Update on Therapeutic Strategies for Chronic AMR in Kidney Transplantation

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Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

REVIEW ARTICLE

Incidence, risk factors, treatment, and consequences of antibody-mediated kidney transplant rejection: A systematic review

Allyson Hart, Devender Singh, Sarah Jane Brown, Jeffrey H. Wang, Bertram L. Kasiske

First published: 17 April 2021 | https://doi.org/10.1111/ctr.14320 | VIEW METRICS

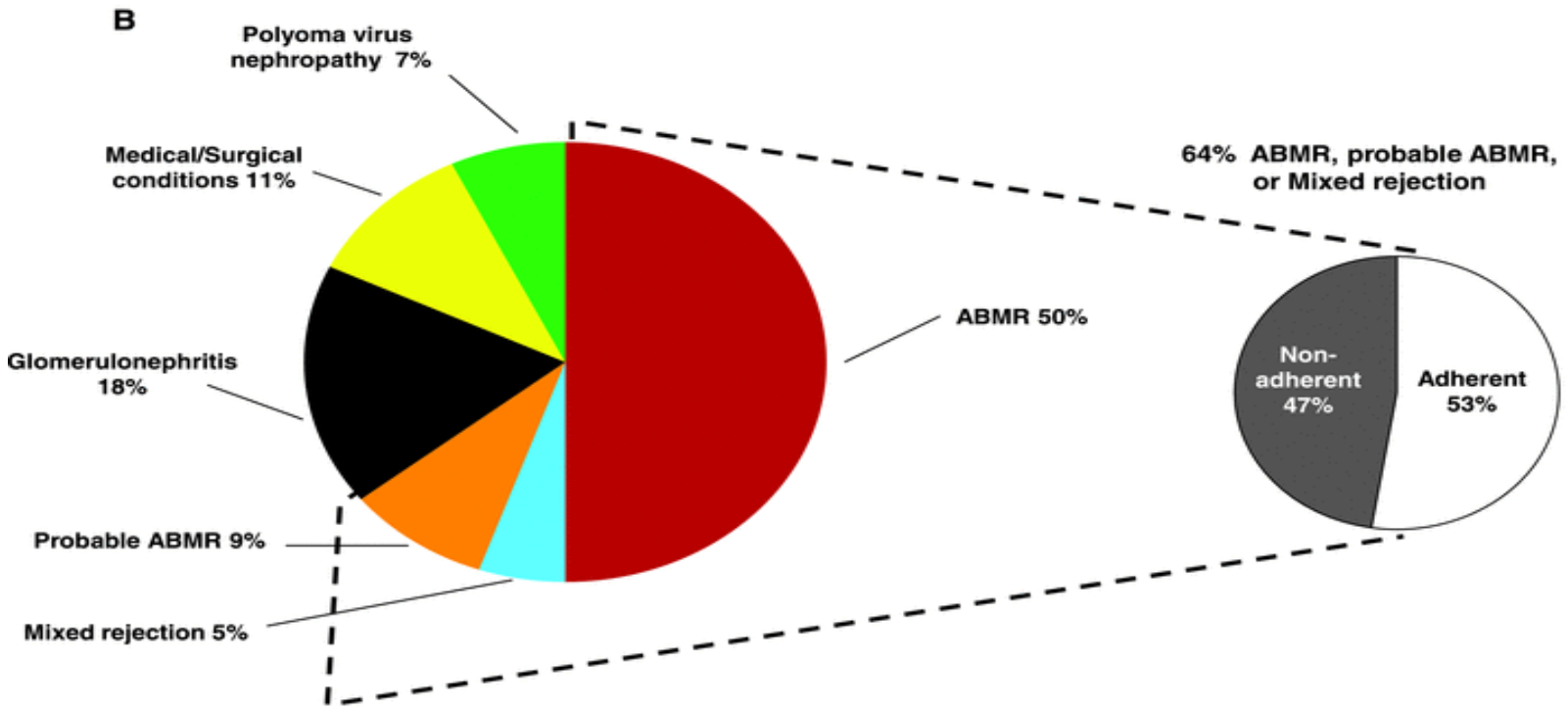
A **systematic review** of **28 studies** reported AMR incidences ranging from 3- 12%, with **chronic AMR** affecting **7.5- 20.1% of patients over 10 years**.

- **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

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,

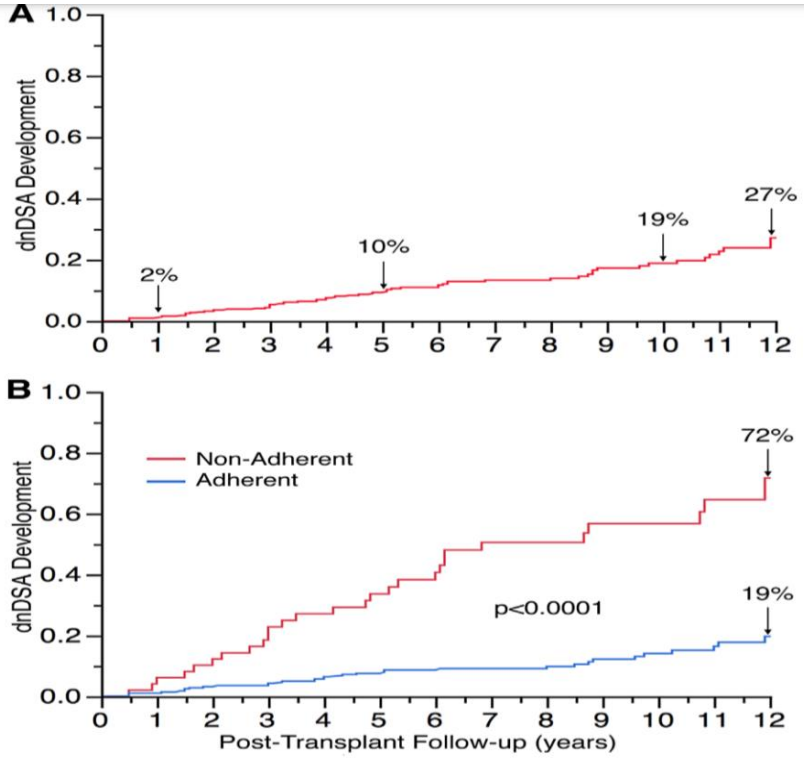


Figure 1: *dn*DSA free survival. Kaplan–Meier plot of *dn*DSA-free survival over time posttransplant (A), split by adherence (B). *dn*DSA, *de novo* donor-specific antibody.

- 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

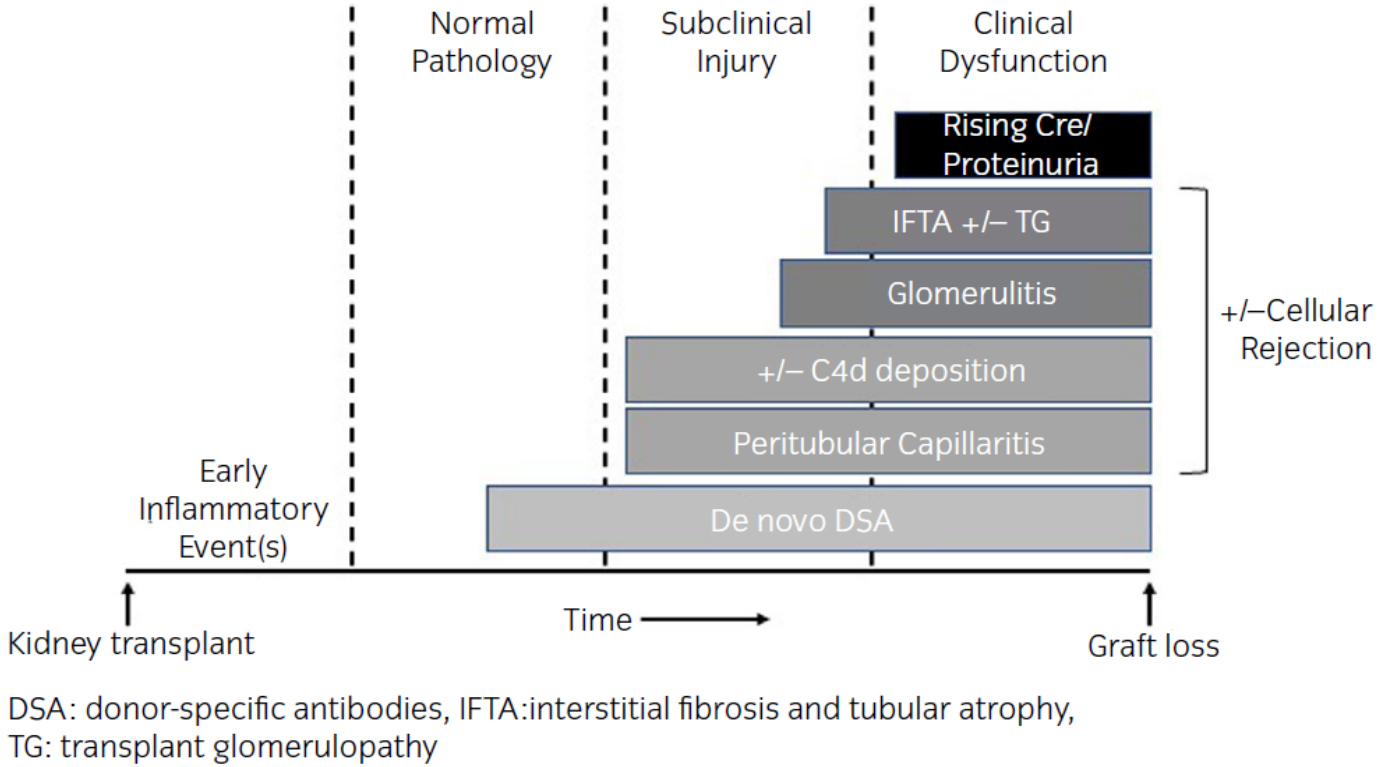


FIGURE 1 A proposed natural history for graft loss due to de novo donor-specific antibodies. Wiebe et al.[8] proposed a model for a continuum of antibody-mediated damage based on the primate studies.[66] The production of dnDSA after transplantation is preceded by early inflammatory events, such as cellular 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]).

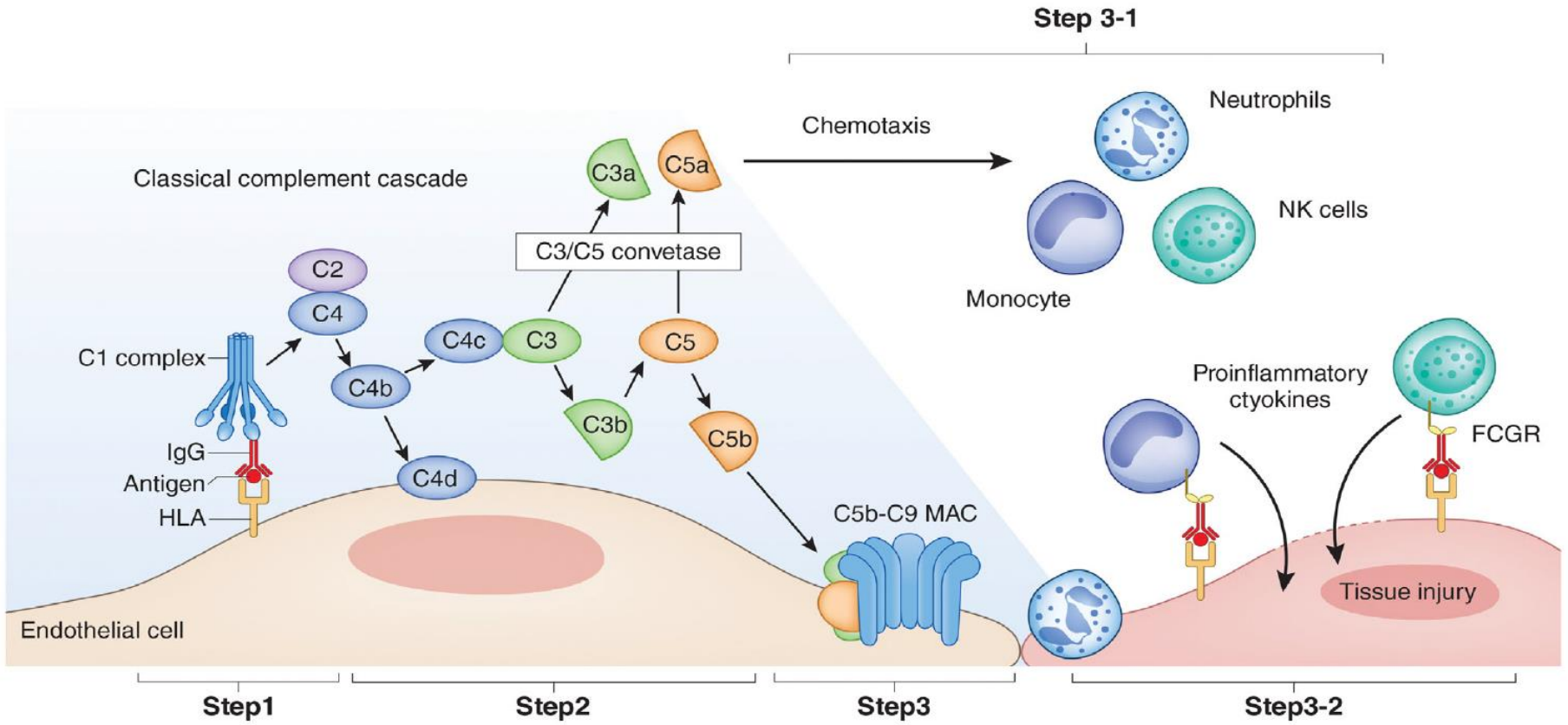
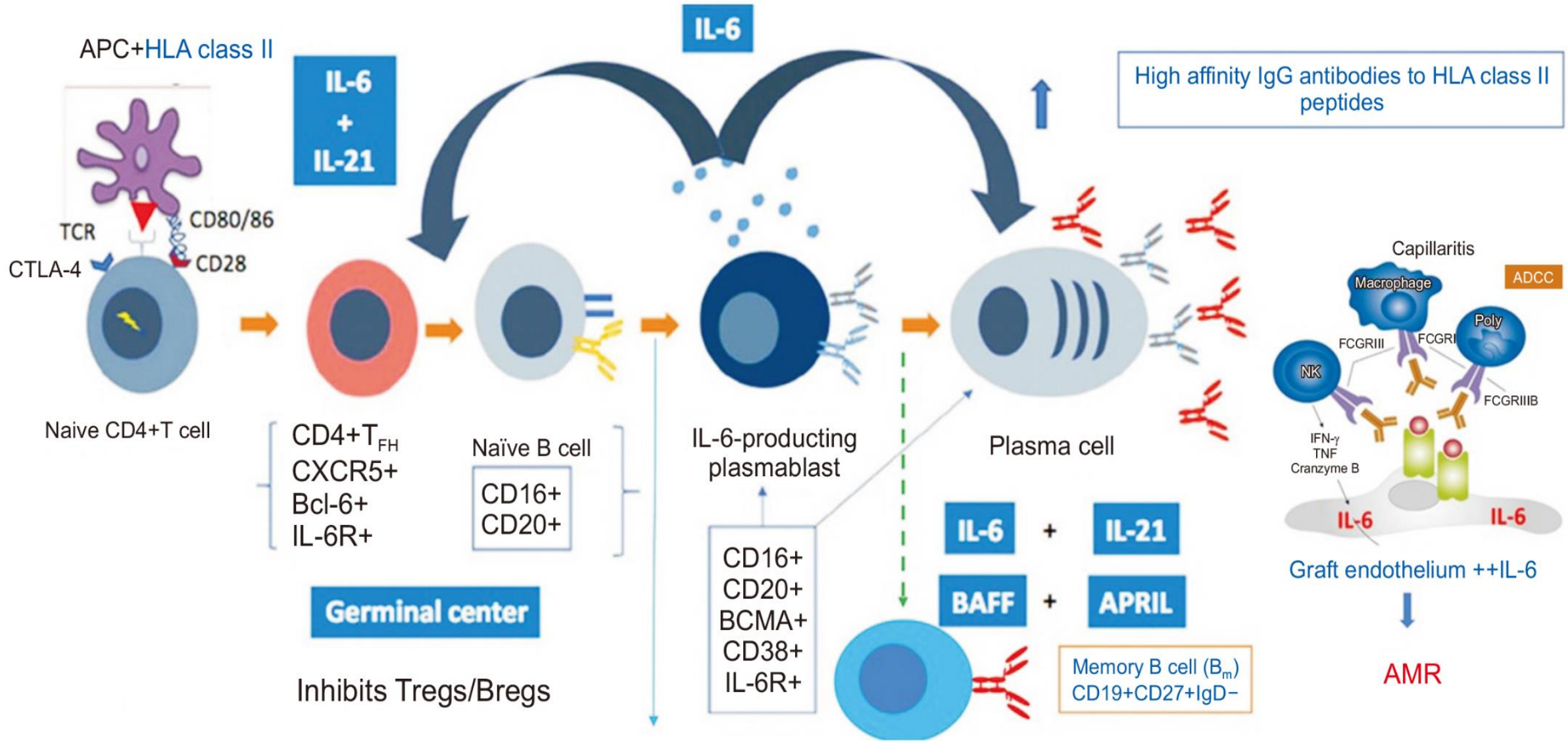


FIGURE 3 Possible mechanism of chronic antibody-mediated injury via donor-specific antibodies and complement activation. The C1 complex is activated by DSA (shown as IgG), resulting in the generation of C3a and C5a. C3a and C5a act as anaphylatoxins to promote the migration of inflammatory cells (natural 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.

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


APC+HLA class II
TCR
CD80/86
CTLA-4
CD28
Naive CD4+T cell
IL-6
+
IL-21
CD4+T$_{FH}$
CXCR5+
Bcl-6+
IL-6R+
Naïve B cell
CD16+
CD20+
Germinal center
Inhibits Tregs/Bregs
IL-6
IL-6-producting plasmablast
CD16+
CD20+
BCMA+
CD38+
IL-6R+
Plasma cell
High affinity IgG antibodies to HLA class II peptides
IL-6 + IL-21
BAFF + APRIL
Memory B cell (B$_m$)
CD19+CD27+IgD−
Capillaritis
ADCC
Macrophage
Poly
NK
FCGRIII
FCGRI
FCGRIIIB
IFN-γ
TNF
Cranzyme B
IL-6
IL-6
Graft endothelium ++IL-6
AMR

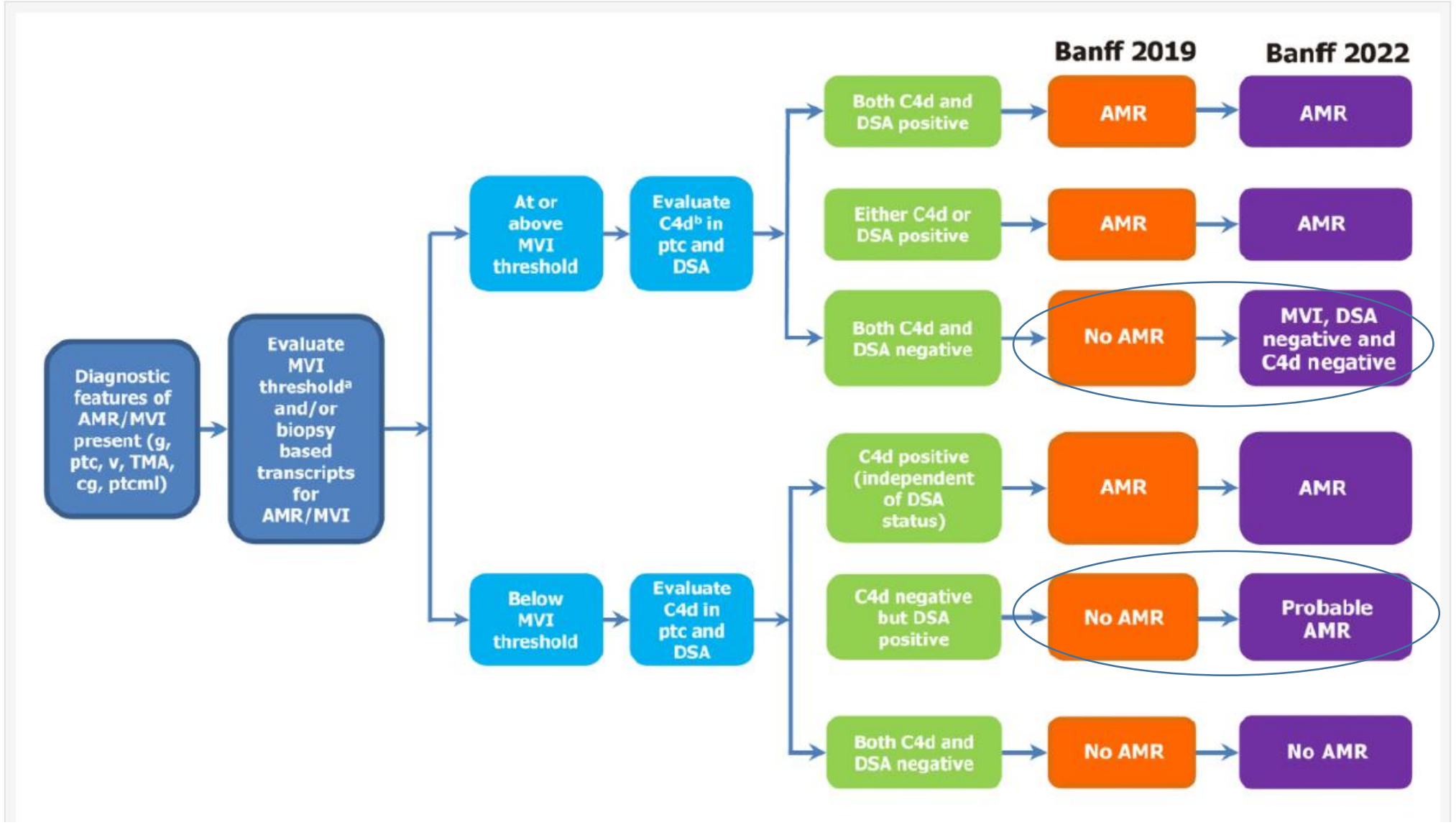
World Journal of Transplantation

Review Open Access

World J Transplant. Mar 18, 2026; 16(1): 111524
Published online Mar 18, 2026. doi: 10.5500/wjt.v16.i1.111524

Update on diagnostic and therapeutic strategies for antibody-mediated rejection in kidney transplantation

Tabassum Elahi, Saima Ahmed, Muhammed Mubarak


Banff 2019
Banff 2022
Diagnostic features of AMR/MVI present (g, ptc, v, TMA, cg, ptcml)
Evaluate MVI threshold[a] and/or biopsy based transcripts for AMR/MVI
At or above MVI threshold
Below MVI threshold
Evaluate C4d[b] in ptc and DSA
Evaluate C4d in ptc and DSA
Both C4d and DSA positive
AMR
AMR
Either C4d or DSA positive
AMR
AMR
Both C4d and DSA negative
No AMR
MVI, DSA negative and C4d negative
C4d positive (independent of DSA status)
AMR
AMR
C4d negative but DSA positive
No AMR
Probable AMR
Both C4d and DSA negative
No AMR
No AMR

- Clinical management of chronic AMR remains particularly challenging.

- Current therapeutic strategies primarily aim to **slow the progression** of graft injury rather than reverse established damage, in part because of the limited availability of agents that effectively target **antibody- producing plasma cells**.

- Emerging therapies such as **IL-6 receptor antagonists** like tocilizumab, clazakizumab, and **CD38 monoclonal antibody** like felzartamab offer promising avenues for intervention and may help to reshape the landscape for Chronic AMR.

World Journal of Transplantation,Mar 18, 2026; 16(1): 11524

Transcriptomic signatures of chronic active antibody-mediated rejection deciphered by RNA sequencing of human kidney allografts.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Cohort

57 adult recipients of kidney allografts

57 allograft biopsies

39 Rejection ← For-cause

18 No Rejection ←Per-protocol

Banff 2019- All criteria met

CA-ABMR: N=15

DSA+ in all & C4d+ in 5

active-ABMR: N=7

DSA+ in all & C4d+ in all

Acute TCMR: N=17

No chronic TCMR features

No Rejection (NR): N =18

Acute Banff lesion scores 0 in all

Methods

RNA-Seq

57 biopsies

Illumina sequencer

Standard bioinformatic pipeline

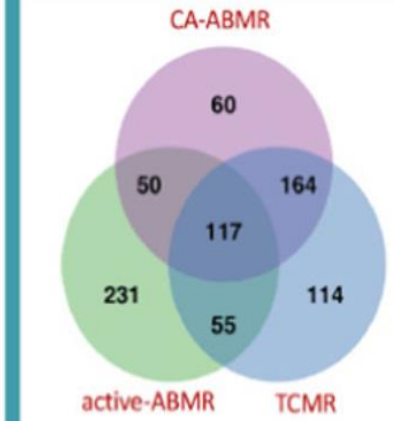
Microarray

Analysis of 2 publicly available kidney allograft datasets

Immunostaining

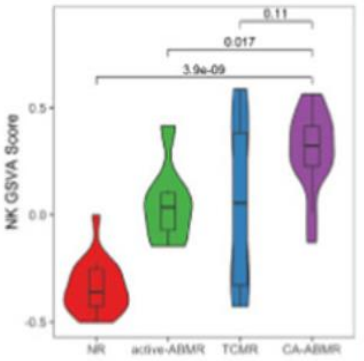
138 consecutive clinically indicated kidney allograft biopsies

Outcomes

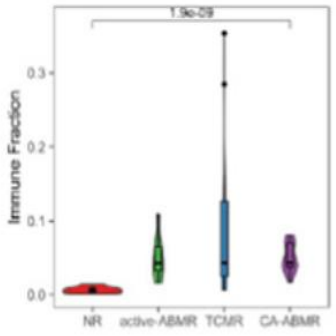


Highly overexpressed genes
(Rejection vs. NR, FDR <0.05 and log_2FC >2)

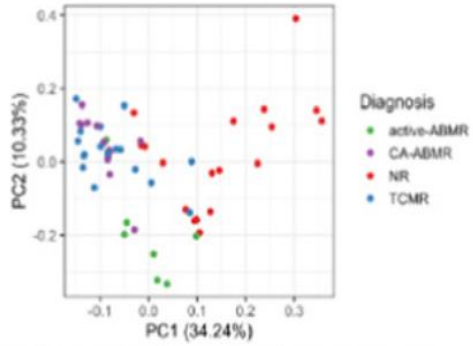
Unique genes (Venn diagram)	PanglaoDB cell type	KEGG pathway
CA-ABMR	NK cells T cells	Allograft rejection NK cell cytotoxicity
Active-ABMR	Neutrophils Monocytes	Cytokine-receptor interaction
TCMR	T cells NK cells	Allograft rejection Th17 differentiation



Gene Set Variation Analysis (GSVA)
NK cell cytotoxicity pathway
Highest score in CA-ABMR



Cellular deconvolution
Immune cell fraction
Similar across the 3 rejection categories



PCA of deconvolved immune cell transcriptomes
CA-ABMR & TCMR separated from
active-ABMR & NR

Microarray datasets
NK cell cytotoxicity pathway GSVA score
Higher in ABMR & TCMR biopsies vs. NR biopsies in GSE36059
Higher in ABMRh biopsies vs. No ABMRh biopsies in GSE147089

Immunophenotyping
Proportion of CD56+ NK cells
Higher in CA-ABMR compared to active-ABMR

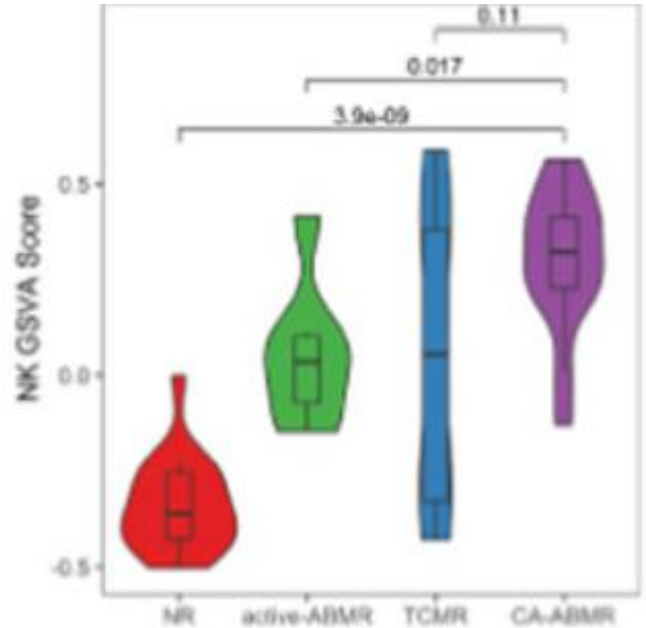
Shah et al., 2023

Conclusions

- CA-ABMR, compared to active-ABMR, is exemplified by the overexpression of the NK cell cytotoxicity pathway gene set
- CA-ABMR is molecularly similar to TCMR than active -ABMR

Highly overexpressed genes
(Rejection vs. NR, FDR <0.05 and log_2FC >2)

Unique genes (Venn diagram)	PanglaoDB cell type	KEGG pathway
CA-ABMR	NK cells	Allograft rejection
	T cells	NK cell cytotoxicity
Active-ABMR	Neutrophils	Cytokine-receptor interaction
	Monocytes	
TCMR	T cells	Allograft rejection
	NK cells	Th17 differentiation



Gene Set Variation Analysis (GSVA)
NK cell cytotoxicity pathway
Highest score in CA-ABMR

Therapeutic goals

- The primary aim is to supress **B cell development,maturation**, and **activity**.
- Initial treatment approach:
- Although **intensifying immunosuppression may seem** logical, the limited supporting data and heightened **risk of infections** warrant a cautious approach
- 2)Firstline therapy: **Glucocorticoids and IVIG**
- 3)Optional addition: **Rituximab** may be considered in patients <70 years age with relatively preserved graft function and severe disease.

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*†]

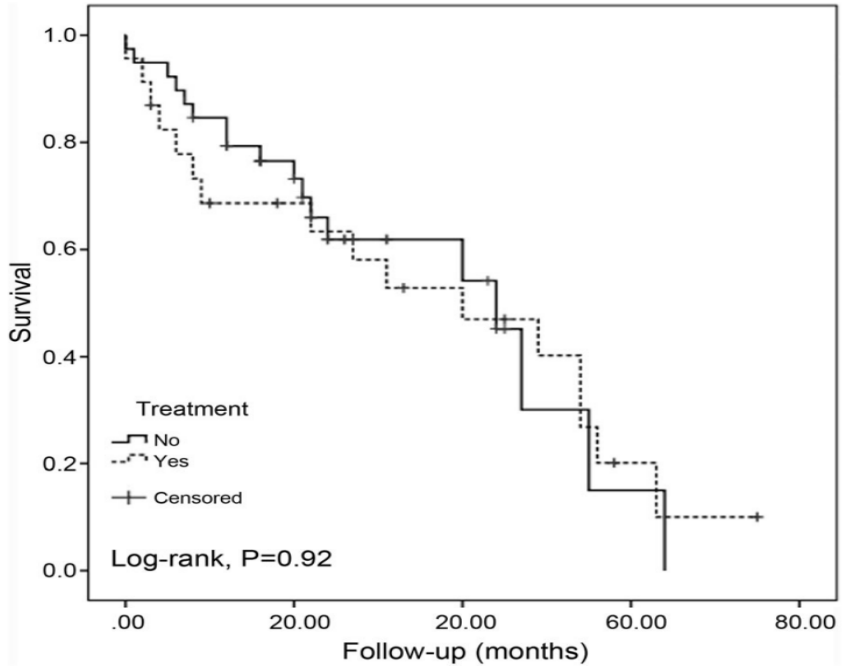


Fig. 1 Renal allograft survival censoring death after c-aABMR diagnose. Treatment: patients under rituximab-containing treatment (yes), control patient group (no). Chronic active antibody-mediated rejection (c-aABMR)

- 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 .

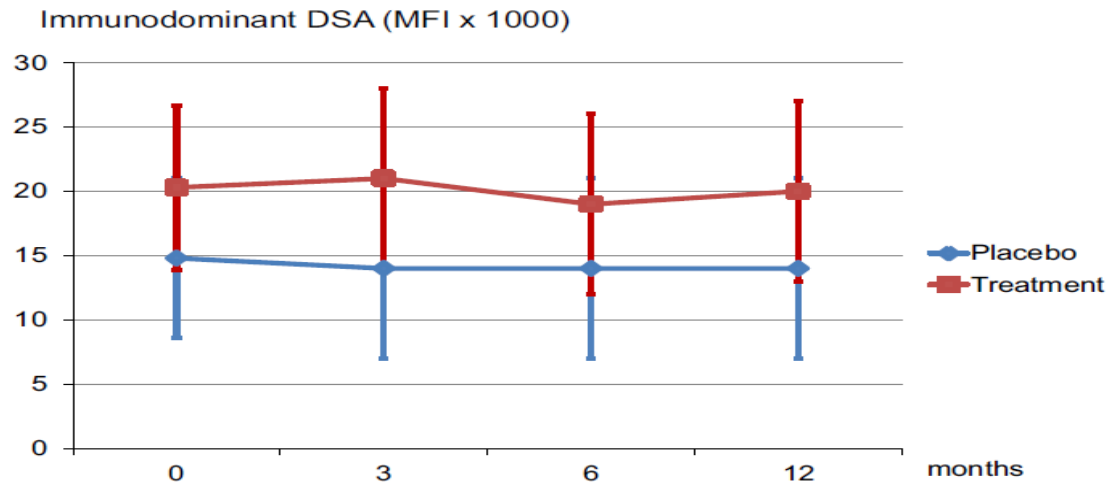


FIGURE 4 Evolution of the MFI of the immunodominant donor specific anti-HLA antibody in the placebo and treatment groups. By mixed linear model *P*-value between groups was .0735; *P*-value 3, 6, and 12 months vs. baseline was >.05. MFI, maximal fluorescence intensity [Color figure can be viewed at wileyonlinelibrary.com]

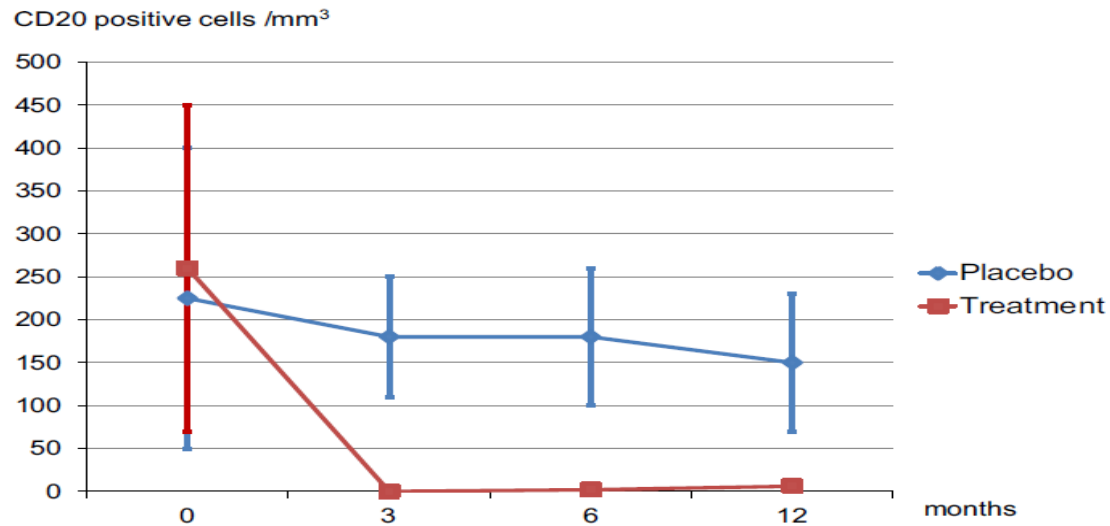


FIGURE 5 Evolution of circulating B lymphocytes in the placebo and treatment groups. By mixed linear model *P*-value between groups was .0036; *P*-value 3, 6, and 12 months vs. baseline was <.001 [Color figure can be viewed at wileyonlinelibrary.com]

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]

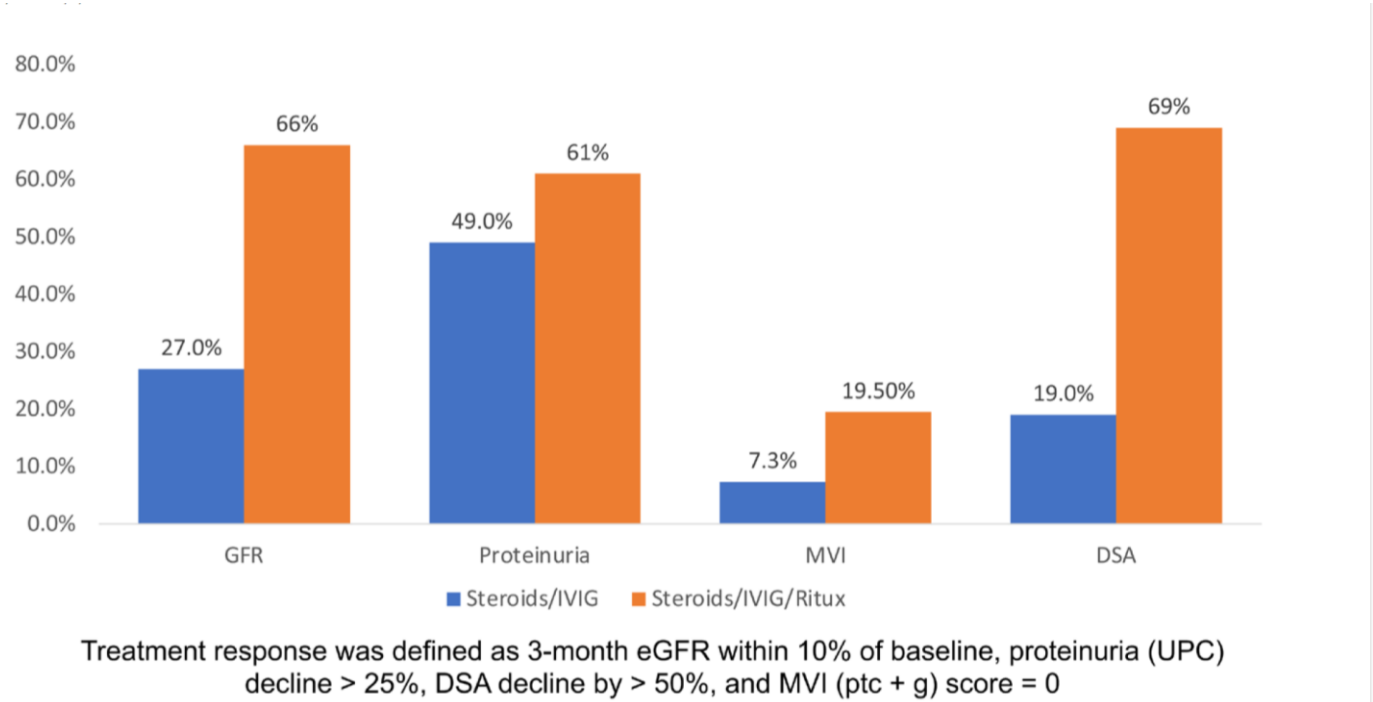


FIGURE 2. Three-month response rates to prescriptions in cAMR. cAMR, chronic active antibody-mediated rejection; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; MVI, microvascular inflammation; UPC, urine-protein creatinine ratio.

n=41 control.n=41 Rituximab

Transplantation Direct 2022;8: e1360

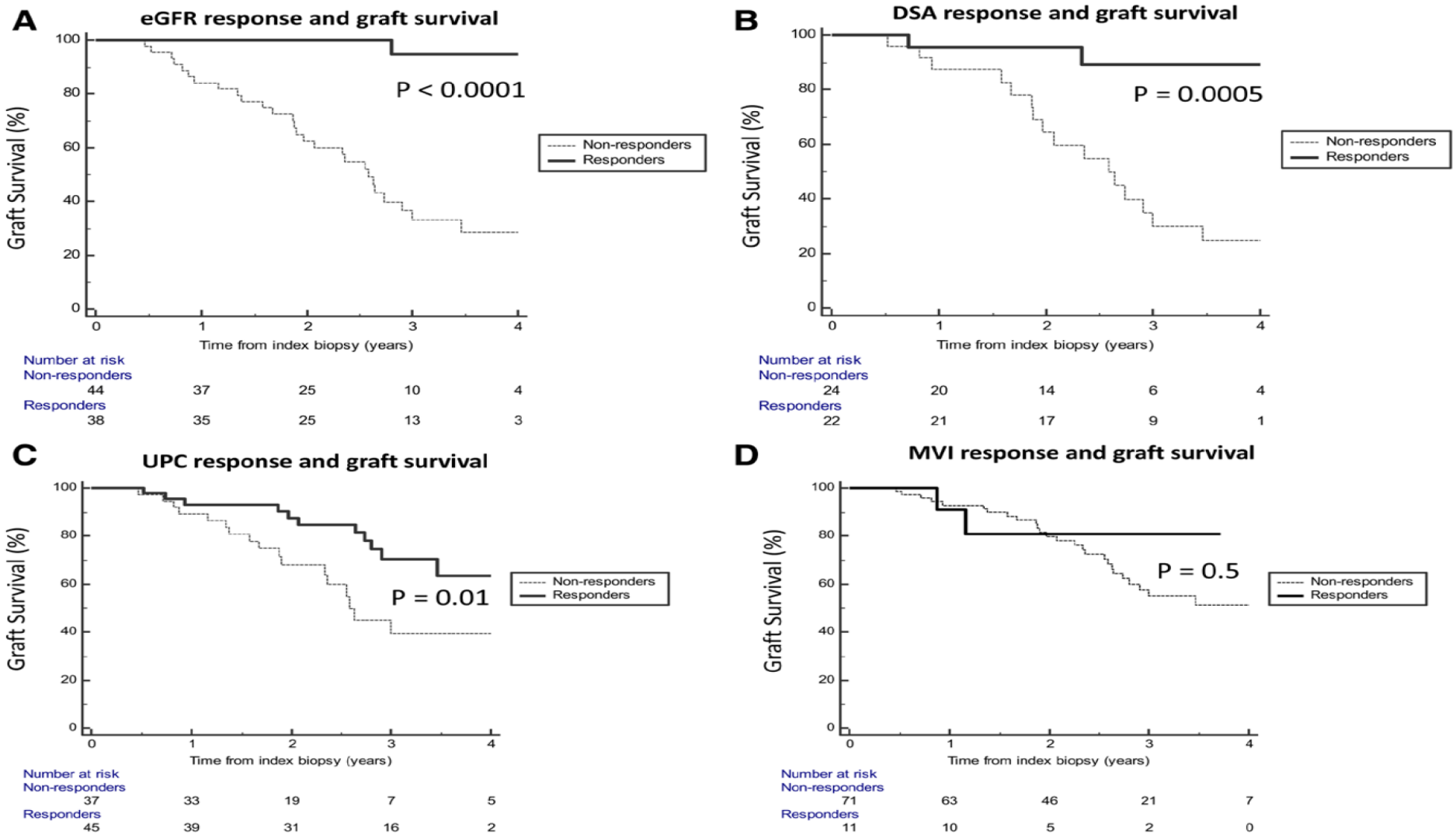


FIGURE 3. Short-term response in kidney function and DSA associated with graft survival. DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; MVI, microvascular inflammation; UPC, urine-protein creatinine ratio.

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	0.013	0.02–0.64
DSA response, yes/no	0.11	0.004	0.026–0.49	1.28		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.

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

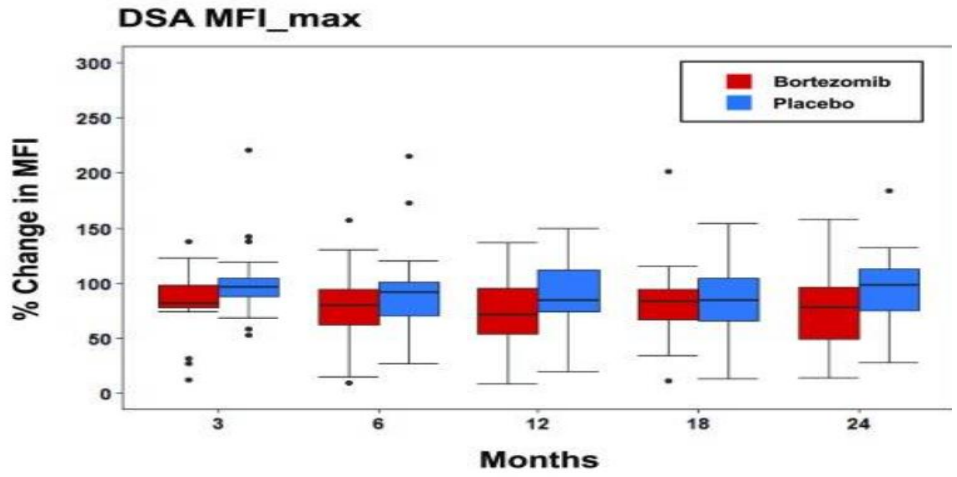
A Randomized Trial of Bortezomib in Late Antibody-Mediated Kidney Transplant Rejection

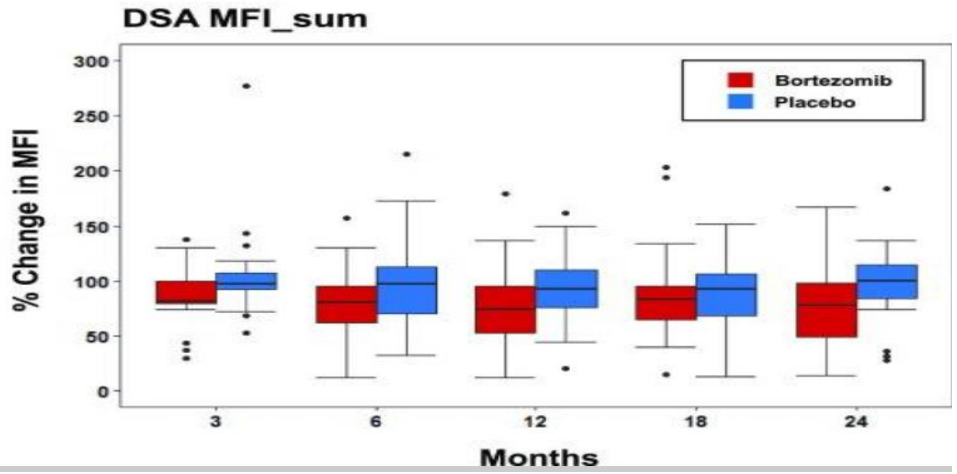
Farsad Eskandary,[1] Heinz Regele,[2] Lukas Baumann,[3] Gregor Bond,[1] Nicolas Kozakowski,[2] Markus Wahrmann,[1] Luis G. Hidalgo,[4] Helmuth Haslacher,[5] Christopher C. Kaltenecker,[1] Marie-Bernadette Aretin,[6] Rainer Oberbauer,[1] Martin Posch,[3] Anton Staudenherz,[7] Ammon Handisurya,[1] Jeff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

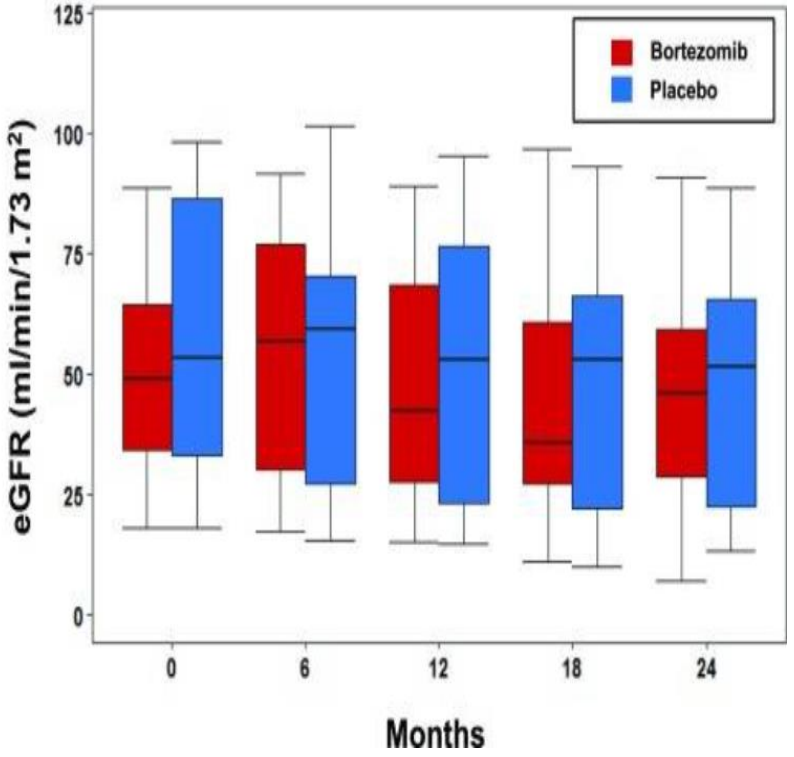
N=44 patients were randomly assigned to receive **two cycles** of either **bortezomib n=21** or **placebo n=23**, at **3-month intervals** in **double-blinded** fashion.

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

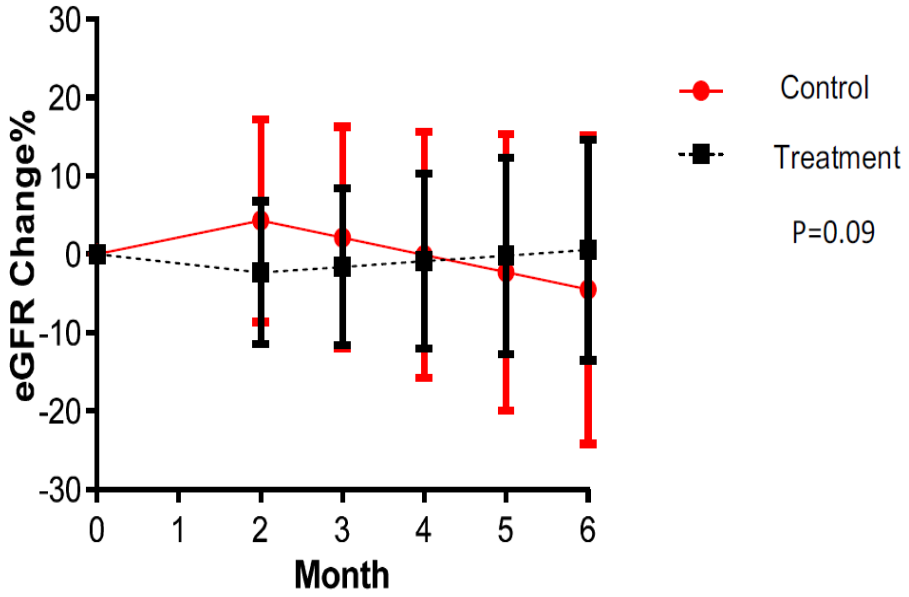
Eculizumab

- 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.

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



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

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

Management of non-responders

- **Tocilizumab** :An anti IL6 receptor monoclonal antibody(8mg/kg IV,max 800mg,monthly)

- **ClazaKizumab**: Another IL6/IL6 receptor antibody

- **Felzartamab**: A CD38 monoclonal antibody targeting **plasma cells** and **NK cells**.

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%**
- **increase regulatory T lymphocyte numbers by 10%**

in a murine skin transplantation model.

- **IL-6** is a relevant target for the treatment of antibody-mediated disorders given its role in driving **B-cell proliferation** **and the maturation** of naive B cells into **plasmablasts** and **long-lived antibody-producing plasma cells**. Both **B cells and plasma cells express IL-6 receptors**, and experimental models have observed that **IL-6 blockade reduces IgG and DSA** production and promotes allograft.
- Importantly, recent data in humans and animal models show that anti-IL-6 treatment **inhibits CD8+ T-effector/memory cells** and induces **T-regulatory cell** populations, which are critical for the prevention of DSA rebound and rejection and extending graft survival

Index and 1 year post–tocilizumab allograft biopsies

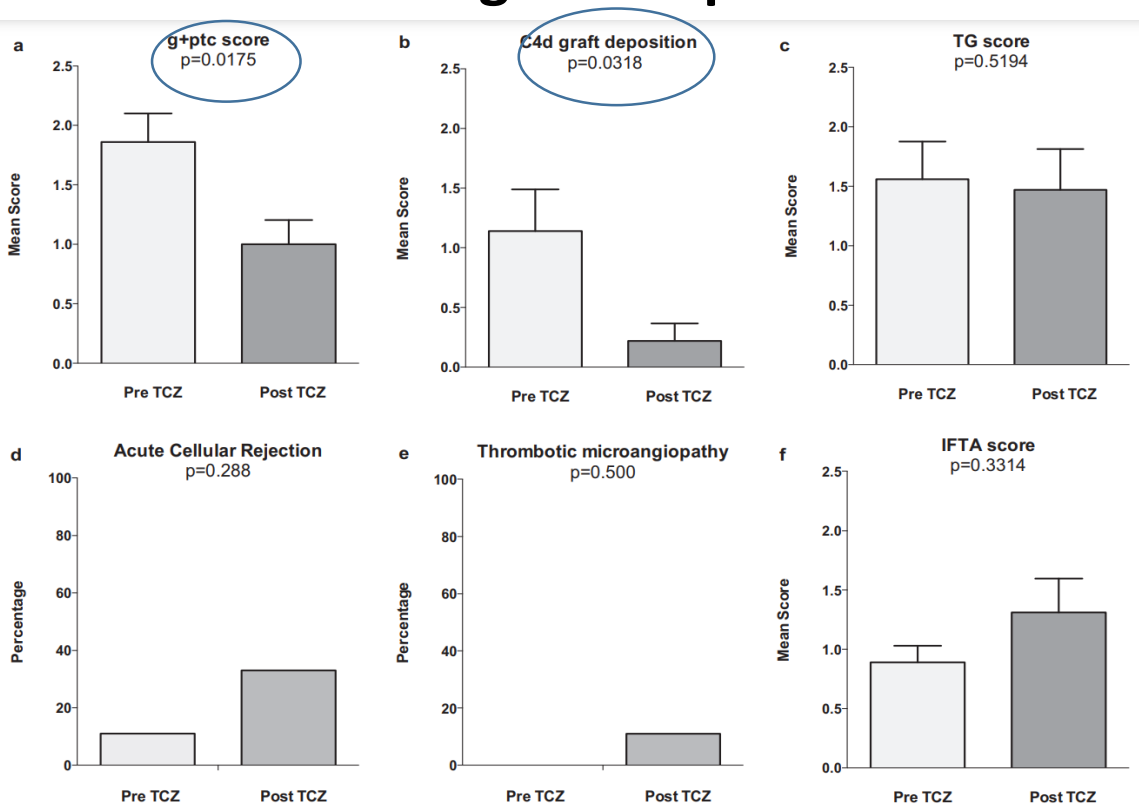


Figure 1: Index and 1 year post–tocilizumab allograft biopsies. (A) Kidney allograft index biopsy phenotypes at the initiation of tocilizumab treatment were obtained for 36 patients. All patients had significant glomerulitis (g), peritubular capilaritis (ptc), C4d positivity, and chronic changes in the 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

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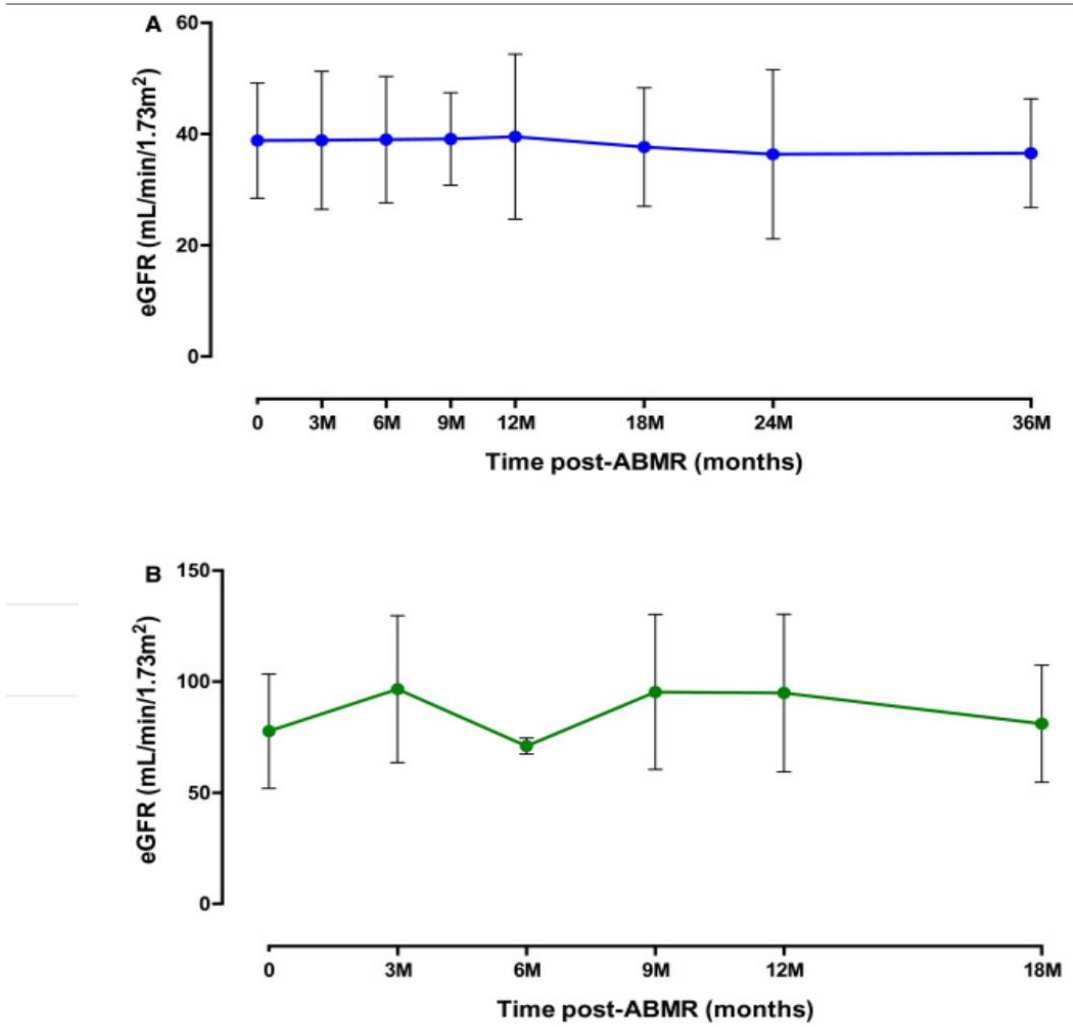
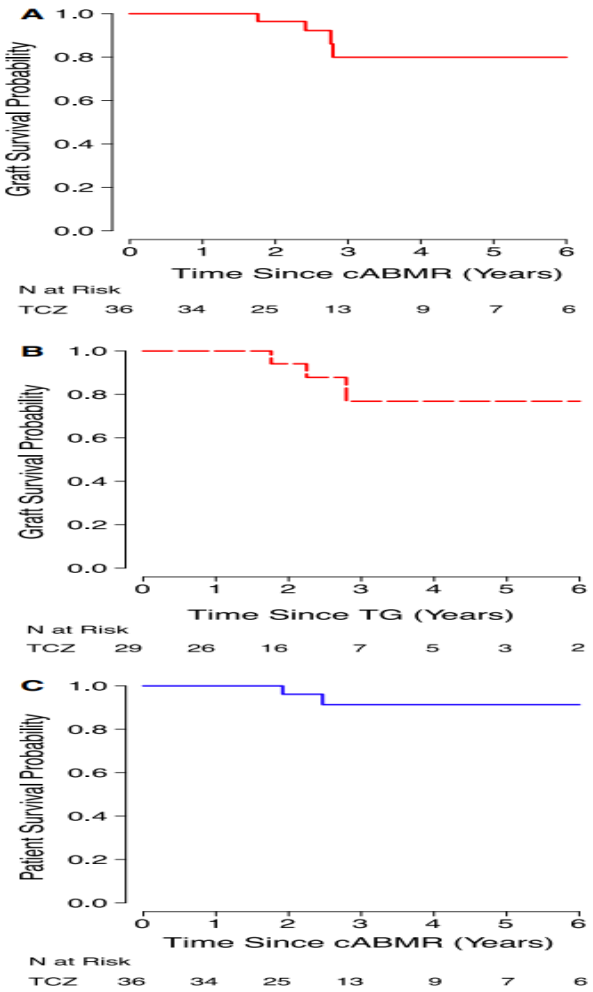


Tocilizumab-treated patients demonstrated graft survival and patient survival rates of 80% and 91% at 6 years, respectively. Significant reductions in DSAs and stabilization of renal function were seen at 2 years. No significant adverse events or severe adverse events were seen.

Kaplan–Meier curves of kidney allograft and patient survival after treatment with -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

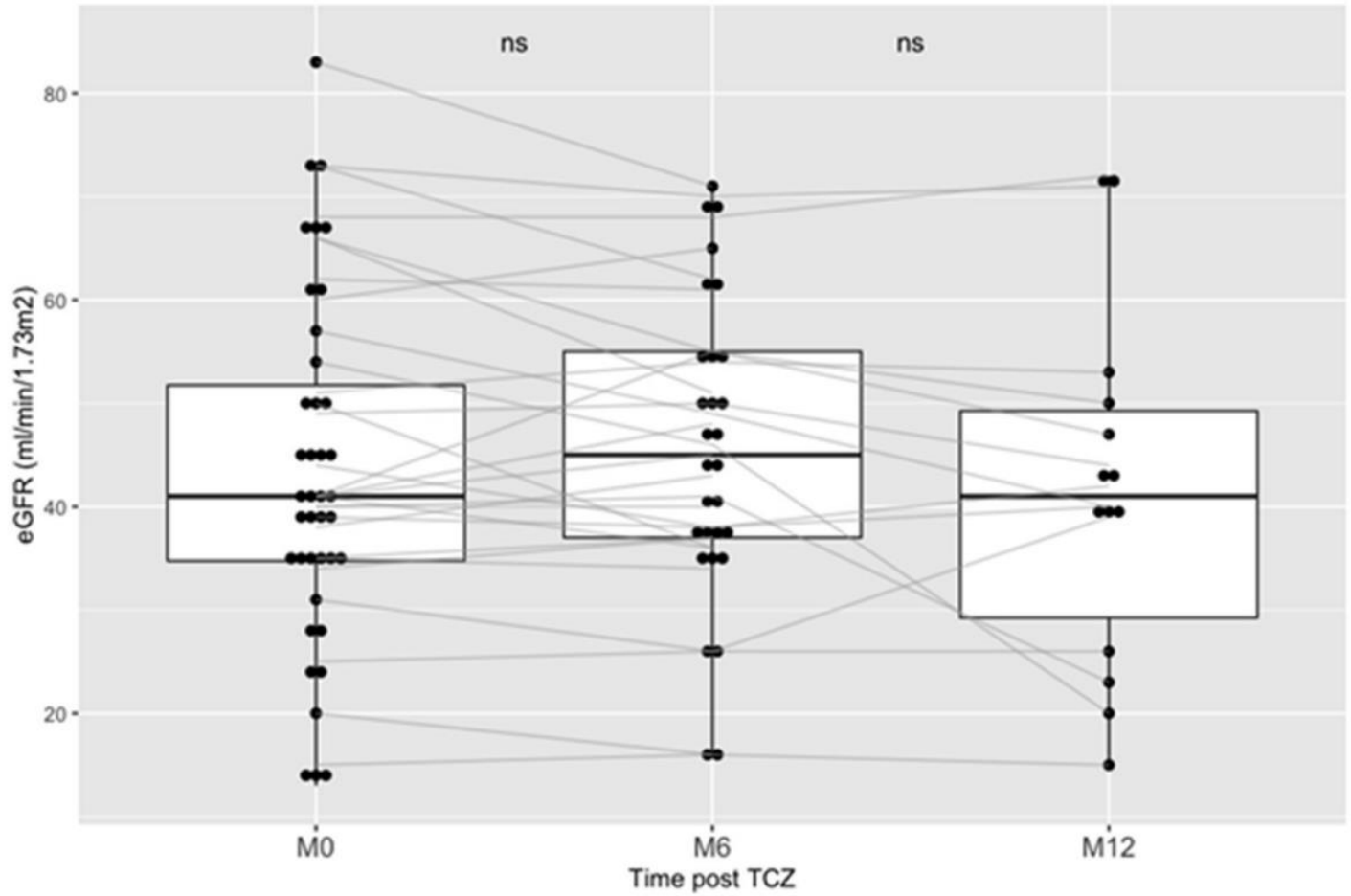


FIGURE 1 | Outcome of eGFR post Tocilizumab in kidney transplanted patients treated for chronic ABMR. Boxplots shows the eGFR (CKD-Epi) of p
of the introduction of TCZ, at Month-6 (M6) and at Month-12 (M12). TCZ stands for Tocilizumab. AMBR stands for antibody-mediated rejection.

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

DOI: 10.1111/ajt.17207

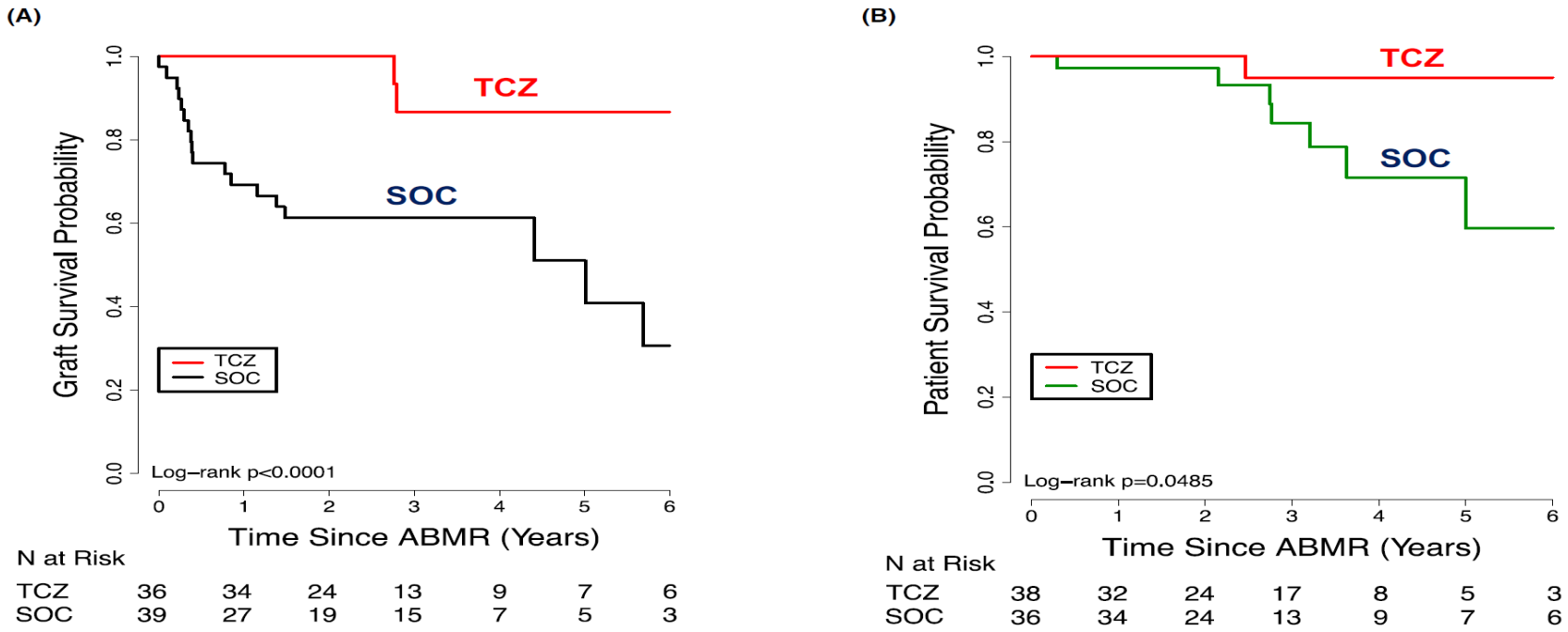
SPECIAL ARTICLE

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

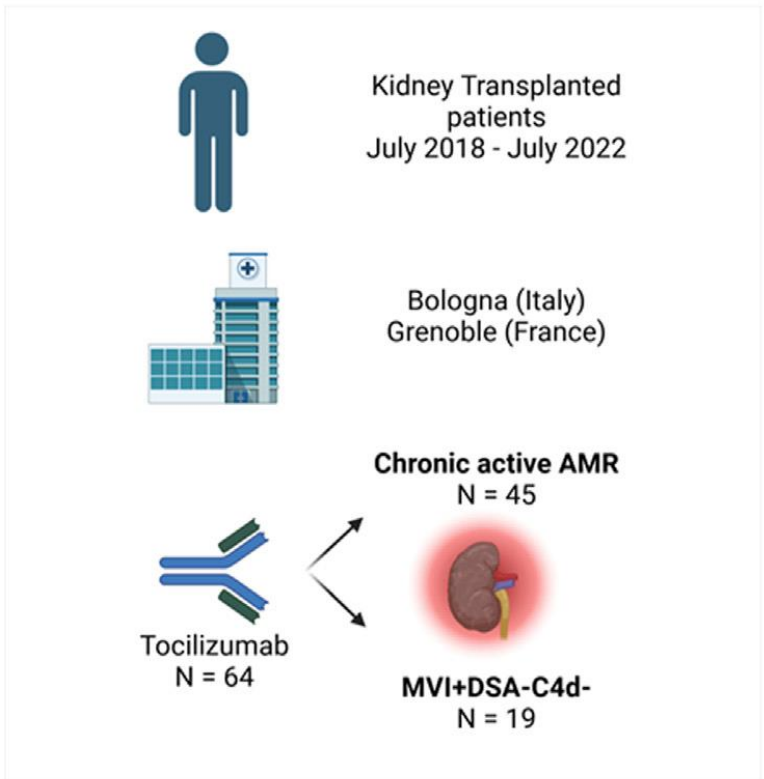
patients with cAMR + TG receiving6–12 months of tocilizumab ***N* = 37** treatment compared to a historical cohort of patients treated with PLEX , IVIg, and rituximab (*N* = 39)

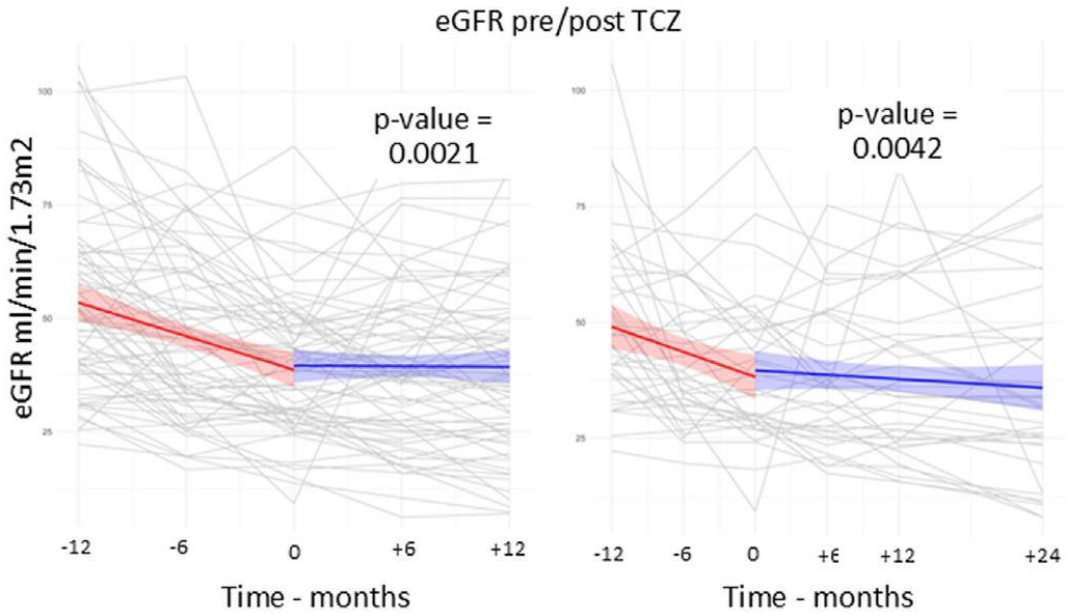


Kaplan–Meiergraph assessment of allograft survival and patient survival in patients with cAMR who were treated with standard of care SOC) consisting of IVIg + Rituximab ±PLEX versus patients who failed SOC and were treated with tocilizumab (TCZ) for 6-12M.

Tocilizumab-Based Treatment of Microvascular Inflammation in Kidney Transplant Recipients: A Retrospective Study

Johan Noble[1,2,3†], Giorgia Comai[4,5†], Valeria Corredetti[4†], Reda Laamech[1†], Celine Dard[6], Thomas Jouve[1,2], Diane Giovannini[7], Audrey Le Gouellec[8], Shivani Wadnerkar[3], Paolo Cravedi[3], Della Apuzzo[4,5], Daniele Vetrano[4,5], Marco Busutti[4], Chiara Abenavoli[4,5], Paolo Malvezzi[1], Lionel PE Rostaing[1,2†] and Gaetano Lamanna[4,5†]*





In multivariate analysis, tocilizumab response (trajectory ≥ 0) was associated with: **younger age** (OR=0.95), **lower chronic glomerulopathy score** (OR=4.5) and **MVI+DSA-C4d- phenotype** (OR=5.2)

Noble J, et al. *Transpl. Int.* 2025
doi: 10.3389/ti.2025.14502

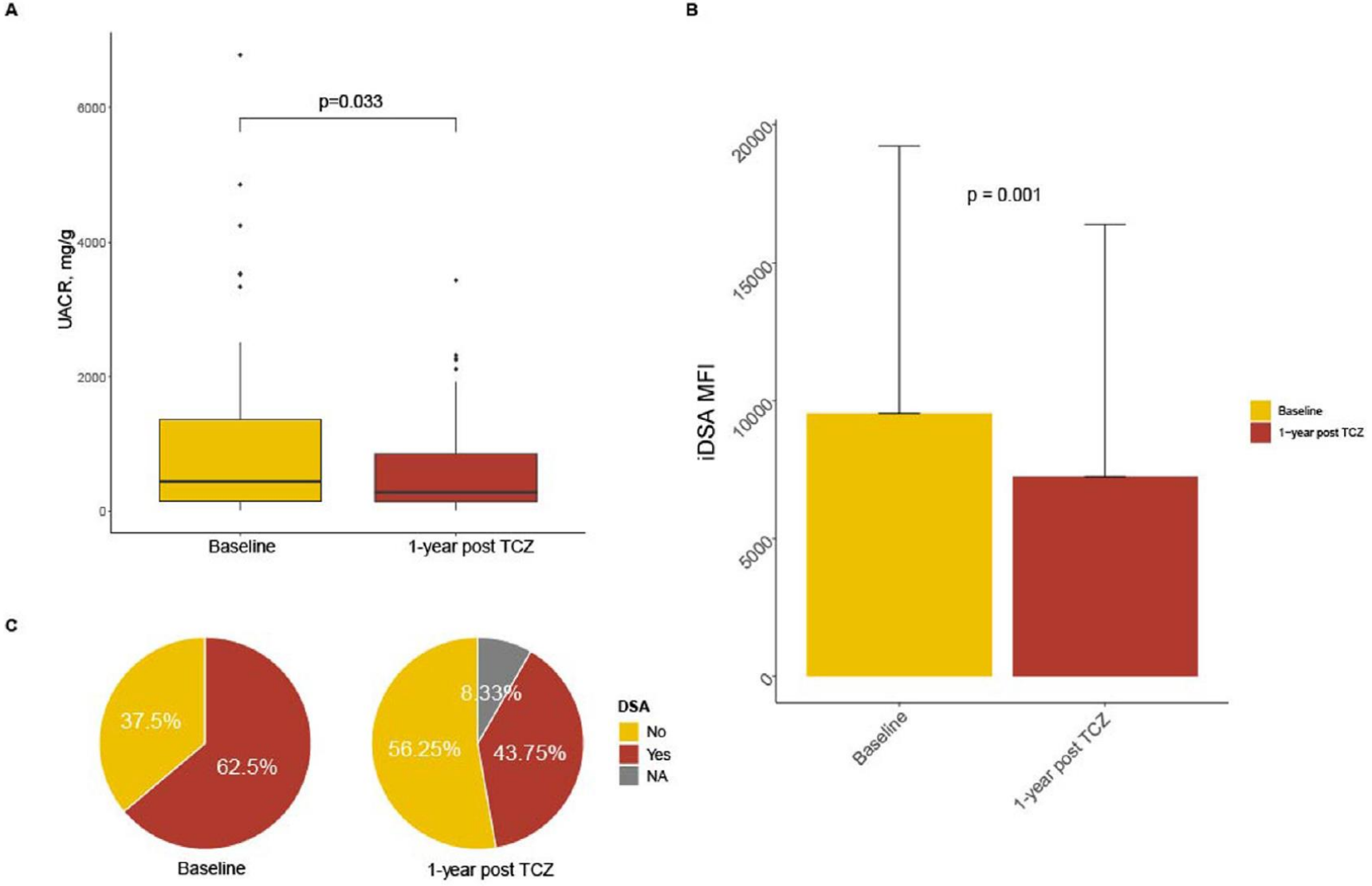


FIGURE 2 | Evolution of Donor-specific antibodies (DSA) and albuminuria post tocilizumab (TCZ). Panel **(A)** shows boxplots of urinary albuminuria over creatininuria (mg/g) at baseline and at 1-year post TCZ. Panel **(B)** shows the MFI of the immunodominant DSA (iDSA) at the time of diagnosis (baseline) and after 1-year post TCZ (median and SD). Panel **(C)** chows Pie chart of the presence of at least one DSA at the time of diagnosis (baseline) and after 1-year post TCZ treatment.

Tocilizumab in chronic active antibody-mediated rejection: rationale and protocol of an in-progress randomized controlled open-label multi-center trial (INTERCEPT study)

Lillian Streichart[1], Marie Felldin[1], Jana Ekberg[1], Lars Mjörnstedt[1], Per Lindnér[1], Annette Lennerling[1], Verena Bröcker[2], Johan Mölne[2], Jan Holgersson[3], Kristien Daenen[4], Lars Wennberg[5], Tomas Lorant[6] and Seema Baid-Agrawal[1*]

A total **of 50 recipients with biopsy-proven caAMR** at least 12 months after transplantation will be randomized to receive either **tocilizumab (*n* = 25**) added to our standard of care (SOC) maintenance treatment or **SOC alone (*n* = 25**) for a period of 24 months. Patients will be followed for an additional 12 months after cessation of study medication. After the inclusion biopsies at baseline, protocol kidney graft biopsies will be performed at 12 and 24 months.

- The primary endpoint is the **slope of eGFR at 24 months** after the start of treatment.
- The secondary endpoints include assessment of the following **at 12, 24, and 36 months**: composite **risk score iBox**, **safety, evolution,** and characteristics of donor-specific antibodies **(DSA**), **graft histology**, **proteinuria**, kidney function assessed by measured GFR (**mGFR)**, **patient- and death-censored graft survival**, and patient-reported outcomes that include transplant-specific wellbeing, adherence to immunosuppressive medications, and perceived threat of the risk of graft rejection.

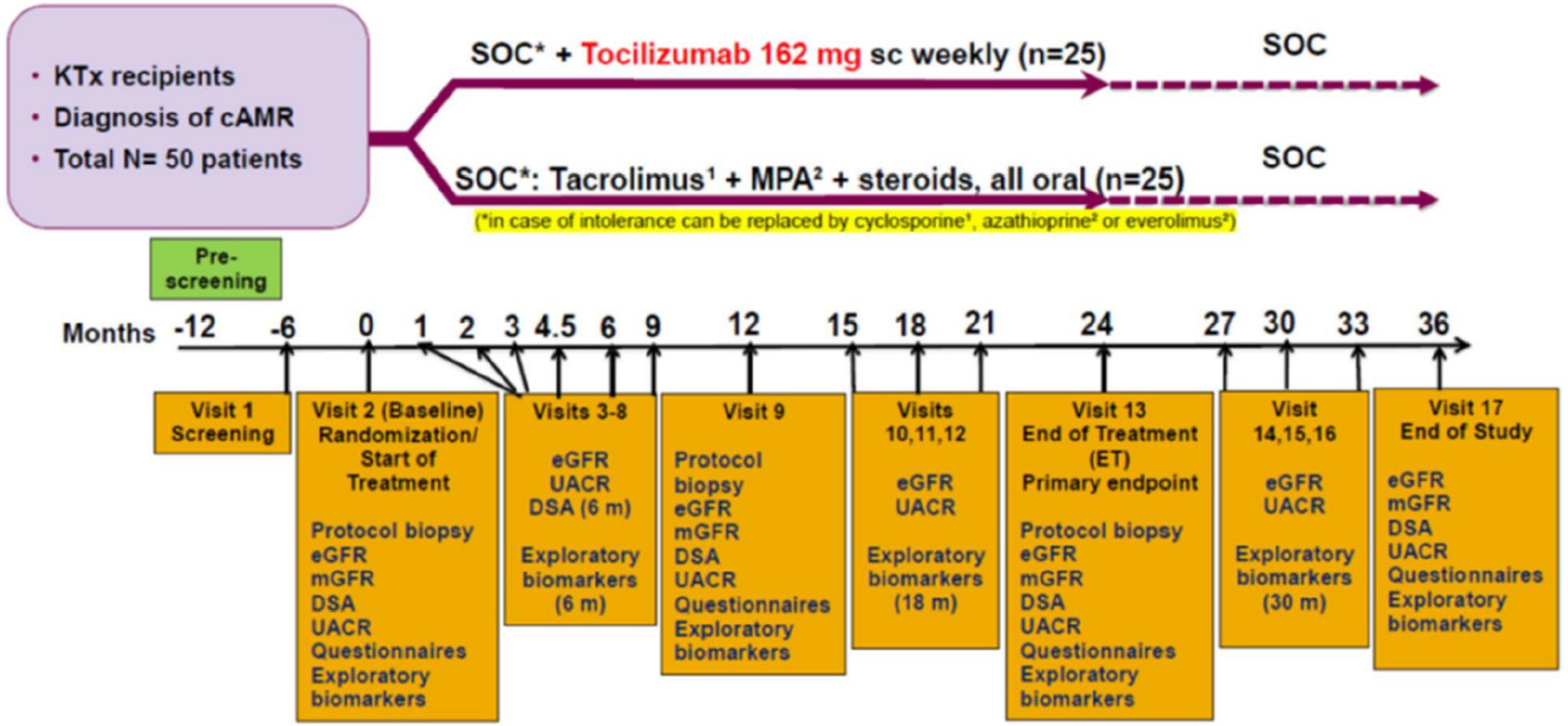


Fig. 1 Flow chart of the Intercept-study. DSA donor-specific antibodies, eGFR estimated glomerular filtration rate, KTx kidney transplant, m months, mGFR measured glomerular filtration rate, MPA mycophenolic acid, sc subcutaneous, SOC standard of care, UACR urine albumin:creatinine ratio

Streichart et al. Trials,BMC(2024) 25:213

pharmaceutics

MDPI

Systematic Review

The Promising Effect of Tocilizumab on Chronic Antibody-Mediated Rejection (cAMR) of Kidney Transplant

Łukasz Świątek [1], Miłosz Miedziaszczyk [2,3], Dominik Lewandowski [1], Filip Robakowski [1], Piotr Tyburski [1], Marta Jakubowska [1], Marek Karczewski [2] and Ilona Idasiak-Piechocka [2,*]

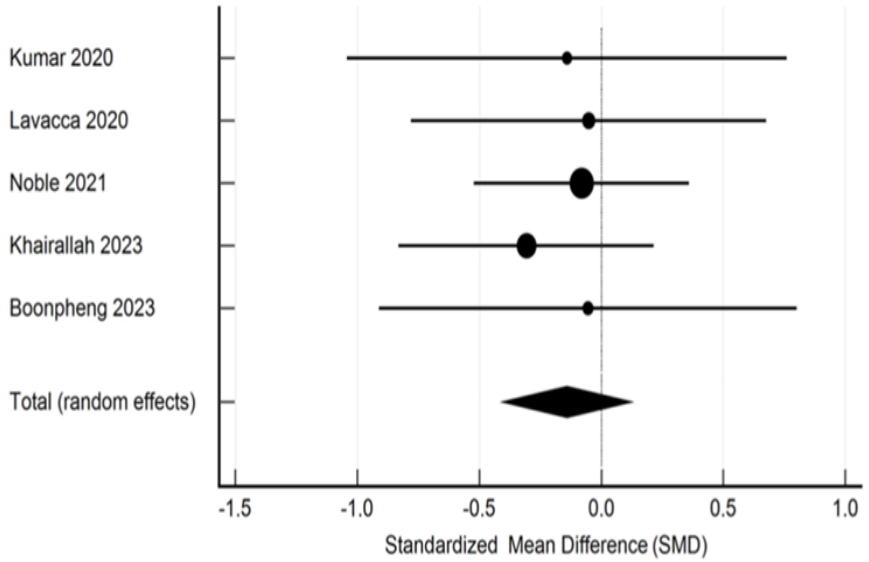


Figure 2. Forest plot presenting the results of our random effects meta-analysis for changes in eGFR [17,27–30].

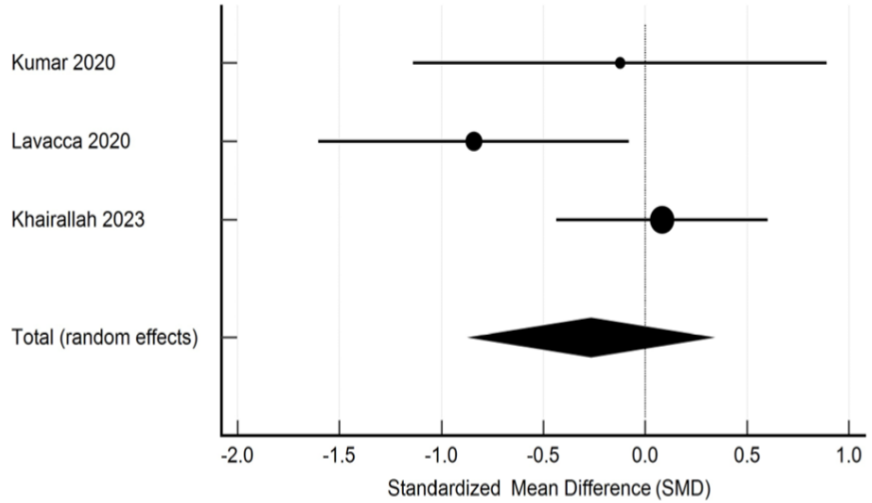


Figure 4. Forest plot demonstrating the results of our random effects meta-analysis in terms of changes in DSA titer [27–29].

Five clinical trials with a total number of **105 patients** were included in our review.

- The **mean loss of eGFR in time was −0.141 mL/min/1.73 m2** (95% CI: −0.409 to 0.126; p = 0.298) and was found to be **statistically insignificant**.
- The heterogeneity was low and was equal to I2 = 0.00%.
- The authors demonstrated **a reduction in DSA titer by TCZ** (−0.266 MFI (95% CI: −0.861 to 0.329; p = 0.377)).
- **In the majority of studies, eGFR stabilization was associated with a reduction in DSAs.**
-

Kidney Transplantation

OPEN

Tocilizumab Treatment for Microvascular Inflammation and Chronic Active Antibody-mediated Rejection in Kidney Transplantation

Edmund Huang, MD,[1] Michie Adjei, MD,[2] Alice Peng, MD,[1] Reiad Najjar, MD,[1] Jun Shoji, MD,[1] Sindhu Chandran, MD,[1] Ashley Vo, PharmD,[1] and Stanley C. Jordan, MD[1]

Kidney Transplantation. 2025 Oct 3;11(11):e1867

- **85 adult kidney transplant** patients with histologic features of **chronic active AMR** treated with monthly **tocilizumab 8 mg/kg** intravenous infusions were identified. Piecewise linear mixed effects models were fitted to compare eGFR trajectories **12 mo before and after tocilizumab** initiation.
- **Results. The eGFR declined at a rate of –0.70 mL/min/1.73 m2/mo** (95% confidence interval, –1.03 to –0.36) preceding tocilizumab initiation and stabilized after treatment onset to a slope of **–0.07 (–0.35 to 0.21) mL/min/1.73 m2/mo** (slope difference: 0.59 [0.22-0.97] mL/min/1.73 m2/mo, *P* = 0.002).
- The **distribution of the sum mean fluorescence intensity of donor specific antibodies (DSA) among 65 DSA+ patients remained unchange**d from baseline to 1 y after treatment; however, 14 of 65 DSA+ patients (**22%) no longer had DSA at 1 y**.
- There was **1 graft loss and 2 deaths, both COVID-19-related**, by 12 mo after treatment onset.
- **Conclusions.** This study suggests that monthly treatment with the anti-IL-6 receptor monoclonal antibody, tocilizumab, **may stabilize allograft function** among kidney transplant patients with chronic active AMR and that further studies to confirm its efficacy should be conducted.

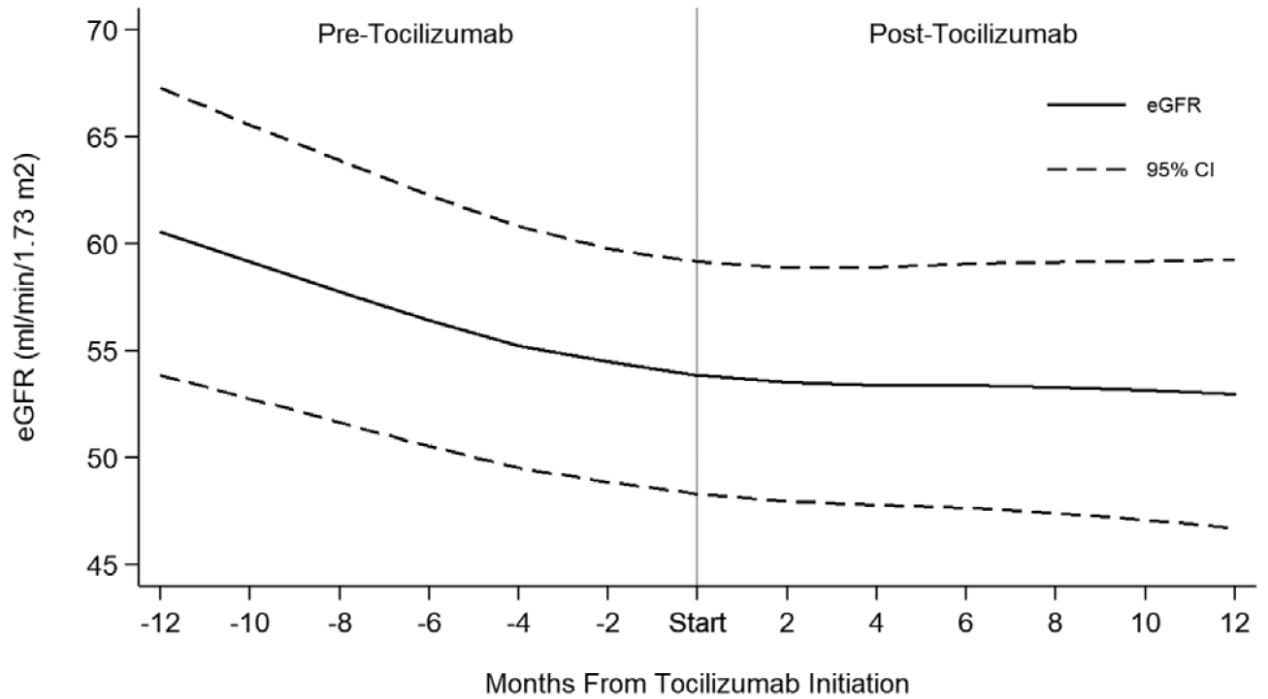


FIGURE 2. Trend in eGFR (mL/min/1.73 m^2) with 95% CIs before and after tocilizumab initiation. CI, confidence interval; eGFR, estimated glomerular filtration rate.

- **Infections During Tocilizumab Treatment**
- . A total of **75 infections** developed among **47 of 85 patients (55**%) during 118 person-years of follow-up, yielding an incidence rate of **0.64 infections/person-year**.
- **Most infections were minor** and treated in the outpatient setting. The most common infections were **upper respiratory infections (19/75; 25%)** and **urinary tract infections** (17/75; **23%**).
- Only **1 case of cytomegalovirus** viremia and no cases of BK viremia or nephropathy were observed.
- **Seven patients (8%) discontinued** tocilizumab treatments because of *infection concerns*.

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

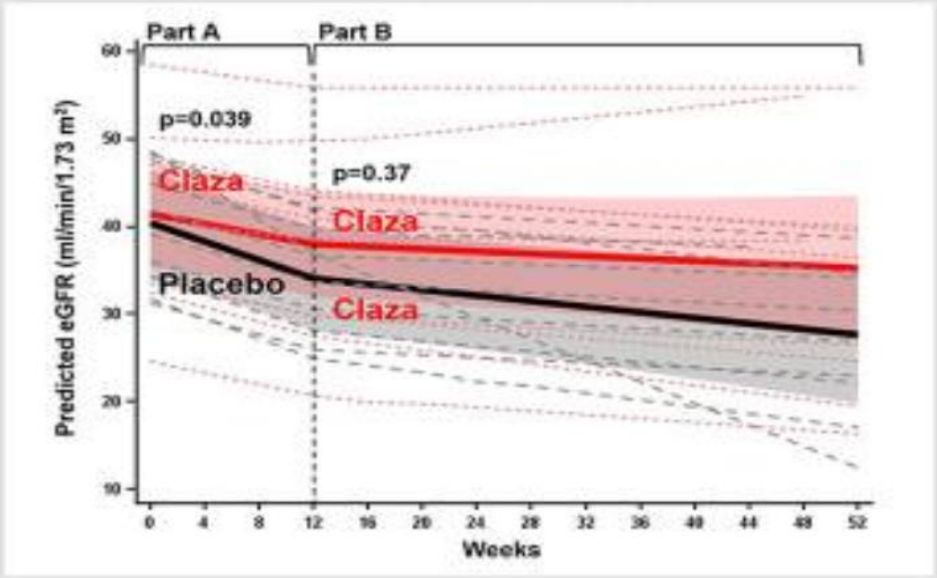
Part B: Clazakizumab (25 mg SC, monthly) | Clazakizumab (25 mg SC, monthly)

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

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

Doberer et al.

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

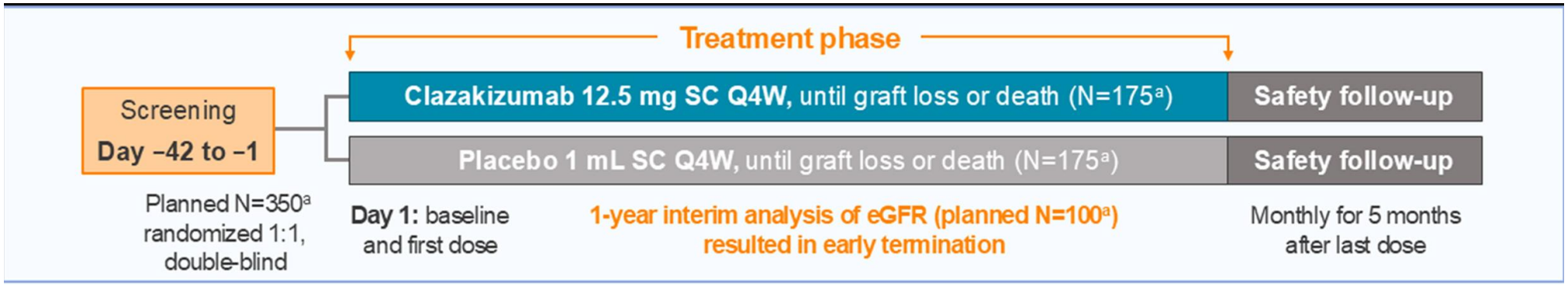
Conclusion In this small cohort of cAMR patients, a trend towards stabilization of eGFR, reductions in DSA, and graft inflammation. No significant safety issues were observed. A trial (IMAGINE) of Clazakizumab in cAMR treatment is underway [NCT03744910].

Jordan et al

Original Article

Clazakizumab in the treatment of chronic active antibody-mediated kidney transplant rejection: Results from the IMAGINE phase 3, randomized, double-blind, placebo-controlled study

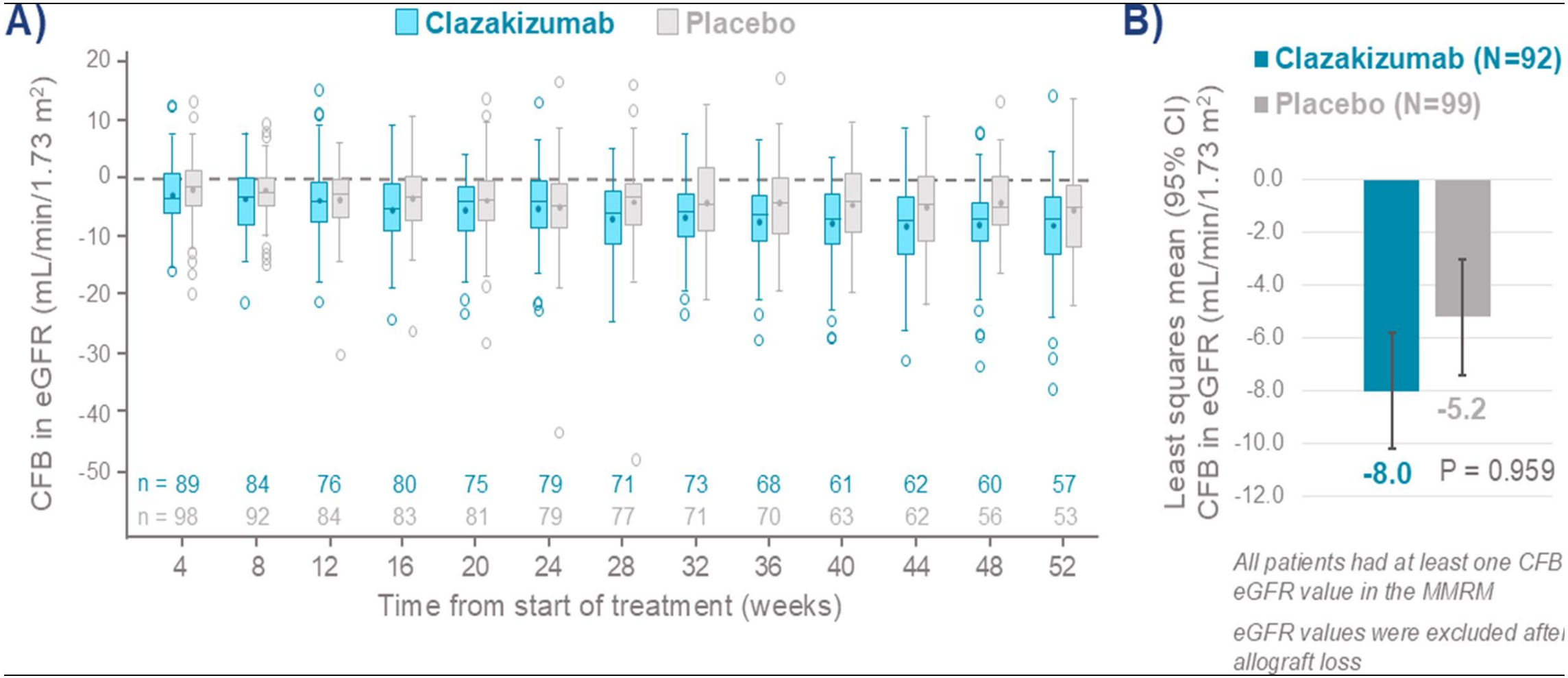
Arjang Djamali [1], Georg A. Böhmig [2], Roslyn B. Mannon [3], Steve Chadban [4], Deepali Kumar [5], Teun van Gelder [6], Gabriele Schultz-Hauser [7], Gabriela Alperovich [8], Ralph Preiss [9], Laurie A. Lee [10], Tobias Rogosch [7], Isabelle Morin [11], Charles Luo [12], Klemens Budde [13], Michael Mengel [14], Peter W. Nickerson [15]

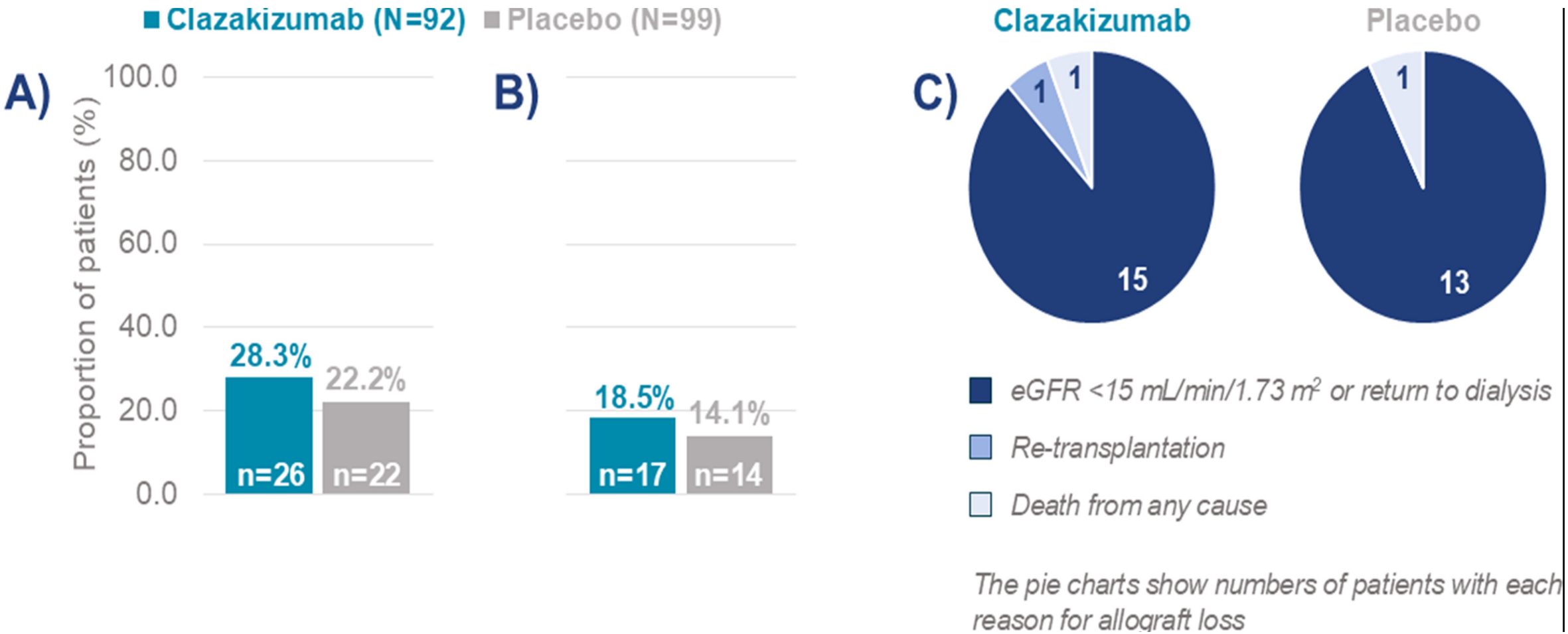


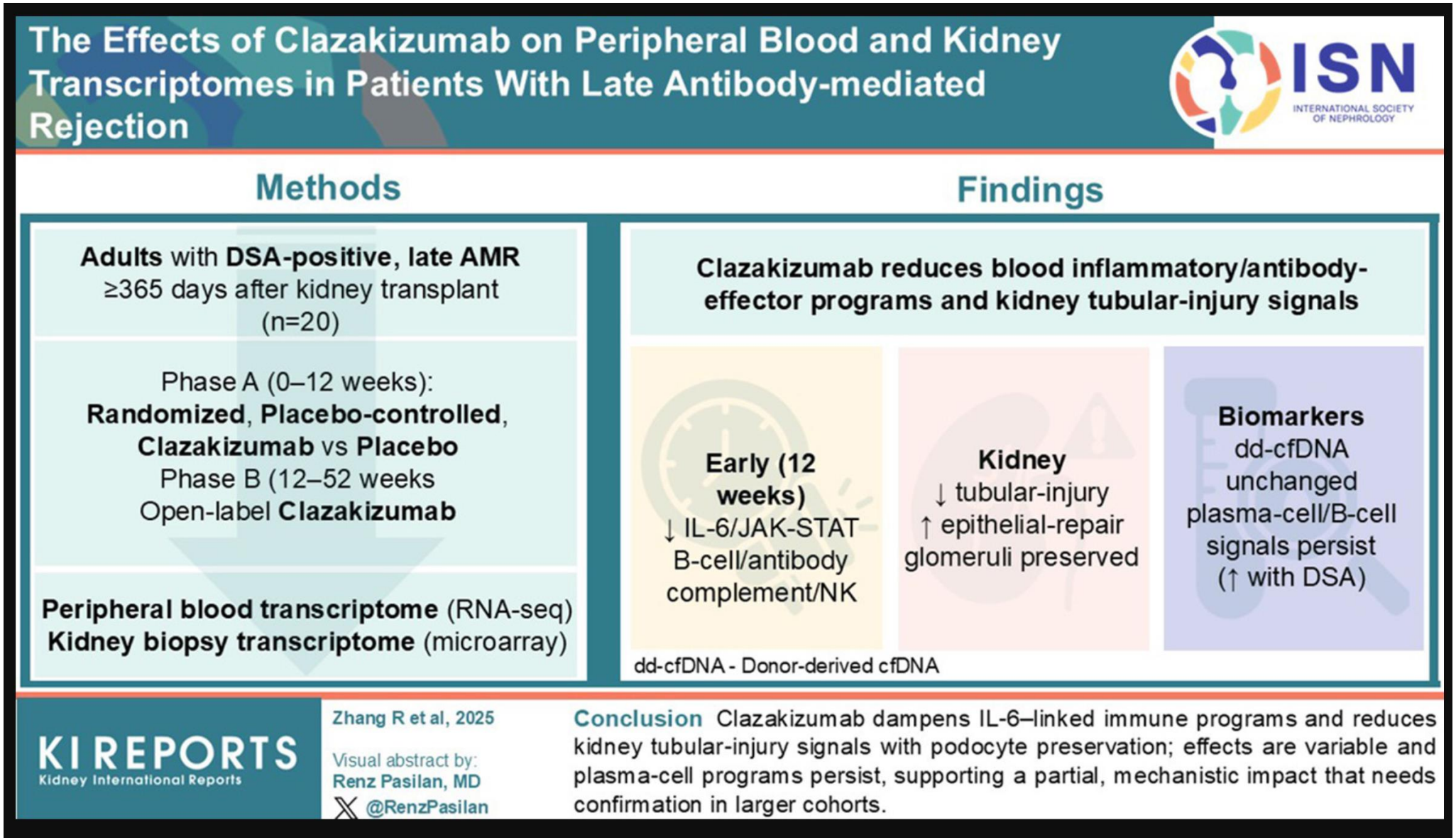
- IMAGINE was a global phase 3 study (NCT03744910)
- The **largest placebo-controlled study** in adult KTx recipients with caAMR (determined by kidney biopsy and Banff 2015)

- **Primary endpoint:** time to a composite of all-cause allograft loss or irreversible loss of allograft function[b]
- **Event-driven design:** primary endpoint due for analysis after 221 events occurred

- IMAGINE was the **first KTx study with 1-year analysis of eGFR as a surrogate endpoint** accepted by the FDA as reasonably likely to reflect clinical benefit
- **We report the final analysis following early termination**, after 1-year interim analysis of eGFR


A)
Clazakizumab
Placebo
CFB in eGFR (mL/min/1.73 m²)
20
10
0
-10
-20
-30
-40
-50
n = 89 84 76 80 75 79 71 73 68 61 62 60 57
n = 98 92 84 83 81 79 77 71 70 63 62 56 53
4 8 12 16 20 24 28 32 36 40 44 48 52
Time from start of treatment (weeks)
B)
Clazakizumab (N=92)
Placebo (N=99)
Least squares mean (95% CI) CFB in eGFR (mL/min/1.73 m²)
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
-5.2
-8.0
P = 0.959
All patients had at least one CFB eGFR value in the MMRM
eGFR values were excluded after allograft loss


Clazakizumab (N=92)
Placebo (N=99)
A)
Proportion of patients (%)
100.0
80.0
60.0
40.0
20.0
0.0
28.3%
22.2%
n=26
n=22
B)
18.5%
14.1%
n=17
n=14
C)
Clazakizumab
Placebo
1
1
15
1
13
eGFR <15 mL/min/1.73 m² or return to dialysis
Re-transplantation
Death from any cause
The pie charts show numbers of patients with each reason for allograft loss



Zhang R et al,KI REPRTS, 2025

American Journal of
TRANSPLANTATION

The Impact of Tocilizumab and Clazakizumab on Molecular Rejection and Injury Scores in Chronic-Active Antibody-Mediated Rejection in Kidney Transplantation: A Case Series

K. Castrezana Lopez · S. von Moos · D. Harmacek · L. Weidmann · F. Westphal · E. Rho · K. Huebel · T. Schachtner Show less

We analyzed **14 KTRs** transplanted at the University Hospital Zurich with histological and molecular caAMR who underwent an initial (t1) and a **12-months follow-up biopsy** (t2).

Biopsy-based transcriptomics were assessed using the Molecular Microscope Diagnostics System (**MMDx**).

5 KTRs received monthly TCZ (8 mg/kg IV) plus optimized IS, **4 KTRs received monthly CKZ (12.5 mg SC)** plus optimized IS, and **5 KTRs received optimized IS** alone.

Volume 25, Issue 8, Supplement 1, S697, August 2025

- Results: There was **no difference** **in semiquantitative lesion scores** for **glomerulitis (g)** or **peritubular capillaritis (ptc**) before or after treatment.
- **Molecular rejection classifier** and molecular AMR classifier scores **did not change** in the TCZ or CKZ group compared to optimized IS alone.
- However, an **initial molecular archetype cluster of early-stage AMR (R4 score, median at t1: 0.55, median at t2: 0.26; p=0.027) more frequently progressed to fully-developed AMR in the TCZ** group (R5 score, 0.22, 0.43; p=0.055). In contrast, the molecular rejection archetypes did not change in the CKZ group.
- **Regarding molecular injury dimension** scores, a **trend towards decreased injury-repair associated transcripts (IRRAT) scores** was **observed in the TCZ group** (-0.02, -0.03; p=0.823), a shift not seen in the CKZ or optimized IS group.
-

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

Kidney International Reports
Volume 10, Issue 10, October 2025, Pages 3506-3515

Clinical Research

Anti-CD38 Daratumumab Treatment of Chronic Active Antibody-Mediated Kidney Allograft Rejection

Wai-Choong Lye [1], Hwai-Liang Loh [2]

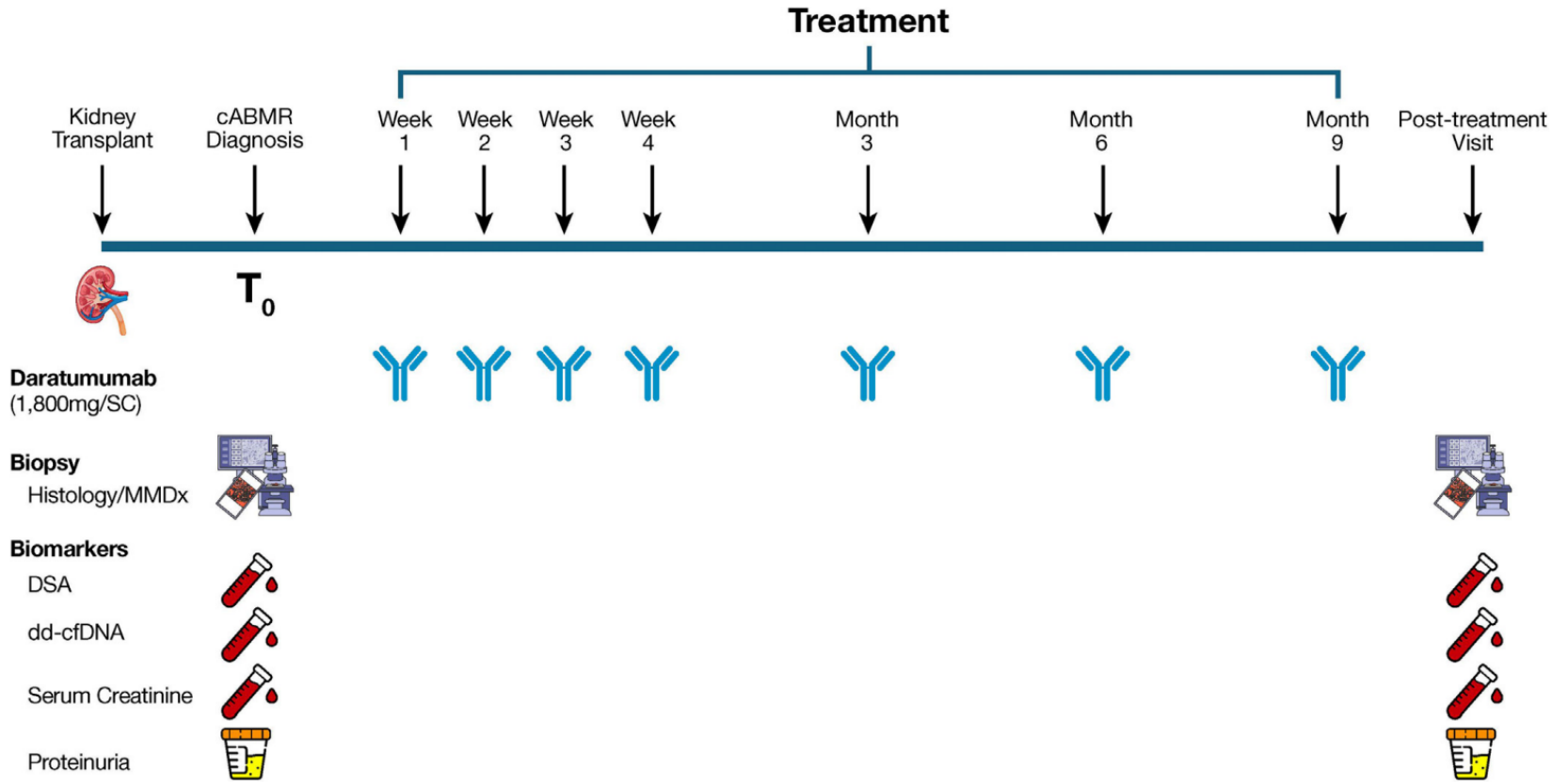


Figure 1. Timeline of daratumumab treatment and data collection. cABMR, chronic active antibody-mediated rejection; dd-cfDNA, donor-derived cell-free DNA; DSA, donor-specific antibody; MMDx, molecular microscope diagnostic.

Anti-CD38 Daratumumab Treatment of Chronic Active Antibody-mediated Kidney Allograft Rejection

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Study Design & Cohort

- Retrospective Review
- Adult KTR
  Feb 2022 – Aug 2023
- KTR with cABMR diagnosed > 6 months post-transplant
- Monitored Outcomes: eGFR, uACR, dd-cfDNA, DSA, renal biopsy, adverse events

Intervention

Subcutaneous Daratumumab

Flat dose 1,800 mg

Weekly for 4 weeks, followed by 3 quarterly doses

Findings

N=16
Adults with KTR diagnosed with cABMR
Median time transplant to treatment = 9 years

Biopsy Histology, 10 months After Treatment

- 13/16 showed improved microvascular inflammation scores
- 8/16 showed ABMR score decline (median ↓74%)

- eGFR levels remained stable
- 11/16 showed uACR improvement
- dd-cfDNA significantly decreased (median ↓85%)

eGFR, estimated glomerular filtration rate; uACR, urine albumin/creatinine ratio; DSA, donor-specific antibody

KI REPORTS
Kidney International Reports

Lye WC et al, 2025

Visual abstract by:
Jade Teakell, MD PhD
@jmteakell

Conclusion Subcutaneous daratumumab may be an effective treatment for chronic active antibody-mediated rejection (cABMR); larger randomized trials are warranted to study its role in the treatment for cABMR in kidney transplant recipients (KTR). Donor-derived cell-free (dd-cfDNA) may be a useful monitoring tool to predict and detect relapses.

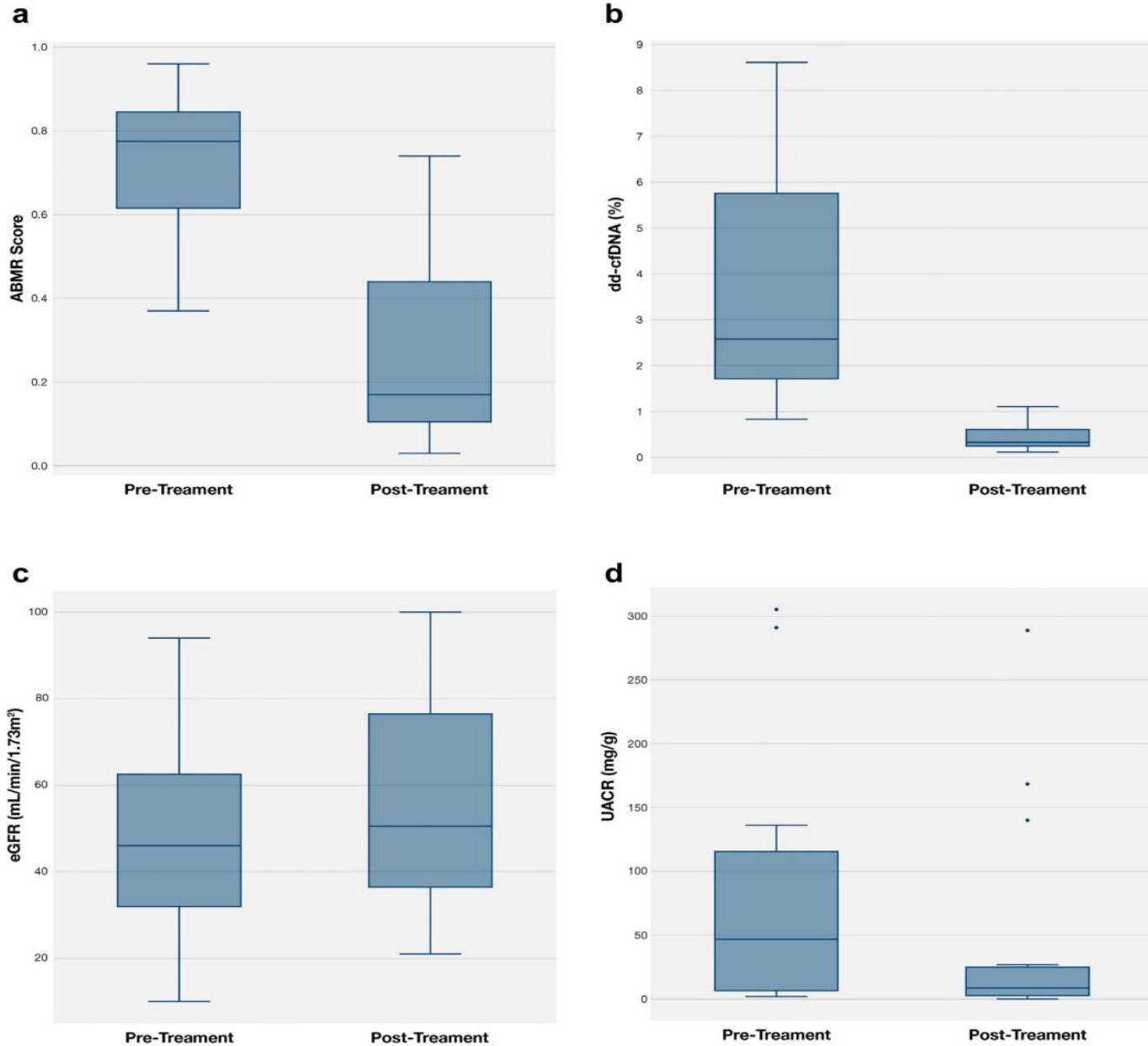


Figure 2. Boxplots showing the median and interquartile biomarker results at the pre- and post-treatment time points for (a) molecular microscope diagnostic (MMDx) antibody-mediated rejection (ABMR) scores, (b) donor-derived cell-free DNA (dd-cfDNA) fraction, (c) estimated glomerular filtration rate (eGFR) levels, and (d) urine albumin-to-creatinine ratios (UACR).

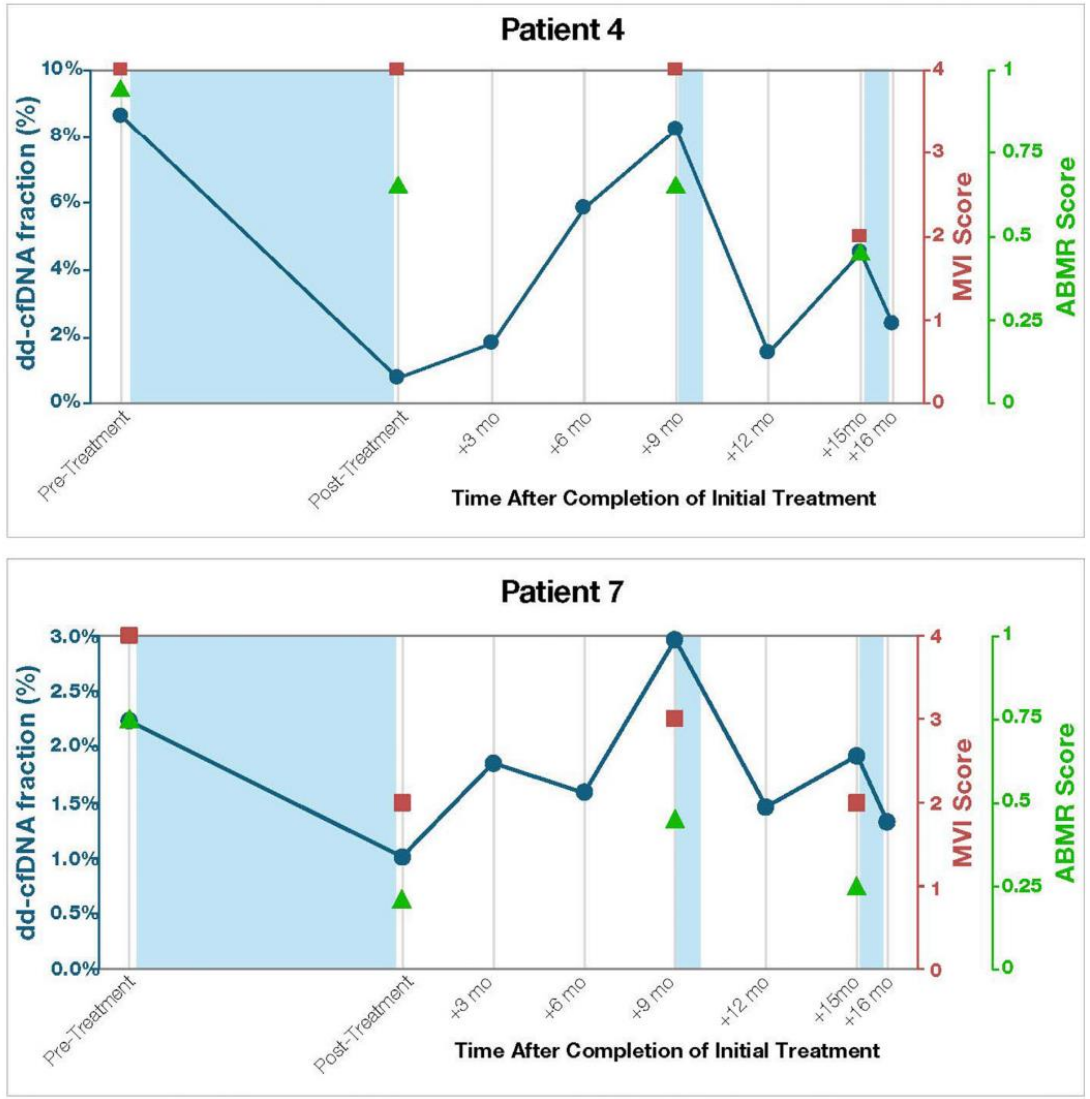


Figure 3. Donor-derived cell-free DNA (dd-cfDNA) timeline for 2 patients with dd-cfDNA rebound, along with the daratumumab treatment windows and relevant biopsy results.

- In conclusion, daratumumab appears to be **effective** in the treatment of biopsy confirmed chronic ABMR according to both **histological** and **molecular biopsy** assessments and led to a stabilization of renal function in a majority of treated patients.
- **dd-cfDNA was strongly correlated** with the administration of daratumumab and the resultant molecular ABMR scores, providing a **noninvasive way to monitor treatment response**.
- Furthermore, dd-cfDNA **appeared predictive of ABMR relapse**.
-

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection

K.A. Mayer, E. Schrezenmeier, M. Diebold, P.F. Halloran, M. Schatzl, S. Schranz, S. Haindl, S. Kasbohm, A. Kainz, F. Eskandary, K. Doberer, U.D. Patel, J.S. Dudani, H. Regele, N. Kozakowski, J. Kläger, R. Boxhammer, K. Amann, E. Puchhammer-Stöckl, H. Vietzen, J. Beck, E. Schütz, A. Akifova, C. Firbas, H.N. Gilbert, B. Osmanodja, F. Halleck, B. Jilma, K. Budde, and G.A. Böhmig

In this **phase 2**, **double-blind**, **randomized**, placebo-controlled trial,
to receive **nine infusions** of the CD38 monoclonal antibody **felzartamab (at a dose of 16 mg per kilogram** of body weight) or **placebo for 6 months**,
The primary outcome was the **safety and side-effect profile** of felzartamab.
Key secondary outcomes were **renal-biopsy results at 24 and 52 weeks**, **donor-specific antibody level**s, **peripheral NK-cell** counts, and **donor-derived cell-free DNA levels**.
A total of 22 patients underwent randomization (**11 to receive felzartamab** and **11 to receive placebo**). The median time from transplantation until trial inclusion was 9 years.

N Engl J Med 2024;391:122-32.

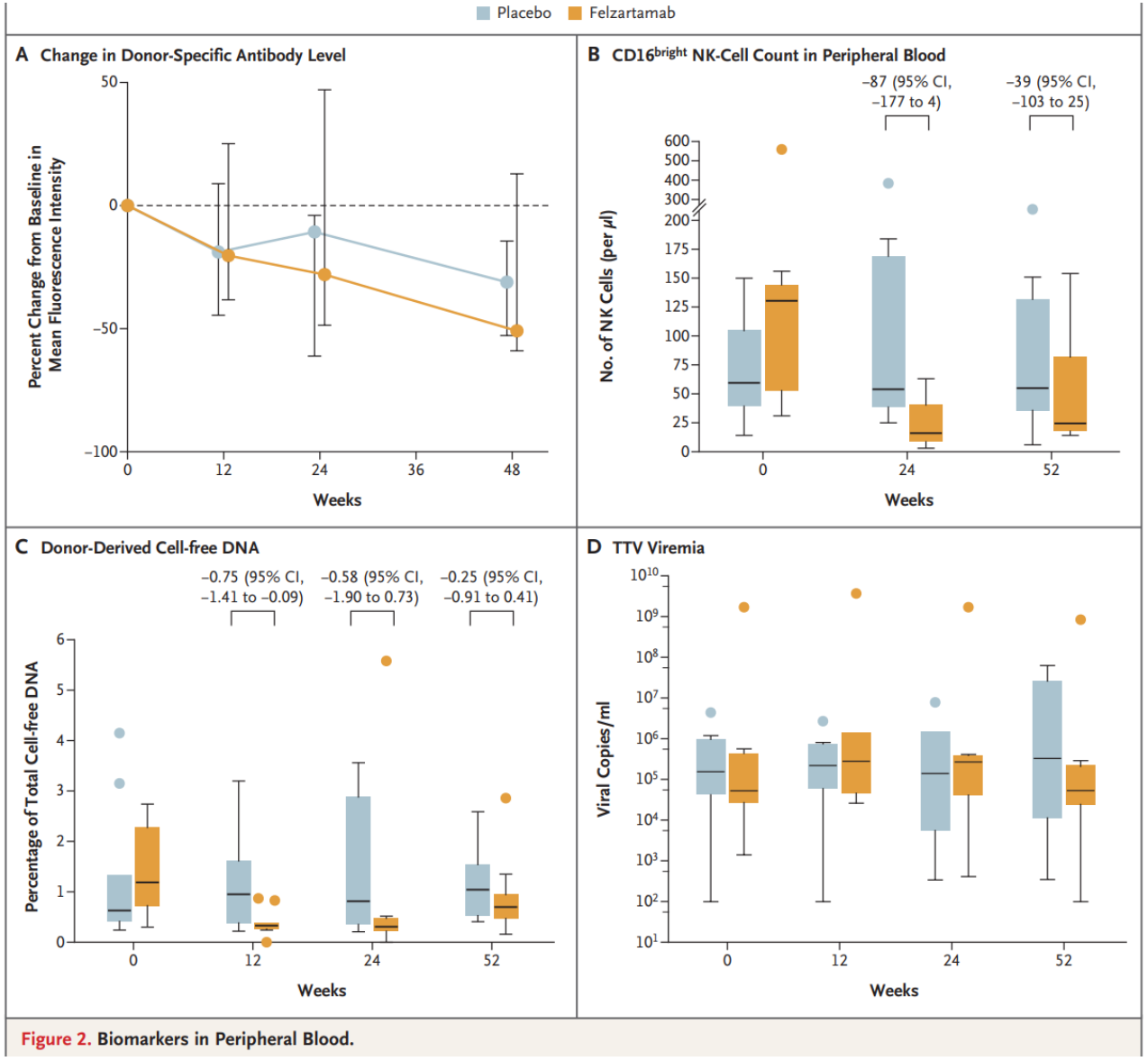


Figure 2. Biomarkers in Peripheral Blood.

At 1 year, survival was 100% in the two trial groups. **One graft loss in the placebo group** had occurred because of persistent chronic active antibody-mediated rejection. The 1-year eGFR slope was **−0.39 ml per minute per 1.73 m$_2$ (95% CI, −5.47 to 4.69) in the felzartamab** group and **−4.53 ml per minute per 1.73 m$_2$ (95% CI, −9.83 to 0.77) in the placebo group** (difference, 4.14 ml per minute per 1.73 m$_2$; 95% CI, −3.20 to 11.48) (Fig. S13).

In the two groups, the **ratio of spot urinary protein to creatinine did not change over time (**Fig. S14).

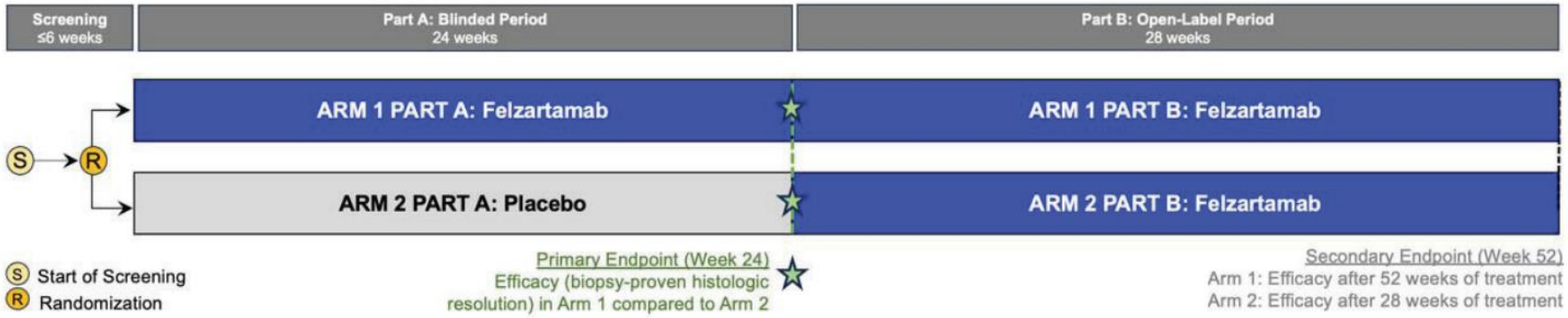
American Journal of
TRANSPLANTATION

ABSTRACT ONLY · Volume 25, Issue 8, Supplement 1, S699, August 2025

TRANSCEND: A Phase 3 Trial of the Anti-CD38 Antibody Felzartamab in Kidney Transplant Recipients with Late Antibody-Mediated Rejection

G. Bohmig [1] · K. Budde [2] · D. Cibrik [3] · ... · L. Micsa [7] · U.D. Patel [7] · R. Mannon [8] ... Show more

Figure. TRANSCEND Study Schematic



TRANSCEND (NCT06685757) is a **double-blind, placebo-controlled, multicenter, randomized Phase 3 trial.**
120 participants with late (≥6 months) active or chronic active AMR post-kidney transplant will be randomized to receive felzartamab or placebo.

Emerging therapies under investigation for AMR

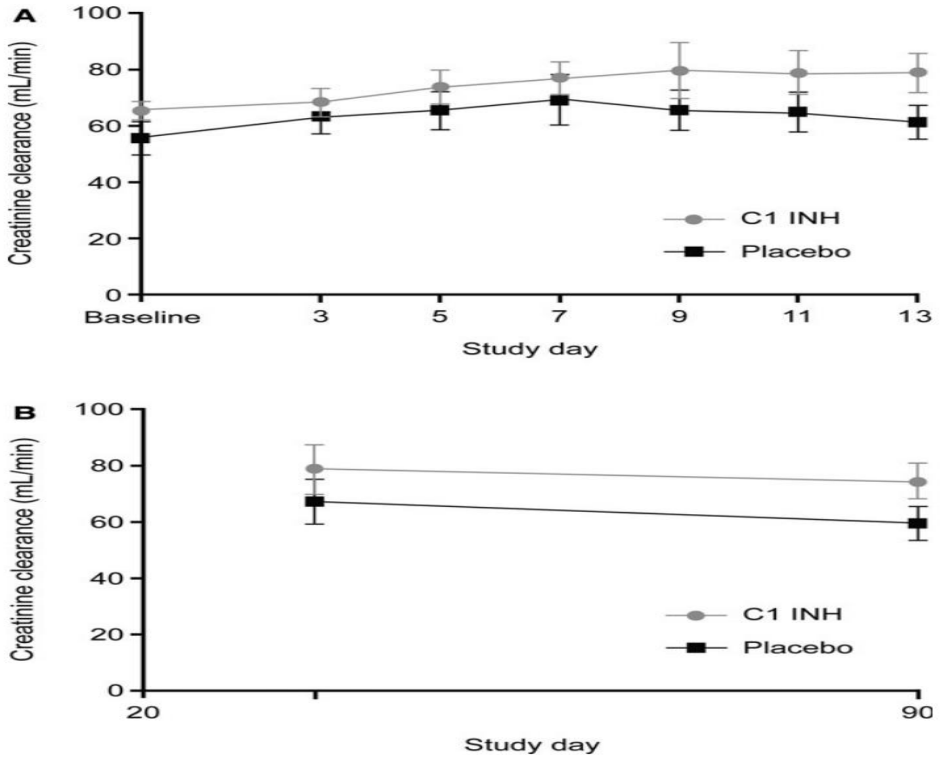
- **Fostamatinib**: Preclinical studies in sensitized rat models suggests that fostamatinib a spleen tyrosine kinase inhibitor ,may suppress the production of DSAs.A phase 2clinical trial is currently evaluating its potential in treating chronic active AMR.
- **High –dose IVIG** : The efficacy of prolonged high-dose IVIG therapy, administered over 6 months alongside steroid pulse therapy ,is being explored in a randomized open-label trial conducted in Australia.
- **BIVV020**: This next generation **anti-C1s monoclonal antibody** targets the classical complement pathway. A phase 2 trial is underway to assess its safety and efficacy in both the prevention and treatmentof AMRwhen used with standard care of therapy.
- **Efgartigimod:** An **FcRn antagonist** approved for myasthenia gravis, efgartigimod works by inhibiting neonatal Fc receptor –mediated IgG recycling, thereby reducing circulating IgG levels. A **phase 2 trial** is currently investigated its role in managing **late stage AMR.**

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

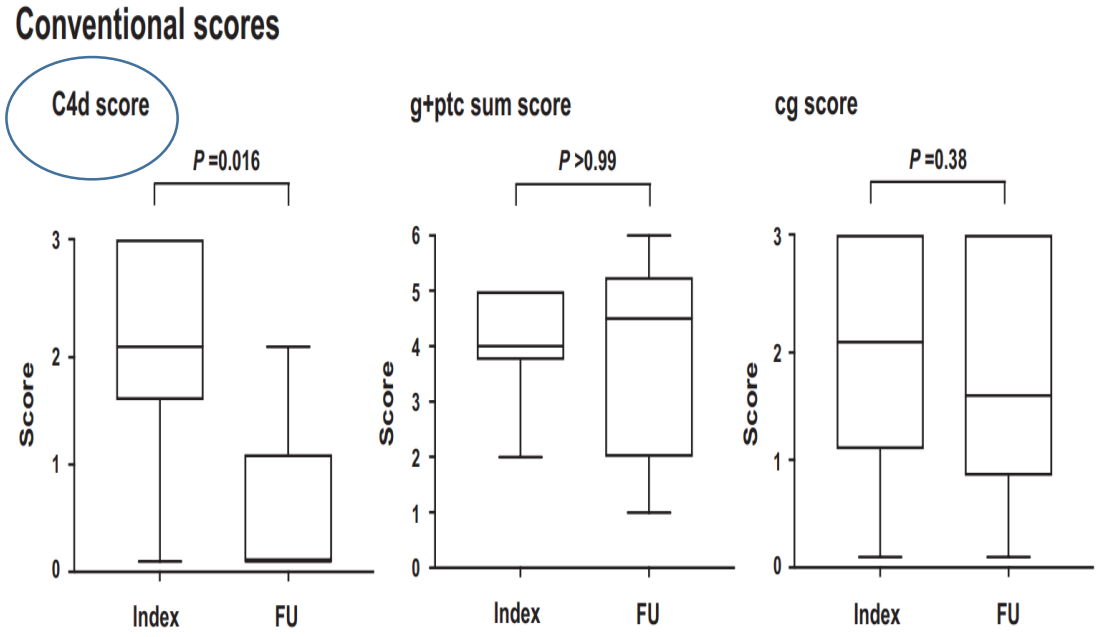
R. A. Montgomery[1,*], B. J. Orandi[1], L. Racusen[2], A. M. Jackson[3], J. M. Garonzik-Wang[1], T. Shah[4], E. S. Woodle[5], C. Sommerer[6], D. Fitts[7], K. Rockich[7], P. Zhang[7] and M. E. Uknis[7]

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.

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

REVIEW ARTICLE

Impact of C1-Inhibitor on Renal Function and Safety Outcomes in Kidney Transplant Recipients: A Meta-Analysis of Randomized Controlled Trials

Xinmiao Feng, Di Zhang, Yang Qiu, Haowei Zhu, Xinzhe Wu, Boqun Zha, Zhigang Wang, Wenjun Shang

First published: 11 February 2026 | https://doi.org/10.1111/ctr.70479 |

- This study included **four randomized controlled trials** encompassing **148** kidney transplant recipients.
- The findings suggest that treatment with C1-INH **may be associated** with **an improvement in renal function, as reflected by eGFR**.
- **No statistically significant difference** was observed in the incidence of **delayed graft function or antibody-mediated rejection** between the treatment and control groups.
- The overall **incidence of serious adverse events was comparable** between groups, with no significant differences detected in infection-related, renal, cardiovascular, or gastrointestinal events.

A randomized controlled trial of intravenous immunoglobulin vs standard of care for the treatment of chronic active antibody-mediated rejection in kidney transplant recipients

kidney INTERNATIONAL

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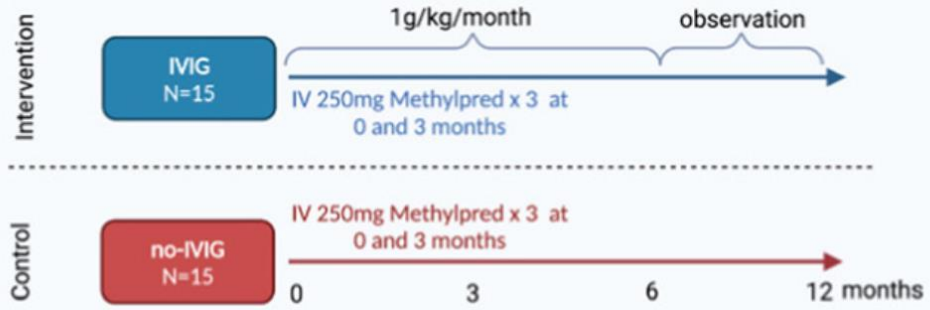
Cohort/Methods

- Kidney transplant recipients with chronic active antibody mediated rejection were randomized 1:1 to intravenous immunoglobulin (IVIG) or standard of care.

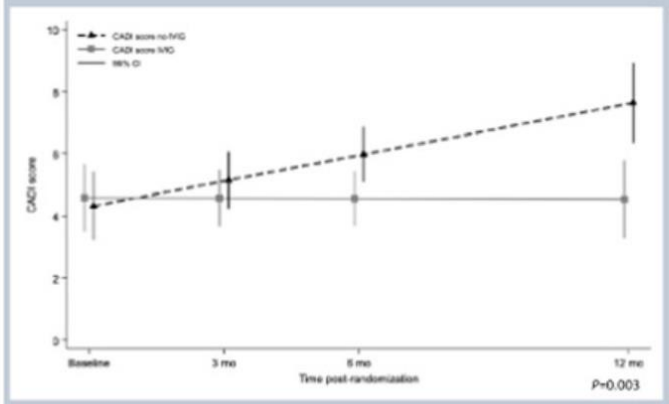


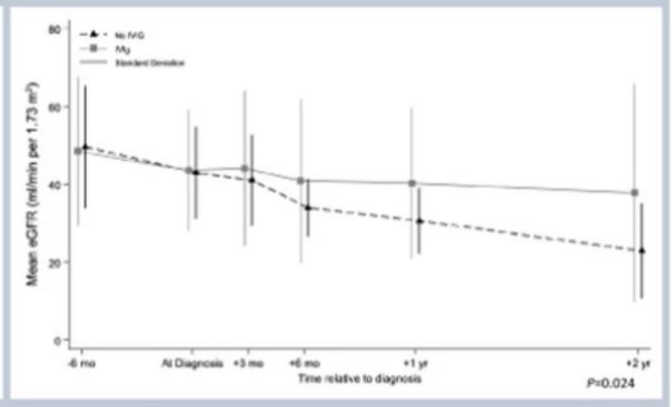
Investigations (clinical, biopsy, serology) performed at 0,3,6,12 months

Endpoints:

- **Primary** – chronic allograft damage index (CADI)
- **Secondary** – estimated glomerular filtration rate (eGFR), donor specific anti-HLA antibodies (DSA), allograft & patient survival and intragraft mRNA expression.

Findings:





1. IVIg stabilized histological damage
2. IVIg stabilized eGFR
3. IVIG did not reduce donor specific antibodies or proteinuria
4. Patient and allograft survival was similar at 12 months
    - At 5 yrs, 0 deaths in IVIG and 5 deaths in no-IVIG group
5. IVIg stabilized/reduced intragraft gene transcripts – particularly B-cell, T-cell, NK-cell and fibrosis associated transcripts.

Mulley et al, 2025

CONCLUSION: In kidney transplant recipients with chronic active antibody mediated rejection, IVIG therapy stabilized allograft histology, function and intragraft gene transcripts.

Clinical Trial > Cytotherapy. 2025 Oct;27(10):1199-1207. doi: 10.1016/j.jcyt.2025.05.011.
Epub 2025 Jun 4.

Clinical trial assessing the safety and efficacy of human bone marrow-derived allogeneic mesenchymal stem cell therapy for chronic active antibody-mediated rejection in kidney transplant recipients

Hyeran Park [1], Xianying Fang [2], Hanbi Lee [1], Tae Hyun Ban [3], Eun-Jee Oh [4], Hye Eun Yoon [1], Hyung Duk Kim [5], Byung Ha Chung [6]

Affiliations + expand

PMID: 40663031 DOI: 10.1016/j.jcyt.2025.05.011

Cytotherapy . 2025 Oct;27(10):1199-1207.

- Abstract
- This study evaluated the **safety and efficacy** of allogenic human bone marrow-derived mesenchymal stem cell (**hBM-MSC)** therapy in kidney transplant recipients (KTR) with chronic active antibody-mediated rejection (cABMR).

- Methods: **Seven cABMR patients** received four infusions of **hBM-MSC (1 × 10^6 cells/kg), one every other week**. The primary outcome was clinical **safety,** focusing on short-term adverse events. Secondary outcomes included changes in allograft function, mean fluorescence intensity **(MFI)** of Anti(HLA-DSA), allogenic immune response as determined by **ELISPOT**, lymphocyte subset analysis, **infection-free survival**, and **graft survival** compared to 18 historical controls via propensity score matching.

- Results: **Seven patients** received **hBM-MSC therapy ,8.5 months (range, 1.2-20.6) after the diagnosis of cABMR**.
- **Six patients completed treatment**, and one patient received two doses. **No immediate side effects** were observed. **One** patient developed Pneumocystis jirovecii pneumonia (**PJP) 3 weeks after treatment** and died 6 weeks post-treatment.
- Among those **who completed therapy**, the **eGFR slope shifted from -Δ16.6% to -Δ2.4%** over the 6 month periods before and after treatment, suggesting a **stabilization of eGFR** decline, proteinuria decreased, and **MFI of HLA-DSA declined**.
- **T-cell subset analysis** showed **increased CD8+CD45RA+CCR7- T cells** and **CD4+CD25+CD127low T cells** with **decreased CD8+CCR7+CD45RO+/CD45RA+ T cells.**
- Kaplan-Meier analysis demonstrated **no significant difference in infection-free survival** or **death-censored graft survival** compared to those of the propensity score-matched control group.
-

- Conclusions: hBM-MSC therapy was generally **well tolerated** for KTR with cABMR and demonstrated **favorable immunomodulatory effects**.