Complement blockade Post-Kidney Transplantation

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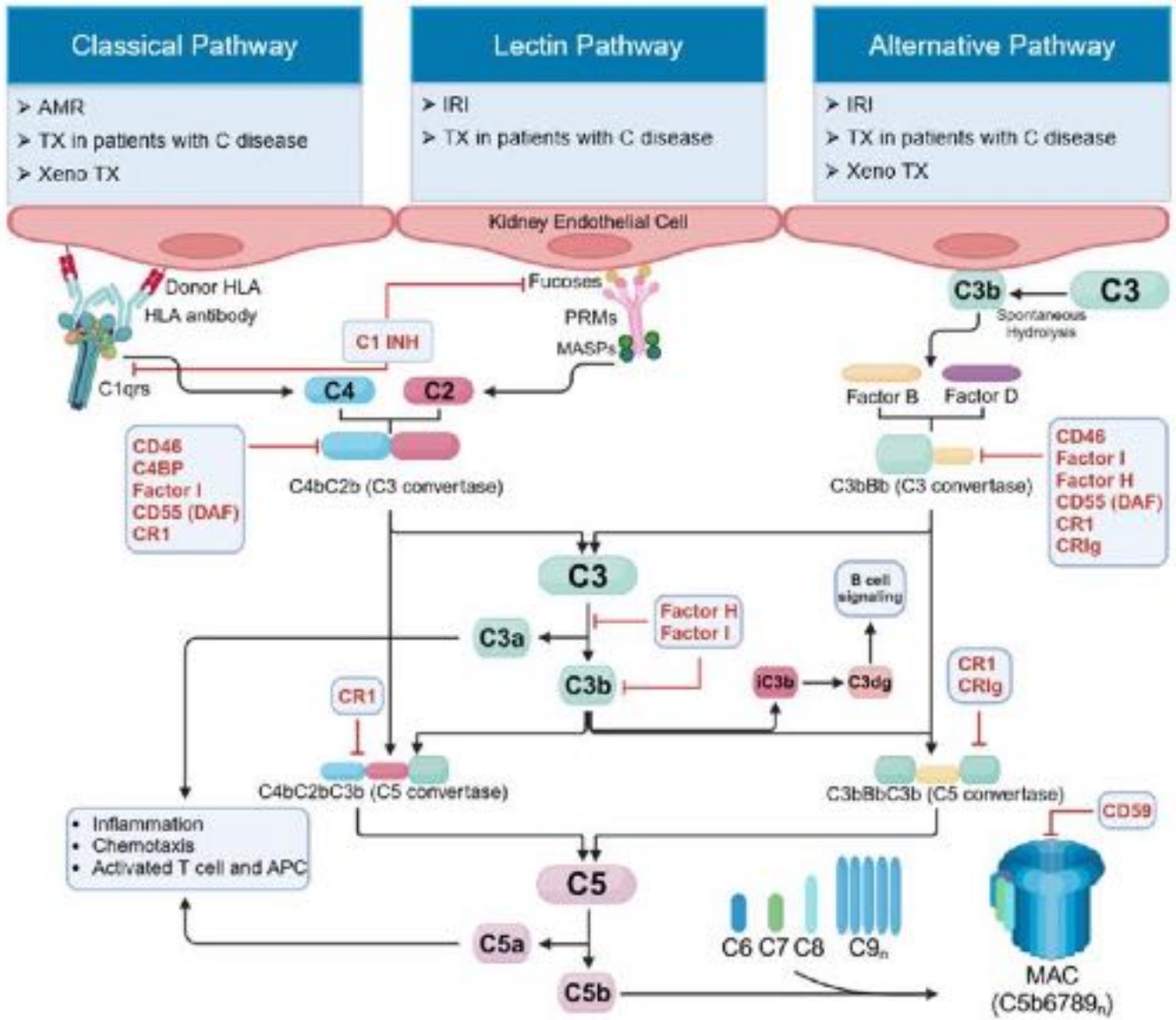
Agenda

- Introduction
- Indications
  - Prophylactic
  - Therapeutic
- Complement-targeting therapy in transplantation
- Risk and side effects
- Considerations

Introduction

- Complement system is an essential component of the innate immune system
- It has a protective role for defence against pathogens, the clearance of immune complexes and cell debris
- Complement activation occurs through 3 pathways: classical, lectin and alternative
- All three complement activation pathways converge with the cleavage of C3 into C3b and C3a by the C3 convertases, which starts the terminal pathway and ends in formation of the MAC through the assembly of C5b-C9


Classical Pathway
➢ AMR
➢ TX in patients with C disease
➢ Xeno TX
Lectin Pathway
➢ IRI
➢ TX in patients with C disease
Alternative Pathway
➢ IRI
➢ TX in patients with C disease
➢ Xeno TX
Kidney Endothelial Cell
Donor HLA
HLA antibody
C1qrs
C1 INH
Fucoses
PRMs
MASPs
C4
C2
C4bC2b (C3 convertase)
CD46
C4BP
Factor I
CD55 (DAF)
CR1
C3b
C3
Spontaneous Hydrolysis
Factor B
Factor D
C3bBb (C3 convertase)
CD46
Factor I
Factor H
CD55 (DAF)
CR1
CRIg
C3
C3a
Factor H
Factor I
C3b
B cell signaling
iC3b
C3dg
CR1
CR1
CRIg
C4bC2bC3b (C5 convertase)
C3bBbC3b (C5 convertase)
CD59
• Inflammation
• Chemotaxis
• Activated T cell and APC
C5
C5a
C5b
C6 C7 C8 C9n
MAC
(C5b6789n)

Introduction

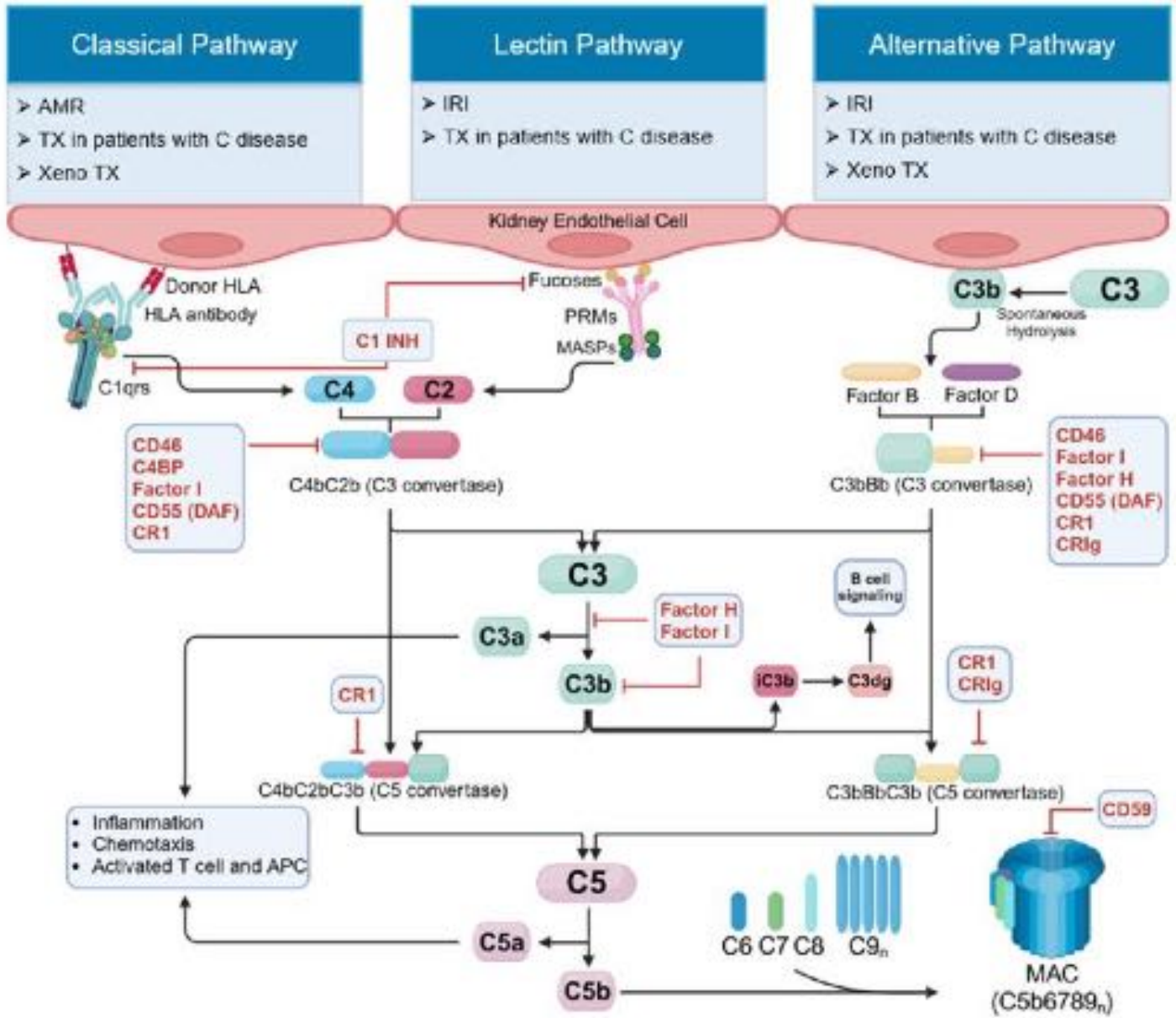
- Complement activation post kidney transplantation could lead to severe damage in the allograft affecting the outcome of transplantation
- It is involved in:

➢ **Recurrence of the primary kidney disease** (complement-mediated)

- Atypical hemolytic uremic syndrome
- C3 glomerulopathy

➢ **Ischemia–reperfusion injury (I/R) and delayed graft function (DGF)**

➢ **Antibody-mediated rejection**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Introduction

- Many drugs acting by complement inhibition that have been studied in kidney transplantation
- Currently, the bulk of data concerns complement factor 5 inhibitor

Indications

Prevention and treatment of recurrence of the primary kidney disease

Atypical hemolytic uremic syndrome

- Complement factor 5 inhibitor is used for **prophylaxis** in high-risk and moderate-risk recipients to prevent recurrence

- **High risk:**

- History of recurrence with a previous allograft
- Pathogenic variant of the CFH/C3/CFB genes

Atypical hemolytic uremic syndrome

- **Moderate risk:**

➢Negative complement screening result

➢Pathogenic variant in the CFI gene

➢Detectable circulating anti-CFH antibody

- **Low risk:**

➢Isolated pathogenic variants in MCP or DGKE genes

➢Anti-CFH antibodies no longer detected at the time of transplantation

C3 glomerulopathy

- Clinical trials in native and recurrent C3 glomerulopathy after kidney transplant
- Complement factor 5 inhibitor

➢ Stabilization of the graft function with mild histological improvement

➢ When?

C3 glomerulopathy

- Clinical trials focused on factor B inhibitor and C3 and C3b inhibitor.

➢Reduction in proteinuria, stabilization of eGFR and reduction in C3c staining

➢Waiting for approval

Indications

Prevention of ischemia reperfusion and delayed graft function

Ischemia–Reperfusion Injury

- All kidney grafts suffer from I/R but to a variable extent
- A part of this injury is complement dependent, resulting in extensive endothelial cell damage
- So, blockade of complement could protect the organ
- I/R….. complement activation (locally and systemically)…...inflammation…. tubular cell injury and delayed graft function

Ischemia–Reperfusion Injury

- Tubular cells produce C3 leading to the activation of the C5 convertase, the release of C3a and C5a (anaphylatoxins) recruiting inflammatory cells, and tubular cells are injured by the C5b-9 complex.
- It is currently admitted that the lectin pathway is the main activation pathway, whereas the alternative amplified the injury.

Ischemia–Reperfusion Injury

- Increased levels of soluble C5b-9 detected after reperfusion of deceased donor kidneys but not in living donor kidneys
- Complement activation was shown to be observed in brain death donors before I/R as demonstrated by increased expression of complement factors in donor organs and systemic complement activation

Clinical trials targeting complement in ischemia reperfusion and delayed graft function

Prevention of DGF	Eculizumab 1200 mg IV prior to reperfusion of the allograft and 900 mg 12–24 h post-transplantation ($n = 142$) vs placebo ($n = 146$)	Eculizumab treatment did not significantly reduce DGF in transplanted kidneys	Completed
Prevention and treatment of IRI in pediatric kidney transplantation	Eculizumab 1200 mg/m^2 IV 1 h before graft reperfusion in pediatric patients ($n = 29$) vs nontreated ($n = 28$)	Eculizumab was associated with better early graft function and improved graft morphology; however, there was an unacceptably high number of early graft losses among the eculizumab-treated children	Completed
Prevention DGF and IRI	C1 Esterase inhibitor (Berinert®): 50 U/kg bw IV on day of transplantation and 24 h post-transplantation ($n = 35$) vs placebo ($n = 35$)	No significant difference in frequency of DGF but duration was shorter in C1-esterase inhibitor group. Treatment of patients at risk for IRI and DGF with	Completed

Indications

Prevention and treatment of Antibody-mediated rejection

Antibody-mediated rejection

- It is one of the most common causes of graft deterioration
- It is associated with the presence of DSAs in the circulation of sensitized recipients
- Inhibition of the terminal complement pathway by the C5 inhibitor has been used for the treatment of ABMR with some success in patients with evidence for complement-dependent ABMR (C5b-9 positivity)
- Particularly with early-onset rejection and high HLA antibody reactivity
- Additionally, C3b, by converting to C3dg, promotes the activation of B cells, enhancing their proliferation and antibody production

Antibody-mediated rejection

- C5b-9 plays a pathogenic role only in selected ABMR cases, and such patients should be accurately identified before treatment
- Eculizumab can be broadly applied in ABMR remains debatable
- **C5 blockade** has the advantage of leaving the C3b-opsonization capacity intact for defence against pathogens, the clearance of immune complexes and cell debris but also allows excessive production of C3a possessing inflammatory properties

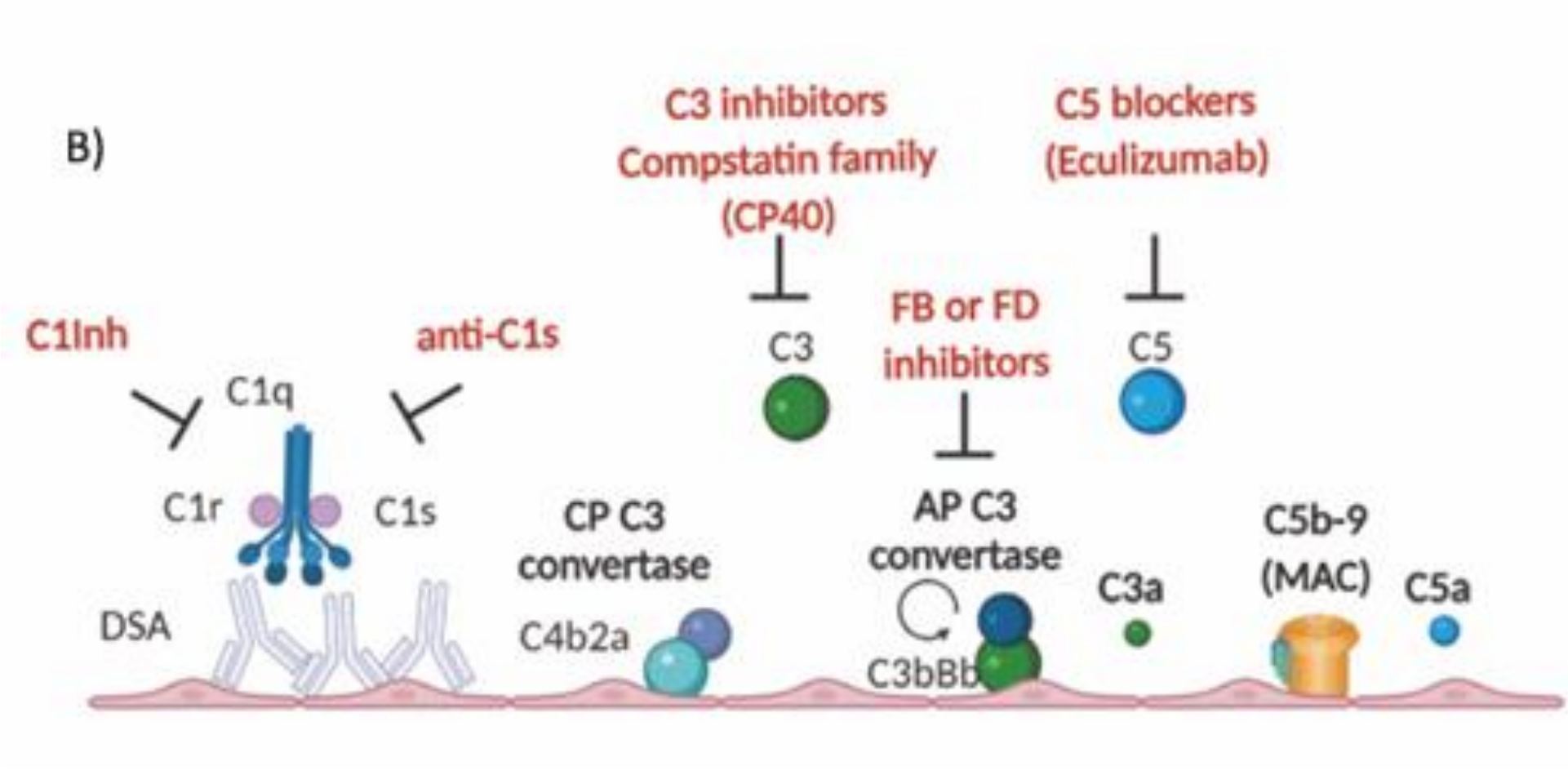
Antibody-mediated rejection

- Other complement blocking strategies are also currently available in clinical trials.
- **C3 inhibitory peptide**, Cp40, was administered to HLA-sensitized primates to prevent ABMR after kidney transplantation (non human)

Clinical trials targeting complement in ABMR

Purpose	Study group	Results	Status
Prevention of ABMR in positive crossmatch living donor kidney transplantation	Eculizumab 1200 mg IV prior to surgery and doses of 600 mg on day 1 followed by 4 weekly doses. After testing for DSAs, treatment was continued or discontinued ($n = 26$)	Inhibition of terminal complement activation with eculizumab decreases the incidence of early ABMR in sensitized renal transplant recipients compared with a historical control group without eculizumab treatment	Completed
Prevention of ABMR in living donor kidney transplant recipients requiring desensitization therapy	Eculizumab 1200 mg administered IV before reperfusion of the allograft (day 0) with subsequent 900-mg doses given on days 1, 7, 14, 21 and 28 and 1200 mg at post-transplant weeks 5, 7, 9 ($n = 80$)	Eculizumab was well tolerated and no new safety concerns were identified. Eculizumab has the potential to provide prophylaxis against injury caused by active ABMR	Completed
Treatment of active ABMR in recipients of donor-sensitized kidney transplants	C1-esterase inhibitor CINRYZE®: 7 doses over a 2-week period: an initial IV infusion of 5000 U on day 1, followed by 2500 U IV on days 3, 5, 7, 9, 11, and 13 ($n = 9$) vs placebo ($n = 9$)	While the study's primary endpoint, a difference between groups in day 20 pathology or graft survival, was not achieved, the C1 INH group demonstrated a trend toward sustained improvement in renal function. Six-month biopsies performed in 14 subjects (C1 INH = 7, placebo = 7) showed no transplant glomerulopathy (TG) (PTC+cg≥1b) in the C1 INH group, whereas 3 of 7 placebo subjects had TG	Completed

Antibody-mediated rejection



Complement-targeting therapies in transplantation

- Many clinical studies are underway on complement-targeting therapies.
- These drugs are being investigated to reduce risks in organ transplantation, prevent rejection, treat ABMR, and decrease DGF and IR

Eculizumab

- C5 Inhibitor
- Monoclonal antibody blocking the complement cascade at the C5
- IV infusion
- Its efficacy has been demonstrated in the treatment and prevention of recurrence of atypical HUS with an overall good safety profile
- Prevention of I/R and DGF after kidney transplantation
- Prevention and treatment of ABMR

Iptacopan

- Factor B inhibitor
- Oral
- Approved by for the treatment of high-risk native IgA nephropathy based on trials
- Case series in recurrent IgA nephropathy: (in combination with short-term steroids)

➢ Significant reductions in proteinuria

➢ Resolution of microscopic hematuria

➢ But one individual developed progressive graft dysfunction

Iptacopan

- Clinical trials in native and recurrent C3 glomerulopathy after kidney transplant:

➢Reduction in proteinuria

➢Stabilization of eGFR

➢Reduction in C3c staining

Pegcetacoplan

- C3 and C3b inhibitor
- Subcutaneous
- Clinical trials in native and recurrent C3 glomerulopathy after kidney transplant

➢Reduction in proteinuria

➢Stabilization of eGFR

➢Reduction in C3c staining

C1 Esterase inhibitor

- It is a glycosylated serine protease inhibitor
- It limits proinflammation and coagulation by clearing C3 and C4 fragments
- IV infusion
- It has shown promise in:

➢Managing ABMR

➢Improved eGFR in refractory ABMR with high dose IVIG

C1 Esterase inhibitor

- Reducing IRI and DGF risk by
  - Inhibiting complement activation
  - Decreasing inflammation, tubulointerstitial damage
  - Reduced dialysis requirements
  - Improved renal function and lowered graft loss rates without increasing adverse events

Risk and side effects

- **Infections** that endanger the transplant and the patient
- One threatening side effect of eculizumab therapy is the occurrence of meningococcal infections

Considerations

- **Vaccination**

➢Critical prerequisite before treatment

➢Immunosuppressed patients is challenging and sometimes fails

➢It may be possible to lower the doses of standard therapy (tacrolimus, mycophenolate mofetil and prednisolone) to minimize side effects when combining them with complement inhibitors

Considerations

- **Cost:**

Very expensive especially in developing countries

- **The appropriate timing:**
  - For initiating
  - For discontinuing
- **Indications:**
  - Prophylactic
  - Therapeutic

Take home massage

- Complement-targeting therapy had a great potential role for graft protection and rejection prevention.
- It reduce recurrence rates in complement mediated diseases.
- It improves overall transplant success rates.
- Eculizumab remains the most extensively studied agent.
- Emerging proximal complement inhibitors have shown encouraging efficacy in both native and recurrent disease.

Take home massage

- Critical issues remain challenging in transplant recipients regarding:
  - Cost
  - Optimal timing
  - Prophylactic use
  - Long-term safety
- Further studies are still needed.


THANK
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