Management of Antibody Mediated Rejection in Adult Patients

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INTRODUCTION

- Despite modern immunosuppression, ongoing kidney injury and graft loss due to alloantibody-induced immunity remains an important issue.
- Driving this response are polymorphic HLA antigens.
- While the impact of antibodies to HLA on kidney allograft survival has been known for some time, only recently, with the advent of sensitive solid-phase assays to detect donor-specific anti-HLA antibodies (DSA) and the development of the Banff diagnostic criteria for antibody-mediated rejection (AMR), has the size of the problem been realized.

INTRODUCTION

- By 10 years, after kidney transplant, up to 25% have developed de novo DSA (dnDSA).
- Thus, it is not surprising that AMR was the most common cause of allograft failure in a cohort of renal transplant recipients with indication biopsies before graft failure.
- Moreover, in a multicenter cohort study, antibody-mediated damage caused allograft dysfunction late posttransplant in nearly 60% of renal transplan trecipients.

INTRODUCTION

- Given the scope and severity of the problem, it is unfortunate that there are no commonly accepted guidelines for treatment.
- To date, clinical trials of AMR have been small or inconclusive, and there are no Federal Drug Administration (FDA)-approved therapies for the prevention and treatment of the condition.

CLINICAL PHENOTYPES OF AMR

- AMR can present with abrupt allograft dysfunction early posttransplant but can also have an insidious or subclinical onset, presenting later posttransplant.
- Anti-HLA antibody can also be present before transplant (preexisting DSA) or develop after transplant (dnDSA) in the setting of under-immunosuppression.

CLINICAL PHENOTYPES OF AMR

- In some circumstances, the histological features suggestive of AMR are present, but anti-HLA antibody is not detected.
- Incorporating these clinical features of AMR into the current Banff classification while considering the likely underlying immunologic mechanisms is critical to appropriately guide therapeutic decisions and ultimately design efficient and effective therapeutic clinical trials.
- Therefore, we recommend considering the timing of presentation, and type of DSA (preexisting or de novo), in relation to the histological classification

Early Posttransplant (<30 Days) Active AMR

- In patients who have measurable DSA at the time of kidney transplant or who have an immunologic amnestic response due to previous exposure to allo-HLA, active AMR can occur within the first 30 days posttransplant.
- The risk of early posttransplant AMR increases with growing DSA strength or breadth at the time of transplant as determined by DSA mean fluorescence intensity (MFI), the degree of flow cytometric crossmatch positivity, and the number or breadth of cross-reactive DSA specificities.

Early Posttransplant (<30 Days) Active AMR

- In general, this form of AMR is uncommon, as it is common practice to avoid allocating kidneys to patients with known preformed DSA, as early posttransplant AMR occurs in up to 40% of patients with preformed DSA and a positive flow cytometric crossmatch.
- This aggressive form of active AMR typically presents with an abrupt increase in DSA accompanied by allograft dysfunction (increased creatinine and oliguria with or without proteinuria).

Early Posttransplant (<30 Days) Active AMR

- If not recognized and treated quickly, it can lead to cortical necrosis and allograft loss within days.
- From a histological perspective, the criteria for Banff active AMR are met and C4d is usually positive.
- There is often interstitial hemorrhage, glomerular fibrin thrombi, and microvascular coagulative necrosis.

Early Posttransplant (<30 Days) Active AMR

- With prompt diagnosis and treatment, patients can recover allograft function and histological features of active AMR frequently resolve completely.
- In other cases, the histological features of active AMR persist and chronic active AMR, allograft dysfunction, and ultimate allograft failure ensues.

Late (>30 Days) Posttransplant AMR With Preexisting DSA

- While many patients with preexisting DSA do not develop an aggressive early AMR as described above, they can develop an indolent and progressive form of AMR that is usually initially detected on a surveillance biopsy (in the setting of stable function) or on a for-cause biopsy for mild allograft dysfunction.

Late (>30 Days) Posttransplant AMR With Preexisting DSA

- Histological findings are dependent on the timing of the biopsy. When detected early, microvascular inflammation (MVI) in glomeruli and peritubular capillaries is the predominant finding and C4d staining may or may not be present.
- MVI tends to persist and is later accompanied by chronic histological features including transplant glomerulopathy and peritubular basement membrane multilayering.

Late (>30 Days) Posttransplant AMR With Preexisting DSA

- At diagnosis, there is often minimal if any reduction in glomerular filtration rate (GFR) or proteinuria even when mild chronic features are present.
- Overtime, however, the GFR declines and the patient becomes proteinuric with graft failure often occurring several years after transplant.

Late (>30 Days) Posttransplant AMR With Preexisting DSA

- In an observational prospective cohort study of >100 renal transplant recipients who underwent surveillance biopsy at 1 year, patients with AMR were the most likely to experience allograft failure.
- Allograft survival was only 56% at 8 years posttransplant compared with 88% if subclinical TCMR was present, and 90% if the biopsy was normal.

Late (>30 Days) AMR Associated With dnDSA

- In the current era of sensitive DSA testing and a general avoidance of preexisting DSA, the most common form of AMR is associated with dnDSA.
- In general, dnDSA is a new DSA detected after >3 months posttransplant in the context of inadequate immunosuppression which is either due to patient nonadherence, physician directed, or genetically determined variability in metabolism of immunosuppressive drugs.

Late (>30 Days) AMR Associated With dnDSA

- This form of AMR often presents with allograft dysfunction and concomitant or preexisting TCMR.
- Results from 2 recent studies have suggested that AMR with dnDSA is associated with inferior allograft survival when compared with AMR from preexisting DSA after adjusting for clinical, histological, and immunologic characteristics.
- Allograft survival was 63% in patients with preexisting DSA and only 34% in patients with dnDSA 8 years after the rejection diagnosis.

Late (>30 Days) AMR Associated With dnDSA

- Compared with patients with preexisting DSA, those with dnDSA tend to have increased proteinuria and increased expression of interferon-γ–inducible, natural killer cell, and T-cell transcripts at presentation.

Antibody-mediated rejection phenotypes

Timing	DSA	Histology[a]	Clinical presentation	Pathophysiology	Prognosis	Features associated with reduced allograft survival
Early[a] Acute (<30 days posttransplant)	Preexisting DSA (or nonimmunologically naive)	Banff 2017 active AMR Usually C4d+ Thrombotic microangiopathy often present	Abrupt allograft dysfunction correlating with increased DSA MFI or titer usually 7–10 days posttransplant[15]	Memory B-cell response	Graft loss within days if not treated[15]	Pretransplant crossmatch (+T-AHG-CDC+[15] or high-flow cytometric crossmatch)[15]
Late (>30 days posttransplant)	Preexisting DSA	Banff 2017 active or chronic active AMR May be C4d±	± Allograft dysfunction and proteinuria	Preexisting plasma cell response	Graft loss within months to ys[16-20]	Histological Banff cg >0 lesion[19,21,22] Degree of IFTA[23-25] Concomitant TCMR[22-24,26,27] Banff cv score >0[24] C4d positivity[28-30] Clinical Proteinuria[19,25,31,32] Allograft dysfunction[19,22,24,25,31,33] Ys posttransplant[24,25] Patient nonadherence or physician-directed immunosuppression reduction[22,25] DSA characteristics C1q-positive DSA[24,34,35] High DSA MFI or titer and pretransplant crossmatch[16,18,31,36,37] Anticlass II DSA[17,36]
	De novo DSA	Banff 2017 active or chronic active AMR May be C4d± Concomitant TCMR often present	± allograft dysfunction and proteinuria	Under-immunosuppression	Graft loss within months to ys 28-30,32	

[a]Hyperacute rejection is associated with very high DSA (positive complement-dependent cytotoxicity crossmatch) at the time of transplant and results in graft loss within minutes to hours posttransplant. This type of AMR is virtually nonexistent in the current era and not addressed in this article.

AMR, antibody-mediated rejection; CDC, complement-dependent cytotoxicity; cg, chronic glomerulitis; cv, chronic vasculopathy; DSA, donor-specific antibody; IFTA, interstitial fibrosis and tubular atrophy; MFI, mean fluorescence intensity; TCMR, T-cell mediated rejection.

Monitoring for De Novo DSA

- Monitoring for dnDSA is recommended in the following settings:

1. immunosuppression reduction by physician for any reason,
2. known patient medication nonadherence,
3. at the time of rejection episode (T cell or antibody mediated) (2B).

THE TREATMENT OF ACTIVE AND CHRONIC ACTIVE AMR

- Plasma Exchange and IVIG
- Complement Inhibitors
- Rituximab
- Imlifidase
- Antithymocyte Globulin
- Splenectomy
- Proteasome Inhibitor: Bortezomib
- Cyclophosphamide
- Interleukin-6 Inhibitors

Plasma Exchange and IVIG

- The primary aims of nearly all therapeutic approaches for AMR are removing circulating DSA and reducing DSA production.
- In this sense, the strongholds for contemporary treatment of AMR are represented by plasma exchange (PLEX) and IVIG, although neither of these have FDA approval.
- This treatment regimen is most commonly used to treat active AMR, although frequency, modality, and dosing may vary.

Plasma Exchange and IVIG

- The rationale for using PLEX and IVIG is to combine removal of circulating DSA with immunomodulation of the antigraft immune response and in particular modulation of the B-cell response.
- In experimental models, IVIG has been shown to inhibit B-cell responses by the Fc portion of the Ig binding the Fc fragment of IgG2b receptor on B cells, and sialylated IVIG binds CD22, inducing apoptosis of mature B cells.
- It also functions as a scavenger of activated complement.

Evidence for use of plasma exchange and intravenous immune globulins as SOC in active AMR

Criterion	Evidence	Reference
Biological rationale	Anti-HLA antibodies activate complement and interact with Fc receptors and endothelium.	Akiyoshi et al[63]
	Removal of anti-HLA Ab via plasma exchange correlates with better clinical response in kidney transplant recipients.	Gelfand[64]
	Intravenous immune globulins have pleiotropic effects including neutralization of antibodies/cytokines/activated components of complement, effects on B cells, T cells, and Fc receptors.	
Benefit in clinical (observational) studies	Humoral rejection treated with PE/IVIG results in improved renal function.	Rocha et al[65]
	The combination PE/IVIG leads to better removal of anti-HLA antibodies and correlates with better graft survival.	Lefaucheur et al[66]
International recommendations	FDA 2017 Public workshop: Antibody removal therapies, generally in combination with low- or high-dose IVIG (immunomodulation) form the SOC in many institutions.	Velidedeoglu et al[67] Kasiske et al[68]
	KDIGO 2010: Recommendation for PE and IVIG in association with corticosteroids.	
Most used combination in clinical practice	American Society of Transplantation survey: Most centers utilize a combination of IVIG and plasmapheresis for treatment.	Burton et al[69]
	The treatment of AMR in kidney transplant recipients: a systematic review.	Roberts et al[55]

Ab, antibody; AMR, antibody-mediated rejection; Fc, fragment crystallizable; IVIG, intravenous immune globulins; PE, plasma exchange; FDA, Federal Drug Administration; KDIGO, Kidney Disease: Improving Global Outcomes; SOC, standard of care.

Complement Inhibitors

- The main goal of using complement inhibitors is to avoid the downstream damage to the allograft from DSA.
- Eculizumab results in terminal complement blockade as a monoclonal antibody targeting C5.
- A single-center study showed that among patients who received positive crossmatch HLA-incompatible transplants, the incidence of early active AMR was decreased from approximately 40% in historical controls to 7% among treated patients.

Complement Inhibitors

- A single-center small case series has also shown that eculizumab has effectiveness in treating early active AMR that occurs within the first month posttransplant.
- Despite these promising results, long-term follow-up of eculizumab-treated positive crossmatch patients in a single-center study has shown that despite prevention of early active AMR, the long-term incidence of chronic AMR and allograft survival is comparable to historical controls.

Complement Inhibitors

- Proximal complement inhibition has also been studied as a therapeutic target.
- The plasma C1 esterase inhibitors Berinert (CSL Behring) and Cinryze (Takeda/Shire/ ViroPharma) have been tested in 2 pilot studies and indicate a possible improvement in allograft function in kidney recipients with AMR.

Rituximab

- Rituximab, a B-cell–depleting agent, was suggested as a treatment option by KDIGO guidelines.
- Despite its frequent use, the evidence is low and 3 small randomized trials have investigated its utility without demonstrating a clear benefit.

Rituximab

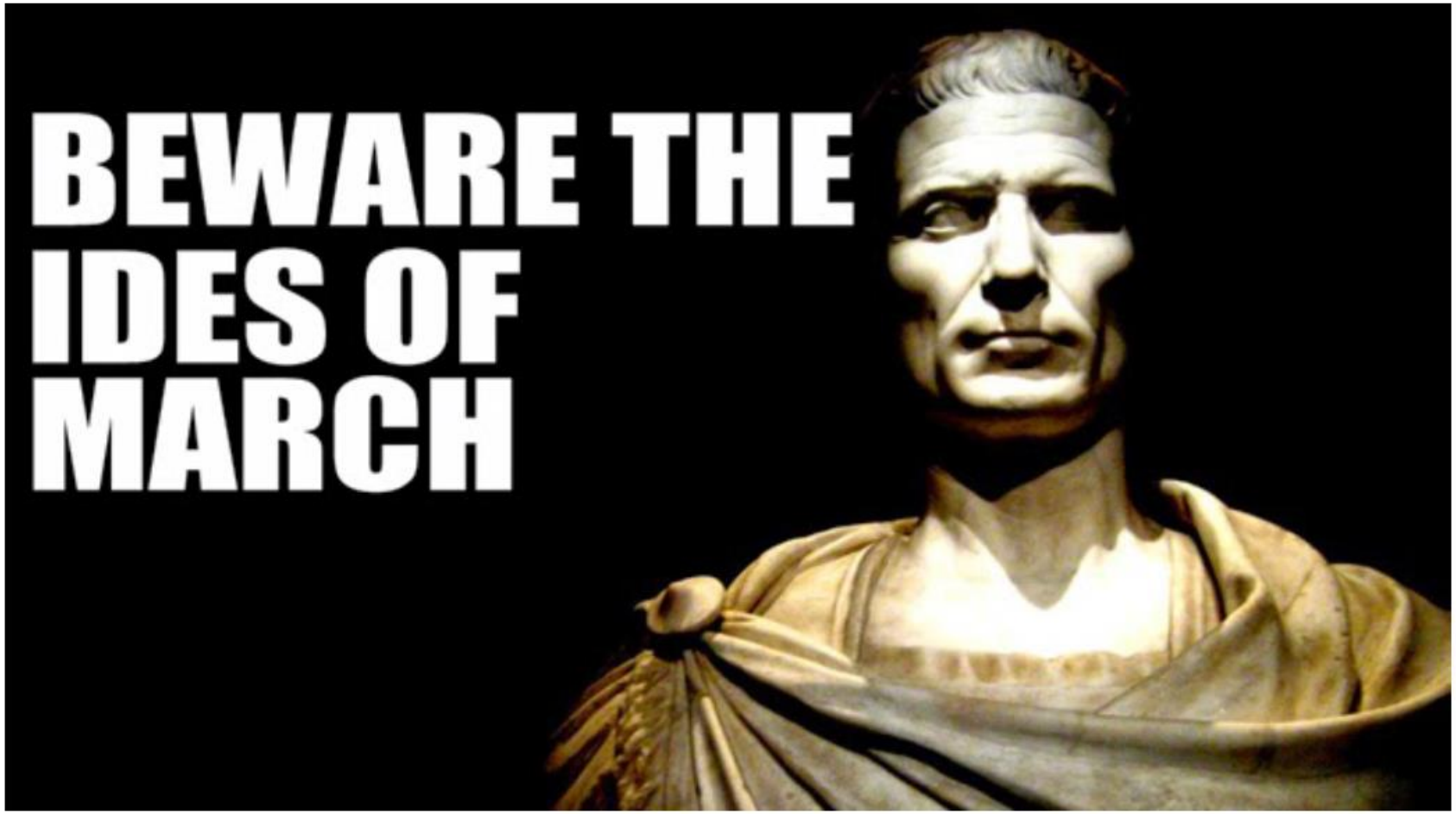
- In contrast to these prospective RCTs, several retrospective analyses have suggested some positive effects of rituximab in multimodal treatment regimens together with steroids, plasmapheresis, and high-dose IVIG, especially on patients with vascular AMR.

Rituximab

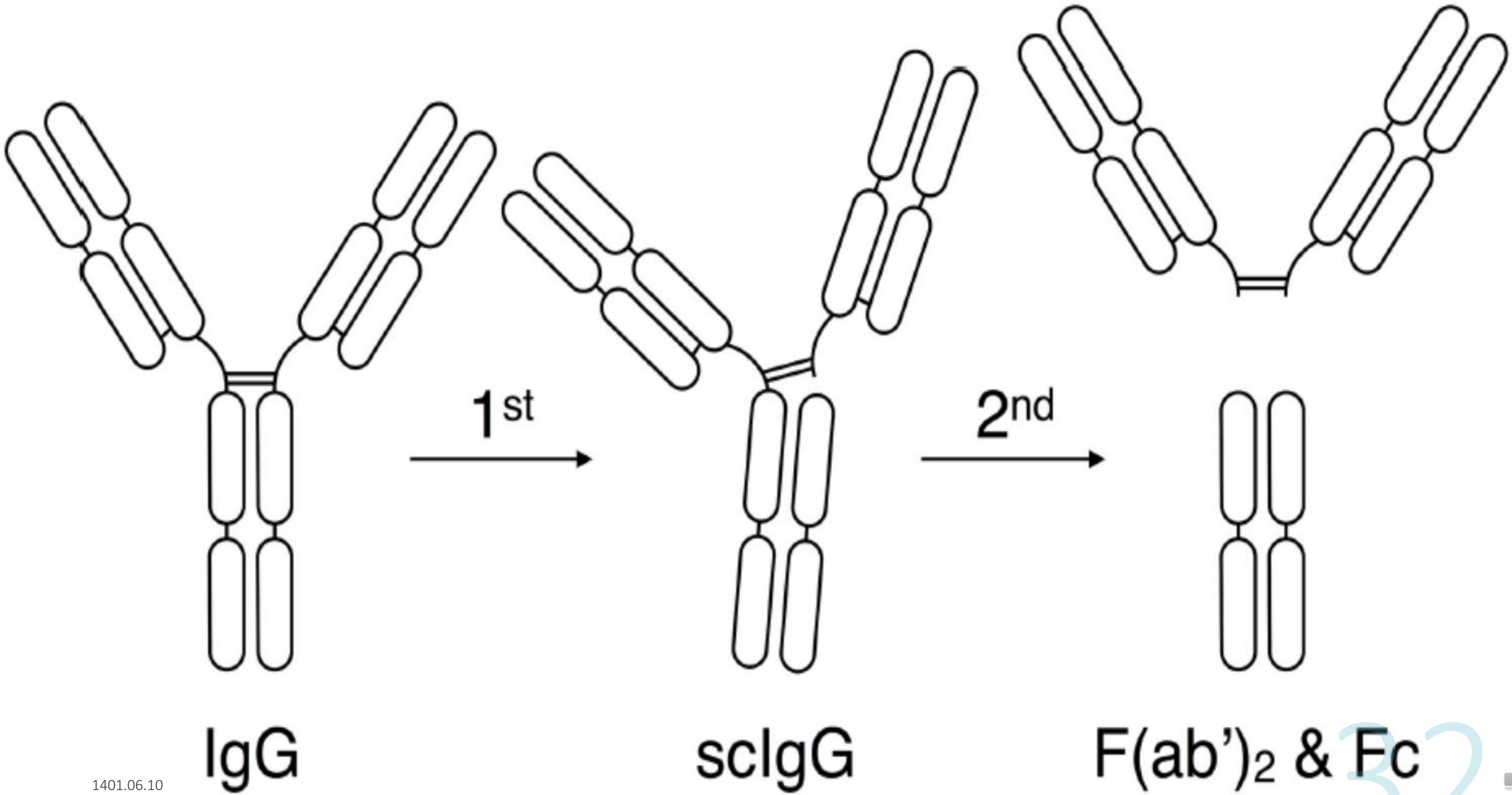
- A recent study developed a prognostic score on the basis of a treatment response to a regimen with Rituximab in the context of multimodal therapy.
- However, optimal doses, number of treatment cycles, and the effect on patients without a vascular component remain unclear, as is the need for Rituximab within a multimodal regimen

Imlifidase

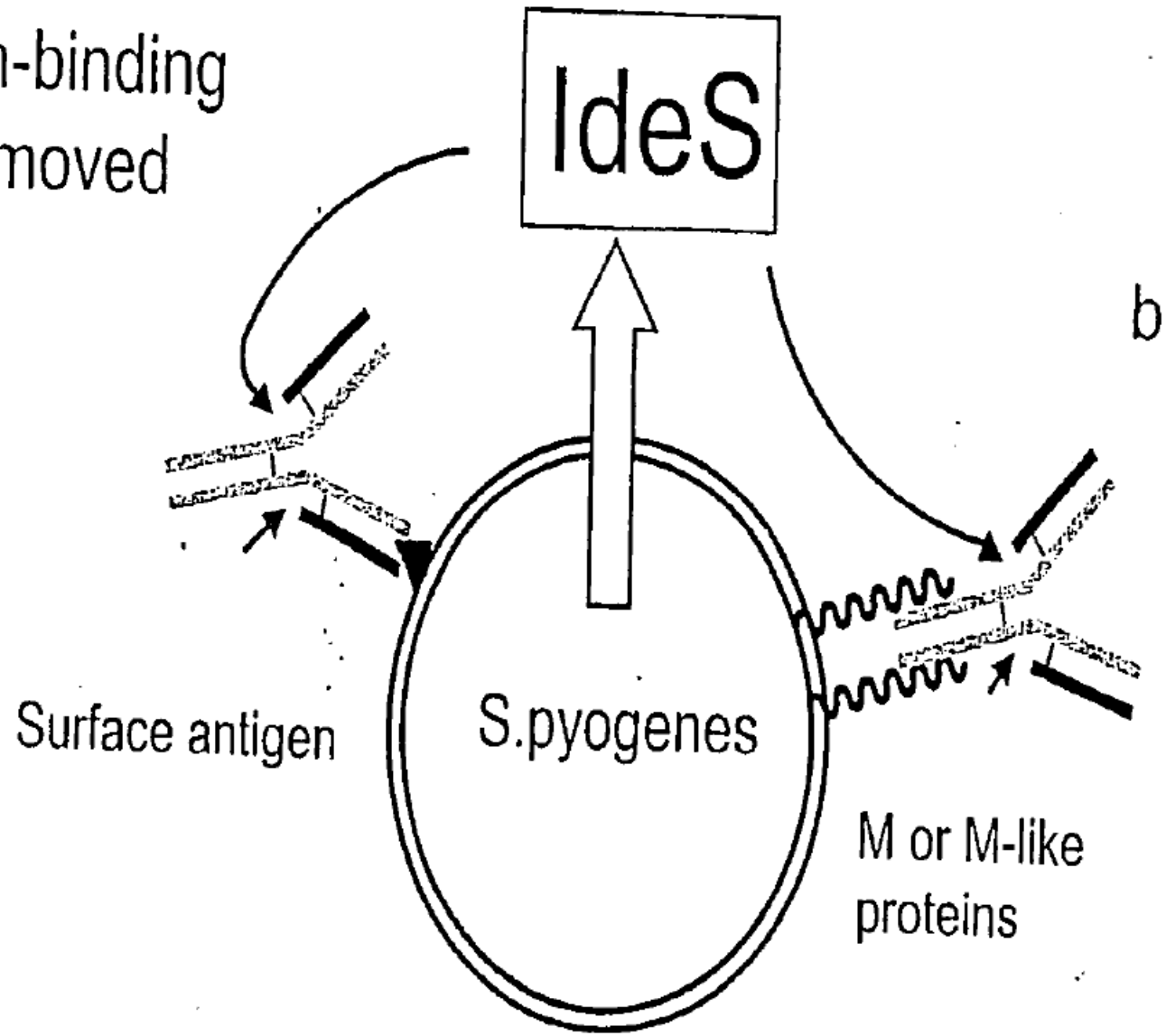
- Imlifidase (Hansa Biopharma AB), an IgG-degrading enzyme of Streptococcus pyogenes (IdeS), can rapidly reduce or even eliminate anti-HLA DSA and is undergoing clinical trials in AMR.
- IdeS cleaves human IgG at a highly specific amino acid sequence within the hinge region producing Fc and F(ab)2 fragments and effectively blocking CDC and antibody-dependent cellular cytotoxicity.



IdeS: IgG-degrading enzyme of S. pyogenes
Cysteine proteinase that cleaves extracellular IgG with unique specificity in the hinge region


1st
2nd
IgG
scIgG
F(ab')2 & Fc

a) Fc and non-binding Fab are removed



b) Fab's are removed and Fc is blocked

Antithymocyte Globulin

- Since its introduction, antithymocyte globulin (ATG) or other T-cell–depleting antibodies have been used for treatment of refractory rejection, vascular rejection, mixed rejections, and AMR.
- Although depleting antibodies were proposed by KDIGO guidelines as potential treatment options, no benefit has been demonstrated for treatment of pure AMR with T-cell–depleting therapy.

Splenectomy

- There are several case series of surgical splenectomy, splenic embolization, and splenic radiation being used as a salvage procedure for severe early AMR.
- It must be performed rapidly after the onset of early AMR to be effective.
- Most of these AMR cases occur in the first week after transplantation and result in profound graft dysfunction and a sudden rise in DSA strength, usually from an anamnestic response.
- Some patients who recover develop transplant glomerulopathy and premature graft loss.

Proteasome Inhibitor: Bortezomib

- Bortezomib is a proteasome inhibitor approved for the treatment of multiple myeloma that directly targets antibody-producing plasma cells making it an attractive candidate for the treatment of active AMR.
- Data supporting its use are limited to case series suggesting a positive effect within a multimodal treatment regimen of PLEX, IVIG, steroids, and depleting antibodies.

Proteasome Inhibitor: Bortezomib

- The only prospective randomized, double-blind, placebo-controlled trial was in “late” AMR and did not demonstrate any beneficial effect of bortezomib alone.
- The drug has well-documented side effects, and at the present time, there are no trial data to support its use.

Cyclophosphamide

- Cyclophosphamide is used for the treatment of antibody smediated diseases such as anti-neutrophil cytoplasmic antibody vasculitis or lupus nephritis.
- Previous anecdotal reports describe its use within a multimodal treatment regimen for the treatment of refractory rejections.
- While it is relatively inexpensive, there are no trial data to support its use.

Interleukin-6 Inhibitors

- A single-center, nonrandomized trial of tocilizumab (anti-interleukin-6 receptor monoclonal antibody) was undertaken in 36 patients with chronic active AMR that had failed IVIG plus rituximab.
- Patient and graft survival at 6 years (91% and 80%, respectively) were found to be superior to historical controls, with significant reductions in DSA and stabilization of renal function

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REVIEW
published: 14 April 2022
doi: 10.3389/fimmu.2022.839380

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Tocilizumab and Active Antibody-Mediated Rejection in Kidney Transplantation: A Literature Review

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Introduction: Chronic kidney disease (CKD) is a major public-health problem that increases the risk of end-stage kidney disease (ESKD), cardiovascular diseases, and other complications. Kidney transplantation is a renal-replacement therapy that offers better survival compared to dialysis. Antibody-mediated rejection (ABMR) is a significant complication following kidney transplantation: it contributes to both short- and long-term injury. The standard-of-care (SOC) therapy combines plasmapheresis and Intravenous Immunoglobulins (IVIg) with or without steroids, with or without rituximab: however, despite this combined treatment, ABMR remains the main cause of graft loss. IL-6 is a key cytokine: it regulates inflammation, and the development, maturation, and activation of T cells, B cells, and plasma cells. Tocilizumab (TCZ) is the main humanized monoclonal aimed at IL-6R and appears to be a safe and possible strategy to manage ABMR in sensitized recipients. We conducted a literature review to assess the place of the anti-IL-6R monoclonal antibody TCZ within ABMR protocols.

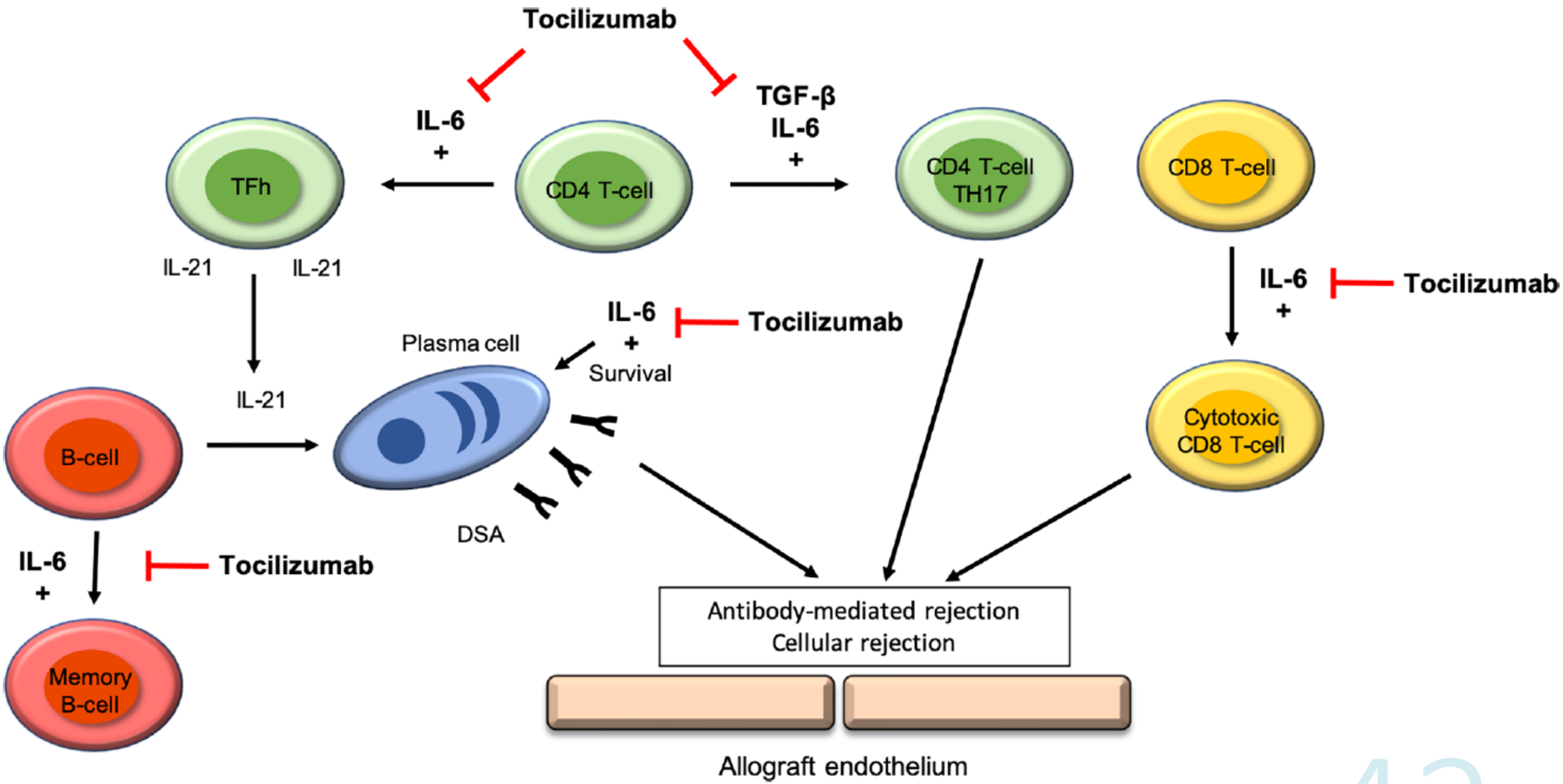

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FIGURE 1 | IL-6 receptor targets of Tocilizumab in the development if antibody-mediated rejection.

Results: Most studies report a significant reduction in levels of Donor Specific Antibodies (DSAs) and reduced inflammation and microvascular lesions (as found in biopsies). Stabilization of the renal function was observed. Adverse events were light to moderate, and mortality was not linked with TCZ treatment. The main side effect noted was infection, but infections did not occur more frequently in patients receiving TCZ as compared to those receiving SOC therapy.

Conclusion: TCZ may be an alternative to SOC for ABMR kidney-transplant patients, either as a first-line treatment or after failure of SOC. Further randomized and controlled studies are needed to support these results.

Consensus treatment recommendations based on available evidence and expert opinion

Timing	DSA	Histology (Banff 2017)	Standard of care[a]	Consider adjunctive therapies
Early[a] Acute (<30 days posttransplant)	Preexisting DSA (or nonimmunologically naive)	Active AMR	Plasmapheresis (daily or alternative day × 6 based on DSA titer) (1C)[b] IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (1C) Corticosteroids (EO)	Complement inhibitors (2B) Rituximab 375 mg/m^2 (2B) Splenectomy (3C)
Late (>30 days posttransplant)	Preexisting DSA	Active AMR	Plasmapheresis (daily or alternative day × 4–6 based on DSA titer) (2C)[b] IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (2C) Corticosteroids (EO)	Rituximab 375 mg/m^2 (2B)
		Chronic AMR	Optimize baseline immunosuppression (eg, add steroids if on a steroid-free regimen) (1C)	IVIG (3C)
	De novo DSA	Active AMR	Optimize baseline immunosuppression (eg, add steroids if on a steroid-free regimen) (1C) Evaluate and manage nonadherence	Plasmapheresis and IVIG (3C) Rituximab (3C)
		Chronic AMR		IVIG (3C)

[a]For all cases, treatment of concomitant T-cell–mediated rejection (≥borderline) and optimizing immunosuppression is recommended. Optimizing immunosuppression includes the use of tacrolimus with goal trough of >5 and use of maintenance steroid equivalent to prednisone 5 mg daily.
[b]Fresh-frozen plasma to be used for replacement fluid for plasmapheresis if a biopsy was performed within 24–48 h. The codes for grades of evidence have been taken from KDIGO.[54,56]
AMR, antibody-mediated rejection; DSA, donor-specific antibody; EO, expert opinion; IVIG, intravenous immune globulins; KDIGO, Kidney Disease: Improving Global Outcomes.

Received: 27 November 2020 | Revised: 12 January 2021 | Accepted: 31 January 2021

DOI: 10.1111/iji.12532

INVITED REVIEW

INTERNATIONAL JOURNAL OF IMMUNOGENETICS WILEY

NK cells in antibody-mediated rejection – Key effector cells in microvascular graft damage

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Abstract

Antibody-mediated rejection (ABMR) stands as the major limitation to long-term transplant outcome. The immunologic understanding of ABMR continues to progress and has identified natural killer (NK) cells as key effector cells promoting and coordinating the immune attack on the graft microvascular endothelium. This review discusses the current concepts outlining the different ways that allow for NK cell

8 | SUMMARY

NK cells are powerful immune effector cells with multiple ways to engage and damage graft endothelial cells in organ transplants. We have mainly discussed NK cell properties in the context of DSA causing ABMR as that is where the bulk of the literature exists. ABMR caused by antibody has until now been assumed to the sole cause of MVI in a transplant. However, the newly described ability for NK cell recognition of missing self on graft endothelium that also results in MVI challenges this. The message stemming from the compilation of studies of NK cells in organ transplants is that

NK cell engagement of donor microvascular endothelium, whether DSA- or MS-mediated, is deleterious to graft survival. This places NK cells at the centre of the immunologic picture of factors directly contributing to graft failure. The concepts discussed in this review warrant not only further studies but also diagnostic application of currently known NK cell characteristics that dictate immunologic risk by affecting the potential to engage graft endothelium. Additionally, in clinically relevant settings, more investigation into immunosuppression and the impact this has on NK cell function in ABMR is needed.