Kidney Transplantation in Sensitized Patients

Induction and Maintenance immunosuppression

Treatment of Rejection

Dr. Atefeh Amouzegar

Introduction

- For many highly allosensitized renal transplant candidates, an acceptable donor is never identified, and the patient remains on dialysis indefinitely.
- In an attempt to ameliorate this situation, several desensitization protocols have been developed that permit positive-crossmatch kidney transplantation.

Introduction

- Sensitized patients are a unique group of allograft recipients having memory B and T cells that elicit immunologic recall responses, which may lead to early and often severe AMR.
- Since donor-reactive cells rapidly expand by immunologic recall in a short time frame of days to weeks after engraftment, the use of induction agents with cell-depleting capabilities appears to be a reasonable and efficient way to reduce the size of, albeit not eliminate, donor-specific clones, and improve graft outcomes in sensitized renal- allograft recipients.

Introduction

- Immunologic rejection, antibody-mediated rejection (AMR) in particular, has higher incidence in sensitized patients, and graft loss secondary to acute or chronic rejection is also more frequent than in non-sensitized patients.
- Patient death, mostly due to infectious complications associated with over-immunosuppression, also has higher incidence in these recipients.
- Immunosuppressive regimens for sensitized patients, therefore, should be at a proper balance between graft protection from immune injury and the adverse consequences of over-immunosuppression.

Introduction

- It is expected that those patients with preexisting donor-specific anti-HLA antibodies (DSA) will also harbor donor-specific memory B and T cells.
- Upon antigen re-exposure, memory B cells elicit a secondary immune response involving:

I. activation

II. clonal expansion, and

III. differentiation into plasma cells or germinal center B cells,

IV. as well as functioning as antigen-presenting cells and directly facilitating T cell responses.

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ELSEVIER

Successful Kidney Transplantation After Desensitization Using Plasmapheresis, Low-Dose Intravenous Immunoglobulin, and Rituximab in Highly Sensitized Patients: A Single-Center Experience

M.-K. Jin, J.-H. Cho, O. Kwon, K.-D. Hong, J.-Y. Choi, S.-H. Yoon, S.-H. Park, Y.-L. Kim, and C.-D. Kim

Results. Seven patients with positive-crossmatch tests or high levels of panel-reactive antibody (PRA) were included. Their mean age was 51.4 ± 3.3 years. The average number of human leukocyte antigen mismatchs was 3.4 ± 0.5. The mean percent PRA was 41.7% ± 6.1%. Six patients were crossmatch-positive, and one patient was crossmatch-negative but had high PRA levels. The mean follow-up period was 33.2 ± 5.4 months after transplantation. The all patients showed no AR episodes for follow-up period, and the patient and graft survival rates were 100%. The mean serum creatinine concentration at last follow-up was 0.92 ± 0.11 mg/dL.

Conclusions. Our experiences suggest that the combination of PP and low-dose IVIG with or without rituximab may prove effective as a desensitization regimen for positive-crossmatch and/or highly sensitized living donor renal transplant recipients. Further investigations are needed to evaluate the long-term clinical efficacy and safety of this approach.

Transplantation Proceedings, 44, 200–203 (2012)

Kidney Transplantation After Desensitization in Patients With CD Crossmatch(-), Flowcytometric Crossmatch(+), and C1q Assay(-).

Methods : 11 patients with CDCXm (-), FCXm(+) and donor-specific antibody (DSA) detected in single antigen assay (SAA) using Luminex were selected. Before kidney transplantation, plasma exchange was done and rituximab (375mg/m2) was administered.

Results : Acute rejection developed in 6 (54.5%) patients; 2 (18.2%) biopsy-proven acute T-cell mediated rejection, 3 (27.2%) biopsy-proven acute antibody-mediated rejection (AMR), 1 (9.1%) presumed acute rejection.

Of 4 patients with MFI levels of DSA greater than 10000, only 1 patient was clinically diagnosed with acute rejection. Three cases of acute AMR showed MFI level of DSA between 1000-2000. All cases of acute rejection were recovered after anti-rejection treatment. The mean eGFR (MDRD) at 3 months after transplantation was 55.45 ± 11.56 mL/min/1.73m2 showing stable renal function.

Conclusion : Kidney transplant patients with CDCXm(-), FCXm (+), and C1q (-) showed high rate of acute rejection. However, rate of acute AMR was acceptable and acute rejection can be well treated with stable renal function.

Original article

Kidney transplantation of 32 patients from HLA-incompatible live donors: Efficacy and outcome after desensitization☆

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The complement-dependent cytotoxicity (CDC) cross-matching test was positive in 18 patients, flow cytometry was positive in 7 patients and donor-specific antibodies (DSA) were detected in 7.

The protocol used was rituximab, plasmapheresis/immunoadsorption(8 ± 3 sessions) , immunoglobulins, tacrolimus, mycophenolic acid derivatives and prednisone.

23 patients were transplanted (71.9%) and desensitization was ineffective in 9.

After follow-up of 43 ± 30 months, 3 (13%) delayed graft function, 4 (17.4%) acute rejection, 6 (26%) Five-year patient survival was 90%, with 86% allograft survival.

Five-year creatinine was 1.5 ± 0.4 and proteinuria was 0.5 ± 0.7.

Conclusions: Kidney transplantation from HLA-incompatible live donors after desensitization was possible in 71.9% of patients.

nefrologia. 2017

Kidney transplant in sensitized patients: A case series from a premier teaching hospital in Malaysia

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Results: Five patients were analyzed for this report. The first two patients developed antibody-mediated rejection (ABMR) immediately, post-transplant. Learning from initial experience, we have adopted our own desensitization protocol and subsequent to that, all three patients had IGF. Three out of five patients have borderline rejection on protocol biopsy but did not require pulse with methylprednisolone or intensification of immunosuppression. Three patients had negative preformed DSAs at 3-month post-transplant.

Conclusion: Desensitization protocols may help to overcome incompatibility barriers in live-donor renal transplantation. Based on our experiences we have adopted a protocol that comprises of intravenous rituximab, plasma exchange and intravenous thymoglobulin.

Transplantation Reports 3 (2018) 1–4

Pretransplant Desensitization with Costimulation Blockade and Proteasome Inhibitor Reduces DSA and Delays Antibody-Mediated Rejection in Highly Sensitized Nonhuman Primate Kidney Transplant Recipients

proteasome inhibitor (carfilzomib) and costimulation blockade agent (belatacept) was administered to six animals weekly for 1 month; four controls received no treatment.

Results: Compared with controls, carfilzomib- and belatacept-treated animals had significantly prolonged graft survival (P=0.02), and renal biopsy at 1 month showed significantly reduced antibody-mediated rejection scores (P=0.02). However, four of five animals with long-term graft survival showed gradual rebound of donor-specific antibodies and antibody- mediated rejection.

Conclusions: Desensitization using proteasome inhibition and costimulation blockade reduces bone marrow plasma cells, disorganizes germinal center responses, reduces donor-specific antibody levels, and prolongs allograft survival in highly sensitized nonhuman primates. Most animals experienced antibody- mediated rejection with humoral-response rebound, suggesting desensitization must be maintained after transplantation using ongoing suppression of the B cell response.

JASN 30: 2399–2411, 2019

Induction Immunosuppressive Regimen

- Currently available cell-depleting induction agents such as rabbit antithymocyte globulin (ATG, Thymoglobulin®), rituximab, a humanized anti-CD20 monoclonal antibody, alemtuzumab, and bortezomib, a proteasome inhibitor.

Antithymocyte Globulin

- ATG is a purified polyclonal immunoglobulin harvested from rabbits after immunizing them with a suspension of human thymic tissue which predominantly depletes T cells.
- ATG has numerous other immune modulatory actions, because this polyclonal antibody also contains antibodies against B cell antigens, plasma cell antigens, dendritic cells antigens, natural killer- cell antigens, adhesion molecules.
- The depleting ability of ATG on plasma cells seems to be limited to circulating plasmacytes.

Observational Study > Transplantation. 2014 Mar 27;97(6):612-7.
doi: 10.1097/TP.0000000000000031.

Antithymocyte globulin is associated with a lower incidence of de novo donor-specific antibodies in moderately sensitized renal transplant recipients

Marissa M Brokhof [1], Hans W Sollinger, David R Hager, Brenda L Muth, John D Pirsch, Luis A Fernandez, Janet M Bellingham, Joshua D Mezrich, David P Foley, Anthony M D'Alessandro, Jon S Odorico, Maha A Mohamed, Vijay Vidyasagar, Thomas M Ellis, Dixon B Kaufman, Arjang Djamali

Study population comprised 114 consecutive moderately sensitized (positive DSA and negative flow crossmatch) recipients who received deceased donor renal transplants between December 2009 and November 2011.

Results: Patients in the ATG group received a mean dose of 4.98 mg/kg ± 7.9 mg/kg, had a significantly higher PRA, and received more plasmapheresis and IVIG at the time of transplant.

The incidence of dnDSA (P=0.02, HR=0.33, 95% CI 0.09-1.24) and ABMR (P=0.002, HR=0.2, 95% CI 0.04-0.87) was significantly lower in the ATG group.

Conclusions: In moderately sensitized deceased donor renal transplant recipients, induction with ATG is associated with a reduction in the occurrence of dnDSA and ABMR when compared with basiliximab.

ATG vs IR2R antagonists

- ATG appears to reduce the risk of AMR in patients with preformed DSA, presumably by removing T cell help for alloreactive B cells and via B cell depletion by antibodies that directly bind B cells.
- Given ATG induction, compared with no induction, is consistently associated with lower incidence of acute rejection (AR).
- interleukin-2 receptor antagonist (IL2RA)(Basiliximab, Daclizumab) is the most popular induction agent in kidney recipients, it is reasonable to assess the efficacy of ATG by comparing ATG with IL2RA.

Table 4.1 Randomized controlled trials of ATG vs. IL2RA induction in kidney transplant patients

Authors	N	Immunologic risk status	ATG dose	Maintenance immunosuppression	Follow-up duration (months)	Outcomes (ATG vs. IL2RA)	
						Acute rejection (%)	Graft survival[a] (%)
Lebranchu 2002 [10]	100	Low; first graft, PRA <25%	1.0–1.5 mg/kg/d 6–10 d	Cyclosporine-based	12	8.0 vs. 8.0 p = n.s.	100 vs. 96 p = n.s.
Mourad 2004 [11]	105	Low; patients with a previous graft survival ≤1y excluded, PRA ≤20%	1.0 mg/kg Mean 5.4 Infusions	Cyclosporine-based	12	9.4 vs. 9.6 p = n.s.	98 vs. 98 p = n.s.
Brennan 2006 [6]	278	High; Regraft, PRA > 20%, African American,higher DGF risk	1.5 mg/kg/d Days 0–4	Cyclosporine-based	12	15.6 vs. 25.5 p = 0.02	97.2 vs. 92.0 p = n.s.
Abou-Ayache 2008 [12]	109	Low; first graft, PRA ≤20%	1.0–1.5 mg/kg 4–9 infusions	Cyclosporine-based	12	14.5 vs. 16.7 p = n.s.	96 vs. 97 p = n.s.
Noel 2009 [7]	227	High; Regraft, current PRA ≥30%, peak PRA ≥50%	1.25 mg/kg/d Days 0–7	Tacrolimus-based	12	15.0 vs. 27.2 p = 0.016	85.0 vs. 89.5 p = n.s.
Ciancio[c] 2014 [13]	85	Low; PRA ≤5% in 95–98% of patients	1 mg/kg/d Days 0–7	Tacrolimus-based	95	18.6 vs. 28.6 p = n.s.	88.4 vs. 88.1 p = n.s.
Pilch[d] 2014 [9]	200	Mixed; subgroup analyses of PRA >20% (high risk, n = 63) and PRA <20% (low risk, n = 137)	1.5 mg/kg/d, 5 doses	Tacrolimus-based	12	High risk; 6 vs. 14 p = 0.39 low risk; 6 vs. 9 p = 0.74	High risk; 6 vs. 7 p = n.s. low risk; 6 vs. 7 p = n.s.

Randomized Controlled Trial > J Am Soc Nephrol. 2009 Jun;20(6):1385-92.
doi: 10.1681/ASN.2008101037. Epub 2009 May 21.

Daclizumab versus antithymocyte globulin in high-immunological-risk renal transplant recipients

Christian Noël [1], Daniel Abramowicz, Dominique Durand, Georges Mourad, Philippe Lang, Michèle Kessler, Bernard Charpentier, Guy Touchard, François Berthoux, Pierre Merville, Nacera Ouali, Jean-Paul Squifflet, François Bayle, Karl Martin Wissing, Marc Hazzan

We randomly assigned 227 patients (multicenter study)
High risk: current panel reactive antibodies (PRA) >30%; peak PRA >50%; loss of a first kidney graft from rejection within 2 year of transplantation; or two or three previous grafts.
Maintenance immunosuppression comprised tacrolimus, mycophenolate mofetil, and steroids.
Compared with the daclizumab group, patients treated with Thymoglobulin had a lower incidence of both biopsy-proven acute rejection (15.0% versus 27.2%; P = 0.016) and steroid-resistant rejection (2.7% versus 14.9%; P = 0.002) at one year.
One-year graft and patient survival rates were similar between the two groups.
Overall graft survival was significantly higher in the rejection-free group (87.2% versus 75.0%; P = 0.037) Conclusion, among high-immunological-risk renal transplant recipients, Thymoglobulin is superior to daclizumab for the prevention of biopsy-proven acute rejection, but there is no significant benefit to one-year graft or patient survival.

Retuximab

- Rituximab is known to eliminate circulating CD20+ B cells and to reduce the numbers of these cells populating the spleen and lymph nodes.
- In secondary immune responses seen in sensitized patients, memory B cells expand rapidly and generate a burst of plasma cells, mostly donor-specific, that peak on day 7 in peripheral blood, followed by secondary memory B cells that peak on 14 to 21 days.
- This plasma cell burst coincides with a sharp increase in serum antibodies that reach a plateau on day 10, indicating that the vast majority of the plasma cells generated are short-lived.

Retuximab

- These short-lived plasma- blasts and memory B cells, mobilized from the protective niche of bone marrow, are subject to depletion by rituximab.
- Peri-transplant administration of rituximab thus reduces the size of donor-reactive B cell lineage by depleting these young plasma- blasts and memory B cells, although long-lived plasmacytes cannot be lysed by rituximab and the memory B cells are unlikely to be completely eliminated.
- In summary, rituximab appears to be a very valuable induction agent for sensitized renal transplant patients, because it has the capability to mitigate the secondary immune response seen in these patients.

Bortezomib (Velcade)

- Bortezomib is a selective inhibitor of the 26S proteasome, which is present in both the cytoplasm and the nucleus of eukaryotic cells.
- Bortezomib as an induction therapy in organ transplantation has not been adequately evaluated, although there are many reports of the use of this drug for the treatment of AMR and for desensitization.
- Since sensitized kidney transplant patients develop secondary immune response characterized by rapidly proliferating donor-specific plasmablasts within days after transplantation, bortezomib might be a valuable option for reducing the number of donor-specific clonal cells.

Alemtuzumab

- Alemtuzumab is a humanized anti-CD52 pan- lymphocytic (both B and T cells) monoclonal antibody that is approved for treatment of chronic lymphocytic leukemia.
- One of concerns regarding alemtuzumab is that, its benefits in reducing AR may decrease over time.
- Other long-term outcomes, including graft and patient survival and development of chronic allograft nephropathy, may also be worse in patients receiving alemtuzumab compared with ATG.
- Thus, alemtuzumab may not be an appropriate induction agent for sensitized patients.

Alemtuzumab Vs ATG

- In the high- risk cohort, there was no difference in AR between alemtuzumab and ATG groups at 12 months (10% vs. 13%, respectively).
- However, late acute rejection, defined as rejection that occurs between 12 and 36 months in patients who did not have AR in the first 12 months, was more common with alemtuzumab (10% vs. 2%), although this difference did not reach statistical significance.
- In the low-risk group, the AR rate was lower in patients who received alemtuzumab, but again, late rejection was more common in the alemtuzumab (8% vs. 3%, respectively).
- In post hoc analyses, C4d-positive AR was more prevalent in the alemtuzumab group.

Maintenance Immunosuppression

Q: What is the most appropriate maintenance regimen for sensitized kidney transplant patients?

Maintenance Immunosuppression

- A triple-drug regimen consisting of tacrolimus, mycophenolate, and prednisolone appears to be most appropriate in sensitized, high-immunologic-risk transplant patients.
- Alternative regimens that use cyclosporine in place of tacrolimus and sirolimus in place of mycophenolate have shown **inferior** outcomes such as **higher incidence of AR and/or graft loss**.
- Steroid withdrawal or avoidance and calcineurin-inhibitor withdrawal or avoidance **should** also **not** be considered in sensitized patients since these regimens have shown to increase AR.

- The optimal trough level of tacrolimus in sensitized patients has not been established.
- It is obvious that the higher the exposure to tacrolimus, the lower the risk of dn DSA and rejection, but higher trough level at the same time increases the risk of infection or nephrotoxicity.
- The optimal dose should be determined in the context of overall immunosuppression.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

Henrik Ekberg, M.D., Ph.D., Helio Tedesco-Silva, M.D., Alper Demirbas, M.D., Štefan Vítko, M.D., Björn Nashan, M.D., Ph.D., Alp Gürkan, M.D., F.A.C.S., Raimund Margreiter, M.D., Christian Hugo, M.D., Josep M. Grinyó, M.D., Ulrich Frei, M.D., Yves Vanrenterghem, M.D., Ph.D., Pierre Daloze, M.D., and Philip F. Halloran, M.D., Ph.D., for the ELITE–Symphony Study*

Efficacy Limiting Toxicity Elimination (ELITE)-Symphony trial

Conclusions A regimen of daclizumab (as induction), mycophenolate mofetil, and corticosteroids in combination with low-dose tacrolimus may be advantageous for renal function, allograft survival, and acute rejection rates, as compared with regimens containing daclizumab induction plus either low-dose cyclosporine or low-dose sirolimus or with standard-dose cyclosporine without induction.

December 20, 2007

JASN

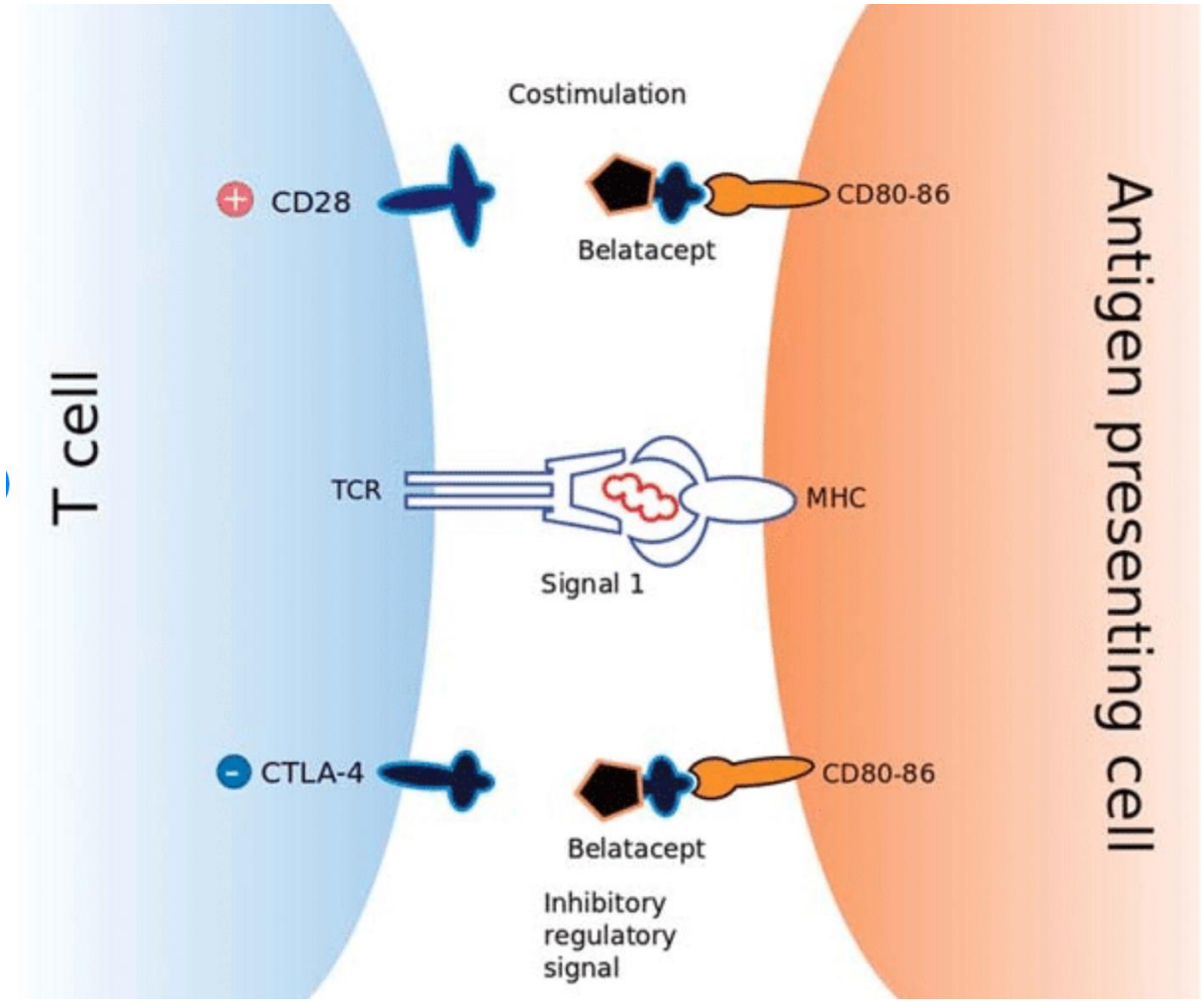
J Am Soc Nephrol. 2011 Sep; 22(9): 1758–1768.
doi: 10.1681/ASN.2011010006

PMCID: PMC3171946
PMID: 21807891

Randomized Trial of Immunosuppressive Regimens in Renal Transplantation

We conducted a randomized trial involving 150 kidney transplant recipients to compare tacrolimus/sirolimus, tacrolimus/mycophenolate mofetil (MMF), and cyclosporine/sirolimus. All patients received daclizumab induction and maintenance corticosteroids. Median follow-up was 8 years post-transplant. Acute rejection (AR) occurred significantly less often among those treated with tacrolimus/MMF (12%) than among those treated with tacrolimus/sirolimus (30%) or cyclosporine/sirolimus (28%). Taken together, these results suggest that maintenance therapy with tacrolimus/MMF is more favorable than either tacrolimus/sirolimus or cyclosporine/sirolimus.

Two recent RCTs comparing belatacept, an inhibitor of the CD28-CD80/86 costimulatory pathway, with a tacrolimus-based regimen showed increased AR in the belatacept arm.



since memory T cells lack CD28 expression, belatacept appears to have limited efficacy in sensitized patients

Official Journal of The Transplantation Society & International Liver Transplantation Society

Transplantation

ORIGINAL CLINICAL

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

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

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.

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.

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Free Access

Immunosuppression with Belatacept-Based, Corticosteroid-Avoiding Regimens in *De Novo* Kidney Transplant Recipients

This 1-year, randomized, controlled, open-label, exploratory study assessed two belatacept-based regimens compared to a tacrolimus (TAC)-based, steroid-avoiding regimen. Recipients of living and deceased donor renal allografts were randomized 1:1:1 to receive belatacept-mycophenolate mofetil (MMF), belatacept-sirolimus (SRL), or TAC-MMF.

All patients received induction with 4 doses of Thymoglobulin (6 mg/kg maximum) and an associated short course of corticosteroids.

Eighty-nine patients were randomized and transplanted.

In conclusion, primary immunosuppression with belatacept may enable the simultaneous avoidance of both CNIs and corticosteroids in recipients of living and deceased standard criteria donor kidneys, with acceptable rates of acute rejection and improved renal function relative to a TAC-based regimen.

› Am J Transplant. 2018 Apr;18(4):907-915. doi: 10.1111/ajt.14504. Epub 2017 Oct 24.

Lower tacrolimus exposure and time in therapeutic range increase the risk of de novo donor-specific antibodies in the first year of kidney transplantation

Scott Davis [1], Jane Gralla [2], Patrick Klem [3], Suhong Tong [2], Gina Wedermyer [4], Brian Freed [4], Alexander Wiseman [1], James E Cooper [1]

Patients at higher immunologic risk (calculated PRA > 20%, repeat transplant, African-American race, cold ischemiatime>24h) received rATG induction and the majority of the remainder received no induction.
The authors' target therapeutic-range was 6–9 ng/mL for months 0–3, and 5–8 ng/mL for months 4–12.
A mean trough <8 ng/mL and time in the therapeutic range of <60% was associated with dnDSA
When patients were grouped according to mean trough levels during the first year, those groups with a mean trough of 6–7.9 ng/mL and ≥ 8 ng/mL developed similar incidences of dnDSA, while which were significantly lower than those in the groups with trough <6 ng/mL.
These results indicate that higher trough levels are associated with lower incidence of dnDSA, and the minimal trough level to be maintained for the prevention of dnDSA is 6 ng/mL.

- The dose of mycophenolate and corticosteroid should be optimized and preferably individualized in the context of overall immunosuppression status, and patient's immunologic risk and general health.
- Mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium(EC-MPS)have equivalent efficacy.
- It is necessary to reduce the MMF dose in tacrolimus-treated patients, because tacrolimus, compared with cyclosporine, increases MMF exposure by 20–30%.

Methylprednisolone

- Intravenous methylprednisolone should be a part of initial immunosuppression since this has lymphocyte-depletive action and may help to diminish donor-reactive cells in the early post- transplant period.
- The initial dose and tapering protocol of prednisolone varies among institutions.
- In the absence of AR, tapering to 5 mg/ day by 1–3 months is a common practice.
- Steroid withdrawal should not be attempted in sensitized patients since this increases the risk of AR.

Treatment of Rejection in Desensitized KT Patients

- Many cases of ABMR in renal allografts associated with de novo DSAs can present as mixed ABMR and TCMR.
- When antibody-mediated rejection is diagnosed, pathologically T cell-mediated rejection is accompanied or antibody mediated rejection is processed causing acute cellular rejection.
- It is well known that CD4+ helper T cells can activate B cells.
- The purpose of the antibody-mediated rejection treatment is to:

a. Remove the donor-specific antibody
b. Suppress the donor-specific antibody production in B cell or plasma cells,
c. Suppress the body response to suppress inflammation in the implantation body.

What kinds of medications can be used to treat ABMR?

- Plasmapheresis
- IV Ig
- Rituximab
- Corticosteroid
- Bortezomib
- Eculizumab
- C1 esterase inhibitor
- Ig G endopeptidase
- Tocilizumab

Is the combination therapy of plasmapheresis and IVIG the best way of treatment for antibody-mediated rejection?

- The most commonly used treatment methods for acute antibody-mediated rejection are plasmapheresis and IVIG
- Therapeutic apheresis selectively removes cells or other targeted abnormal substances from circulation.
- By removing the HLA- specific antibody, the plasmapheresis removes the circulatory donor-specific antibodies.
- During acute antibody-mediated rejection, donor-specific antibody generation is increased because of B cell clonal expansion.
- IVIG has been used to suppress alloantibody and modulate immune responses.

- For a plasmapheresis, 1–1.5 plasma volume exchanged, 60–70% of plasma is removed.
- The plasma volume is calculated as:

$$\text{plasma volume} = \text{total blood volume} \times (1 - \text{hematocrit})$$

- The total volume of replacement fluid is usually 1 plasma volume (40 mL/kg) or 1.5 plasma volumes (60 mL/kg).
- Plasmapheresis is performed four to six times, and sometimes performed three or seven times.
- If necessary, additional plasmapheresis may be performed.
- Therapeutic plasma exchange and IVIG eliminate rate 60–75% of HLA anti- bodies

Two general treatment protocols have been developed utilizing IVIG

- The first is the use of high- dose IVIG (2 mg/g) alone and
- The second is to combine lower-dose IVIG with plasmapheresis

But 100 mg/kg/day of IVIG is the most common dose.

- In general, high doses of IVIG are relatively safe.
- However, serious side effects have been reported including acute renal dysfunction likely related to high osmotic load, thrombotic events with rapid infusions, and aseptic meningitis

> Am J Transplant. 2009 May;9(5):1099-107. doi: 10.1111/j.1600-6143.2009.02591.x.

Comparison of combination Plasmapheresis/IVIg/anti-CD20 versus high-dose IVIg in the treatment of antibody-mediated rejection

C Lefaucheur [1], D Nochy, J Andrade, J Verine, C Gautreau, D Charron, G S Hill, D Glotz, C Suberbielle-Boissel

Group A (12 patients) was treated with high-dose IVIg between January 2000 and December 2003; group B (12 patients) was treated by Plasmapheresis/IVIg/anti-CD20 between January 2004 and December 2005.

Graft survival at 36 months was 91.7% in group B versus 50% in group A ($p = 0.02$).

Donor-specific human leukocyte antigens (DSA) levels detected by Luminex single antigen (Luminex SA) and ELISA, 3 months post-rejection are significantly lower in group B than in group A

Conclusions:

high dose IVIg alone is inferior to Plasmapheresis/IVIg/anti-CD20 as therapy for AMR

Rituximab

- Rituximab causes a reduction in B cells in the peripheral blood within 1–3 days of administration, and complete B cell depletion in the majority of patients within 1–6 week

  The effect continues beyond the expected 3–12 months

- Single-dose rituximab in kidney transplant recipients evokes a long-term elimination of B cells in peripheral blood as well as within the kidney transplanted.

Rituximab

- As B lymphocytes also function as antigen presenting cells, rituximab is also likely to indirectly suppress T lymphocyte activity
- In many studies, doses of rituximab 375 mg/m2 for antibody rejection therapy was commonly used.
- But low dose of rituximab (200mg) is the sufficient dose in kidney transplantation.

Rituximab

- In the chronic antibody-mediated rejection, only retrospective study of rituximab was investigated, and most studies did not favor both graft and graft function.
- Currently, it is considered to use rituximab after administration of plasmapheresis and IVIG, because retrospective study showed a positive effect in rituximab although random controlled trial did not show a good result.

Corticosteroid

- Corticosteroids inhibit T cells, so it can be considered primarily in acute T cell-mediated injection.
- Corticosteroids inhibit cytokine transcription and production, with multiple downstream effects on lymphocyte function, decreasing inflammation caused by donor-specific antibodies in graft.
- Thus, in the treatment of acute antibody-mediated rejection, the use of corticosteroids as well as IVIG and plasmapheresis is possible.
- In acute rejection, methylprednisolone is used at a dose of 0.5–1 g per day for 3–5 days.
- After the steroid pulse, reduce the corticosteroids and keep dosage higher than before acute rejection

Bortezomib

Bortezomib in Late Antibody-Mediated Rejection (BORTEJECT trial)

METHODS

Randomized controlled trial

44 renal allograft recipients
Key inclusion criteria:
DSA+ and ABMR morphology
≥6 months post-Tx
eGFR ≥20mL/min/1.73 m²

- Bortezomib (2 cycles) 21 patients
- Placebo (2 cycles) 23 patients

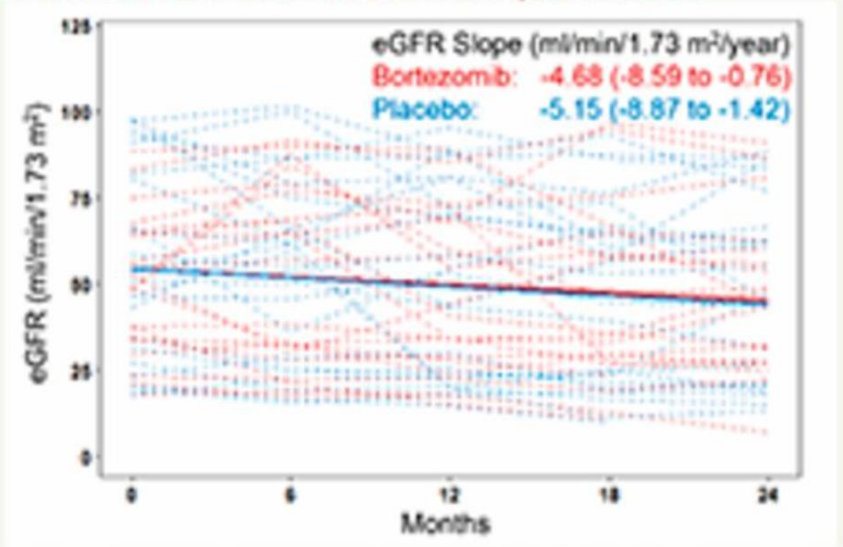
24-month follow-up

Primary endpoint
eGFR slope

Secondary endpoints
mGFR, DSA, 24-mo Bx, survival

OUTCOMES

► Bortezomib did not affect the slope of eGFR



► No difference in secondary endpoints ► More AEs

CONCLUSION

Bortezomib may not halt the progression of late ABMR

doi: 10.1681/ASN.

JASN

J Am Soc Nephrol 29: 591–605, 2018.

Eculizumab

- Eculizumab is a monoclonal antibody that targets the complement component C5 and has been approved for the treatment of two complement mediated diseases, paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.
- Data on desensitization and ABMR therapy by eculizumab are inadequate.
- A more diverse and randomized controlled study is needed.

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CLINICAL AND TRANSLATIONAL RESEARCH

Report of the Inefficacy of Eculizumab in Two Cases of Severe Antibody-Mediated Rejection of Renal Grafts

Methods and results: We present two cases of AMR resistant to eculizumab after renal transplantation. One patient received the anti-C5 antibody curatively, and the other patient developed AMR while being treated with eculizumab after a relapse of atypical hemolytic uremic syndrome. The peculiarity of these two cases was the absence of C4d deposition in peritubular capillaries as well as the absence of C1q-binding donor-specific anti-human leukocyte antigen alloantibody, as determined retrospectively, suggesting that a complement-independent mechanism underlies the pathogenesis of these AMR.

Conclusion: The use of eculizumab in C4d-negative or C1q-negative AMR does not seem effective.

Transplantation 2014 Nov 27

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CLINICAL AND TRANSLATIONAL RESEARCH

Eculizumab and Splenectomy as Salvage Therapy for Severe Antibody-Mediated Rejection After HLA–Incompatible Kidney Transplantation

Results: The study population was 267 consecutive patients with donor-specific antibody undergoing desensitization. In the first 3 weeks after transplantation, 24 patients developed sudden onset oliguria and rapidly rising serum creatinine with marked rebound of donor-specific antibody, and a biopsy that showed features of AMR.

No patients treated with splenectomy plus eculizumab experienced graft loss.

There was more chronic glomerulopathy in the splenectomy-alone and eculizumab-alone groups at 1 year, whereas splenectomy plus eculizumab patients had almost no transplant glomerulopathy.

Conclusion: These data suggest that for patients manifesting early severe AMR, splenectomy plus eculizumab may provide an effective intervention for rescuing and preserving allograft function.

Transplantation 2014 Oct 27

Eculizumab

- Two pre- liminary RCT studies are underway;
- Randomized, open-label, multicenter phase 2 study to determine the safety and efficacy of eculizumab in the prevention of ABMR
- Efficacy and safety of eculizumab for the treatment of antibody-mediated rejection following renal transplantation.
- In both studies, eculizumab showed no significant differences in the occurrence of ABMR and the therapeutic effect (transplant glomerulopathy progression, graft loss, and patient death) compared with the control group using standard therapy.
- In the future, eculizumab is more likely to be used as potential co-therapy to reduce DSA levels than eculizumab alone.

Tocilizumab

- Tocilizumab is the first monoclonal antibody to IL-6R.
- Tocilizumab reduced peripheral pre- and post-switch B cells, IgG+ and IgA+ B cells, IgG and IgA, and significantly reduced B cell hypersensitivity in rheumatic arthritis patients.
- Interleukin-6 was initially identified as B cell stimulatory factor-2.
- Interleukin-6 has also been recognized as an important mediatory of allograft rejection.

ORIGINAL CLINICAL SCIENCE—GENERAL

A Phase I/II Trial of the Interleukin-6 Receptor–Specific Humanized Monoclonal (Tocilizumab) + Intravenous Immunoglobulin in Difficult to Desensitize Patients

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Methods: From July 2012 to November 2013, 10 patients unresponsive to DES with IVIg + Rituximab were treated with IVIg + TCZ. Patients received IVIg on days 0 and 30 at 2 g/kg and TCZ 8 mg/kg on day 15 then monthly for 6 months. If transplanted, patients received IVIg once and TCZ monthly for 6 months.

Results: Five of 10 patients were transplanted. Mean time to transplant from first DES was 25 +/- 10.5 months but after TCZ was 8.1 +/- 5.4 months. Six-month protocol biopsies showed no antibody-mediated rejection. Donor-specific antibody strength and number were reduced by TCZ treatment. Renal function at 12 months was 60 +/- 25 mL/min.

Conclusions: Tocilizumab and IVIg appear to be safe. From this pilot trial, we are cautiously optimistic that targeting the IL-6/IL-6R pathway could offer a novel alternative for difficult to desensitize patients. Larger controlled studies are essential to prove efficacy

Transplantation. 2015 Nov

› Am J Transplant. 2017 Sep;17(9):2381-2389. doi: 10.1111/ajt.14228. Epub 2017 Mar 10.

Assessment of Tocilizumab (Anti-Interleukin-6 Receptor Monoclonal) as a Potential Treatment for Chronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients

36 renal transplant patients with cAMR plus DSAs and TG who failed standard of care treatment with IVIg plus rituximab with or without plasma exchange were identified. Patients were offered rescue therapy with the anti-IL-6 receptor monoclonal tocilizumab with monthly infusions and monitored for DSAs and long-term outcomes. Tocilizumab-treated patients demonstrated graft survival and patient survival rates of 80% and 91% at 6 years, respectively.

Tocilizumab provides good long-term outcomes for patients with cAMR and TG, especially compared with historical published treatments. Inhibition of the IL-6-IL-6 receptor pathway may represent a novel approach to stabilize allograft function and extend patient lives.

STUDY PROTOCOL Open Access

Clazakizumab in late antibody-mediated rejection: study protocol of a randomized controlled pilot trial

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Trial registration: NCT03444103

Methods: This investigator-driven RCT was designed to assess the safety and efficacy of clazakizumab, a genetically engineered humanized monoclonal antibody directed against IL-6. The study will include 20 DSA-positive kidney allograft recipients diagnosed with ABMR ≥ 365 days after transplantation. Participants will be recruited at two study sites in Austria and Germany.

Discussion: Currently, there is no treatment proven to be effective in halting the progression of late ABMR.

Based on the hypothesis that antagonizing the effects of IL-6 improves the outcome of DSA-positive late ABMR by counteracting DSA-triggered inflammation and B cell/plasma cell-driven alloimmunity, we suggest that our trial has the potential to provide proof of concept of a novel treatment of this type of rejection.

Eskandary et al. Trials (2019) 20:37