The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023
Homa Hotel, Tehran

Novel Therapies In Chronic antibody mediated rejection

Farahnaz Dadras,MD.

Iran University Of Medical Sciences

TEHRAN 2023

✓**Chronic antibody-mediated rejection** of kidney transplantation is a major cause of **late-stage graft loss**.

✓Sellares et al. showed that **50% of cases with graft loss** were chronic active AMR.

International Journal of Urology (2023) 30, 624--633

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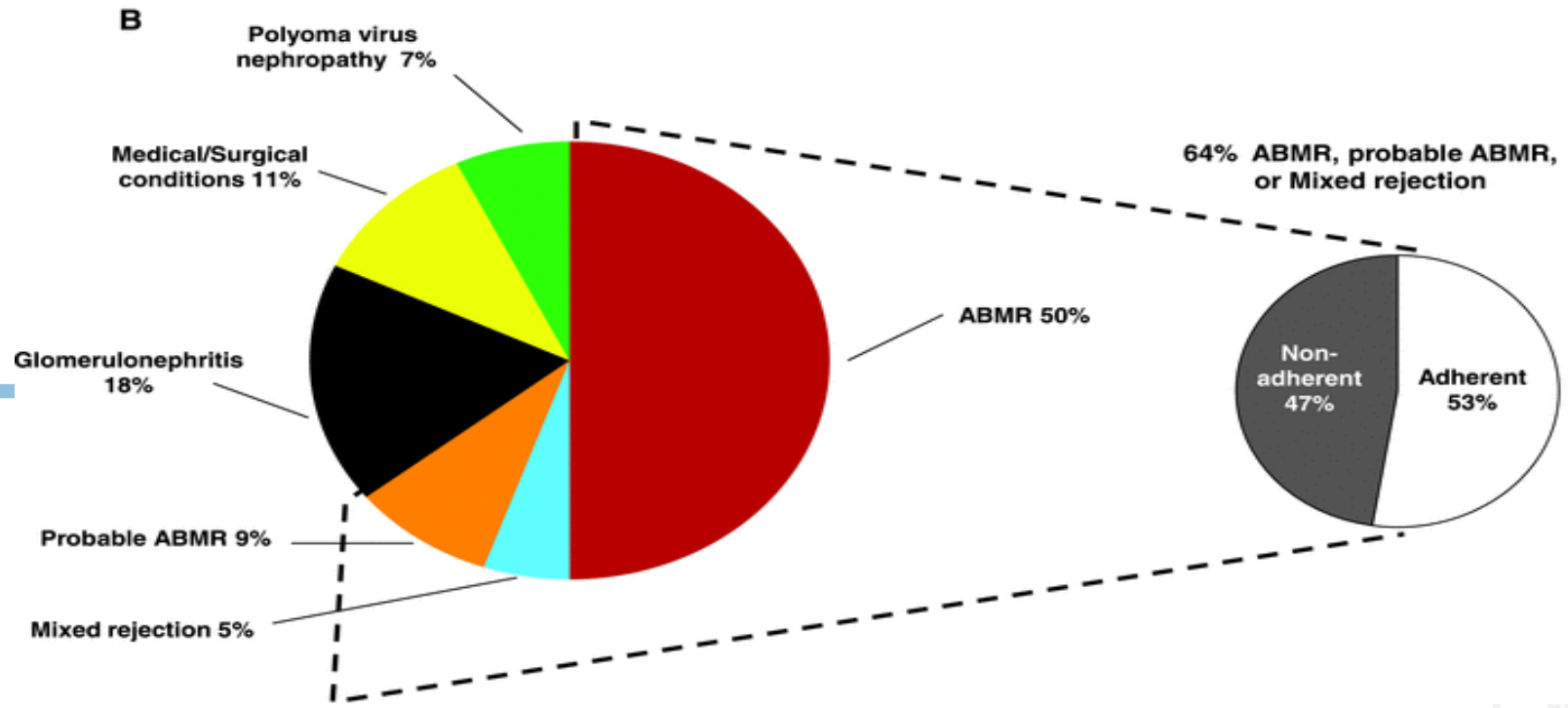
Understanding the Causes of Kidney Transplant Failure: The Dominant Role of Antibody-Mediated Rejection and Nonadherence



American J Transplantation, Volume: 12, Issue: 2, Pages: 388-399, First published: 14 November 2011, DOI: (10.1111/j.1600-6143.2011.03840.x)

- ✓Donor-specific antibodies are the main cause of antibody-mediated rejection in particular, de novo donor-specific antibodies are a risk factor for chronic active AMR.

- ✓The **level** of **de novo donor-specific antibodies** tends to increase with time throughout long-term graft survival.

International Journal of Urology (2023) 30, 624--633

Rates and Determinants of Progression to Graft Failure in Kidney Allograft Recipients With *De Novo* Donor-Specific Antibody

C. Wiebe[1,†], I. W. Gibson[2,†], T. D. Blydt-Hansen[3], D. Pochinco[4], P. E. Birk[5], J. Ho[6], M. Karpinski[7], A. Goldberg[5,7], L. Storsley[7], D. N. Rush[7] and P. W. Nickerson[8,*]

were multivariate predictors of IFTA. Independent risk factors for post-*dn*DSA graft survival available prior to, or at the time of, *dn*DSA detection were delayed graft function, nonadherence, *dn*DSA mean fluorescence intensity sum score, tubulitis, and cg. Ultimately,

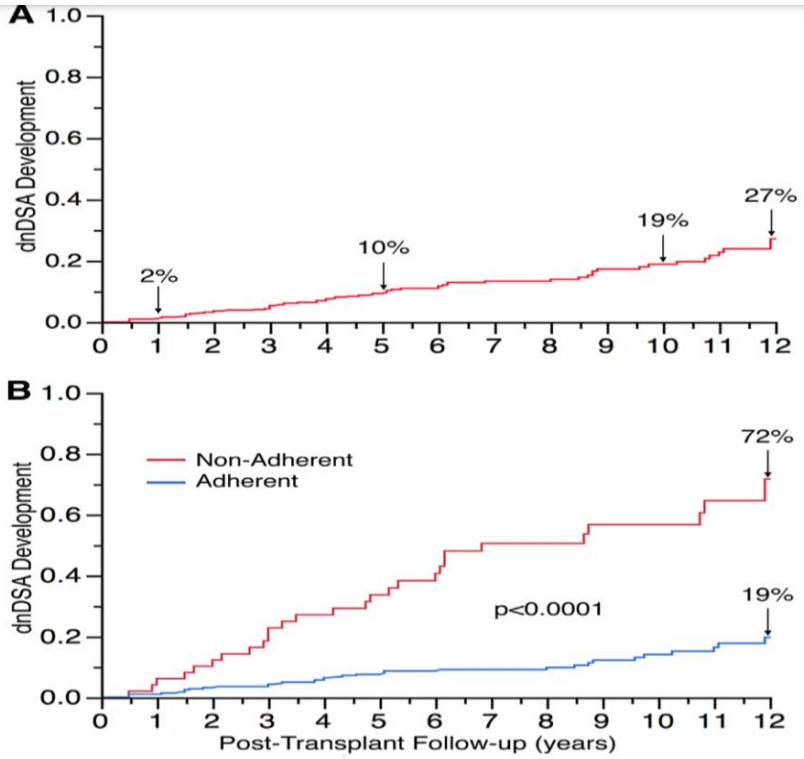


Figure 1: *dn*DSA free survival. Kaplan–Meier plot of *dn*DSA-free survival over time posttransplant (A), split by adherence (B). *dn*DSA, *de novo* donor-specific antibody.

- ✓560 adult and pediatric consecutive renal transplants between January 1999 and July 2012 . 508 recipients (adult n = 459, pediatric n = 49) included for analysis.The incidence of dnDSA is reported to be approximately 20% at 10 years.
- ✓American Journal of Transplantation 2015; 15: 2921–2930

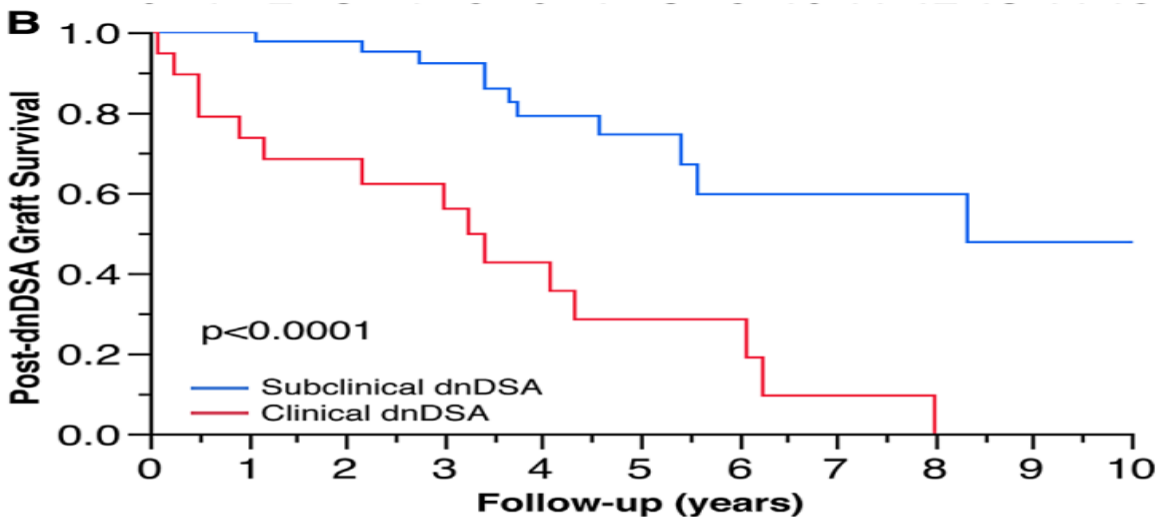


Figure 2: Death-censored graft survival. (A) Kaplan–Meier plot of renal allograft survival by clinical phenotype. (B) Kaplan–Meier survival plot of post-*dn*DSA graft survival by clinical phenotype at the time of *dn*DSA detection. *dn*DSA, *de novo* donor-specific antibody.

Antibody-mediated rejection: prevention, monitoring and treatment dilemmas

Sonia Rodriguez-Ramirez[a,b], Ayman Al Jurdi[c,d], Ana Konvalinka[a,b,e,f,g] and Leonardo V. Riella[c,d]

✓Risk Factors for dnDSA formation:

- ✓Non-adherence
- ✓Reduced immunosuppression
- ✓Higher eplet mismatch
- ✓Younger age
- ✓Preceding TCMR
- ✓

Current Opinion,Volume 27 Number 5 October 2022

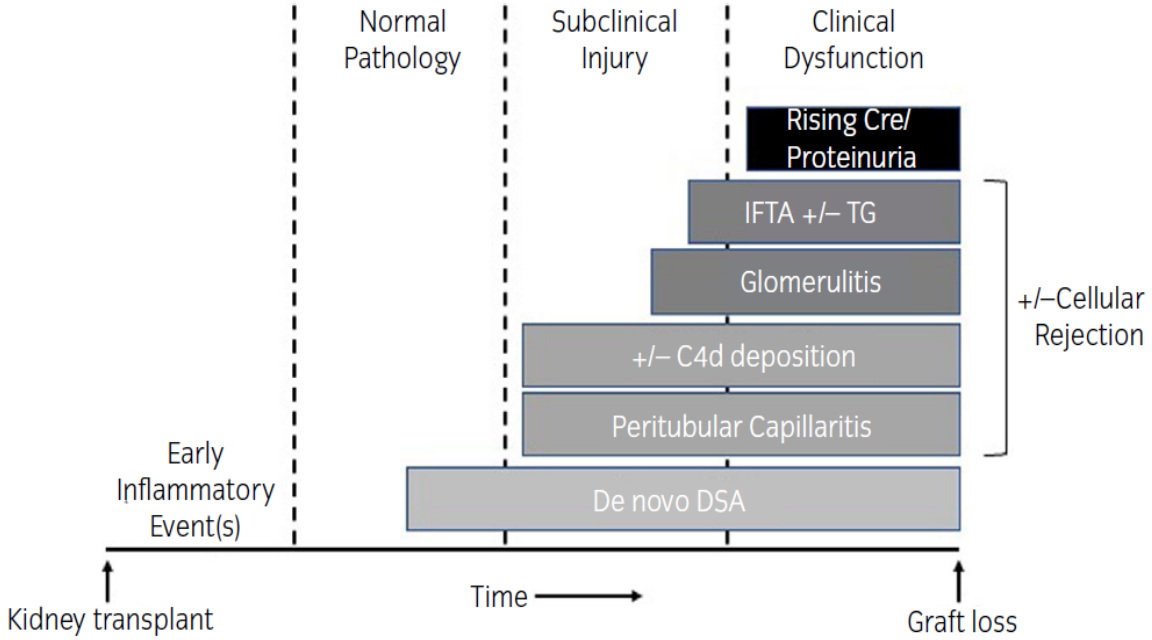
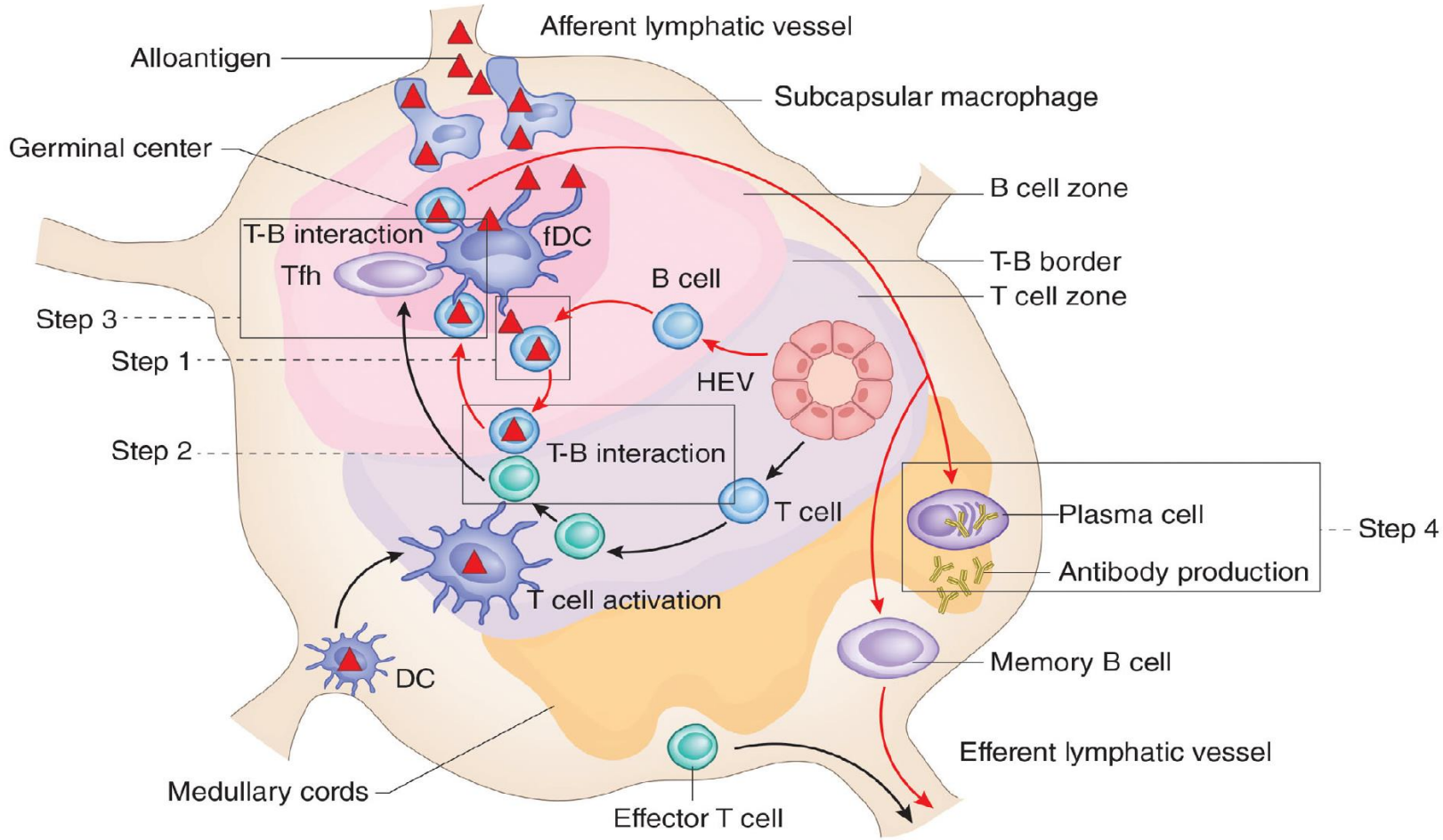


FIGURE 1 A proposed natural history for graft loss due to de novo donor-specific antibodies. Wiebe et al.[8] proposed a model for a continuum of antibody-mediated damage based on the primate studies.[66] The production of dnDSA after transplantation is preceded by early inflammatory events, such as cellular rejection and graft infection. Those events trigger an upregulation of HLA expression on vascular endothelial cells, thus, enhancing alloresponses of B cells and leading to subsequent induction of dnDSA-producing plasma cells. In the early phase of dnDSA development, the pathology may appear normal until dnDSA binds to the vascular endothelium, inducing vascular endothelial injury through activation of complement or recruitment of innate immunity. Microvascular inflammation (i.e., glomerulitis, peritubular capillaritis, and vasculitis) eventually leads to progressive tissue fibrosis (i.e., transplant glomerulopathy and IFTA), resulting in graft dysfunction. dnDSA, de novo donor-specific antibodies; IFTA, interstitial fibrosis and tubular atrophy; TG, transplant glomerulopathy (Adapted from Wiebe et al.[8]).

B cell maturation and de novo donor-specific antibody production via follicular dendritic cells and T follicular helper cells in lymph nodes.



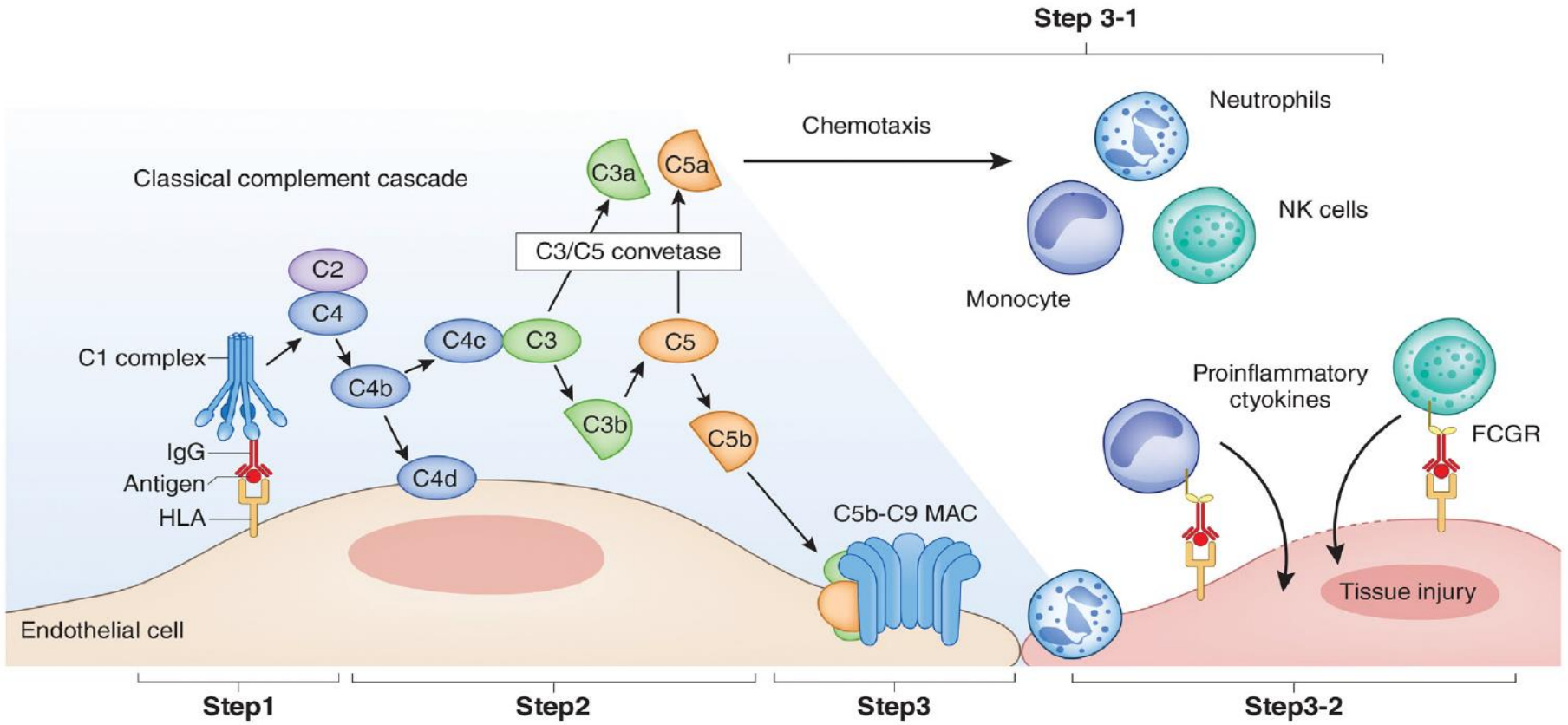


FIGURE 3 Possible mechanism of chronic antibody-mediated injury via donor-specific antibodies and complement activation. The C1 complex is activated by DSA (shown as IgG), resulting in the generation of C3a and C5a. C3a and C5a act as anaphylatoxins to promote the migration of inflammatory cells (natural killer [NK] cells, monocytes, and neutrophils). NK cells and monocytes, which bind to IgG via Fc gamma receptors, produce proinflammatory cytokines, and increase endothelial damage. Activation of the classical complement cascade leads to the formation of the membrane attack complex (MAC) C5b–C9, which destroys the membrane of vascular endothelial cells. C4d, a degradation product of C4, remains bound to vascular endothelial cells at the site of complement activation and can be detected using immunohistochemistry (Adapted with modification from Loupy et al.[25] and Stegall et al.[23]). FCGR, Fc gamma receptor; HLA, human leukocyte antigen; MAC, membrane attack complex; NK, natural killer.

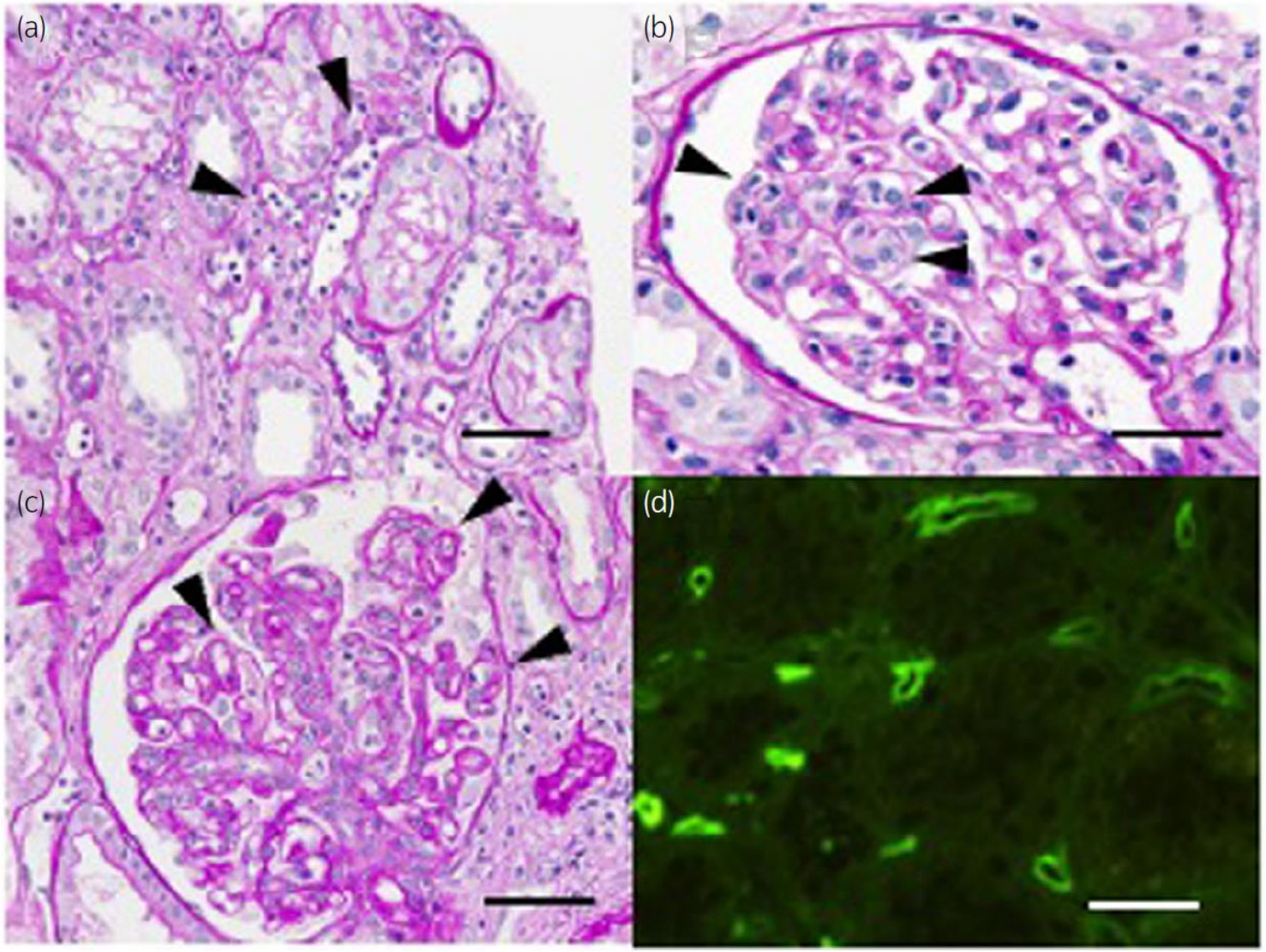
TABLE 1 Antibody-mediated change in Banff classification 2019.

	Active AMR: All 3 criteria must be met for diagnosis	Chronic active AMR: All 3 criteria must be met for diagnosis	Chronic inactive AMR	C4d staining without evidence of rejection: All 4 features must be present for diagnosis
Criteria 1: Histological findings	Including 1 or more of the following: • g ≥ 1 and/or ptc ≥ 1 • v ≥ 1 • acute thrombotic microangiopathy • acute tubular injury		≥ 1 and/or ptcml1	• Criterion 1 for AMR not met • No acute or chronic TCMR or BLC
Criteria 2: Antibody interaction with the vascular endothelium			ence of criterion 2	• ≥ C4d2 (IF) or ≥ C4d1 (IHC) • No molecular evidence of AMR
Criteria 3: Serological evidence of circulating DSA			r diagnosis of AMR and/or prior evidence of DSA	No mention

Including 1 or more of the following:
. cg≥1
ptcml 1
Arterial intimal fibrosis

Including 1 or more of the following:
≥C4d2(IF) or ≥C4d1 (IHC)
g+ ptc ≥2 , g must be ≥1
Increased expression of gene transcripts/classifiers associated with AMR

DSA positive
Criteria 2 may substitute for DSA


(a)
(b)
(c)
(d)

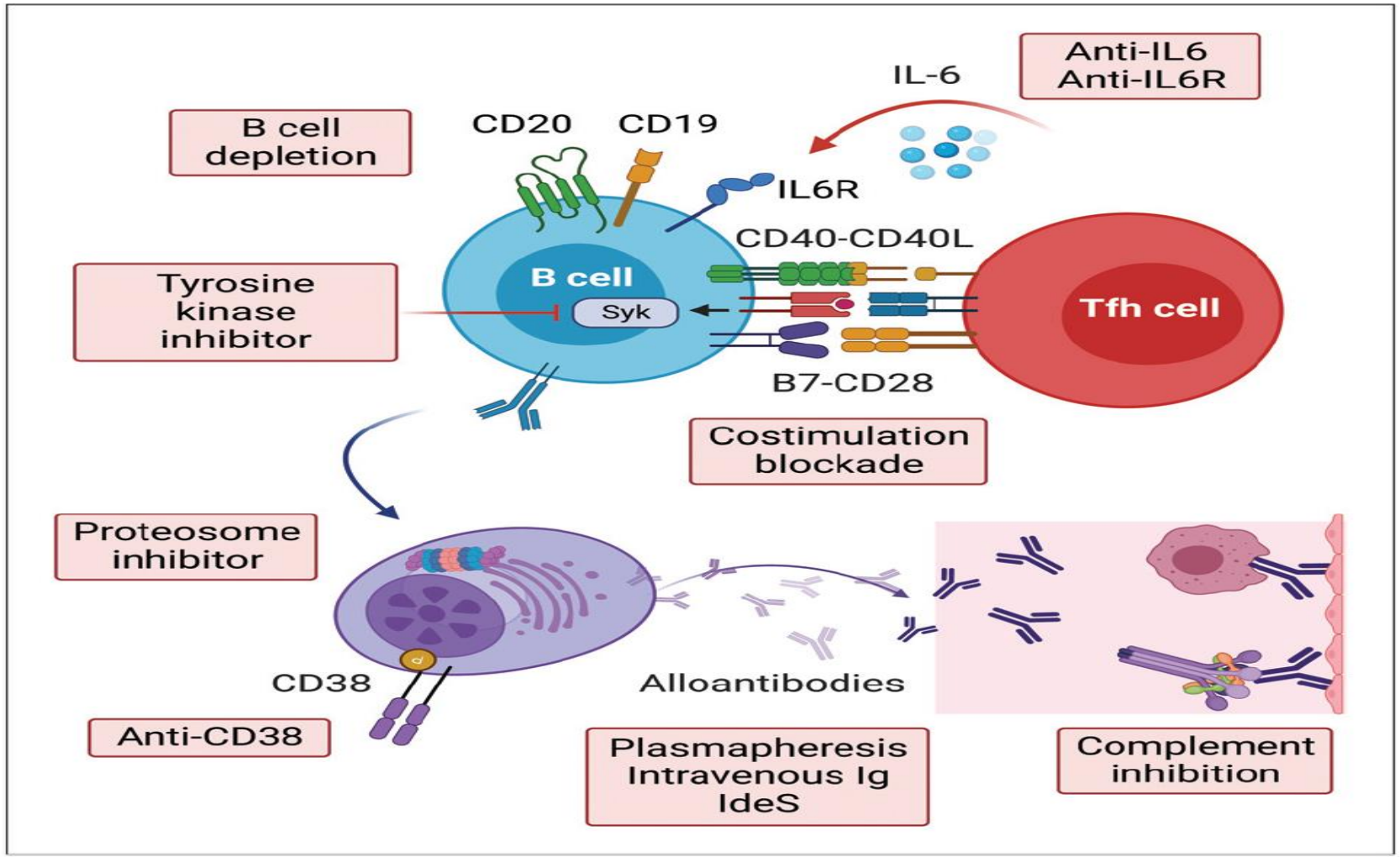


FIGURE 2. Currently used and investigational drugs for kidney transplant recipients with antibody-mediated rejection.

TREATMENT OF CHRONIC AMR

✓The process from **de novo DSA production** to **irreversible tissue**
✓injury is **a sequential change**, leading to **sub-clinical injury** and
✓then to **clinical dysfunction**.

✓**Therapeutic intervention during sub-clinical injury improves graft outcome**.

✓Surveillance protocols with **donor-derived cell-free DNA** and **gene profile testing** have been established, can lead to the **early detection of AMR**.

Treatment Of Chronic ABMR

- ✓According to the consensus treatment recommendations based on the
- ✓available evidence and expert opinion, treatment of active AMR due to
- ✓de novo DSA should :
- ✓**Optimize baseline immunosuppression**
- ✓**Manage nonadherence**
- ✓ **Adjunctive therapies,** such as PEX and IVIG.
- ✓The use of **PEX + IVIG has not been shown to improve** the outcomes

  in patients with **chronic active AMR**.

✓The therapeutic concept is to

✓**Remove circulating DSA**

✓**Block their effects**

✓**Reduce their production, or both.**

Investigational drugs for the treatment of kidney transplant rejection

Lukas K van Vugt, Maaike R Schagen, Annelies de Weerd, Marlies EJ Reinders, Brenda CM de Winter & Dennis A Hesselink

Table 1. Summary of investigational drugs for the treatment of kidney transplant rejection.

Type of immunosuppression	Mechanism of action	Therapeutic effect	Advantages	Disadvantages	Reference
Cellular-depleting therapies					
Alemtuzumab	B/T lymphocyte and NK cell depletion	In retrospective analysis, allograft survival comparable to rATG	Applicable in ABMR, TCMR and mixed rejection	Long-lasting lymphocyte depletion with risk of infection, malignancy, auto-immunity	[8]
Rituximab	B lymphocyte depletion	No clear evidence for beneficial effect in ABMR	Specifically targets B lymphocytes	Higher risk of infection, plasma cells unaffected	[26]
Bortezomib	Inhibits degradation intracellular protein	No conclusive evidence for beneficial effect in ABMR	Specifically targets plasma cells	High rate of gastro-intestinal and hematological toxicity	[32]
Daratumumab	Plasma cell, B/T lymphocyte and NK cell depletion	Anecdotal evidence only, regarding use in ABMR	Targets plasma cells and lymphocytes	Possibly increased rejection rate due to loss of regulatory cells	[36–38]

EXPERT OPINION ON INVESTIGATIONAL DRUGS
2022, VOL. 31, NO. 10, 1087–1100

Rituximab

✓**Rituximab**, a CD20 monoclonal antibody, is a novel treatment option for **desensitization therapy in ABO-incompatible**

and **highly sensitized recipients**undergoing renal transplantation.

✓ However, **no beneficial effect** of **rituximab** in addition to PEX + IVIG + steroids was observed for established acute AMR or **in addition to IVIG for chronic AMR**.

A systematic review of the use of rituximab for the treatment of antibody-mediated renal transplant rejection ☆, ☆☆, ★

Philip S. Macklin [a], Peter J. Morris [a b], Simon R. Knight [a b]

- ✓CAMR, 10 records relating to **7 studies**.
- ✓This contrasts with CAMR in which
- ✓**only one of seven studies reported improved graft outcomes** with a rituximab-based regimen;
- ✓**three studies** reported **inferior** outcomes
- ✓ **three** reported **no difference**.
- ✓Only one study reported that rituximab was associated with an increase in adverse effects.

Transplantation reviews, 2017 Apr;31(2):87-95.

Rituximab, plasma exchange and immunoglobulins: an ineffective treatment for chronic active antibody-mediated rejection

Gastón J Piñeiro[1,2], Erika De Sousa-Amorim[1], Manel Solé[3], José Ríos[4,5], Miguel Lozano[6], Frederic Cofán[1], Pedro Ventura-Aguiar[1,2], David Cucchiari[1,2], Ignacio Revuelta[1,2,7], Joan Cid[6], Eduard Palou[8], Josep M Campistol[1,7], Federico Oppenheimer[1], Jordi Rovira[2,7*†] and Fritz Diekmann[1,2,7*†]

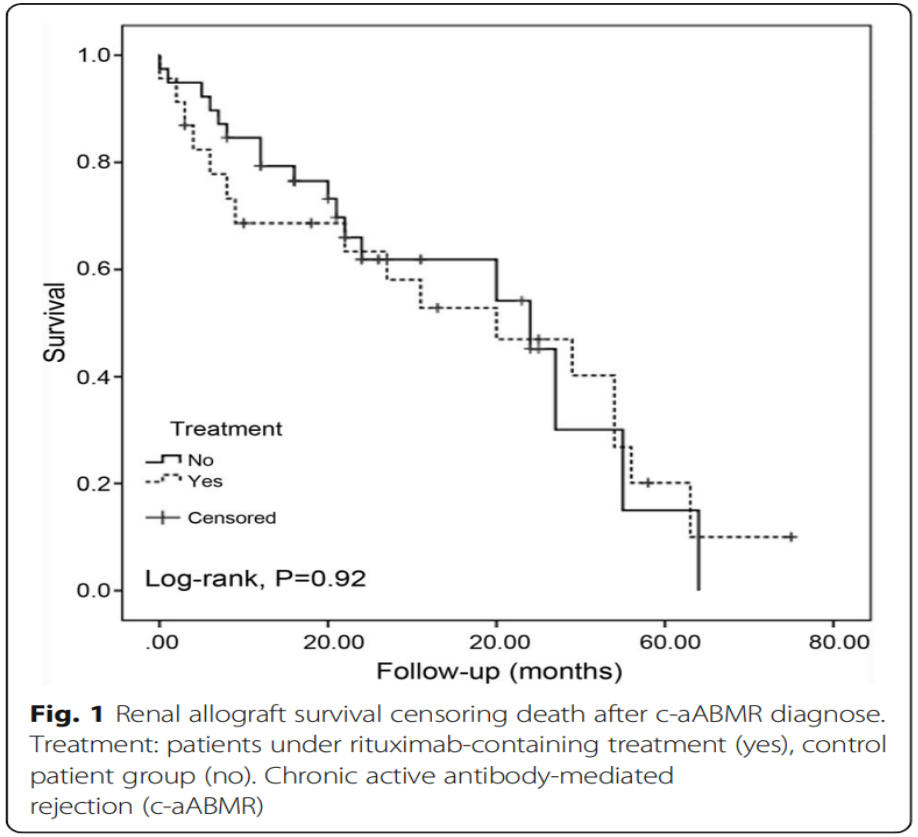


Fig. 1 Renal allograft survival censoring death after c-aABMR diagnose. Treatment: patients under rituximab-containing treatment (yes), control patient group (no). Chronic active antibody-mediated rejection (c-aABMR)

- ✓In this retrospective study,n=62, and **n=23** received treatment with rituximab + IVIG, and PE was not associated with improved graft survival when compared with the control group.
- ✓On the other hand, the incidence of infections requiring hospitalization within 1 year after treatment was more than doubled in the treated group.

Piñeiro et al. BMC Nephrology (2018) 19:261

Received: 13 April 2017 | Revised: 13 September 2017 | Accepted: 18 September 2017
DOI: 10.1111/ajt.14520

ORIGINAL ARTICLE

AJT

Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: A multicenter, prospective, randomized, double-blind clinical trial

Francesc Moreso[1] | Marta Crespo[2] | Juan C. Ruiz[3] | Armando Torres[4] | Alex Gutierrez-Dalmau[5] | Antonio Osuna[6] | Manel Perelló[1] | Julio Pascual[2] | Irina B. Torres[1] | Dolores Redondo-Pachón[2] | Emilio Rodrigo[3] | Marcos Lopez-Hoyos[7] | Daniel Seron[1]

our study (**n=25**)suggests that **treatment with IVIG and RTX** does **not significantly** modify the natural history **of chronic ABMR with transplant glomerulopathy**.

absence of any effect on circulating DSA .

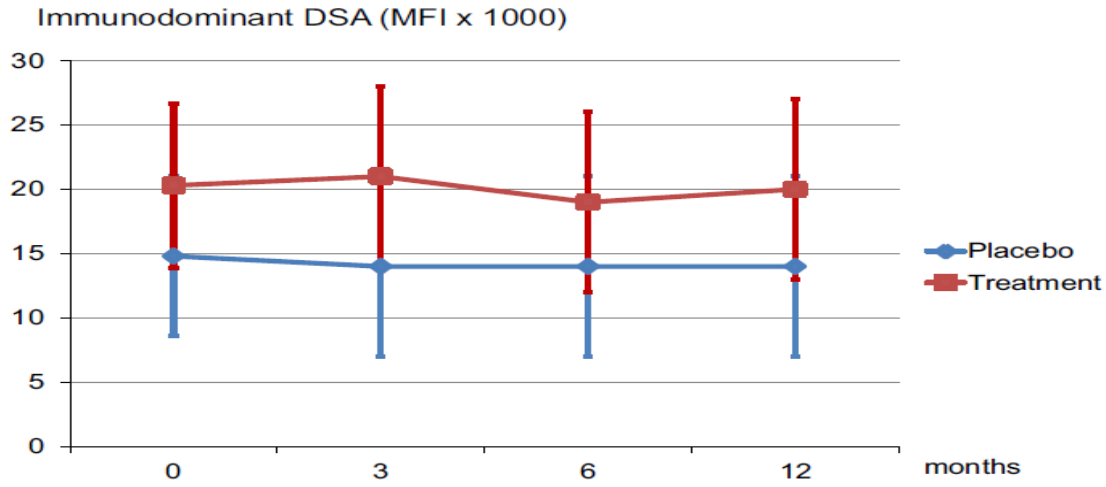


FIGURE 4 Evolution of the MFI of the immunodominant donor specific anti-HLA antibody in the placebo and treatment groups. By mixed linear model *P*-value between groups was .0735; *P*-value 3, 6, and 12 months vs. baseline was >.05. MFI, maximal fluorescence intensity [Color figure can be viewed at wileyonlinelibrary.com]

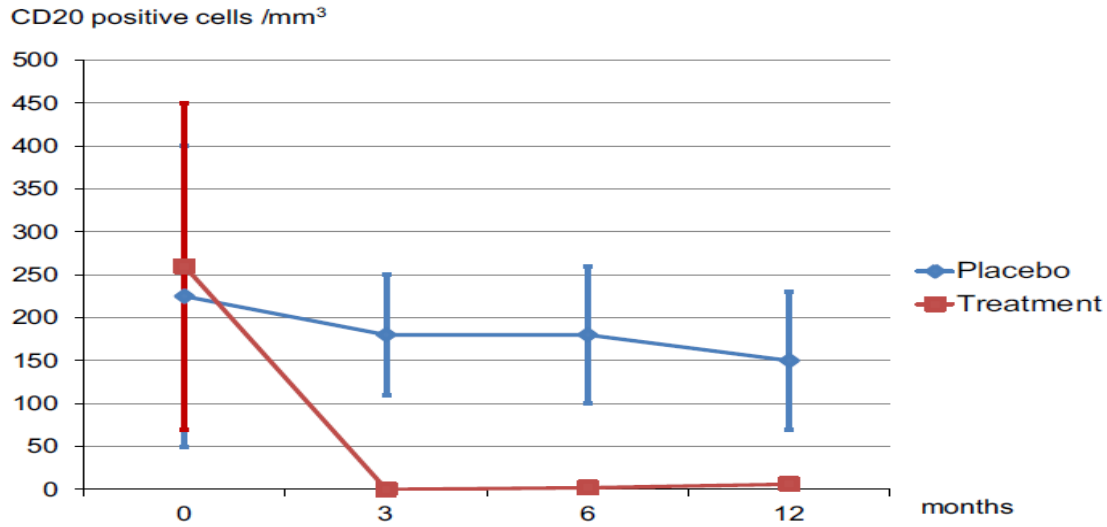


FIGURE 5 Evolution of circulating B lymphocytes in the placebo and treatment groups. By mixed linear model *P*-value between groups was .0036; *P*-value 3, 6, and 12 months vs. baseline was <.001 [Color figure can be viewed at wileyonlinelibrary.com]

OPEN

Chronic Active Antibody-mediated Rejection in Kidney Transplant Recipients: Treatment Response Rates and Value of Early Surveillance Biopsies

Fahad Aziz, MD,[1] Sandesh Parajuli, MD,[1] Margaret Jorgenson, PharmD, BCPS,[2] Neetika Garg, MD,[1] Venkata Manchala, MD,[1] Elsadiq Yousif, MD,[1] Didier Mandelbrot, MD,[1] Luis Hidalgo, PhD,[3] Maha Mohamed, MD,[1] Weixiong Zhong, MD,[4] and Arjang Djamali, MD[5]

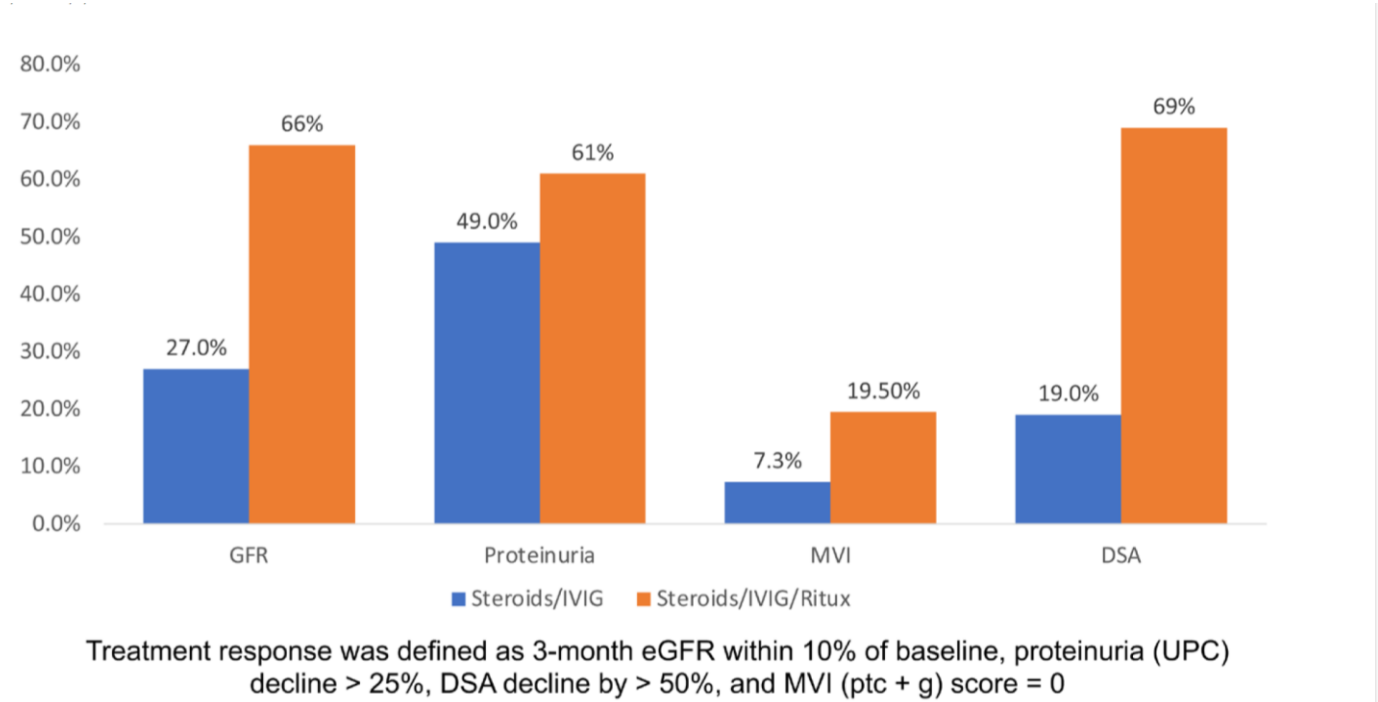


FIGURE 2. Three-month response rates to prescriptions in cAMR. cAMR, chronic active antibody-mediated rejection; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; MVI, microvascular inflammation; UPC, urine-protein creatinine ratio.

n=41 control.n=41 Rituximab

Transplantation Direct 2022;8: e1360

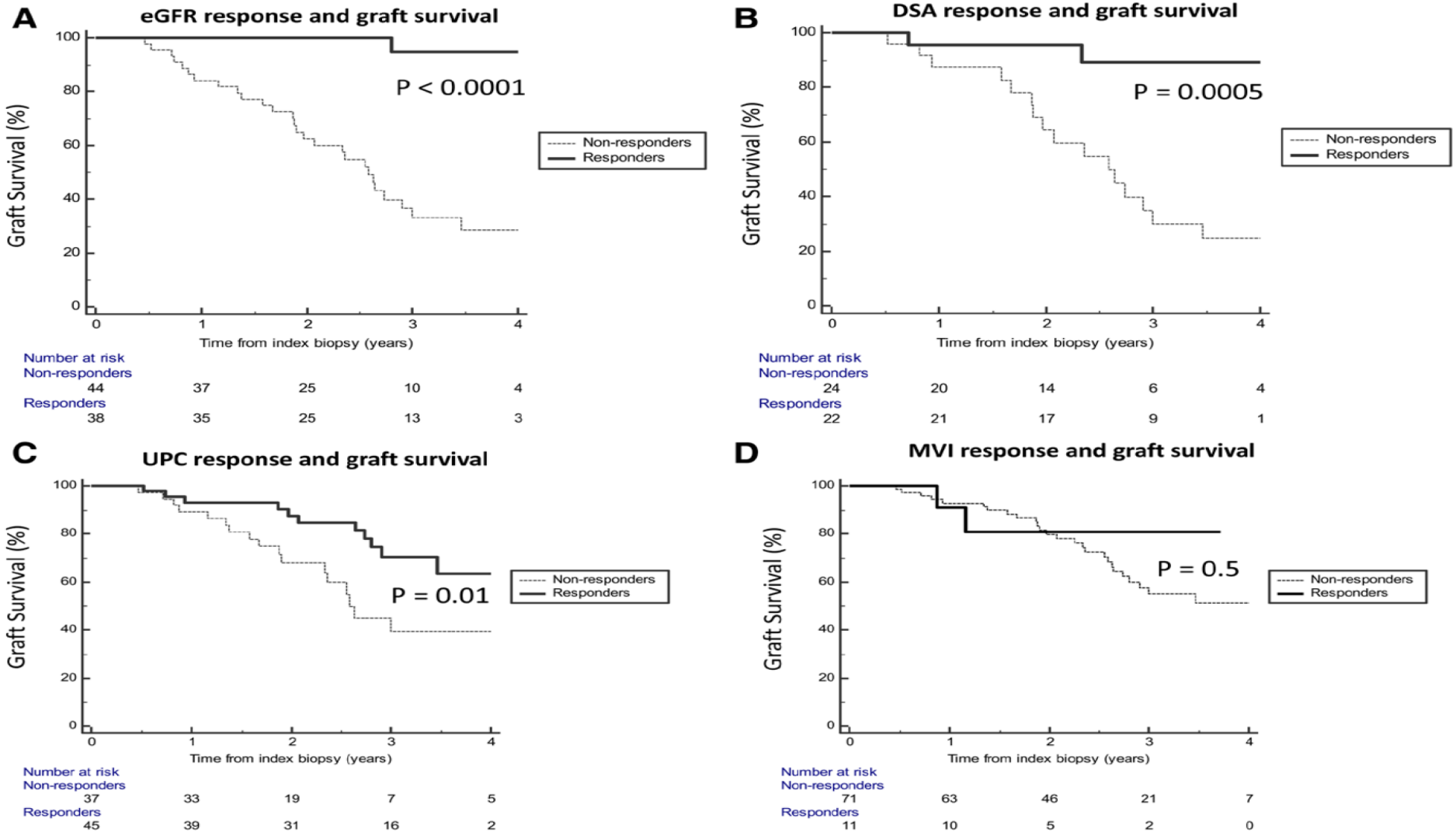


FIGURE 3. Short-term response in kidney function and DSA associated with graft survival. DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; MVI, microvascular inflammation; UPC, urine-protein creatinine ratio.

TABLE 4.

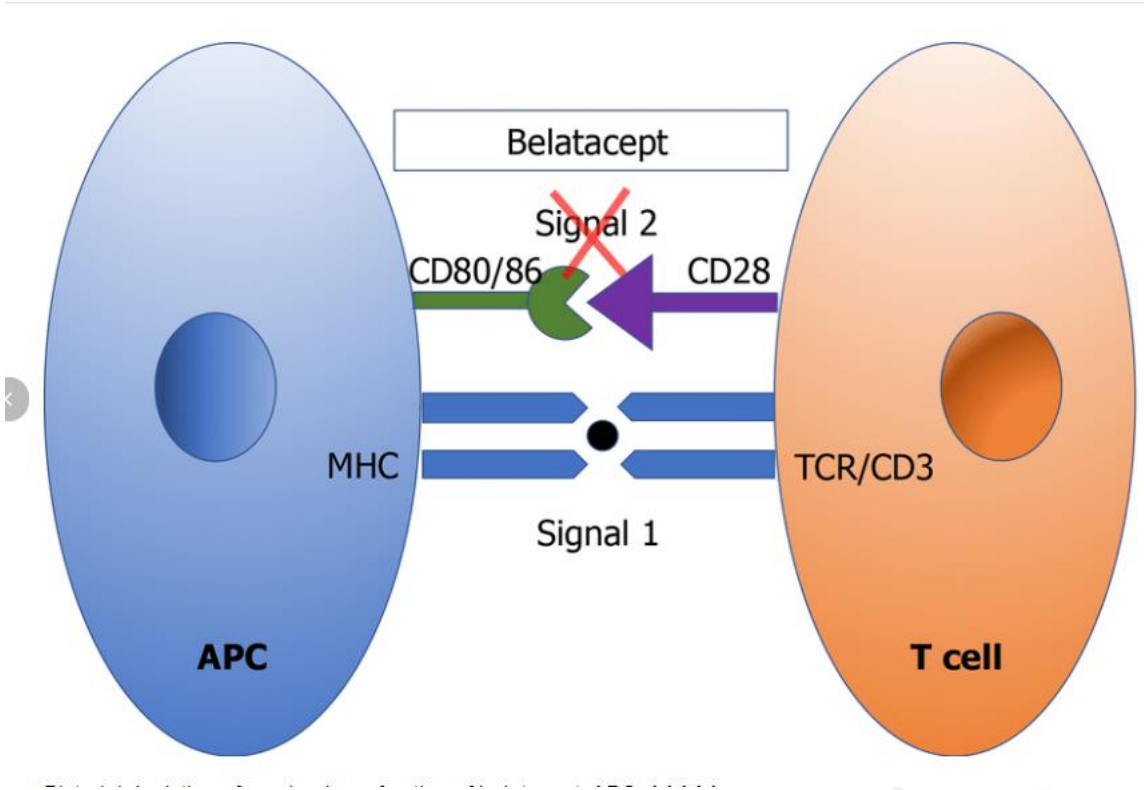
Variables associated with death-censored graft loss

	Univariate analyses			Multivariate analyses		
Variables	**HR**	***P***	**95% CI**	**HR**	***P***	**95% CI**
Age >55 at txp	1.01	0.97	0.41–2.49			
Male	1.17	0.68	0.53–2.60			
White	0.67	0.36	0.28–1.58			
History of failed transplant	0.85	0.73	0.34–2.12			
DM as cause of ESRD	0.51	0.27	0.15–1.71			
Living donor transplant	1.76	0.13	0.83–3.74			
Depleting Induction	1.38	0.39	0.65–2.94			
DSA present at biopsy	1.18	0.66	0.55–2.55			
Chronicity score >8	11.91	0.0001	5.38–26.33	1.54	0.48	0.45–5.25
eGFR response, yes/no	0.03	0.001	0.004–0.26	0.12		0.02–0.64
DSA response, yes/no	0.11	0.004	0.026–0.49	1.28	0.013	0.21–7.77
UPC response, yes/no	0.38	0.01	0.18–0.82	1.02	0.96	0.32–3.20
MVI response, yes/no	0.65	0.55	0.15–2.75			
C4d response, yes/no	1.61	0.45	0.42–6.08			
Change in MVI between two biopsies	0.86	0.2	0.69–1.09			
Rituximab use	0.13	0.0001	0.05–0.34	0.27	0.10	0.05–1.29

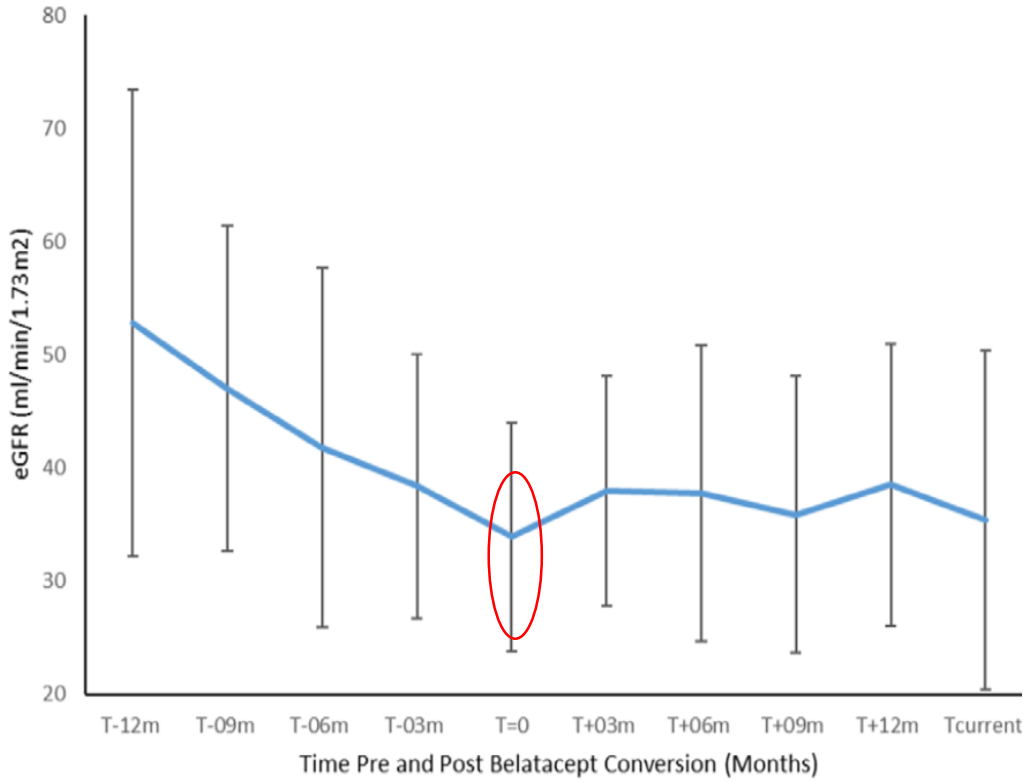
CI, confidence interval; DM, diabetes mellitus; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; ESRD, End-Stage Renal Disease; HR, hazard ratio; MVI, microvascular inflammation; txp, transplantation; UPC, urine-protein creatinine ratio.

Belatacept

- ✓Targeting **Tfh–B cells costimulation** signal by **belatacept** may prevent dnDSA and AMR .
- ✓.



Mean estimated glomerular filtration rate trend: prebelatacept and postbelatacept conversion



Original Clinical Science—General

Impact of Belatacept Conversion on Renal Function, Histology, and Gene Expression in Kidney Transplant Patients With Chronic Active Antibody-mediated Rejection

Dhiren Kumar, MD,[1] Marc Raynaud, PhD,[2] Jessica Chang, BS,[3] Jeff Reeve, PhD,[3] Idris Yakubu, PharmD,[1] Layla Kamal, MD,[1] Marlon Levy, MD,[1] Chandra Bhati, MD,[1] Pamela Kimball, PhD,[1] Anne King, MD,[1] Davis Massey, MD,[1] Philip Halloran, MD,[3] and Gaurav Gupta, MD[1]

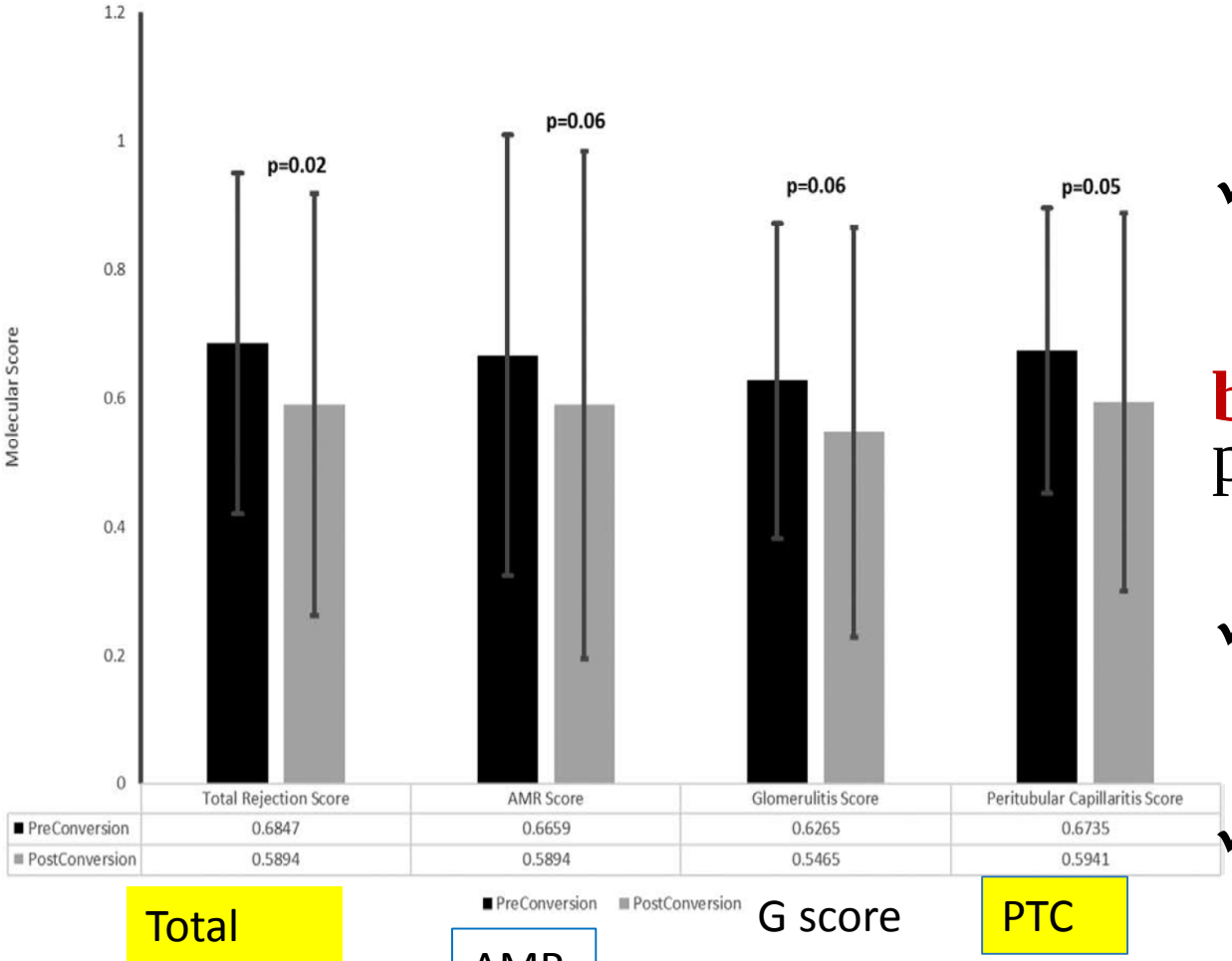
We converted **19** patients (mean age, 45 ± 12 y) with biopsy-proven caAMR from tacrolimus to belatacept at a median of 44 months

post–kidney transplant.

the belatacept group had progressive improvement (*P* = 0.02) in eGFR

In patients diagnosed with caAMR who were **not subjected to intensive salvage immunosuppressive therapies**, isolated belatacept conversion alone was associated with stabilization

in renal function.



- ✓Seventeen-paired preconversion and postconversion surveillance biopsies were subjected to intragraft **mRNA-based gene expression** using the MMDx platform.
- ✓Previously validated gene expression scores for total rejection and peritubular capillaritis improved.
- ✓.

Histology—pre conversion and post conversion chronicity score.

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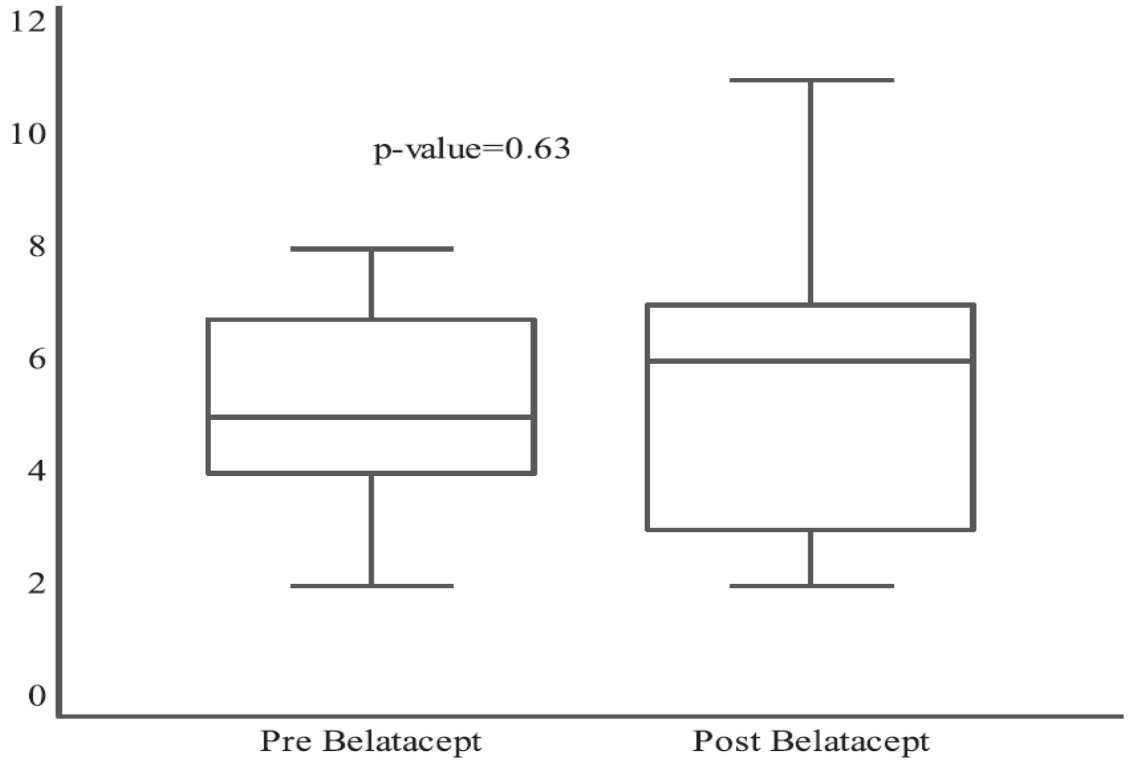


Transplant Immunology
Volume 76, February 2023, 101737

Conversion to Belatacept in kidney transplant recipients with chronic antibody-mediated rejection (CAMR)

Mahmoudreza Moein [a], Shuqi X. Gao [a 1], Samuel J. Martin [a 1], Katie M. Farkouh [a 1], Benson W. Li [a 1], Angela S. Ball [a], Reut Hod Dvorai [b], Reza F. Saidi [a]

We conclude that compared to the standard Tacrolimus/MMF/Prednisone regimen, Belatacept did not significantly benefit in preserving the GFR in long-term follow-ups and stabilizing the DSA production, which is one of the main factors resulting in chronic graft failure.

N=48

Bortezomib

- ✓Bortezomib is a proteasome inhibitor that is registered for the treatment of multiple myeloma .

- ✓Its mechanism of action is to **inhibit the degradation of intracellular proteins**, which in the end causes **apoptosis.**

- ✓**In vitro**, bortezomib caused **human plasma cell apoptosis** and **prevented DSA production**.

J Am Soc Nephrol. 2018 Feb; 29(2): 591–605.
Published online 2017 Dec 14. doi: 10.1681/ASN.2017070818
PMCID: PMC5791086
PMID: 29242250

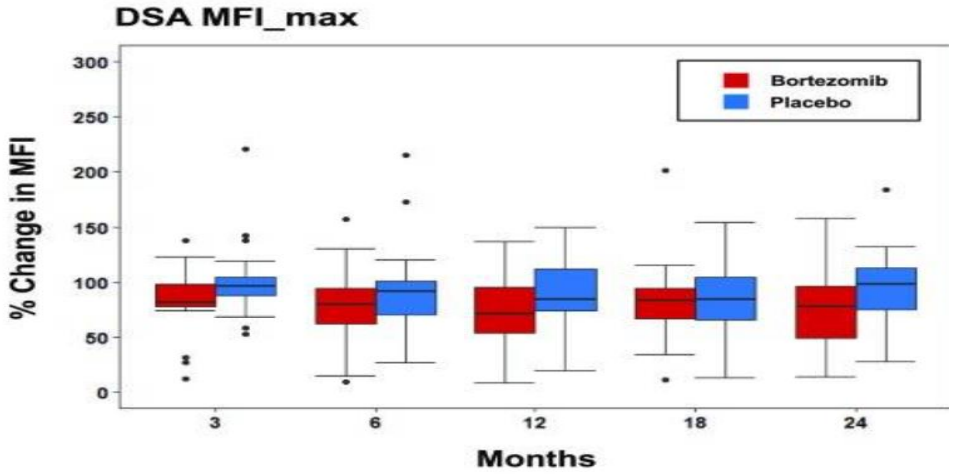
A Randomized Trial of Bortezomib in Late Antibody-Mediated Kidney Transplant Rejection

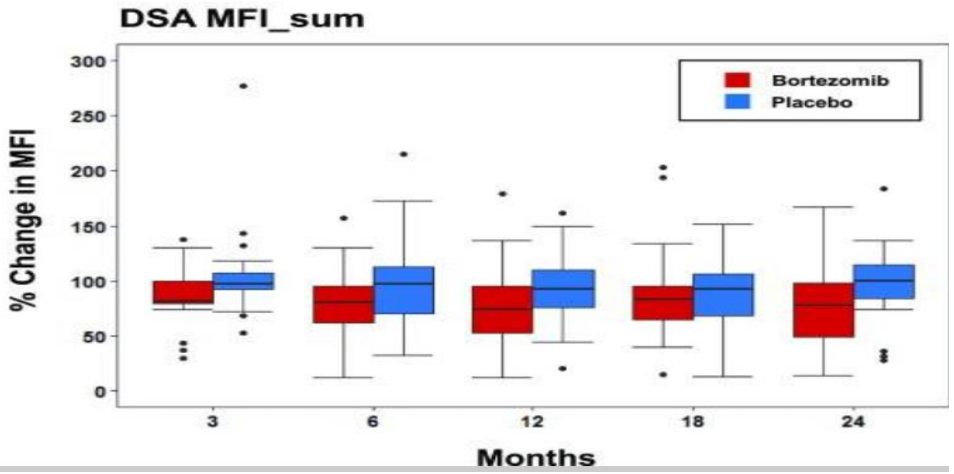
Farsad Eskandary,[1] Heinz Regele,[2] Lukas Baumann,[3] Gregor Bond,[1] Nicolas Kozakowski,[2] Markus Wahrmann,[1] Luis G. Hidalgo,[4] Helmuth Haslacher,[5] Christopher C. Kaltenecker,[1] Marie-Bernadette Aretin,[6] Rainer Oberbauer,[1] Martin Posch,[3] Anton Staudenherz,[7] Ammon Handisurya,[1] Jeff Reeve,[8] Philip F. Halloran,[8] and Georg A. Böhmig[1]

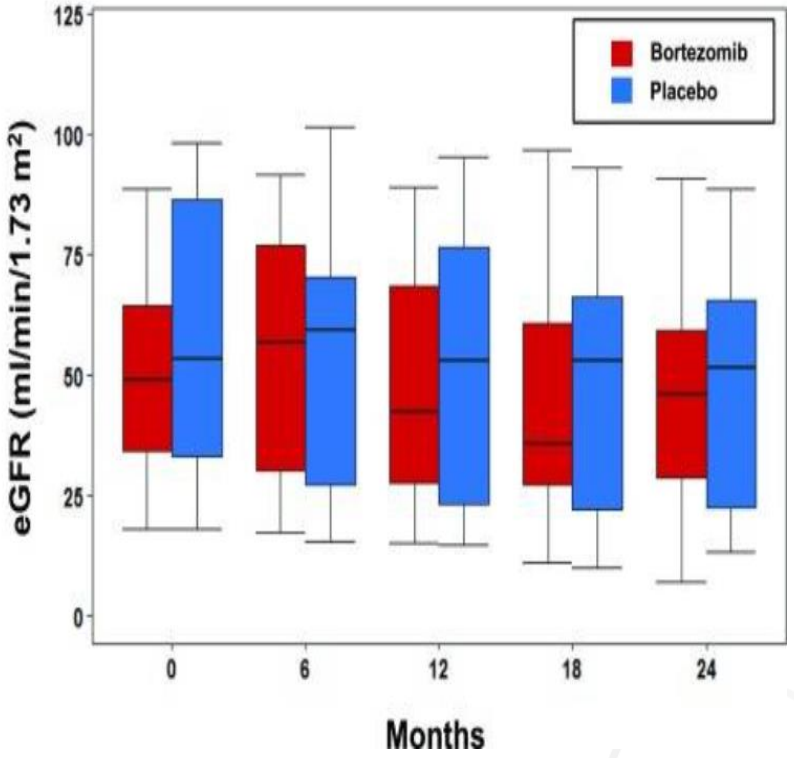
N=44 patients were randomly assigned to receive **two cycles** of either **bortezomib n=21** or **placebo n=23**, at **3-month intervals** in **double-blinded** fashion.

Each treatment cycle consisted of bortezomib at **1.3 mg/m²** administered intravenously **twice weekly** on days **1, 4, 8, and 11.**

There were also **no significant differences** **in measured GFR**, **urinary protein levels**, **DSA**, or the **morphologic and molecular features** of disease activity in follow-up biopsies







In conclusion, this randomized trial **was not able to show that bortezomib prevents** the progression of graft dysfunction or reduces features of disease activity in late DSA-positive ABMR.
This and the **observed increase in the number of AEs** do not support the use of bortezomib in the treatment of this type of rejection

Carfilzomib

✓Carfilzomib is a second-generation **irreversible proteasome inhibitor.** Its mechanism of action is similar to that of bortezomib.

✓**Six non human primate** kidney transplant recipients

Its effectiveness in humans was studied only in **lung and heart transplant**

✓ J. Clin. Med. **2023**, 12, 4916. https://doi.org/10.3390/jcm12154916

Investigational drugs for the treatment of kidney transplant rejection

Lukas K van Vugt, Maaike R Schagen, Annelies de Weerd, Marlies EJ Reinders, Brenda CM de Winter & Dennis A Hesselink

Complement inhibition				
C1 esterase inhibitors	Binding and inactivating C1 esterase	No conclusive evidence for beneficial effect acute and late, active ABMR	Specifically targets complement, modulating immune responses without cellular depletion	Gastro-intestinal toxicity
Eculizumab	Inhibits cleavage of C5 in active components	No conclusive evidence for beneficial effect in ABMR	Specifically targets complement, modulating immune responses without cellular depletion	Increased meningococcal infections and hepatotoxicity
Anti-C1s antibodies	Binds and blocks activated C1 protein	No conclusive evidence in ABMR, only phase I trials	Specifically targets complement, modulating immune responses without cellular depletion	Safety unclear. Safety data only available from small patient numbers

Eculizumab

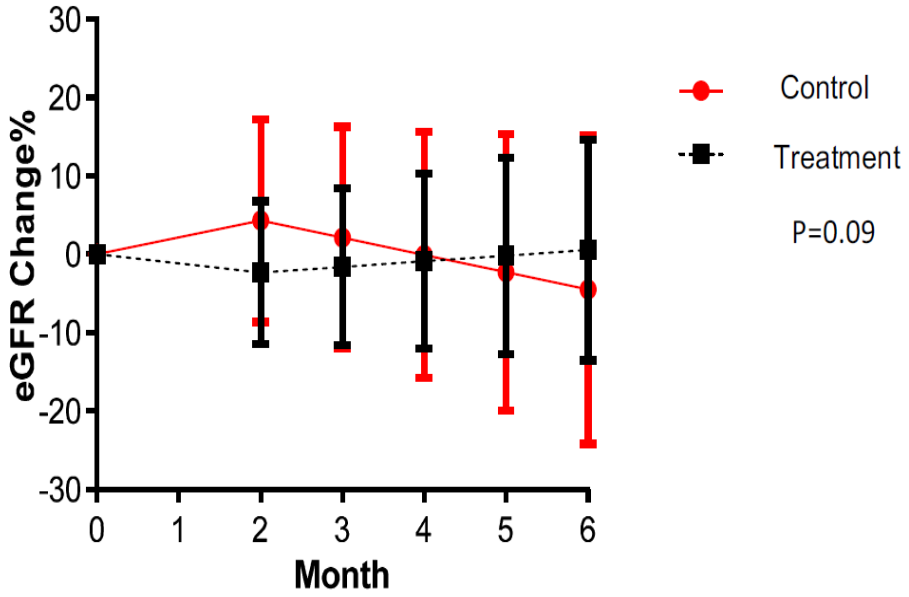
- ✓Eculizumab, an **anti-C5 monoclonal antibody**, inhibits terminal complement activation.
- ✓A **pilot randomized** controlled trial of chronic AMR with de novo DSA showed **modest improvement in the (eGFR).**
- ✓ However, a cohort with significantly **lower TG levels** in the control group may not have provided a high level of evidence.

Eculizumab Therapy for Chronic Antibody-Mediated Injury in Kidney Transplant Recipients: A Pilot Randomized Controlled Trial

S. Kulkarni[1,2,*], N. C. Kirkiles-Smith[3], Y. H. Deng[4], R. N. Formica[1,2], G. Moeckel[5], V. Broecker[6], L. Bow[1], R. Tomlin[1] and J. S. Pober[3,5]

Abbreviations: +, C4d positive; –, C4d negative; cDNA, complementary DNA; DSA, donor-specific antibody; eGFR, estimated GFR; ENDAT, endothelial cell–associated transcript; MFI, mean fluorescence

Mixed model analysis of eGFR slope comparing study arms during the first 6 mo



In total, 15 participants (5 control, n=10 treatment).

The treatment group received 6 mo of eculizumab followed by 6 mo of observation.

The primary end point was percentage change in (eGFR) trajectory over the treatment period. The treatment group had an improved eGFR trajectory versus control, based on our predetermined two-sided 0.10 significance level (p = 0.09)

American Journal of Transplantation 2017; 17: 682–691

ENDAT analysis of kidney biopsies performed at baseline and at 3, 6, and 12 mo.

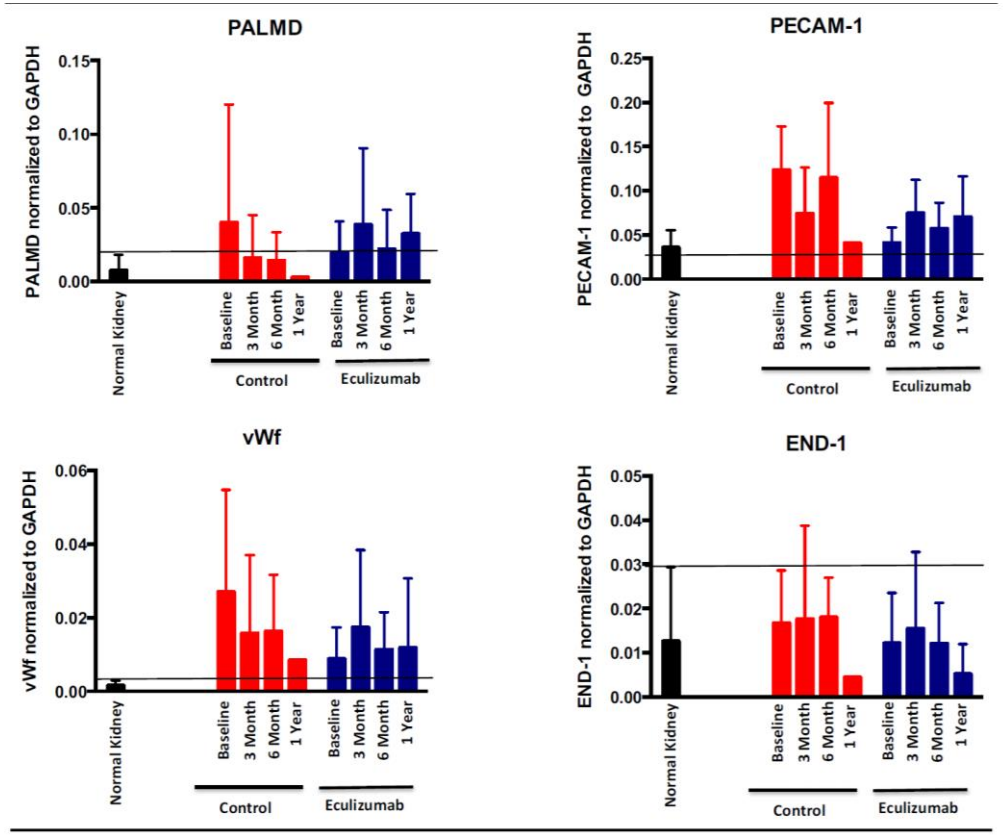


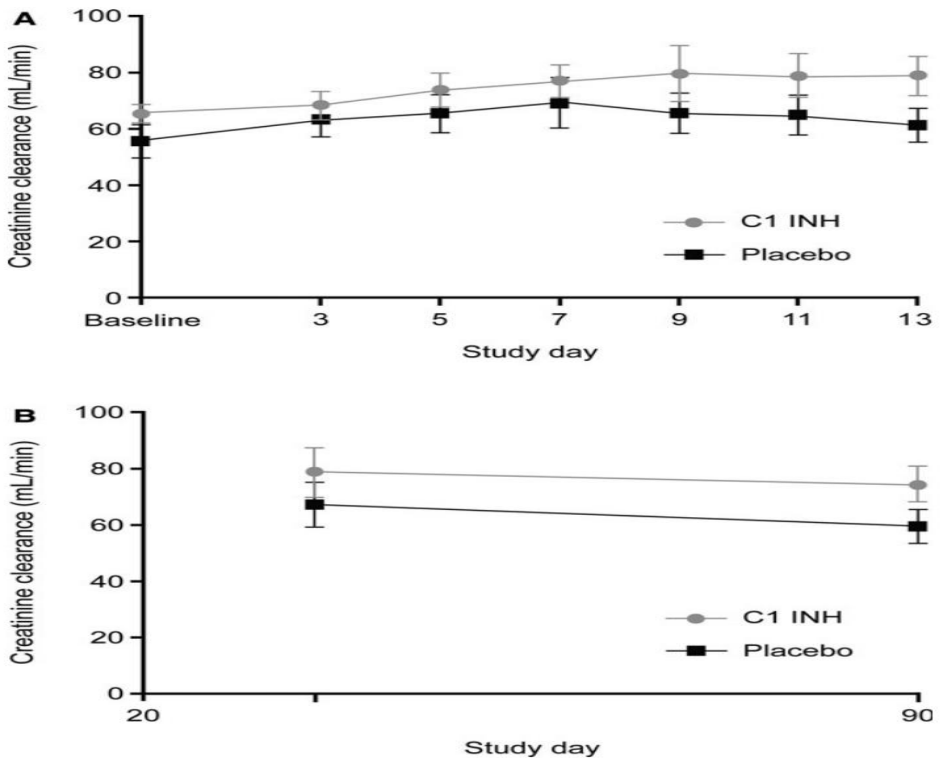
Figure 6: ENDAT analysis of kidney biopsies performed at baseline and at 3, 6, and 12 mo. ENDAT expression of *SELE*, *PECAM1*, *VWF*, and *PALMD* were noted to be higher than levels in normal kidneys for both groups; however, there was no reduction in ENDAT expression in eculizumab-treated patients. ENDAT, endothelial cell–associated transcript.

C1 esterase inhibitors

- ✓C1 esterase inhibitors are serine proteases isolated from human plasma.
- ✓Their mechanism of action is to **inactivate C1esterase** by binding to its reactive site, thus **inhibiting the classical pathway of complement** activation.

- ✓Berinert R and Cinryze™ are currently on the market and are registered for the treatment of hereditary angio-edema.

(A) Mean (SE) creatinine clearance on therapy (baseline through day 13). Baseline levels obtained at screening, before study dose on day 1. (B) Mean (SE) creatinine clearance after therapy (day 20 through day 90).



American Journal of Transplantation 2016; 16: 3468–3478
Wiley Periodicals Inc.

doi: 10.1111/ajt.13871

Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study

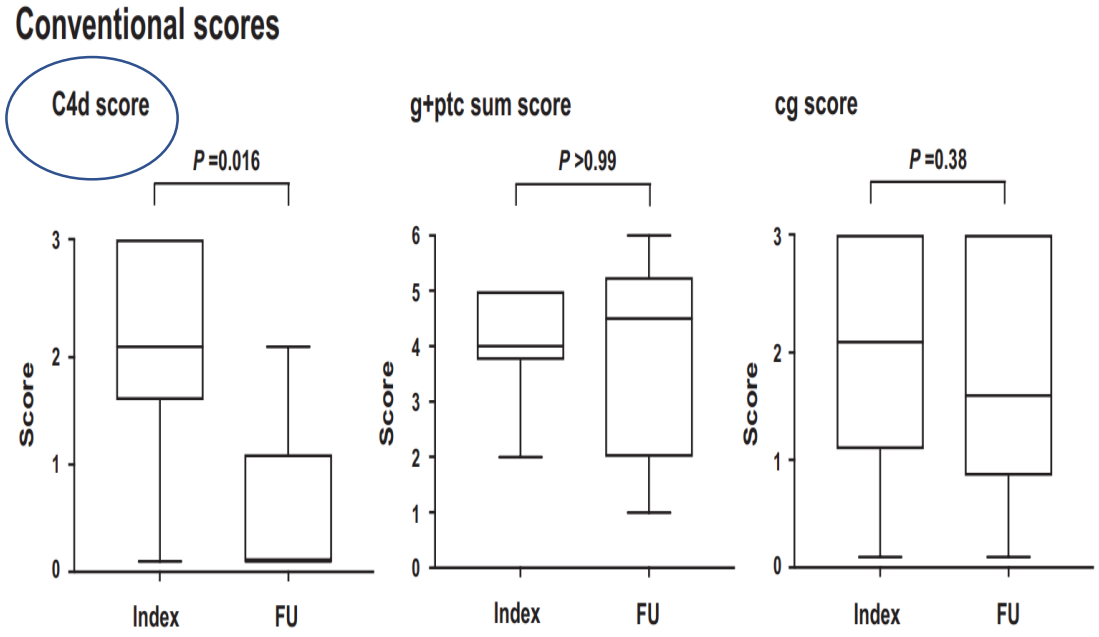
R. A. Montgomery[1,*], B. J. Orandi[1], L. Racusen[2], A. M. Jackson[3], J. M. Garonzik-Wang[1], T. Shah[4], E. S. Woodle[5], C. Sommerer[6], D. Fitts[7], K. Rockich[7], P. Zhang[7] and M. E. Uknis[7]

patients achieved supraphysiological levels throughout. This new finding suggests that C1 INH replacement may be useful in the treatment of AMR.

Abbreviations: AMR, antibody-mediated rejection; AE, adverse event; C1 INH, C1 esterase inhibitor; C4d, fourth complement protein degradation pro-

Eighteen patients were enrolled (C1 INH n = 9, placebo n = 9).They found a decrease in TG development after 6 months of treatment with a C1 esterase inhibitor.

Effect of BIVV009 on morphologic and molecular biopsy results. C4d staining in peritubular capillaries (C4d score) and antibody mediated rejection (ABMR) histomorphology



ORIGINAL ARTICLE

AJ

Anti-C1s monoclonal antibody BIVV009 in late antibody-mediated kidney allograft rejection—results from a first-in-patient phase 1 trial

F. Eskandary[1] | B. Jilma[2] | J. Mühlbacher[3] | M. Wahrmann[1] | H. Regele[4] | N. Kozakowski[4] | C. Firbas[2] | S. Panicker[5] | G. C. Parry[5] | J. C. Gilbert[6] | P. F. Halloran[7] | G. A. Böhmig[1]

Here we describe the results in a cohort of 10 kidney transplant recipients (median of 4.3 years post transplantation) with late active ABMR .

During 7 weeks follow-up, no severe adverse events were reported.

Five of 8 C4d-positive recipients turned C4d-negative in 5-week follow-up biopsies, while another 2 recipients showed a substantial decrease in C4d scores. There was, however, no change in MVI, gene expression patterns, DSA levels, or kidney function.

Tocilizumab

✓Tocilizumab is a recombinant, **monoclonal antibody** with specificity for both soluble and membrane-bound **IL-6 R**.

✓ Anti-IL-6 therapy was found to significantly **reduce the number of pro-inflammatory T helper lymphocytes by 10%** and **increase regulatory T lymphocyte numbers by 10%** in a murine skin transplantation model.

Index and 1 year post–tocilizumab allograft biopsies

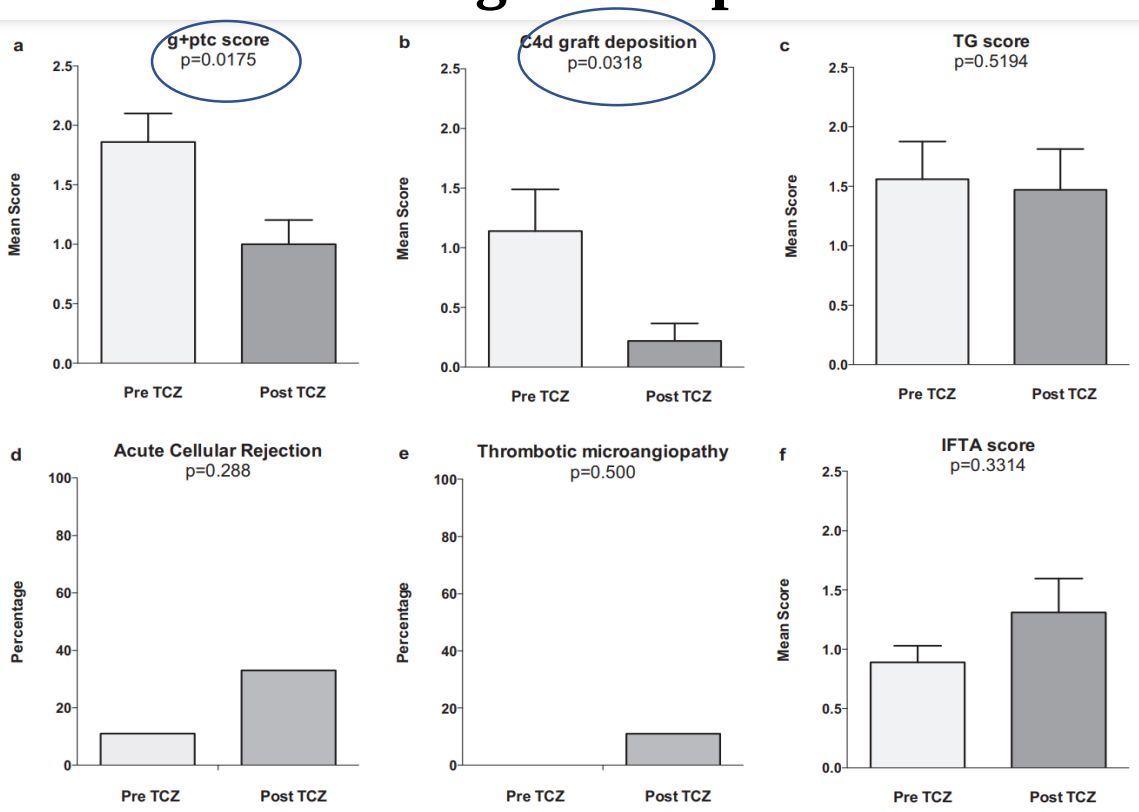


Figure 1: Index and 1 year post–tocilizumab allograft biopsies. (A) Kidney allograft index biopsy phenotypes at the initiation of tocilizumab treatment were obtained for 36 patients. All patients had significant glomerulitis (g), peritubular capilaritis (ptc), C4d positivity, and chronic changes in the glomerulus (cg), interstitium (ci), and tubules (ct). (B) This figure shows kidney allograft biopsy phenotypes before and after tocilizumab treatment (N = 9). Allograft biopsy specimens were obtained 1 year after tocilizumab treatment and compared with pretocilizumab chronic active antibody-mediated rejection biopsy specimens in nine patients. Significant reductions in g plus ptc scores and C4d deposition were seen with tocilizumab treatment. Other parameters were stable. TG, transplant glomerulopathy; IF/TA, Interstitial fibrosis/tubular atrophy.

American Journal of Transplantation 2017; 17: 2381–2389
Wiley Periodicals Inc.

doi: 10.1111/ajt.14228

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

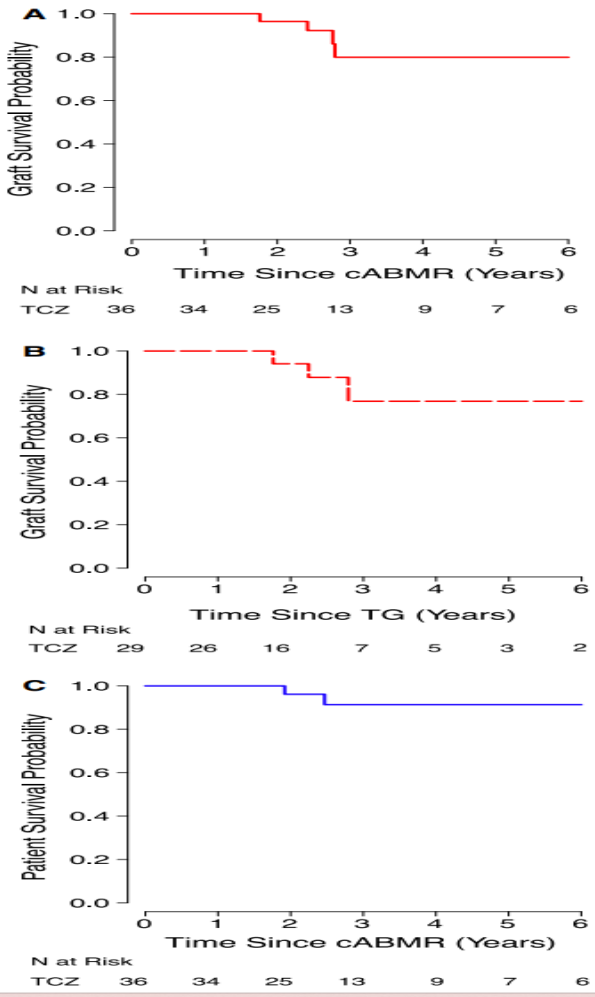
J. Choi[1,*], O. Aubert[2], A. Vo[1], A. Loupy[2], M. Haas[3], D. Puliyanda[1], I. Kim[1], S. Louie[1], A. Kang[1], A. Peng[1], J. Kahwaji[1], N. Reinsmoen[3], M. Toyoda[4] and S. C. Jordan[1]

Abbreviations: AE, adverse event; AMR, antibody-mediated rejection; cAMR, chronic active antibody-mediated rejection; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; iDSA, immunodomi-

We identified 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.

Patients were offered rescue therapy with the anti–IL-6 receptor monoclonal tocilizumab with monthly infusions .

Kaplan–Meier curves of kidney allograft and patient survival after treatment with tocilizumab for chronic active antibody-mediated rejection (cAMR)



- ✓**Tocilizumab-treated** patients demonstrated **graft survival 80%and patient survival rates 91%, at 6 years**.
- ✓Significant reductions in DSAs and **stabilization of renal function** were seen at 2 years.
- ✓**No significant adverse events** or severe adverse events were seen.
- ✓Tocilizumab provides good long-term outcomes for patients with **cAMR and TG**, especially **compared with historical published treatments**.

Tocilizumab in the Treatment of Chronic Antibody-Mediated Rejection Post Kidney Transplantation: Clinical and Histological Monitoring

Johan Noble[1,2], Diane Giovannini[3], Reda Laamech[1], Farida Imerzoukene[1], Bénédicte Janbon[1], Laura Marchesi[1], Paolo Malvezzi[1], Thomas Jouve[1,2] and

- ✓A retrospective study in **40 kidney transplant recipients** who received
- ✓monthly tocilizumab for chronic active AMR.(no control group)
- ✓At **12 months follow-up**, **renal function** and **proteinuria remained stable, no clinical or histological worsening** was seen, except for those whose clinical condition was more severe at the time of initiation.

Front. Med. 8:790547. doi: 10.3389/fmed.2021.790547

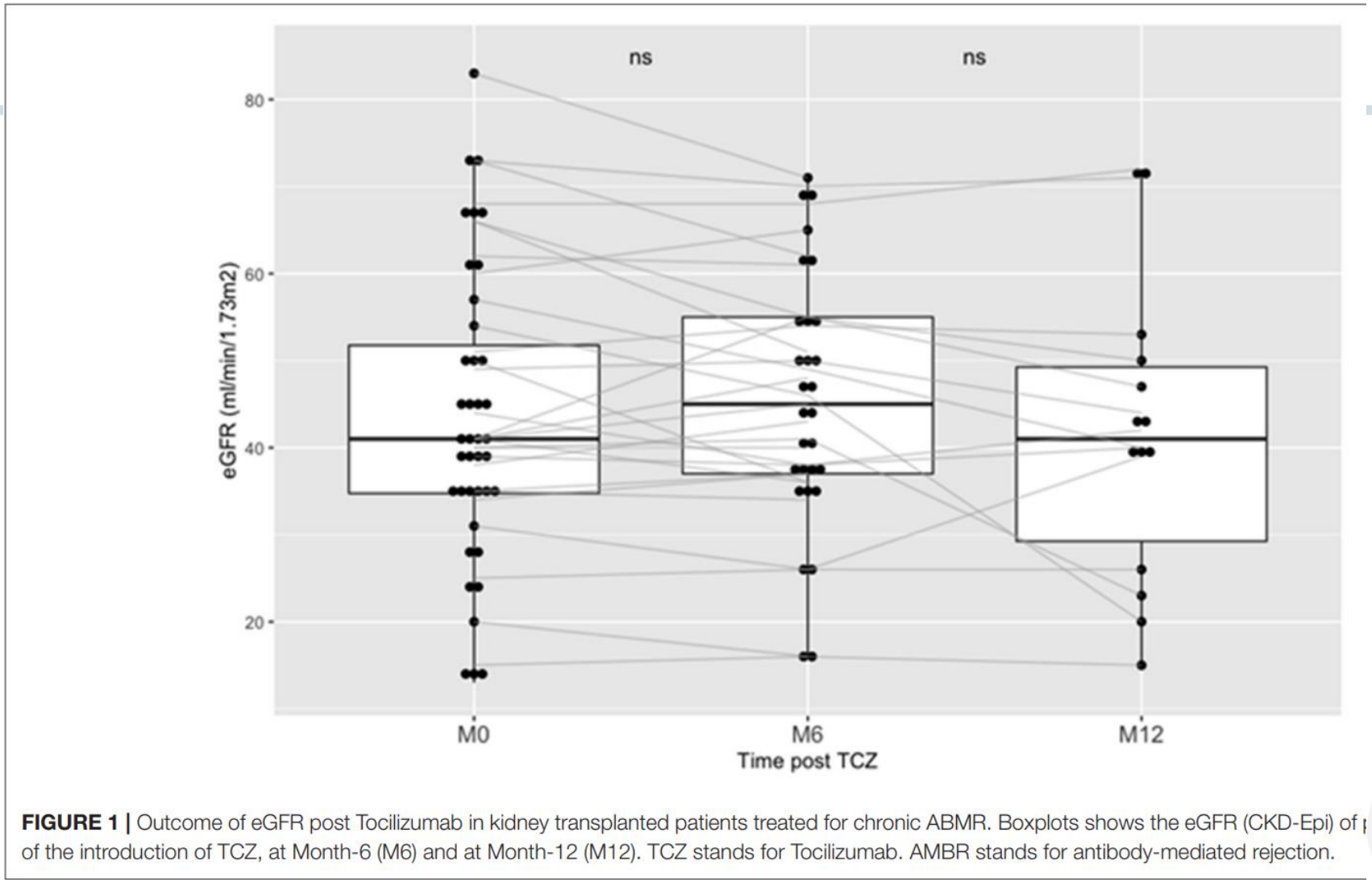


FIGURE 1 | Outcome of eGFR post Tocilizumab in kidney transplanted patients treated for chronic ABMR. Boxplots shows the eGFR (CKD-Epi) of p
of the introduction of TCZ, at Month-6 (M6) and at Month-12 (M12). TCZ stands for Tocilizumab. AMBR stands for antibody-mediated rejection.

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

ORIGINAL ARTICLE

Early effects of first-line treatment with anti-interleukin-6 receptor antibody tocilizumab for chronic active antibody-mediated rejection in kidney transplantation

Antonio Lavacca, Roberto Presta, Chiara Gai, Alberto Mella, Ester Gallo, Giovanni Camussi, Isabella Abbasciano, Antonella Barreca, Cristiana Caorsi, Fabrizio Fop ... See all authors

First published: 15 May 2020 | https://doi.org/10.1111/ctr.13908 | Citations: 44

n= **15,**first-line therapy , **stabilization of (GFR) and proteinuria , a significant reduction in DSA titers, and Histological improvementon the protocol biopsies after 6 months.**

Original Investigation

Kidney360

Lack of Histological and Molecular Signature Response to Tocilizumab in Kidney Transplants with Chronic Active Antibody Mediated Rejection: A Case Series

Dhiren Kumar,[1] Idris Yakubu,[1] Frough Safavi,[1] Marlon Levy,[1] Irfan Moinuddin,[1] Pamela Kimball,[1] Layla Kamal,[1] Anne King,[1] Davis Massey,[1] Philip Halloran,[2] and Gaurav Gupta [1]

N=10, black (70%), underwent **regrafts (40%),** and were sensitized (mean **cPRA541%).** median of **six doses of TCZ** (range53–10). At a **median follow-up of 12 months** (range58–24 months), **Patient survival was 90%,** one patient death :hip infection.
Overall death censored **graft survival was 80%,** with two graft losses.

KIDNEY360 1: 663–670, July, 2020

Table 2. Results

Measure	*N*	Mean (SD)		*P* Value
		Pre-TCZ	Post-TCZ	
Graft function				
eGFR T_0 versus T_{3m}	10	41.6 (18.8043)	42.2 (17.6937)	0.71
eGFR T_0 versus T_{6m}	10	41.6 (18.8043)	39.2 (19.0193)	0.43
eGFR T_0 versus T_{12m}	6	41.7 (20.2846)	41 (26.6983)	0.88
Proteinuria T_0 and T_c	10	1.61 (1.1426)	1.85 (2.3244)	0.70
Slope eGFR (T_0−12 m versus T_0+12 m)	10	−0.14 (0.9082)	−0.33 (1.0724)	0.60
Histology				
MVI	6	4.8333 (1.472)	4.1667 (2.0412)	0.39
Total chronicity score	6	4.3333 (1.9664)	5.6667 (3.4448)	0.29
IFTA	6	2.5 (0.8367)	3.3333 (1.7512)	0.38
MMDx scores				
AbMR	5	0.792 (0.1681)	0.776 (0.2615)	0.86
Total rejection	5	0.83 (0.1454)	0.79 (0.1488)	0.51
Atrophy fibrosis	5	0.362 (0.2374)	0.584 (0.1494)	0.21
Global disturbance	5	0.884 (2.243)	1.646 (1.2158)	0.44

TCZ, tocilizumab; T_0, at time of initiation of TCZ; T_{3m}, 3 months after initiation of TCZ; T_c, at time of most recent followup; MVI, microvascular inflammation (glomerulitis plus peritubular capillaritis score); IFTA, interstitial fibrosis and tubular atrophy; MMDx, Molecular Microscope Diagnostic System; AbMR, antibody-mediated rejection.

Received: 29 April 2020 | Revised: 25 October 2020 | Accepted: 27 October 2020

DOI: 10.1111/ajt.16391

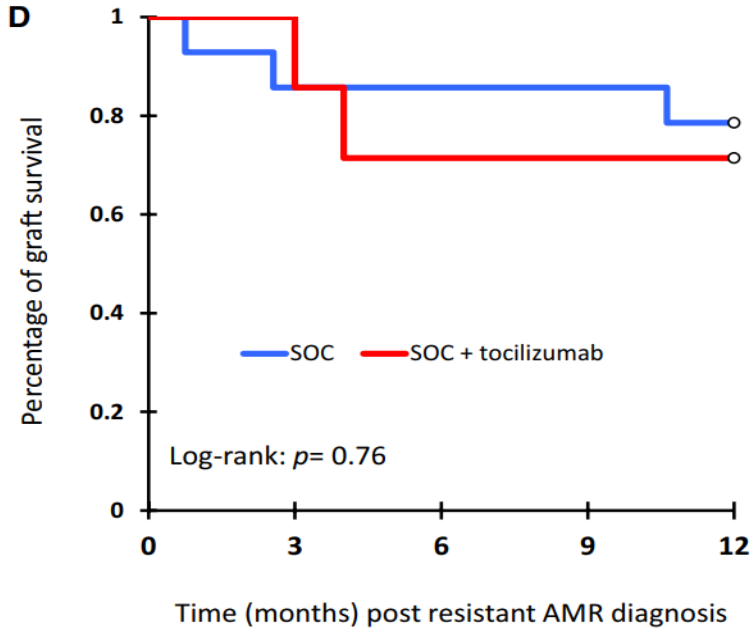
CASE REPORT

AJT

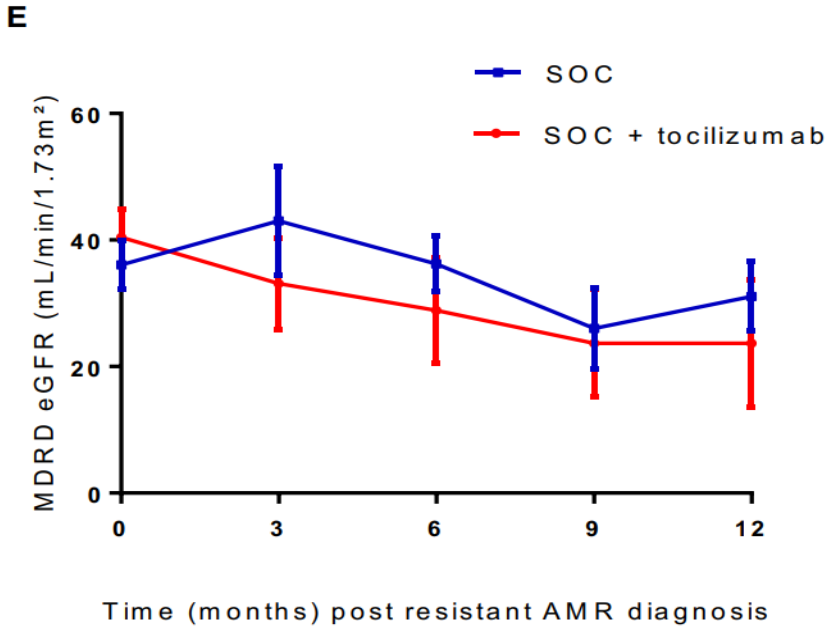
Do anti-IL-6R blockers have a beneficial effect in the treatment of antibody-mediated rejection resistant to standard therapy after kidney transplantation?

Maéva Massat[1] | Nicolas Congy-Jolivet[2,3,4] | Anne-Laure Hebral[1] | Laure Esposito[1] | Olivier Marion[1,2,5] | Audrey Delas[6] | Magali Colombat[2,6] | Stanislas Faguer[1,2,7] | Nassim Kamar[1,2,5] | Arnaud Del Bello[1,2,5] | the Toulouse Acquired Immune Deficiency,

Retrospective, propensity score matched comparative study of **n = 9** patients who received **rescue treatment** with tocilizumab **after treatment with rituximab, plasmapheresis, and IVIG** and compared this with **n = 37 patients**



SOC	n= 14	12	12	12	11
SOC+ tocilizumab	n = 7	6	5	5	5



SOC	n= 14	12	12	12	11
SOC+ tocilizumab	n = 7	6	5	5	5

It should be noted that the included patients suffered from both **acute and chronic ABMR** , as well as **mixed-type rejection**, which may have influenced the outcomes.

Received: 15 July 2022 | Revised: 30 August 2022 | Accepted: 23 September 2022

DOI: 10.1111/ajt.17207

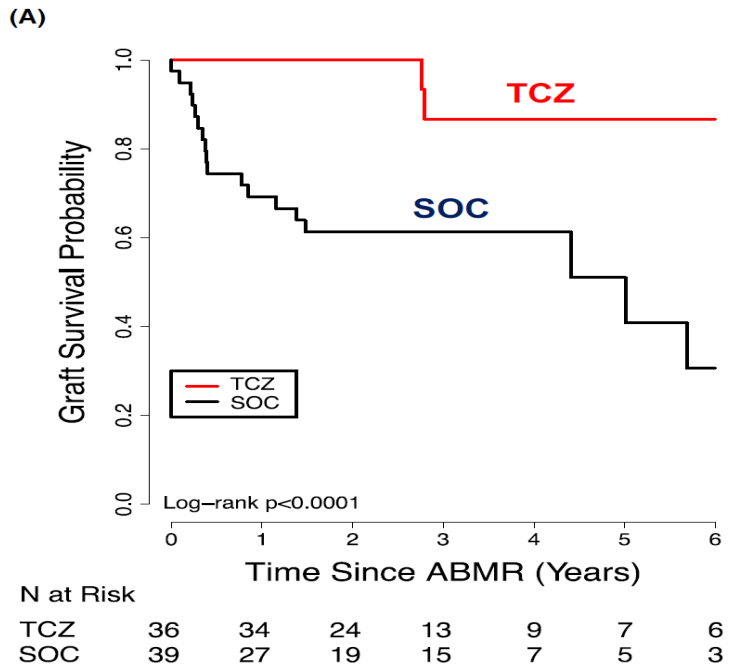
SPECIAL ARTICLE

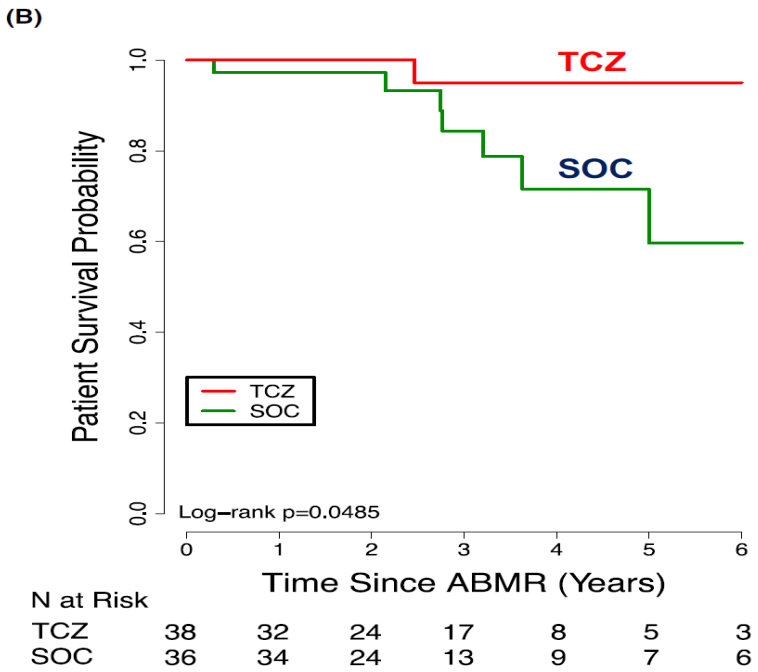
AJT

Importance of IL-6 inhibition in prevention and treatment of antibody-mediated rejection in kidney allografts

Stanley C. Jordan | Noriko Ammerman | Edmund Huang | Ashley Vo

patients with cAMR + TG receiving6–12 months of tocilizumab ***N* = 37** treatment compared to a historical cohort of patients treated with PLEX , IVIg, and rituximab (*N* = 39)





Kaplan–Meiergraph assessment of allograft survival and patient survival in patients with cAMR who were treated with standard of care SOC) consisting of IVIg + Rituximab ±PLEX versus patients who failed SOC and were treated with tocilizumab (TCZ) for 6-12M.

Clazakizumab

✓Clazakizumab is a humanized monoclonal antibody with a high affinity for the **cytokine IL-6 receptor**(not its soluble) which is the target of tocilizumab.

✓Its mechanism of action is to **bind to IL-6 cytokines**, which prevents association of IL-6 with IL-6 R and inhibits its effector functions.

✓It is the **most potent and longest-acting** in the **IL-6/IL-6R blocking Category.**

Anti-Interleukin-6 Antibody Clazakizumab in Late Antibody-Mediated Rejection

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

Phase 2 RCT (Vienna, Berlin)

20 renal allograft recipients
DSA-positive ABMR
≥365 days after transplantation
eGFR >30 mL/min/1.73 m²

n=10 | n=10

3 months

Part A: Clazakizumab (25 mg SC, monthly) | Placebo (monthly)

9 months

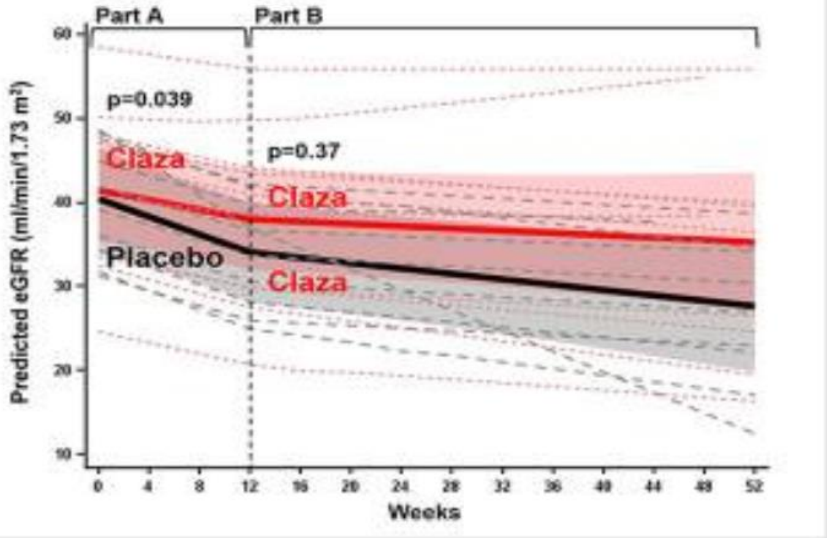
Part B: Clazakizumab (25 mg SC, monthly) | Clazakizumab (25 mg SC, monthly)

Primary endpoint
Safety & tolerability

Key secondary endpoints
DSA levels, biopsy results, eGFR decline

OUTCOME

- 5 serious infections, 2 diverticular disease complications
- Reduction of DSA levels & ABMR activity
- Modulation of eGFR decline



Conclusion
- Safety signals warrant careful evaluation in future trials
- Preliminary outcome results suggest potential efficacy

doi: 10.1681/ASN.2020071106

Doberer at al.

J Am Soc Nephrol. 2021 Mar; 32(3): 708–722.

Evaluation of Clazakizumab (anti-IL-6) in Patients with Treatment-Resistant Chronic Active Antibody Mediated Rejection of Kidney Allografts

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods

Single center
Phase 2, Open label
Feb '18 - Jan '19

n = 10
Age = 15 to 75 years

Biopsy proven chronic active antibody mediated rejection (cAMR)

Intervention

Clazakizumab
25 mg s/c

Monthly x 12

6 month protocol biopsy

At 12 months, stable patients entered a long term extension (LTE)

Results

In months		eGFR ml/min/1.73m²	DSAs mean MFI
At	-24 M	52.8 ± 14.6	-
	-12 M	-	7,412 ± 5,228
	0 M	38.1 ± 12.2	9,625 ± 5,745
	+12 M	41.6 ± 14.2	5,469 ± 7,675
	+24 M	38.1 ± 20.3	4,167 ± 7,188

Banff 2017 analysis of pre- and post-treatment biopsies showed reductions in g+ptc & C4d scores

- Adverse effects minimal
- Graft loss in 2 patients who discontinued Clazakizumab at 6 M and 12 M

eGFR - estimated glomerular filtration rate DSAs - donor specific antibodies g+ptc - glomerulitis + peritubular capillaritis

KI REPORTS
Kidney International Reports

Jordan et al, 2021

Visual abstract by:
Krithika Mohan, MD, DNB
@krithicism

Conclusion In this small cohort of cAMR patients, a trend towards stabilization of eGFR, reductions in DSA, and graft inflammation. No significant safety issues were observed. A trial (IMAGINE) of Clazakizumab in cAMR treatment is underway [NCT03744910].

Non depleting antibodies
Belimumab

- ✓Belimumab is a humanized **anti-B lymphocyte stimulator (BLyS) IgG1 monoclonal antibody**.

- ✓Binding of **belimumab to the TNF receptor** prevents the **survival**, **maturation** and **activation of B lymphocytes** and their **differentiation**

  into plasma cells.

- ✓**Belimumab** has been studied for the **prevention of AMR in a phase 2** randomized controlled trial of **28** kidney transplant recipients

- ✓Belimumab therapy in kidney transplant recipients with **active AMR has not been well studied**.

- ✓In a **case report of a combined kidney–pancreas** transplant recipient with **mixed rejection of the kidney allograft**, belimumab was utilized for **persistent DSA and inflammation** following
- ✓conventional treatment with TPE, rituximab, and IVIg.

- ✓The patient was noted to have a **reduction in class II DSA improved graft function**.

Antibody targeted therapy

- ✓**Imlifidase**
- ✓an **IgG-degrading enzyme** of streptococcus pyogenes, may rapidly reduce or even eliminate anti-HLA DSA, and is currently undergoing clinical trials in AMR.

- ✓This enzyme **cleaves human IgG** at a highly specific amino acid sequence and **effectively blocks complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity**.

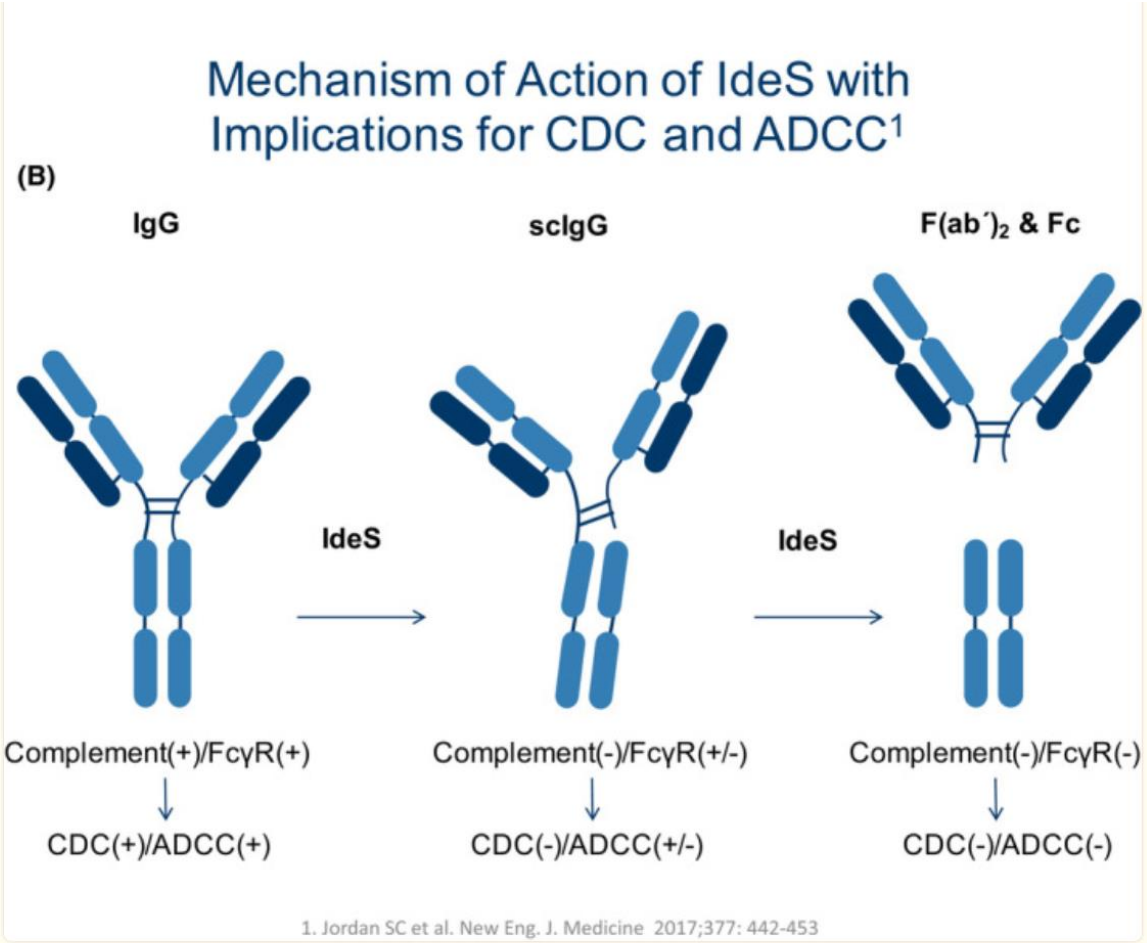


FIGURE 1

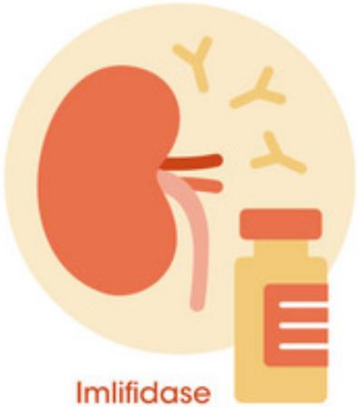
(A) Mechanisms of action of IdeS (IgG endopeptidase). (B) Implications of IdeS on IgG-mediated effector functions

Am J Transplant. 2022;22:691–697

- ✓Winstedt *et al.studied* **n = 29** healthy male subjects in a phase I.
- ✓In contrast to plasma exchange, imlifidase rapidly depletes **IgG within hours** and also cleaves **extravascular IgG**.
- ✓doses of 0.12 or 0.24 mg/kg IV
- ✓ However, imlifidase has a **short-term effect** since intact IgG **returned within one week to two months** .

Outcomes at 3 years post-transplant in imlifidase-desensitized kidney transplant patients

What are the clinical outcomes for crossmatch positive kidney Tx recipients who receive imlifidase prior to transplant?



4

Pooled analysis of four single-armed open-label phase II studies (39 patients)

At 3 years postTx, assessed:

- Patient survival
- Graft survival / function
- DSA levels
- AMR rates

At 3 years postTx, recipients of imlifidase-enabled allografts had comparable outcomes to other highly sensitized patients undergoing HLA-incompatible Tx

90% Patient survival

84% Graft survival

38% AMR rate

AJT

Kjellman et al | *Created by the AJT Editorial Office* | 10.1111/ajt.16754

Am J Transplant. 2021. https://doi.org/10.1111/ajt.16754 .

CD38-directed therapy

- ✓**CD38** is a glycoprotein which is expressed on the **surface of plasma cells**, as well as **NK cells**, **B-** and **T lymphocytes**.
- ✓**Daratumumab** is a monoclonal antibody directed against CD38.
- ✓ In **macaques**, treatment with daratumumab significantly reduced DSA concentrations and prolonged kidney graft survival.
- ✓However, **regulatory lymphocytes were also depleted** after daratumumab, which could have contributed to the development of TCMR.

- ✓ For the treatment of ABMR in kidney transplantation, daratumumab has only been described in **three case reports** .

- ✓ Doberer *et al.* described **a kidney transplant recipient** with both **smoldering myeloma and chronic, active ABMR** in which **graft function stabilized** after a **nine-month course of daratumumab**
- ✓ This was accompanied by **improved histology on kidney biopsy (**resolution of the microvascular inflammation.**1**
- ✓ **Jordan *et al*.** reported **a patient** with **severe ABMR that was resistant** to plasma exchange, IVIG, rituximab, and complement-inhibition who was treated with four-weekly doses of daratumumab (16 mg/kg).
- ✓ After treatment, **ABMR resolved but the patient developed severe TCMR. 2**

Spica *et al*. presented a patient with **ABMR due to anti-blood group antibodies**. This patient did not respond to immunoadsorption, high-dose glucocorticoids, rATG and complement inhibition and was then treated with daratumumab because of

- ✓ persistent antibody formation After daratumumab treatment, **kidney function recovered** and antibody titers decreased.**3**

1Transplantation 105(2):p 451-457, February 2021

2*Blood* (2023) 142 (Supplement 1):.
3Case Rep Nephrol Dial 2019;9:149–157

Review

Emerging Therapies for Antibody-Mediated Rejection in Kidney Transplantation

Farah Abuazzam [1], Casey Dubrawka [2], Tarek Abdulhadi [1], Gwendolyn Amurao [1], Louai Alrata [1], Dema Yaseen Alsabbagh [1], Omar Alomar [1] and Tarek Alhamad [1,3,*]

Name of Drug	Mechanism of Action	Use in Kidney Transplant	Type of Study	Participants	Efficacy Measures	Reported Side Effects
Carflizomib	Protesome inhibitor	Acute AMR	Clinical Trial	6 non-human subjects	DSAs, kidney rejection scores	Acute kidney injury, thrombocytopenia, infections
Tocilizumab	IL-6 receptor inhibitor	Desensitization	Phase I/II clinical trial	10	DSA titers, prevention of AMR	Infections, gastrointestinal perforation, elevation of transaminases
		Acute AMR	Clinical Trial	7	DSA titers	
		Chronic AMR	Multitude of Studies	36/15/10	DSA titers, histology, proteinuria	
Clazakizumab	IL-6 inhibitor	Refractory AMR, currently being studied for use in chronic AMR	Phase II single center open label study	10	eGFR, DSA titers, graft inflammation	Diverticulitis, pleural effusion, acute kidney injury
Daratumumab	Monoclonal antibody targeting CD38	Desensitization	Clinical trial	8 non-human subjects and 2 human subjects	DSA titers	Infusion-related reaction, volume overload, hypogammaglobulinemia, myelosuppression, gastrointestinal upset, infection
		Acute AMR	Multiple case reports	multiple	Graft function	
		Chronic AMR	Case report	2	DSA titers, graft function	
Belimumab	Anti-B lymphocyte simulator (BLyS)	Prevention of AMR	Phase II clinical trial	28	Comparison to standard of care results and infection rates	Gastrointestinal upset, dizziness, infection, depression, diabetes
Imlifidase	Recombinant cysteine protease	Desensitization	Multicenter clinical trial	39	Graft survival, patients survival, rates of AMR	Well tolerated, safety is currently being studied
Obintuzumab	Anti-CD20	Desensitization	Phase I clinical trial	24	Adverse events, B-Cell depletion	Infections, thrombocytopenia, infusion-related reactions, cardiac events

Conclusions

- ✓ **Conventional therapies for AMR are still not optimal**, with high rates of graft loss leading to poor patient outcomes.
- ✓ Clearly, additional studies to define the optimal treatment of AMR are needed.

- ✓ Surveillance protocols with **donor-derived cell-free DNA** and **gene profile testing** have
- ✓ been established, leading to the **early detection of AMR**.

- ✓ A multitude of clinical trials are ongoing, opening numerous opportunities for improving outcomes in kidney transplant recipients

- ✓ Newer therapies that target novel pathways in the AMR pathologic process are promising, but **randomized studies are vital** given the lack of randomized studies with **adequate statistical power** to compare the safety and efficacy of these novel therapeutics.

Thank you for you attention