Chronic Active Kidney Transplant Rejection

Dr. Shahrzad Shahidi - Dr. Pegah Hedayat

Nephrologist - Pathologist

Isfahan University of Medical Sciences

Objects

1. Introduction
2. Abbreviates in Histopathology
3. Banff classification for allograft pathology
4. Chronic Active TCMR
   - Ca TCMR is variably responsive to immunosuppressive therapy
   - Do we need to treat CA TCMR?
5. Chronic Active AMR
   - Treatment response rate
   - IL6
   - IMAGINE study
   - Splenic irradiation
6. Summary

Introduction

- There were **>25 000** KTs in the US in 2022.
- Approximately **250 000** individuals are living with functioning grafts.
- About **50%** of all transplanted kidneys will fail within **8–11 y**.
- Graft failure has **high physical, emotional, & financial costs**.
- Chronic active AMR (caAMR) is arguably the **most important** cause of late graft failure.

Berger M. Transplantation. 2022

Banff Classification for Allograft Pathology

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV
	1991	1993	1995	1997	1999	2001	2003	2005	2007	2009	2011	2013	2015	2017	2019
Change	n/a		x	x		x		x	x			x	x	x	x

☐ minor change

"The banff classification is changing too often"

Abbreviates in Histopathology

- **ah**, arteriolar hyalinosis
- **cg**, glomerular BM double contours
- **ci**, interstitial fibrosis
- **ct**, tubular atrophy
- **cv**, vascular fibrous intimal thickening
- **g**, glomerulitis
- **i**, interstitial inflammation
- **t**, tubulitis
- **v**, intimal arteritis
- **ptc**, peritubular capillaritis
- **mvi**, microvascular inflammation(sum of g + ptc)

Aziz F. Transplant Direct. 2022

The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection

Chronic Active T cell- Mediated Rejection

Chronic active T cell–mediated rejection is variably responsive to immunosuppressive therapy.

Case selection

- Retrospective single institution review
- 44 cases of treated, pure CA TCMR without antibody-mediated rejection or intimal arteritis

Primary observation

20% of patients responded (had ≥50% eGFR recovery at 4 weeks post initiation of immunosuppressive therapy)

Possible features of immunosuppressive therapy resistant CA TCMR

Histology → Severe tubulitis

Transcriptional profiling → Increased mast cells and altered fatty acid metabolism

CONCLUSION:
CA TCMR is not a homogenous entity, and in a subset of cases, improvement in kidney function can be achieved with immunosuppressive therapy.

kidney INTERNATIONAL ISN

Kung et al, 2021

Do we need to treat chronic active T cell–mediated rejection?

Michael Mengel[1] and Michelle Lubetzky[2]

Chronic active T cell–mediated rejection, demonstrated by the presence of inflammation in areas of fibrosis, is associated with long-term allograft loss. Kung *et al.*, in this issue of *Kidney International*, describe a series of cases of CA TCMR and analyze their clinical, molecular, and pathologic features as well as their response to therapy. Their translational study aids in understanding this diverse phenotype and provides future direction for managing these patients.

Kidney International (2021) **100,** 275–277; https://doi.org/10.1016/j.kint.2021.04.031

see clinical investigation on page 391

Do we need to treat ca TCMR?

- In acknowledgement of the lack of specificity of i-IFTA for TCMR, the Banff 2017 definition of CA TCMR grade I is quite conservative.
- Furthermore, other diagnoses (e.g., polyomavirus, ABMR, & GN) need to be ruled out, making CA TCMR essentially a **diagnosis of exclusion**.

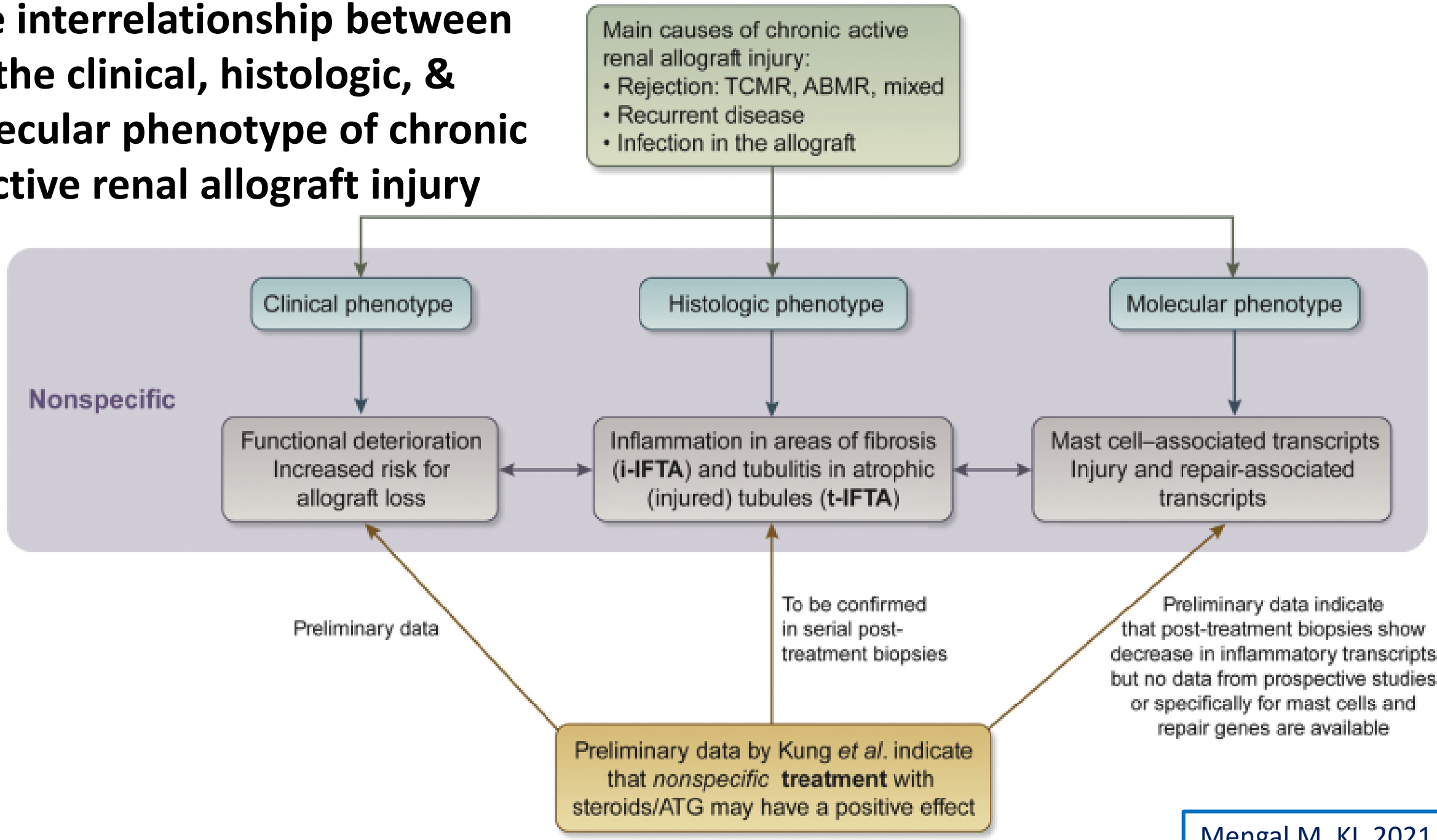
Mengal M. KI. 2021

Do we need to treat ca TCMR?

Despite the **lack** of diagnostic specificity of i-IFTA & the consensus based nature of the initial diagnostic criteria for CA TCMR, the **main rationale** for including it into the Banff classification was to provide an international basis to explore

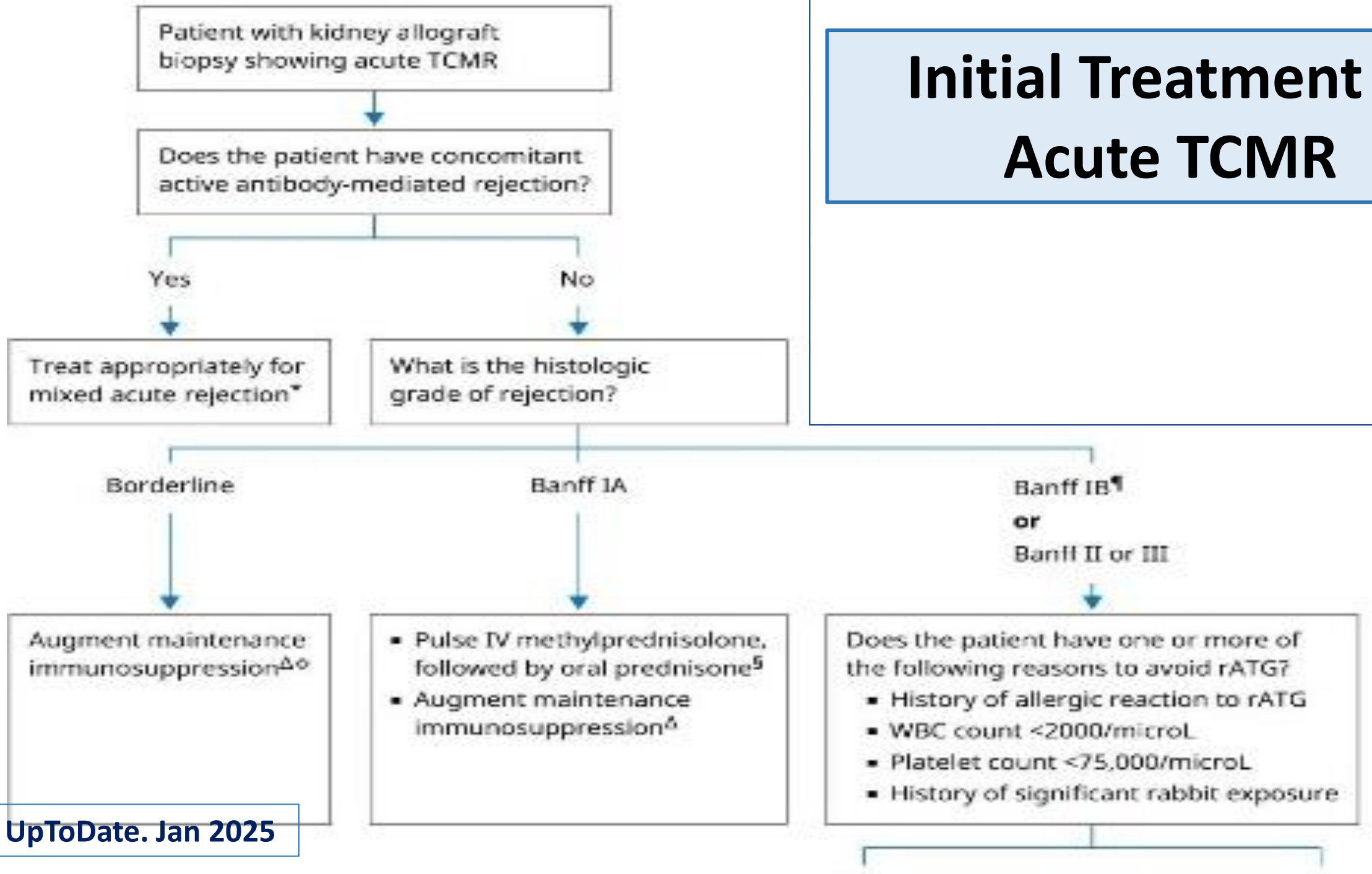
Mengal M. KI. 2021

The interrelationship between the clinical, histologic, & molecular phenotype of chronic active renal allograft injury



Mengal M. KI. 2021

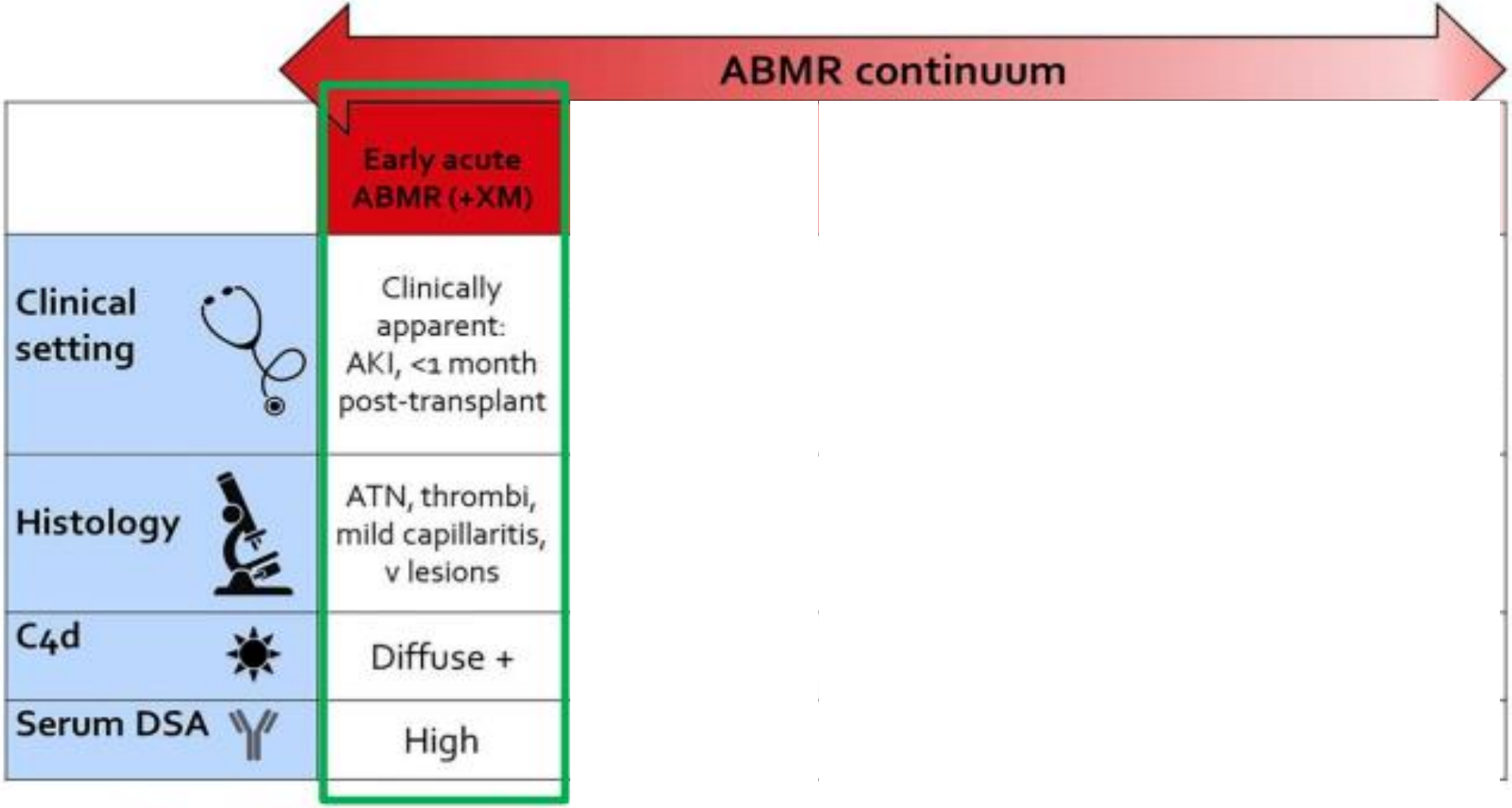
Initial Treatment of Acute TCMR



UpToDate. Jan 2025

Chronic Active Antibody-Mediated Rejection

The Banff schema overly simplifies the full spectrum of anti-HLA DSA associated AMR



"Need to recognize exceptions"

Transplantation DIRECT
The Transplantation Society

IF: 2

KIDNEY TRANSPLANTATION

Aziz F. Transplantation Direct. 2022

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

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

Author Information

Transplantation Direct 8(9):p e1360, September 2022. | *DOI:* 10.1097/TXD.0000000000001360

Ca ABMR in Kidney Transplant Recipients

- **Background.** There is limited information on the value of short-term invasive & noninvasive monitoring in KTRs undergoing therapy for chronic active antibody-mediated rejection .
- **Methods.** We describe response rates in patients with cAMR receiving pulse steroids/IVIG ± rituximab 3-mo after index biopsy.

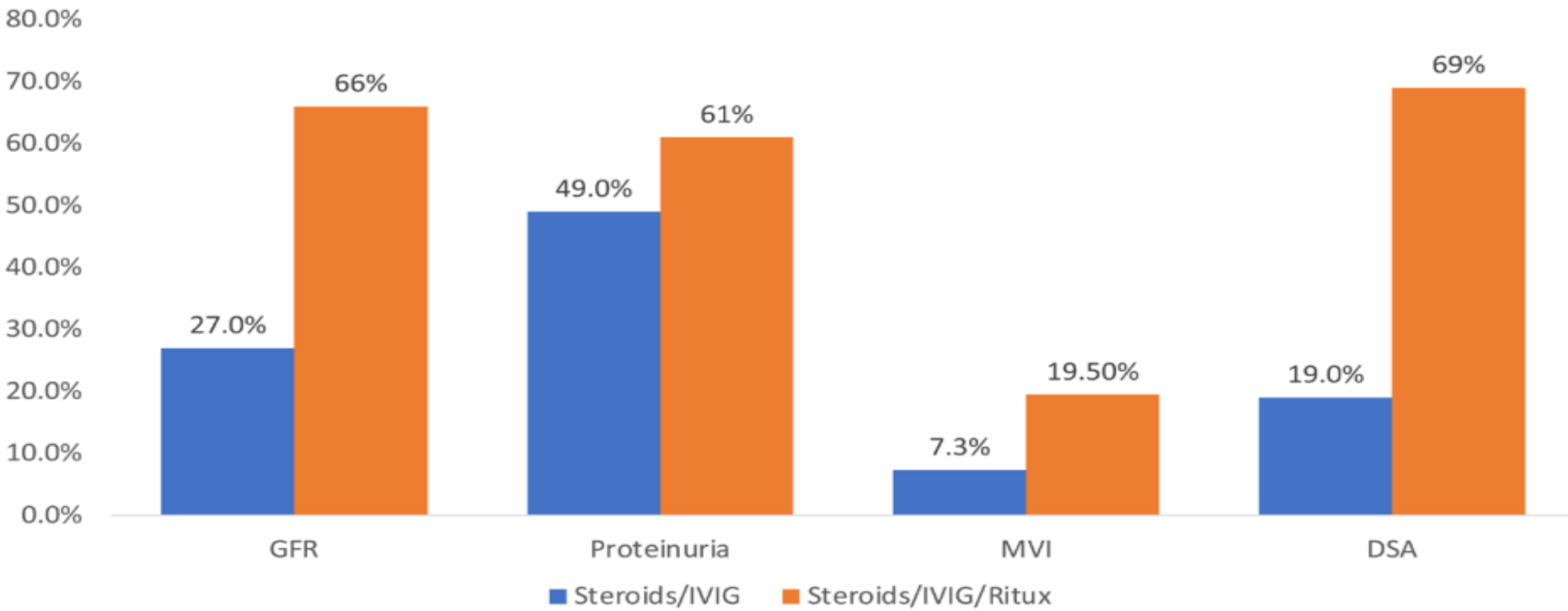
Aziz F. Transplant Direct. 2022

Ca ABMR in Kidney Transplant Recipients

- **Results.** The study included **82** consecutive KTR.
- Mean time from transplant to caAMR was **10 y**.
- Mean eGFR & UPC ratio were 38mL/min & 1.6 g/g, respectively.
- Thirty (37%) patients lost their allograft during the mean follow-up of 2.4 y.
- Univariate analysis identified response in **eGFR** (HR = 0.03; *P* = 0.001; 95% CI, 0.004-0.26), **UPC** (HR = 0.38; *P* = 0.01; 95% CI, 0.18-0.82), & **DSA** (HR = 0.11; *P* = 0.004; 95% CI, 0.02-0.49) as predictors of graft survival.
- **Multivariate analysis** only retained **eGFR** response (HR = 0.12; *P* = 0.01; 95% CI, 0.02-0.64).

Aziz F. Transplant Direct. 2022

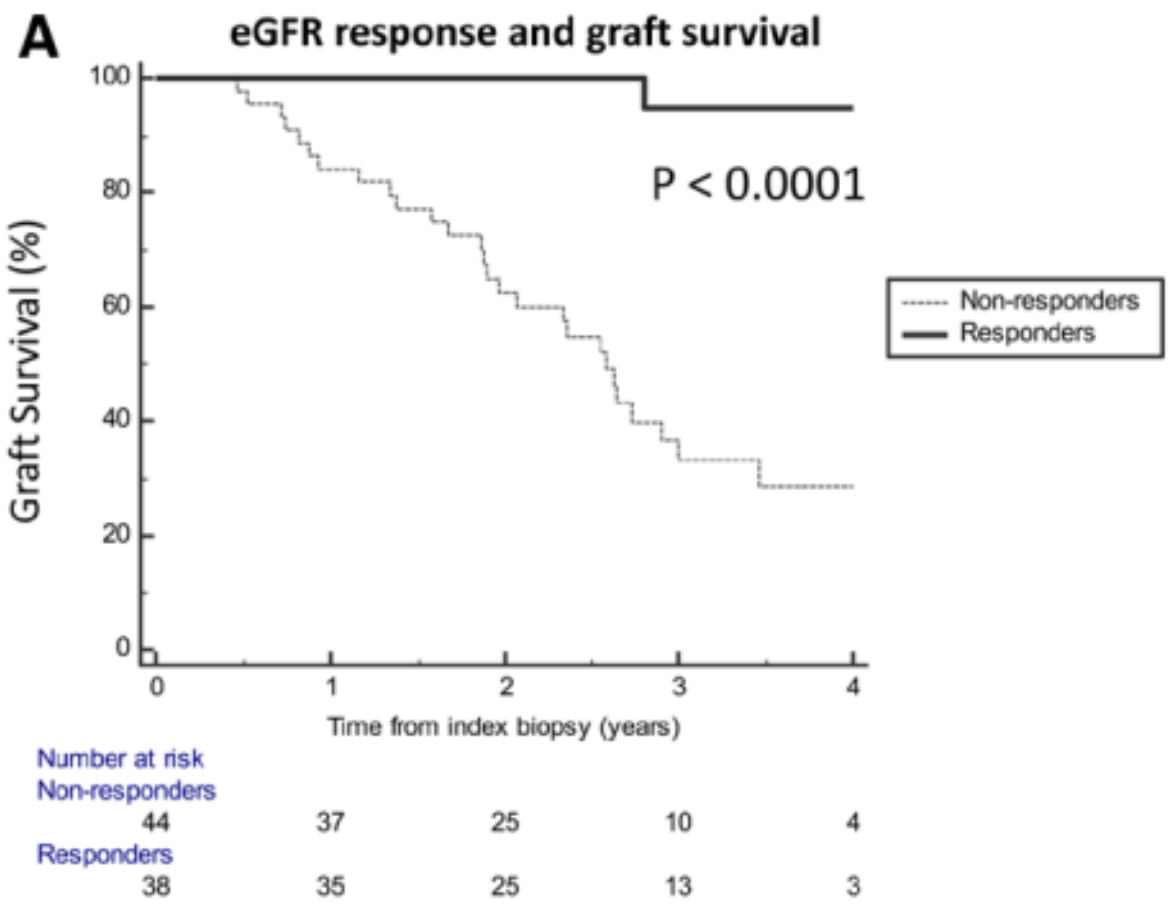
3-month response rates to prescriptions in Ca ABMR

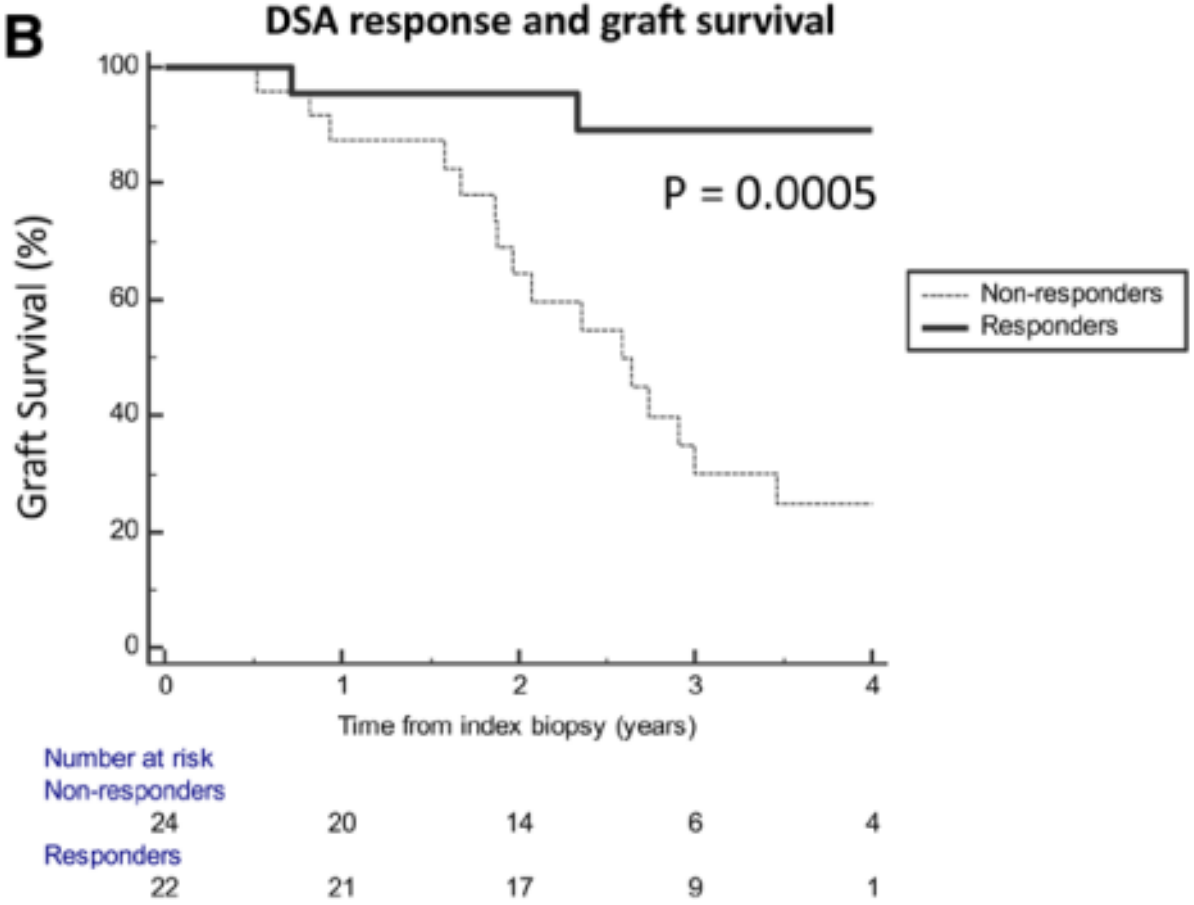


Treatment response was defined as 3-month eGFR within 10% of baseline, proteinuria (UPC) decline > 25%, DSA decline by > 50%, and MVI (ptc + g) score = 0

Aziz F. Transplant Direct. 2022

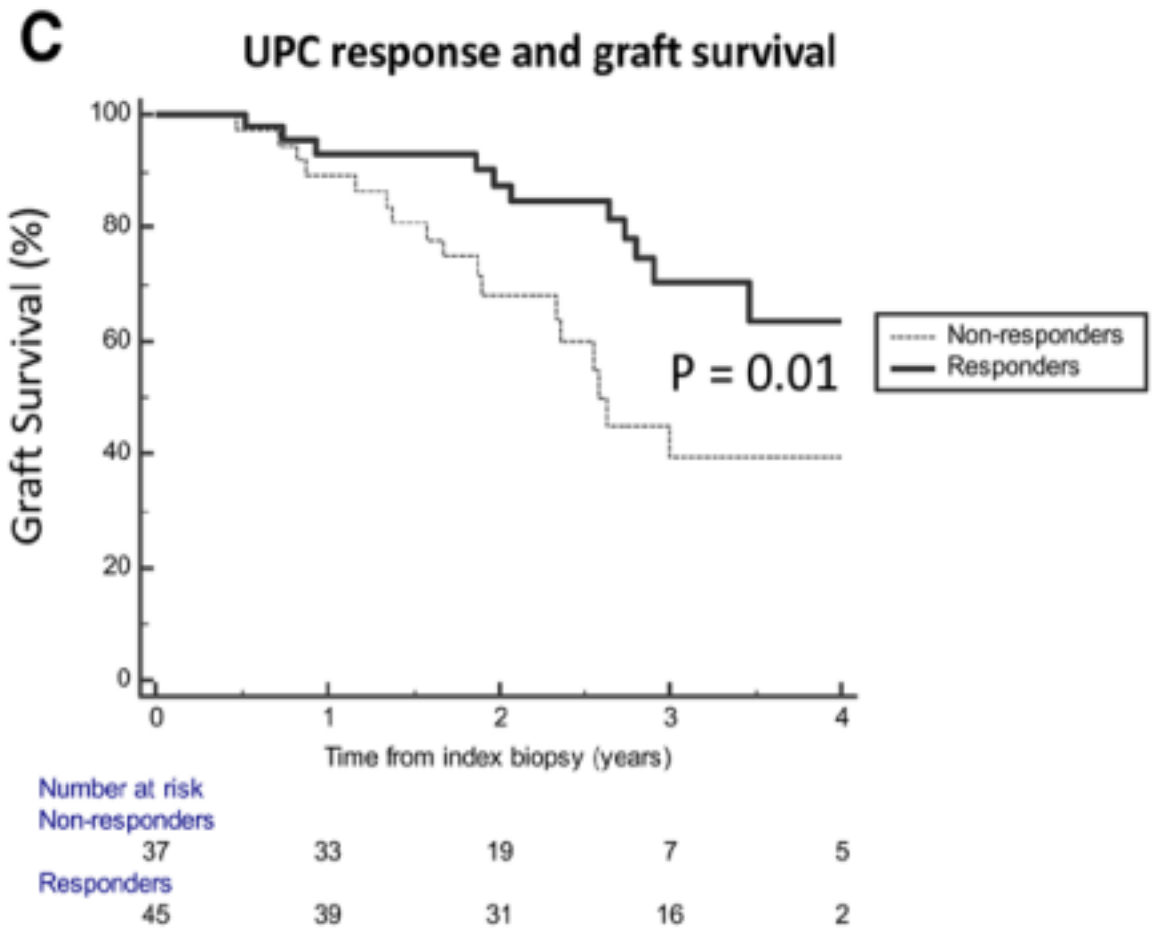
Short-term response in kidney function & DSA associated with graft survival

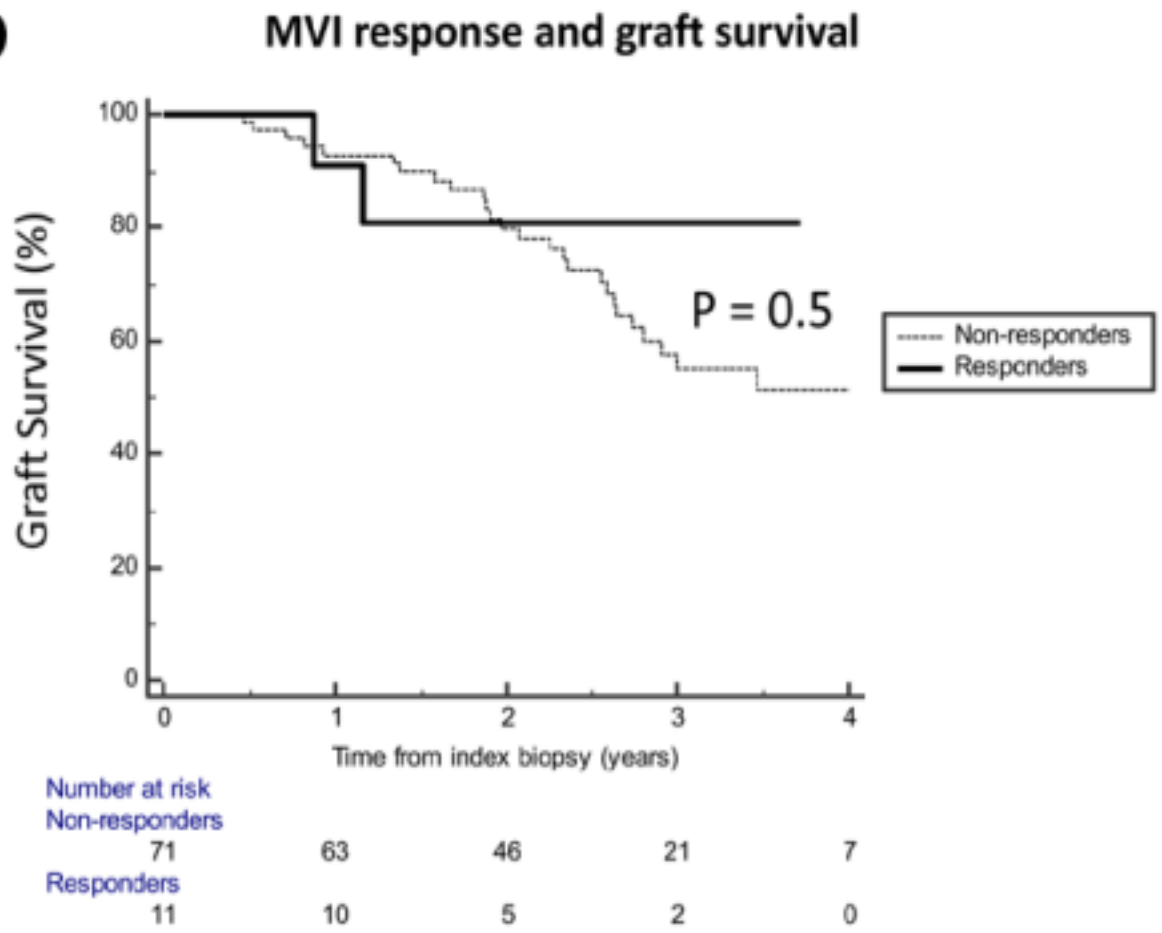




Aziz F. Transplant Direct. 2022

Short-term response in kidney function & DSA associated with graft survival





Aziz F. Transplant Direct. 2022

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	0.78	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

Aziz F. Transplant Direct. 2022

Ca ABMR in Kidney Transplant Recipients

- **Conclusions:** In Ca ABMR, short-term response to treatment for kidney function & DSA was associated with graft survival, but the role of early surveillance biopsies needs further evaluation.
- **eGFR** response 3-mo after cAMR treatment to be the single most important factor in predicting long-term graft survival.

Aziz F. Transplant Direct. 2022

Transplantation DIRECT
The Transplantation Society

KIDNEY TRANSPLANTATION

The Trend of Serum Creatinine Does Not Predict Follow-Up Biopsy Findings Among Kidney Transplant Recipients With Antibody-Mediated Rejection

Parajuli, Sandesh MD[1]; Zhong, Weixiong MD[2]; Pantha, Monika BS[1]; Sokup, Megan PA[1]; Aziz, Fahad MD[1]; Garg, Neetika MD[1]; Mohamed, Maha MD[1]; Mandelbrot, Didier MD[1]

The Trend of SCr Does Not Predict F/Up Biopsy Findings Among KTRs With AMR

- A total of **183** KTRs were included, 66 in the responder group & 177 in the nonresponder group.
- The MVI scores & sum chronicity scores, along with transplant glomerulopathy scores, were higher in the nonresponder group.
- Scr at index biopsy was similar in responders versus nonresponders (*P*=0.39), as were the delta Scr at various time points.
- Being a nonresponder was significantly associated with an increased risk of graft failure at the last follow-up in univariate analysis but was not in multivariate analysis (hazard ratio 1.35; 95% CI, 0.58-3.17; *P*=0.49).

Parajuli S. Transplant Direct. 2023

The Trend of SCr Does Not Predict F/Up Biopsy Findings Among KTRs With AMR

- **Conclusions.** We found that **Scr** is **not** a good predictor of the resolution of MVI, supporting the utility of follow-up biopsies after treatment of AMR.

Parajuli S. Transplant Direct. 2023

IF: 5.3

▸ Transplantation. 2023 Nov 9;108(5):1109–1114. doi: 10.1097/TP.0000000000004822

Chronic Active Antibody-mediated Rejection: Opportunity to Determine the Role of Interleukin-6 Blockade

Mel Berger [1], Mary Baliker [2], Teun Van Gelder [3], Georg A Böhmig [4], Roslyn B Mannon [5], Deepali Kumar [6], Steve Chadban [7], Peter Nickerson [8], Laurie A Lee [9], Arjang Djamali [10,✉]

▸ Author information ▸ Article notes ▸ Copyright and License information

Patient Perspective

- **When I was 9**, I was diagnosed with MPGN.
- I have undergone HD & 4 KTs.
- My **first** was my brother. But I lost it 4 y later because my disease returned.
- **Second** Tx: I received a deceased-donor kidney, which failed after 4 y as well.
- At age 24, I had my **third** transplant, which was complicated by DGF & acute rejection. After 11 y, while...
- I received my **fourth** kidney at the age of 35. Fortunately, that last transplant is still strong after 23 y.

Berger M. Transplantation. 2024


Maria Never Gives Up
ARE YOU BRAVE LIKE ME?
A Story About A Child With A Chronic Illness
Mary Baliker

Reasons for the Lack of Standard Therapy for caAMR

- Current recommendations for caAMR focus on supportive care & optimized baseline immunosuppression.
- Median graft survival in patients with caAMR is **<2 y** after diagnosis.

Berger M. Transplantation. 2024

Reasons for the Lack of Standard Therapy for caAMR

- There are **2 key reasons** for the lack of new approved therapies for >30 y.
  - Evolving understanding of caAMR & changes in the Banff criteria made it difficult to define a homogenous group of patients for clinical trials at any given time.
  - The rigor of published studies suffered from limited sample size, lack of controls, & poor-quality clinical endpoints.

Berger M. Transplantation. 2024

IL 6

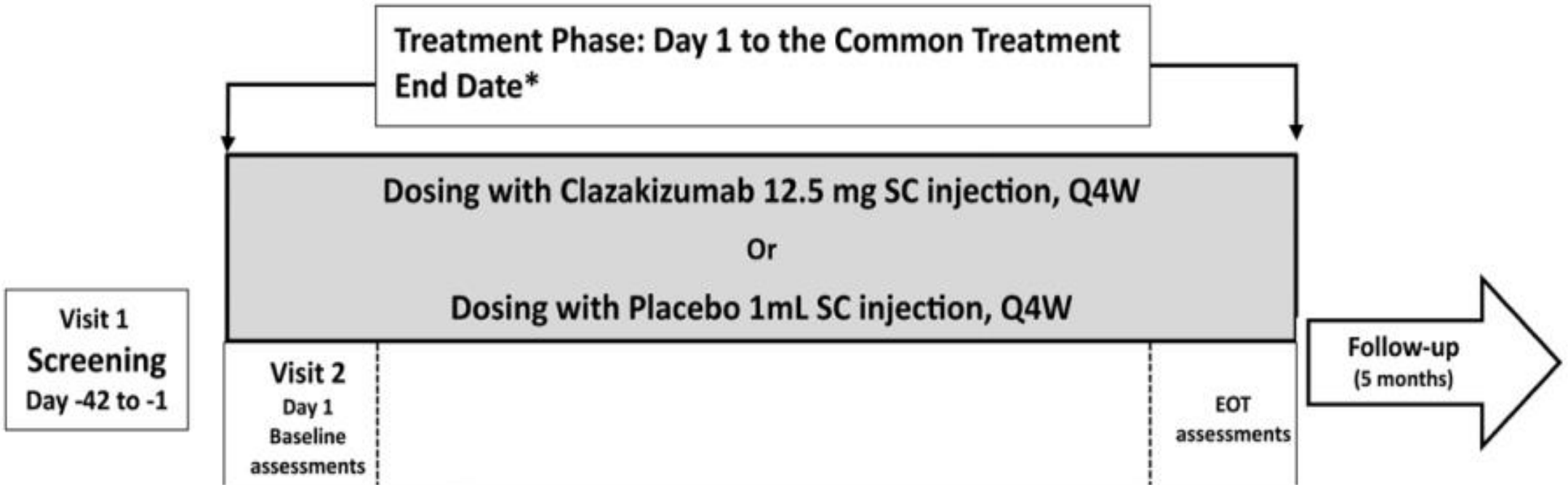
- IL-6 is implicated in T-cell activation, reducing Treg, stimulating T-follicular helper cells & germinal centers, as well as driving B-cell proliferation, maturation, & class-switching.
- IL-6 also induces APR, activates endothelial cells, & promotes vascular injury.
- **IL-6 gene polymorphisms** correlate with graft survival, & elevated circulating IL-6 correlates with increased morbidity.
- Multiple monoclonal antibodies against IL-6 or its receptors are in clinical use &/or studies across a broad spectrum of diseases.

Berger M. Transplantation. 2024

IMAGINE study

- ***I***nterleukin-6 Blockade ***M***odifying ***A***ntibody-mediated ***G***raft ***In***jury & ***E***stimated GFR Decline
- Clazakizumab is a humanized monoclonal antibody against IL-6 manufacture, Vitaeris

Schematic for event-driven IMAGINE study



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**.

Berger M. Transplantation. 2024

frontiers in Immunology

CASE REPORT
published: 15 April 2021
doi: 10.3389/fimmu.2021.661614

Zhu L. Front in Immunolo. 2021

Case Report: Splenic Irradiation for the Treatment of Chronic Active Antibody-Mediated Rejection in Kidney Allograft Recipients With *De Novo* Donor-Specific Antibodies

OPEN ACCESS

Lan Zhu[1,2], *Zhiliang Guo*[1], *Rula Sa*[1], *Hui Guo*[1,2], *Junhua Li*[3] *and Gang Chen*[1,2*]

Case-Report: Splenic Irradiation

- Historically, splenectomy was routinely performed in **ABO incompatible KT**, & it has been further used with success in the rescue of **early severe acute AMR**.
- In a recently published case report, splenic irradiation was added to the conventional treatment (PP/IVIG, rituximab, & eculizumab) to rescue early severe acute AMR in **2 KTRs**, achieving excellent therapeutic effects in both patients.
- Owing to the difference in immunological mechanisms between late chronic AMR & early acute AMR, whether splenic irradiation can also play an important complementary role in the treatment of ca AMR remains to be determined.

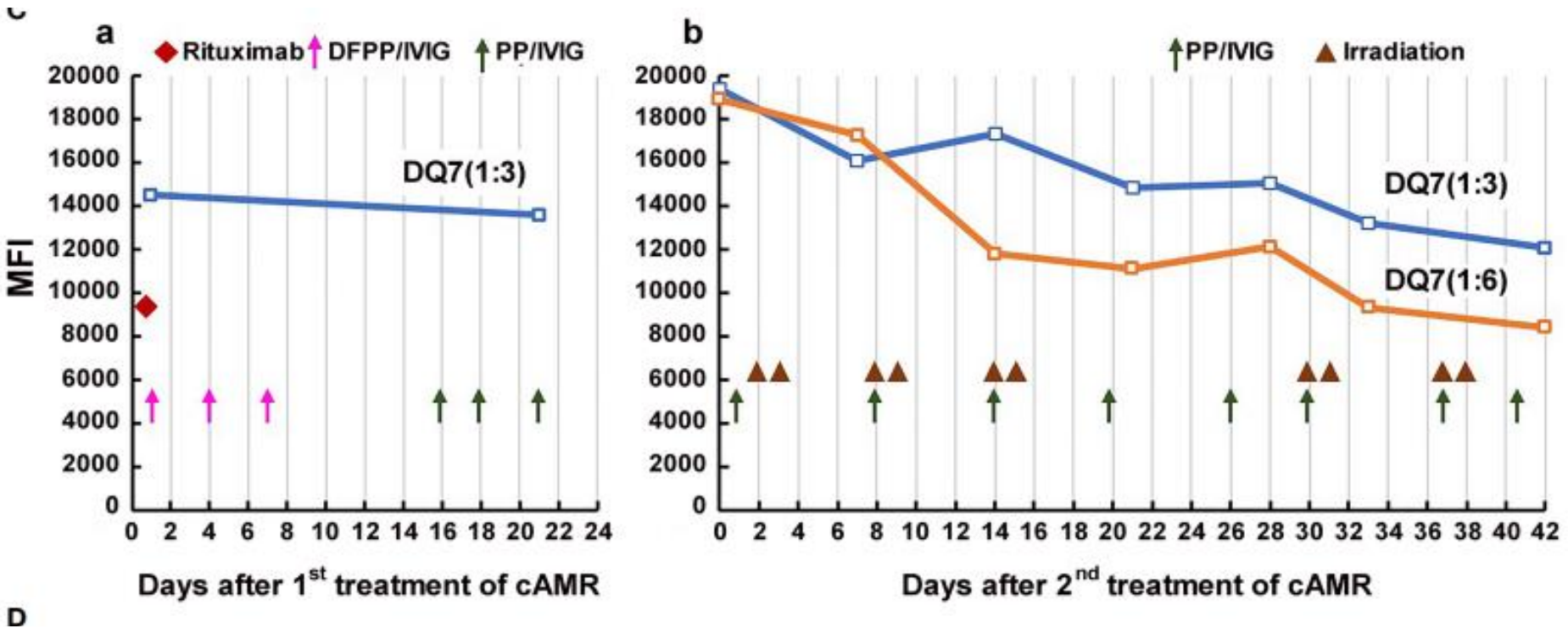
Zhu L. Front in Immunolo. 2021

Case 1: Splenic Irradiation

- A 38-year-old man LRKT for his IgA nephropathy 8 ys ago (January 2013) following 4 ys of HD.
- The donor was his father (59 years old at that time).

HLA	A	B	DRB1	DQB1
D	2.11	44.54	9.12	7.9
R	1.11	44.60	8.9	5.9

Zhu L. Front in Immunolo. 2021



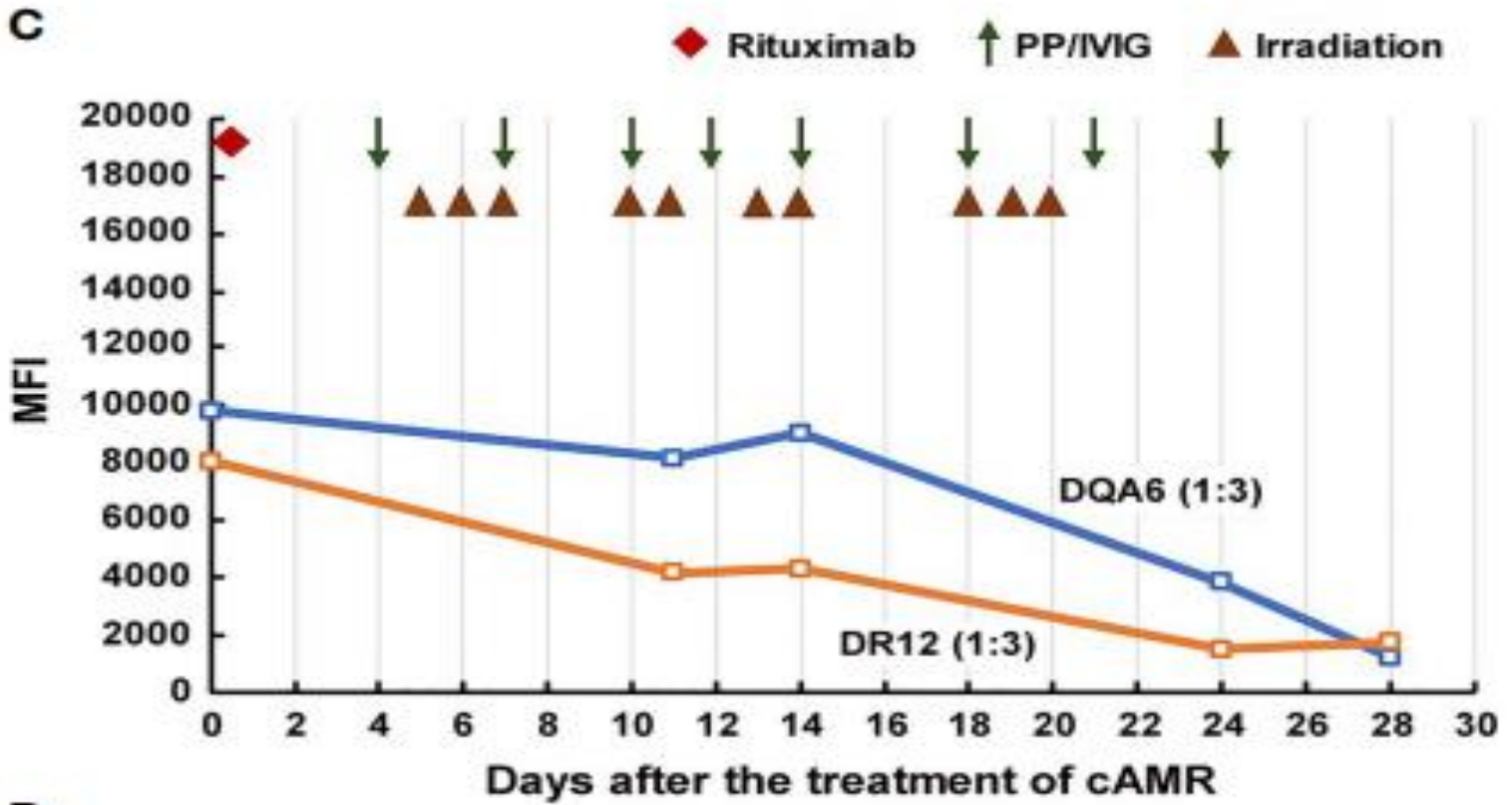
Case 1: Splenic Irradiation

hu L. Front in Immunolo. 2021

Case 2: Splenic Irradiation

- A 44-year-old man who received a LKT from his 34-year-old wife in June, 2012 after 1.5 ys of HD. In Sep 2019, the patient underwent a biopsy because of proteinuria (676 mg/24h).

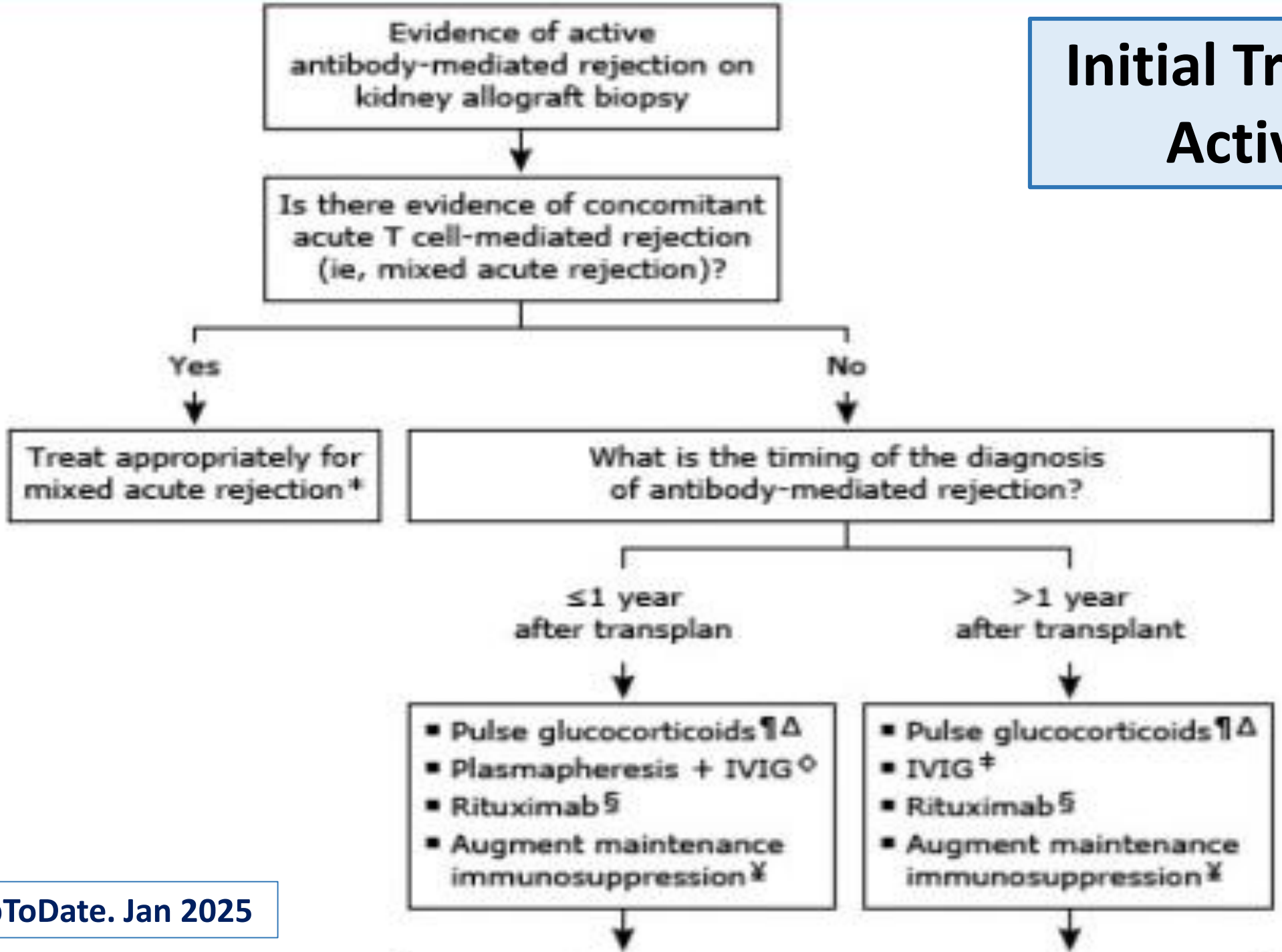
Zhu L. Front in Immunolo. 2021



Case 2: Splenic Irradiation

Zhu L. Front in Immunolo. 2021

Initial Treatment of Active AMR



UpToDate. Jan 2025

Summary

- Interestingly, a survey done at the 2019 Banff meeting revealed that 90% of pathologists at the meeting already diagnose CA TCMR & indicated that for **>80%** at least some of these cases were treated, despite **no data** published in the literature providing evidence for any treatment effect.
- The introduction of the Banff category for CA TCMR in 2017 represented the starting point to segregate out the disease processes driving renal allograft deterioration through ongoing injury & inflammation.

Summary

- The intent was to **facilitate studies** & to make the findings **comparable** to other centers, ultimately increasing our understanding of **i-IFTA** & increasing the precision of diagnosis & risk stratification of renal allografts with i-IFTA.
- We are still **not** at the point to recommend evidence-based treatment of CA TCMR.

"با تشکر از توجه شما "

پاییز در بیمارستان خورشید اصفهان