Nephrology and Transplantation Department
Labbafinejad Medical Center

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Chronic Active Antibody Mediated-Rejection

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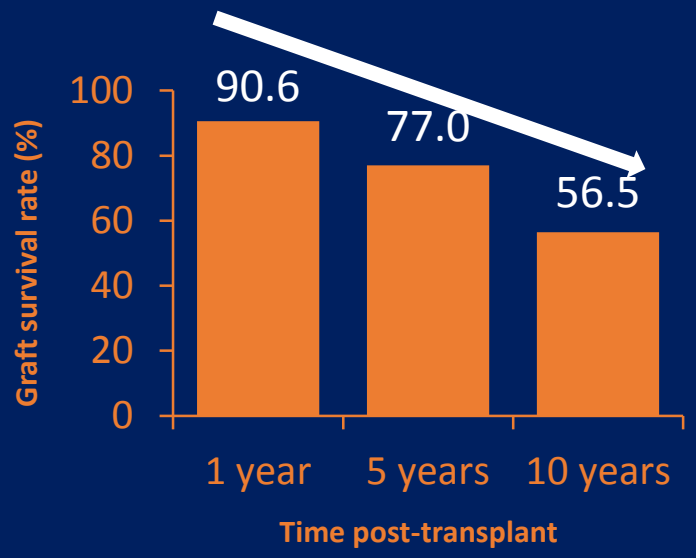
2024.12.12

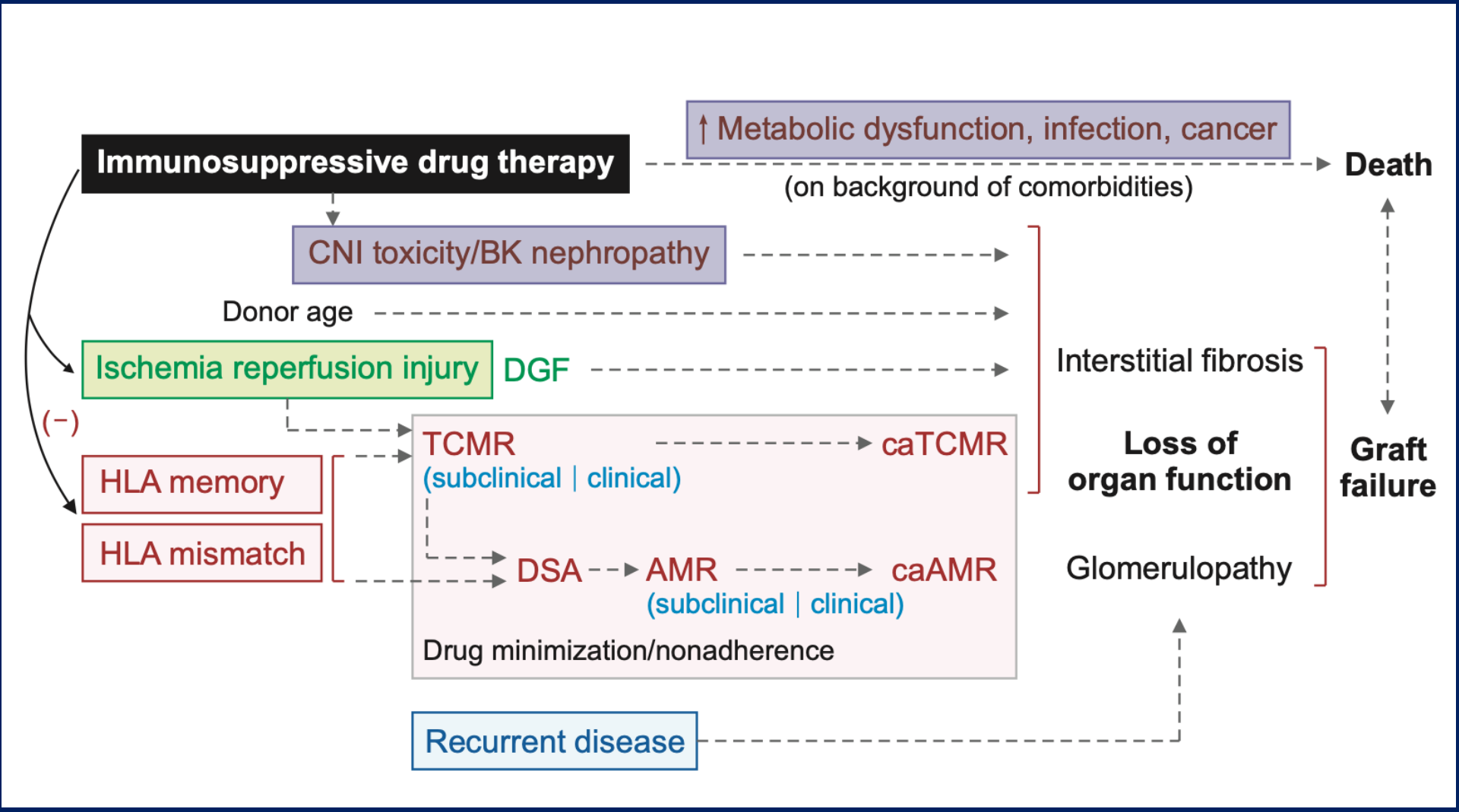
Maintaining long-term graft survival remains a challenge: Kidney transplantation

Kidney graft survival by post-transplant years (CTS Europe)

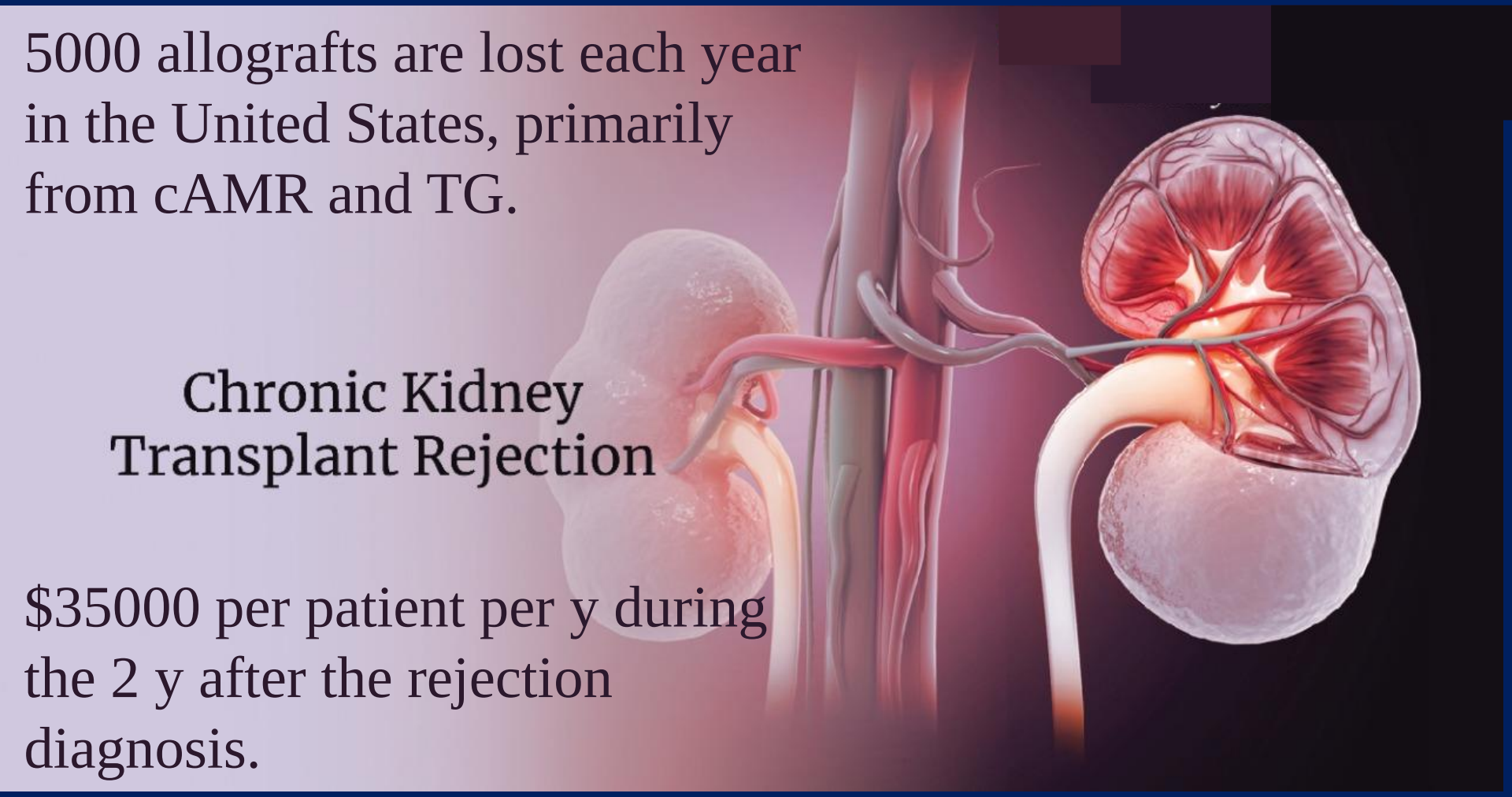


"10-year kidney graft survival rate: <60%

CTS, Collaborative Transplant Study,
Gondos A, et al. Transplantation 2013;95:267-274.


↑ Metabolic dysfunction, infection, cancer
Immunosuppressive drug therapy
Death
(on background of comorbidities)
CNI toxicity/BK nephropathy
Donor age
Ischemia reperfusion injury
DGF
Interstitial fibrosis
(−)
TCMR
caTCMR
(subclinical | clinical)
Loss of organ function
Graft failure
HLA memory
HLA mismatch
DSA
AMR
caAMR
(subclinical | clinical)
Glomerulopathy
Drug minimization/nonadherence
Recurrent disease

5000 allografts are lost each year in the United States, primarily from cAMR and TG.



$35000 per patient per y during the 2 y after the rejection diagnosis.

American Journal of Transplantation 2017; 17: 2381–2389

Future disease risk

Risk markers:
- HLA mismatches
- HLA antibodies
- HLA-DSA
- Missing self
- Non-HLA antibodies
- …

Ongoing disease probability

Non-invasive diagnostics:
- Serum creatinine/eGFR
- Proteinuria
- Blood markers (dd-cfDNA, mRNA)
- Urinary markers
- Polyomavirus PCR
- …

Disease diagnosis

Biopsy-based diagnosis:
- Histological Banff classification
- Biopsy-based molecular diagnostics
- HLA-DSA, non-HLA antibodies

Disease stage/severity

Disease stage:
- Active disease
- Chronic/active disease
- Chronic disease

Disease severity/extent
- Activity index?
- Chronicity index?

Prognostication

Outcome prognostication:
- Single markers (e.g., eGFR evolution)
- Multidimensional markers (iBox)
- Patient comorbidities

Prediction of therapy response

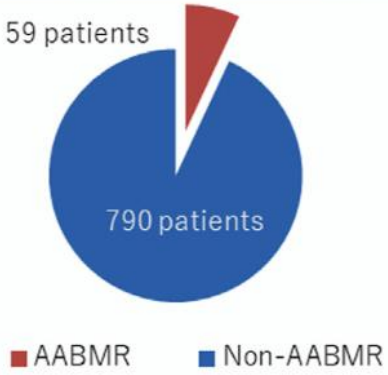
Predictive markers:
- None available

RISK FACTORS FOR DEVELOPING CHRONIC AMR

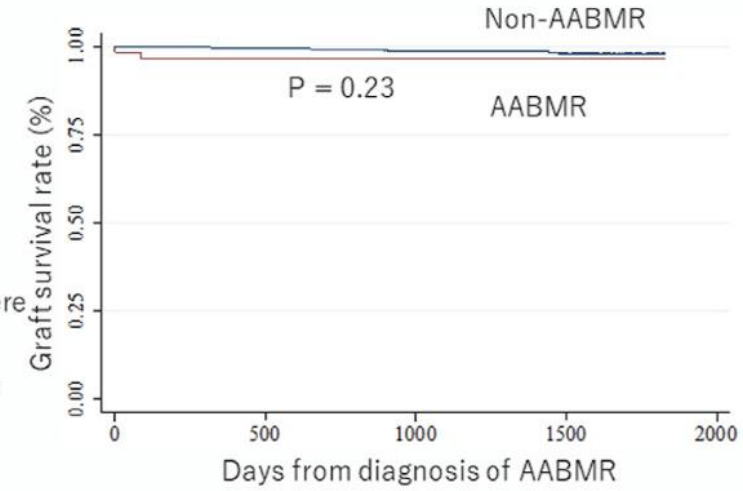
- DSA (Preformed or *de novo*)
- A higher risk of graft loss correlated with DSA strength.
- The impact of preformed DSA on graft survival may depend on whether the DSA persists 3 months posttransplantation, with persistence influenced by the strength and specificity of the DSA.

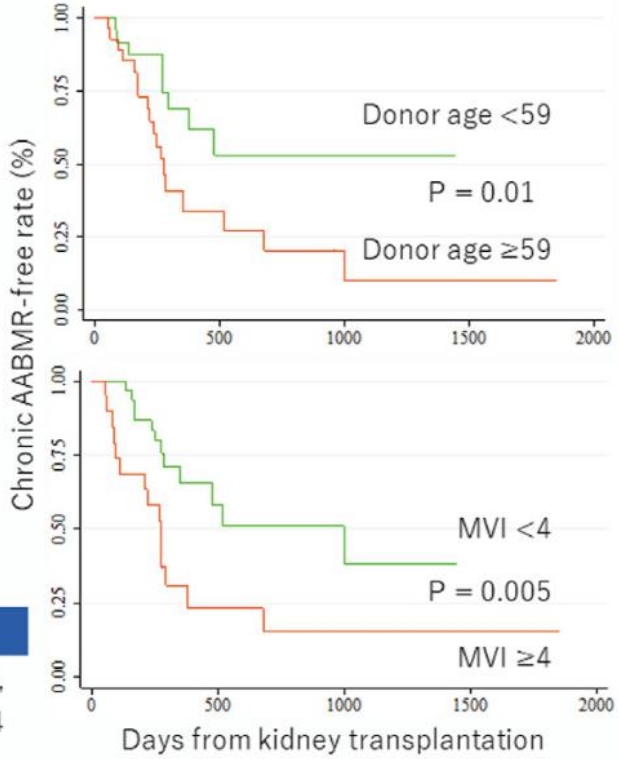
- Known risk factors for de novo DSA are:
  - HLA mismatches, particularly the number of epitope mismatches in HLA-DR/ DQ
  - Inadequate immunosuppression
  - Medication nonadherence
  - TCMR
  - Viral infection
  - Ischemia-reperfusion injury

Higher donor age and severe microvascular inflammation are risk factors for chronic rejection after treatment of active antibody-mediated rejection



Fifty-nine of 849 patients (6.9%) were diagnosed with active antibody-mediated rejection (AABMR) within one-year after living-donor kidney transplantation.

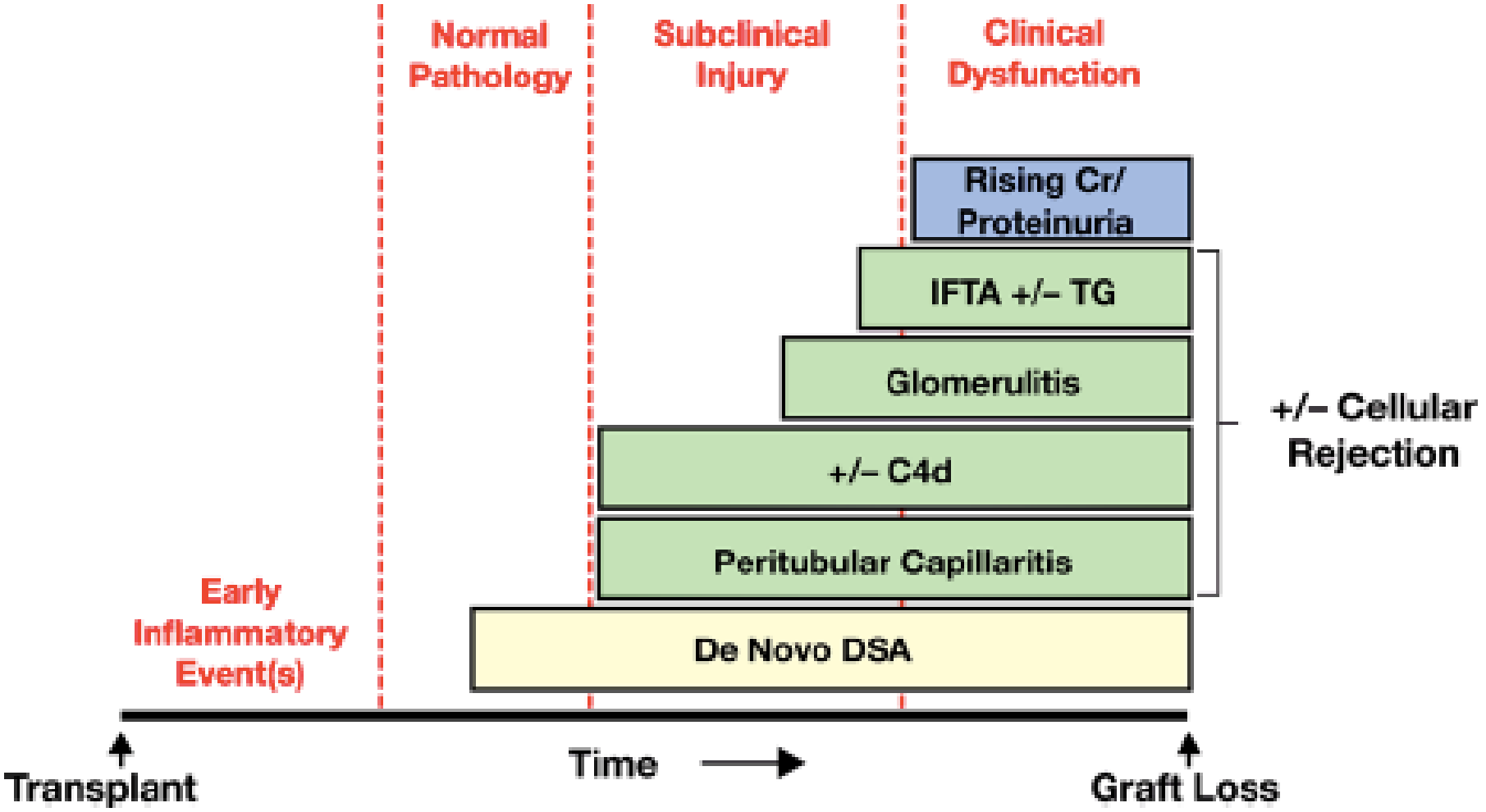




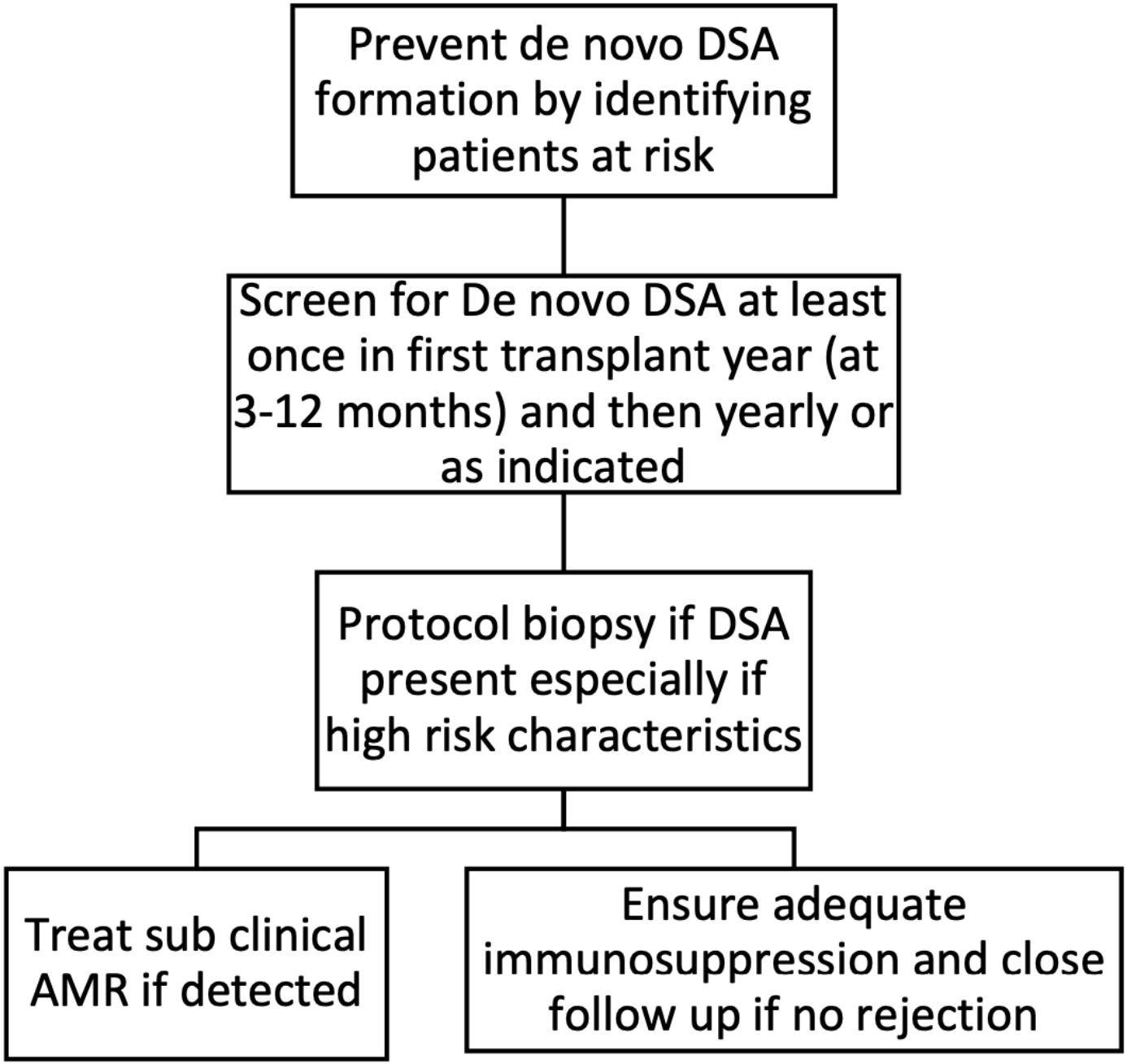
Conclusion

While 5-year death-censored graft survival is good in both AABMR and non-AABMR groups, AABMR patients with donor age ≥59 or microvascular inflammation (MVI) (g + ptc) score ≥4 significantly developed chronic AABMR.

Banno T, et al. *Transpl. Int.* 2024
doi: 10.3389/ti.2024.11960


Normal Pathology
Subclinical Injury
Clinical Dysfunction
Rising Cr/ Proteinuria
IFTA +/– TG
Glomerulitis
+/– C4d
Peritubular Capillaritis
De Novo DSA
+/– Cellular Rejection
Early Inflammatory Event(s)
Transplant
Time
Graft Loss

- Ideally, patients should be captured at an early stage of the disease:
- Serial surveillance biopsies
- eGFR or proteinuria
- dd-cfDNA release together with DSA screening,



Pak J Kidney Dis 2020;4(3):264-272

DIAGNOSTIC CRITERIA

Banff Classification

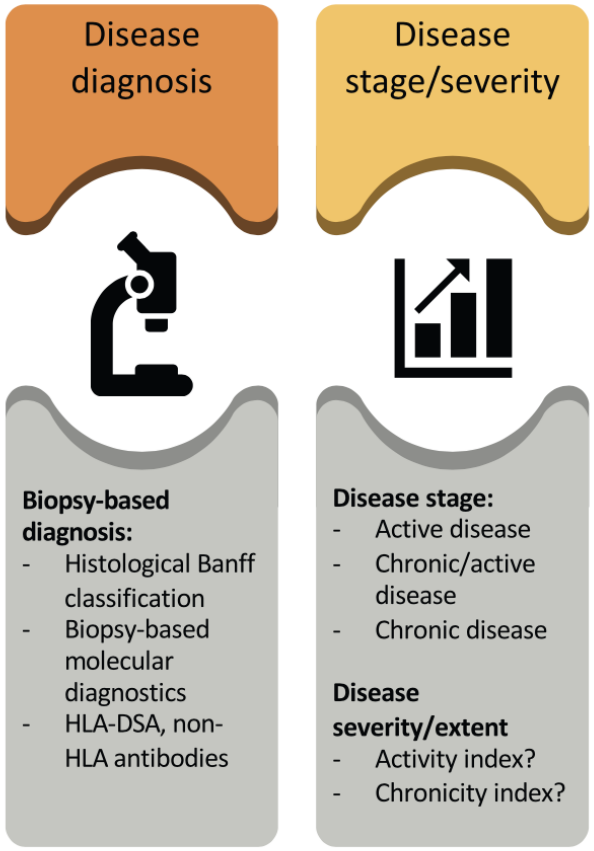
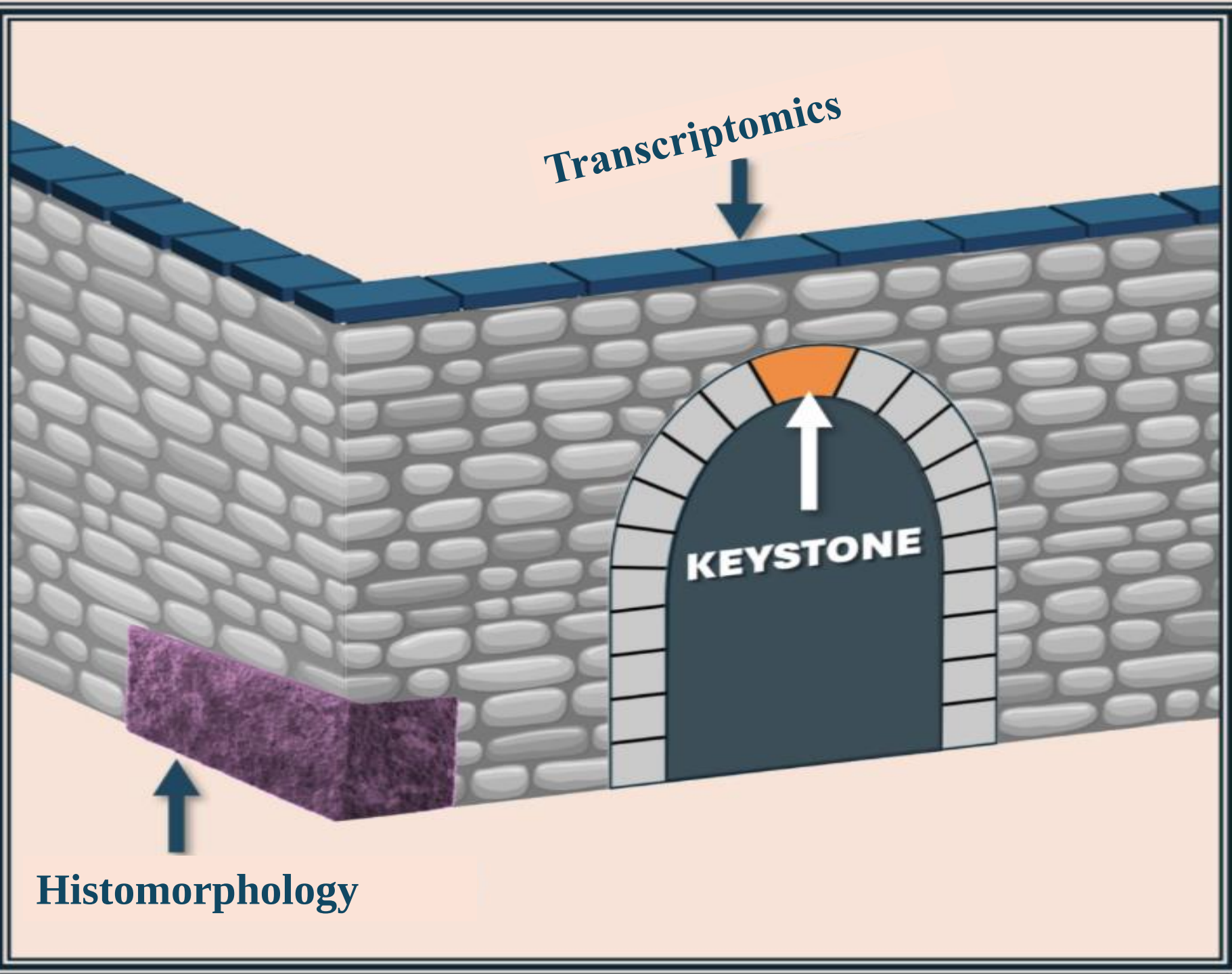


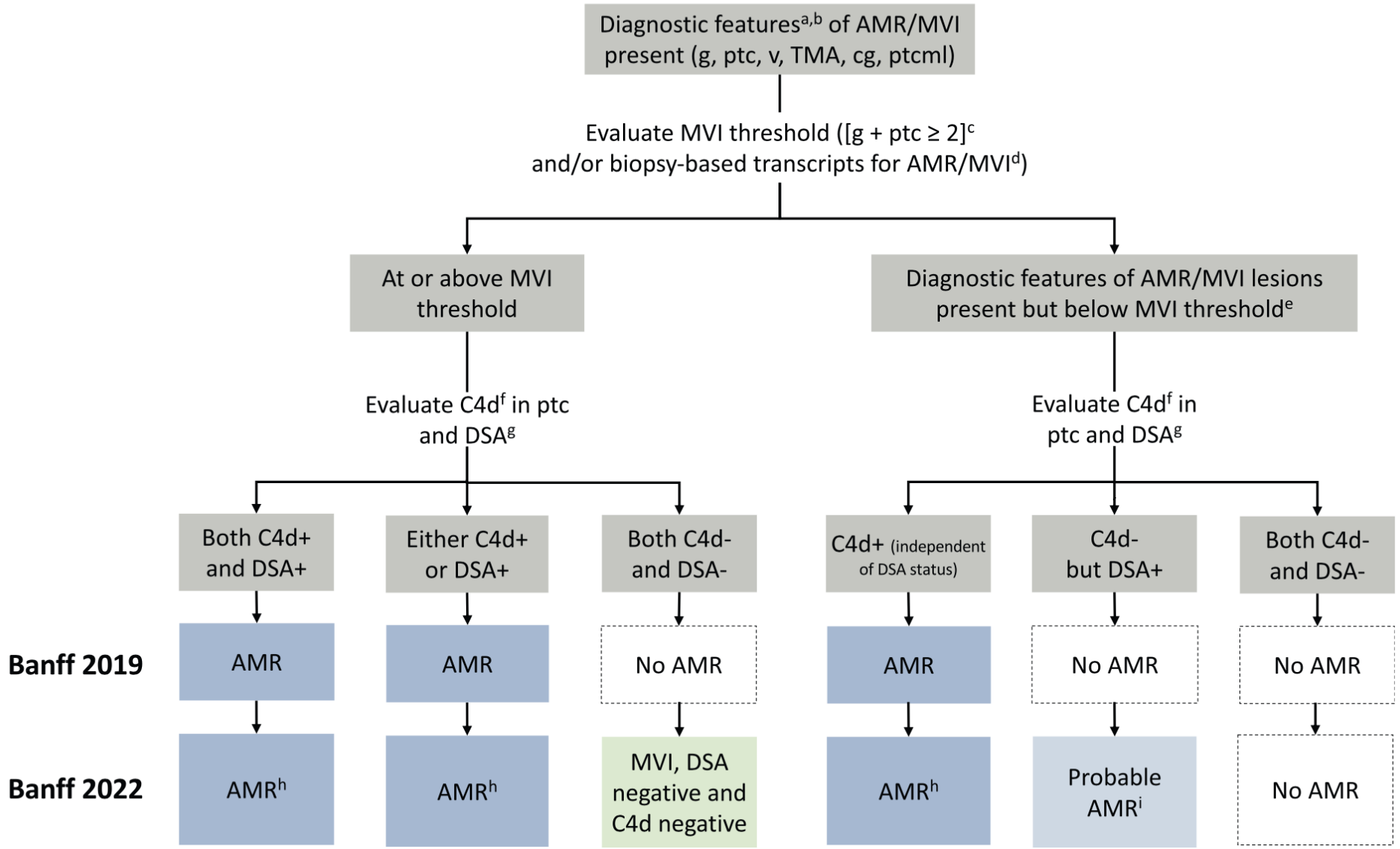
TABLE 3 Candidate biomarkers for antibody-mediated

Biomarker	Type of sample	Type of rejection
gp130, SH2D1B, TNFα, and CCL4	Plasma	AMR
miR-142-5p↓, miR-486-5p↑	PBMC	CAAMR
CIITA↓, CTLA-4 mRNA↑	PBMC	CAAMR+dnDSA
ETV7, RSAD2	PBMC	AMR
Eight-gene assay	Plasma	AMR
synaptotagmin-17↑	Urine	CAAMR
orosomucoid 1↑	Urine	CAAMR
AZGP1↑	Urine	CAAMR

International Journal of Urology (2023) **30**, 624–633

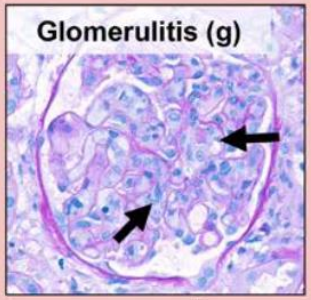

Transcriptomics
KEYSTONE
Histomorphology

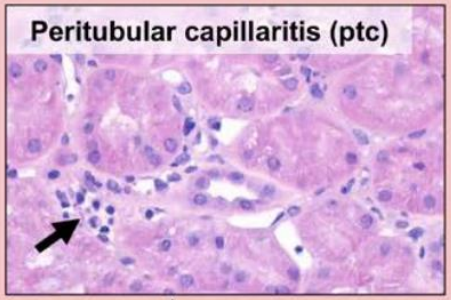
American Journal of Transplantation 24 (2024) 338–349



AMR/MVI (Banff 2022)

Active





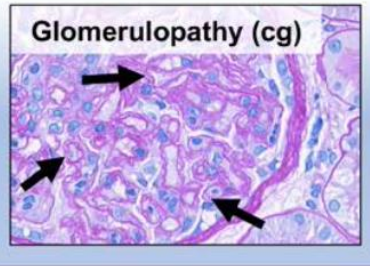
MVI (g+ptc)

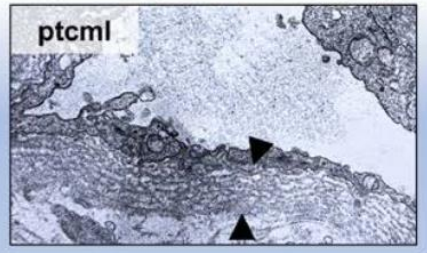
Active AMR:
MVI ≥ 2 AND **C4d ± DSA**
C4d WITH **MVI = 1** OR **v > 0** OR **TMA**

Probable active AMR:
DSA AND **MVI = 1** OR **v > 0** OR **TMA**

MVI, C4d negative, DSA negative:
MVI ≥ 2, BUT NO **C4d** OR **DSA**

Chronic active / inactive

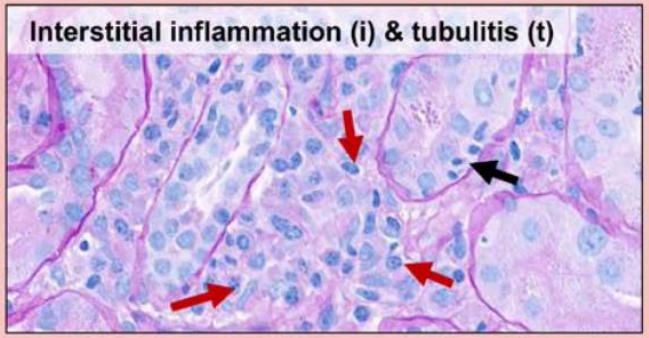




Chronic active AMR: Active lesions* AND **cg > 0** AND/OR **severe ptcml**

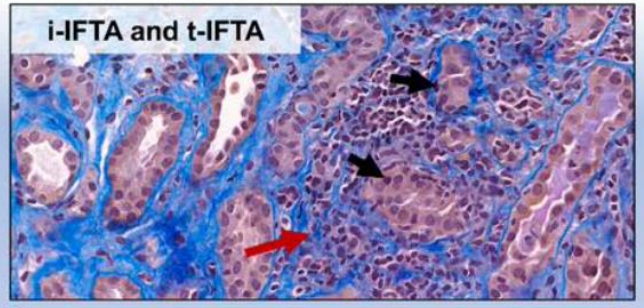
Chronic AMR: **cg > 0** AND/OR **severe ptcml** WITHOUT **active lesions****

TCMR (Banff 2019)



Borderline: t ≥ 1 AND i1 OR **t1 AND i ≥ 2**

TCMR:
Grade IA: i ≥ 2 AND **t2**
Grade IB: i ≥ 2 AND **t3**
Grade IIA: v1 ± i AND/OR **t**
Grade IIB: v2 ± i AND/OR **t**
Grade III: v3 ± i AND/OR **t**



Chronic active TCMR:
Grade IA: (i-IFTA ≥ 2 AND **ti ≥ 2)** AND **(t2** OR **t-IFTA2)**
Grade IB: (i-IFTA ≥ 2 AND **ti ≥ 2)** AND **(t3** OR **t-IFTA3)**
Grade II: Neointima with mononuclear cells

DOI: 10.1097/TP.0000000000005187

Disease stage/severity

Disease stage:
- Active disease
- Chronic/active disease
- Chronic disease

Disease severity/extent
- Activity index?
- Chronicity index?

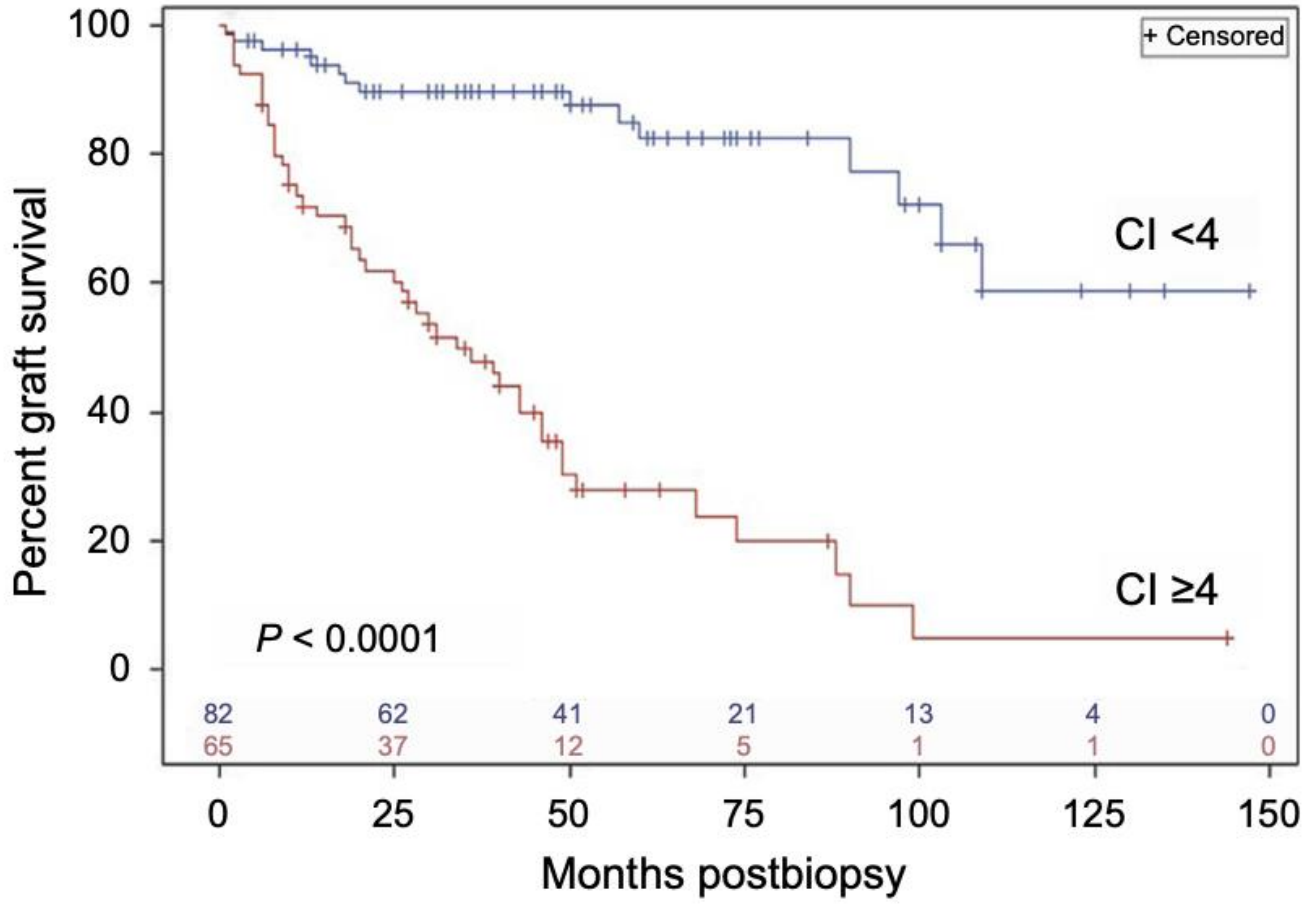
Activity index

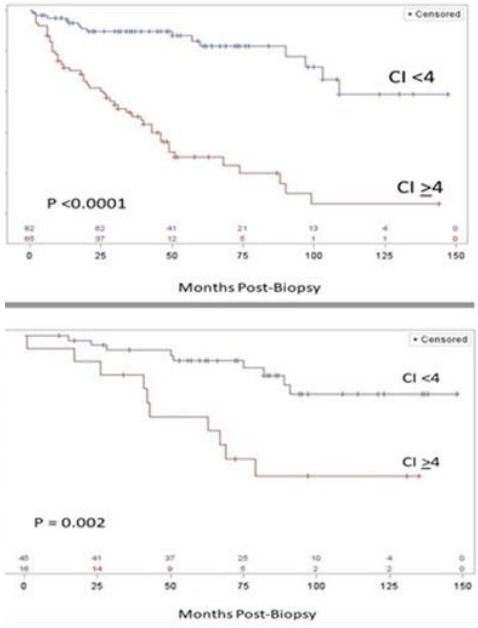
g + ptc + v + C4d

Chronicity index

i + ct + cv + 2*cg

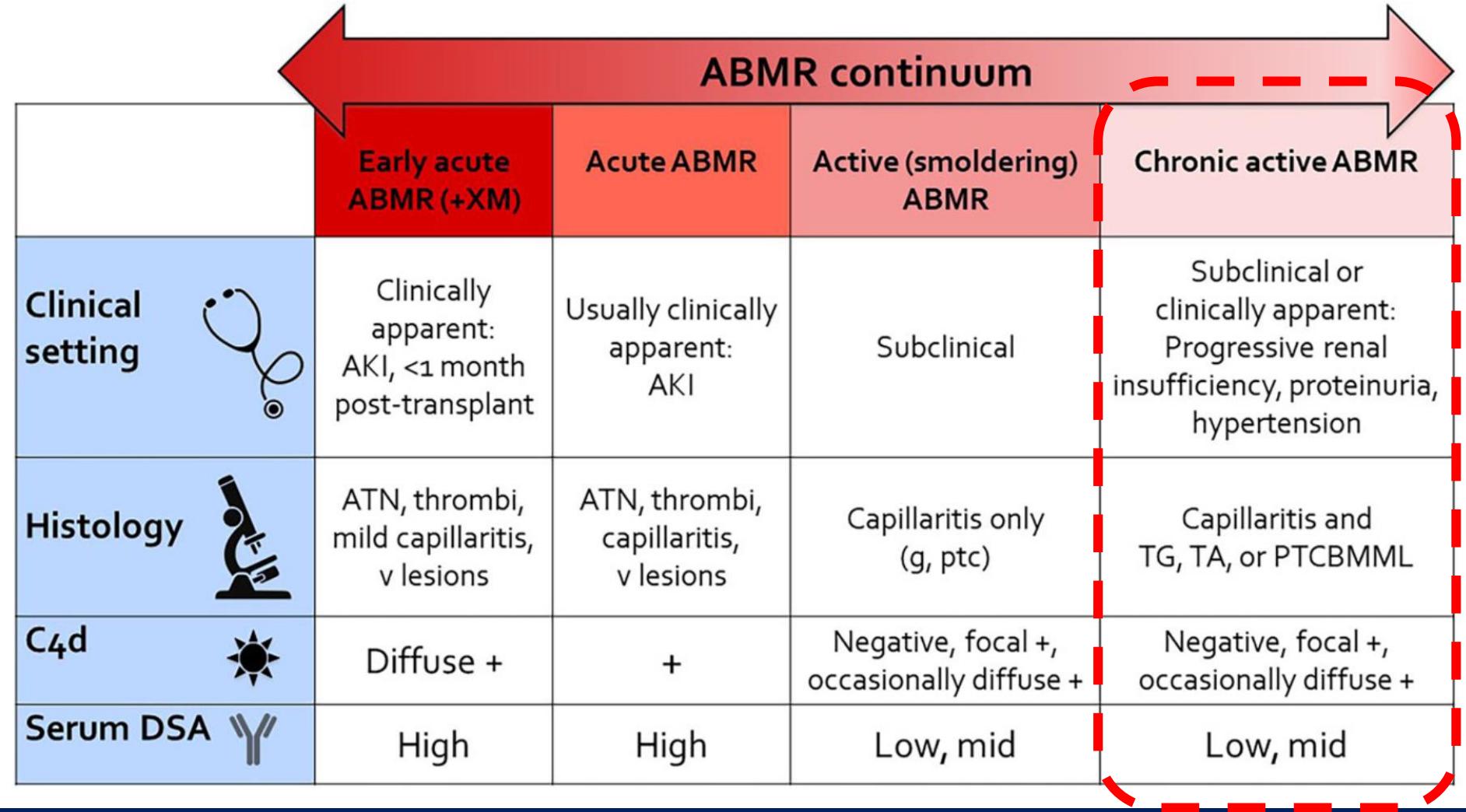
A Banff-based histologic chronicity index is associated with





renal allograft biopsy with an
strongly associated with graft
tive patients, respectively.

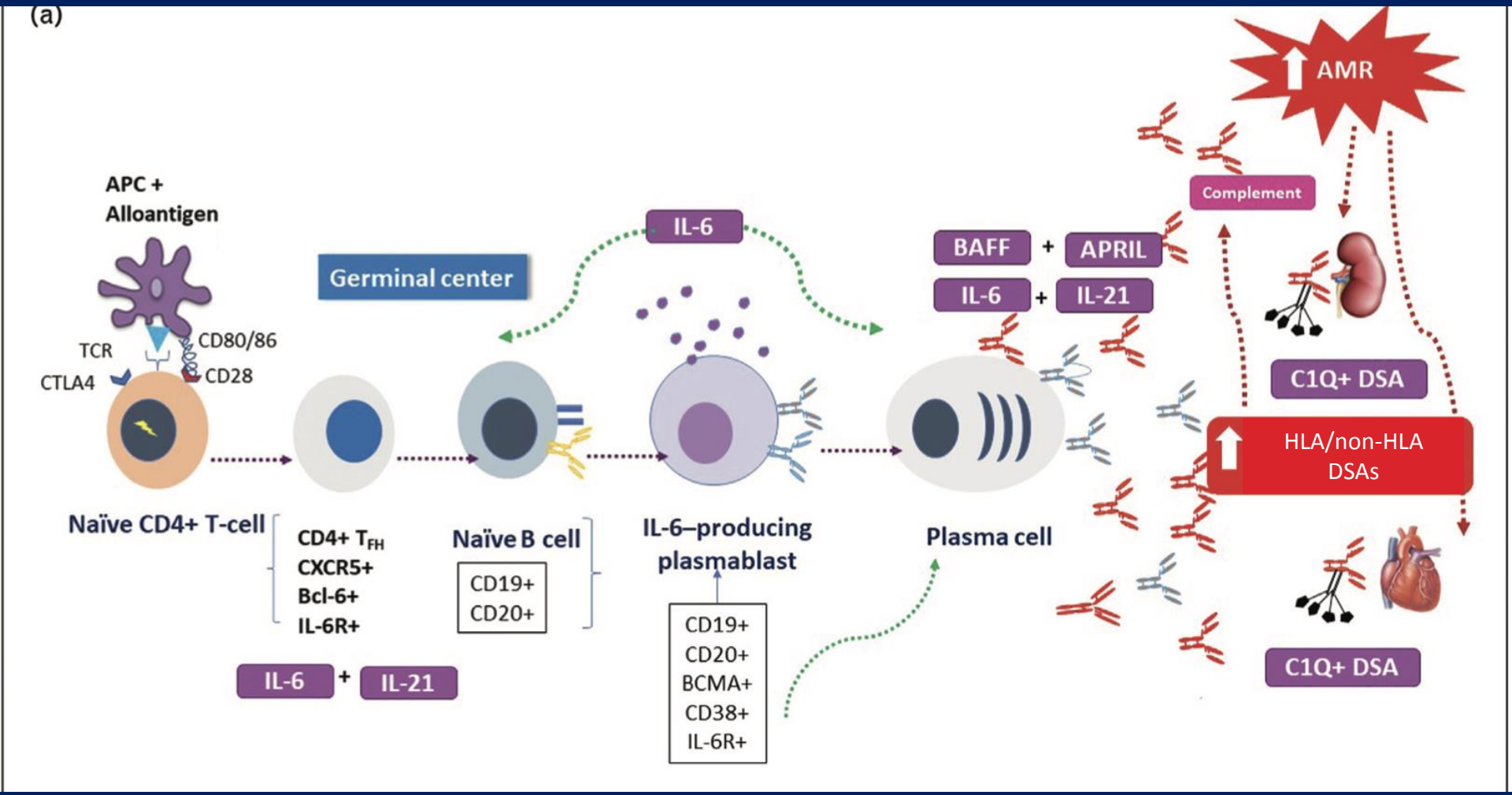
The continuum of "pure ABMR" in kidney transplant recipients with preformed DSA



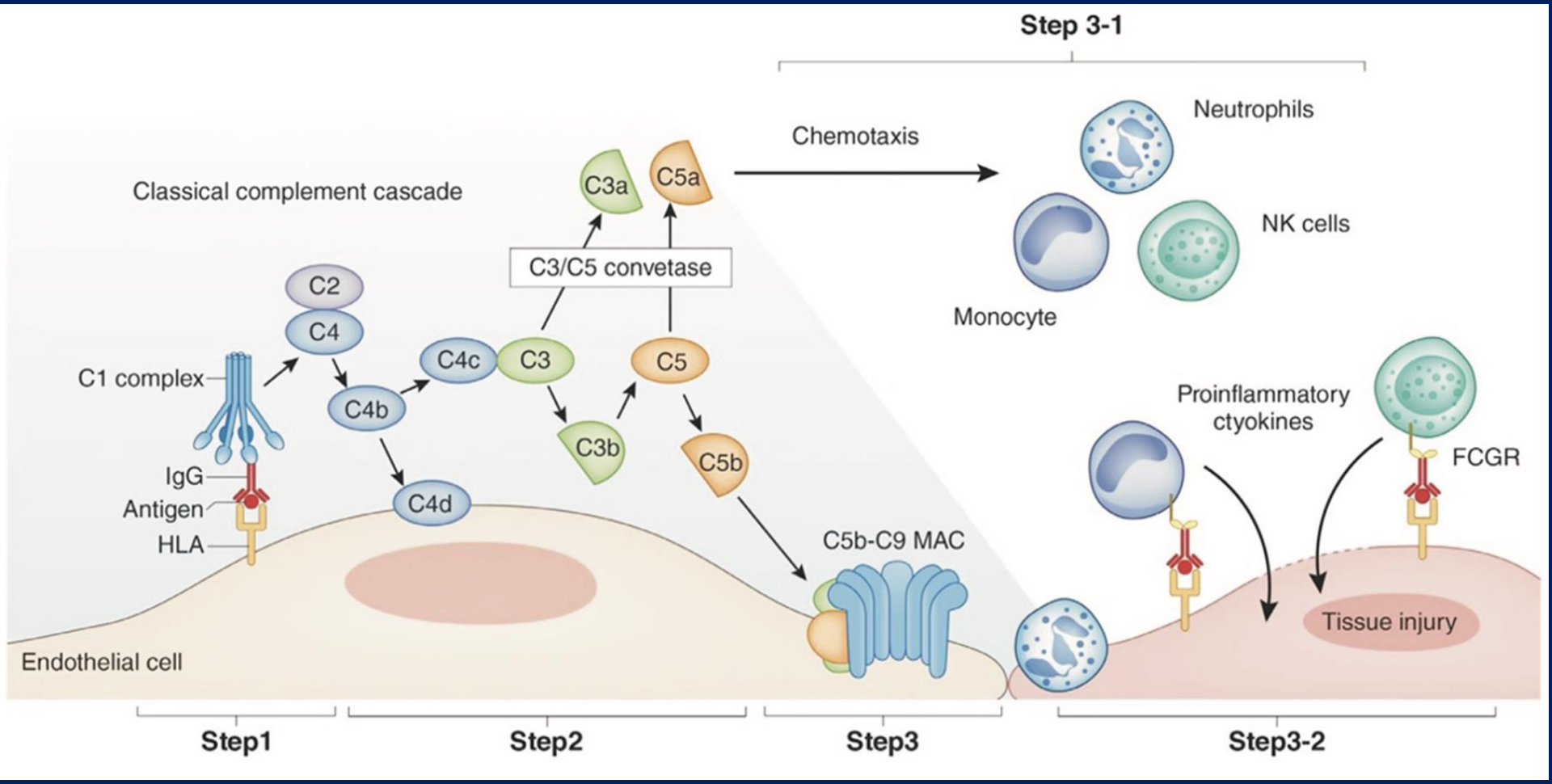
Frontiers in Immunology

doi: 10.3389/fimmu.2021.718122

IMMUNOLOGIC MECHANISMS



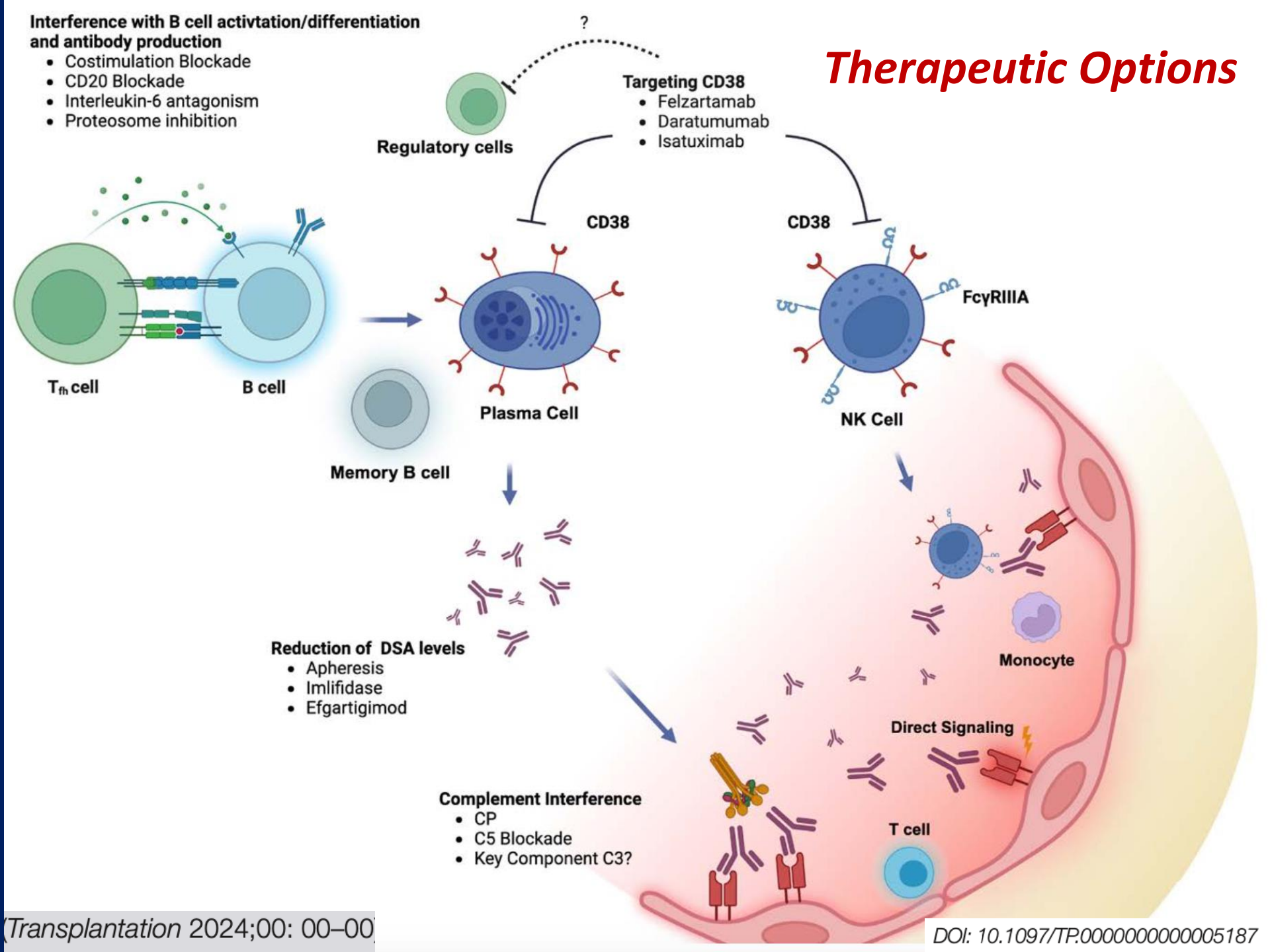
Curr Opin Organ Transplant 2024, 29:104–120
DOI:10.1097/MOT.0000000000001131


Step 3-1
Neutrophils
Chemotaxis
Classical complement cascade
C3a
C5a
NK cells
C3/C5 convetase
C2
C4
Monocyte
C1 complex
C4c
C3
C5
Proinflammatory
ctyokines
C4b
C3b
FCGR
IgG
Antigen
HLA
C4d
C5b
C5b-C9 MAC
Tissue injury
Endothelial cell
Step1
Step2
Step3
Step3-2

- The current treatment paradigms rely on reduction of antibody levels to prevent AMR.

- This raises the importance of maintaining immunosuppression and investigating novel methods to prevent and treat AMR/cAMR that directly address the reduction of DSAs and antibody-producing cells.

Therapeutic Options



(Transplantation 2024;00: 00–00)

DOI: 10.1097/TP.0000000000005187

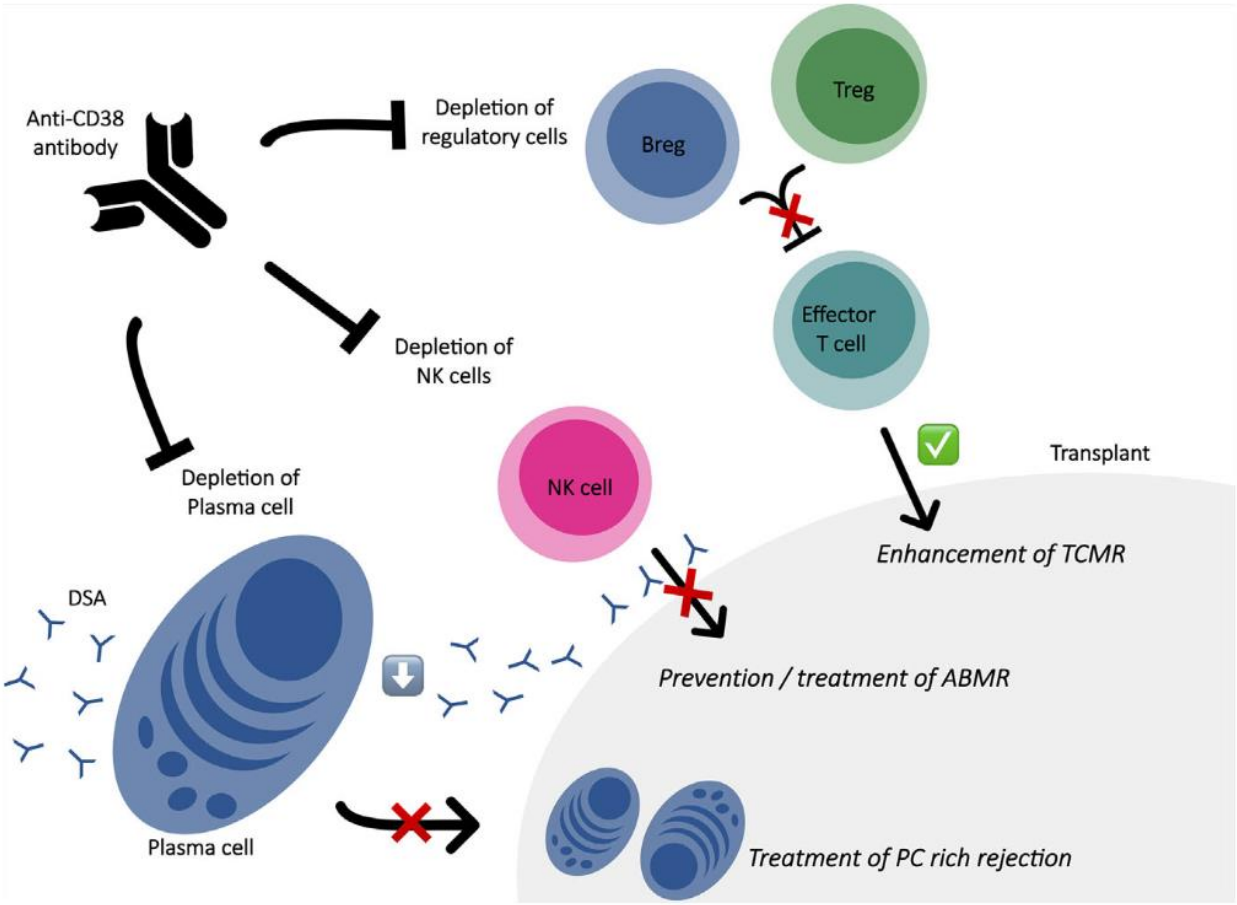


FIGURE 1 | Immune effects of anti-CD38 antibody in the context of solid organ transplantation. ABMR, antibody mediated rejection; Breg, regulatory B cell; DSA, donor specific antibodies; PC, plasma cell; TCMR, T cell mediated rejection; Treg, regulatory T cell.

doi: 10.3389/fimmu.2021.688301

Major Therapeutic Concepts

- CD20 antibody rituximab as a sole treatment or in combination with IVIG (phase 2)
- Proteasome inhibition using bortezomib (phase 2)
- Targeting IL-6 with the anti-IL-6 antibody clazakizumab (phase 2 and phase 3)
- DSA cleavage with imlifidase (phase 2)
- Targeting CD38 with felzartamab (phase 2).

Review

OPEN

Recommended Treatment for Antibody-mediated Rejection After Kidney Transplantation: The 2019 Expert Consensus From the Transplantion Society Working Group

There was no conclusive evidence to support any specific therapy

There are no FDA-approved treatments for acute or chronic AMR

Transplantation. 2018;102:e257–e264.

(*Transplantation* 2020;104: 911–922).

Post-transplant surveillance and management of chronic active mediated rejection in renal transplant patients in Europe

BACKGROUND

Antibody mediated rejection (ABMR) is the leading cause of immune-related allograft failure following kidney transplantation. Chronic active ABMR (CABMR) typically occurs after one-year post-transplant and is the most common cause of late allograft failure

STUDY AIM

To assess common practices in Europe for post-transplant surveillance one year after kidney transplant, and diagnosis and management of CABMR.

METHODS AND COHORT

Online survey
15 minutes

58 questions
multiple-choice/open

Transplant nephrologists
Transplant surgeons
Nephrologists
N=56

CRITERIA
Practicing 3-30 years
5 patients/year with CABMR
Perform DSA testing

February – November 2022

RESULTS

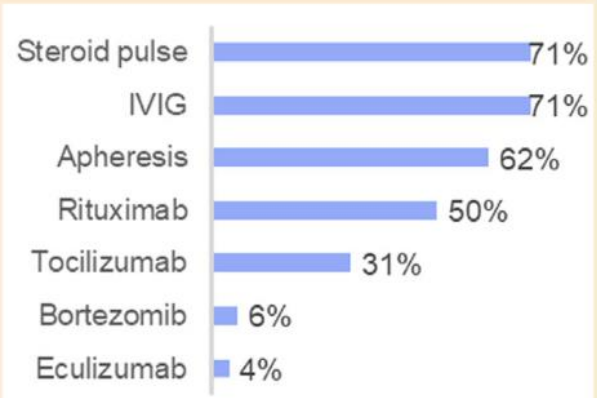
POST TRANSPLANT SURVEILLANCE

Observing clinical measures of graft function forms the cornerstone of post-transplant surveillance. This may be suboptimal, leading to late diagnoses and untreatable disease.

Less than half of patients who develop CABMR receive treatment beyond optimization of immune suppression

CABMR TREATMENT

Intravenous Immunoglobulin (IVIG), steroid pulse and apheresis are most prescribed to treat CABMR. While biologics can feature as part of treatment, there is no single preferred agent



Rostaing, et al. Transpl. Int. 2023
doi: 10.3389/ti.2023.11381

Systematic trials in late and chronic active antibody-mediated rejection

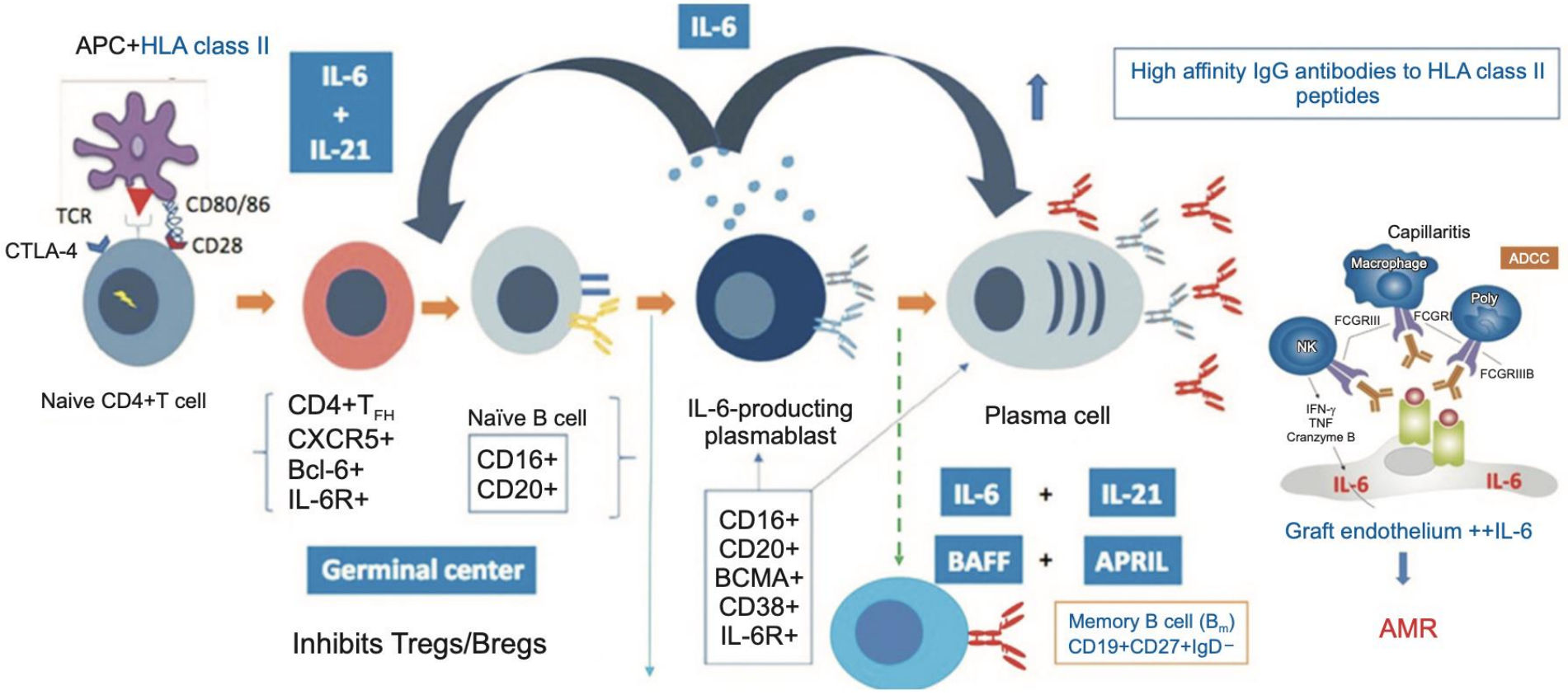
Primary target	Compound	Mechanism of action	Stage of development	Trial acronym	Identifier[a]	Study	Main trial results
PC	Bortezomib	Proteasome inhibition	Phase II (finished)	BORTEJECT	NCT01873157	Eskandary et al[91]	No effect on DSA levels, morphologic/molecular biopsy results, and eGFR slope
			Phase II (finished)	TRIBUTE	NCT02201576	—	Finalized, but not yet published
			Phase II (recruiting)	—	NCT03737136	—	Not yet finalized
PC/NK cells	Felzartamab	CD38 binding	Phase II (finished)	—	NCT05021484	Mayer et al[44]	Reduction/resolution of morphologic/molecular AMR activity; NK cell depletion; decrease in plasma dd-cfDNA
B cells	Rituximab	$CD20^+$ B cell depletion	Phase II (prematurely terminated)	TRITON	2010-023746-67	Moreso et al[107]	No effect on morphologic biopsy results and eGFR course
			Phase IV (prematurely terminated)	RituxiCAN-C4	NCT00476164	Shiu et al[108]	No effect on clinical outcomes
			Phase III (recruiting)	TAR:GET-1	NCT03994783		Not yet finalized
	Fostamatinib	SYK inhibition	Phase II (recruiting)	FOSTAMR	NCT03991780	—	Not yet finalized

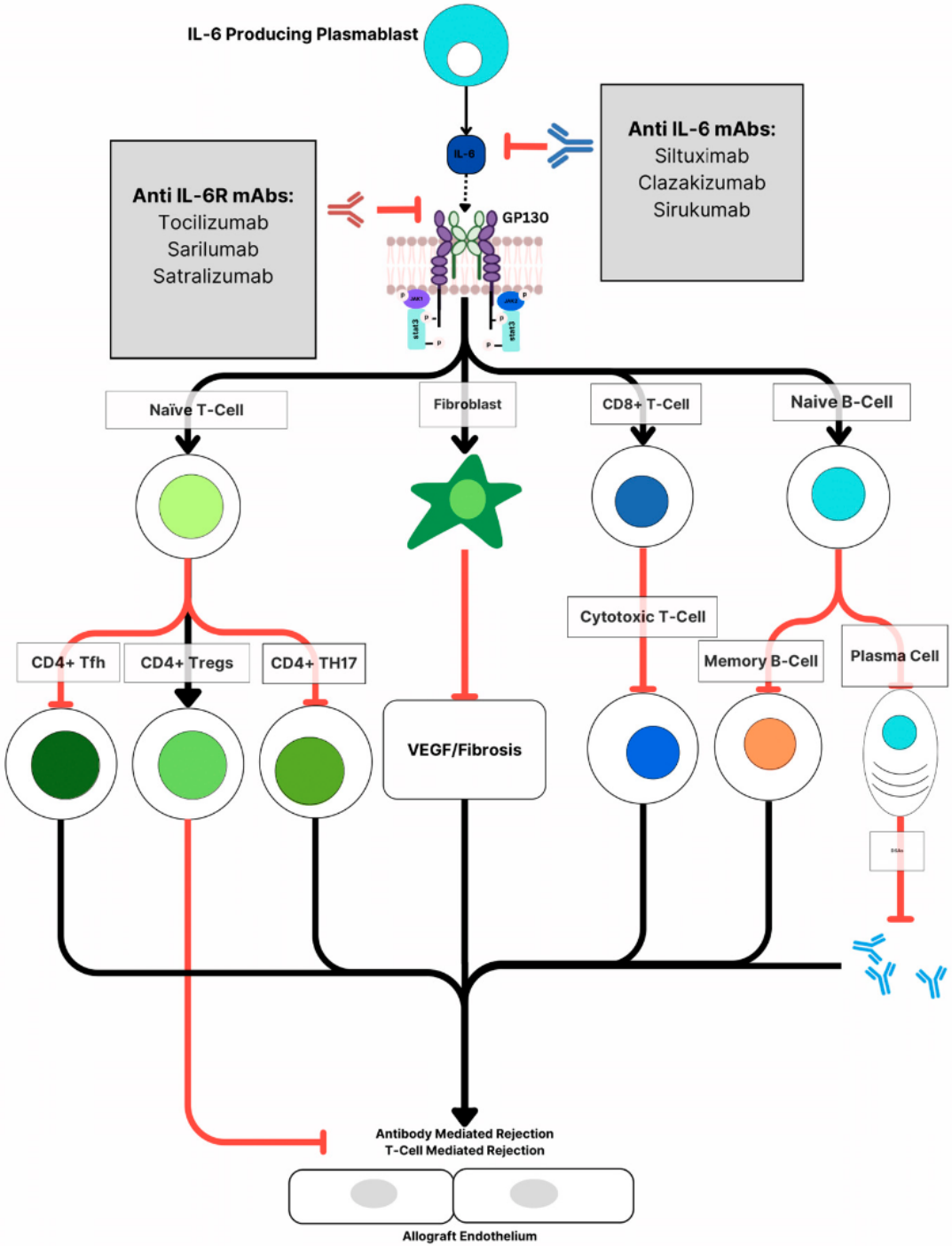
DOI: 10.1097/TP.0000000000005187

Systematic trials in late and chronic active antibody-mediated rejection

Primary target	Compound	Mechanism of action	Stage of development	Trial acronym	Identifier[a]	Study	Main trial results
IL-6/IL-6R	Clazakizumab	IL-6 neutralization	Phase II (finished)	—	NCT03444103	Doberer et al[92]	Moderate DSA reduction; modest effect on molecular AMR activity after 12 mo; effect on eGFR slope
			Phase III (prematurely terminated)	IMAGINE	NCT03744910	Nickerson et al[109]	No effect on eGFR slope (not yet published)
	Tocilizumab	IL-6R blockade	Phase III (recruiting)	INTERCEPT	NCT04561986	Streichart et al[110]	Not yet finalized
Complement	BIVV009	Inhibition of C1s	Phase I (finalized)	—	NCT02502903	Eskandary et al[47]	Marked complement inhibition (ex vivo; C4d staining); no effect on morphologic/molecular AMR activity
	BIVV020	Inhibition of C1s	Phase II (recruiting)		NCT05156710		Not yet finalized
	Eculizumab	C5 cleavage inhibition	Phase III (finished)	—	NCT01327573	Kulkarni et al[111]	No impact on biopsy results. Possible effect on eGFR course

DOI: 10.1097/TP.0000000000005187


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
Macrophage
ADCC
Poly
FCGRIII
FCGRI
NK
FCGRIIIB
IFN-γ
TNF
Cranzyme B
IL-6
IL-6
Graft endothelium ++IL-6
AMR


IL-6 Producing Plasmablast
IL-6
Anti IL-6 mAbs:
Siltuximab
Clazakizumab
Sirukumab
Anti IL-6R mAbs:
Tocilizumab
Sarilumab
Satralizumab
GP130
Naïve T-Cell
Fibroblast
CD8+ T-Cell
Naive B-Cell
Cytotoxic T-Cell
CD4+ Tfh
CD4+ Tregs
CD4+ TH17
Memory B-Cell
Plasma Cell
VEGF/Fibrosis
Antibody Mediated Rejection
T-Cell Mediated Rejection
Allograft Endothelium

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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].

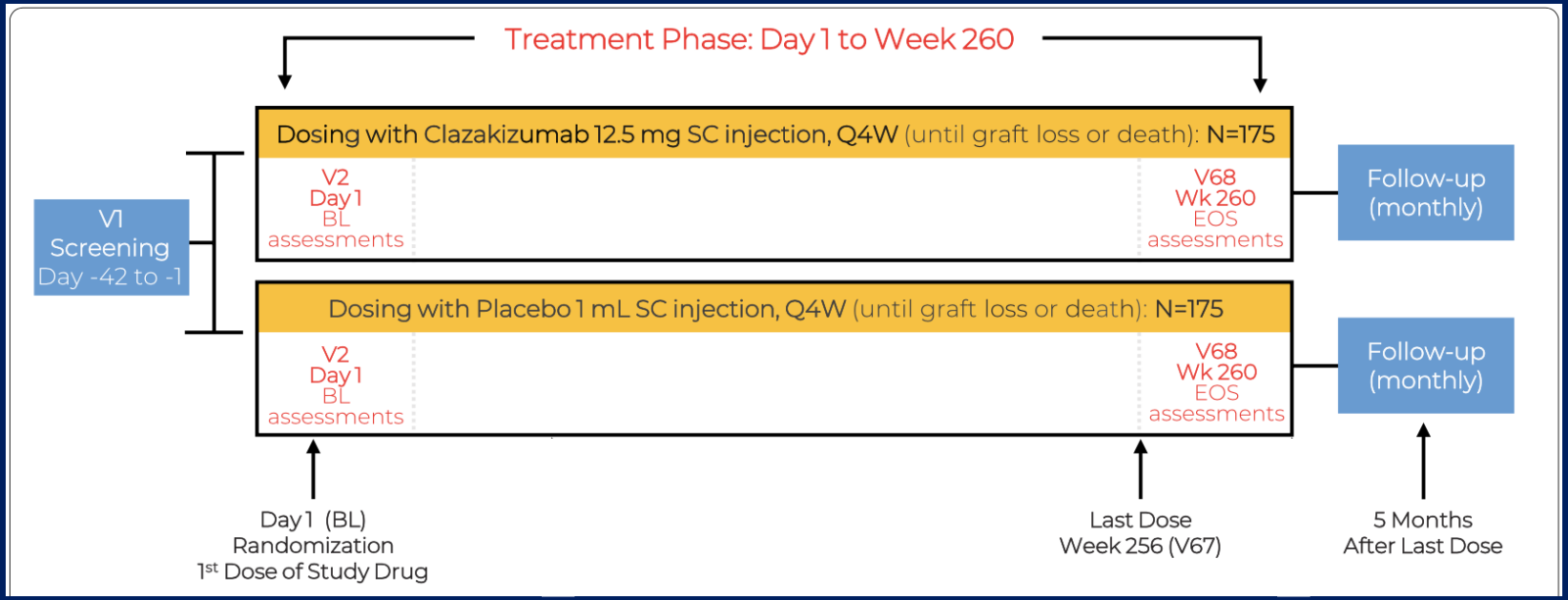
Nickerson *et al. Trials* (2022) 23:1042
https://doi.org/10.1186/s13063-022-06897-3

Trials

STUDY PROTOCOL Open Access

Clazakizumab for the treatment of chronic active antibody-mediated rejection (AMR) in kidney transplant recipients: Phase 3 IMAGINE study rationale and design

Peter W. Nickerson[1], Georg A. Böhmig[2], Steve Chadban[3], Deepali Kumar[4], Roslyn B. Mannon[5], Teun van Gelder[6],



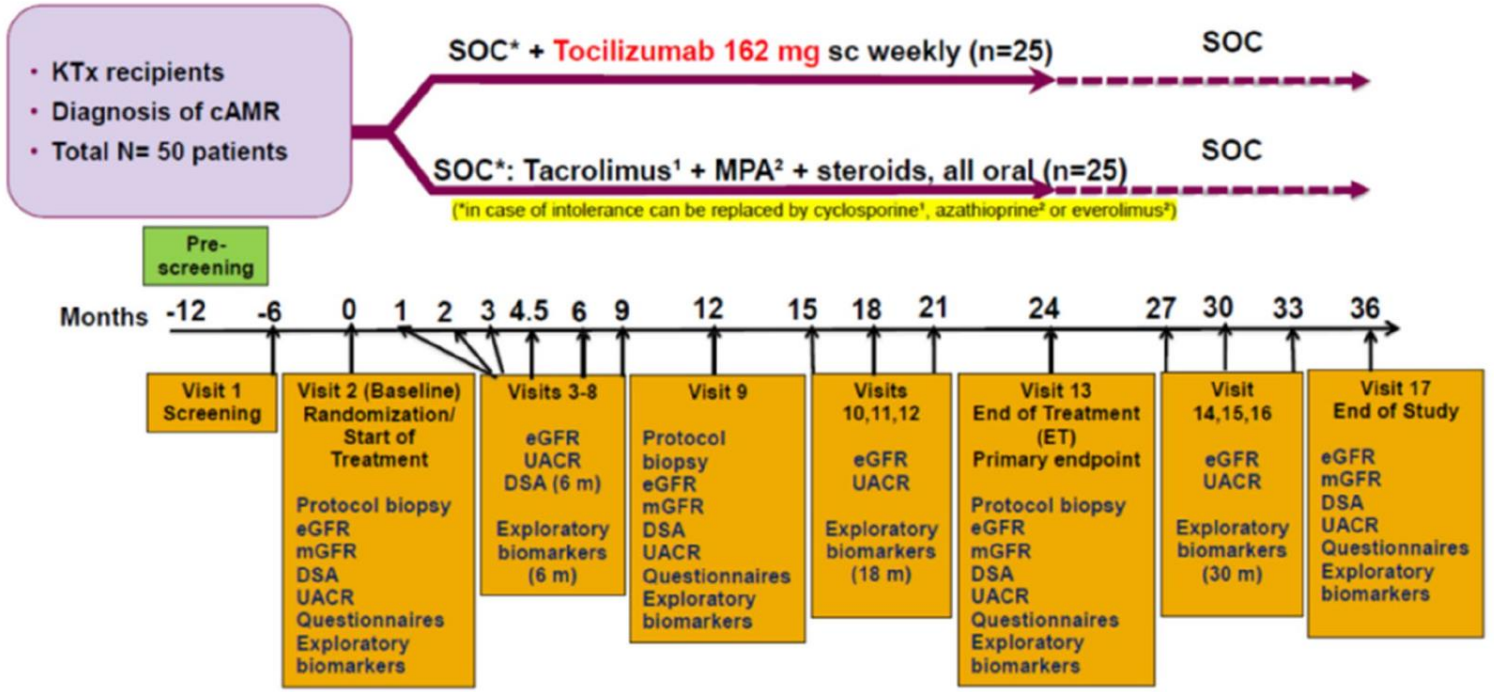
ADDENDUM

Since acceptance of this paper for publication, the results of the first planned interim analysis of the IMAGINE trial have become available, indicating the trial was unlikely to meet the ultimate primary efficacy outcome. Therefore, enrollment to the study has been stopped. The recommendation to stop the study was not based on safety concerns. Communications with investigators and site staff are ongoing for scheduling an end-of-treatment study visit with patients currently participating in the trial. It is clear that we need to continue to search for a solution for transplant recipients at risk of allograft failure and do it in a robust manner that enables a clear decision. We thank the study participants and study staff for participating in the largest placebo-controlled study in caAMR and the transplant community for their advocacy.

Streichart *et al. Trials* (2024) 25:213
https://doi.org/10.1186/s13063-024-08020-0

STUDY PROTOCOL **Open Access**

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



Systematic trials in late and chronic active antibody-mediated rejection

Primary target	Compound	Mechanism of action	Stage of development	Trial acronym	Identifier[a]	Study	Main trial results
PC	Bortezomib	Proteasome inhibition	Phase II (finished)	BORTEJECT	NCT01873157	Eskandary et al[91]	No effect on DSA levels, morphologic/molecular biopsy results, and eGFR slope
			Phase II (finished)	TRIBUTE	NCT02201576	—	Finalized, but not yet published
			Phase II (recruiting)	—	NCT03737136	—	Not yet finalized
PC/NK cells	Felzartamab	CD38 binding	Phase II (finished)	—	NCT05021484	Mayer et al[44]	Reduction/resolution of morphologic/molecular AMR activity; NK cell depletion; decrease in plasma dd-cfDNA
B cells	Rituximab	$CD20^+$ B cell depletion	Phase II (prematurely terminated)	TRITON	2010-023746-67	Moreso et al[107]	No effect on morphologic biopsy results and eGFR course
			Phase IV (prematurely terminated)	RituxiCAN-C4	NCT00476164	Shiu et al[108]	No effect on clinical outcomes
			Phase III (recruiting)	TAR:GET-1	NCT03994783		Not yet finalized
	Fostamatinib	SYK inhibition	Phase II (recruiting)	FOSTAMR	NCT03991780	—	Not yet finalized

DOI: 10.1097/TP.0000000000005187

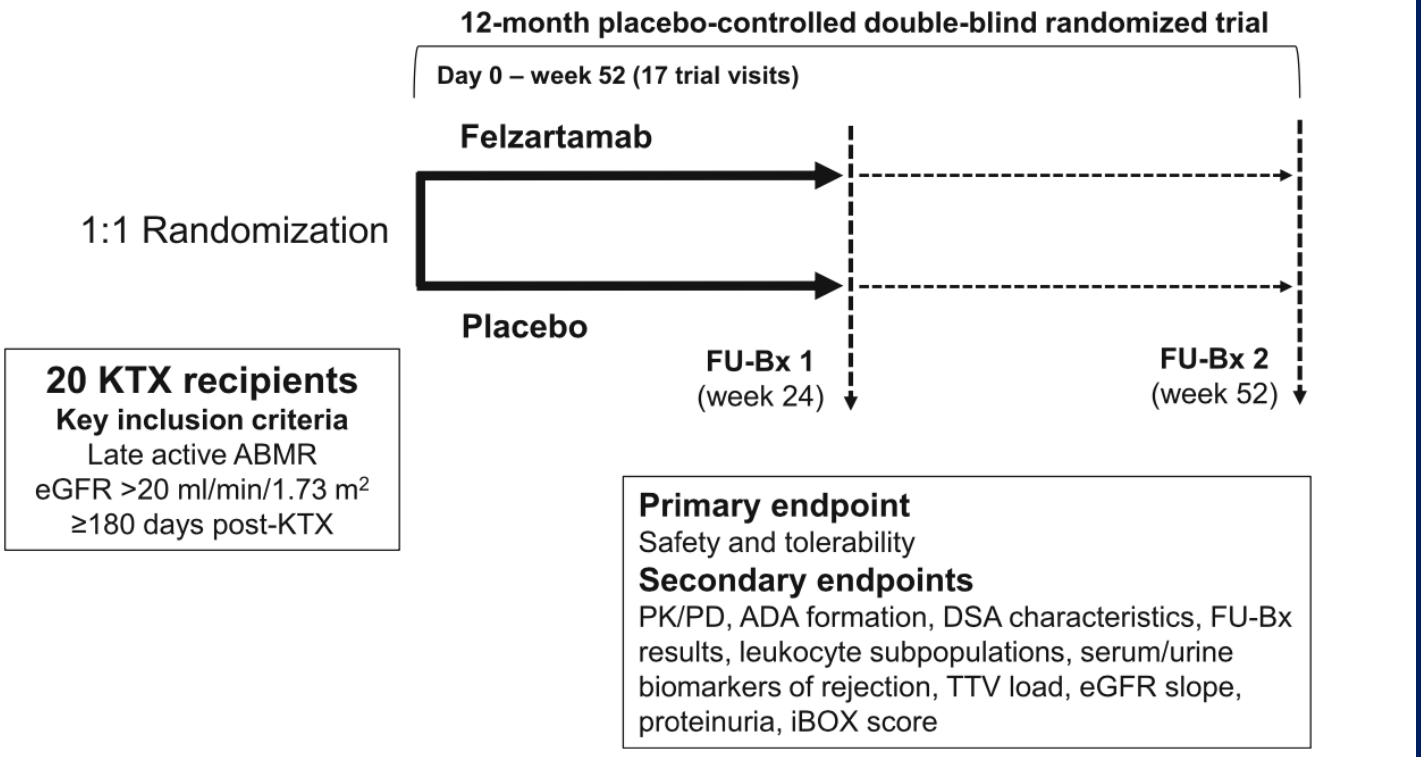
Mayer *et al. Trials* (2022) 23:270
https://doi.org/10.1186/s13063-022-06198-9

Trials

STUDY PROTOCOL Open Access

Safety, tolerability, and efficacy of monoclonal CD38 antibody felzartamab in late antibody-mediated renal allograft rejection: study protocol for a phase 2 trial

Katharina A. Mayer[1], Klemens Budde[2], Philip F. Halloran[3], Konstantin Doberer[1], Lionel Rostaing[4], Farsad Eskandary[1],

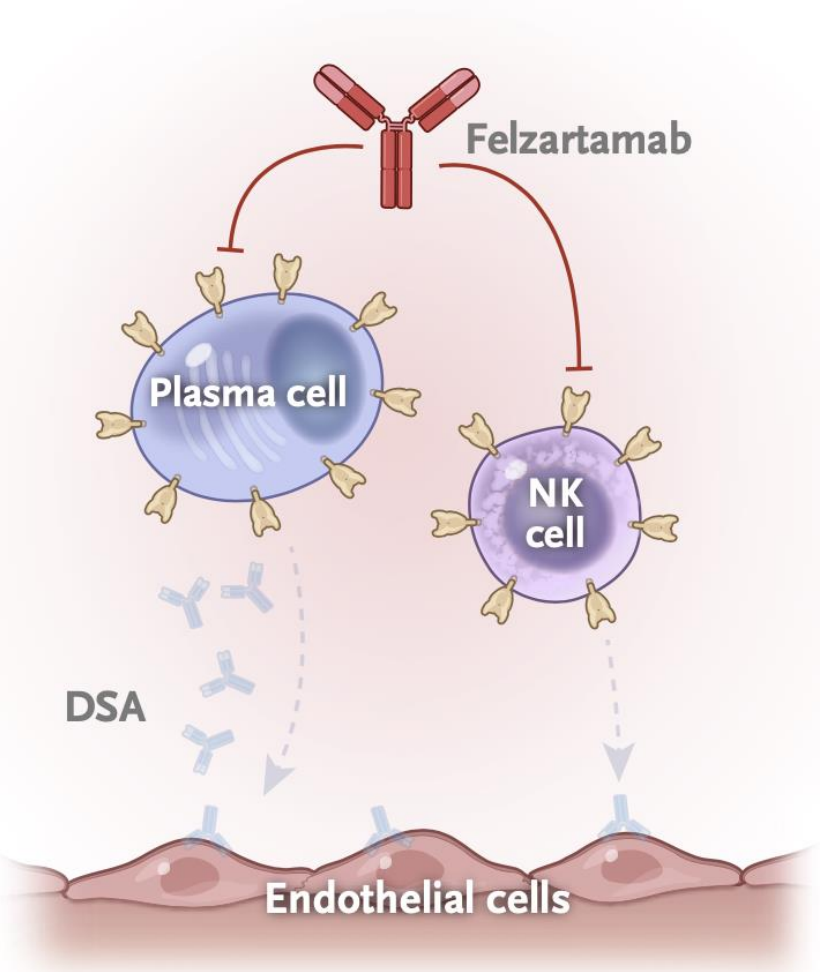


The NEW ENGLAND JOURNAL of MEDICINE

Felzartamab for Antibody-Mediated Rejection

A PLAIN LANGUAGE SUMMARY

Based on the NEJM publication: A Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection by K.A. Mayer et al. (published May 25, 2024)



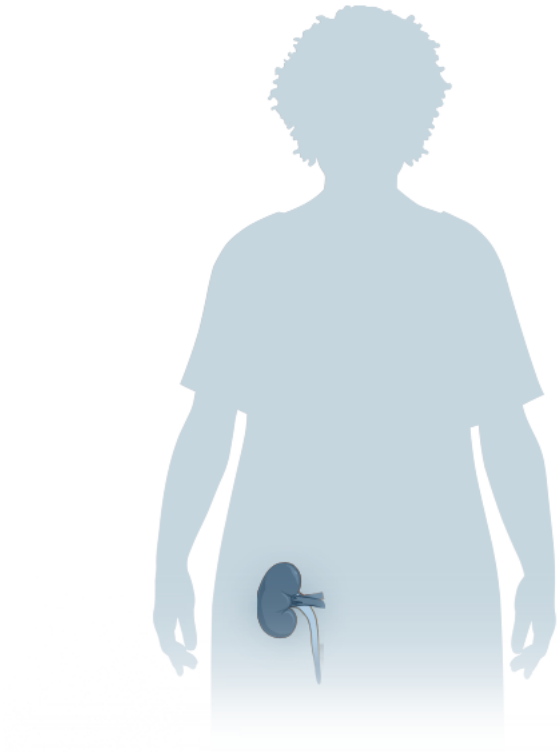
TRIAL DESIGN

- PHASE 2
- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- DURATION OF TREATMENT: 24 WEEKS; TOTAL FOLLOW-UP: 52 WEEKS
- LOCATIONS: VIENNA AND BERLIN

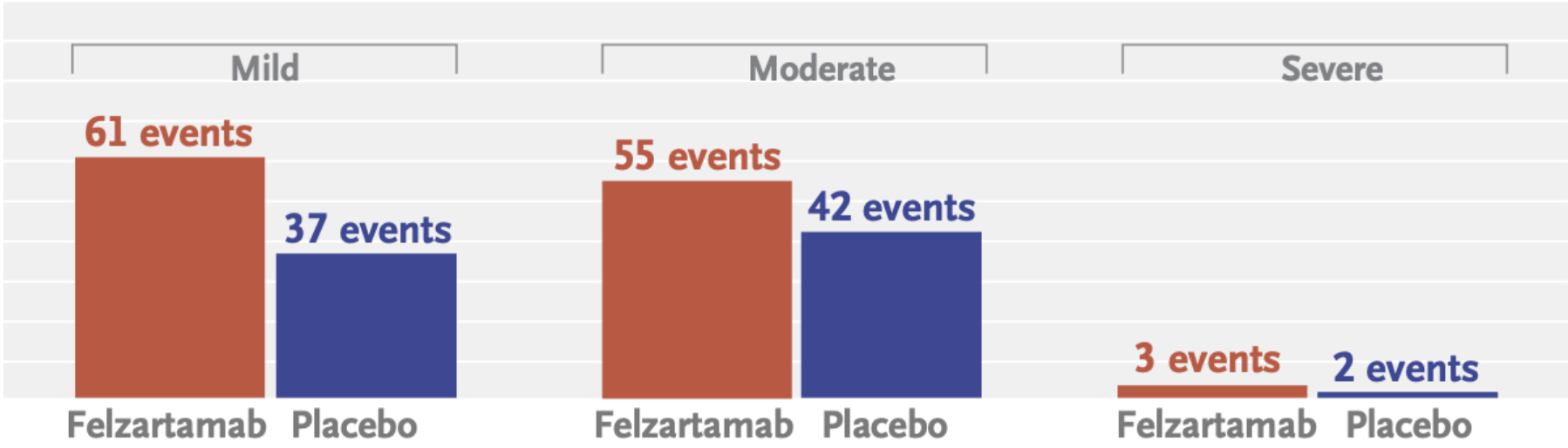
PATIENTS

WHO	22 adults Median age, 39 years
CLINICAL STATUS	Biopsy-diagnosed antibody-mediated kidney-transplant rejection Estimated glomerular filtration rate of at least 20 ml/min/1.73 m^2 Presence of donor-specific antibody

RESOLUTION



At 24 weeks, resolution of antibody-mediated kidney-transplant rejection (a key secondary outcome) was **four times** as likely with felzartamab as with placebo.



LIMITATIONS AND REMAINING QUESTIONS

- The trial was exploratory, with a primary safety objective.
- The sample size was small, and the duration of the trial was short.
- The trial was conducted in Europe in a primarily White population; the findings may not be generalizable to transplant populations in other regions, including North America.

CONCLUSIONS

In patients with antibody-mediated kidney-transplant rejection, treatment with intravenous felzartamab over 24 weeks had acceptable safety and side-effect profiles.

A thorough analysis of follow-up biopsies did not reveal any molecular features of TCMR.

Response to treatment

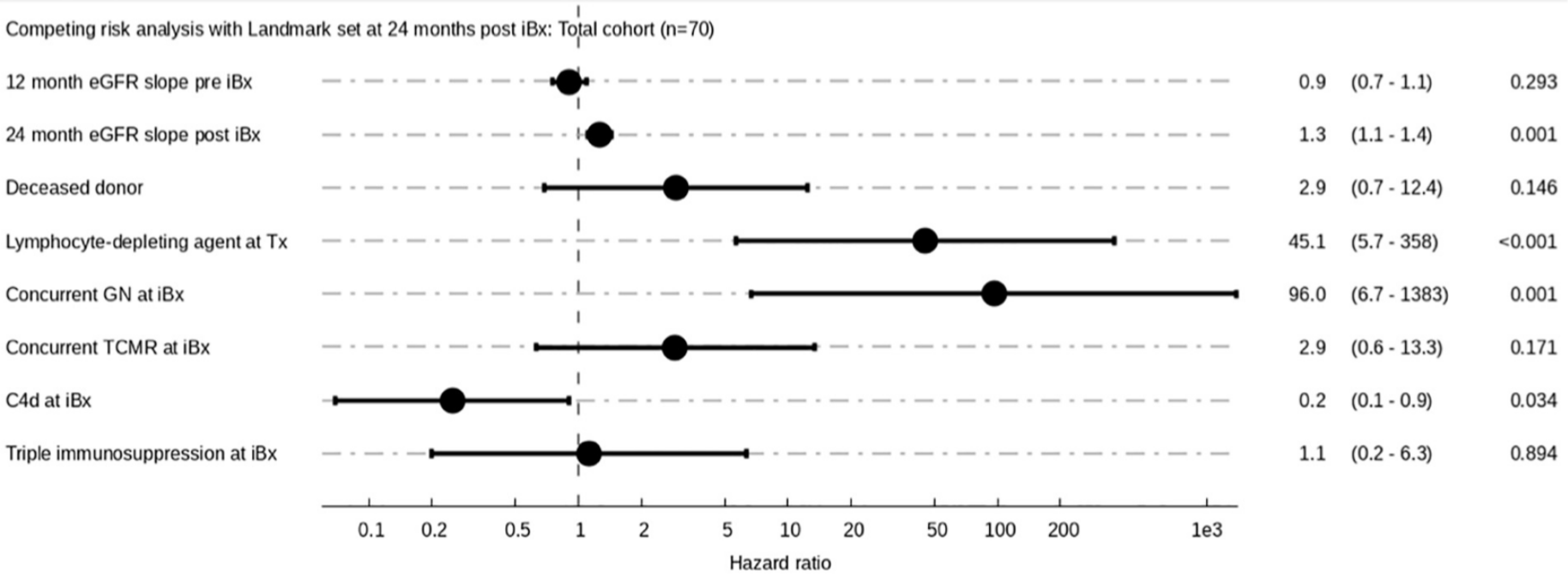
- eGFR returned within 10% of baseline
- Urine protein decline >25%
- Immune-dominant DSA MFI or cumulative DSA MFI decline >50%
- MVI (ptc +g) = 0

TABLE 2 Challenges and opportunities to improve studies in ABMR.

Challenges	Opportunities
Heterogenous cases with varied clinical outcomes	
• Varied baseline DSA quantity • Preexisting versus *de novo* DSA • ABMR detected via surveillance or indication biopsy	• Plan to enroll patients with a similar risk profile as those included in pilot and early observational studies. • Balance the inclusion of patients with preexisting and *de novo* DSA. Adjust for whether the ABMR diagnosis was made via indication or surveillance biopsy
Difficult to conduct clinical trials because of low enrollment and need for prolonged follow-up	
• The time to graft loss after ABMR detection can be several years. • High risk transplants with DSA and positive crossmatch are done less often making it more difficult to enroll patients in clinical trials. • The downside of improving the homogeneity in the studied patient population is a decrease in patients who meet inclusion criteria. • Patients with chronic ABMR often not found early because these patients may be followed by non-transplant nephrologists and/or do not get surveillance DSA or biopsies	• Develop international consortia. • To account for long follow-up, consider using reliable qualified surrogate endpoints such as slope of eGFR, and plan for long term extension studies to verify results. • Be realistic about enrollment and include centers experienced in transplantation with donor specific antibody. • Develop decentralized clinical trials and partner with local general nephrologists to enroll and identify patients who do not have long term follow-up in an academic medical center. • Consider novel clinical trial design to overcome small patient numbers
Lack of standardized reporting limit the ability to communicate or combine results for meta-analysis	
• Key details about DSA, histology, and patient characteristics often missing in the literature	• Collaboration and development of minimum standards for reporting by major transplant groups (e.g., Banff). • Minimal standard reporting consistently followed by industry and enforced by major clinical journals

DOI 10.3389/frtra.2024.1389005

OUTCOME PREDICTORS IN LATE/CHRONIC AMR



Concurrent glomerulonephritis was the only biopsy-based predictor of eGFR slope.

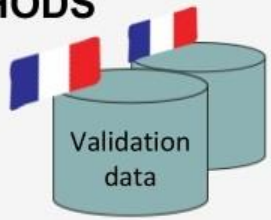
frontiers | Frontiers in Medicine published: 21 April 2022 doi: 10.3389/fmed.2022.817127

Data-Driven Chronic Allograft Phenotypes: A Novel and Validated Complement for Histologic Assessment of Kidney Transplant Biopsies

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

3549 biopsies from 1 Belgian kidney transplant center



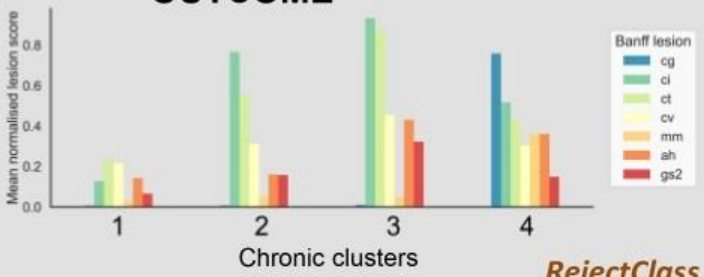
4031 biopsies from 2 French transplant centers

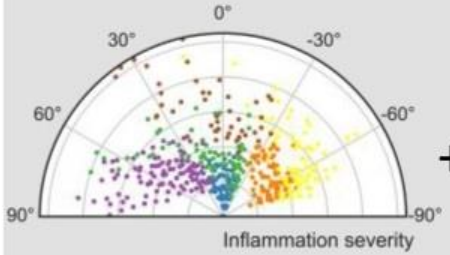
Time-dependent Banff chronic lesion scores

Semi-supervised consensus clustering

OUTCOME

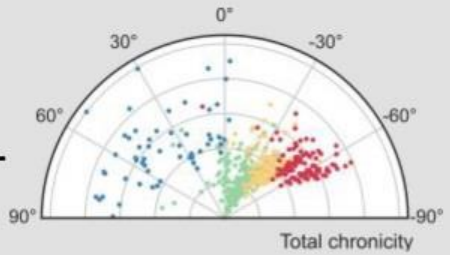
4 data-driven clusters of various degrees of chronicity, **independent** of acute lesions





Acute component

+



Chronic component

=

RejectClass, a holistic online assessment tool for kidney transplant biopsies

Conclusion

The evaluation of total chronicity provides complementary information of kidney transplant pathology on top of the estimation of disease activity from acute lesion scores.

doi: 10.1681/ASN.

Morphologic and molecular features of antibody-mediated transplant rejection: Pivotal role of molecular injury as an independent predictor of renal allograft functional decline

OBJECTIVE

To assess the prognostic potential of histomorphologic and molecular biopsy scores in predicting graft loss and eGFR decline among patients with late antibody-mediated rejection (ABMR)

METHODS – Patients & analysis

75 allograft recipients/biopsies with DSA+ ABMR

MMDx

- IRRAT: injury-repair associated transcript set
- ciprob: probability for ci lesion score > 1

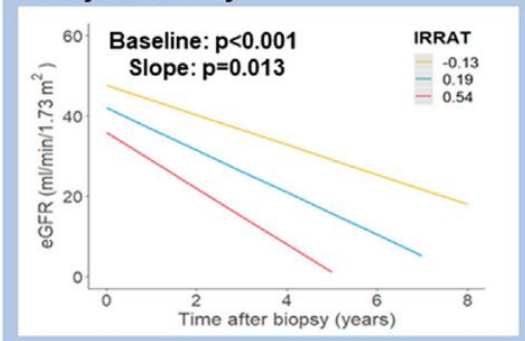
Histology

- CI_{3comp}: chronicity index (ci+ct+cg[x2])
- AI_{3comp}: activity index (g+ptc+C4d)

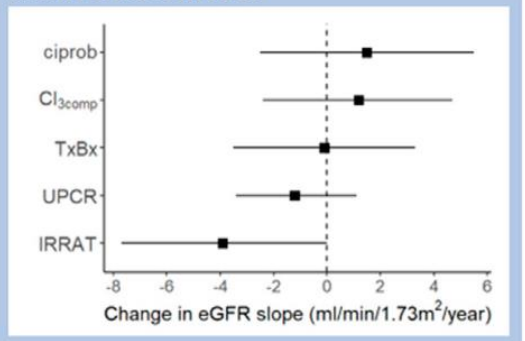
→ Allograft outcome

RESULTS – eGFR trajectory

Unadjusted analysis



Multivariable model



CONCLUSION

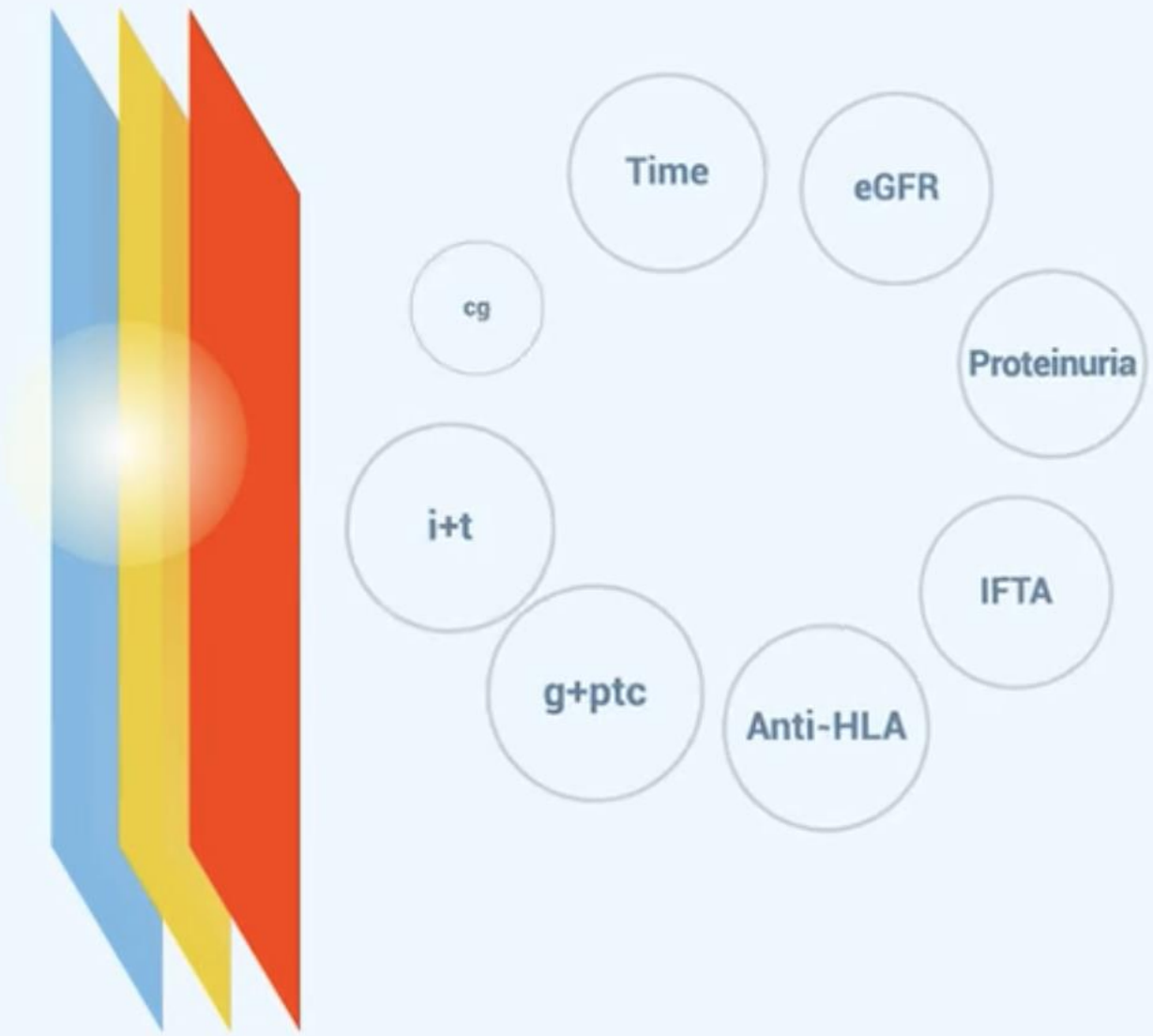
The molecular assessment of tissue injury-repair responses indicative of a persisting maladaptive disease process holds promise in the identification of ABMR associated with unfavorable graft outcomes

Herz, et al. *Transpl. Int.* 2023

doi: doi: 10.3389/ti.2023.12135

GRAPHICAL ABSTRACT |

The iBox technology:
Leading the way to prevent and treat organ failure with AI.


Time
eGFR
cg
Proteinuria
i+t
IFTA
g+ptc
Anti-HLA

Patient

Patient — New Patient

Mike D. Strickland (557-19-XXXX)

Date of risk evaluation — 21 months after transplantation

March 26, 2019

DSA

- (•) Not Available
- ( ) Anti-HLA DSA MFI

0 — 20 000

- ( ) Available (qualitative)
  - ( ) Presence
  - ( ) Absence

Estimated GFR (MDRD)

- ( ) Available (eGFR - mL/min/1.73m°)

0 — 42 — 120

Prediction of Graft Survival

90%	77%	65%
at 3 years	at 5 years	at 7 years

iBox is highly reliable

C-index=0.81; 95% CI, 0.79 to 0.83

Male and female

Europe and US

Different ethnic and social backgrounds

Different allocation systems

Clinical scenarios

Different treatments

Next Generation of Clinical Trials

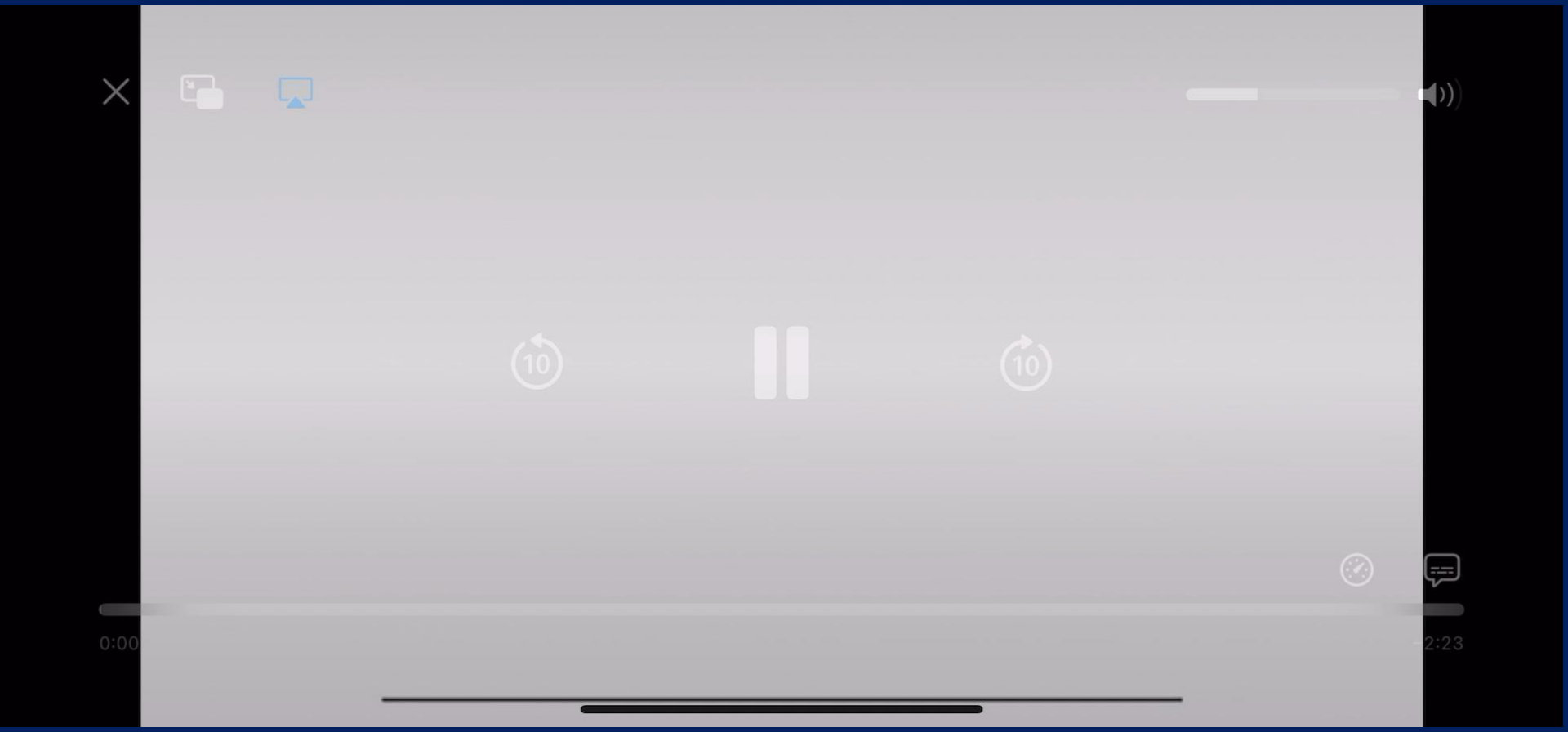
Design study

Surrogate Endpoint

Prediction system for risk of allograft loss in patients receiving kidney transplants: international derivation and validation study

Alexandre Loupy,[1,2] Olivier Aubert,[1,2] Babak J Orandi,[3] Maarten Naesens,[4] Yassine Bouatou,[1] Marc Raynaud,[1] Gillian Divard,[1] Annette M Jackson,[5] Denis Viglietti,[1,6] Magali Giral,[7] Nassim Kamar,[8] Olivier Thaunat,[9] Emmanuel Morelon,[9] Michel Delahousse,[10] Dirk Kuypers,[4] Alexandre Hertig,[11] Eric Rondeau,[11] Elodie Bailly,[11] Farsad Eskandary,[12] Georg Böhmig,[12] Gaurav Gupta,[13] Denis Glotz,[1,6] Christophe Legendre,[1,2] Robert A Montgomery,[14] Mark D Stegall,[15] Jean-Philippe Empana,[1,16] Xavier Jouven,[1] Dorry L Segev,[17] Carmen Lefaucheur[1,6]

thebmj | *BMJ* 2019;366:l4923 | doi: 10.1136/bmj.l4923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مرکز پزشکی آموزشی و درمانی

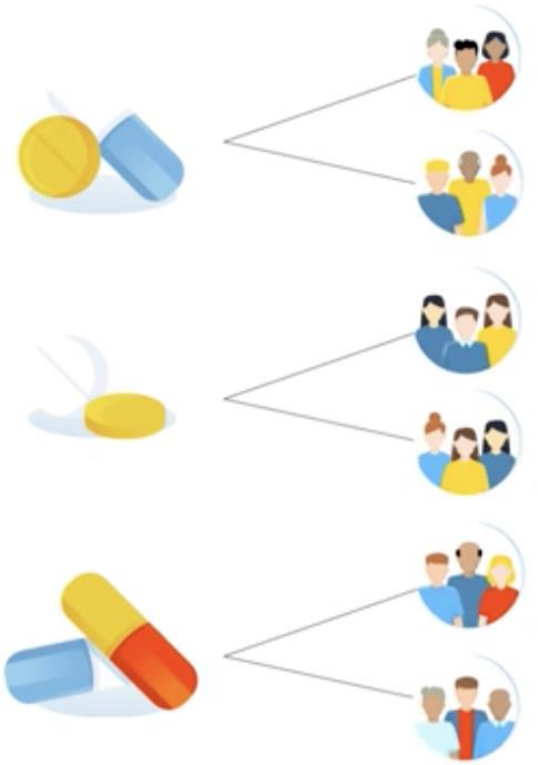
Table 4 iBox variables

Risk factor	Full model	Simplified model	Quantification	Type
Time from transplant to evaluation	X	X	-	Continuous
eGFR	X	X	-	Continuous
Proteinuria (log transformed)	X	X	-	Continuous
iDSA MFI category	X	X	< 5000 ≥ 500-3000 ≥ 3000-6000 ≥ 6000	Categorical
Interstitial fibrosis/tubular atrophy (IFTA)	X		0/1 2 3	Categorical
Microcirculation inflammation (g+ptc)	X		0-2 3-4 5-6	Categorical
Interstitial inflammation and tubulitis (i+t)	X		0-2 ≥ 3	Categorical
Transplant glomerulopathy	X		0 ≥ 1	Categorical

DSA Donor-specific antibodies, *eGFR* Estimated glomerular filtration rate, *MFI* Mean fluorescence intensity

iBox validation

4000 patients



3 RCTs

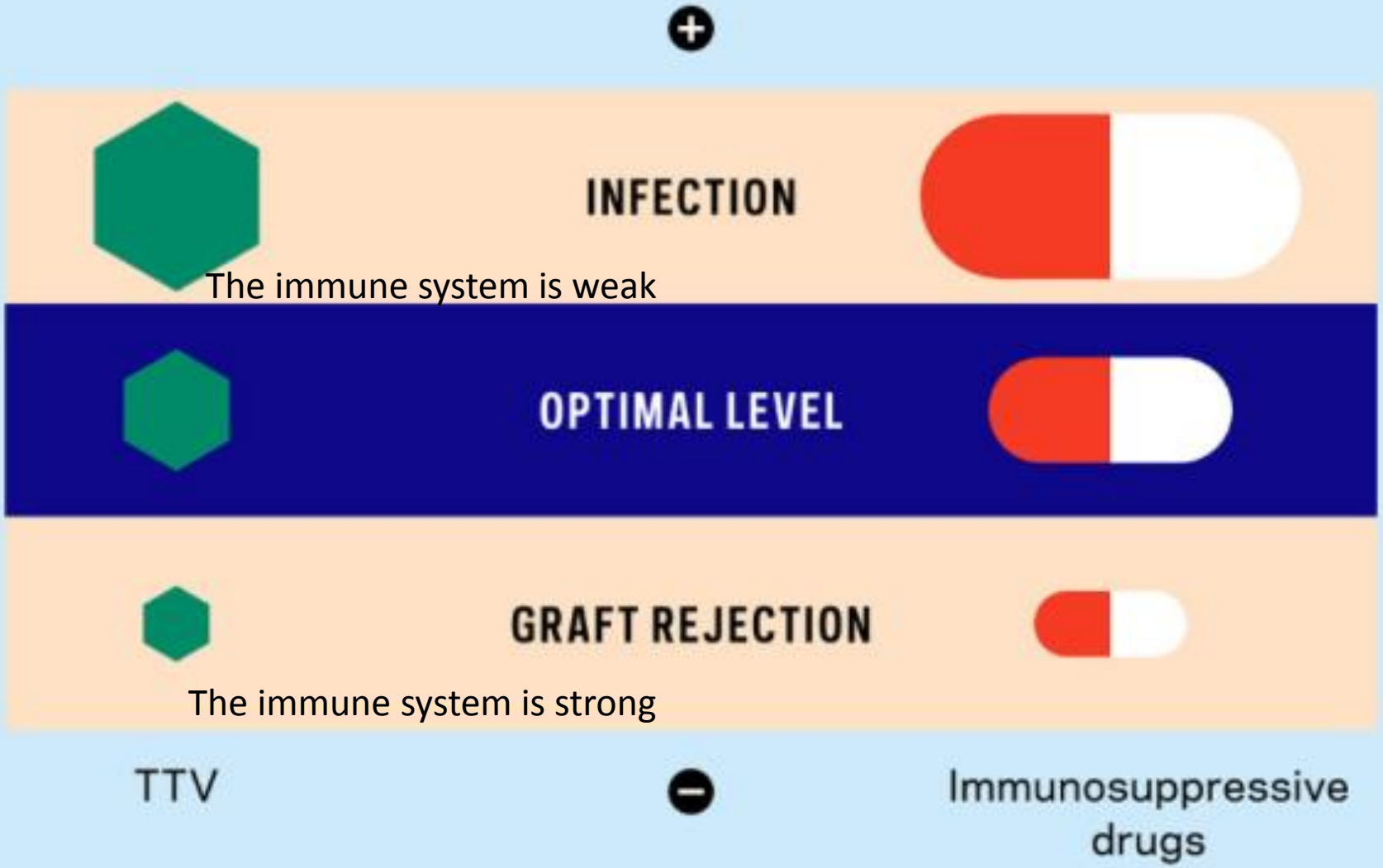
A NOVEL CONCEPT

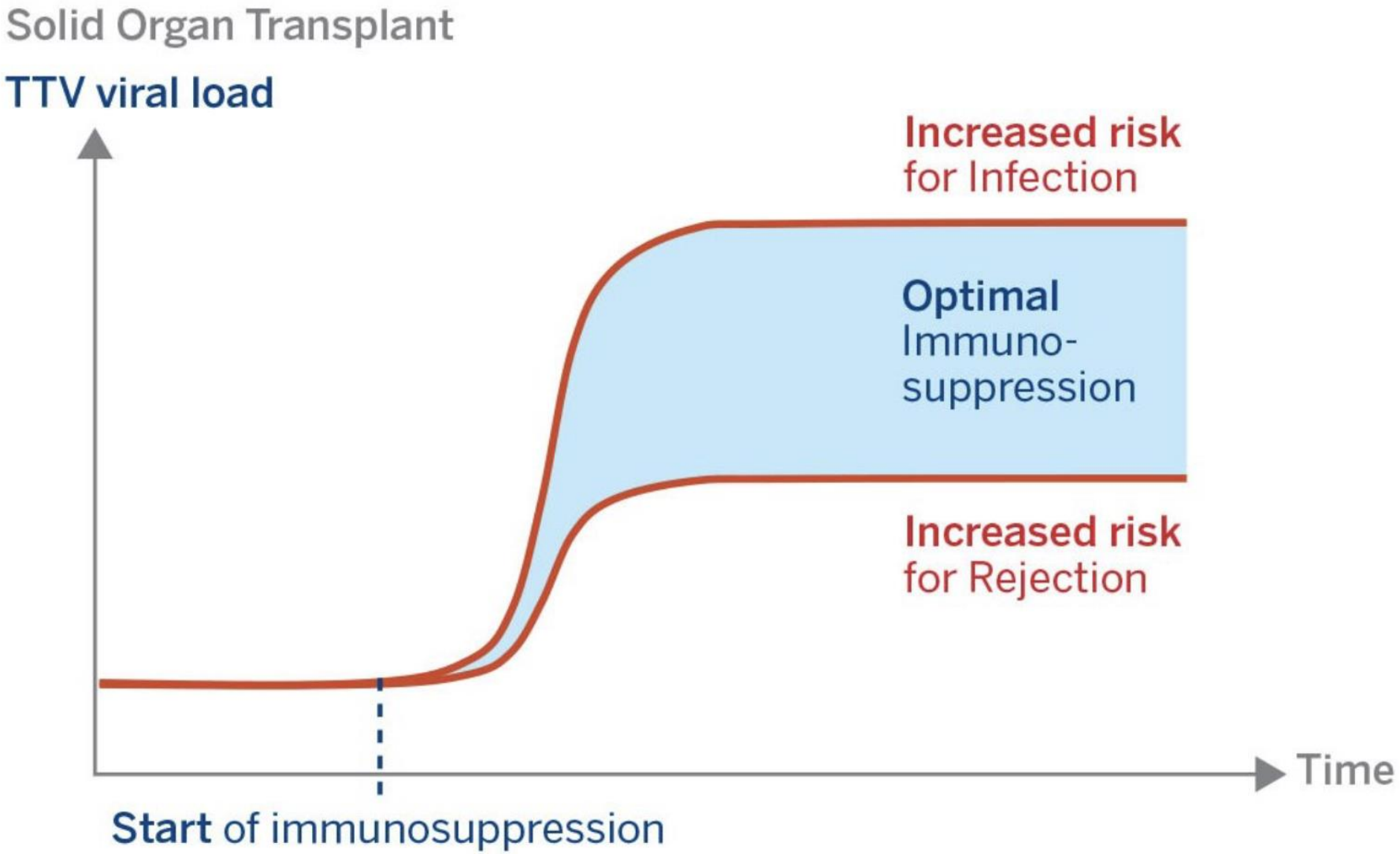
Torque Teno Virus (TTV)

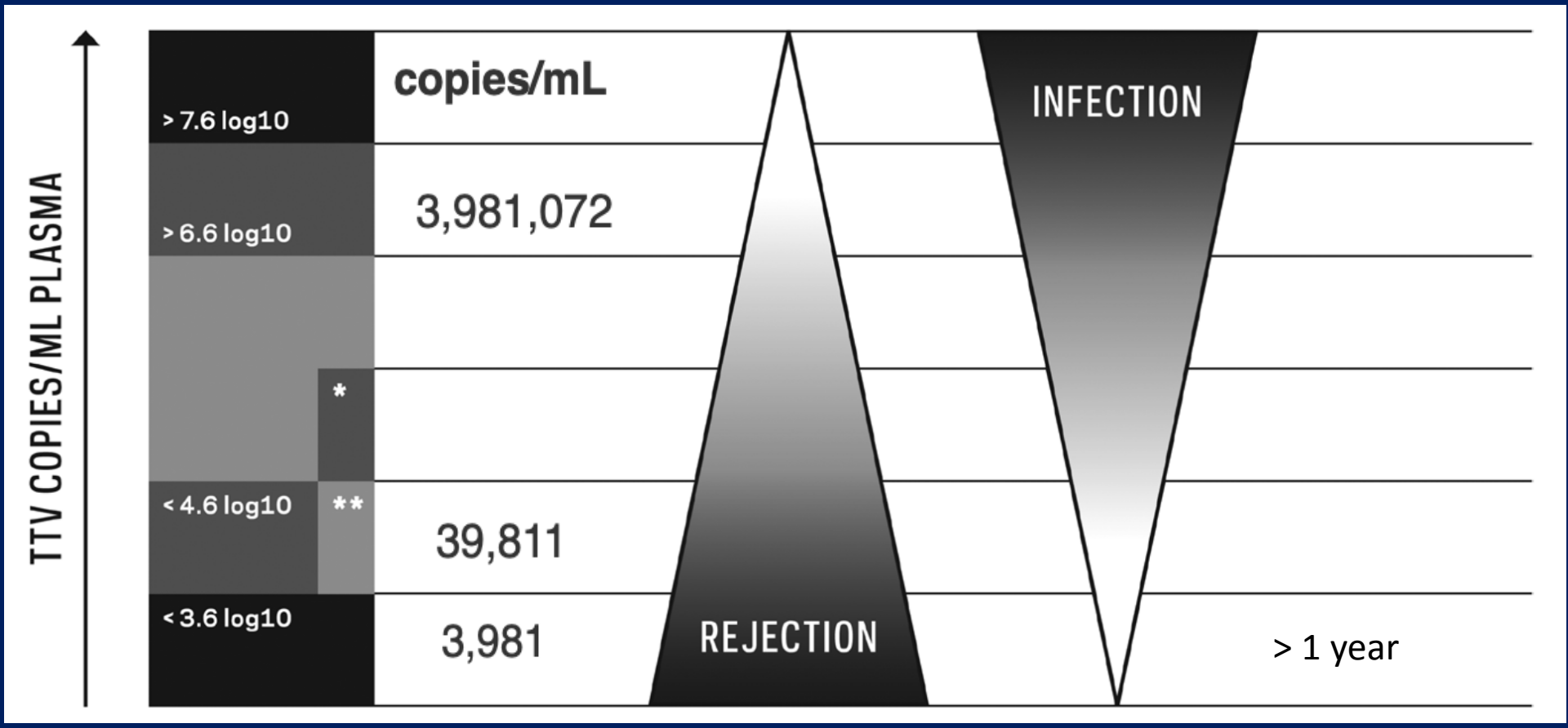
Immune monitoring by TTV

- DETECTABLE IN THE BLOOD OF ALL KIDNEY TRANSPLANT RECIPIENTS
- CAUSES NO DISEASE
- REFLECTS THE IMMUNE FUNCTION OF THE HOST
- TTV LEVEL IN THE BLOOD ASSOCIATES WITH INFECTION AND GRAFT REJECTION

TTV mirrors the immune function

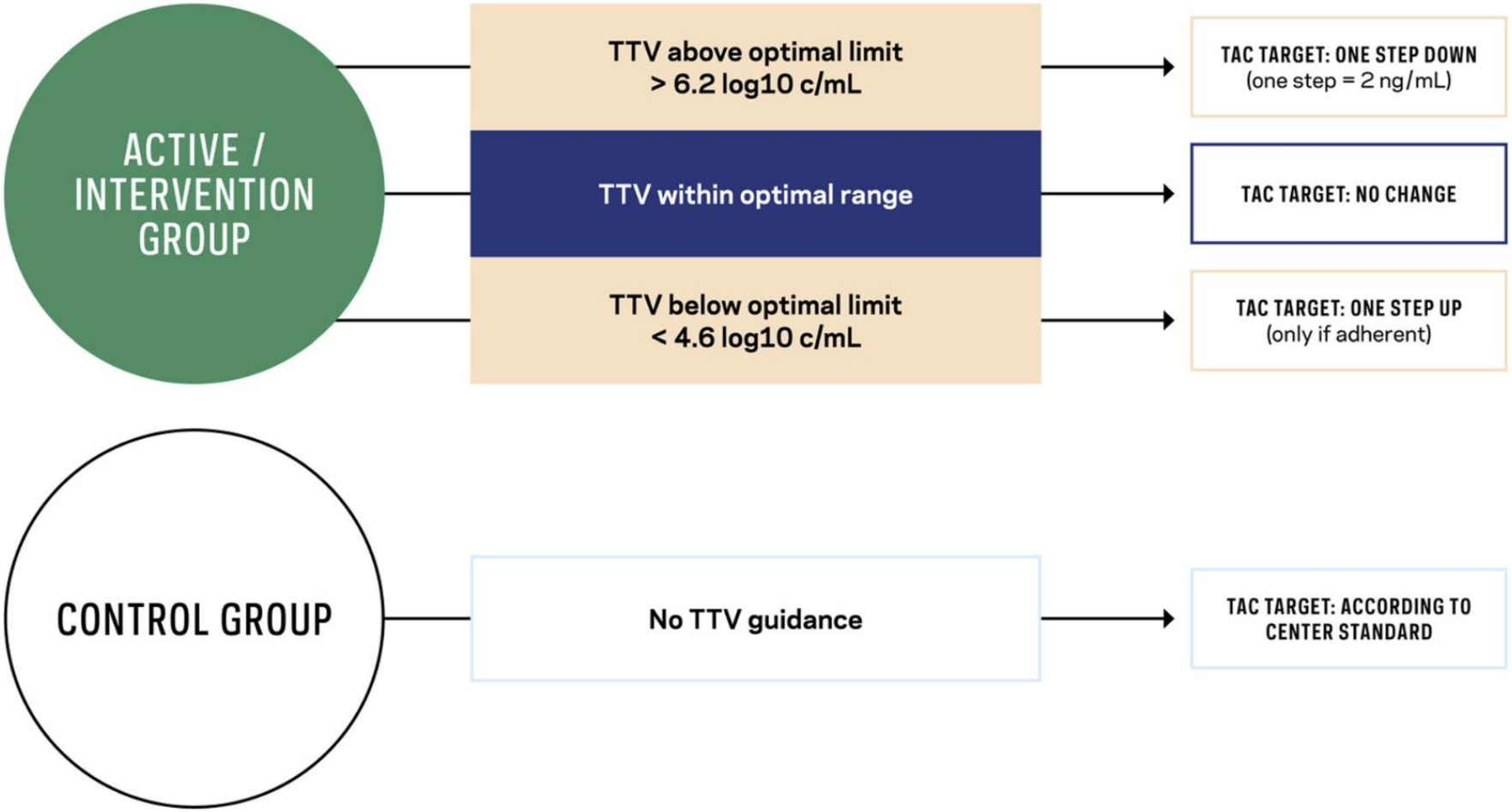



Solid Organ Transplant
TTV viral load
Increased risk
for Infection
Optimal
Immuno-
suppression
Increased risk
for Rejection
Time
Start of immunosuppression



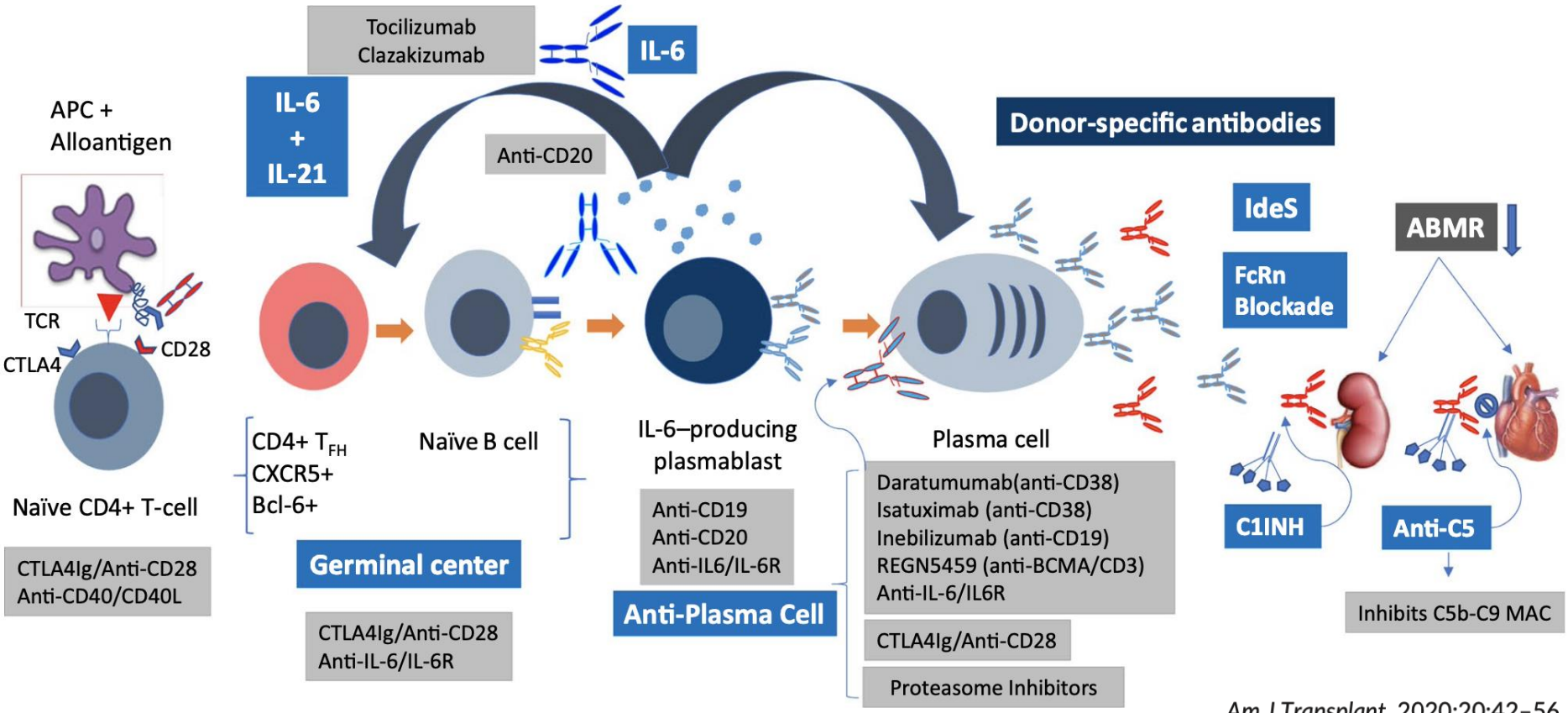
Transplantation ■ October 2022 ■ Volume 106 ■ Number 10

TAC DOSING



Haupenthal *et al. Trials* (2023) 24:213

Emerging Therapeutic Approaches to Reducing Alloantibody Injury to Allografts



Am J Transplant. 2020;20:42–56.

REASONS FOR THE LACK OF STANDARD THERAPY FOR CAAMR

- Summary of 2017 FDA public workshop:

- "there are no FDA-approved treatments for acute or chronic AMR.
- Similar to desensitization protocols, plasmapheresis or high-dose IVIG constitute standard of care with different add-on treatments per center preference."

Transplantation. 2018;102:e257–e264.

- Current recommendations for caAMR focus on supportive care and optimized baseline immunosuppression. Meanwhile, median graft survival in patients with caAMR is <2 y after diagnosis

Is Lack of Consensus on the Management of Chronic Active Antibody-Mediated Rejection Harming Renal Transplant Recipients?

Author: *Lionel Rostaing[1]

TABLE 1 Framework of ABMR clinical phenotypes.

Timing	Donor specific antibody		Histology	Clinical presentation
Hyperactive rejection (hours post-transplant)	Preexisting		Diffuse inflammation, necrosis, and thrombotic microangiopathy	Abrupt graft loss
Early active (<30 days post-transplant)	Preexisting (or patient is Non immunologically naïve with history of sensitizing events including pregnancy, transplant, or blood transfusion)	Can have similar histologic features depending on time of detection	Banff active ABMR C4d positivity and thrombotic microangiopathy usually present. Banff cg = 0	Abrupt allograft dysfunction correlating with increased DSA quantity usually 7–14 days post-transplant
Late (>30 days post-transplant)	Preexisting		Banff active or chronic active ABMR (continuum) +/− C4d positivity	+/− allograft dysfunction and proteinuria Can occur in patients with or without Early active (<30 days post-transplant active ABMR)
	De novo (MOST COMMON)		Banff active or chronic active ABMR (continuum) +/− C4d positivity Concomitant TCMR often present with *de novo* DSA	+/− allograft dysfunction and proteinuria

PUBLISHED 12 June 2024
DOI 10.3389/frtra.2024.1389005

Active AMR; All 3 criteria must be met for diagnosis

1. Active lesions* of AMR present, at least 1 of the following:

- Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 1 alone is not sufficient and g must be ≥ 1
- Intimal or transmural arteritis (v > 0)
- Acute thrombotic microangiopathy, in the absence of any other cause

2. At least 1 or more of the following:

- Linear C4d staining in peritubular capillaries or medullary vasa recta (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
- At least moderate microvascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥1
- Biopsy-based transcript diagnostics for AMR/MVI above a defined threshold, if thoroughly validated for use as substitute for MVI and available

3. Evidence of circulating donor-specific antibodies (DSA to HLA or other antigens). If thorough testing for DSA (anti-HLA or other specificity) has not yet been performed, this should be done, following the STAR guidelines. Detection of non-HLA antibodies (including ABO antibodies in ABO-incompatible transplantation) can be used as serologic Banff criterion for diagnosis of AMR, if the testing protocols are sufficiently standardized and clinically validated for the appropriate clinical context. C4d staining as noted above in Criterion 2 may substitute for DSA.

*Can be observed in AMR and strengthen the diagnosis but not diagnostic in itself: acute tubular injury, in the absence of any other apparent cause

Chronic active AMR; all 3 criteria must be met for diagnosis

1. Chronic lesions* of AMR present, at least 1 of the following:

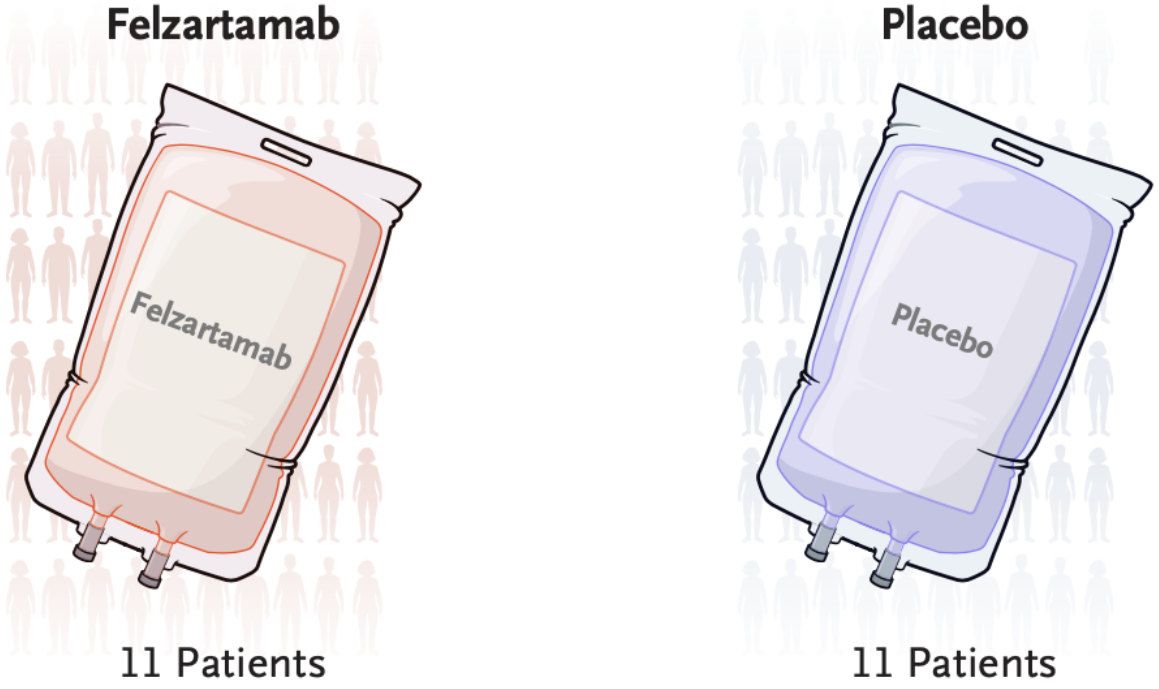
- Transplant glomerulopathy (cg > 0) if no evidence of chronic TMA or chronic recurrent/de novo glomerulonephritis; includes changes evident by electron microscopy (EM) alone (cg1a)
- Severe peritubular capillary basement membrane multilayering (requires EM)

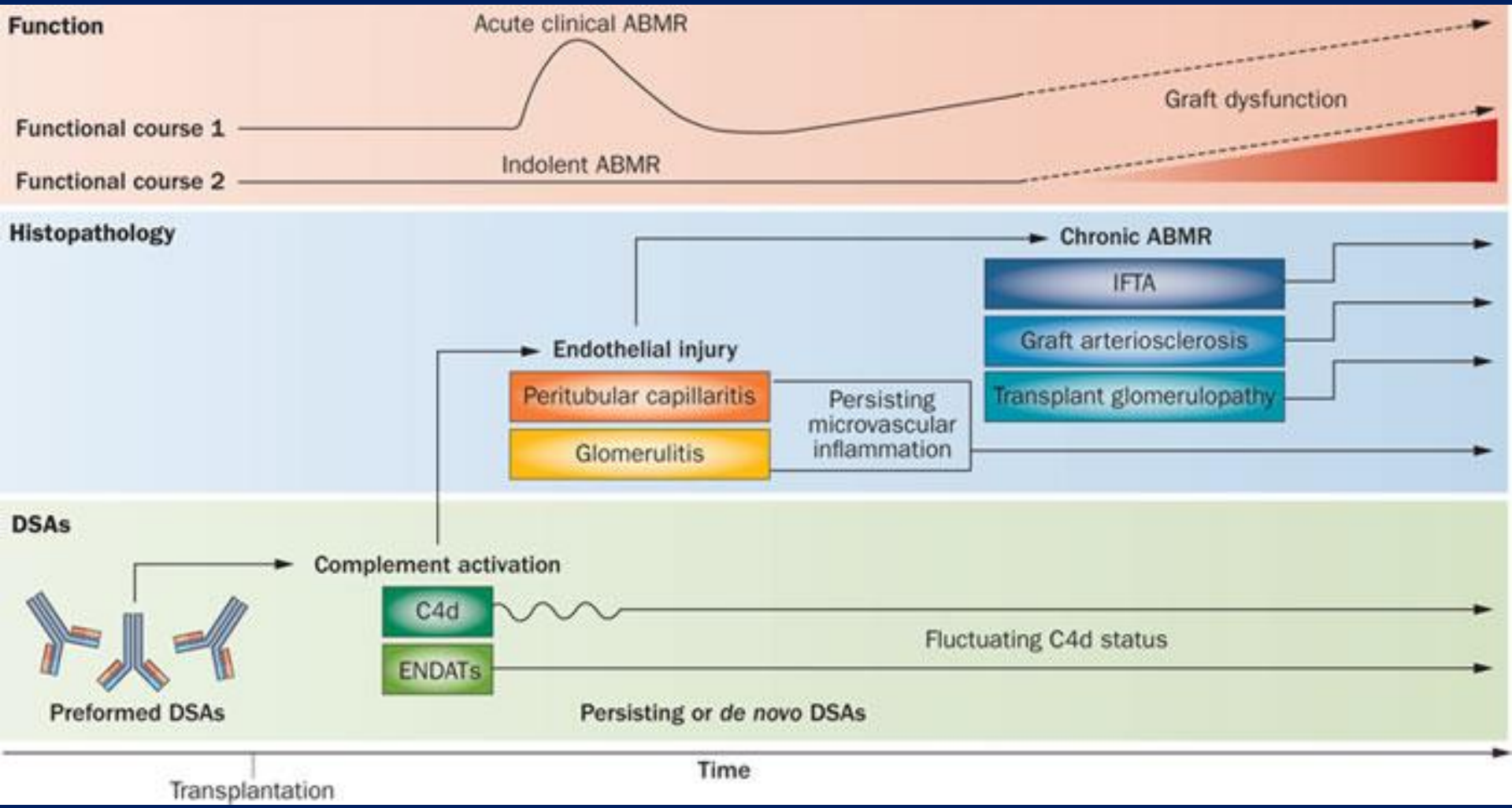
2. Identical to criterion 2 for active AMR, above
3. Identical to criterion 3 for active AMR, above, including strong recommendation for DSA testing whenever criteria 1 and 2 are met.

*Other lesions can be observed in AMR and strengthen the diagnosis but are not diagnostic by themselves: arterial intimal fibrosis (cv) of new onset, excluding other causes; leukocytes within the sclerotic intima favour chronic AMR if there is no prior history of TCMR;

HOW WAS THE TRIAL CONDUCTED?

22 patients with antibody-mediated rejection of a functioning kidney allograft at least 180 days after transplantation, diagnosed through biopsy results, were assigned to receive nine intravenous infusions of either felzartamab (16 mg/kg) or placebo over 24 weeks. The primary outcome was the safety and side-effect profile of felzartamab over 52 weeks.





Loupy, A. *et al. Nat. Rev. Nephrol.* **8**, 348–357 (2012)