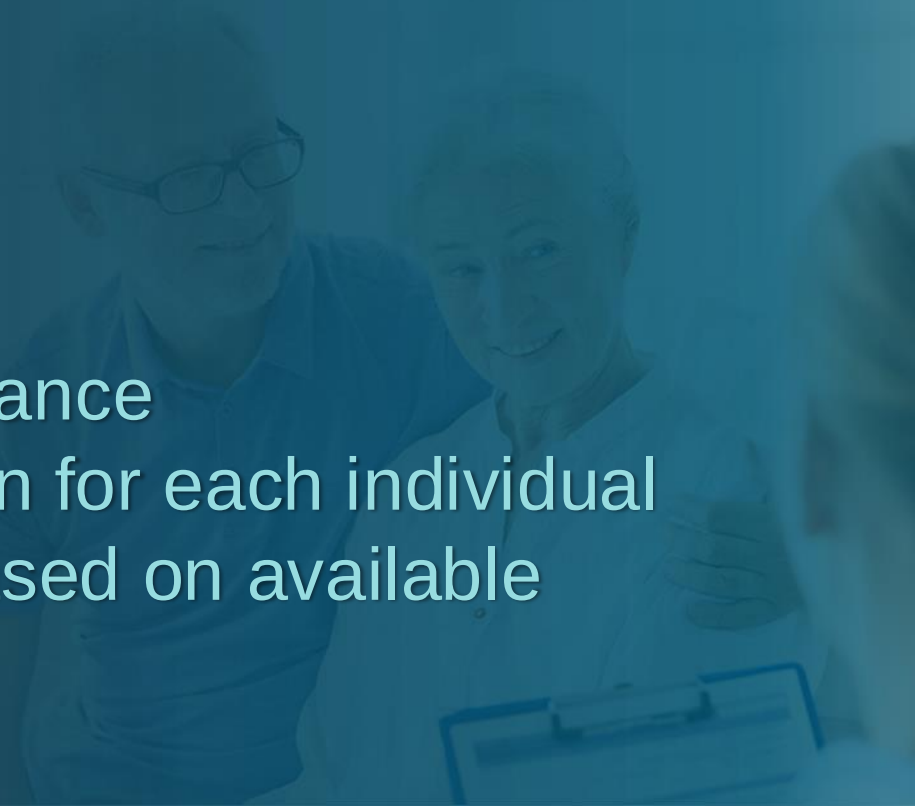
LEARNING OBJECTIVE 1

Identify the optimal maintenance immunosuppressive regimen for each individual renal transplant recipient based on available safety and efficacy data.



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LEARNING OBJECTIVE 2

Develop individualized management plans for patients who fail initial immunosuppressive therapy to sustain long-term graft survival.

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LEARNING OBJECTIVE 3

Counsel patients with renal transplant on long-term immunosuppressive therapy, emphasizing the balance between short- and long-term goals.

Struggles with the "Troubled Kidney" Patient

Determining the optimal treatment of recipients with late graft dysfunction ("the troubled transplant") has been limited for a number of reasons

- Allograft injury subclinical can begin at any time following kidney transplantation and can be insidious
- There are likely many causes: immunologic, nephrotoxic, vascular, and glomerular disease
- There are only a limited number of cases in any given year at a single institution
- Biopsy is usually done late in the clinical course, after the active causative phase of damage has occurred and mostly fibrosis is observable. Protocol biopsies are not done routinely at all centers and even well immunosuppressed patients demonstrate subclinical rejection.

The DeKAF study confirmed a few findings

- Inflammation in area of atrophy is associated with increasingly worse post biopsy death-censored graft survival
- C4d−/DSA− recipients had significantly better (and C4d+/DSA+ worse) death-censored graft survival than other groups. C4d+/DSA− and C4d−/DSA+ had similar intermediate death-censored graft survival.

Matas AJ, et al. *Am J Transplant*. 2019;19(5):1432-1443. Gourishankar S, et al. *Am J Transplant*. 2010;10(2):324-330.

Summary of Costimulation Blockade in Kidney Transplant

1. CNI-based regiments have served as the backbone of transplant immunosuppression for most renal transplant recipients over the past 40 years
- Currently tacrolimus, mycophenolic acid +/- steroids are considered standard of care

2. Although CNI therapy has secured exceptional short-term outcomes with transplantation, progress in improving long-term renal allograft survival has stagnated for many years, spurring other immunosuppressive strategies

3. The nephrotoxicity and well-defined adverse metabolic effects of CNIs have also driven a desire to explore alternative immunosuppressive agents.

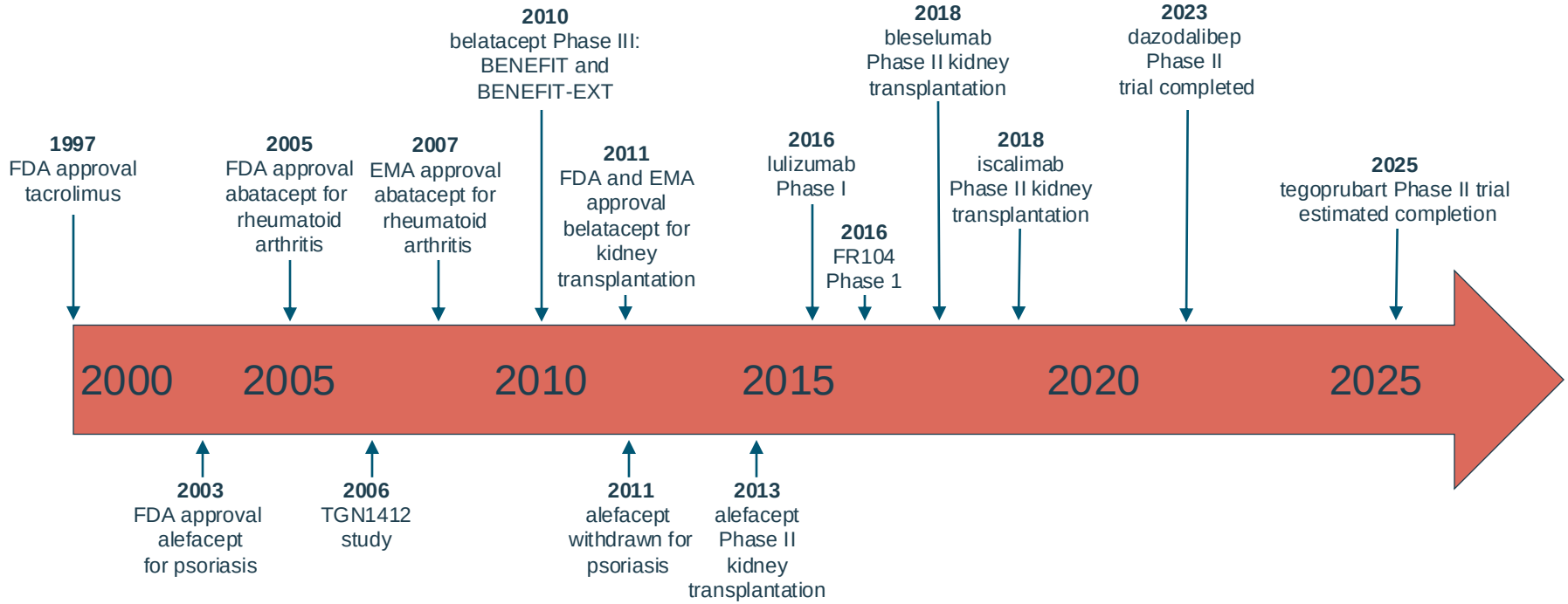
4. Costimulation blockade emerged as a promising immunosuppression strategy- blockade of critical costimulatory pathways (such as CD28-CD80/86 and CD40-CD154 interaction) could substantially prolong allograft survival

5. Many unmet needs associated with costimulation blockade in kidney remain

CNI = calcineurin inhibitor

Kitchens WH, et al. *Kidney Int Rep*. 2023;8(12):2529-2545.

Summary of Costimulation Blockade in Kidney Transplant



- Belatacept is the first and only costimulatory blockade agent FDA-approved for transplant immunosuppression.
- The development of abatacept therapy for transplantation was discontinued
- Bleselumab and iscalimab failed in clinical trials for immunosuppression in kidney transplant patients.
- Biologics targeting the CD40L are in development (tegoprubart and dazodalibep)

van der Zwan M, et al. *Drugs*. 2020;80(1):33-46.

Unmet Needs and Challenges

Conversion to costimulating agent

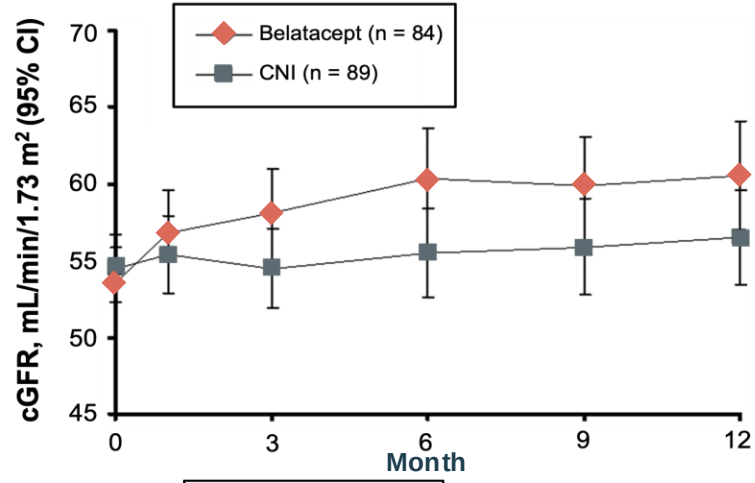
- No standardized protocol for de-novo use
- Excellent results of clinical trials for conversion from CNI to belatacept after 6 months in patients with stable renal function
- Quality conversion trials in patients with troubled kidneys are lacking
- Desensitization may benefit from the use of costimulation blockade
- Special populations

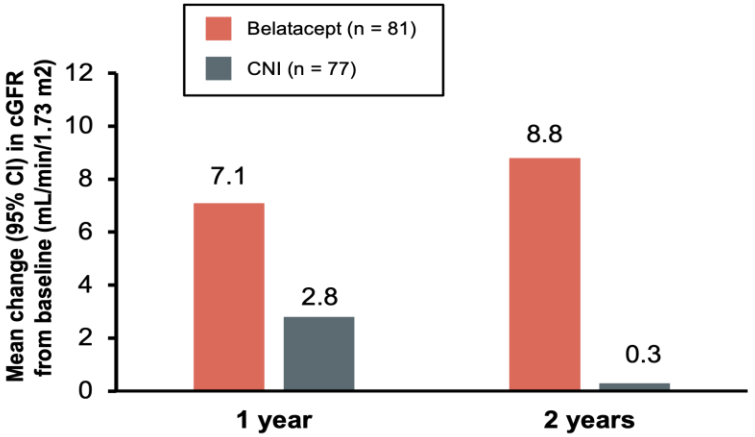
Unmet Needs and Challenges

No clear-cut trials for conversion

- Only 2 randomized multicenter trials of late (> 6 months) conversion in stable patients are available
- Data on early conversion(< 6 months) and high-risk groups are retrospective and mostly single centers

Switching from Calcineurin Inhibitor-based Regimens to a Belatacept-based Regimen in Renal Transplant Recipients: A Randomized Phase II Study





Secondary outcomes at month 12

	Belatacept (*n* = 84)	CNI (*n* = 89)
Acute rejection incidence, *n* (%)	6 (7)	0
95% CI	1.6 to 12.7	
Banff grade, *n* (%)		
mild acute (IA)	1 (1)	0
mild acute (IB)	1 (1)	0
moderate acute (IIA)	3 (4)	0
moderate acute (IIB)	1 (1)	0
severe acute (IIA)	0 (0)	0
Patient/graft survival, *n* (%)	84 (100)	88 (99)
95% CI		96.7 to 100.0
Graft loss or death, *n* (%)	0	1 (1)
graft loss	0	0
death	0	1 (1)
death with functioning graft	0	1 (1)

Rostaing L, et al. *Clin J Am Soc Nephrol*. 2011;6(2):430-439.

Conversion from Calcineurin Inhibitor- to Belatacept-Based Maintenance Immunosuppression in Renal Transplant Recipients: A Randomized Phase IIIb Trial

Methods

Prospective randomized open-label Phase IIIb trial

466 kidney transplant recipients

- 6 – 60 months post-transplant
- On CNI-based immunosuppression

R

1:1

Convert to belatacept
n = 223

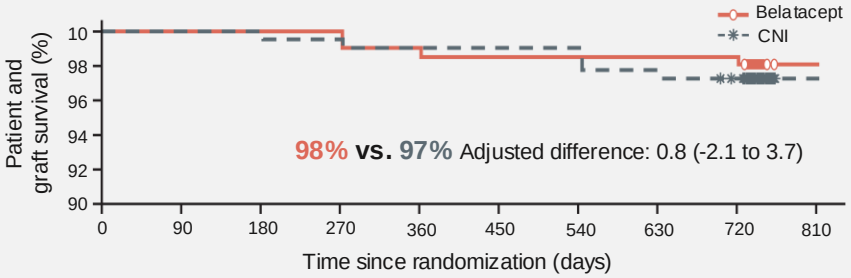
Continue CNI regimen
n = 223

Primary analysis at 24 months
Primary endpoint: survival with functioning graft at 24 months

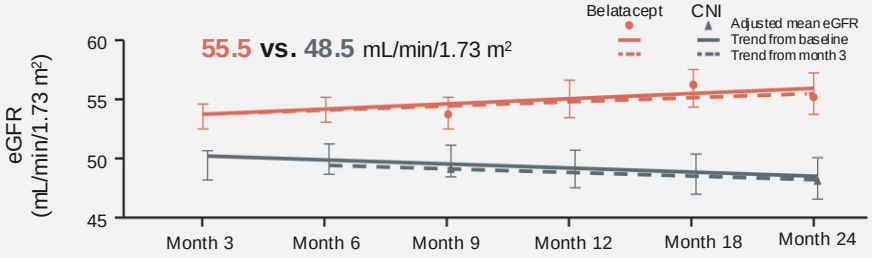
Outcomes

Belatacept Conversion vs. CNI Continuation

Patient and graft survival



Renal function



BPAR
8% vs. 4%

dnDSAa
1% vs. 7%

Serious AEs
48% vs. 43%

Serious infections
17% vs. 20%

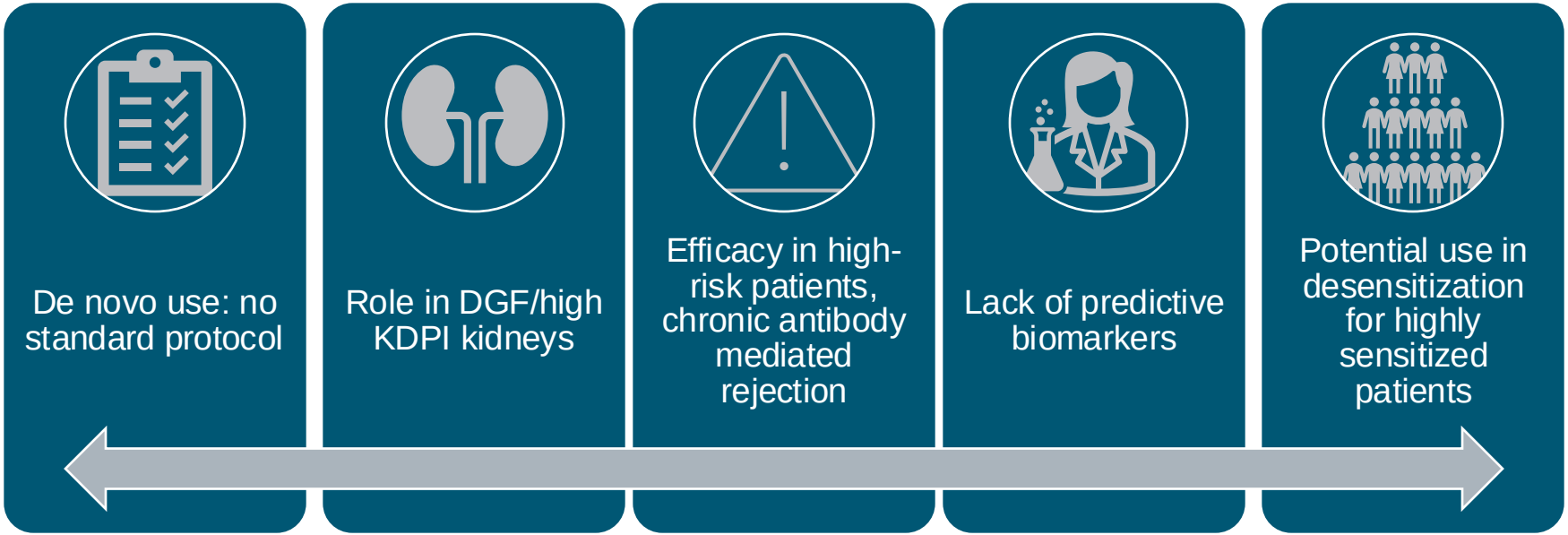
AE-related discontinuations
5% vs. 4%

AEs = adverse events

Budde K, et al. *J Am Soc Nephrol*. 2021;32(12):3252-3264.

Unmet Needs and Challenges

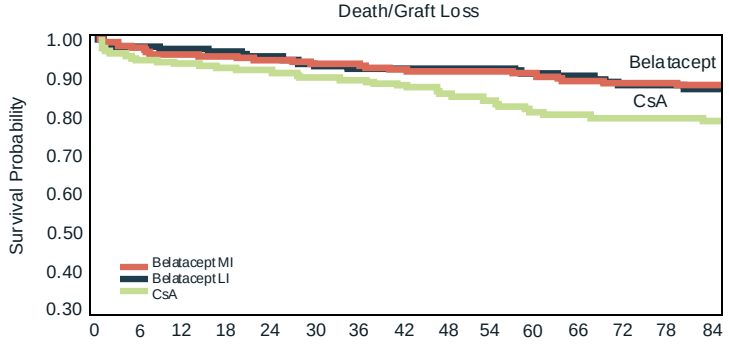
Important Issues Still to Be Determined



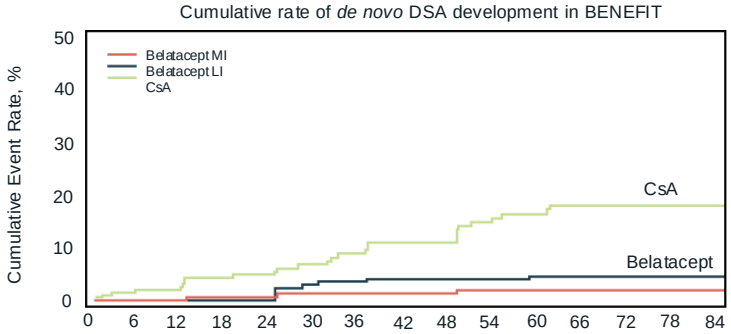
Rigorous trials in troubled kidneys treated with belatacept are needed

DGF = delayed graph function; KDPI = The Kidney Donor Profile Index

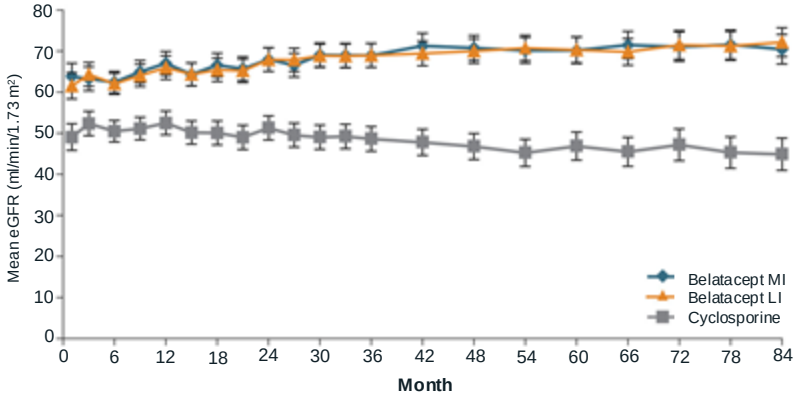
Belatacept and Long-Term Outcomes in Kidney Transplantation



HR Graft loss, Belatacept LI vs. CsA: 0.570 (0.348, 0.935) *P* = .02



HR DSA, Belatacept LI vs. CsA: 0.245 (0.111, 0.539) *P* < .0001



Differences in eGFR favored belatacept (*P* < .001)

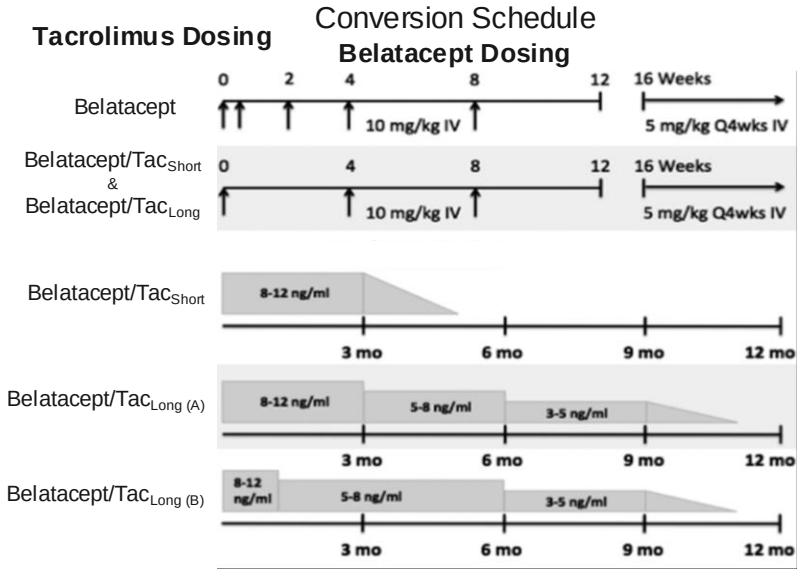
Acute Rejection Rates

	MI Belatacept	LI Belatacept	CsA
Acute Rejection	24.4%	18.3%	11.4%

CsA = cyclosporine

Vincenti F et al. *N Engl J Med*. 2016;374(4):333-343. Bry RA, et al. *Am J Transplant*. 2018;18:1783-1789.

Standard of Care for De Novo Use of Belatacept with Tacrolimus at Emory



Steroid Dosing

All patients received steroids indefinitely

day 0	500 mg
day 1	250 mg
day 2	125 mg
Belatacept$_A$ day 3 ->	5 mg ->
Belatacept$_B$ day 3-42 ->	20 -> 5 mg ->
Belatacept/Tac day 3 ->	5 mg ->

Initial belatacept treatment (n = 97)

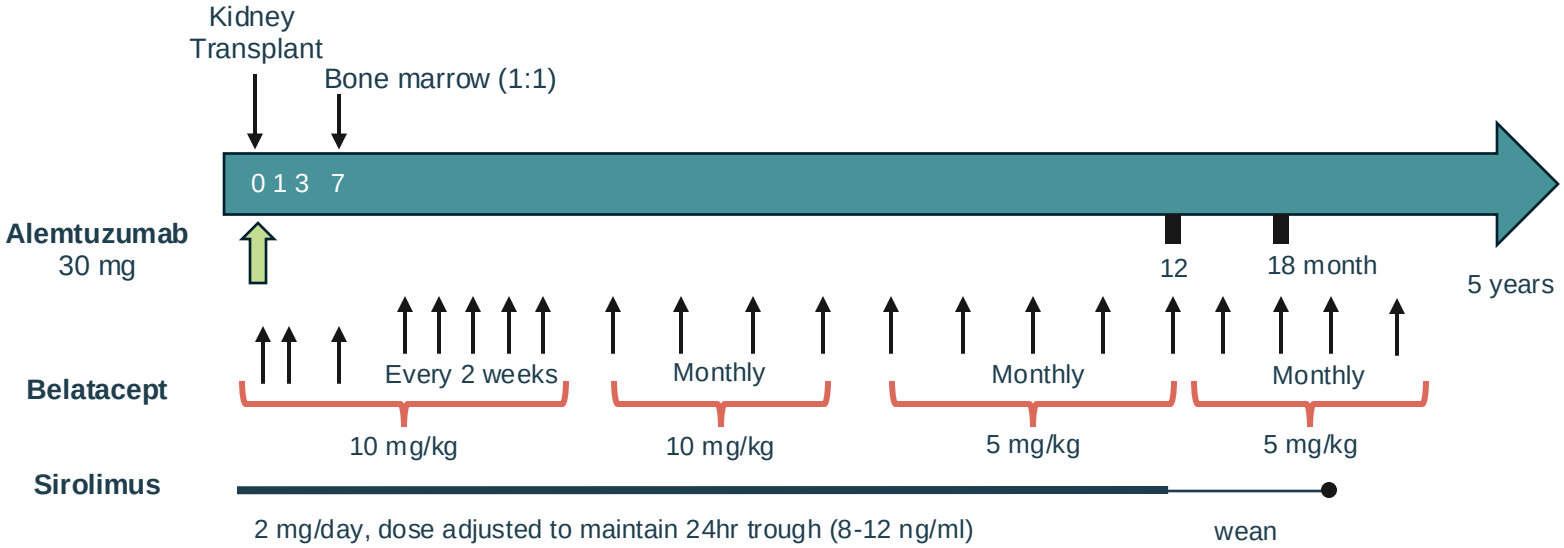
- AR rate month 12: 50.5%
- Graft survival month 12: 100%

Results

- Belatacept/Tacro (n = 87)
  - AR rate month 12: 20.5%
  - Graft survival month 12: 99.5%

Adams AB, et al. *Am J Transplant*. 2017;17(11):2922-2936.

CNI-Sparing Regimen with Belatacept



- Sirolimus (n = 20)
  - AR rate month 12: 0%
  - Graft survival month 12: 100%
  - Mean eGFR month 12: 89 mL/min

*Alemtuzumab is not FDA approved for prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants
eGFR = estimated glomerular filtration rate
Kirk AD, et al. *Am J Transplant*. 2014;14(5):1142-1151.

CNI-Sparing Regimen with Belatacept

	Anti-Thymocyte Globulin	Steroids	Belatacept	MMF	Everolimus*
Dose	2-3 days: 3 mg/kg total dose	Methylprednisolone Days 0-4: 500,250,125,60 mg Prednisone: Day 5 30 mg/d, tapered by 10 mg weekly to final maintenance dose 5 mg/d	POD 1,7: 10 mg/kg Weeks 2,4: 10 mg/kg Weeks 8,12: 10 mg/kg Dosing onwards: 5 mg/kg Q4W	Started POD 0: 2 g/d	Starting dose: 0.75 mg BID
Considerations		Maintenance CS use determined by treating physician		Converted to everolimus 1-month post-transplant	Titrated to trough level 3-8 ng/mL

*Everolimus is FDA approved for prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants

Wojciechowski D, et al. *Clin Transplant*. 2017;31(9):e13042.

Conversion Protocol

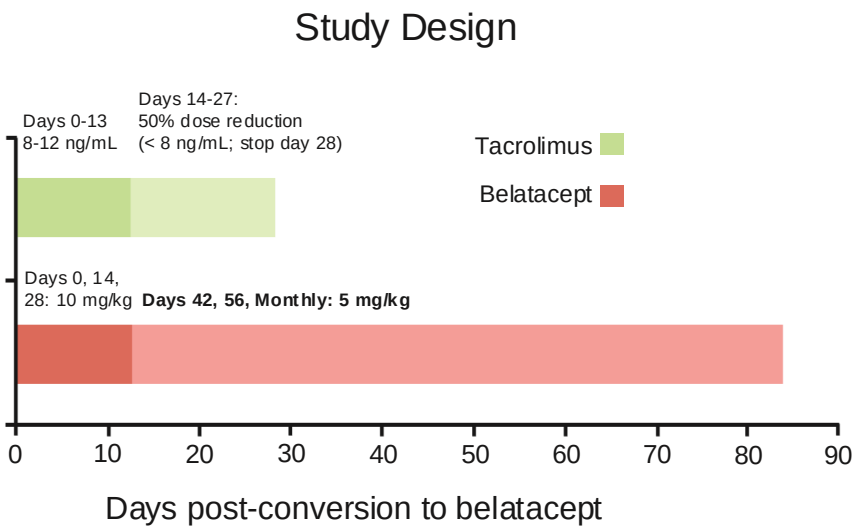
Day	Steroid	< 6 Months Post-Transplant		> 6 Months Post-Transplant	
		CNI Dose*	Belatacept	CNI Dose*	Belatacept
0	Add Prednisone 5 mg daily (if not already taking)	100%	10 mg/kg	100%	10 mg/kg
14		50%	10 mg/kg	50%	5 mg/kg
28		Stop	10 mg/kg	Stop	5 mg/kg
42			5 mg/kg		5 mg/kg
56, then every 4 weeks (± days)			5 mg/kg		5 mg/kg

*No need to overall CNI if switching for CNI-related TMA

Viral monitoring for all patients on belatacept (same for *de novo* or conversion)

1. Monitor CMV PCR and EBV PCR at 3 and 6 months after 1st dose of belatacept
2. Start CMV prophylaxis as outlined in infection prophylaxis section below

Early Post-Transplant Conversion from Tacrolimus to Belatacept for Prolonged Delayed Graft Function Improves Renal Function in Kidney Transplant Recipients



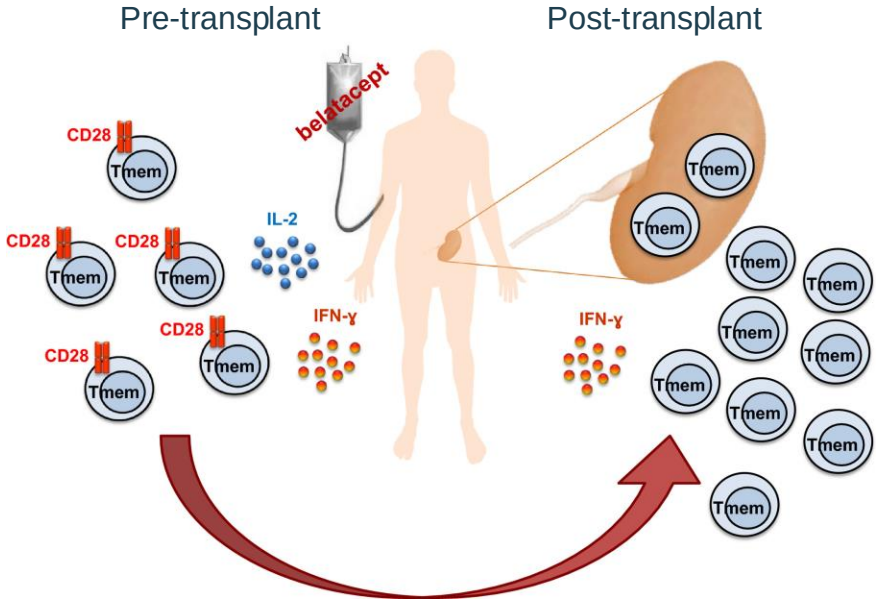
	Group 1 Belatacept 30, n = 8	Group 2 Belatacept 31-60, n = 6	Group 3 Belatacept 61-90, n = 6	*P* Values
eGFR mL/min/1.73 m^2, mean (SD)	–	–	–	–
Day of conversion	9.5 (11.4)	15 (13.8)	25.7 (7.7)	1 vs. 2: .42; **1 vs. 3: .016**; 2 vs. 3: .17
30 days post-conversion	50.6 (20.9)	41.2 (10.6)	35 (7.6)	1 vs. 2: .56; 1 vs. 3: .017; 2 vs. 3: .31
12 months post-transplant	65.1 (19.4)	52.2 (18)	39 (7.5; n = 5)	1 vs. 2: .24; **1 vs. 3: .03**; 2 vs. 3: .18

Results:

- 20 patients converted to belatacept for prolonged DGF. Prior to conversion, patients underwent an allograft biopsy to rule out rejection and confirm tubular injury.
- The primary outcome: eGFR 12 months post transplant; secondary outcome change in eGFR 30 days post belatacept conversion
- The acute rejection was 20% with 100% patient survival at 12 months post-transplant. There was one graft loss in the setting of an invasive Aspergillus infection that resulted in withdrawal of immunosuppression and transplant nephrectomy.

Wojciechowski D, et al. *Clin Transplant*. 2017;31(5):e12930.

Biomarkers



- T-cell profiling pre-transplant may assist in determining which patients are at an increased risk of cellular rejection in patients treated with costimulation blockade agents
- However, no biomarker of a specific T-cell phenotype has been definitively proven to predict an increase in cellular rejection
- Some promise has been identified regarding specific biomarkers:
  - CD57+ CD4 T-cells
  - CD28- CD4 T-cells
  - CD28- CD8 T-cells

Figure: Patients with a high pre-transplant frequency of CD28+ memory T cells are at increased risk of acute rejection under belatacept therapy. Upon transplantation, CD28+ memory T cells proliferate and produce IL-2 and IFN-ɣ despite belatacept treatment. Many of these cells lose expression of CD28, turning into CD28- memory T cells. These cells lose their ability to produce IL-2, but they retain the potential to produce IFN-ɣ and to infiltrate the graft during rejection.

Wekerle T. *Am J Transplant*. 2017;17(9):2235-2237. Espinosa J, et al. *Am J Transplant*. 2016;16(4):1102-1112.

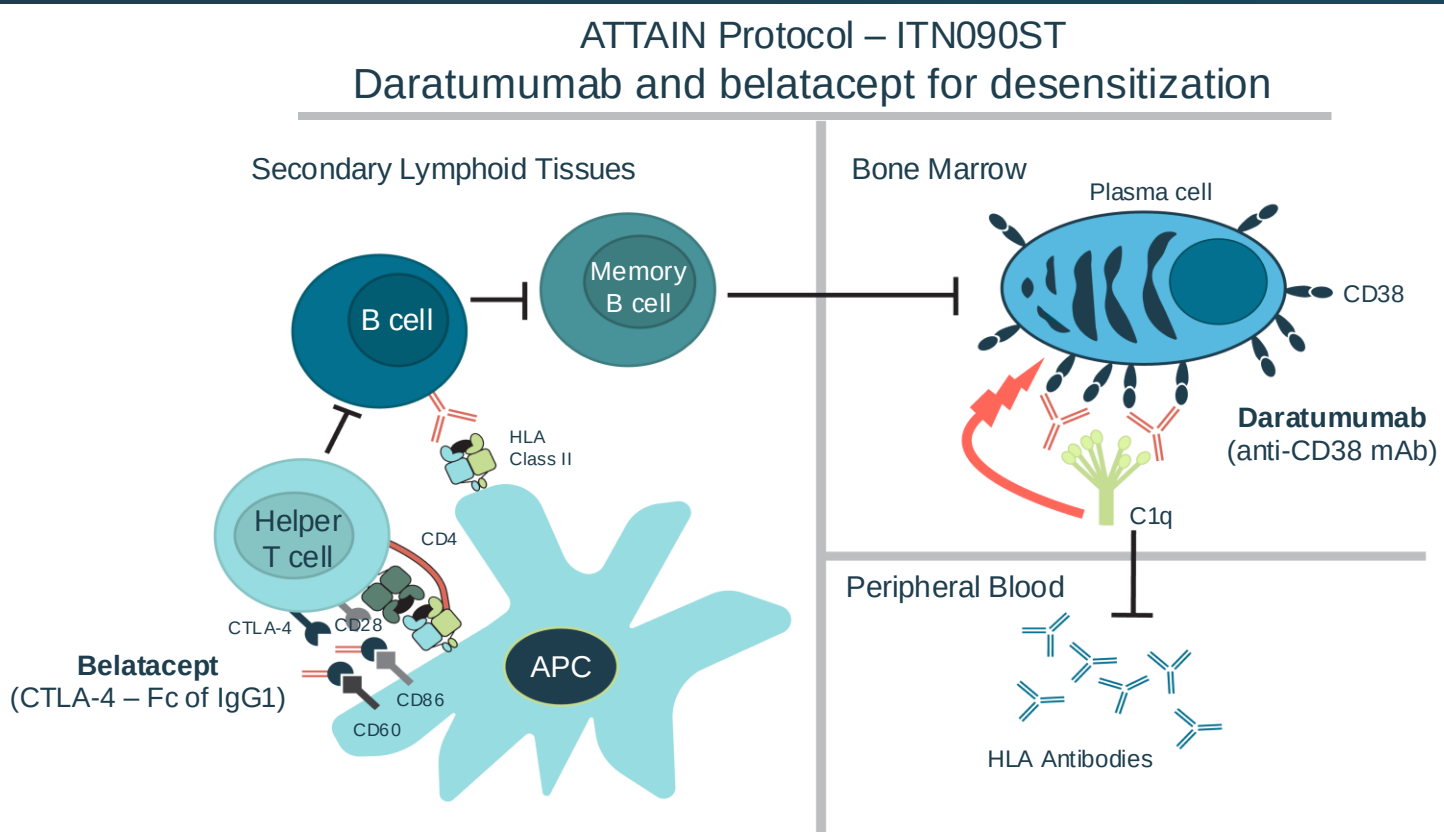
Use in Highly Sensitized Patients

Desensitization

- Desensitization allows for kidney transplantation in highly sensitized and incompatible patients
- Most desensitization protocols include plasmapheresis to reduce circulating HLA antibody and intravenous immunoglobulin for its immunomodulatory effects and to prevent hypogammaglobinemia, but many other therapies have been added or used alone
- Drugs utilized for desensitization include rituximab (RTX)*, proteasome inhibitors*, daratumumab*, isatuximab*, and belatacept*

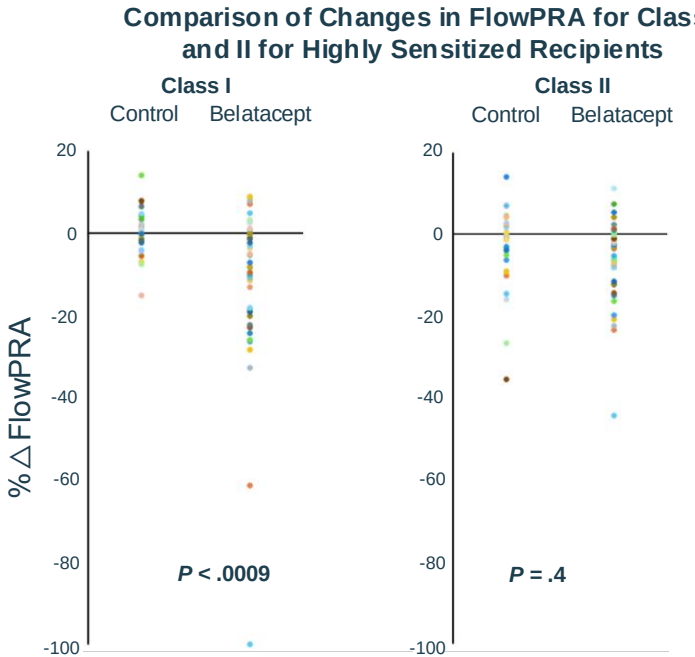
*Not FDA approved for desensitization in patients receiving allogeneic liver, kidney, or heart transplants
ATG = anti-thymocyte globulin; HLA = human leukocyte antigen
Schinstock C, et al. *Front Immunol*. 2021;12:686271.

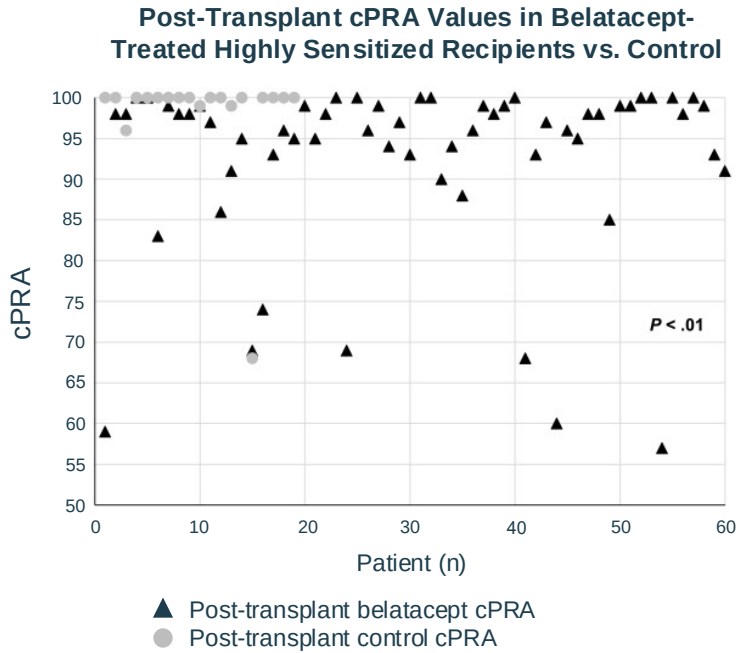
Desensitization



National Institute of Allergy and Infectious Diseases (NIAID). *Daratumumab and Belatacept for Desensitization (ATTAIN)*. Identifier: NCT04827979. 2021. Accessed September 4, 2024.

The Impact of Belatacept on Third-Party HLA Alloantibodies in Highly Sensitized Kidney Transplant Recipients





Findings

- Significant HLA antibody reduction was evident for class I ($P < .0009$)
- Post-transplant belatacept-treated patients also had a clinically significant reduction in their cPRA compared to controls ($P < .01$)

cPRA = calculated panel reactive antibody

Parsons RF, et al. *Am J Transplant*. 2020;20(2):573-581.

Outcomes With Belatacept Exposure During Pregnancy in Kidney Transplant Recipients: A Case Series

Pre-pregnancy

- Belatacept (16 pregnancy events)
  - Median SCr: 0.9 mg/dL (o.8-1.37 mg/dL)
  - 31% taking MPA at time of conception
- Tacrolimus (578 pregnancy events)
  - Medical SCr: 1.0 mg/dL (0.9-1.3)

Pregnancy Events

- Belatacept: 13 (81%) live births, 3 (19%) miscarriages
  - All three miscarried first trimester
  - 2/3 did not transition off MPA before conception
  - Preeclampsia complicated 5/13 (38%) of pregnancies
  - Renal function stable for duration of pregnancy 12/13 patients
  - No rejection episodes were observed
  - Complications: CMV reactivation (1), COVID-19 (2), gestational diabetes (1)
- Tacrolimus: 75% live births, 22% miscarriages, 1% terminations, 1% ectopic pregnancies, 1% stillbirths
  - Complications: hypertension (48%), infection (16%), gestational diabetes (11%), rejection (2%), preeclampsia (40%)

Post-pregnancy

- Belatacept:
  - Median SCr 1.09 mg/dL (1-1.5 mg/dL)
  - Allograft loss due to nonadherence to belatacept (1)
  - Renal function declining (2)
  - No neonatal deaths or infant complications observed
  - 5 chose to breastfeed, no issues reported
- Tacrolimus:
  - Median SCr 1.0mg/dL (0.9-1.4 mg/dL)
  - Graft loss (3%)
  - Birth defects (4%)

SCr = serum creatinine

Coscia L, et al. *Transplantation*. 2023;107(9):2047-2054.

Logistics Behind Administration

- Biggest hurdles to belatacept treatment
  - IV access
  - Monthly vs. every 2 months administration
  - Access and administration logistics
    - Insurance
    - Rural vs. urban areas

Faculty Discussion Question
- How can we help patients overcome logistical barriers?

Badell IR, et al. *Am J Transplant*. 2021;21(9):3066-3076.

Emerging Options for Costimulation Blockade

A Pilot Study Evaluating Dual Co-Stimulation Blockade with Dazodalibep (HZN4920) and Belatacept for Prophylaxis of Kidney Allograft Rejection

- Phase IIa, single-arm, open-label, pilot study in adults of low immunologic risk undergoing a first kidney transplant (N = 23)
- Graft and patient survival were 100%. Both drugs were well tolerated; The incidence of composite efficacy failure was 5/20 (25%) at Week 24 and 48. The mean (SD) eGFR of patients at Week 48 was 71.3 (12.7) mL/min/1.732.
- There were no ABMRs and 5/20 (25.0%) treated acute rejections by Week 48 (five diagnosed within 12 weeks). The most frequently reported AEs (≥ 4 patients) were COVID-19, anemia, BK virus infection, hypophosphatemia, and leukopenia. Nine patients experienced ≥ 1 serious AE and seven experienced ≥ 1 AE of special interest.

WCN23-0454 Tegoprubart for the Prevention of Rejection in Kidney Transplant Recipients: A Snapshot of Emerging Data from an Ongoing Trial

- 12 adults receiving a kidney transplant from either a living or deceased donor will be enrolled.
- Eligibility: this must be their first transplant, seropositive for EBV, free of donor specific antibodies, low panel reactive antibodies, organ cannot be from an extended criteria donor or have a prolonged cold ischemia time.
- All participants will receive rATG and a regimen consisting of tegoprubart 20 mg/kg IV administered every 3 weeks after initial loading, mycophenolate and corticosteroids.
- The primary endpoint is safety at one year. Secondary endpoints include characterizing the pharmacokinetic profile of tegoprubart, the incidence of biopsy proven rejection (BPAR) and changes in estimated glomerular filtration rate (eGFR).

Kirk, AD. *American Transplant Congress.* June 7, 2023. Tchervenkov J, et al. *Kidney International Reports.* 2023;8(3):S391-S392.

Faculty Discussion

What needs to be discussed with patients when initiating belatacept?

What impact does multidisciplinary/ coordinator involvement and outreach have on outcomes?

How do we improve patient engagement?

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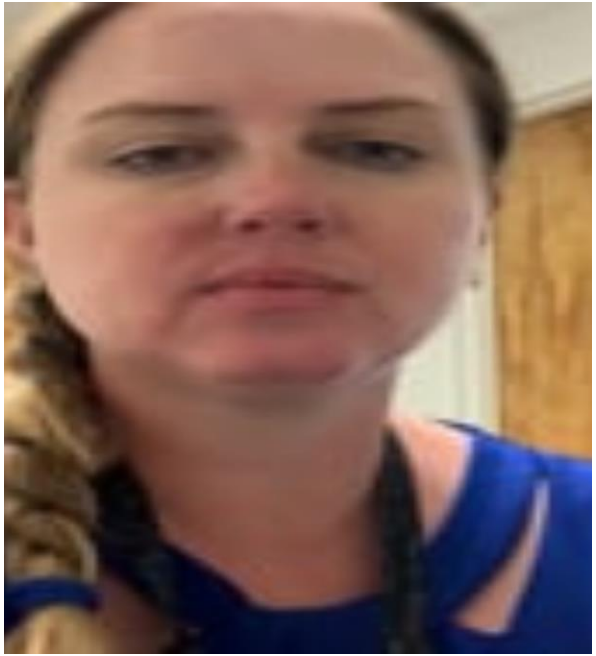
Patient Cases

Patient Case 1

- 38-year-old woman with ESRD secondary to IgA nephropathy who is status post second kidney transplant (living unrelated) for IgA nephropathy
- 1/25/2019: baseline creatinine 1.0-1.1 mg/dl was maintained on a Belatacept-based immunosuppression regimen. Underwent two uneventful pregnancies on a Belatacept-based regimen

ESRD = end stage renal disease; IgA = immunoglobulin A

Patient Case 1



Patient Case 1

Patient Case 2

Patient Characteristics

- 55-year-old Black man admitted for a second deceased donor kidney transplant
- Medical history
  - ESRD associated with T2DM, HTN
  - Underwent deceased kidney transplant 2 years prior, complicated by renal vein thrombosis, day 4 post-op underwent transplant nephrectomy

Pre-Transplant

- Patient blood group B, cPRA 74%
- Negative virtual crossmatch with donor. Kidney procured from a CDC donor with KDPI 42%

Transplantation/Post-Transplant

- Surgery uneventful, induced w/thymoglobulin 1.5 mg/kg/d x4d, maintained on Tac, MMF, prednisone

CDC = complement dependent cytotoxicity; CPRA = calculated panel reactive antibody; HTN = hypertension; MMF = mycophenolate mofetil; T2DM = type 2 diabetes mellitus

Patient Case 2 (cont.)

Post-Transplant

- Patient was oliguric, requiring hemodialysis
- D/c and continued outpatient hemodialysis
- Three weeks post-transplant continued to require hemodialysis despite increase in urine output to 800 ml/d, underwent percutaneous kidney biopsy
- Renal function not improving

Pathology

- Widespread tubular epithelial cell injury with identified mitotic figures
- Banff scores: g0, ptc0, t0, i0, C4d-

Labs

- Tac levels ~6 ng/ml

Patient Case 2 (cont.)

8 Weeks Post-Biopsy

- 55-year-old Black male admitted for a second deceased donor kidney transplant

- Converted to belatacept per protocol:

- Dose 725 mg belatacept IV
- Tac decrease 2 mg BID → 1 mg BID
- Maintained for 4 weeks then d/c tac
- Tac levels decreased 6.3 → 3.2 ng/ml and was undetectable few days after d/c

- 3 weeks post-conversion SCr decreased to 4.1 mg/dl and soon after hemodialysis was d/c
- SCr decreased to 3 mg/dl ~8 weeks after conversion
- Patient converted from MMF to everolimus

- 6 months post-transplant patient had stable renal function,
  no DSAs and protocol biopsy showed no evidence of rejection or tubular injury with mild fibrosis

- 2 years post-transplant SCr was 1.5 mg/dl and eGFR was 56 ml/mn

Faculty Discussion: Shared Decision-Making

How do we define short- and long-term goals with patients?

How can we support adherence?

What is the best way to utilize a multidisciplinary approach to treatment?

What tools and resources are available to encourage patient self-management?

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Identify situations where costimulation blockade agents may be optimal in conjunction with other treatments for patients requiring immunosuppression post-kidney transplant
- Individualize treatment plans and conversion regimens for patients eligible for management with costimulation blockade agents or who are failing current immunosuppressive therapy
- Provide customized counsel and support for patients undergoing changes in immunosuppression regimens, with emphasis on both short- and long-term goals

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Versatility of Therapeutic Uses of Costimulation Blockade in Kidney Transplantation

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