AJKD

Principles of Immunosuppression in the Management of Kidney Disease: Core Curriculum 2022

Sam Kant, Andreas Kronbichler, and Duvuru Geetha

The management of immunosuppression utilized in glomerular diseases requires highly nuanced care. Timely recognition and management of these disorders is essential to mitigate the extent of kidney damage. This involves being cognizant of the various classes of immunosuppression, which includes alkylating agents, antimetabolites, calcineurin inhibitors, anti-CD20 therapy, complement inhibitors, corticosteroids, and intravenous immunoglobulin. The mechanisms of action of these drugs, along with associated pharmacokinetics and pharmacodynamics, facets of monitoring, and adverse effects are important aspects with which nephrologists are required to be well versed. In addition, an understanding of therapeutic decisions such as induction and maintenance regimens in the setting of glomerular disease and alteration based on trajectory of disease and subsequent response is imperative. The overarching principle of these strategies of immunosuppression is to achieve a balance of disease mitigation without exposure to inadvertent harm. Special groups such as pregnant women, elderly patients, and patients treated with dialysis are especially susceptible to immunosuppression and thus need highly weighed therapeutic strategies and enhanced surveillance of adverse effects.

Introduction

The immune system can inflict kidney damage through myriad processes. Indirect and direct mechanisms can lead to acute kidney injury (AKI), development of chronic kidney disease, and even kidney failure. In some cases, the immune system directly targets various antigens in the kidneys; in others, inadvertent harm can be caused by systemic dysfunction of the immune system via indirect pathways. Immunosuppression is frequently employed to abate these immune processes. An understanding of not only these processes but also the nuances of immunosuppression is required to institute rapid and effective disease control to minimize kidney injury. The main tenet of immunosuppression in management of kidney disease is equipoise of achieving disease control and treatment-related adverse events.

In direct immune-mediated kidney diseases, the differences in presentation are based on the structures that are specifically targeted by autoantibodies or circulating factors. For example, anti-glomerular basement membrane (GBM) disease is due to autoantibody-induced vascular damage. For focal segmental glomerulosclerosis (FSGS), the mechanism is podocyte injury due to circulating autoantibodies/factors.

Kidney injury can occur inadvertently as a result of systemic immune disorders manifesting primarily as glomerular and vascular disease. The predominant mechanism of indirect immune-mediated kidney disease is a consequence of autoimmunity, with a smaller proportion due to hematological malignancies and genetic aberrations in the complement system. Four primary mechanisms are implicated in the indirect immune-mediated kidney injury: systemic autoantibody-induced vascular damage, circulating immune complex deposition, monoclonal immunoglobulin deposition, and dysregulation of the alternate complement pathway.

The understanding of the principles of immunosuppression lies at the confluence of elucidation of various drug classes with their mechanisms of action (Fig 1), pharmacological aspects (kinetics, dynamics, and genetic influences), indications, adverse effects, and monitoring. In addition, pertinent facets such as induction, maintenance, and monitoring of disease activity and immunosuppression in special groups (pregnant individuals, elderly persons, and patients treated with dialysis) require nuanced discussion.
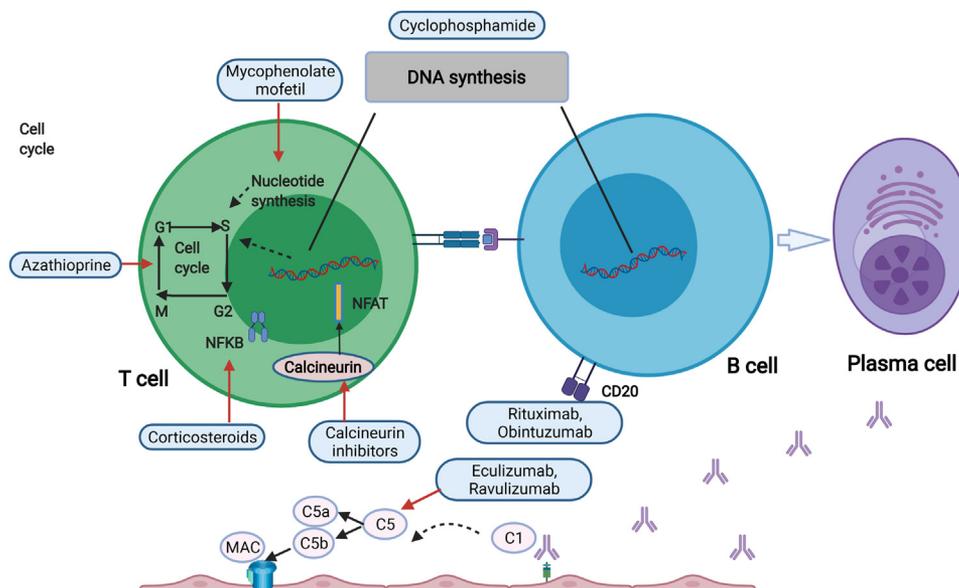
Figure 1. Sites of action of various immunosuppressive drugs. Abbreviations: MAC, membrane attack complex; NFAT, nuclear factor of activated T cells; NFKB, nuclear factor-κB. Created with Biorender.

Immunosuppressive Drug Classes

Alkylating Agents

Case 1: A 50-year-old woman with a history of hypertension reports a 3-week duration of generalized malaise and diffuse joint pain. She is noted to have decreased kidney function, with a serum creatinine level (Scr) of 2.0 mg/dL, urinalysis showing 2+ protein (quantified as a protein-creatinine ratio of 2.1 g/mg), and 25 red blood cells (RBCs) per high-power field. Additionally, her antinuclear antibody (ANA) titer is 1:320, and tests for antibodies to double-stranded DNA (anti-dsDNA) are positive. The kidney biopsy shows class IV lupus nephritis with crescents. She was commenced on the National Institutes of Health (NIH) cyclophosphamide protocol. Her laboratory values are reviewed before her next cyclophosphamide dose after a month: her white blood cell (WBC) count is noted to have dropped from 8,400/μL to 4,500/μL.

Question 1: What would be your next step in dosing cyclophosphamide?
a) Proceed with no change in cyclophosphamide dosing as per NIH protocol
b) Administer granulocyte colony-stimulating factor (G-CSF)
c) Administer half of the planned dose of cyclophosphamide
d) Switch to mycophenolate mofetil (MMF)

For the answer to the question, see the following text.

Cyclophosphamide is the predominantly used alkylating agent in glomerular disease. Phosphoramide mustard is the active alkylating agent, which accelerates cell apoptosis by crosslinking between and within DNA fragments at guanine positions. This effect extends to both T and B cells, with high efficacy in rapidly reducing in antibody production. The action of cyclophosphamide is not only limited to actively dividing cells but also extends to cells in an inactive state.

Cyclophosphamide is an inactive prodrug; oral formulations are well absorbed with oral bioavailability of >75%. The metabolism is primarily hepatic (cytochrome P450 system) with generation of the active metabolites 4-aldophosphamide, 4-hydroperoxycyclophosphamide, acrolein, and phosphoramide mustard (the latter 3 are found in the urine). The elimination half-life of the intravenous formulation is 6-8 hours, with the drug cleared almost completely from plasma by 24 hours after administration. Polymorphisms in genes such as CYP2B6 and CYP2C19 may explain the significant variability in metabolism of cyclophosphamide, with a small proportion of patients—known as low carboxylators—susceptible to increased toxicity.

Cyclophosphamide has demonstrable efficacy in minimal change disease, membranous nephropathy, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), anti-GBM disease, and lupus nephritis.

The following are major adverse effects associated with cyclophosphamide:

1. *Bone marrow suppression.* The occurrence of leukopenia predominates over anemia and thrombocytopenia, with nadir WBC counts at 8-14 days after administration (resurgence occurs after 18-25 days). Patients with decreased kidney function are at risk, given reduced clearance of cyclophosphamide.

2. *Infections.* Patients will be at risk for sepsis and opportunistic infections. The likelihood of infections is greater with WBC counts < 3,000/μL, lymphocyte

Box 1. Common Adverse Effects Associated With Cyclophosphamide, Along With Measures to Mitigate Toxicity

- Hemorrhagic cystitis

  Mesna (2-mercaptoethanesulphonate) binds to the metabolite acrolein, thereby preventing its irritant effects on the bladder epithelium. Optimize oral fluid intake and frequent voiding (risk highest with continuous daily oral administration).
- Bone marrow suppression

  Administer half-dose if white blood cell count is <5,000/µL or age is >65 years or eGFR<40 mL/min/1.73 m² (reduce dose by one-third or less for patients on dialysis). Cease medication if white cell count is <3,000/µL. More common with increasing doses and is also more likely to occur with a longer duration of use.
- Bacterial, opportunistic, and viral infections

  Appropriate dose adjustment, along infection prophylaxis and vaccination.
- Gonadal toxicity

  Cryopreservation of eggs or sperm should be considered. Gonadotropin agonists can be used to reduce risk of ovarian failure (lower risk of infertility in those treated before the age of 25 than those treated after the age of 30).

Abbreviation: eGFR, estimated glomerular filtration rate.

count < 500/µL, and sequential intravenous and oral therapy.

3. *Bladder injury.* Acrolein, an inactive metabolite excreted in the urine, is injurious to the bladder epithelium. The most frequent manifestation of this toxicity is hemorrhagic cystitis, which can be alleviated with concomitant administration of mesna. The other serious adverse effects include transitional cell carcinoma and bladder fibrosis (the risk of bladder cancer is 3.6 times greater for patients administered >36 g of cyclophosphamide than those receiving less than this cumulative dose).

4. *Malignancy.* Leukemia and bladder cancer are the most reported malignancies associated with cyclophosphamide use. The risk correlates with a cumulative dose threshold of 36 g, duration of treatment, and development of agranulocytosis.

5. *Infertility.* Cyclophosphamide has been associated with development of amenorrhea, ovarian failure, and oligoazoospermia. In addition to correlating with dose and duration of therapy, higher patient age is associated with onset of infertility.

6. *Rare adverse effects.* These include interstitial pneumonitis, acute liver injury, cardiac toxicity, and hyponatremia.

Box 1 lists measures to mitigate the adverse effects of cyclophosphamide. As elucidated in Box 1, the best answer to Question 1 is (c).

Additional Readings

➢ Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis.* 2012;71(6):955-960. https://doi.org/10.1136/annrheumdis-2011-200477

➢ Parikh SV, Almaani S, Brodsky S, Rovin BH. Update on lupus nephritis: core curriculum 2020. *Am J Kidney Dis.* 2020;76(2):265-281. https://doi.org/10.1053/j.ajkd.2019.10.017

➢ Ponticelli C, Escoli R, Moroni G. Does cyclophosphamide still play a role in glomerular diseases? *Autoimmun Rev.* 2018;17(10):1022-1027. https://doi.org/10.1016/j.autrev.2018.04.007

Anti-CD20 Therapy

Rituximab is the prototypical anti-CD20 therapy; more recently, other monoclonal antibodies including obinutuzumab have been developed.

Rituximab is a monoclonal, chimeric IgG1 antibody formulated by fusion of the human Fc region with murine variable domains directed against CD20. Administration of rituximab results in profound and prolonged elimination of peripheral B cells. Cytotoxicity is rendered via antibody-dependent cell-mediated and complement mechanisms. The duration of B-cell depletion is usually 6-12 months, with periods of sustained depletion of up to 30 months reported. It also has effects on podocyte preservation by stabilizing sphingomyelin-phosphodiesterase-acid-like-3b (SMPDL-3b) expression and preventing downregulation of acid-sphingomyelinase activity, thereby reducing actin cytoskeleton disruption and podocyte apoptosis.

Rituximab has an elimination half-life of 3 weeks (which can vary depending on disease), persisting in the circulation for 3-6 months. Body surface area and sex (elimination half-life is prolonged in women) can explain interindividual variability. Of note, there is a propensity of high urinary loss of rituximab in patients with nephrotic-range proteinuria, resulting in lower achieved rituximab levels. With a molecular weight of 145 kDa, rituximab is not eliminated by hemodialysis, and modality of dialysis does not influence half-life. Plasma exchange (PLEX), on the other hand, is associated with removal of a significant proportion of rituximab. PLEX performed 24 hours after rituximab infusion decreases the rituximab area under the curve (AUC) by 26%. The standard recommendation would be, if possible, instituting a delay of 48 hours between rituximab administration and PLEX; however, minimal variation is found in the elimination of rituximab if the delay is 1 versus 3 days.

The formation of human antichimeric antibodies should be suspected in patients with rapid B-cell reconstitution or failure of depletion, with the highest reported incidence in patients with lupus.

Rituximab has been approved for the treatment of AAV and has been increasingly used off-label for the treatment of membranous nephropathy, minimal change disease, lupus nephritis, and cryoglobulinemia.

The following are the adverse effects associated with rituximab:

1. *Infusion reactions.* This is usually encountered during the first infusion, with occurrences possible, albeit rare, during subsequent administrations. These reactions are hypersensitivity reactions that can be of varying severity, generally manifesting as fever, chills, and myalgia but could be life threatening at times. This can be mitigated by pretreatment with acetaminophen, antihistamines, and steroids.

2. *Late-onset neutropenia.* This is an underappreciated adverse effect of rituximab. It is defined as absolute neutrophil count $<1.0 \times 10^9$/L more than 1 month after the last rituximab infusion with spontaneous recovery, when other causes are ruled out. It has been reported to develop 38-175 days after conclusion of therapy, lasting 5-77 days.

   This phenomenon is mostly reported in patients with AAV in comparison with other glomerular disorders. G-CSF administration should be considered in patients at high risk for infection. Encouragingly, late-onset neutropenia is unlikely to recur with repeated administration of rituximab.

3. *Hypogammaglobulinemia.* Up to 30% of patients treated with rituximab can develop hypogammaglobulinemia, which is associated with prior cyclophosphamide exposure, steroid use, AAV diagnosis, and low baseline IgG levels. The decline in IgG levels is associated with severe infections. The decision to start IgG replacement should be informed by the degree of hypogammaglobulinemia; recurrent, persistent, or serious infections; and impaired humoral response to polysaccharide antigens.

4. *Infections.* The frequency of reported infections associated with rituximab use depends on the indication for use, along with other factors such as age, comorbidities, chronic lung disease, and decreased kidney function. Infections can range from common community-acquired organisms to opportunistic, with the majority occurring in the first year of initiation of therapy. The following infections warrant special discussion:

   a. *Pneumocystis jiroveci* pneumonia (PJP). The incidence of PJP in the context of rituximab use is unknown, but the risk of infection is being increasingly recognized, as has been reported in various trials and retrospective analyses. Given the high mortality risk with PJP, prophylaxis should be considered in rituximab use because B cells (in addition to T cells) confer protection against the organism. High-dose steroid use and pulmonary disease in granulomatosis with polyangiitis appear to be associated with the highest risk of PJP.

   b. Hepatitis B virus (HBV) reactivation. A black box warning now exists for the risk of HBV reactivation. Screening for hepatitis serologies is recommended before initiation of rituximab. Patients positive for HBV surface antigen and/or antibody to HBV core antigen should ideally receive antiviral prophylaxis 7 days before initiation, with avoidance of rituximab in active HBV infection. Patients with resolved HBV infection should undergo surveillance laboratory measurements every 3 months for alanine transferase and HBV DNA, with initiation of antiviral therapy on detection of HBV DNA. Recommended duration of antiviral prophylaxis is 1 year after cessation of rituximab, given that immune reconstitution usually ensues after that period.

5. *Progressive multifocal leukoencephalopathy (PML).* This is an extremely rare, albeit devastating central nervous system complication associated with rituximab treatment. An opportunistic infection caused by reactivation of JC virus, PML presents as progressive cognitive decline, unsteady gait, and subtle neurologic deficits. Diagnosis requires characteristic magnetic resonance imaging (MRI) findings and demonstration of the JC virus in cerebrospinal fluid. Patients with lupus and those treated with other immunosuppressive therapies appear to be the most susceptible.

A novel anti-CD20 therapy, obinutuzumab, is being increasingly used for management of glomerular disease. Obinutuzumab is a type II glycoengineered and humanized monoclonal antibody directed against a different CD20 epitope than is recognized by rituximab (which is a classic type I anti-CD20 monoclonal antibody). It has superior in vitro B-cell cytotoxicity by inducing an apoptotic response via antibody-dependent cellular phagocytosis and cytotoxicity. The elimination half-life of obinutuzumab is 25.5-35.3 days. Per the US Food and Drug Administration (FDA), it has "breakthrough" therapy status for lupus nephritis, and it is being employed off-label in membranous nephropathy.

Additional Readings

➢ Gauckler P, Shin JI, Alberici F, et al. Rituximab in membranous nephropathy. *Kidney Int Rep.* 2021;6(4):881-893. https://doi.org/10.1016/j.ekir.2020.12.035

➢ Kronbichler A, Windpessl M, Pieringer H, Jayne DRW. Rituximab for immunologic renal disease: what the nephrologist needs to know. *Autoimmun Rev.* 2017;16(6):633-643. https://doi.org/10.1016/j.autrev.2017.04.007

Antimetabolites

The 2 major antimetabolites used in the kidney disease are MMF and azathioprine. Although they have different mechanisms of action, both result in inhibition of nucleotide synthesis. Lymphocytes are especially sensitive to these agents, given their dependence on de novo DNA synthesis for proliferation.

MMF is derived from the fungus *Penicillium stoloniferum*. It is a prodrug that is converted to an active metabolite

mycophenolic acid (MPA), which reversibly inhibits inosine monophosphate dehydrogenase, thereby blocking the conversion of inosine monophosphate to guanine monophosphate.

The oral bioavailability of MMF is 94%, with half-life of approximately 17.9 ± 6.5 hours. The metabolism of MMF is hepatic, where it is hydrolyzed to MPA and a component of enterohepatic circulation. Dose reduction should be considered in severely decreased kidney function given the MMF AUC is increased 75% with estimated glomerular filtration rate (eGFR) <25-30 mL/min/1.73 m^2, with no adjustment recommended in the setting of severe hepatic parenchymal disease. Given the high proportion of MPA is bound to albumin and bilirubin, surveillance for toxicity should be heightened. Another formulation available, mycophenolate sodium, is not well studied in glomerular disease.

MMF has extensively demonstrated efficacy for induction and maintenance therapy in lupus nephritis. In addition, it has been used to induce remission of refractory nephrotic syndrome in minimal change disease and FSGS, along with C3 glomerulopathies; however, efficacy remains to be confirmed in a randomized control trial.

It is recommended that a complete blood count (CBC) be done 1-2 weeks after commencement of MMF, with monitoring every 6-8 weeks.

Azathioprine is an analog of 6-mercaptopurine. The metabolites interfere with de novo purine synthesis by acting as a purine analog, in addition to having immunomodulatory properties by inducing cell cycle arrest and reducing interleukin 2 secretion.

The bioavailability of azathioprine is 16%-50%, with predominant hepatic metabolism. The elimination half-life is ∼2 hours, with excretion primarily in the urine. Dose reduction is usually recommended in the setting of oliguria/acute tubular injury. Genetic polymorphisms of certain enzymes play an important role in the metabolism of azathioprine, namely thiopurine S-methyltransferase (TPMT) and nucleoside triphosphate diphosphatase (NUD15). Deficiency of TPMT can cause accumulation of 6-thioguanine nucleotides and 6-methylmercaptopurine, leading to hematological toxicity and hepatotoxicity. This enzyme deficiency is the primary cause of azathioprine intolerance in patients of African and European ancestry. The NUD15 polymorphism, predominantly present in Asian and Hispanic populations, leads to a poor metabolizer phenotype. Performing genotyping and functional enzyme assays before initiation of azathioprine is not currently mandatory but is recommended. Xanthine oxidase inhibitors (allopurinol and febuxostat) should be avoided during azathioprine use, given the risk of accumulation of 6-mercaptopurine by slowing elimination, with consequent serious toxicity.

Additional Reading

➤ Appel AS, Appel GB. An update on the use of mycophenolate mofetil in lupus nephritis and other primary glomerular diseases. *Nat Clin Pract Nephrol.* 2009;5(3):132-142. https://doi.org/10.1038/ncpneph1036

Calcineurin Inhibitors

Calcineurin inhibitors (CNIs) bind calcineurin-dependent signaling proteins that initiate T-cell gene transcription required for activation and further proliferation (Fig 2). The development of these agents, tacrolimus and cyclosporine (both derived from fungi), has provided immense benefit not only in the realm of transplantation but also in glomerular disease. Their efficacy in glomerular disease is from a combination of immunosuppressive and podocyte stabilization effects. The latter effect is a consequence of inhibition of synaptopodin degradation, resulting in preservation of actin cytoskeleton with subsequent reduction in proteinuria.

The bioavailability of tacrolimus is variable (17% ± 10%), with a half-life of 23-46 hours; the bioavailability of cyclosporine is 30%-68%, with half-life of 5-18 hours. The suboptimal bioavailability of both drugs is attributed to poor intestinal absorption, partial enzymatic metabolism in gastrointestinal mucosa, and first-pass hepatic metabolism. Both CNIs are metabolized by the CYP3A system and are excreted via the biliary route (liver dysfunction prolongs the half-life of both drugs). African Americans and Hispanics have lower CNI exposure after similar dose administration than those of European ancestry. Genetic polymorphisms of *CYP3A5* that affect absorption and metabolism are considered likely to explain this variation.

It is recommended that tacrolimus immediate release and cyclosporine be monitored with 12-hour trough levels. Dose changes are usually reflected in 2-3 days for both CNIs. For tacrolimus, dose adjustments of 0.5-1.0 mg per dose should occur depending on trough levels; the range for change for cyclosporine is 25-50 mg. It is imperative to verify whether the trough levels guiding these changes are accurate in relation to timing of administration.

Successful use of traditional CNIs (cyclosporin and tacrolimus) has mainly been described in minimal change disease, membranous nephropathy, and FSGS.

A novel CNI, voclosporin, has recently been approved for use in lupus nephritis in combination with MMF and corticosteroids. The half-life of voclosporin can range from 25-36 hours, with mainly hepatic metabolism (CYP3A4). The excretion is mostly fecal (>90%), with minimal amounts excreted in the urine (2%). An advantage of the drug noted in the clinical trials is that it does not require monitoring of serum levels. Most frequently noted adverse effects include hypertension, diarrhea, headache, and reduction in mean eGFR.

Additional Reading

➤ Alsharhan L, Beck LH Jr. Membranous nephropathy: core curriculum 2021. *Am J Kidney Dis.* 2021;77(3):440-453. https://doi.org/10.1053/j.ajkd.2020.10.009
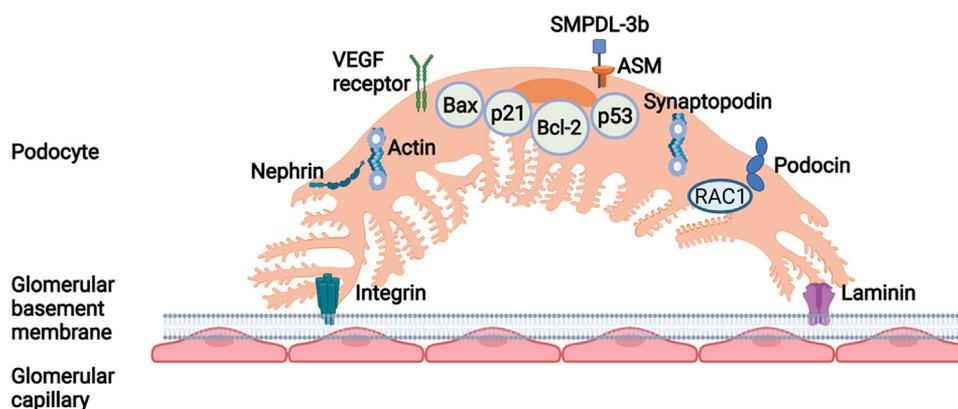
Figure 2. Podocyte-based sites of action of calcineurin inhibitors, corticosteroids, and rituximab. Calcineurin inhibitors sustain nephrin expression, protect synaptopodin, inhibit integrin activation, and promote actin polymerization. Corticosteroids aid in stabilization of actin filament and diminish Rac-1 (a Rho guanosine triphosphatase) overactivity, reducing podocyte motility. They also stimulate podocyte survival pathways and inhibit apoptosis by decreasing the expression of p53, p21, and Bax and elevating the expression of Bcl-2. VEGF secretion and expression are also down-regulated by corticosteroids. Rituximab stabilizes SMPDL-3b expression and prevents down-regulation of ASMase activity, thereby reducing actin cytoskeleton disruption and podocyte apoptosis. Abbreviations: ASMase, acid-sphingomyelinase; SMPDL-3b, sphingomyelin-phosphodiesterase-acid-like-3b; VEGF, vascular endothelial growth factor. Created with Biorender.

Complement Inhibitors

Case 2: A 45-year-old man with a history of type 2 diabetes is admitted with nausea and vomiting. He is noted to have AKI, with an Scr of 4.5 mg/dL. In addition, he has anemia (hemoglobin, 6 g/L) and thrombocytopenia (platelet count of 90 × 10³/mL), with peripheral smear demonstrating schistocytes. He is found to have a normal ADAMTS level. A kidney biopsy shows evidence of thrombotic microangiopathy. While awaiting complement and genetics studies, eculizumab therapy is planned.

Question 2: In addition to administering meningococcal vaccines, what other drug would need to be provided for the duration of eculizumab therapy?
a) Trimethoprim/sulfamethoxazole
b) Angiotensin-converting enzyme (ACE) inhibitor
c) Amoxicillin
d) Hydroxyurea

For the answer to the question, see the following text.

The role of the complement system in kidney disease is being increasingly recognized, and as a consequence multiple therapies targeting various pathways are being developed. Eculizumab and ravulizumab are 2 C5 monoclonal antibodies being used in clinical practice.

Both monoclonal antibodies are humanized and prevent cleavage of C5 into C5a and C5b, thereby preventing the formation of terminal attack complex C5b-9. Ravulizumab has 4 amino acid substitutions in the complementarity-determining and Fc regions of eculizumab, leading to enhanced endosomal dissociation of C5 and recycling to the vascular compartment through the neonatal Fc receptor

pathway. This results in a half-life that is 4 times longer than eculizumab ($\sim$52 vs $\sim$13 days).

Complement blockade and activity can be monitored via total complement testing, with CH50 levels <10% indicative of complete suppression. A complete complement factor H deficiency precludes measurement of CH50; instead, a global complement functional test (Wieslab; with a goal of <30%) is recommended. Alternatively, blood levels of eculizumab can be used for monitoring of treatment: levels >100 mg/mL lead to optimal reduction in CH50 levels.

Life-threatening meningococcal infections appear to be the most severe adverse effect associated with eculizumab therapy. Patients should ideally receive vaccinations for *Neisseria meningitis*, *Streptococcus pneumoniae*, and *Haemophilus influenza type B* before initiation of therapy, along with prophylactic antibiotic coverage for *N. meningitis*. Therefore, the best answer to Question 2 is (c).

Increased risk of hemolytic anemia after receiving the multicomponent meningococcal serogroup B vaccine (MenB-4C [Bexsero]) has been reported among patients who were already being treated with eculizumab. To minimize the risk of hemolysis, vaccination is recommended before the initiation of eculizumab. In the event patients have already been treated with eculizumab before vaccination, the manufacturer of eculizumab recommends that vaccination be carried out when the patient is clinically stable and disease is well controlled. Other reported adverse events in patients with complement-mediated hemolytic uremic syndrome (HUS) treated with eculizumab include hypertension, asymptomatic bacteremia, influenza, peritonitis, and venous sclerosis at the infusion site.

Additional Reading

➢ Thurman JM. Many drugs for many targets: novel treatments for complement-mediated glomerular disease. *Nephrol Dial Transplant.* 2017;32(suppl 1):i57-i64. https://doi.org/10.1093/ndt/gfw228

Corticosteroids

Corticosteroids have been used for a variety of glomerular diseases. They have effects on various components of the immune system as well as on podocytes (Fig 2).

Within the first 90 minutes of corticosteroid administration, immunosuppressive effects occur via alteration of cell signaling cascades. Within 24 hours of administration, steroids bind to nuclear factor-κB (NFκB), thereby decreasing expression of proinflammatory proteins (transrepression) and increasing production of anti-inflammatory protein (transactivation).

With regard to podocytes, steroids exert protective benefits via 4 mechanisms. First, they stabilize actin filaments and diminish Rac-1 overactivity; this reduces podocyte motility, which is important because a hypermobile podocyte after injury is susceptible to foot-process effacement. Second, they inhibit podocyte detachment from the GBM. Third, by blocking proinflammatory mediators in podocytes and restoring differentiation markers, steroids improve survival of podocytes. Fourth, they reduce glycosylation and phosphorylation of nephrin, thereby reducing foot-process effacement and proteinuria.

The 2 most used formulations of steroids in kidney disease include oral prednisone and intravenous methylprednisolone. The absorption of prednisone is 50%-90%, and the onset of action is 2 hours, with metabolism primarily hepatic (leading to conversion to the active metabolite prednisolone); the elimination half-life is 2-3 hours. The onset of action of methylprednisolone is 1 hour with an elimination half-life of 0.15-0.35 hours.

Corticosteroids are used for induction and maintenance regimes for minimal change disease, FSGS, AAV, anti-GBM disease, lupus nephritis, C3 glomerulopathies, and crescentic/rapidly progressive forms of IgA nephropathy.

The adverse effects of corticosteroids are related to the dose and duration of therapy and are multisystemic in nature:

1. *Metabolic and endocrine effects* include impaired glucose tolerance/diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease, and adrenal insufficiency.
2. *Infectious effects* include community-acquired and opportunistic pathogens.
3. *Musculoskeletal effects* include myopathy, osteoporosis, and aseptic necrosis.
4. *Gastrointestinal effects* include peptic ulcer disease.
5. *Psychiatric and ophthalmic (cataract) effects* may also occur.

Additional Reading

➢ Ponticelli C, Locatelli F. Glucocorticoids in the treatment of glomerular diseases: pitfalls and pearls. *Clin J Am Soc Nephrol.* 2018;13(5):815-822. https://doi.org/10.2215/CJN.12991117

Immunomodulatory Drugs

Intravenous immune globulin (IVIG) is used not only for protection against infection and alloimmunization but also immunomodulation. IVIG renders immunomodulatory and anti-inflammatory effects via several mechanisms. First, the increase in immunoglobulin concentrations leads to saturation of the FcRn receptor on vascular endothelial cells, resulting in increased degradation of nonbound immunoglobulin. Second, IVIG leads to proliferation of circulating FOXP3-positive regulatory T cells and inhibition of the proinflammatory T helper 17 pathway. Third, IVIG administration provides an increased number of binding sites for C3b and other active complement components, preventing downstream activation of the complement pathway. In addition, C3a and C5a are neutralized after interaction with the Fab2 region of the immunoglobulin. Importantly, IVIG aids in clearance of the immune complex deposits. A final mechanism is neutralization of cytokines and proinflammatory monocytes and blockade of the binding of leukocyte adhesion molecule to the vascular endothelium.

The elimination half-life of IVIG is 14-24 days; hypermetabolic states lead to shortened half-life. The adverse effects of IVIG are classified as immediate or delayed; the former include the following:

1. *Infusion reactions.* These usually manifest as flu-like symptoms including fever, chills, nausea, flushing,

Table 1. Common Adverse Effects Associated With Immunosuppression Used in Disease Secondary Systemic Autoantibody-Induced Vascular Damage and Circulating Immune Complex Deposition, Along With Measures to Reduce Drug Toxicity

Medication	Adverse Effects	Measures to Mitigate Drug-Related Adverse Effects
Rituximab	Infusion reaction	Acetaminophen, antihistamine, and glucocorticoids
	Hypogammaglobulinemia	Monitor immunoglobulin levels with repeated courses; immunoglobulin replacement with sustained low IgG and severe or recurrent infections
	Opportunistic infections	PJP prophylaxis
	Viral reactivation	Serologic testing for TB, HBV, HCV, and HIV before initiating treatment
Corticosteroids	Metabolic: hyperglycemia, hyperlipidemia	Frequent monitoring of HbA_{1c} and lipids in the setting of long-term use
	Osteoporosis	Calcium and vitamin D if expected duration of therapy >3 months, dose minimization; baseline bone densitometry and fracture risk assessment
	Bacterial, opportunistic, and viral infections	Dose minimization, along with infection prophylaxis and vaccination
	Ophthalmologic: cataracts, glaucoma	Regular follow up with ophthalmology for patients with prolonged moderate or high-dose treatment
Mycophenolate mofetil	Gastrointestinal: diarrhea, abdominal cramping, and nausea	Reduction in dose if possible, trial of enteric-coated mycophenolate sodium
	Bone marrow suppression	Regular monitoring of CBC
Azathioprine	Gastrointestinal: anorexia, nausea, and vomiting; elevation of LFTs; pancreatitis	Reduction in dose, monitoring of LFTs
	Bone marrow suppression	Monitoring of CBC, measurement of TPMT levels

Abbreviations: CBC, complete blood count; HbA_{1c}, hemoglobin A_{1c}; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; LFTs, liver function tests; PJP, *Pneumocystis jiroveci* pneumonia; TB, tuberculosis; TPMT, thiopurine *S*-methyltransferase.

and malaise. These most frequently occur in the first hour of administration, with most episodes within 24 hours. Cytokine and complement activation have been deemed responsible for these reactions and can be alleviated by commencing infusion at a slow rate.

2. *Arrythmia and hypotension.* The most frequent arrythmias include supraventricular tachycardia and bradycardia, noted during administration. It is uncertain whether IVIG is responsible for these arrythmias; however, it is recommended that cardiac monitoring be instituted for patients with cardiac comorbidities. The occurrence of hypotension is rare and usually related to anaphylaxis.

3. *Dermatological.* A number of dermatological conditions can occur with 2 weeks of IVIG administration, including eczema, urticaria, pompholyx, spot papules, lichenoid dermatitis, desquamation, and epidermolysis.

4. *Transfusion-associated lung injury.* This is one of the most serious adverse effects, frequently requires mechanical ventilation, and is associated with high mortality.

Delayed adverse effects include the following:

1. *Neurological.* Headache is noted to be a frequent adverse effect after administration. Other neurological disorders include aseptic meningitis, seizures, abducens nerve palsy, and posterior reversable encephalopathy syndrome.

2. *Thrombotic.* Various presentations of thrombosis are associated with IVIG, such as venous sinus thrombosis, stroke, pulmonary embolism, and myocardial infarction (venous and arterial).

3. *AKI.* This complication has significantly reduced since the use of sucrose-free IVIG formulations (ie, sucrose-based IVIG caused osmotic injury).

4. *Hematologic.* IVIG-associated hemolysis can occur 12 hours to 10 days after administration, usually from those derived from non-O blood group donors. Neutropenia is the other hematological complication; it occurs within 4 days of infusion with recovery usually within 2 weeks.

IVIG has been used as an adjunct therapy in AAV refractory to standard immunosuppression in a small randomized control trial with demonstrable reduction in disease activity. In addition, it has been shown to be as efficacious as cyclophosphamide in maintaining remission in patients with proliferative lupus nephritis in remission after standard immunosuppression.

Box 2 lists the infectious disease screening tests and prophylaxis required at the time of initiation of immunosuppression. Table 1 lists the common adverse effects associated with immunosuppression used in disease secondary systemic autoantibody-induced vascular damage and circulating immune complex deposition, along with measures to reduce drug toxicity.

Additional Readings

➢ Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. *Front Immunol.* 2018;9:1299. https://doi.org/10.3389/fimmu.2018.01299
➢ Jayne DR, Chapel H, Adu D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis

with persistent disease activity. QJM. 2000;93(7):433-439. https://doi.org/10.1093/qjmed/93.7.433

Deciding on Appropriate Immunosuppressive Treatment

Decisions that relate to the timing, intensity, and duration of immunosuppression in immune-mediated kidney disease are critical not only to preserve organ function and life but also to attenuate therapy-related adverse effects. These decisions in turn are centered on the disease trajectory, natural history of the disease, and trends in serologic markers of disease activity in addition to patient-related variables like age and comorbidities. Immunosuppressive therapy frequently results in control of disease activity but therapy-related adverse events lead to comorbidities that can influence quality of life and life expectancy. Therefore, the major challenges are to discern the appropriate timing of initiating immunosuppressive therapy, to identify patients in whom immunosuppressive therapy should not be initiated, and to determine the most appropriate time for withdrawal of immunosuppressive therapy.

The disease phenotype and natural history often determine the timing of initiation of immunosuppressive therapy. Glomerular diseases like membranous nephropathy and IgA nephropathy are frequently initially managed by conservative therapy with renin-angiotensin-aldosterone system (RAAS) inhibitors and lipid-lowering therapy before initiating immunosuppressive therapy, especially when the clinical presentation is limited to sub–nephrotic-range proteinuria and preserved kidney function. Conversely, diseases that present with a rapidly progressive kidney failure such as small vessel vasculitis and lupus nephritis require immediate commencement of immunosuppression for swift control of the inflammatory process. Additionally, in systemic autoimmune diseases, the severity of extrarenal disease manifestations can influence the decision to start immunosuppressive therapy.

The eGFR at diagnosis, the slope of eGFR decline, histologic parameters of disease chronicity, and absence of extrarenal disease in systemic autoimmune diseases are commonly used parameters in deciding when to refrain from initiating immunosuppression and oftentimes these decisions are individualized to the patient. For the most part, a case may be made to hold off on initiating immunosuppressive therapy when the kidney disease is advanced clinically and there is histologic evidence of severe chronicity or in the setting of a serious infection, a scenario where the risks of immunosuppressive therapy often outweigh the benefits. This approach may not be applicable to systemic autoimmune diseases like AAV for which there is no cutoff eGFR, or chronicity score on kidney biopsy where treatment is considered futile, or when immunosuppressive therapy is needed to control extrarenal disease activity.

The immunologic pathways involved in disease pathogenesis, patient comorbidities, and data from observational studies and clinical trials inform the appropriate type of immunosuppressant. Although glucocorticoids are used in a majority of immune-mediated kidney diseases, often in high doses, glucocorticoid sparing or avoidance is desirable for patients with pre-existing diabetes mellitus, atherosclerotic vascular disease, and osteoporosis. Likewise, cytotoxic therapy should be used with caution in patients with active malignancy, active infection, and in the elderly with advanced kidney disease.

The duration of immunosuppressive therapy is determined by the therapeutic response. Treatment response is often defined by clinical criteria for disease remission, which factors in the stability or improvement in eGFR, improvement or resolution of proteinuria, and resolution of hematuria, depending on the disease phenotype. Although immunologic response is measured in phospholipase A_2 receptor (PLA_2R)-positive membranous nephropathy, lupus nephritis, and AAV, the literature is sparse on the utility of immunologic markers to determine treatment duration. Immunosuppressive therapy is frequently continued for 6-12 months beyond clinical remission in a majority of immune-mediated kidney diseases.

Additional considerations include whether the immune-mediated kidney disease has a monophasic course (as in anti-GBM disease) or can have a relapsing course (as is seen in AAV and lupus nephritis). In diseases with a relapsing course, the treatment course involves a 2-stage approach: a remission induction phase, which aims to quell the inflammation to preserve kidney function and control extrarenal disease activity, and a remission maintenance phase, which is designed to prevent disease relapses. Induction of remission often entails using high doses of glucocorticoids in combination with cytotoxic or B-cell–depleting therapy whereas less-intense immunosuppression is sufficient for remission maintenance.

Monitoring of Disease Response

Patients require close surveillance for disease activity and adverse effects during both induction and maintenance phases of therapy. This monitoring comprises 3 important aspects: clinical features, laboratory indices, and histology. Although there is a common approach to disease monitoring among the disease types, patients continue to require nuanced care given permutations of age, comorbidities, and type of immunosuppression.

For direct antibody-mediated diseases, anti-PLA_2R and anti-GBM antibodies are present before onset of the respective diseases. Antibodies to PLA_2R should be monitored because antibody negativity precedes proteinuria decline. Negative results for anti-PLA_2R antibody testing at 6 months predicts remission, and a 50% reduction in PLA_2R antibody titers precedes an equivalent proteinuria reduction by 10 months. Immediate elimination of anti-

GBM antibodies from the circulation and kidney-bound antibodies is desired in anti-GBM disease.

Patients with AAV require close follow-up observation to monitor symptoms, signs of extrarenal disease, and laboratory indices of disease activity (stabilization or improvement in Scr, resolution of hematuria, and Birmingham vasculitis activity score of 0) which in turn guides tapering or transition of induction immunosuppression to maintenance immunosuppression when remission is achieved or escalating immunosuppressive therapy in the event of disease relapse.

From the standpoint of laboratory measurements, checking complete blood counts (assessing for leukopenia in the setting of cyclophosphamide, MMF, and azathioprine use), hepatic function, blood glucose, fasting lipid profile, serum immunoglobulins, and bone densitometry can mitigate therapy-associated morbidity and mortality. Although the clinical utility of serial ANCA monitoring for predicting relapse remains controversial, one scenario where such monitoring can predict relapses is in AAV patients with renal involvement. Histology is usually not required for disease surveillance; however, there should be a low threshold for kidney biopsy if suspicion for recurrence of disease arises.

With respect to diseases secondary to immune complex deposition, an approach akin to that of systemic autoantibody-induced vascular damage could be used. Lupus nephritis, however, has defined criteria for complete response (CR), partial response (PR), and no response. A CR is defined as reduction in protein excretion to <0.5 g/d based on a 24-hour urine collection with normal Scr or Scr within 15% of previous baseline. A >50% reduction in proteinuria and to non–nephrotic-range, with Scr within 25% of previous baseline is consistent with a PR. Patients who do not achieve CR or PR are considered nonresponders.

Proteinuria with protein excretion <800 mg/d at 1 year has been shown to be the best predictor of good long-term renal outcomes, and the absence of hematuria has a good positive predictive value for a favorable long-term prognosis (albeit it does not have a strong negative predictive value). Nevertheless, achieving an inactive urine sediment devoid of RBC casts or dysmorphic RBCs remains a viable treatment goal. Additional laboratory markers of disease include anti-dsDNA and complement (C3 and C4) levels.

In the setting of IgA nephropathy, there are no serological markers to monitor disease activity. Proteinuria >1 g/d is a major risk factor for progression of disease, with treatment centered around its reduction and correlation with improved outcomes. Persistent hematuria is considered a marker of persistent immunologic activity and usually does not reflect progressive disease. A compensatory rise in single-nephron GFR among unaffected glomeruli is expected, so a stable Scr or total eGFR may not indicate stable disease.

In addition to kidney indices, diseases involving deposition of monoclonal immunoglobulin require monitoring of the hematological response to treatment because it closely correlates with renal outcomes. The complete battery of tests includes serum free light chains and difference in free light chains (dFLC); serum protein electrophoresis with immunofixation; 24-hour urine collection for total protein, protein electrophoresis, and immunofixation; and bone marrow for ascertaining percentage of clonal plasma cells.

Additional Readings

➢ Alsharhan L, Beck LH Jr. Membranous nephropathy: core curriculum 2021. *Am J Kidney Dis.* 2021;77(3):440-453. https://doi.org/10.1053/j.ajkd.2020.10.009

➢ Geetha D, Jefferson JA. ANCA-associated vasculitis: core curriculum 2020. *Am J Kidney Dis.* 2020;75(1):124-137. https://doi.org/10.1053/j.ajkd.2019.04.031

➢ Hogan JJ, Alexander MP, Leung N. Dysproteinemia and the kidney: core curriculum 2019. *Am J Kidney Dis.* 2019;74(6):822-836. https://doi.org/10.1053/j.ajkd.2019.04.029

➢ Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis.* 2016;75(9):1583-1594. https://doi.org/10.1136/annrheumdis-2016-209133

Immunosuppression in Special Groups

Pregnancy

Case 3: A 34-year-old kidney transplant recipient with stable kidney function for the past 3 years asks about the possibility to become pregnant. She is receiving a CNI (tacrolimus), an antimetabolite (MMF), and low-dose glucocorticoids as part of her rejection-preventing medication. She has a Scr of 1.2 mg/dL, and her urinary albumin-creatinine ratio is within the normal range.

Question 3: Which of the following is most correct at this point?
a) Pregnancy is absolutely contraindicated because the risks for the mother are considered high.
b) Medication would be unchanged during pregnancy.
c) MMF should be stopped and replaced by azathioprine ahead of conception.
d) Tacrolimus increases the risk of gestational diabetes and should be stopped.
e) A kidney biopsy is needed ahead of conception to rule out chronic kidney transplant rejection.

For the answer to the question, see the following text.

Managing disease before and during pregnancy is a challenge for physicians and should involve a multidisciplinary team of nephrologists and obstetricians experienced with high-risk pregnancies. Kidney transplant recipients and patients with autoimmune kidney diseases have in general a lower pregnancy rate, and these

---

Box 3. Safety of Immunosuppressive Drugs in Pregnancy

Safe
- Cyclosporine/tacrolimus
- Azathioprine
- Glucocorticoids
- Intravenous immune globulin
- Eculizumab

Unclear evidence
- Voclosporin
- Rituximab/obinutuzumab
- Ravulizumab

Not safe
- Cyclophosphamide
- Mycophenolate mofetil
- Mycophenolic acid

---

pregnancies are likely to be complicated by hypertension and a greater risk for small for gestational age, cesarean delivery, prematurity, a diagnosis of preeclampsia, and perinatal mortality. The current recommendations from the American Society of Transplantation highlight that in preparation for pregnancy there should be no rejection within the past year, transplant function should be stable and adequate, there should be no or minimal proteinuria, and the dosing of immunosuppression should be stable. Indeed, an analysis of the UK Pregnancy Registry indicated that pregnancy is not associated with kidney function decline in kidney transplant recipients with a prepregnancy Scr <150 μmol/L. No such recommendations exist for autoimmune kidney diseases, but disease quiescence or minimal disease activity the months before conception should be targeted.

In 2015, the FDA updated the Pregnancy and Lactation Labeling Rule and eliminated the prior grading system, which is still present for most FDA labels of drugs licensed before this time point. No immunosuppressive drugs have been specifically tested in pregnancy, and thus safety and efficacy data are based on reported experience (Box 3).

Cyclophosphamide is absolutely contraindicated in the first trimester of pregnancy because its use in humans is associated with severe embryopathy, including severe bone marrow hypoplasia, craniosynostosis, facial anomalies, distal limb defects, and developmental delay. Reports on its use in autoimmunity during pregnancy are limited, but experience in cases with severe systemic lupus erythematosus have indicated a high possibility of fetal demise after introduction of cyclophosphamide, which might either be disease- or treatment-associated.

MMF and MPA are teratogenic in animal models, and an increasing body of evidence supports its teratogenicity in humans. Patients with a desire to become pregnant should discontinue MMF at least 6 weeks before conception. An increased rate of spontaneous abortion as well as congenital malformations with estimated rate of 25% has been reported, including a distinctive and unique phenotype associated with MMF exposure called the EMFO tetrad (ear, mouth, fingers, ocular/organ malformation). The FDA has issued a black box warning based on the reports of teratogenicity, and contraception is mandatory for women with childbearing potential. An early switch from MMF to azathioprine in women planning pregnancy is advised. Uncertainty remains whether MMF/MPA should be stopped in men, but recent literature has indicated that paternal exposure to MPA is not associated with adverse birth outcomes. After a switch, a longer observational period confirming stable kidney function or disease activity over time is of interest to reduce the complication rate during pregnancy.

Exposure to azathioprine is reported to increase the risk of preterm and low-birth-weight infants, but no specific pattern or increased risk of malformations has been described. The former might be a direct consequence of the underlying disease rather than an effect of drug exposure. Thus, the use of azathioprine during pregnancy seems to be a good option, and the best answer to Question 3 is (c).

Both CNIs used to prevent transplant rejection (cyclosporine A and tacrolimus) are relatively well tolerated during pregnancy: there are consistent reports of low birth weight for gestational age and premature birth but without increased risk of birth defects. Trough levels may fluctuate during pregnancy due to an increase in enzymatic activity of the CYP3A family, altered volume of drug distribution, and changes in drug-binding components as albumin and hemoglobin levels decrease and the unbound fraction of CNIs increases. To maintain a stable trough level, a CNI dose increase of approximately 20%-25% may be required during pregnancy. To date, there is no information about pregnancy outcome after voclosporin exposure, but animal data indicate a similar safety profile as observed for other CNIs.

Glucocorticoids are frequently used to manage kidney transplant recipients and patients with autoimmunity during pregnancy. There is no overall increased rate of fetal malformations in comparison with the general population, but some reports have indicated a higher incidence of oral clefts. Other studies found no association, so the risk for the developing fetus exposed to glucocorticoids might be minimal. Immunomodulation with IVIG is safe for the mother and the newborn.

B-cell–depleting agents should be avoided during pregnancy and at least 12 months before conception because there is only limited documentation on safety. A small single-center study highlighted that the use of rituximab even close to conception resulted in a low rate of adverse effects. Analysis of the global drug safety database revealed that the preterm delivery rate was higher (19%) in comparison with the general population (10%-12%), but the rate of congenital malformations was similar.

Pharmacovigilance data for eculizumab indicate that its use is safe in pregnancy. Among 260 patients receiving eculizumab for either paroxysmal nocturnal hemoglobinuria

or atypical HUS, the live-birth rate was 70%, the miscarriage or spontaneous abortion rate was reported at 15.8%, and the rate of induced abortion was 10.4%. No malformations were reported. Incomplete terminal complement pathway blockade led to an increase of eculizumab dose during most pregnancies, and monitoring is indicated. Similar reports are not available for ravulizumab so far, but its use might be safe during pregnancy as well. Box 3 lists various drugs classified by level of safety during pregnancy.

Elderly Patients

High short-term mortality characterizes this patient group. In autoimmune kidney diseases, a fine balance between over- and underimmunosuppression needs to be discussed critically. In AAV, the standardized mortality rate is 5-fold greater in the first year, and older age and higher Scr are independent risk factors. Importantly, 2-year survival was reported to be better in patients receiving immunosuppression (72.9% and 72.5% for oral and intravenous cyclophosphamide, respectively; 81.3% for rituximab; and 45% for no/other treatment). The reasons for withholding immunosuppression or adequate treatment were not given, but it is likely that these results are confounded by frail patients receiving inadequate AAV management. These results argue for an individualized approach in these vulnerable patients.

The CORTAGE trial included patients with a mean age of 75.2 years receiving either reduced intravenous (IV) cyclophosphamide (cumulative 2.7 g) and 9 months of glucocorticoids or conventional IV cyclophosphamide (5.6 g) and 26 months of glucocorticoids. The number of patients with serious adverse events was reduced in the experimental arm with reduced exposure to immunosuppression; these differences were largely driven by infections, cardiovascular events, and cytopenias. The efficacy of both regimens was not statistically significantly different, with 44% and 29% of patients in the experimental and conventional arms presenting with disease relapses.

A trial conducted in Japan, LOVAS, recruited patients with a median age of 73 years to rituximab (approved dose) and regimens with either reduced glucocorticoid (cumulative dose of 1.3 g) or standard glucocorticoid (cumulative dose of 4.2 g). The rate of serious adverse effects (18.8% vs 36.9%) and especially infections (7.2% vs 20%) were significantly lower with reduced glucocorticoid exposure. In line with this, complications of steroids such as diabetes and insomnia occurred less frequently. A combined treatment of rituximab (1-2 g) and low-dose IV cyclophosphamide (0.5-2 g) with no glucocorticoid exposure in 11 patients with a median age of 82 years induced remission in all patients and provided evidence of a good safety profile, with only 1 patient developing a lower respiratory tract infection. These data clearly indicate that these patients benefit from effective induction therapy with a minimized exposure to glucocorticoids.

Immune system dysregulation needs to be considered when prescribing rejection-preventing immunosuppression in kidney transplant recipients. In transplant recipients aged 65-84 years a 2-fold increase in serum trough levels of CNIs was found compared with younger controls in part due to an age-related decline of CYP3A activity and a significant decline in calcineurin phosphatase activity. In addition, the rate of acute rejection declines with increasing recipient age. Moreover, the rate of comorbidities and complications is increased in elderly transplant recipients, including new-onset diabetes after transplantation (NODAT), cancer development, and the risk of serious bacterial infections. Lower albumin levels and decreased kidney function are associated with increased clearance of MMF, so higher doses might be needed. Clearance of glucocorticoids decreases in the elderly and higher doses might aggravate adrenal suppression and potentiate the risk of NODAT. In elderly transplant recipients with a low immunologic risk profile, reduced doses of immunosuppression are advisable.

A retrospective study among recipients 60 years and older compared a group with an initial tacrolimus trough level of 10-12 ng/mL and MMF at a dose of 2 g/d and another group with a lower tacrolimus dose (trough level 8-10 ng/mL) and reduced MMF exposure (1 g/d). During short-term follow-up (<2 years), graft loss was more frequently observed in the group with higher immunosuppressive density, mainly due to higher mortality rates. There was no difference in rejection rates, BK virus nephropathy, or cytomegalovirus infections.

In conclusion, an individualized approach to elderly patients with autoimmune kidney diseases and transplant recipients seems indicated to reduce the burden of complications of immunosuppression. Ongoing clinical trials will further refine strategies to improve overall and kidney survival.

Patients on Dialysis

The disease entity must factor into considerations regarding initiation of immunosuppression in patients receiving dialysis or with severely decreased kidney function. In anti-GBM disease, patients having anuria for at least 48 hours, a high percentage of crescents on kidney biopsy, advanced age, and high titers of anti-GBM antibodies have low probability of regaining independent kidney function. The picture is different for patients with AAV. A study of patients with a mean age of 75.2 years found the recovery rate might be as low as 25%, but this rate increases with decreasing age and in reports of more contemporary cohorts. Analysis of 41 patients with a median age of 62 years found dialysis-independent kidney function in 73%, while 4 more patients progressed to kidney failure during the follow-up period. At 1 year, the eGFR of patients in the former group was 30 mL/min/1.73 m^2.

The mortality of patients presenting with severely decreased kidney function is high, mainly due to complications of immunosuppressive therapy, as the MEPEX trial has indicated. Analysis of 136 patients with AAV reported from a single center found infectious complications of patients with kidney failure were almost twice as frequent and a major contributor to mortality of these patients, while the relapse rate as compared to before reaching kidney failure was reduced by 60%. These results were confirmed in an analysis of a UK center, which also found a significant number of severe infections; most of these infections occurred during either treatment with glucocorticoids and cytotoxic therapy or glucocorticoids alone. The potential of kidney function recovery of patients with AAV was also underlined by an analysis of the ERA Registry, which found a higher 90-day recovery rate of patients with AAV in comparison with matched control groups. Again, a reduced glucocorticoid-dosing regimen, for example, as used in PEXIVAS, may be associated with fewer treatment-associated side effects.

Once patients with kidney transplants reach kidney failure, maintenance immunosuppression is usually reduced to a certain extent. Most patients will receive low-dose immunosuppression during follow-up. A retrospective study investigated the impact of weaning immunosuppression 6 months after graft failure (prednisolone equivalent dose of <10 mg/d) in comparison with maintaining treatment (prednisolone equivalent dose of ≥10 mg, or prednisolone plus additional treatment). All-cause mortality was significantly greater in patients who had maintained immunosuppression while rejection rates did not differ. An individualized approach to weaning immunosuppression should be adopted, considering the benefits of continuing immunosuppression to preserve residual kidney function and prevent graft-intolerance syndrome, and lower the development of de novo donor-specific antibodies and the risk of infections and malignancy.

Additional Readings

➢ Krenzien F, ElKhal A, Quante M, et al. A rationale for age-adapted immunosuppression in organ transplantation. *Transplantation.* 2015; 99(11):2258-2268. https://doi.org/10.1097/TP.0000000000000842

➢ Moiseev S, Novikov P, Jayne D, Mukhin N. End-stage renal disease in ANCA-associated vasculitis. *Nephrol Dial Transplant.* 2017; 32(2):248-253. https://doi.org/10.1093/ndt/gfw046

➢ Webster P, Lightstone L, McKay DB, Josephson MA. Pregnancy in chronic kidney disease and kidney transplantation. *Kidney Int.* 2017; 91(5):1047-1056. https://doi.org/10.1016/j.kint.2016.10.045

Article Information

Authors' Full Names and Academic Degrees: Sam Kant, MD, Andreas Kronbichler, MD, PhD, and Duvuru Geetha, MD, MRCP (UK).

Authors' Affiliations: Division of Nephrology, Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland (SK, DG); Department of Internal Medicine IV (Nephrology and Hypertension), Medical University Innsbruck, Innsbruck, Austria (AK); and Department of Medicine, University of Cambridge, Cambridge, United Kingdom (AK).

Address for Correspondence: Duvuru Geetha, MD, 301 Mason Lord Dr, Johns Hopkins Bayview Medical Center, Baltimore, MD 21224. Email: gduvura@jhmi.edu