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

12-15 December 2023
Homa Hotel, Tehran

# Treatment of Acute Antibody-Mediated Rejection(ABMR)

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# INTRODUCTION

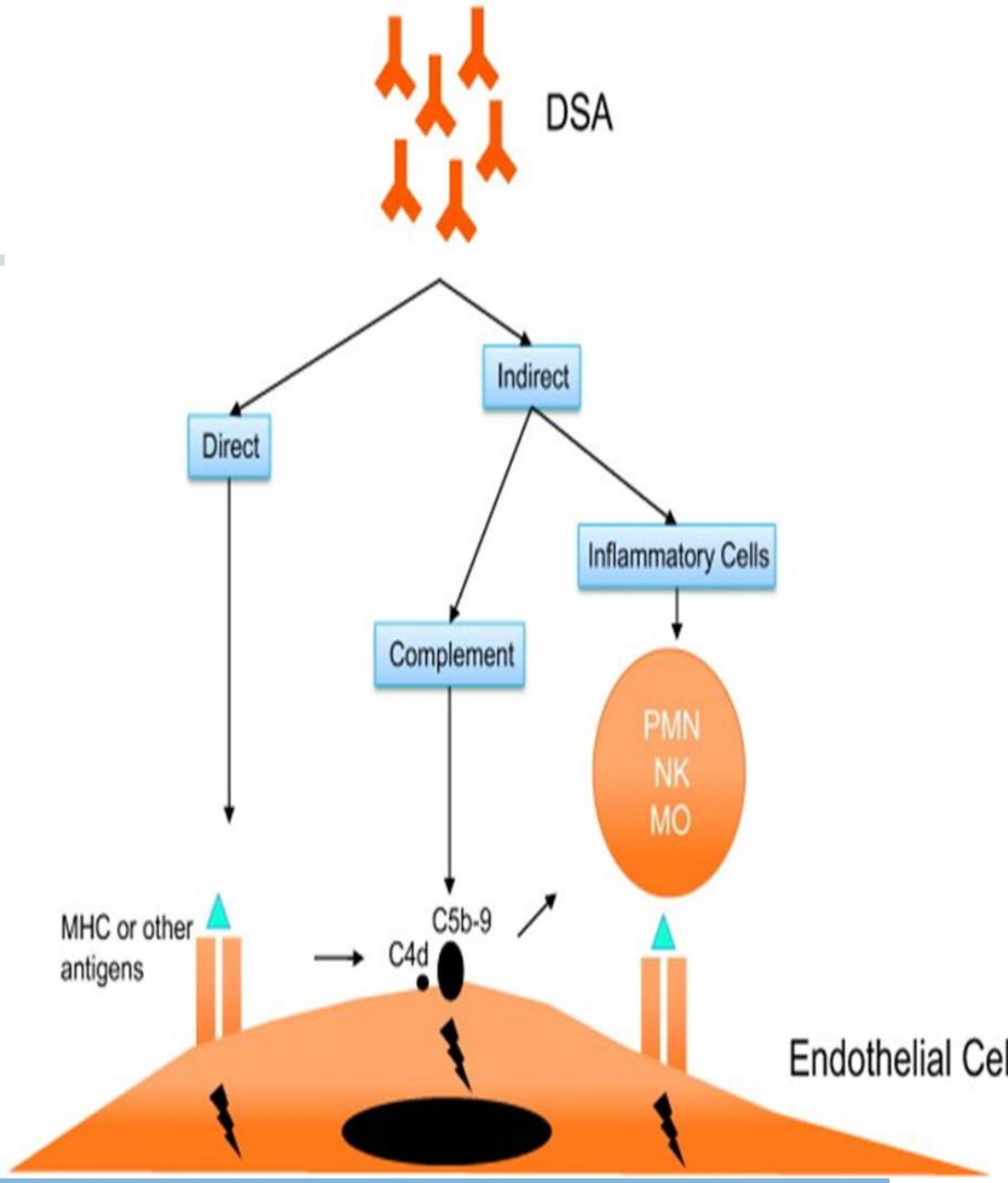
- ✓Antibody-mediated rejection (ABMR) is the most common cause of immune-mediated allograft failure after kidney transplantation
- ✓Active (previously called acute) and chronic active ABMR:
  - Histologic evidence of acute and chronic injury
  - Evidence of current/recent antibody interaction with vascular endothelium
  - Serologic evidence of donor-specific antibodies (DSAs) to human leukocyte antigen (HLA) or non-HLA antigens

# Active ABMR

✓B cell and plasma cell activation:

- Generation of DSAs, which bind to HLA or non-HLA molecules expressed on endothelial cells within the kidney allograft

1. Antibodies bind to graft endothelium
2. Activate complement-dependent and -independent mechanisms
3. Recruit natural killer cells, polymorphonuclear neutrophils, platelets, and macrophages,
4. Peritubular capillaritis, glomerulitis, cellular necrosis, thrombotic microangiopathy,
5. Relatively rapid decline in allograft function



# Chronic ABMR

- ✓Pathophysiological process:
  - Repetitive pattern of thrombotic events
  - Inflammatory changes
    - Endothelial cell injury
    - Allograft matrix remodeling
    - Slow and progressive decline in kidney function

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# PREDICTORS OF OUTCOME

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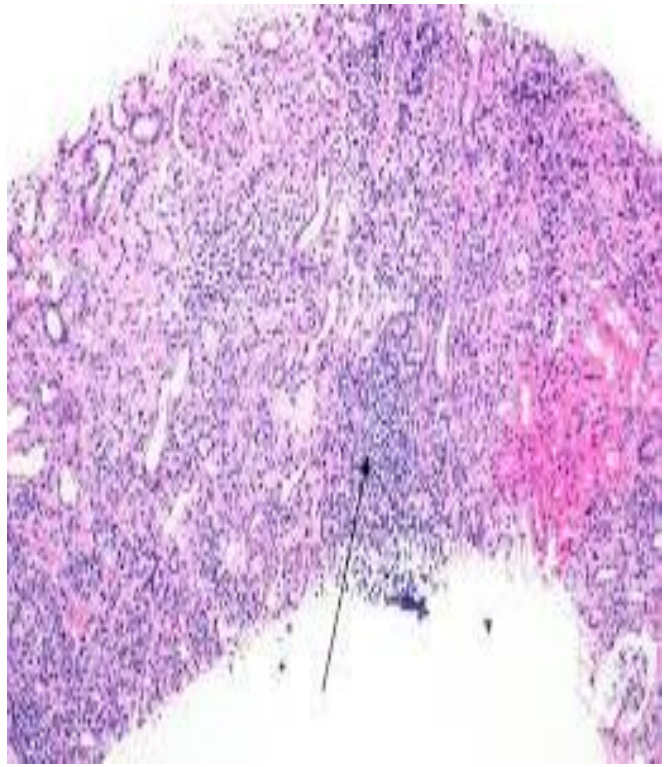
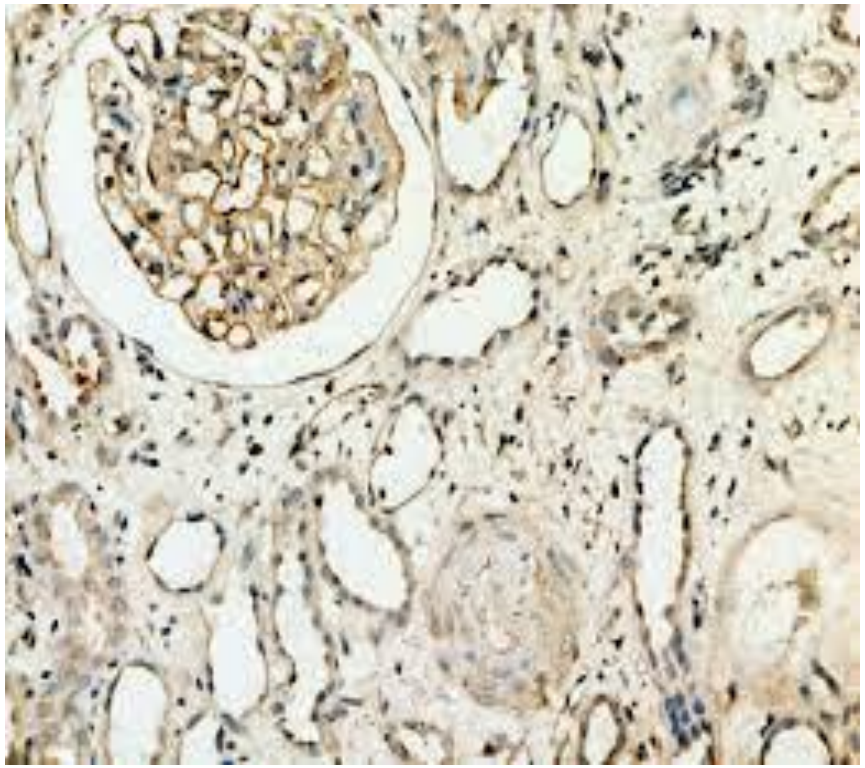
# 1.Histologic features

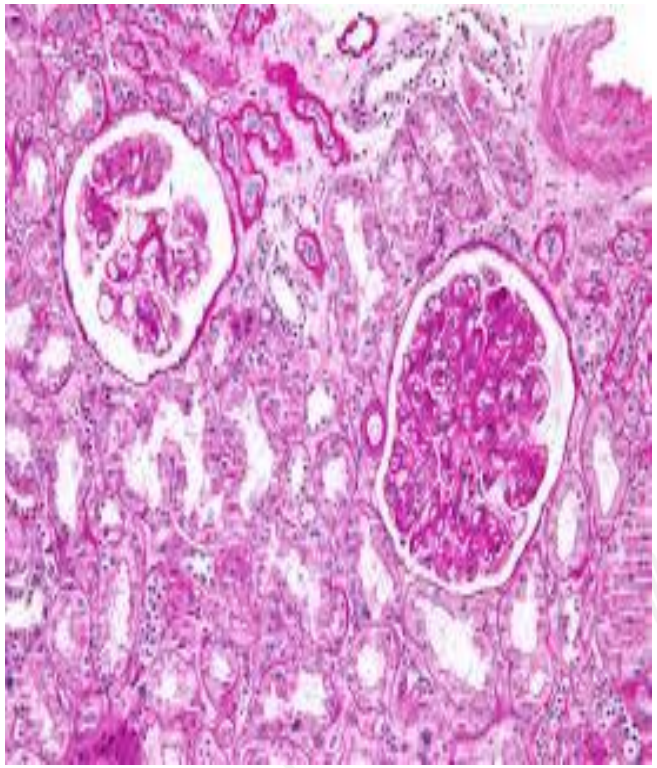
**Acute TCMR**



**Microvascular injury, C4d staining**



**Transplant glomerulopathy**



# 2.Donor-specific antibodies

- ✓**DSA strength:**
  - The risk for both ABMR and graft loss directly correlated with peak preexisting anti-human leukocyte antigen (HLA) DSA strength, (MFI)
- ✓**DSA subclass:**
  - IgG4 immunodominant DSA:
    - Later allograft injury
    - Increased allograft glomerulopathy, interstitial fibrosis/tubular atrophy
  - IgG3 immunodominant DSA:
    - Shorter time to rejection
    - Increased microvascular injury
    - C4d capillary deposition
    - Graft failure

## ✓Complement-binding capacity:

- The C1q assay:
  - C1q-binding activity of DSAs largely reflects differences in antibody strength

## ✓DSA type:

- De novo DSA, associated with poorer outcomes compared with preexisting DSA

## ✓DSA response to treatment:

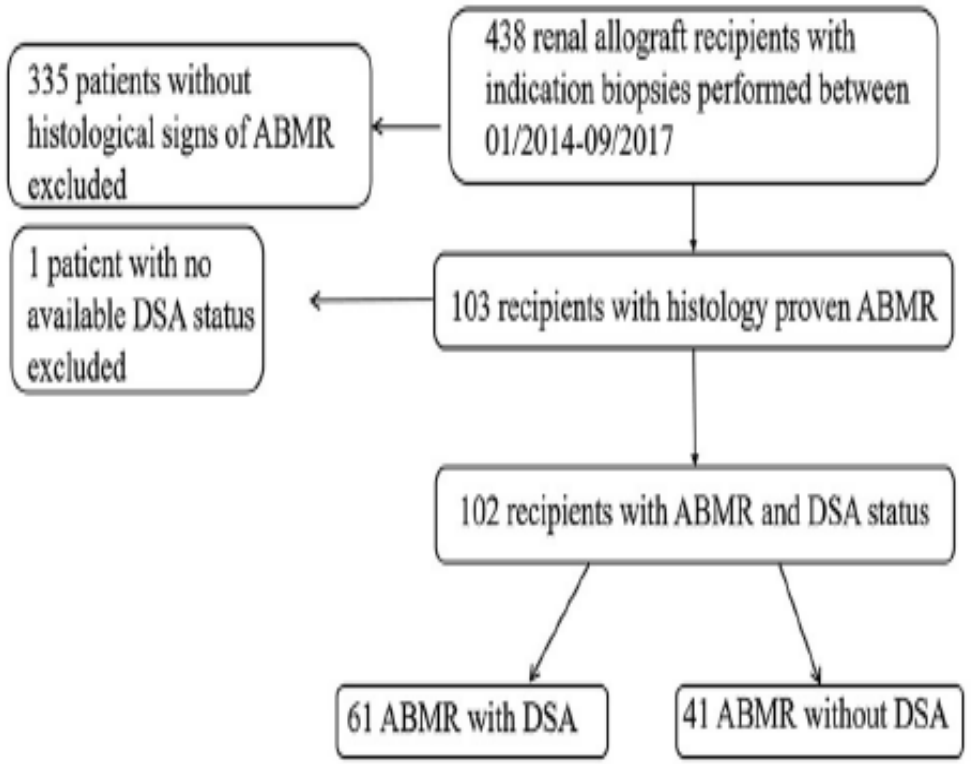
- Decline in DSA strength after treatment is associated with better graft survival

# Differential Treatment Effects for Renal Transplant Recipients With DSA-Positive or DSA-Negative Antibody-Mediated Rejection

*Marius Andreas Koslik[1†], Justa Friebus-Kardash[1†], Falko Markus Heinemann[2], Andreas Kribben[1], Jan Hinrich Bräsen[3] and Ute Eisenberger[1*]*

**Frontiers in Medicine | www.frontiersin.org 2 January 2022 | Volume 9 | Article 816555**

Study population flow chart. ABMR, antibody-mediated rejection; DSA, donor-specific antibody

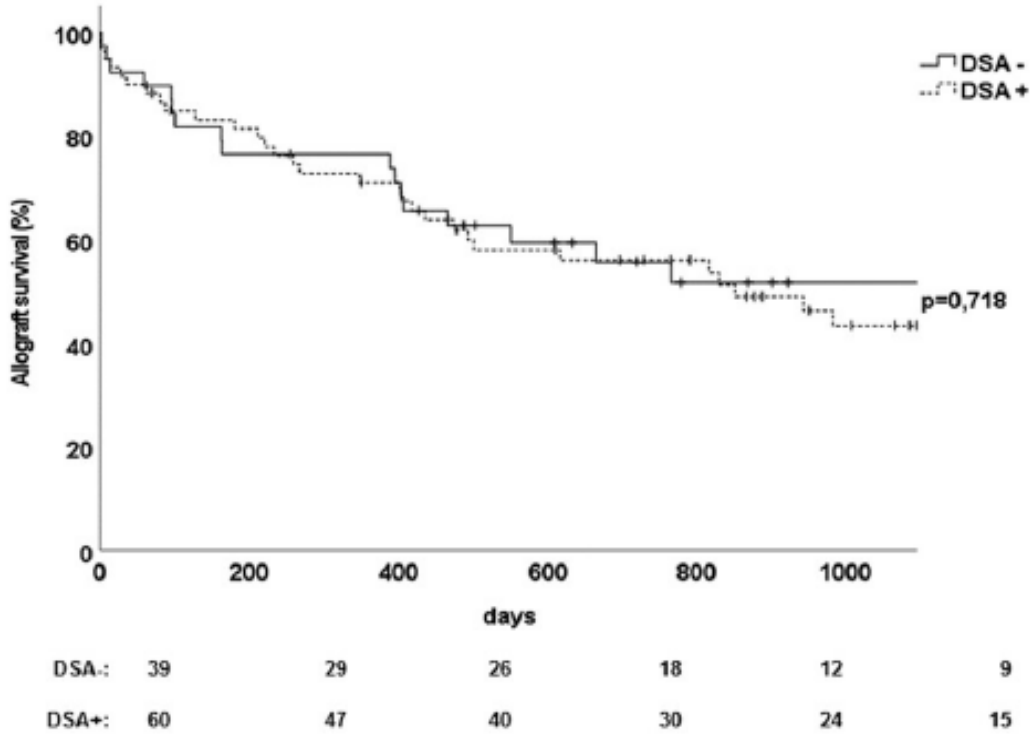



Overview of therapies used to treat biopsy-proven antibody-mediated rejection among 102 renal allograft recipients

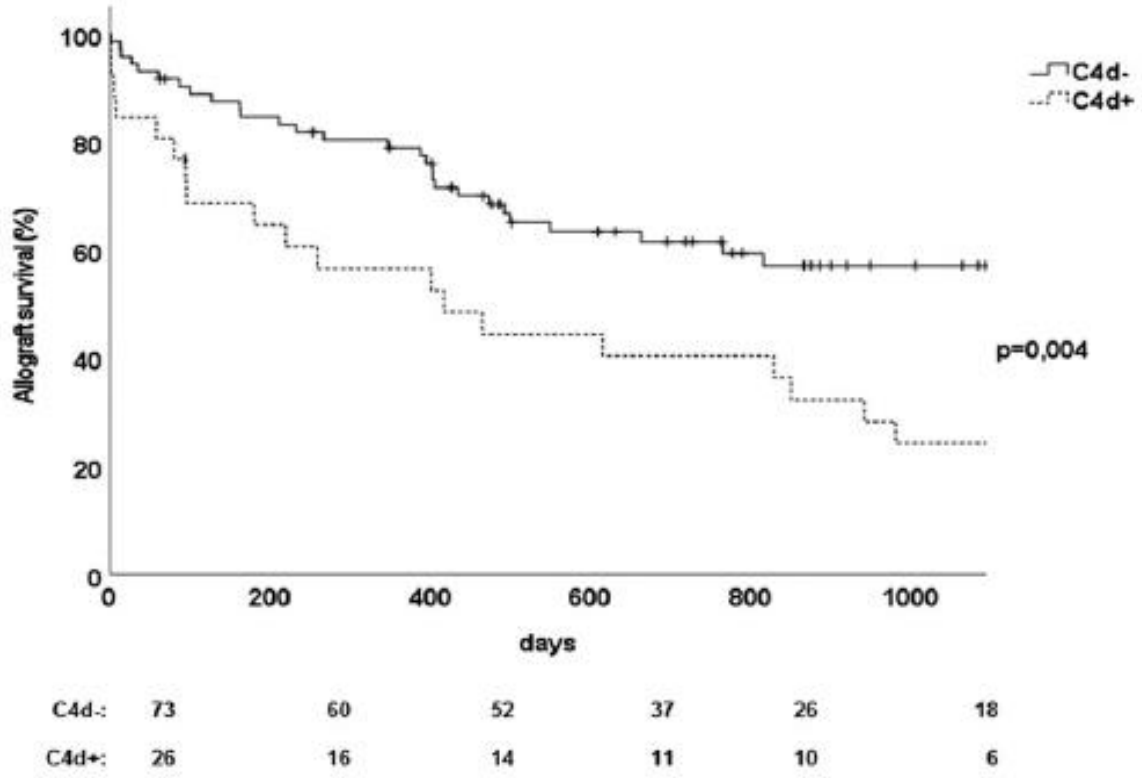
| Primary therapy of ABMR | All patients | Patients with DSA+ ABMR | Patients with DSA− ABMR | *p*-value |
|---|---|---|---|---|
| **No therapy** | 1 | 0 | 1 | n.c. |
| **Thymoglobulin alone** | 1 | 1 | 0 | n.c. |
| **Eculizumab alone** | 1 | 1 | 0 | n.c. |
| **Intensification of maintenance immunosuppression + eculizumab** | 2 | 0 | 2 | n.c. |
| **IVIG alone** | 13 | 6 | 7 | 0.285 |
| **IVIG + IA/PS** | 84 | 53 | 31 | 0.145 |
| *IVIG + PS* | *75* | *46* | *29* | *n.c.* |
| *IVIG + IA* | *9* | *7* | *2* | *n.c.* |
| *IVIG + IA/PS without add-on therapy* | *46* | *27* | *19* | *0.837* |
| *IVIG + IA/PS + add-on therapy* | *38* | *26* | *12* | *0.174* |
| *IVIG + IA/PS + rituximab* | *10* | *8* | *2* | *n.c.* |
| *IVIG + IA/PS + bortezomib* | *11* | *8* | *3* | *n.c.* |
| *IVIG + IA/PS + thymoglobulin* | *9* | *5* | *4* | *n.c.* |
| *IVIG + IA/PS + eculizumab* | *3* | *1* | *2* | *n.c.* |
| *IVIG + IA/PS + multiple add-on therapies* | *5* | *4* | *1* | *n.c.* |
| **Secondary therapy of ABMR** | | | | |
| **Long-term IVIG** | **36** | **27** | **9** | **0.021** |
| Long-term IVIG alone | 6 | 5 | 1 | 0.228 |
| Long-term IVIG + IA/PS without add-on therapy | 11 | 8 | 3 | 0.357 |
| Long-term IVIG + IA/PS with add-on therapy | 19 | 14 | 5 | 0.173 |

*ABMR, antibody-mediated rejection; DSA, donor-specific antibody; IA, immunoadsorption; IVIG, intravenous immune globulin; n.c., not calculated; PS, plasmapheresis.*
*Bold values are significant values ($p < 0.05$).*

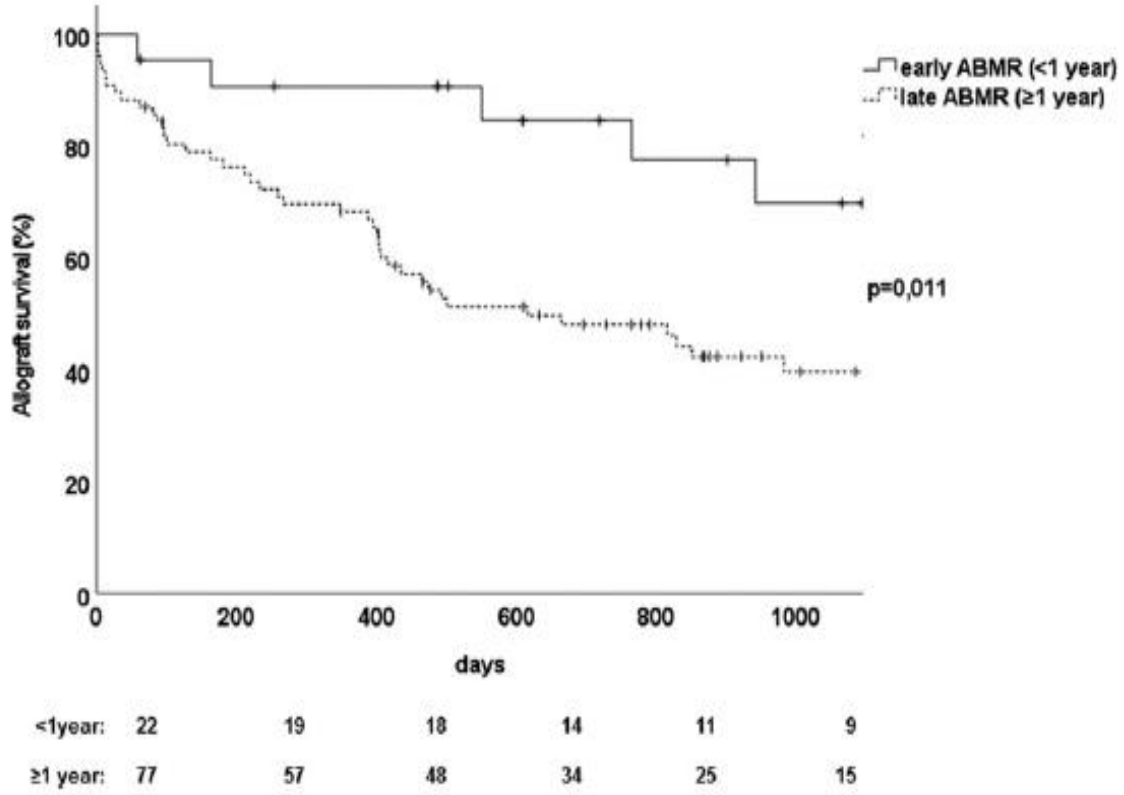
**A** **Influence of DSA status of ABMR on renal allograft survival**



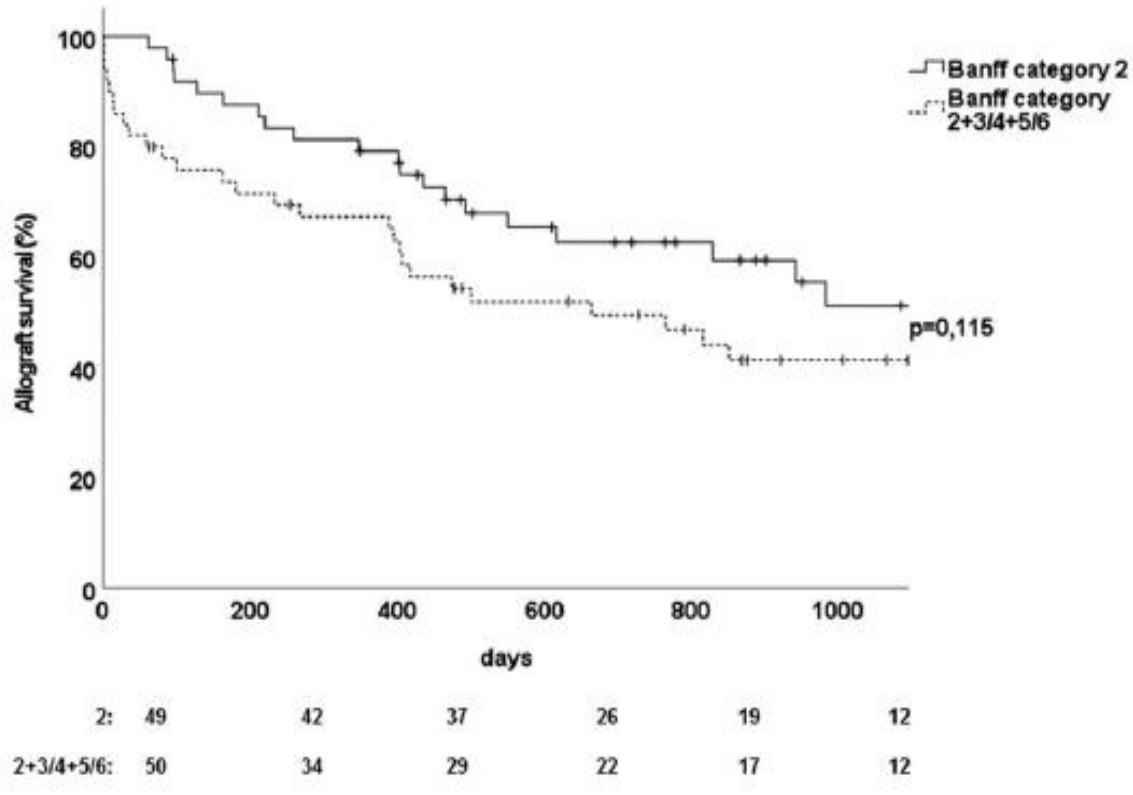

**B** **Influence on renal allograft survival of C4d deposits**



C **Allograft survival in relation to ABMR (the first year)**




D **Allograft survival with ABMR and Banff category 2**



# 3.Graft function

✓The degree of kidney allograft dysfunction at the time of kidney biopsy

- Poor outcome:
  - Lower eGFR
  - Higher urine protein-to-creatinine ratio

# 4.Molecular markers

- ✓Biomarkers of active antibody-mediated injury:
  - Donor-derived cell-free DNA (dd-cfDNA):
    - Nonencapsulated, fragmented DNA continuously shed into the bloodstream from the allograft undergoing injury
      - Half-life of approximately 30 minutes

**Transplant Rev (Orlando)** 2021 Dec;35(4):100649

# 5.Prediction models

- ✓ Novel models are being developed to predict long-term kidney allograft failure, including after the treatment of rejection
  - Functional, histologic, and immunological prognostic factors combined into a risk prediction score (iBox)
  - The iBox system:
    - Accuracy when assessed at different times of evaluation
    - Validated in different clinical scenarios
    - iBox risk prediction score
      - Help to guide monitoring of patients
      - Improve the design and development of a valid and early surrogate endpoint for clinical trials

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# PREVENTION

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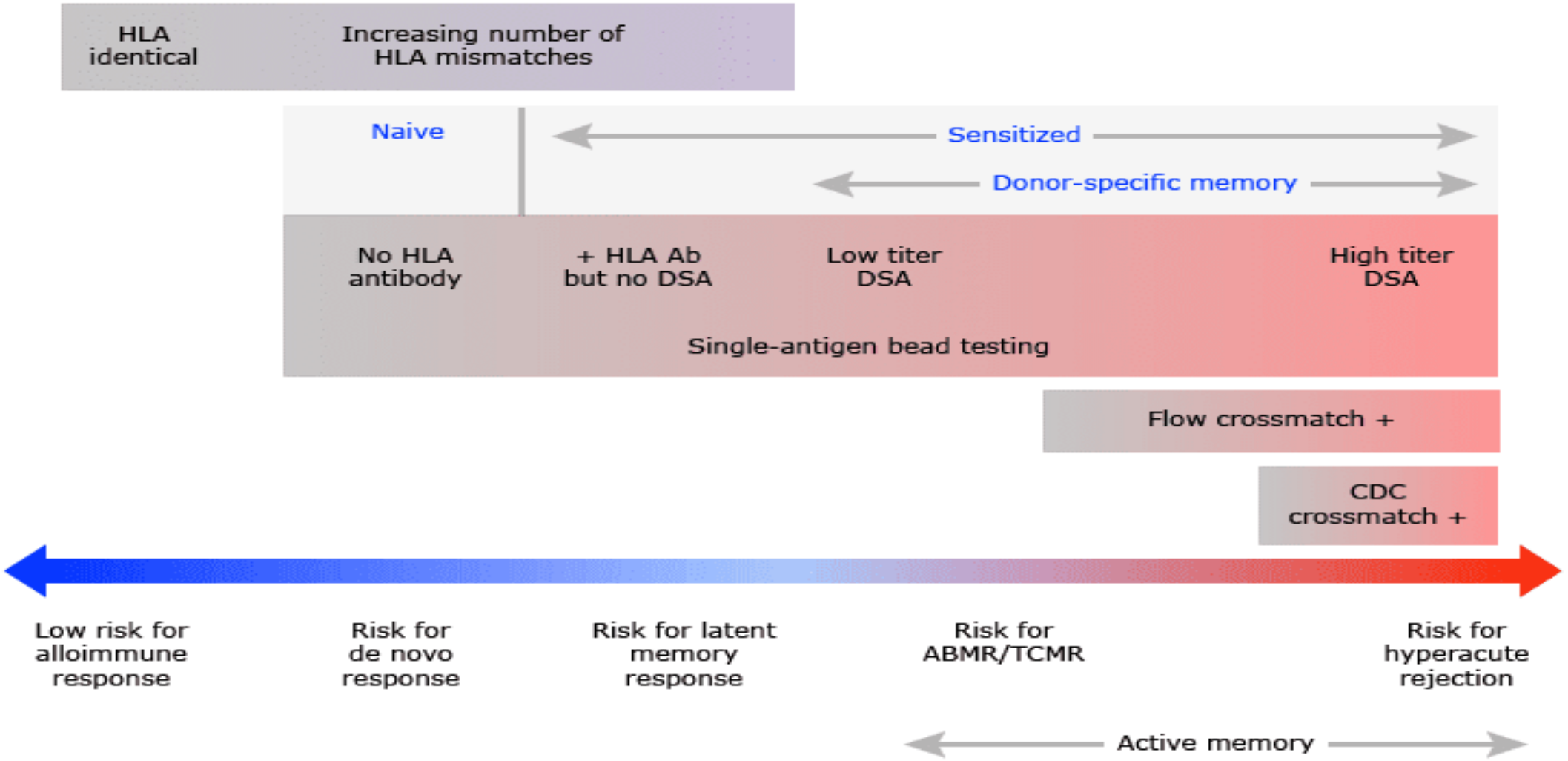
# 1.Patients with preexisting DSA (Immunologic risk assessment)



✓1a.Patients **with** a potential living donor :

- CDC crossmatch Positive **or** flow crossmatch strongly positive:
  - Prefer to use kidney paired donation (KPD) programs, rather than desensitization
    - Enable sensitized patients with immunologically incompatible living donors to be transplanted from other living donors in similar situations who are willing to exchange organs
- Virtual crossmatch positive (antibodies detected by single antigen bead technology) or a mild to moderate flow crossmatch :
  - Human leukocyte antigen (HLA) desensitization strategies:
    - Plasmapheresis
    - rATG -Thymoglobulin
    - Rituximab

✓1b.Patients **without** a potential living donor :

- Employ HLA desensitization strategies

# Monitoring after transplant:

- The monitoring of kidney allograft function in patients with a preexisting DSA before transplant is similar to that performed in nonsensitized patients
  - Monitor  DSA levels at months 1, 3, 6, and 12 posttransplant and then annually
    - Significant rise in DSA or who develop a de novo DSA within the first three months
      - kidney allograft biopsy
  - Pretransplant DSA :
    - Protocol kidney biopsies at months 3 and 12 posttransplant
- Postreperfusion kidney allograft biopsy at the time of transplantation to identify patients at risk for ABMR
  - Positive C4d staining:
    - Plasmapheresis (2-3 sessions), IVIG, Rituximab

# 2.Patients with de novo DSA after transplant

- ✓Common causes :
  - Medication nonadherence
  - Inadequate immunosuppression
    - Use of minimization strategies
  - Acute T cell-mediated (cellular) rejection (TCMR)
  - Malignancy
  - Opportunistic infections
    - BK polyomavirus , CMV infection
- ✓Late-onset ABMR :
  - Monitor DSA annually
  - Allograft biopsies

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# TREATMENT OF ACTIVE ANTIBODY-MEDIATED REJECTION

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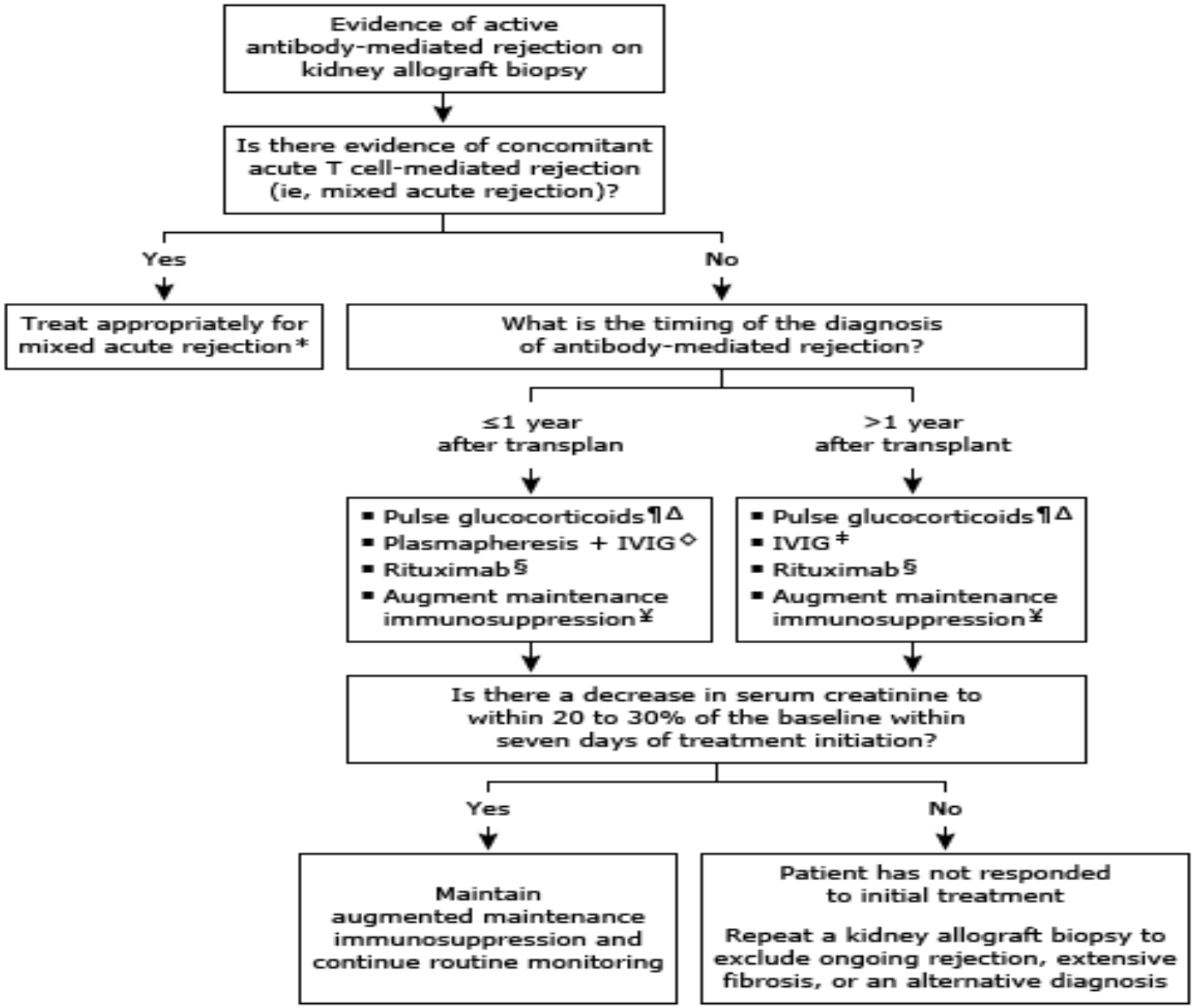
# Goals of therapy

- ✓Reduce the titer of existing pathogenic DSAs
- ✓Eradicate the clonal population of B cells or plasma cells
- ✓Prevent complement activation
- ✓Reduce endothelial injury
- ✓Preserve graft function
  - Complete elimination of DSA commonly does not occur, and to attempt it may lead to dangerous over-immunosuppression
  - **All** patients with evidence of active ABMR on biopsy must be treated
  - C4d-negative ABMR must treated with the same approach that use in C4d-positive ABMR

# Initial treatment of active antibody-mediated rejection of the kidney allograft



# Patients who are ≤1 year posttransplant

- ✓Initial therapy (SOC) combination of:
  - Glucocorticoids
  - Plasmapheresis : Maximum of six sessions
  - IVIG : Total cumulative target dose of at least 1000 mg/kg

- ✓Some experts administer Rituximab:
  - Patient younger than 70 years
  - Better allograft function:
    - eGFR≥20 mL/min/1.73 $m^2$
    - Lower chronicity scores on biopsy
    - Evidence of severe disease (score ≥4 on biopsy)

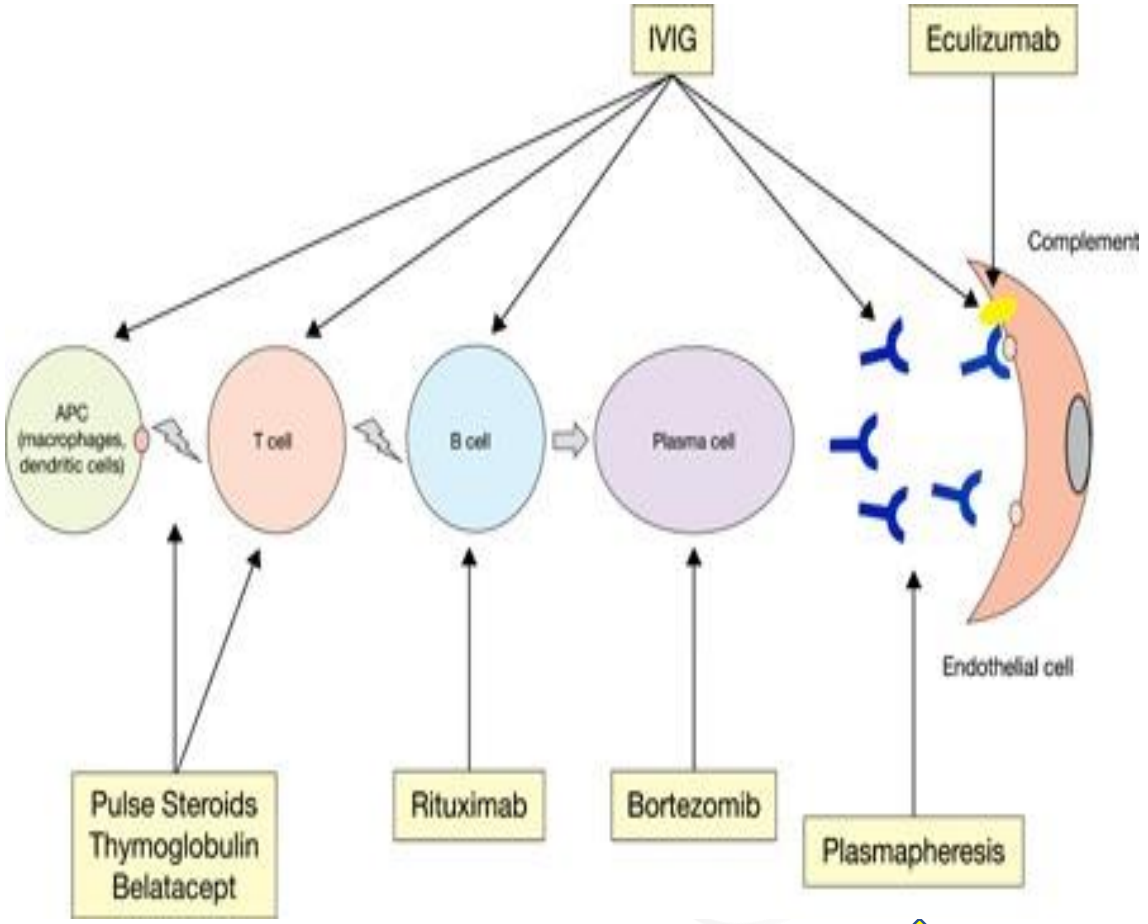
# Glucocorticoids

- ✓Methylprednisolone at a dose of 300 to 500 mg daily for three to five days
  - Followed by a rapid oral prednisone taper to previous maintenance dose
  - Nonadherence :
    - Augment the maintenance prednisone dose

# Plasmapheresis

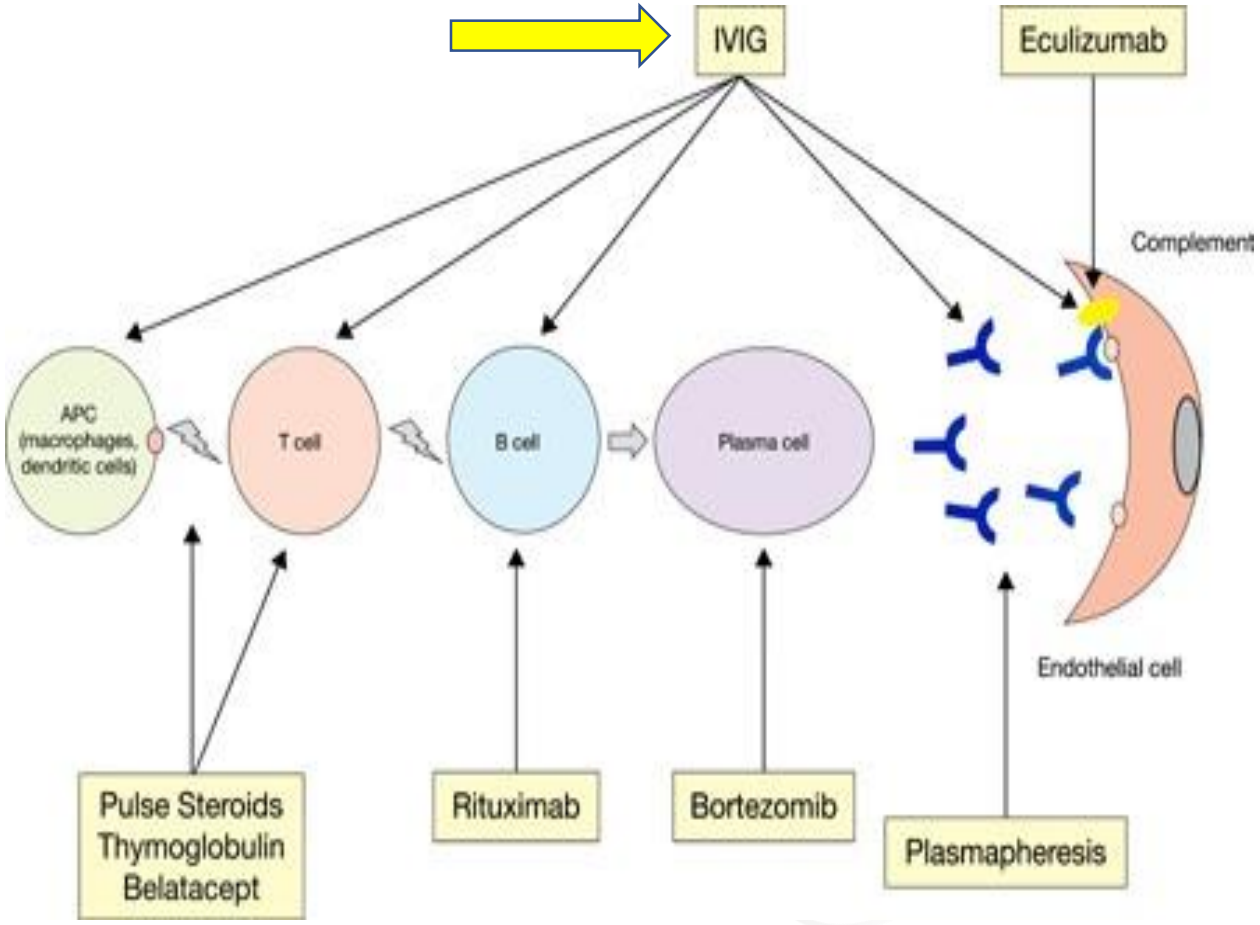
- ✓Daily or every other day for a maximum of six sessions **or**
- ✓Until the serum creatinine is within 20 to 30 percent of the baseline

- ✓Initial treatment is typically a one-and-one-half-volume exchange with albumin
  - Subsequent treatments are a one-volume exchange with albumin
- ✓Every-other-day plasmapheresis schedule as albumin alone:
  - Interval recovery of the PT, PTT, and fibrinogen to acceptable levels
  - Avoids the risk of antigen sensitization



# IVIG

- ✓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
- ✓Scavenger of activated complement



# IVIG

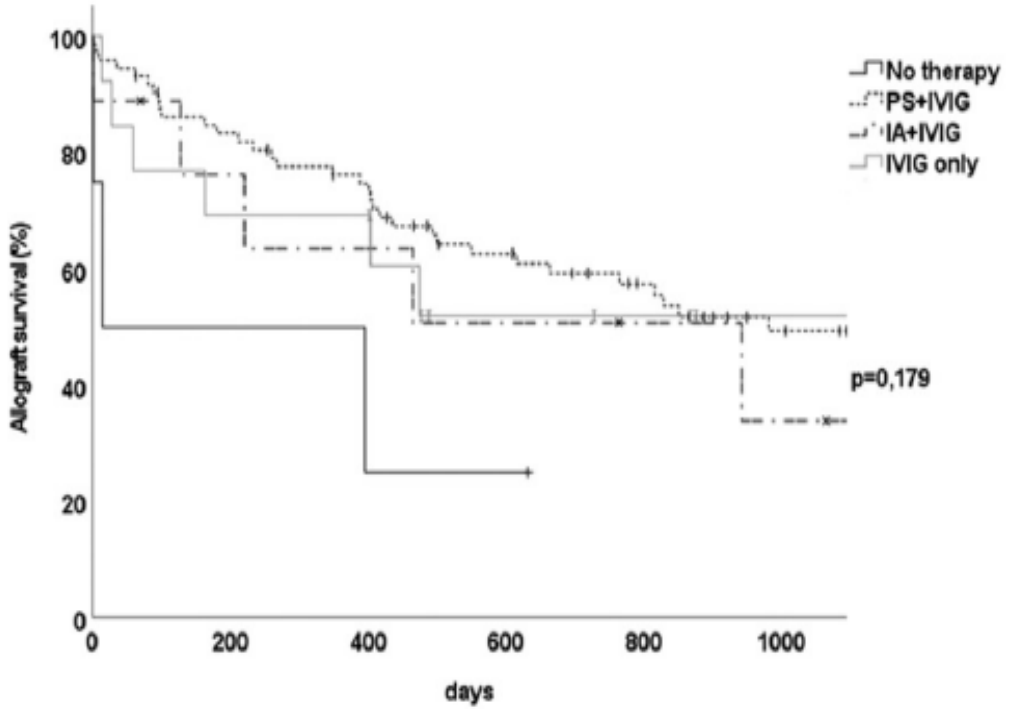
- ✓500 mg/kg/day for one to two days after the final session of plasmapheresis
- ✓In patients with obesity:
  - The IVIG dose based upon the patient's ideal body weight
- ✓Sucrose-free IVIG solutions (5 percent)
  - Decrease the risk of acute kidney injury

# 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.<br>Removal of anti-HLA Ab via plasma exchange correlates with better clinical response in kidney transplant recipients.<br>Intravenous immune globulins have pleiotropic effects including neutralization of antibodies/cytokines/activated components of complement, effects on B cells, T cells, and Fc receptors. | Akiyoshi et al[63]<br>Gelfand[64] |
| Benefit in clinical (observational) studies | Humoral rejection treated with PE/IVIG results in improved renal function.<br>The combination PE/IVIG leads to better removal of anti-HLA antibodies and correlates with better graft survival. | Rocha et al[65]<br>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.<br>KDIGO 2010: Recommendation for PE and IVIG in association with corticosteroids. | Velidedeoglu et al[67]<br>Kasiske et al[68] |
| Most used combination in clinical practice | American Society of Transplantation survey: Most centers utilize a combination of IVIG and plasmapheresis for treatment.<br>The treatment of AMR in kidney transplant recipients: a systematic review. | Burton et al[69]<br>Roberts et al[55] |

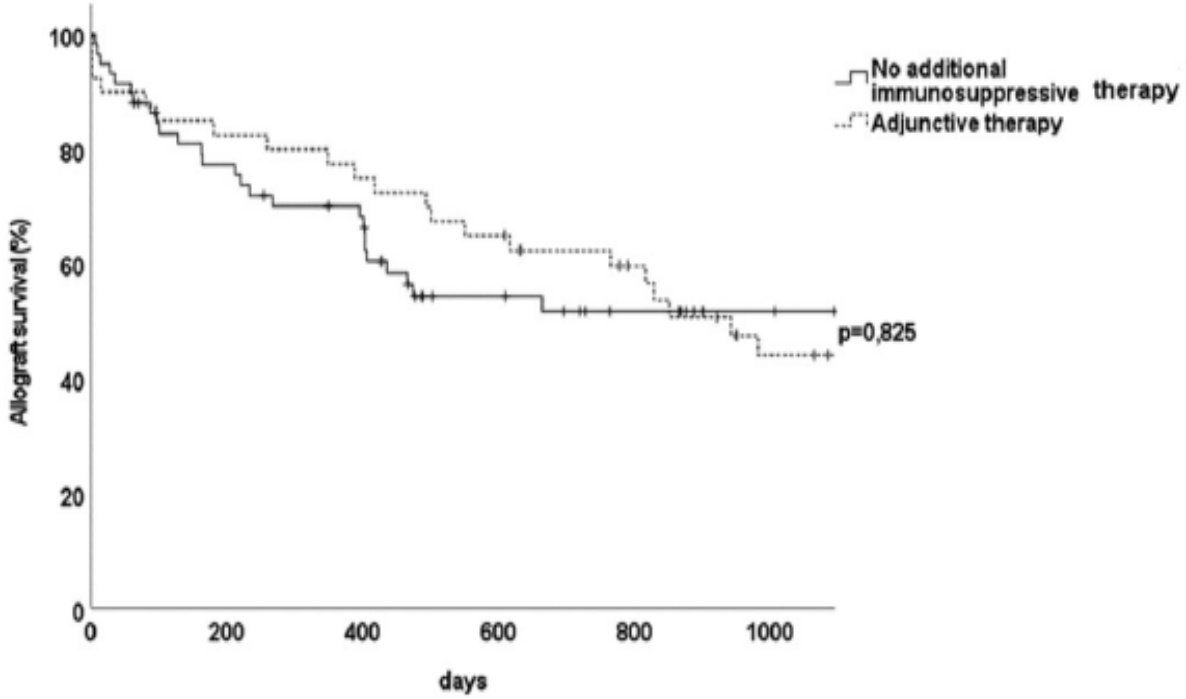
Ab, antibody; AMR, antibody-mediated rejection; Fc, fragment crystallizable; IVIG, intravenous immune globulins; PE, plasma exchange; FDA, Federal Drug Administration; KDIGO, Kidney Disease: Improving Global Outcomes; SOC, standard of care.

## (A) Plasmapheresis plus IVIG vs. immunoadsorption with IVIG and IVIG alone




| | | | | | | |
|---|---|---|---|---|---|---|
| No therapy: | 4 | 2 | 1 | 1 | 0 | 0 |
| PS+IVIG: | 73 | 59 | 51 | 39 | 30 | 21 |
| IA+IVIG: | 9 | 6 | 5 | 4 | 3 | 2 |
| IVIG only: | 13 | 9 | 9 | 4 | 3 | 1 |

## (B) adjunctive immunosuppressive drugs in addition to standard therapy

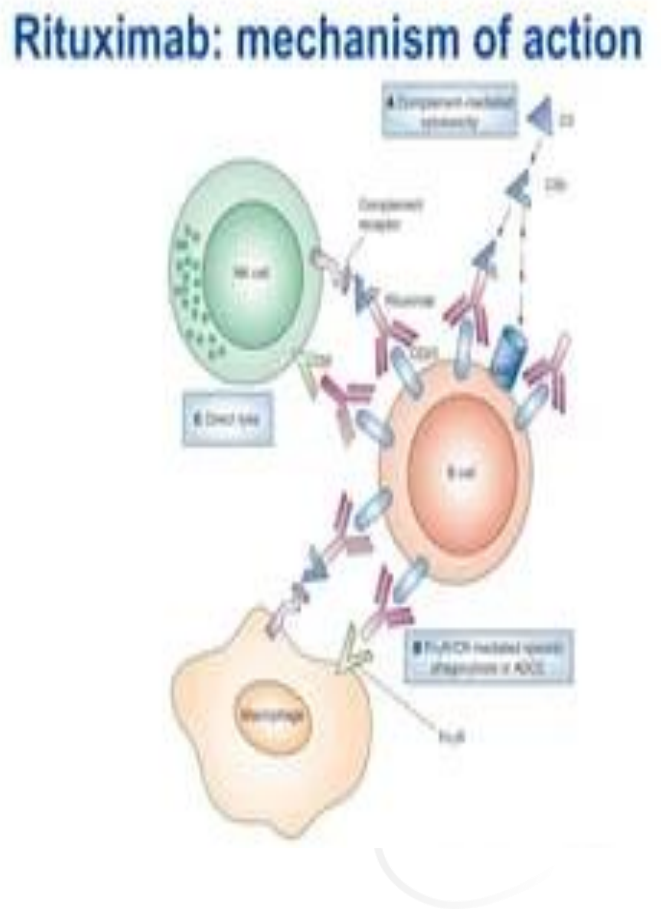



| | | | | | | |
|---|---|---|---|---|---|---|
| No: | 59 | 43 | 36 | 22 | 16 | 11 |
| Adjunctive: | 40 | 33 | 30 | 26 | 20 | 13 |

# Rituximab

- ✓A chimeric monoclonal IgG antibody
- ✓ Against the CD20 antigen expressed on the surface of pre-Band mature B cells
- ✓B cell lysis via both complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity
- ✓If rituximab is given:
  - Single dose of either 200 mg or 375 mg/m$^2$

  After completion of plasmapheresis and <u>IVIG</u>

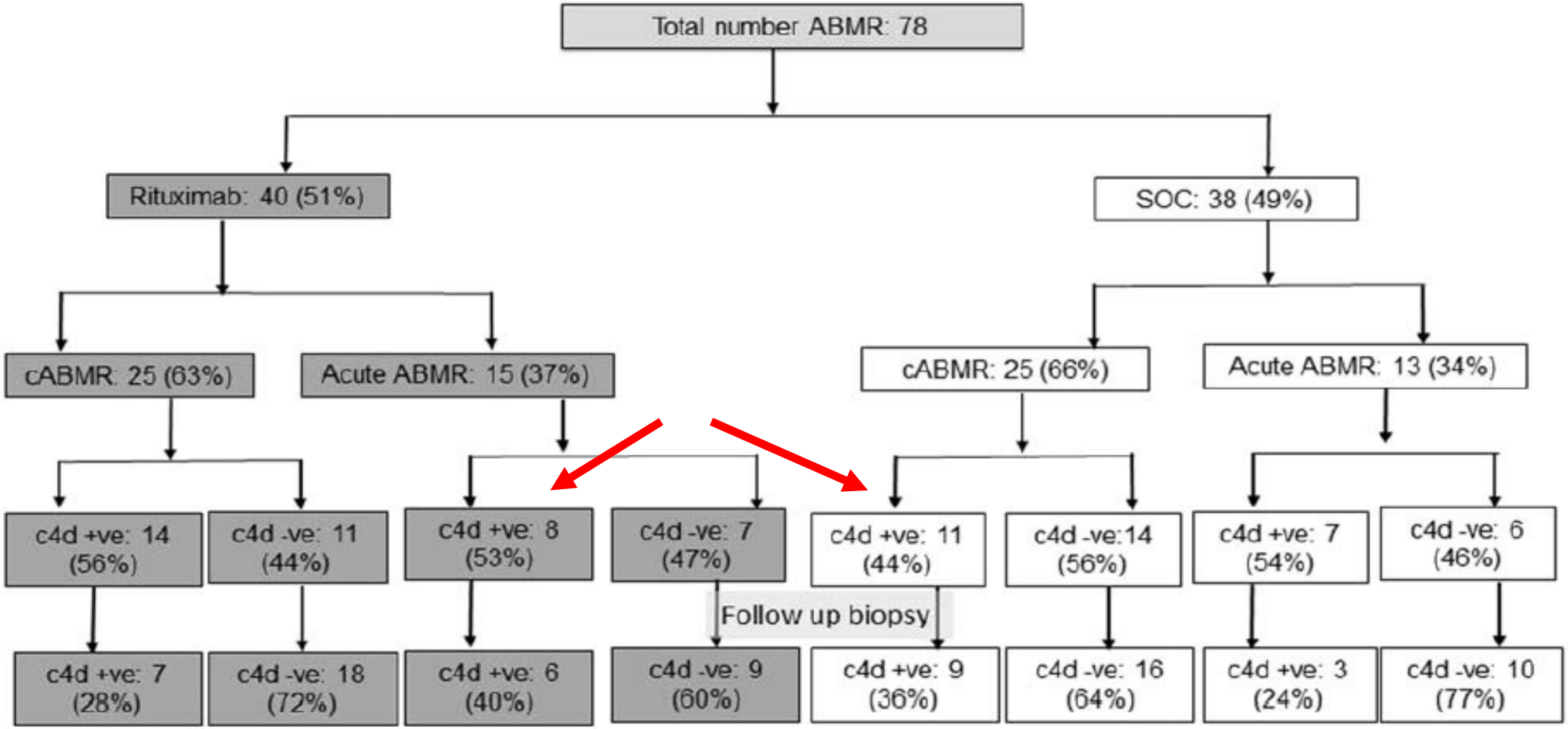


OPEN

# Rituximab and Monitoring Strategies for Late Antibody-Mediated Rejection After Kidney Transplantation

Sandesh Parajuli, MD,[1] Didier A. Mandelbrot, MD,[1] Brenda Muth, NP,[1] Maha Mohamed, MD,[1] Neetika Garg, MD,[1] Fahad Aziz, MD,[1] Robert R. Redfield, MD,[2] Weixiong Zhong, MD, PhD,[3] Brad C. Astor, PhD,[1,4] and Arjang Djamali, MD[1,2]

Transplantation Direct 2017;3:e227; doi: 10.1097/TXD.0000000000000746




C4d positive ABMR decreased on follow-up biopsy in both groups

## Rituximab was associated with improved graft survival

| | | Changes between two biopsies and outcomes | | |
|---|---|---|---|---|
| | | Rituximab | Standard of care | *P* |
| Δ DSA | Mean class I $MFI_{sum}$ | −3637 ± 5134 | −2493 ± 3644 | 0.48 |
| | Mean class II $MFI_{sum}$ | −4559 ± 6938 | −2378 ± 2893 | 0.17 |
| | Mean $MFI_{max}$ | −3033 ± 5179 | −1501 ± 1754 | 0.13 |
| Δ Kidney function | Serum creatinine (mg/dL) | 0 ± 0.6 | 0 ± 0.8 | 0.94 |
| | eGFR (mL/min/1.73 $m^2$) | 0.7 ± 9.2 | −2.8 ± 11.0 | 0.13 |
| | UPC (gm/gm) | 0.2 ± 1.3 | 0.1 ± 1.1 | 0.82 |
| Δ Pathology | Microvascular injury (ptc + g) | −0.9 ± 1.5 | −1.1 ± 1.3 | 0.46 |
| | C4d score (range) | −0.7 ± 1.1 | −0.5 ± 1.1 | 0.43 |
| | Chronicity score (ci + ct + cg + cv) | 0.2 ± 2.1 | 0.6 ± 1.8 | 0.42 |
| Outcome | Serum creatinine 6 months after ABMR (mg/dL) | 1.8 ± 0.7 | 1.8 ± 0.8 | 0.88 |
| | Serum creatinine 12 months after ABMR (mg/dL) | 2.2 ± 1.1 | 2.3 ± 1.2 | 0.76 |
| | Serum creatinine on last follow-up (mg/dL) | 1.96 ± 0.7 | 1.8 ± 0.7 | 0.35 |
| | Mean number of subsequent biopsies | 1.0 ± 1.2 | 1.8 ± 0.8 | <0.001 |
| | Graft loss | 6 | 12 | 0.01 |
| | Death | 0 | 2 | 0.14 |

MFI, mean fluorescence intensity; eGFR, estimated glomerular filtration rate; ABMR, antibody mediated rejection; ptc, peritubular capillaritis; g, glomerulitis; ci, interstitial fibrosis; ct, tubular atrophy; cv, fibrous intimal thickening; cg, allograft glomerulopathy.



Transplantation Direct 2017;3:e227

# A systematic review of the use of rituximab for the treatment of antibody-mediated renal transplant rejection

Transplantation Reviews Volume 31, Issue 2, April 2017, Pages 87-95

## Conclusions

A limited number of published studies suggest that rituximab may have a role in the treatment of AAMR. Therefore, given the current lack of conclusive evidence to support its routine use, it would be more appropriate to view rituximab as a potential **'rescue therapy'** in cases of severe AAMR. However, there is no evidence to support a benefit in the setting of CAMR

# Patients who are ≤1 year posttransplant

- ✓**Not** routinely use in the initial treatment of patients with ABMR:
  - Immunoadsorption
  - Proteasome inhibitors
  - Interleukin (IL)-6 blockade
  - Complement inhibitors
  - Splenectomy

# Patients who are >1 year posttransplant (late onset ABMR)

- ✓Initial therapy with glucocorticoids and IVIG rather than glucocorticoids, IVIG, and plasmapheresis
  - **Lack of evidence supporting the safety and efficacy of plasmapheresis in later-onset ABMR**
- IVIG at a dose of 200 mg/kg every two weeks for three doses
- Some experts administer rituximab_375 mg/m$^2$ after completion of IVIG
  - Patient younger (<70 years)
  - Better allograft function
    - eGFR ≥20 mL/min/1.73 m$^2$
    - Lower chronicity scores on biopsy <8
    - Evidence of severe disease
      - Higher DSA, diffuse C4d staining, or more extensive microvascular inflammation glomerulitis score + peritubular capillary score ≥4 on biopsy

# Patients who are >1 year posttransplant (late onset ABMR)

- ✓There is no high-quality evidence to guide the optimal therapy of patients with ABMR who present after the first year posttransplant

# Prophylactic measures for all patients

- ✓Antimicrobial and antiviral prophylaxis identical to immediate posttransplant period:
  - *Pneumocystis* pneumonia
  - Cytomegalovirus (CMV) infection and disease
  - Herpes simplex infection (in patients who are at low CMV risk) for three months
  - Antifungal prophylaxis
  - Prophylactic histamine-2 (H2) blocker

# Monitoring

- ✓Data on the reversal of ABMR are limited
- ✓One-year graft survival after treatment of clinical and subclinical ABMR is approximately 80 and 95 percent, respectively if they meet all of the following parameters within three months of treatment:
  - Decrease in serum creatinine to within 20 - 30 % of the baseline level
  - Decrease in proteinuria to the baseline level
  - Decrease in immunodominant DSA by >50 percent
  - Resolution of changes associated with ABMR on repeat kidney biopsy
- ✓**Successful response:**
  - **Improvement in serum creatinine within seven days of treatment**

- ✓Patients responsive to initial treatment :
  - Augmented maintenance immunosuppression:
    - Tacrolimus : trough level 20 to 25 percent above the level at the time of rejection
    - Increasing the daily dose of oral prednisone
    - Maximizing the dose of the antiproliferative agent
- ✓Patients unresponsive to initial treatment:
  - Repeat kidney allograft biopsy:
    - Nonviable kidney tissue : discontinue treatment
    - Persistent active ABMR : second-line agents as rescue therapy

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# Second-line therapies for refractory ABMR

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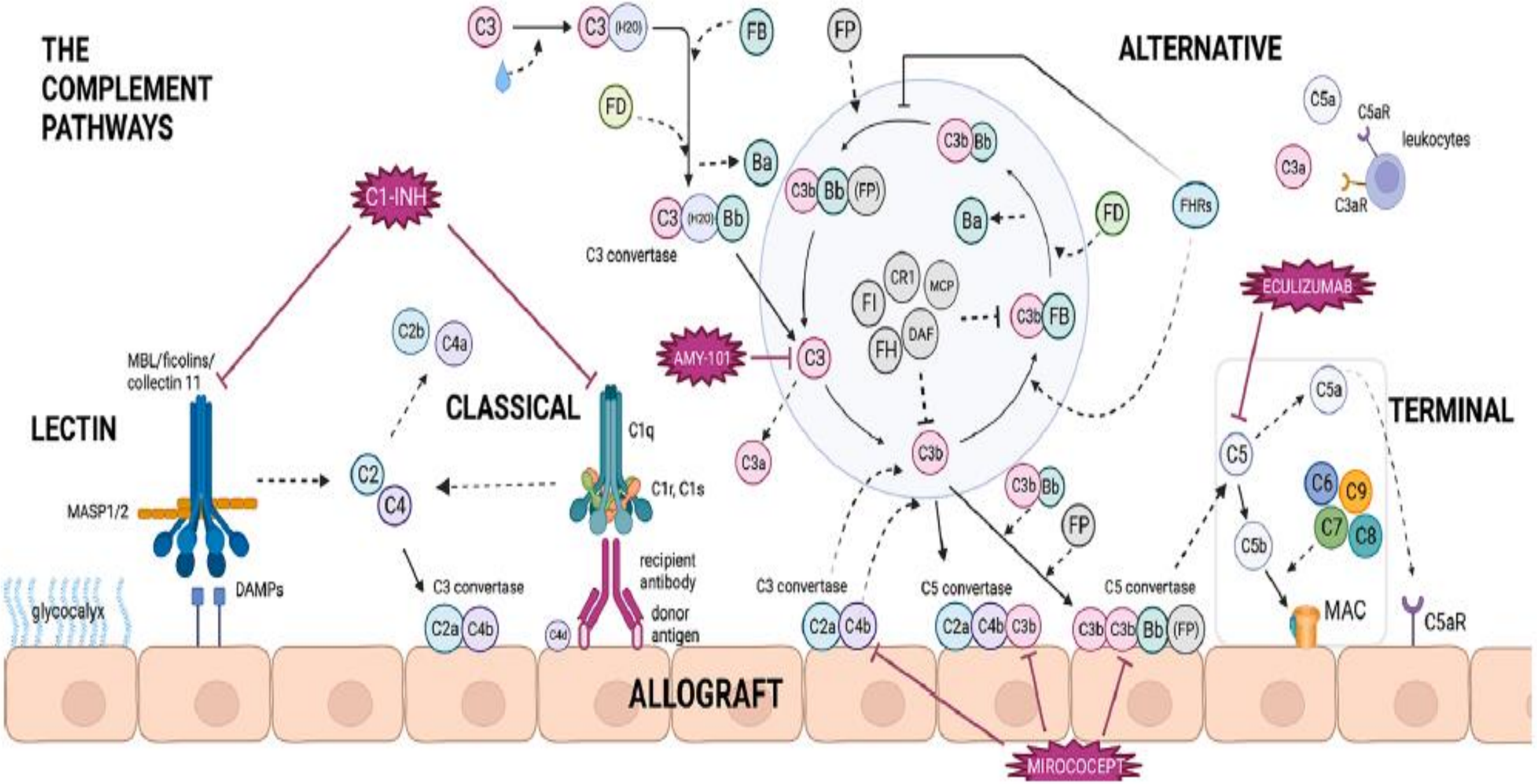
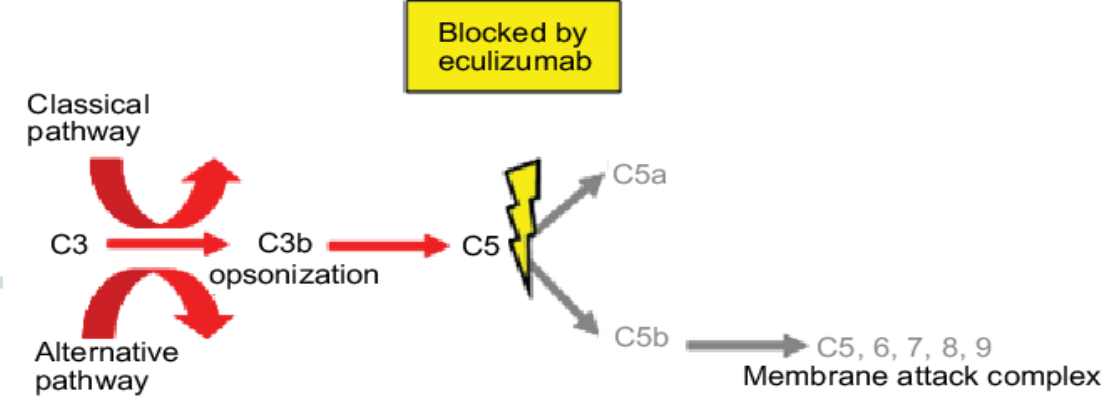


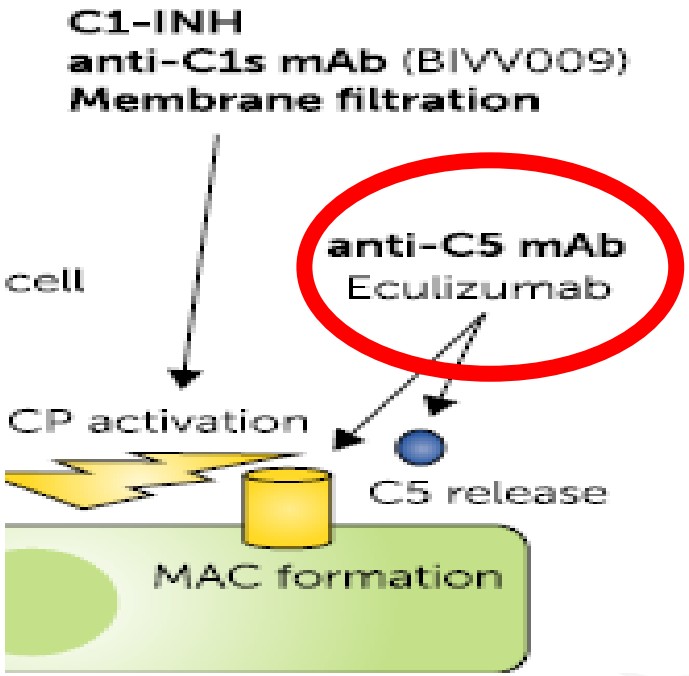



*Immunobiology 228 (2023) 152396*

# Complement inhibitors Eculizumab

- ✓Monoclonal antibody directed against the C5 fragment of the complement cascade and inhibits the generation of the membrane attack complex
- ✓ Eculizumab has not been shown to be effective for the treatment of C4d-negative active and chronic ABMR
  - Limited to acute, complement-mediated processes
- ✓ Warning : life-threatening and fatal meningococcal infections



# Eculizumab

✓Negative results:

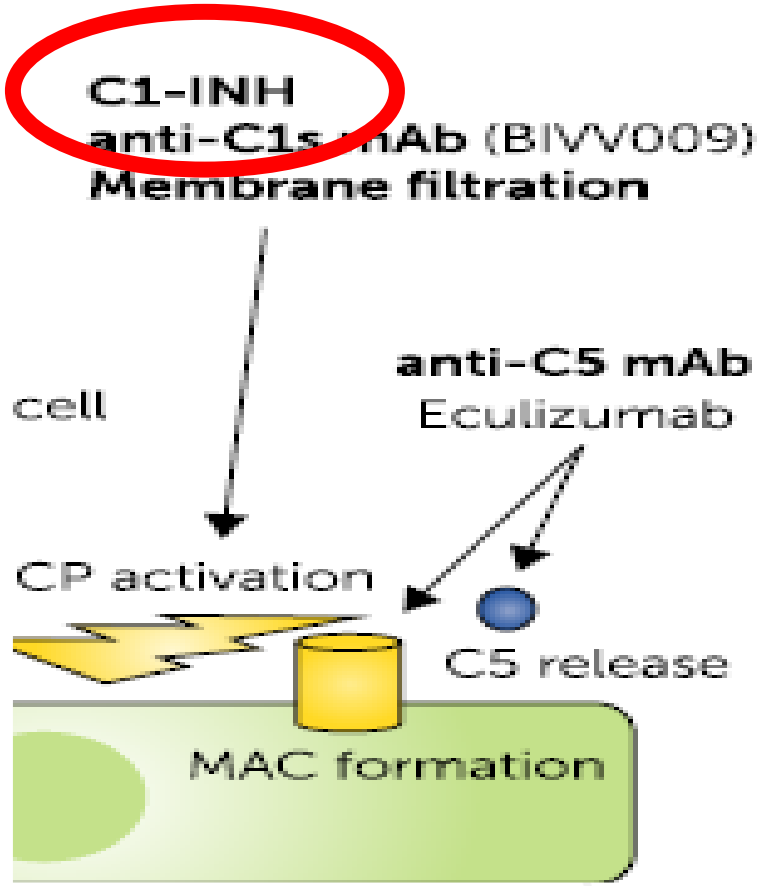
- Not reduce the risk of chronic ABMR **(Cornell et al., 2015)**
- No improve long term outcomes **(Schinstock et al., 2019)**
- No statistical reduction in the primary endpoint (including acute ABMR) **(Marks et al., 2019)**

✓Positive results:

- Treat ABMR with reports of success **(Tan et al., 2019)**
- Success to treat refractory ABMR **(Locke et al., 2009)**
- However, a randomised trial of eculizumab in patients with acute ABMR (NCT01895127) was terminated due to lack of efficacy

# Complement inhibitors
# C1 inhibitors

- ✓Binding of anti-human leukocyte antigen (HLA) DSAs to complement fraction C1q, the first component in the activation of the complement cascade, has been associated with poor graft outcomes and severe phenotypes of ABMR

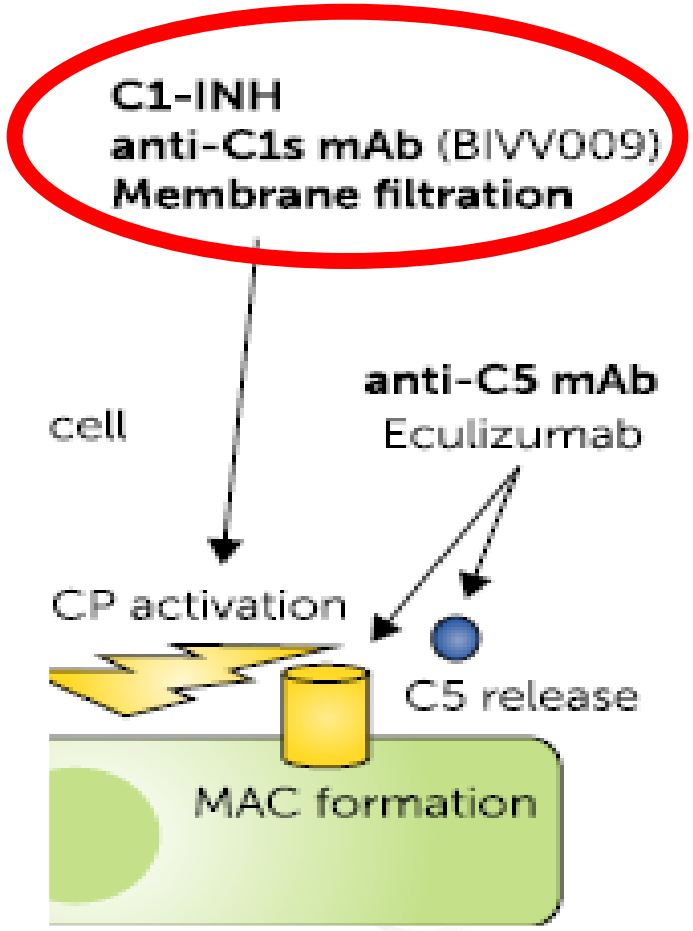


# Complement inhibitors
# C1 inhibitors

- ✓There was no significant difference between the groups in posttreatment kidney histopathology or graft survival on day 20; however, a trend toward sustained improvement in graft function at day 90 was observed in the C1 INH group
  - Am j Transplant 2016 Dec;16(12):3468-3478

# Anti-C1s antibody
## BIVV009

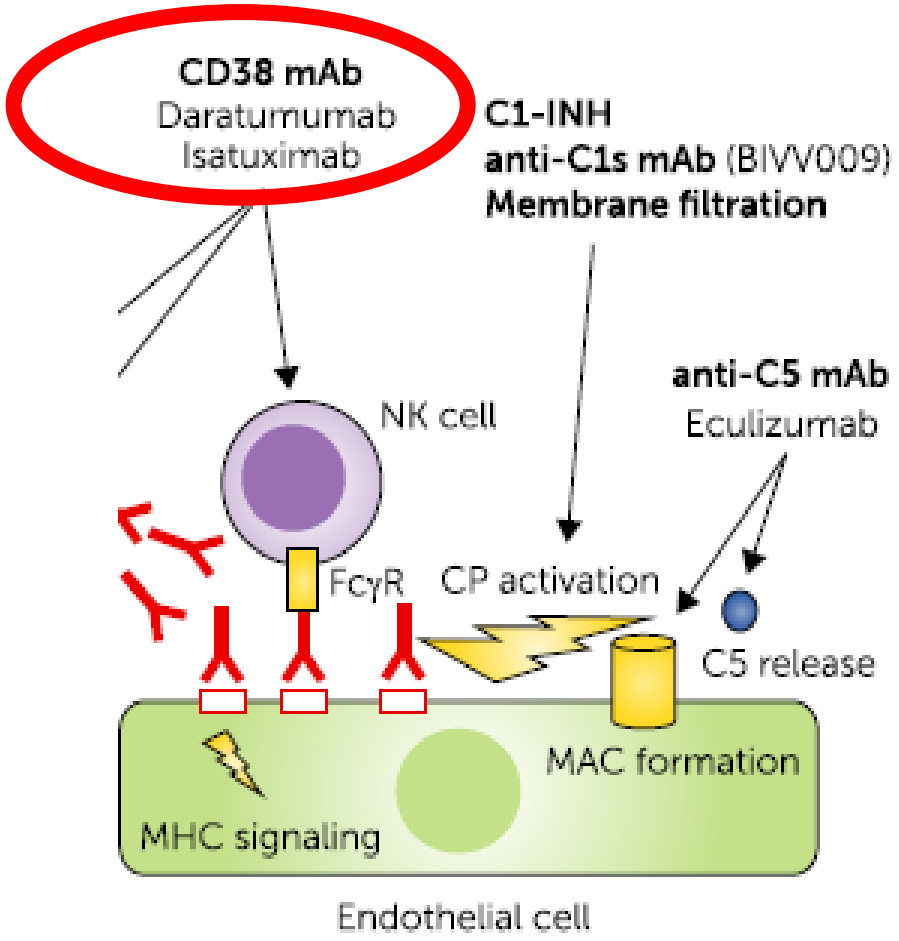
- ✓Selective blockade of the CP
- ✓Follow-up biopsies:
  - C4d staining was markedly reduced, suggesting that CP was also effectively inhibited at tissue level
- ✓No significant effect on features of microcirculation inflammation (glomerulitis or peritubular capillaritis scores)




Am J Transplant 2017; 18: 916

# Targeting CD38
## Daratumumab,Isatuximab

- ✓Induction of complement-dependent cytotoxicity and apoptotic signalling in CD38-expressing cells
- ✓Depletes alloantibody-producing plasma cells
  - An effective way to counteract alloantibody production
- ✓Induction of CD38-expressing NK cells
- ✓Nevertheless, the unique mode of action may be of interest for the prevention and treatment of ABMR

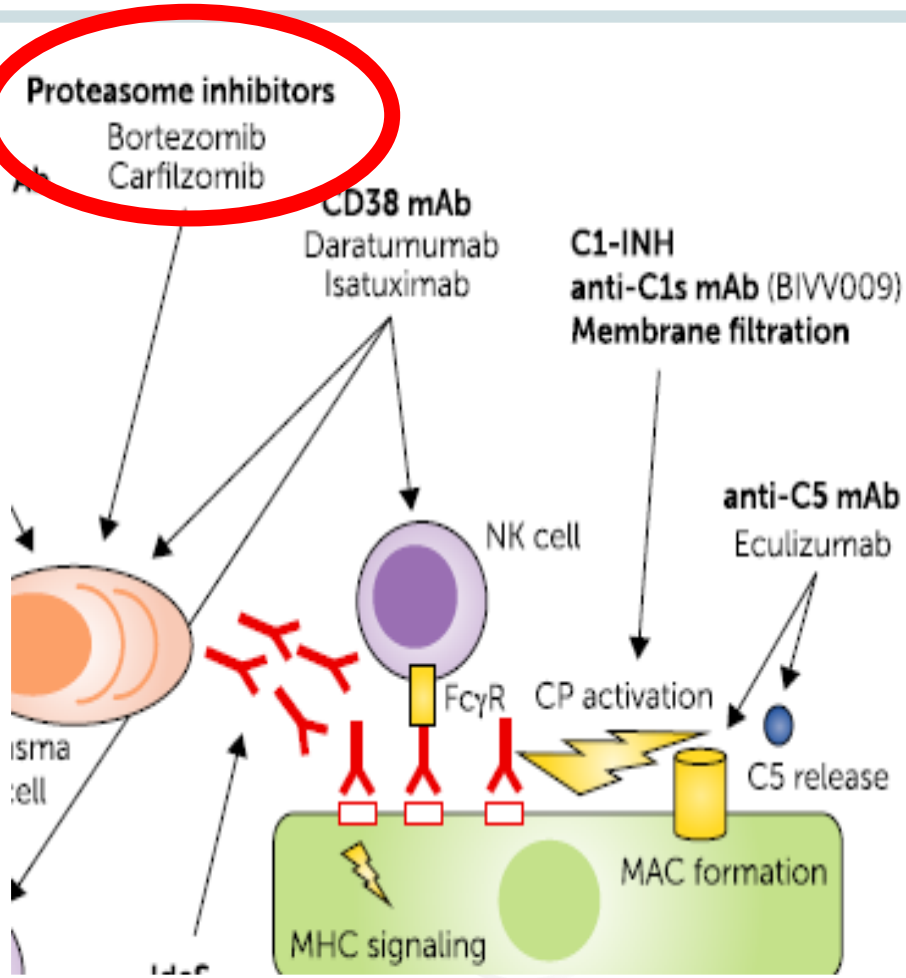



Future Oncol 2018; 14: 1035

# Proteasome inhibitors

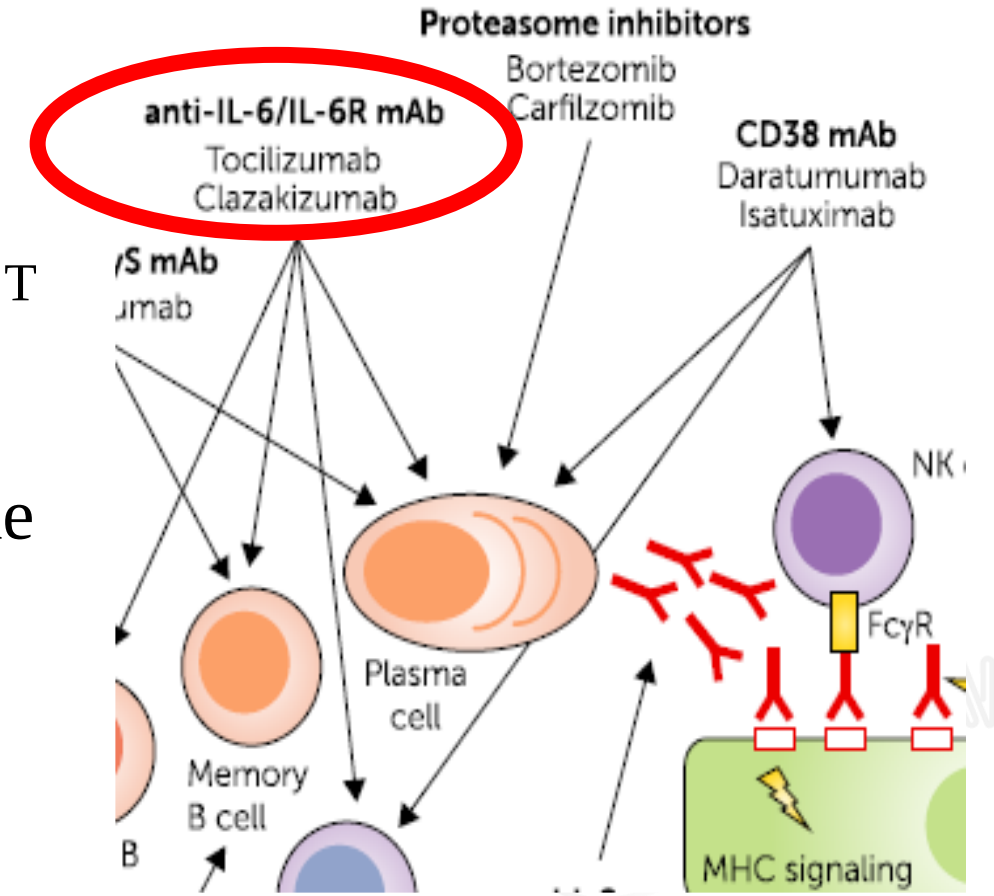
## Bortezomib , Carfilzomib

- ✓ **Early and late acute antibody-mediated rejection differ immunologically and in response to proteasome inhibition** (Transplantation 2011 Jun 15;91(11):1218-26)
- ✓ **Recommended Treatment for Antibody-mediated Rejection After Kidney Transplantation: The 2019 Expert Consensus From the Transplantion Society Working Group** (Transplantation ■ May 2020 ■ Volume 104 ■ Number 5)
  - Follow-up study of 28 patients with active ABMR found that bortezomib therapy was associated with better DSA and histologic response in patients with early (within six months of transplant) rejection but not late ABMR



# IL-6/IL-6R interference
## Tocilizumab , Clazakizumab

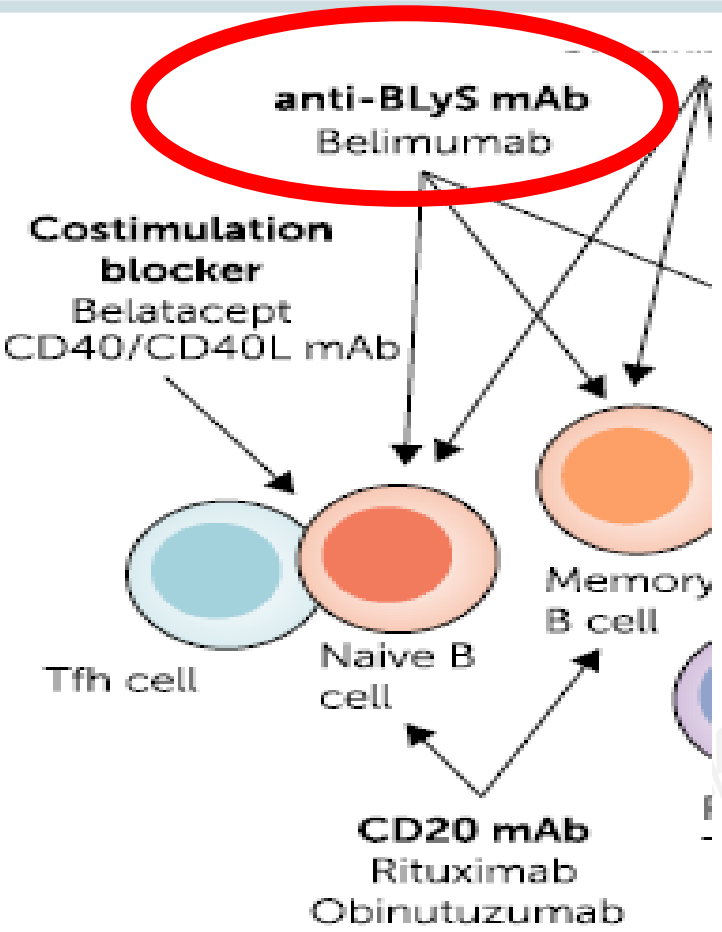
- ✓Slow ABMR progression
  - Effects on B cell immunity
    - Generation and integrity of antibody-producing plasma cells
    - An altered balance between effector and regulatory T cells
- ✓Favourable graft survival rates (80% at 6 y)
- ✓Significant reduction in DSA levels over time
- ✓Stabilization of renal function
- ✓Reduction in microcirculation inflammation and C4d staining in follow-up biopsies




Am J Transplant 2017; 17: 2381.

# Targeting B-lymphocyte stimulator (BLyS)
## Belimumab

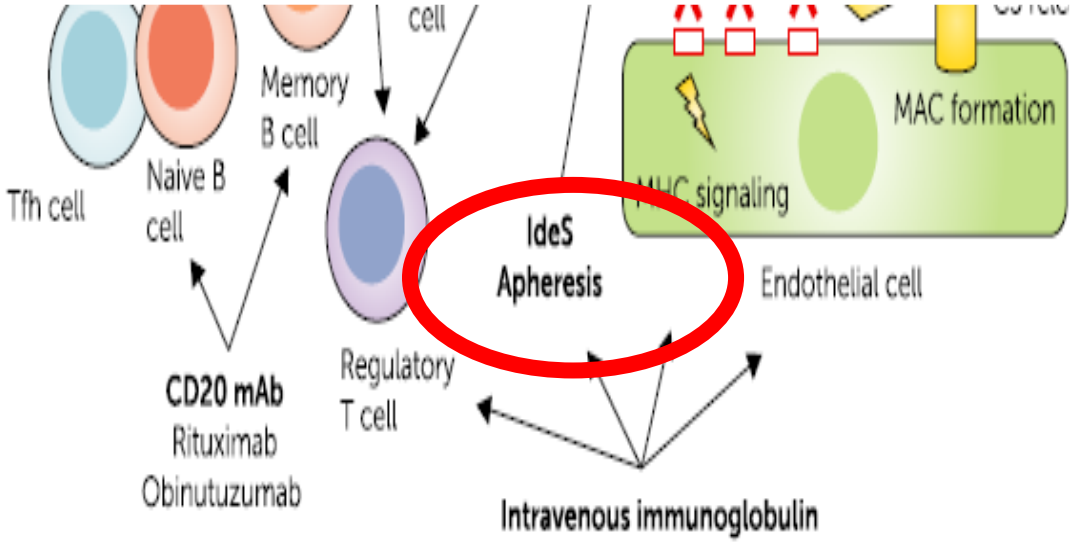
- ✓A cytokine that enhances B cell survival and proliferation and significantly contributes to the plasma cell niche
- ✓There was no significant effect on the primary endpoint, naive B cell counts in peripheral blood from baseline to week 24




Lancet 2018; 391: 2619

# Apheresis (PP, immunoadsorption)

- ✓Deplete circulating alloantibodies
- ✓Combined use of a porous membrane filter and conventional immunoadsorption:
  - Eliminate IgG
  - Markedly enhance the depletion of macromolecules
    - IgM and CP key component C1q




- ✓Treatment of Chronic Active Antibody Mediated Rejection After Kidney Transplantation by Double-Filtration PlasmaPheresis or Plasma Exchange (DFPP)

**NIH U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/show/NCT03436134. Published February 16, 2018.**

# Immunoglobulin G–degrading enzyme of *Streptococcus pyogenes* (IdeS)

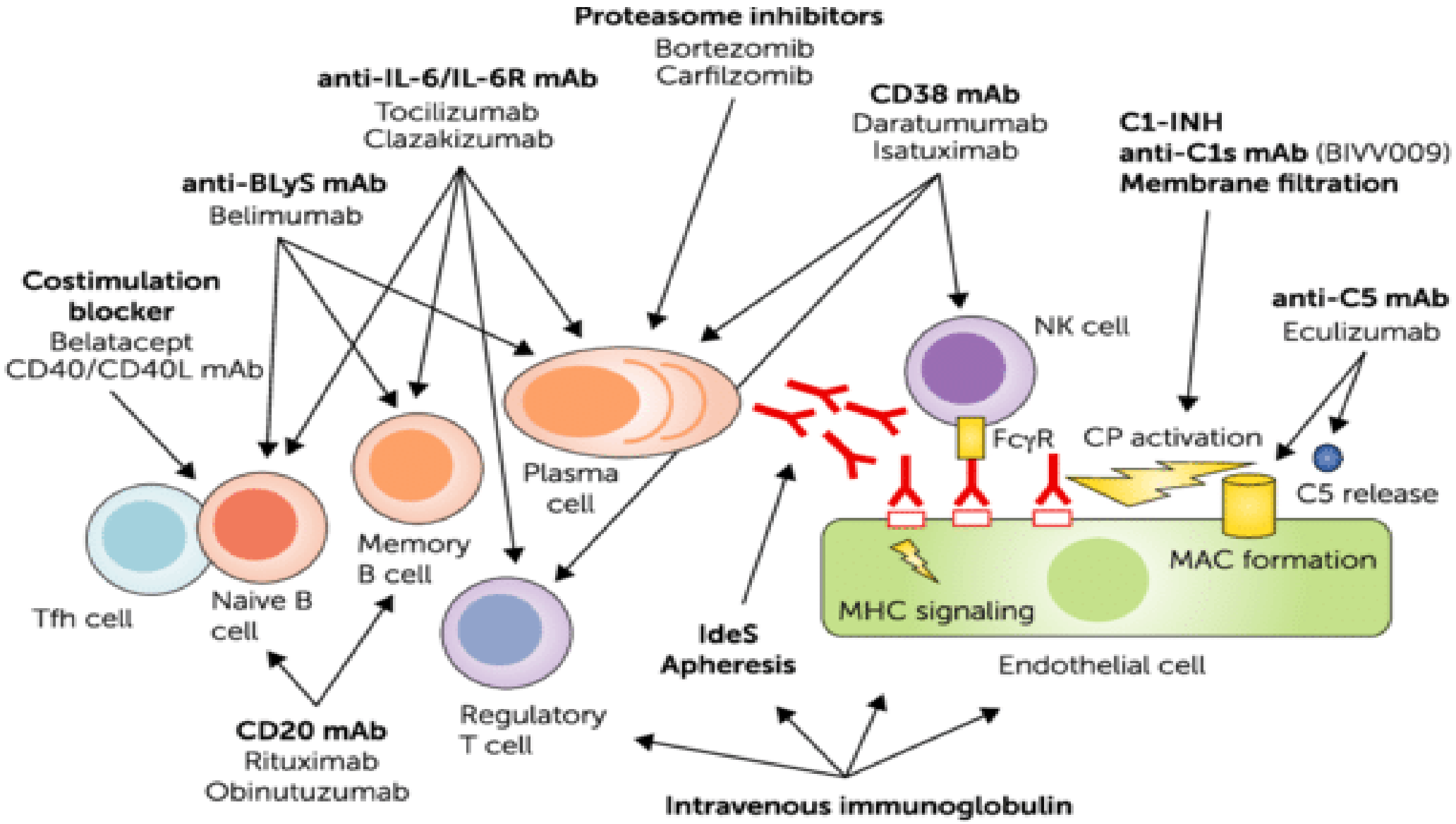
- ✓Enzymatic degradation of alloantibodies
- ✓Transient cleavage of the IgG type of B cell receptor:
  - Profound inhibition of receptor signalling and memory B cell activation
- ✓Major challenges:
  - IdeS also inactivates therapeutic antibodies (IVIG, Rituximab, rATG)
  - May not be able to considerably affect rebound antibody responses

**Lonze BE, Tatapudi VS, Weldon EP, et al. IdeS (Imlifidase): a novel agent that cleaves human IgG and permits successful kidney transplantation across high-strength donor-specific antibody. Ann Surg 2018; 268: 488.**

# Splenectomy

- ✓As a salvage procedure for severe early AMR
- ✓ It must be performed rapidly after the onset of early AMR to be effective
- ✓Designing a proper study would be challenging

**Transplantation ■ May 2020 ■ Volume 104 ■ Number 5**


Proteasome inhibitors
Bortezomib
Carfilzomib
anti-IL-6/IL-6R mAb
Tocilizumab
Clazakizumab
CD38 mAb
Daratumumab
Isatuximab
C1-INH
anti-C1s mAb (BIVV009)
Membrane filtration
anti-BLyS mAb
Belimumab
Costimulation blocker
Belatacept
CD40/CD40L mAb
anti-C5 mAb
Eculizumab
NK cell
Plasma cell
FcγR
CP activation
C5 release
Memory B cell
MAC formation
Tfh cell
Naive B cell
MHC signaling
IdeS
Apheresis
Endothelial cell
Regulatory T cell
CD20 mAb
Rituximab
Obinutuzumab
Intravenous immunoglobulin

Review

OPEN

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

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*Transplantation* 2020;104: 911–922

# CONCLUSIONS

- ✓Despite the severity of the problem and poor outcomes for patients who develop AMR, there is very little high level evidence to support the use of any therapy
- ✓Most trials in this area have been small investigator-initiated studies with small numbers of participants, lacking appropriate controls
- ✓No clear treatment regimens to recommend and there are no approved treatments
- ✓Important to define a standard of care for AMR
- ✓Better characterization of the different forms of AMR based on pathophysiology, histology, as well as clinical and genetic phenotypes is needed