Drug Therapy in the Heart Transplant Recipient

CARDIAC REJECTION AND IMMUNOSUPPRESSIVE DRUGS

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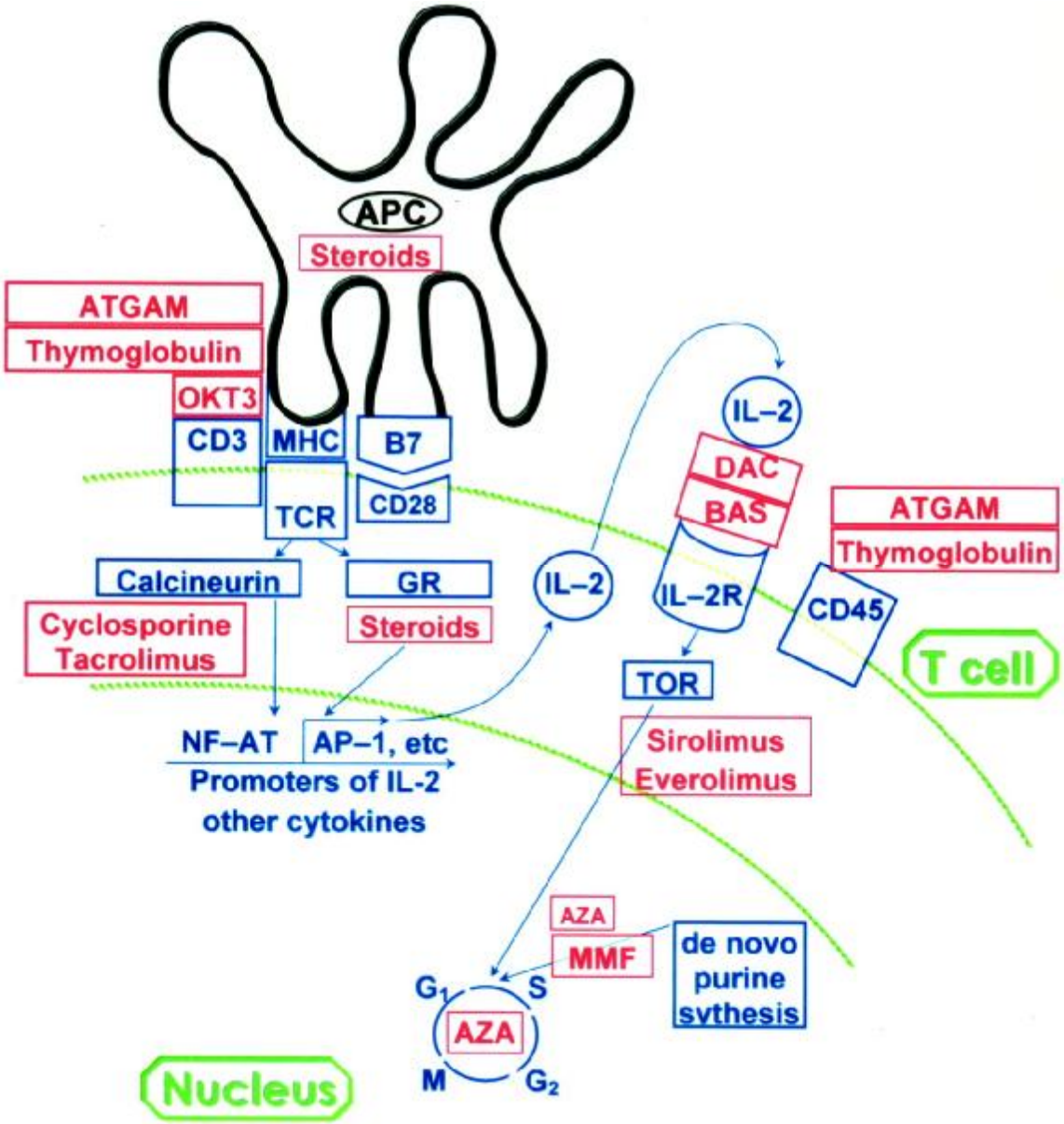
RHC

Rejection

- primarily a T-lymphocyte (T-cell)–mediated event
- humoral (B-cell) responses also contribute
- antigen-presenting cells (APCs).
  - dendritic cells
  - Macrophages
  - B cells
  - endothelial cells
- Donor alloantigens
  - Donor APCs
  - Alloantigens can be shed by cells in the graft
- Recognized by the T-cell receptor (TCR)–CD3 complex on the surface of the T cell

Rejection

- optimal T-cell activation
  - second or costimulatory signal
- activation of calcineurin
  - interleukin-2 (IL-2) and other cytokines
    - clonal expansion of T cells
    - enzyme target of rapamycin (TOR).


APC
Steroids
ATGAM
Thymoglobulin
OKT3
CD3
MHC
B7
CD28
TCR
Calcineurin
GR
Steroids
Cyclosporine
Tacrolimus
NF–AT
AP–1, etc
Promoters of IL-2
other cytokines
IL–2
IL–2
DAC
BAS
IL–2R
ATGAM
Thymoglobulin
CD45
T cell
TOR
Sirolimus
Everolimus
AZA
MMF
de novo
purine
sythesis
G1
S
AZA
M
G2
Nucleus

Immunosuppression Regimens

- Induction
- Maintenance
- Rejection

Induction

- induce tolerance to the graft
- benefits of induction therapy
  - marked reduction in rejection
  - later introduction of calcineurin inhibitors
- Disadvantages of induction therapy
  - increased risk of infection
  - Malignancy
  - Both
  - and increased cost.
- ATGAM, Thymoglobulin and IL-2R antagonists

Maintenance therapy

- Antimetabolite
- Calcineurin inhibitor
- Steroids
- targets several steps in T-cell activation
- allowing lower doses of each individual drug
- Early maintenance therapy
  - steroid,
  - a calcineurin inhibitor with either cyclosporine (target levels, 300 to 350 ng/mL) or tacrolimus (target levels, 10 to 15 ng/mL),
  - and mycophenolate mofetil at 1 g BID.

Maintenance therapy

- gradually decreased over time
  - cyclosporine target levels about 200 ng/mL or tacrolimus target levels at 5 to 10
  - efforts have been made to discontinue maintenance steroid therapy
- Acute cellular rejection has become less frequent

Rejection (or rescue) therapy

- reverse an episode of rejection
- increase in oral therapy
- oral or intravenous pulse steroids
- a change in oral therapy
- or monoclonal or polyclonal anti-lymphocyte agents.

General Comments

- Outcomes:
  - desired immunosuppressive effects
  - the adverse effects of immunodeficiency such as infection and malignancy
  - nonimmune toxicities such as diabetes, hypertension, and renal insufficiency
- Infectious complications,
  - frequent after cardiac transplantation
  - All immunosuppressive drugs
- Malignancy
  - impaired immunoregulation
  - a synergistic effect with other carcinogens
  - Lymphoproliferative diseases, skin and lip cancers, and Kaposi's sarcoma

Specific Drugs

INTRAVENOUS

Anti-Lymphocyte Preparations

Polyclonal Anti-Lymphocyte Antibodies

- ATGAM
  - in horses
- Thymoglobulin
  - in rabbits
- Mechanism of Action
  - substantial lymphocyte depletion
  - antibodies to many surface T- and B-cell molecules
  - Antibodies to CD45
  - early perioperative management of patients with worsening renal insufficiency
- Adverse Effects
  - binding to granulocytes and platelets and a reduction of these cells
  - acute hypersensitivity response or serum sickness on subsequent exposure.
  - Urticaria
  - fever, chills, and rash
  - cytokine release syndrome
  - primary or reactivation cytomegalovirus infections
  - Leukopenia and thrombocytopenia
  - Hypertension,cdiarrhea, and headache are common

Monoclonal Anti-Lymphocyte Antibodies

- Muromonab CD3. Muromonab-CD3 (OKT3)
- Mechanism of Action.
  - binding of OKT3 to CD3 renders the T cell unable to respond to an antigen
- Adverse Effects
  - cytokine releas
    - fever, chills, rigors, dyspnea, wheezing, chest pain or tightness, headache, nausea, vomiting, and diarrhea
    - Cardiogenic and noncardiogenic pulmonary edema
    - aseptic meningitis and encephalopathy
    - antipyretics, intravenous steroids, antihistamines, and occasionally H2 blockers are routinely prescribed 1 hour before administration of OKT3.
    - routine prophylactic treatment with ganciclovir is recommended
  - development of antibodies to the mouse immunoglobulin

Anti-Cytokine Receptor Antibodies

- daclizumab and basiliximab
- Mechanism of Action
  - bind the subunit of IL-2R expressed on antigen-activated T cells
  - prevents binding of IL-2 to the IL-2R, inhibiting proliferation of T cells
- Adverse Effects
  - Few serious common adverse events
  - Hypersensitivity

Corticosteroids (Steroids)

- Mechanism of Action
  - affect the number, distribution, and function of all types of leukocytes (T and B lymphocytes, granulocytes, macrophages, and monocytes), as well as endothelial cells
- standard component of induction, maintenance, and antirejection therapy
  - High-dose steroids
  - Pulse steroids, either oral or intravenous
- Adverse Effects
  - Hypertension
  - emotional lability
  - Cataracts
  - gastric ulcer
  - poor wound healing
  - and proximal myopathy
  - Cosmetic effects
    - hirsutism, acne, easy bruising, skin fragility, moon face, buffalo hump, weight gain, and truncal obesity.
  - chronic adrenal suppression

Antiproliferative Agents

Mycophenolate Mofetil

- Mechanism of Action
  - MMF is a selective inhibitor of lymphocyte proliferation
- Use
  - approved for rejection prophylaxis in renal, hepatic, and cardiac transplant recipients
- Adverse Effects
  - nausea, vomiting, and diarrhea,
  - risk of opportunistic infections

Calcineurin Inhibitors

Cyclosporine

- Prophylaxis of organ rejection in kidney, liver, and heart transplant recipients
- Adverse Effects
  - Nephrotoxicity
    - acute, dose related
    - chronic with arteriolar sclerosis and tubulo-interstitial fibrosis
    - hemolytic-uremic syndrome
  - Hypertension and hyperlipidemia
  - De novo diabetes mellitus
  - Neurological toxicity
    - tremor, paresthesias, headache, seizures, mental status changes, visual symptoms, and insomnia
  - nausea, vomiting, cholestasis, and cholelithiasis
  - Osteoporosis
  - Hypertrichosis
  - gingival hyperplasia

Tacrolimus

- is used in place of CSA
- Adverse Effects
  - Hyperglycemia and neurological toxicity are more common with TAC than with CSA
  - Alopecia

TOR Inhibitors

Sirolimus or Rapamycin

- has been used effectively in heart transplant recipients in place of Cis to treat rejection or to ameliorate renal dysfunction
- Adverse Effects
  - hyperlipidemia with hypertriglyceridemia and increased LDL cholesterol,
  - Thrombocytopenia
  - Neutropenia
  - Anemia
  - adversely affect wound healing
  - noninfectious pneumonitis

Future perspective

Original Article

Belatacept and Long-Term Outcomes in Kidney Transplantation

Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.

N Engl J Med
Volume 374(4):333-343
January 28, 2016

Study Overview

- This study evaluated 7-year efficacy and safety outcomes in transplant recipients assigned to a more-intensive or less-intensive belatacept regimen or cyclosporine for immunosuppression.
- Both belatacept regimens were associated with significantly superior patient and graft survival.

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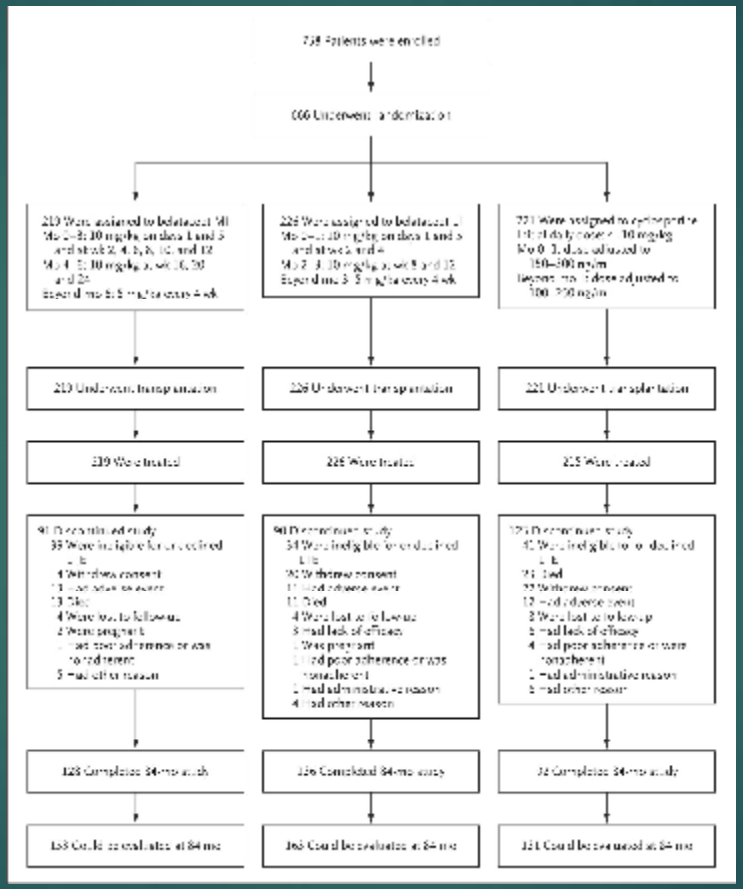
Number of Patients Who Were Enrolled, Underwent Randomization, and Completed the Study.



Vincenti F et al. N Engl J Med 2016;374:333-343

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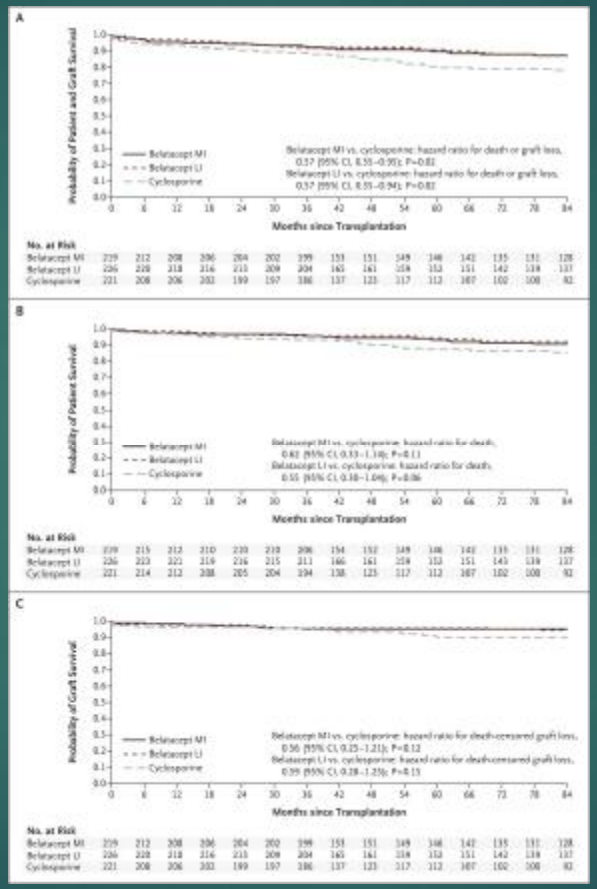
Kaplan–Meier Curves for Patient and Graft Survival.



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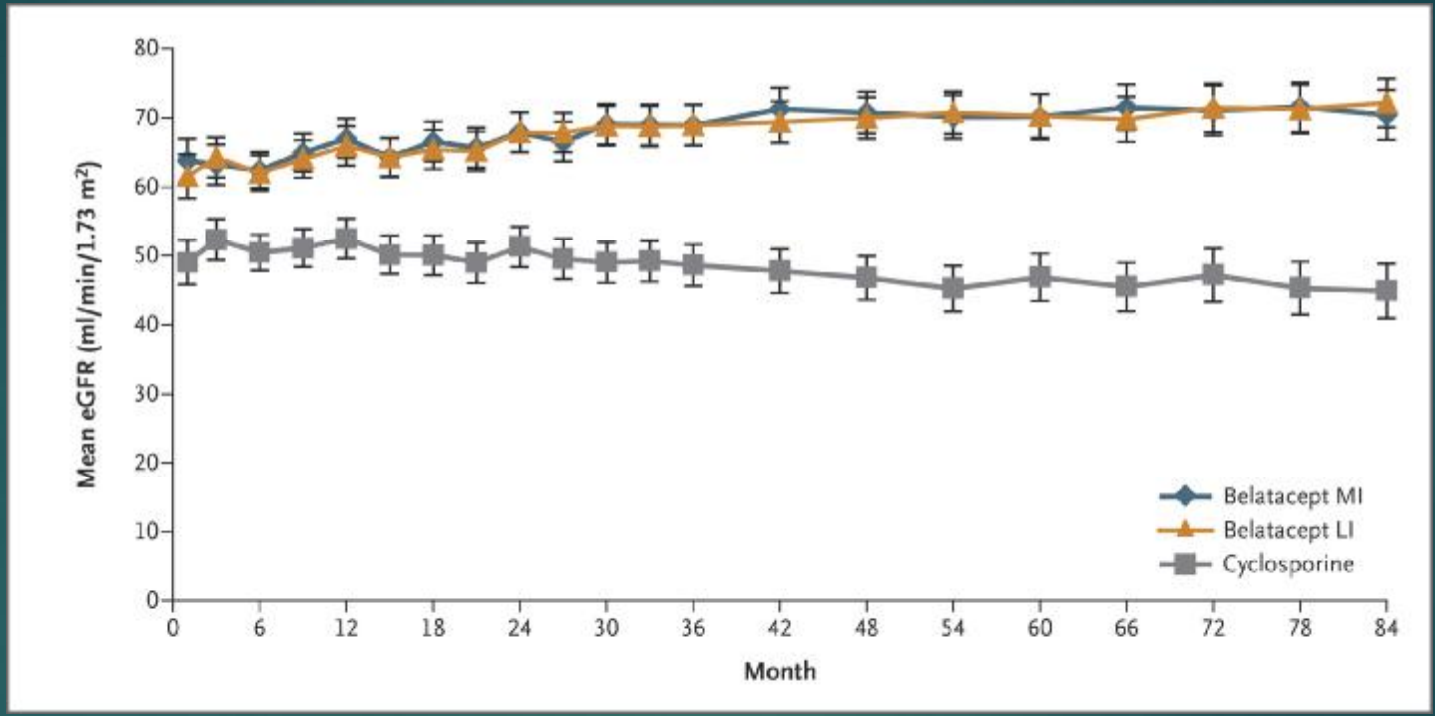
Glomerular Filtration Rate over the Period from Month 1 to Month 84.



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Cumulative Incidence Rates of Selected Adverse Events.

Table 1. Cumulative Incidence Rates of Selected Adverse Events.*

Event	More-Intensive Belatacept (N=219)	Less-Intensive Belatacept (N=226)	Cyclosporine (N=221)
	no. of events/100 person-yr		
Serious infections	10.6	10.7	13.3
Urinary tract infection	1.9	2.0	3.1
Cytomegalovirus infection	1.4	1.1	0.8
Pneumonia	0.7	1.1	1.4
Pyelonephritis	0.7	0.7	0.9
Sepsis	0.8	0.5	0.8
Gastroenteritis	0.7	0.3	0.7
Acute pyelonephritis	0.5	0.3	0.2
Upper respiratory tract infection	0.1	0.2	0.5
Serious gastrointestinal disorders	3.9	2.2	3.8
Serious general disorders and administration-site conditions	2.5	2.3	2.7
Serious cardiac disorders	2.0	1.4	2.2
Serious vascular disorders	1.8	1.5	2.9
Serious blood and lymphatic system disorders	1.6	1.0	1.6
Serious hepatobiliary disorders	0.5	0.3	0.7
Serious endocrine disorders	0.2	0.3	0.5
Cancer of any grade	2.1	1.8	2.6

* Only events occurring at an adjusted rate of 2% or more of patients in any treatment group are reported. Event rates have been adjusted for the duration of treatment exposure (expressed in person-years). For serious infections and cancer of any grade, treatment exposure was calculated from the randomization date to the date of the event, the date of the last follow-up assessment, or month 84, whichever was earliest. For all other events, treatment exposure was calculated from the randomization date to the date of the event, the date of the last dose of study medication plus 56 days, or month 84, whichever was earliest. Infections are classified according to the preferred terms in the *Medical Dictionary for Regulatory Activities*.

Vincenti F et al. N Engl J Med 2016;374:333-343

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Conclusions

- Seven years after transplantation, patient and graft survival and the mean eGFR were significantly higher with belatacept (both the more-intensive regimen and the less-intensive regimen) than with cyclosporine.

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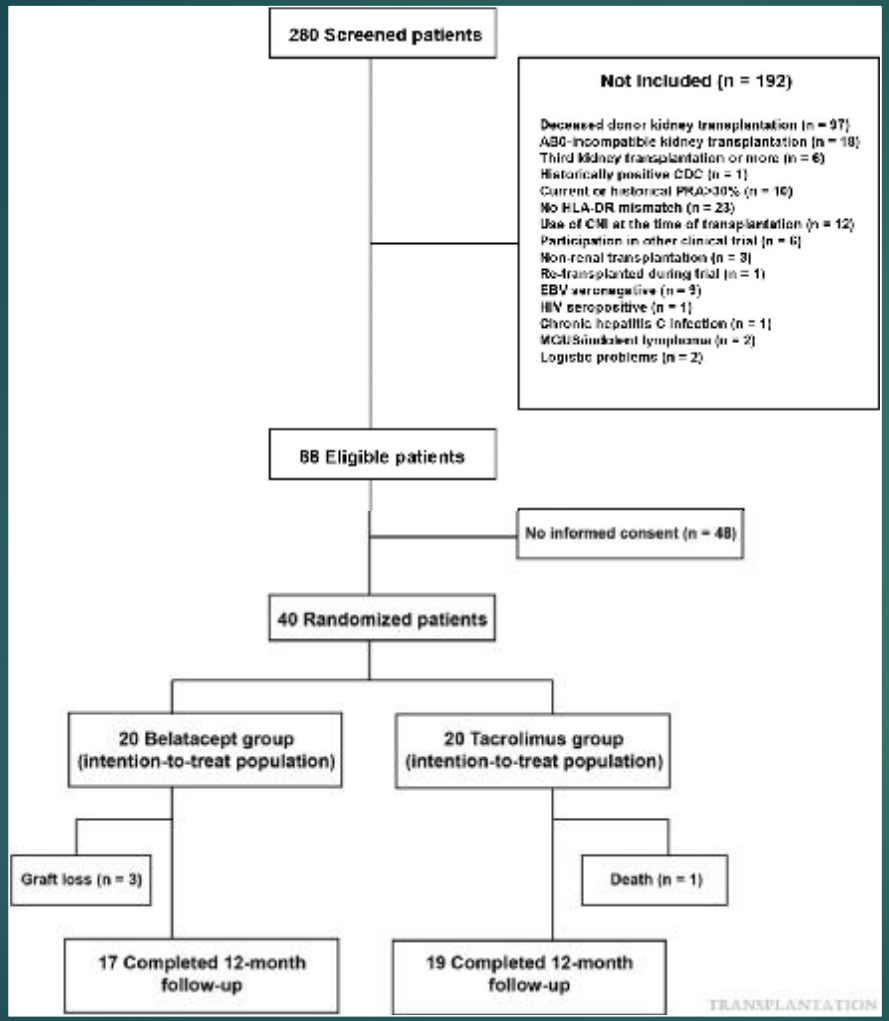
A Randomized Controlled Clinical Trial Comparing Belatacept With Tacrolimus After De Novo Kidney Transplantation

Gretchen N. de Graav, MD,[1] Carla C. Baan, PhD,[1] Marian C. Clahsen-van Groningen, MD, PhD,[2] Rens Kraaijeveld, BSc,[1] Marjolein Dieterich, BSc,[1] Wenda Verschoor, BSc,[1] Jan H. von der Thusen, MD, PhD,[2] Dave L. Roelen, PhD,[3] Monique Cadogan, BSc,[1] Jacqueline van de Wetering, MD, PhD,[1] Joost van Rosmalen, PhD,[4] Wilem Weimar, MD, PhD,[1] and Dennis A. Hesselink, MD, PhD[1]

Background. Belatacept, an inhibitor of the CD28-CD80/86 costimulatory pathway, allows for calcineurin-inhibitor free immunosuppressive therapy in kidney transplantation but is associated with a higher acute rejection risk than ciclosporin. Thus far, no biomarker for belatacept-resistant rejection has been validated. In this randomized-controlled trial, acute rejection rate was compared between belatacept- and tacrolimus-treated patients and immunological biomarkers for acute rejection were investigated. **Methods.** Forty kidney transplant recipients were 1:1 randomized to belatacept or tacrolimus combined with basiliximab, mycophenolate mofetil, and prednisolone. The 1-year incidence of biopsy-proven acute rejection was monitored. Potential biomarkers, namely, $CD8^+CD28^-$, $CD4^+CD57^+PD1^-$, and $CD8^+CD28^{++}$ end-stage terminally differentiated memory T cells were measured pretransplantation and posttransplantation and correlated to rejection. Pharmacodynamic monitoring of belatacept was performed by measuring free CD86 on monocytes. **Results.** The rejection incidence was higher in belatacept-treated than tacrolimus-treated patients: 55% versus 10% ($P = 0.006$). All 3 graft losses, due to rejection, occurred in the belatacept group. Although 4 of 5 belatacept-treated patients with greater than 35 cells $CD8^+CD28^{++}$ end-stage terminally differentiated memory T cells/μL rejected, median pretransplant values of the biomarkers did not differ between belatacept-treated rejectors and nonrejectors. In univariable Cox regressions, the studied cell subsets were not associated with rejection-risk. CD86 molecules on circulating monocytes in belatacept-treated patients were saturated at all timepoints. **Conclusions.** Belatacept-based immunosuppressive therapy resulted in higher and more severe acute rejection compared with tacrolimus-based therapy. This trial did not identify cellular biomarkers predictive of rejection. In addition, the CD28-CD80/86 costimulatory pathway appeared to be sufficiently blocked by belatacept and did not predict rejection.

(*Transplantation* 2017;101: 2571–2581)

FIGURE 1



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Transplantation101(10):2571-2581, October 2017.

doi: 10.1097/TP.0000000000001755

Trial flowchart. All patients who were included in the study were randomized, underwent transplantation and received at least 1 dose of belatacept or tacrolimus. CDC, cytotoxicity-dependent crossmatch; CNI, calcineurin inhibitor; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; MGUS, monoclonal gammopathy of unknown significance.

TABLE 3

	Belatacept group (n = 20)	Tacrolimus group (n = 20)	*P*
Borderline	0 (0%)	0 (0%)	—
Type 1			1.00
• 1A	0 (0%)	0 (0%)	
• 1B	1 (5%)	1 (5%)	
Type 2			0.003
• 2A	2 (10%)	1 (5%)	
• 2B	6 (30%)	0 (0%)	
Type 3	1 (5%)	0 (0%)	1.00
Mixed	1 (5%)	0 (0%)	1.00
Total BPAR	11 (55%)	2 (10%)	0.006

The incidence of the first rejection episodes is given. The highest Banff score is depicted if sequential biopsies were performed.

TRANSPLANTATION

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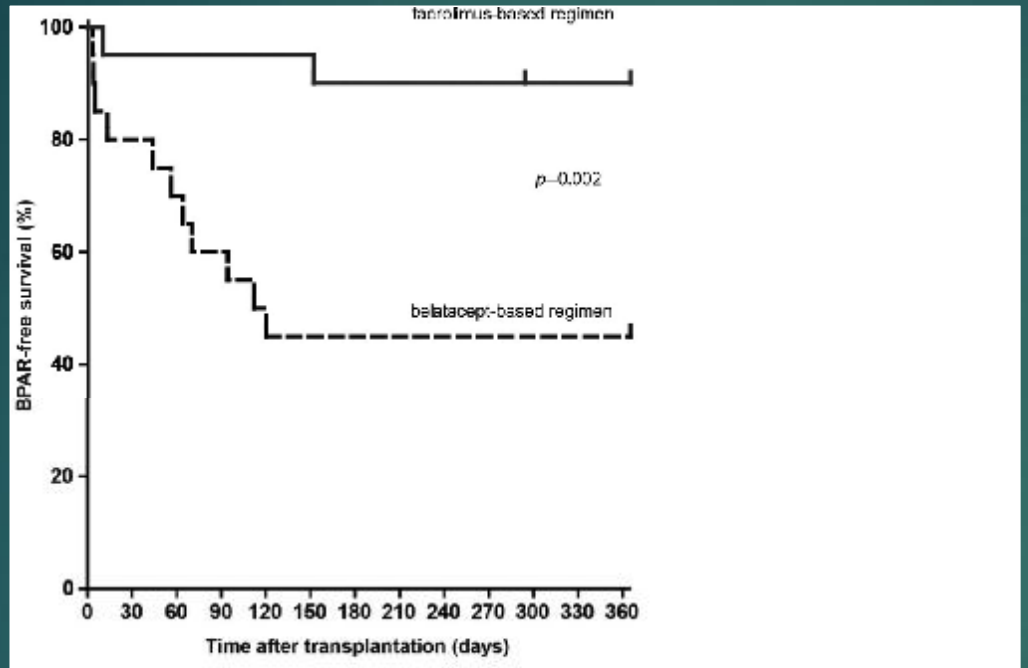
Incidence of rejection per the treatment group

FIGURE 2



Days after transplantation	0	3	4	5	10	13	44	56	64	70	94	112	120	152	294	365
Belatacept-based regimen (No. at risk)	20	20	19	18	18	17	16	15	14	13	12	11	10	10	10	9
Tacrolimus-based regimen (No. at risk)	20	20	20	20	19	19	19	19	19	19	19	19	19	19	18	17

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BPAR-free survival. The time to first BPAR is depicted for the belatacept (dotted line) and the tacrolimus (solid line) group. In the tacrolimus group 1 patient died 294 days after transplantation due to traumatic head injury.

Anti-CD28 Antibody and Belatacept Exert Differential Effects on Mechanisms of Renal Allograft Rejection

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ABSTRACT

Belatacept is a biologic that targets CD80/86 and prevents its interaction with CD28 and its alternative ligand, cytotoxic T lymphocyte antigen 4 (CTLA-4). Clinical experience in kidney transplantation has revealed a high incidence of rejection with belatacept, especially with intensive regimens, suggesting that blocking CTLA-4 is deleterious. We performed a head to head assessment of FR104 (n=5), a selective pegylated Fab' antibody fragment antagonist of CD28 that does not block the CTLA-4 pathway, and belatacept (n=5) in kidney allotransplantation in baboons. The biologics were supplemented with an initial 1-month treatment with low-dose tacrolimus. In cases of acute rejection, animals also received steroids. In the belatacept group, four of five recipients developed severe, steroid–resistant acute cellular rejection, whereas FR104-treated animals did not. Assessment of regulatory T cell–specific demethylated region methylation status in 1-month biopsy samples revealed a nonsignificant trend for higher regulatory T cell frequencies in FR104-treated animals. Transcriptional analysis did not reveal significant differences in Th17 cytokines but did reveal higher levels of IL-21, the main cytokine secreted by CD4 T follicular helper (Tfh) cells, in belatacept-treated animals. *In vitro*, FR104 controlled the proliferative response of human preexisting Tfh cells more efficiently than belatacept. In mice, selective CD28 blockade also controlled Tfh memory cell responses to KLH stimulation more efficiently than CD80/86 blockade. Our data reveal that selective CD28 blockade and belatacept exert different effects on mechanisms of renal allograft rejection, particularly at the level of Tfh cell stimulation.

J Am Soc Nephrol 27: 3577–3588, 2016. doi: 10.1681/ASN.2015070774