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Review Article

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Optimizing Immunosuppression in Glomerular Diseases

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Abstract

Dysregulation of the immune system can cause various glomerular diseases. Immunosuppressive drugs may be required to manage or retard their progression. Though a variety of immunosuppressive agents are available, there is seldom consensus on the choice of drugs, their combination, frequency, and duration. As most of these drugs have significant toxicity and can contribute to morbidity and mortality, their use should be optimized to obtain the best clinical effects while minimizing their adverse effects and cost. Herein, we review the published data on various drugs to treat common glomerular diseases like idiopathic nephrotic syndrome, primary membranous nephropathy, immunoglobulin A nephropathy, lupus nephritis, and renal vasculitis as the information may help to optimize individualized immunosuppressive treatment of these diseases.

Keywords: Immunosuppressive drugs; Idiopathic nephrotic syndrome; Membranous nephropathy; IgA nephropathy; Lupus nephritis; Renal vasculitis; Cost-effective immunosuppression.

Introduction

Glomerular diseases are a major cause of renal diseases worldwide and account for almost 25% of nondiabetic chronic kidney diseases.[1] Several of them can progress to end stage renal disease and are an important cause of morbidity and mortality. Dysregulation of the immune system with resultant immune-mediated renal injury is the predominant pathogenic cause of most glomerular diseases.[2] Hence, immunosuppressant drugs form the mainstay of treatment for most of them.

Nevertheless, suppressing the immune system can be fraught with danger as it alters the host defense systems, thus predisposing patients to the risk of infections and even malignancies.[3] Tolerability of these immunosuppressants is also a major problem as a prolonged duration of treatment may be necessary. To add to these concerns, the financial implications of using immunosuppressive agents often limit their use in conventional dosages and frequencies, with cost-cutting measures frequently employed in lower economic countries. Strategies for using the optimal dose and choice of drugs in order to attain the desired clinical benefit with better tolerability and cost advantages could have significant therapeutic benefits in the management of these patients. Consensus on the ideal choice of drugs, need for combination, dose, frequency, and duration is often lacking, with guidelines changing frequently. Literature evidence on clinical efficacy with the least immunosuppression may help to develop ideal management strategies for glomerular diseases.

Immunosuppression in glomerular diseases

The most common glomerular diseases that often require therapeutic immunosuppression worldwide include idiopathic nephrotic syndrome, immunoglobulin A (IgA) nephropathy, primary membranous nephropathy (MN), lupus nephritis, and renal vasculitis.

Idiopathic nephrotic syndrome

More than 75% of idiopathic nephrotic syndrome cases in childhood are steroid responsive and are managed as presumed minimal change disease (MCD) without a renal biopsy.[4,5] In those with frequently relapsing or steroid-dependent nephrotic syndrome (SDNS), renal biopsy reveals MCD in the majority of cases and focal segmental glomerulosclerosis or mesangial proliferation in some.[6] In adults with nephrotic syndrome, the need for immunosuppression is decided after a renal biopsy.[7] Unlike in children, MCD accounts for only 30% of idiopathic nephrotic syndrome in adults.[8]

Treatment with corticosteroids

Treatment of childhood nephrotic syndrome dramatically changed with the advent of corticosteroids in the 1950s, with almost 90% responding to a 4–6-week course.[3] The suggested dose is 60 mg/m^2 (or 2 mg/kg) of prednisolone for 4 weeks followed by conversion to a reduced dose (40 mg/m^2 per dose) on alternate days for 4 weeks.[9] Though initially it

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was suggested that steroids may be given in divided doses, giving it as a single morning dose had a similar effect with less toxicity.[10] Reducing the duration to 2 weeks after attaining remission was shown to be noninferior to the 4-week therapy.[11] The high prevalence of relapse with the 4-week therapy prompted suggestions to increase the initial duration of daily steroids to 6 weeks and then to administer it on alternate days for 6 weeks, with a reported benefit in some studies,[12] but not others where extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome.[13] Unfortunately, around 70% of patients relapse despite prompt initial response necessitating further therapy. Patients who relapse two or more times within 6 months or four or more times within 12 months are termed as having frequent relapsing nephrotic syndrome (FRNS), and those having two relapses with a steroid taper or within 1 month of ending therapy are termed as having SDNS, which may require prolonged exposure to steroids.[14]

It is recommended that relapses are treated with a single daily dose of 2 mg/kg/day or 60 mg/m^2/day (maximum of 60 mg) until complete remission (urine protein creatinine ratio ≤ 20 mg/mmol or negative, or trace dipstick on three or more consecutive days) and then decreased to alternate days (1.5 mg/kg/dose or 40 mg/m^2/dose, maximum of 40 mg) for 4 weeks.[3] This can result in significant toxicity like growth retardation, steroid facies, obesity, hypertension, diabetes mellitus, bone abnormalities, weight gain, psychiatric disorders, gastrointestinal bleeding, and long-term cardiovascular disease.[15] Decreasing the cumulative steroid doses to the minimum to achieve and maintain remission would be ideal. Yet some centers advocate a prolonged steroid course of several months to years in doses of around 0.25 mg/kg/day or 0.5 mg/kg on alternate days in frequent relapsers, with the aim to decrease relapses and limit high-dose steroids in the latter situation.[16] Though this may be cost effective, it is associated with significant steroid toxicity.

In adults, MCD is steroid sensitive, but steroid resistance is seen in 5–20% of cases.[17] They may need a longer initial duration, and the response is less than that for children.[18] Although 95% of children attain remission by 8 weeks, only 50–75% of adults do so. When steroid resistance is observed, focal segmental glomerulosclerosis is often noted on re-examination of the initial biopsy or on rebiopsy.[19]

Additional immunosuppression may be needed for FRNS and SDNS patients, while it is occasionally used for those with steroid-resistant nephrotic syndrome.[17] In adults, the initial course of prednisone is given at a dose of 1 mg/kg (up to 80 mg) once daily in the morning or 2 mg/kg (up to 120 mg) on alternate days. The administration of steroids on alternate days has been shown to have fewer side effects and a comparable efficacy.[20] A longer treatment duration for up to 16 weeks is recommended, even if early remission is obtained.[7]

Relapses occur in 65–80% of adults with MCD, with the majority happening within the first 3–6 months. Frequent relapse is seen in 10–30% of cases, and 15–30% of cases are steroid dependent.[6] Because the repeated use of steroids in FRNS and SDNS increases the risk of severe adverse events, the use of extremely "low-dose" prednisone or steroid-sparing immunosuppressive agents, such as alkylating agents (cyclophosphamide), antimetabolites (mycophenolate mofetil; MMF), or calcineurin inhibitors (CNIs; e.g., cyclosporin or tacrolimus), is advocated. They may also be used in those with obesity and diabetes mellitus, in whom a steroid-sparing approach may have advantages.[21]

Treatment with cyclophosphamide

Cyclophosphamide at a daily dose of 2 mg/kg for 12 weeks or 3 mg/kg for 8 weeks has been tried in relapsing nephrotic syndrome patients to prevent or reduce relapses, preferably after attaining remission and thereby decreasing overall steroid exposure.[3] Subsequent courses may occasionally be required, though it is recommended that the cumulative cyclophosphamide dose should not exceed 168 mg/kg to limit bone marrow suppression and gonadal toxicity in children.[22] Administering monthly boluses of cyclophosphamide at 500 mg/m^2 has been tried for up to 6 months to achieve a longer duration with a lower cumulative dose and better compliance in the pediatric group.[23] In adults, after attaining a remission with prednisone, treatment with oral cyclophosphamide is initiated at 1–2 mg/kg/day, and treatment is given for 8–12 weeks. It is advisable to monitor the white blood count weekly and to adjust the dose to prevent leukopenia (count <3,000/mm^3). The cumulative dose of cyclophosphamide given for 8–12 weeks is generally well under that associated with infertility (>200–300 mg/kg) or malignancy (cumulative dose of >36 g).[7] Once on cyclophosphamide, the prednisone dose is tapered over 4 weeks. This often results in a remission rate of up to 80%, with a relapse rate of <10% at 1 year.[24]

Treatment with chlorambucil

Chlorambucil is another alkylating agent used to prevent relapses. A dose of 0.2 mg/kg for 8 weeks has been used, but it has been largely replaced by cyclophosphamide due to its wider availability and tolerability.[25]

Treatment with CNIs

CNIs have been widely used to treat FRNS and SDNS as they have the ability to reduce the cumulative steroid dose. Initially, cyclosporine was used in two divided doses of 3–5 mg/kg. Monitoring the drug levels and targeting the dose to keep the C0 (trough) levels around 75–100 nmol/L or the C2 levels between 150–300 nmol/L has been beneficial for optimizing the dose needed. Targeting the dose to be 50% of the standard area-under-the-curve dose can result in a significant reduction in the cyclosporine dose.[26] Relapse of nephrotic syndrome is frequent during cyclosporin tapering, often leading to the need for long-term treatment resulting in a tradeoff of steroid dependency for cyclosporin dependency and the potential for associated nephrotoxicity.[27] To minimize the potential for cyclosporin nephrotoxicity, the dose should be slowly tapered to the lowest dose that maintains a remission.[28]

The later availability of tacrolimus has made it more acceptable due to fewer cosmetic side effects and a better efficacy at a dose of 0.1–0.2 mg/kg in two divided doses to a target C0 level of 3–7 ng/dL. It has been shown that the CNI blood levels are dependent on the ability to metabolize the drug, which may be inherited based on the *CYP3A* genetic polymorphism. Those with low levels of the genetically determined enzyme may achieve the desired target therapeutic blood levels with a lower dose.[29] Concomitant use of drugs that can inhibit the metabolism of the CYP450 pathway, like ketoconazole, erythromycin, and diltiazem, could aid in re-

ducing the dose needed for adequate blood levels.[30] The main drawbacks of CNIs are the need for prolonged therapy, relapses on tapering, and nephrotoxicity, which may necessitate renal biopsy for its early detection, making it a less-than-ideal immunosuppressant in FRNS and SDNS, even though micro-emulsified cyclosporine may have less nephrotoxicity.[31] The risk of new-onset diabetes mellitus with tacrolimus is also of concern.

Treatment with MMF

The use of MMF at a dose of 1,200 mg/m^2/day divided into two doses has been shown to be effective in the treatment of FRNS and SDNS with MCD. However, patients treated with MMF often tend to relapse when the drug is discontinued, resulting in MMF dependence.[32] Hence, this often requires a prolonged duration of treatment and may not be cost effective.

Treatment with levamisole

Levamisole is an immunomodulatory drug that has been shown to decrease the frequency of relapse and steroid exposure in FRNS patients at a dose of 2–2.5 mg/kg three times a week for 6–12 months.[33] Though generally well tolerated and cheap, its low efficacy compared to other drugs has limited its widespread use.

Treatment with rituximab

Rituximab is a monoclonal antibody targeting CD20 B cells, resulting in the suppression of nephrotic syndrome. It was found to be effective in preventing relapses in MCD in the pediatric population as well as in adults.[34] The appropriate dose and duration, however, are still contentious. The high dose and frequency used for treating B-cell lymphoproliferative disorders (375 mg/m^2 weekly for 4 doses) was extrapolated for the management of FRNS and SDNS. The resultant high cost and uncertainty of long-term effects might have accounted for it not being considered as the initial choice in this setting.[3] Yet, there are suggestions that a lower initial dose of 100 mg and targeting subsequent doses based on the CD19 count and clinical response may suffice to produce adequate and prolonged suppression of B cells with a significant benefit in preventing relapses.[35] The relatively lower cumulative dose, lower cost, tolerability, lack of nephrotoxicity, shorter duration, and efficacy compared to those of drugs like CNIs and MMF make it attractive as a possible first-line medication to prevent relapses once remission has been achieved. The significantly lower cost of immunosuppression may benefit low-income nations and those not having insurance coverage or government funding.

Recommended treatments

It appears that initial daily prednisolone treatment for 4–6 weeks, followed by 6 weeks of alternate-day steroid treatment and abrupt stopping may reduce relapses. Once relapse takes place, giving daily steroids until remission occurs for three consecutive days and then shifting to alternate days for around 6 weeks appears to be effective with the least amount of steroid toxicity. Using low-dose rituximab in FRNS and SDNS patients once remission occurs and targeting the next dose based on the B-cell reconstitution has been shown to be effective in some individuals in single-center studies, providing the least cost and toxicity. Larger randomized multicenter trials may be needed to see if this holds true for the majority of patients across the world.

MN

MN is a common cause of nephrotic syndrome in adults that is characterized by the presence of IgG deposition in the subepithelial space of glomerular capillaries and glomerular basement membrane thickening. It is broadly classified as primary, when there is no underlying systemic illness or infection, and secondary, which may be associated with infections, drug use, or systemic disorders. The treatment of secondary MN is primarily aimed at managing the underlying cause. Primary MN has been associated with antibodies directed against phospholipase A2 receptor (PLA2R), which is located in the glomerular basement membrane in 70% of cases, while it has been associated with other antibodies in the rest.[36,37] As some patients with primary MN can go into spontaneous remission and many patients are at low risk of progression because proteinuria may subside with drugs targeting the renin–angiotensin–aldosterone system, immunosuppressive therapy in MN is generally reserved for those at a high risk of progression, like those with proteinuria exceeding 4 g/day, those with renal dysfunction, and those in whom proteinuria fails to respond to renin–angiotensin–aldosterone system blockade.[1] As steroids alone have not been effective in attaining remission and decreasing proteinuria, they are often combined with cytotoxic agents like chlorambucil or cyclophosphamide,[38] CNIs like cyclosporine or tacrolimus,[39] and agents targeting B cells like rituximab,[40,41] ofatumumab, and obinutuzumab.[42,43] A six-month course starting with three daily boluses of 1 g of methyl prednisolone followed by 27 days of oral prednisolone (0.5 mg/kg) and repeated on the third and fifth months, with daily oral chlorambucil (0.2 mg/kg) in the second, fourth, and sixth months could induce remission in almost 70% of patients.[44] Using a lower dose of 500 mg instead of 1 g of methyl prednisolone was also found to be effective, suggesting a better tolerability.[45] In the modified Ponticelli regime, cyclophosphamide (2 mg/kg) was substituted for chlorambucil, with more than 50% of patients responding after 6 months and a better tolerability.[46] However, in those who fail to respond or in those who relapse, there are concerns about giving subsequent cycles due to risk of infection, bone marrow suppression, hemorrhagic cystitis, infertility, and malignancies when the dose exceeds 20 g, suggesting need for alternate immunosuppressive agents.[47] CNIs like cyclosporine have been used at a dose of 3–5 mg/kg, aiming to keep a trough blood level of 125–225 ng/mL, with 75% of patients going into remission by 6 months. In addition, tacrolimus at a dose of 0.75–1 mg/kg has been used to keep a trough level of 5–8 ng/mL.[39] However, the response to CNIs is inferior to that of the modified Ponticelli regime, with higher relapse rates and the need for a longer duration with the risk of relapse occurring on tapering or withdrawal.[48] CNIs also are associated with the risk of nephrotoxicity, thus making its prolonged use less than ideal. As antibodies against PLA2R antigens and other antigens have been implicated in the majority of primary MN,[36] B cell-directed therapies like rituximab have been tried and shown to be noninferior to cyclosporine,[49] though it was inferior when the PLA2R antibody titers were high.[50] However, there is no consensus on the ideal dose

and frequency. A high dose of 1–2 g was initially used, with the subsequent dose being given weekly or fortnightly, without a protocol for targeting the subsequent dose based on monitoring the CD19 count. Some centers decided on giving subsequent doses based on the CD19 counts and PLA2R antibody titers. Such a strategy showed a similar efficacy with a lower cost and total dose of rituximab.[40] Even a single low dose of rituximab has been shown to decrease the CD19 B-cell count and induce remission.[35,51,52]

Giving 500 mg of methylprednisolone instead of 1 g and substituting cyclophosphamide for chlorambucil in the Ponticelli regime appears to have a lower toxicity and comparable efficacy.[44] Rituximab may have a better tolerability than other nonsteroidal alternatives; and in a low dose, it may be cheaper. While low-dose rituximab and targeting subsequent boosters based on the CD19 B-cell reconstitution has shown efficacy with cost benefits in some single-center studies, even larger more frequent doses of rituximab have not shown efficacy in all cases. It is possible that there could be differing responses to rituximab based on the individual. There is also a chance that those who respond to higher doses of rituximab may have responded to a lower dose. This raises the suggestion that a lower dose should be given initially and then a higher dose should be subsequently administered if the response is unsatisfactory, depending on the CD19 count as well as an increase in the PLA2R antibody titer. Controlled multicenter studies comparing lower initial dose of rituximab and CD19 count-based boosters with a conventional higher dose and CD19 count targeted boosters with an adequate sample size and a prolonged follow-up period may help to clarify the best protocol.

IgA nephropathy

IgA nephropathy is the most common type of glomerulonephritis worldwide. It is characterized by predominant deposition of IgA in the kidney. In addition, increased mucosal B-cell production of galactose-deficient polyclonal IgA1 (pIgA1) and subsequent deposition of IgG-pIgA1 compexes in the glomerulus can lead to complement, cytokine, and chemokine activation with mesangial cell proliferation, inflammation, and kidney damage.[53] Though initial studies have suggested some benefit with corticosteroids in reducing progression,[54] it was associated with serious adverse effects due to infections and even death following a trial of methylprednisolone, resulting in early halting in the TESTING trial.[55] Others (Stop-IgAN Trial) also have observed no benefit in attaining remission with steroids and other immunosuppressants compared to supportive care in a follow-up of up to 10 years, with more adverse effects with the former.[56]

Though MMF at a dose of 1.5 g/day for 12 months was shown to have renal protection in progressive IgA nephropathy, it was confined to a Chinese cohort.[57] No benefit was seen in trials conducted in other countries.[58] It is possible that benefits of immunosuppression may be restricted to patients having associated crescentic glomerulonephritis, endocapillary proliferation, and if proteinuria persists despite nonimmunosuppressive medication for at least 90 days.[59,60]

As the lymphoid follicles at the level of Peyer's patches of the distal ileum may be the cause of excess pIgA1 production, it was felt that targeted therapy of the B cells in the ileum by using budesonide at a dose of 16 mg/day for up to 9 months was the best treatment. As budesonide undergoes extensive first pass metabolism, there is minimal systemic absorption and few side effects with a decrease in proteinuria and renal protection.[61] Drugs targeting both endothelin type A and angiotensin receptors like sparsentan at a dose of 400 mg are being evaluated; if they are found to be effective, they may mitigate the need for immunosuppressants.[62] Recent observations also have suggested a beneficial role of sodium/glucose cotransporter 2 inhibitors like dapagliflozin at a dose of 10 mg/day, which could also avoid the need for immunosuppression.[63] Though rituximab targets circulating B cells, it has not been shown to be effective, possibly because of the lack of inhibition of tissue or mucosal B cells.[64]

Indications for systemic steroids and other immunosuppressants in IgA nephropathy appear to be dwindling with recent trials. Probably, they may be reserved for those with progressive renal failure, crescentic variants, or if nephrotic range proteinuria persists despite supportive treatment. If shown to be effective in large multicenter trials, the local delivery of budesonide, dapagliflozin, dual endothelin and angiotensin receptor blockers may avoid the systemic toxicity of steroids and other immunosuppressants in several cases.

Lupus nephritis

Systemic lupus erythematosus is an autoimmune disease with autoantibodies targeting various organs. The kidneys tend to be affected in around 60% of cases. Decisions regarding the type of immunosuppression needed to decrease the production of autoantibodies in lupus nephritis patients are mostly based on the histological class. While steroids alone may suffice in class I and class II lupus nephritis, they may need to be combined with additional immunosuppressants, such as common cytotoxic agents like cyclophosphamide, mycophenolic acid derivatives, and occasionally azathioprine in classes III, IV, and V.[65] Most proliferative lupus patients are treated with three doses of methyl prednisolone (0.5–1.5 g) followed by oral steroids at 0.5–1 mg/kg daily for 2–4 months and then tapered. The previously poor outcome of proliferative lupus nephritis patients dramatically changed with the National Institutes of Health regime of adding six monthly boluses of cyclophosphamide at a dose of 0.5–1 g/m^2 followed by six more doses given at three-month intervals.[66] However, this was associated with the risk of gonadal toxicity, bone marrow suppression, and future malignancies.[47] The Euro lupus regime used a lower dose of 500 mg of cyclophosphamide at 2-week intervals for six doses with comparable efficacy.[67] Meanwhile, MMF at a dose of 2–3 g/day was found to be noninferior to cyclophosphamide in the induction phase, with better tolerability.[68] There are also some single-center reports of azathioprine being comparable to cyclophosphamide in the initial phase.[69] For maintenance therapy after the initial induction therapy, both azathioprine and mycophenolate have been used as alternatives to the National Institutes of Health protocol of cyclophosphamide, showing a better safety profile. While there are reports of MMF at a dose of 2 g daily being superior to azathioprine at a dose of 2 mg/kg in preventing relapses in the maintenance phase,[70,71] other studies did not show superiority of MMF.[72] Moreover, azathioprine was superior to mycophenolate in the maintenance phase of renal vasculitis.[73] These results suggest the need for further multicenter trials comparing the

roles of azathioprine and mycophenolate in the maintenance phase of lupus nephritis. If found to be noninferior, azathioprine could be a cheaper alternative in the maintenance phase of lupus nephritis.

In patients who failed to respond to these drugs, the addition of CNIs like cyclosporine and tacrolimus was found to be beneficial.[74] CNIs also have been used in lupus complicating pregnancy with maternal and fetal acceptability.[75] In cases resistant to conventional therapies, rituximab has been tried with limited success. Recently, belimumab,[76,77] a monoclonal antibody targeting B cells, and a novel CNI called voclosporin also have been tried in resistant lupus nephritis.[78]

In addition, the use of autologous T cells from patients with systemic lupus erythematosus transduced with anti-CD19 chimeric antigen receptor was shown to induce and maintain remission for up to 8–12 months in refractory lupus patients.[79] If further multicenter studies confirm its efficacy, this method could help to reduce immunosuppression in lupus patients.

The Euro-Lupus regime as induction and azathioprine as maintenance appears to be the regime offering minimal side effects and cost-effective immunosuppression. Other protocols should be restricted to those who fail to respond or have other reasons where this might not be ideal. The use of chimeric antigen receptor T cells transduced with anti-CD19 antibodies could result in less immunosuppression in lupus nephritis patients in the future.

Renal vasculitis

The kidneys are a common target of systemic vasculitides like microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatous polyangiitis, IgA vasculitis, cryoglobulinemic vasculitis, etc. The majority of renal vasculitis cases are associated with antineutrophil cytoplasmic antibodies (ANCAs), which may be directed against proteinase 3 or myeloperoxidase. Immunosuppression has drastically reduced mortality, with remission rates of 53–90%; hence, it is a cornerstone therapy.[80] Yet infections due to immunosuppression along with malignancy and cardiovascular disease are the major cause of death at 1 year after the onset of treatment rather than active disease.[81] Tailored and personalized immunosuppressive therapies may thus be needed to avoid over-immunosuppression.

Immunosuppression commonly includes initial induction treatment aiming to attain remission within the first 3 months with methyl prednisolone pulses followed by oral steroids (prednisolone at 1 mg/kg) and varying combinations of cyclophosphamide, rituximab, and azathioprine. While cyclophosphamide has been found to be effective, its limitation is the risk of cumulative dose-related toxicity as vasculitis generally requires a prolonged course and relapses are not infrequent. Oral cyclophosphamide at a dose of 1–2 mg/kg for 6 months or more has been shown to have more toxicity than single monthly boluses of 500 mg/m^2 in the CYCLOPS trial, with comparable efficacy; hence, it seems to be less preferred.[82]

Rituximab may have a better tolerability than cyclophosphamide. When comparing multiple boluses of rituximab versus oral cyclophosphamide, it was found to be noninferior, with a better tolerability and higher remission rates.[83,84] This was also shown when rituximab was compared to monthly cyclophosphamide boluses.[85] This finding suggests that rituximab could be a better alternative to cyclophosphamide and may be the best first-line treatment.[86] Though a dose of 375 mg/m^2 weekly for 4 weeks initially has been tried, there is no consensus on the dose or frequency of initial and subsequent boluses.[85,86] Moreover, there are no guidelines on titrating the doses to keep the CD19 count suppressed or deciding on further boosters depending on B-cell repopulation. If studies show that the clinical efficacy could be decided on B-cell suppression, it could help to limit the initial dose as well as decrease the frequency of administration of rituximab as has been shown to be effective when rituximab was used in SDNS and MN.[35] Determination of the effect of rituximab on decreasing ANCA titers, proteinuria, and stabilizing renal functions also may need multicenter trials for clarification on its appropriate dose and frequency.

MMF given orally at a dose of 2–3 g daily had comparable remission rates as pulse cyclophosphamide by the sixth month, but those taking it had more subsequent relapses. Furthermore, considering the clinical and cost effectiveness, this drug may not be ideal.[87]

Maintenance immunosuppression after the induction phase is necessary as relapses are frequent. A regime that is more effective in preventing relapses would be advantageous. The CYCAZAREM trial found that azathioprine was as effective as cyclophosphamide in preventing relapses, with a better safety profile.[88] Meanwhile, the IMPROVE trial showed that MMF was associated with more relapses compared to azathioprine.[73]

Subsequently, the MAINRITSAN study demonstrated that rituximab at a biannual dose of 500 mg was better than azathioprine in preventing relapses.[89] However, the optimal dose of rituximab in preventing relapses is unclear, with 1 g every four months being used in the RITAXAREM trial. As relapses are more common with proteinase 3 ANCA vasculitis, these patients may need a longer duration of maintenance therapy than others, which may extent to 4–5 years. As there is a possibility of developing antirituximab antibodies that may affect its action, alternate humanized antibodies against B cells like ofatumumab may have a role in this setting.[90] Whether monitoring the CD19 B-cell count or deciding the need for subsequent boluses based on the B-cell reconstitution is useful needs further study, although the MAINRITSAN II study reported relapses even when B cells were suppressed.[91] Recent studies have suggested CD19-targeting chimeric antigen receptor T cells can be useful in several autoimmune disorders, and it may be possible to limit the cumulative dose of drugs for total immunosuppression.[92]

Steroids given initially as pulse methyl prednisolone followed by oral prednisolone and monthly cyclophosphamide boluses for 6 months followed by prednisolone and azathioprine as maintenance appears to be an effective, better tolerated, and a cheaper option. In addition, rituximab may have a role in those prone for frequent relapses like those with proteinase 3-associated ANCA vasculitis. Nevertheless, the role of CD19-targeted initial and booster doses needs further study.

Table 1 shows the details of drugs used in common glomerular diseases, the rationale for their use as per the pathogenetic mechanisms, dose, adverse effects, and comments regarding their choice. Suggestions based on the literature review of possible methods for optimizing immunosuppression are summarized in Table 2.[10-12,20,23,26,30,35,45,46,51,52,59-63,67,69,72,78,79]

Table 1. Summary of rationale, dosage, adverse effects and comments on use of commonly used drugs various glomerular diseases

Glomerular disease	Postulated pathogenesis	Treatment modalities	Dosage	Postulated mechanisms	Adverse effects	Comments
Idiopathic nephrotic syndrome	a) Disorder of T cells b) Circulating permeability factors c) Disorder of B cells	Corticosteroids	60 mg/m2 or 2 mg/kg daily initially and later alternate days	Inhibits Tcells May decrease circulating permeability factors	Steroid facies Growth retardation Obesity Diabetes mellitus Bone abnormalities	Drug of first choice May need alternate drugs in case of relapses
		Cyclophosphamide	2–2.5 mg/kg 500 mg/m2 monthly pulses	Inhibits Tcells May decrease circulating permeability factors	Bone marrow suppression Gonadal toxicity Alopecia Haemorrhagic cystitis	Useful in steroid dependent and frequently relapsers
		Chlorambucil	0.2 mg/kg	Targets T,B cells	Bone marrow suppression	Rarely used at present due to toxicity
		Cyclosporine	3–5 mg/kg	Targets T,B cells, decreases permeability factors Decreases proteinuria due to hemodynamic effects	Hirsuitism Gingival hyperplasia Diabetes mellitus Nephrotoxicity	Used in relapsers High chance of relapse on withdrawal Nephrotoxicity could limit its prolonged use
		Tacrolimus	0.1 to 0.2 mg/kg			
		Mycophenolate Mofetil	1–2 gm/day	Targets T, B cells	Bone marrow suppression	Needs prolonged duration Costly
		Levamisole	2–2.5 mg/kg twice a week	Immunomodulator	Minimal side effects	Needs prolonged duration Limited efficacy
		Rituximab	100 mg to 375 mg/m2 in varying frequency	B cell depletion by targeting CD19 cells	Pyrogenic reactions Activation of Hepatitis B Rash, Bronchospasm	Dose highly variable No consensus on appropriate dose Highly effective in frequent relapsers and steroid dependent nephrotic syndrome

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Table 1. *(continued)*

Glomerular disease	Postulated pathogenesis	Treatment modalities	Dosage	Postulated mechanisms	Adverse effects	Comments
Primary Membranous Nephropathy	a) Antibodies against PLA2R antigens in glomerular basement membrane b) Antibodies against Thrombospondin type1 domain containing 7 A c) Antibodies against NELL d) Antibodies against other antigens	Methyl prednisolone pulses for 3 days followed by oral prednisolone for 27 days repeated on months 3 and 5	500–1 gm 0.5 mg/kg	Decrease circulating antibodies Anti inflammatory effect	Mentioned above	Time tested
		Cyclophosphamide	2 mg/kg orally on months 2,4 and 6	Targets T,B cells Decreases Antibody production	Mentioned above	Toxicity could limit its use Cost effective
		Chlorambucil	0.2 mg/kg on months 2,4 and 6	Targets T,B cells, Decreases Antibody production Targets T, B cells	Mentioned above	Rarely used at present due to toxicity Needs prolonged duration
		Cyclosporine	3–5 mg/kg/day	Decreases proteinuria due to hemodynamic effects	Mentioned above	Costly Nephrotoxicity could limit its prolonged use Less effective
		Tacrolimus	0.75 to 1 mg/kg/day			
		Rituximab	100 mg to 375 mg/m2 and upto 1–2 grams in varying frequency	B cell depletion by targeting CD19 cells Decreases antibodies against target antigens	Mentioned above	Dose highly variable No consensus on appropriate dose Costly
IgA Nephropathy	a) Activation of mucosal B cells b) Increased concentration of galactose deficient polyclonal IgA1(pIgA1) c) Deposition of pIgA1 and IgG compexes in the glomerulus d) Complement, cytokine and chemokine activation e) Mesangial cell proliferation, Glomerular inflammation, Glomerulosclerosis	Corticosteroids	1–2 mg/kg 500 mgIV	Decreases B cell activation	Mentioned above	Systemic steroids may cause infections/death

(continued)

Table 1. *(continued)*

Glomerular disease	Postulated pathogenesis	Treatment modalities	Dosage	Postulated mechanisms	Adverse effects	Comments
		Budesonide	16 mg daily	Decreases mucosal pIgA1 production	Mild	Minimal systemic effects
		Mycophenolate mofetil	1.5 gm daily	Suppresses IgG production	Mentioned above	As above
		Renin angiotensin blockers	Variable depending on type	Decreases intraglomerular pressure Decreases proteinuria	May cause worsening renal function, Hyperkalemia	Immunosuppression sparing therapy
		Endothelin receptor blocker, (Sparsentan)	400 mg/day	Decreases intraglomerular pressure Decreases proteinuria	Hepatotoxicity	Immunosuppression sparing therapy
		SGLT2 inhibitors (eg. Dapaglifozin)	10 mg daily	Activation of tubuloglomerular feedback causing afferent arteriolar constriction Decreases intraglomerular pressure Decreases proteinuria	Urinary tract infection, worsening renal function	Immunosuppression sparing therapy
Lupus Nephritis	a) Production of autoantibodies targeting various organs b) Defective clearance of circulating immune complexes c) Disorder of B cells	Methyl prednisolone Prednisolone	a) Methyl prednisolone 0.5 to 1.5 gm pulses for 3 days in active lupus followed by Oral predisolone 0.5 to 1 mg/kgdaily and later tapered to alternate day	Targets T,B cells Decreases levels of autoantibodies Anti inflammatory effect	Mentioned above	Drug of first choice in active lupus Needs to be combined with other agents in Class 3 and Class 4 lupus
		Cyclophosphamide	Monthly pulses 500–750 mg/ m2 pulses for 6 doses then once in 3 months OR 500 mg every 2 weeks for 6 doses initially	Targets T,B cells Decreases levels of autoantibodies	Mentioned above	Risk of infertility Contraindicated in pregnancy

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Table 1. *(continued)*

Glomerular disease	Postulated pathogenesis	Treatment modalities	Dosage	Postulated mechanisms	Adverse effects	Comments
		Mycophenolate Mofetil	2–3 gm/day	Targets T,B cells Decreases levels of autoantibodies	Mentioned above	Useful in both induction and maintenance phase Contraindicated in pregnancy
		Cyclosporine	3–5 mg/kg/day	Targets T, B cells Decreases levels of autoantibodies	Mentioned above	Can be used in pregnancy Nephrotoxicity could limit its prolonged use Can be used in resistant lupus as part of multitargeted therapy
		Tacrolimus	0.75 to 1 mg/kg/day			
		Voclosporin	64 mg twice daily		Same as for Cyclosporine	
		Rituximab	375 mg/m2 in varying frequency	B cell depletion by targeting CD19 cells Decreases proteinuria due to hemodynamic effects	Mentioned above	Tried in resistant lupus with limited efficacy
		Azathioprine	1–2 mg/kg	Targets T,B cells Decreases levels of autoantibodies	Mentioned above	Not ideal in induction phase Cheap Useful in maintenance phase
		Belilumab	10 mg/kg	Decreases autoantibody levels Targets B cells Decreases levels of autoantibodies	Infusion reactions	Useful in resistant lupus

(continued)

Table 1. *(continued)*

Glomerular disease	Postulated pathogenesis	Treatment modalities	Dosage	Postulated mechanisms	Adverse effects	Comments
Renal vasculitis	Antibody mediated Eg: a) Antibodies against neutrophilic cytoplasmic antigens(ANCA) eg Proteinase 3 (p-ANCA) b) Myeloperoxidase (c-ANCA) b) Immune complexes mediated glomerular damage c) Inflammatory cells/ cytokine mediated damage	Methyl prednisolone Prednisolone	a) Methyl prednisolone 0.5 to 1.5 gm pulses for 3 days in active lupus followed by Oral prednisolone 0.5 to 1 mg/kgdaily and later tapered to alternate day	Targets T,B cells Decreases levels of autoantibodies Anti inflammatory effect	Mentioned above	Useful in initial active phase
		Cyclophosphamide	Oral: 1–2 mg/ kg for 6 months 500 mg/m2 monthly pulses	Targets T,B cells Decreases levels of autoantibodies	Mentioned above	Proven efficacy but increase toxicity IV Pulses may have less toxicity
		Azathioprine	1–2 mg/kg	Targets T,B cells Decreases levels of autoantibodies	Mentioned above	Preferred in maintenance phase Better tolerability than cyclophosphamide Decreases relapses Less toxic Cost effective
		Mycophenolate Mofetil	2–3 gm/day	Targets T, B cells	Mentioned above	Better tolerability than cyclophosphamide Not shown to be better than Azathioprine in preventing relapses Costlier than Azathioprine
		Rituximab	No consensus on ideal dose Variable dose schedule in various trials 375 mg/m2/week for 4 weeks then every 6 months or 1 gm every 4 months tried	B cell depletion by targeting CD19 cells	Mentioned above	Comparable efficacy with cyclophosphamide with lesser toxicity, no risk of infertility Effective in preventing relapses especially in those with PR3+veANCA Costly

ANCA, Antineutrophil Cytoplasmic Antibody; CD19, Cluster of Differentiation 19; IgA, Immunoglobulin A; PLA2R, Phospholipase A2 Receptor; PR3, Proteinase 3; SGLT2, Sodium-Glucose Co-Transporter 2.

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Table 2. Summary of alterations suggested for optimizing immunosuppression in various glomerular diseases.

Glomerular disease	Drug	Suggested alteration	Proposed advantage	Reference
Idiopathic nephrotic syndrome	Corticosteroids	Using single dose rather than divided dose	Decreases steroid toxicity	Ekka BK *et al*[10]
		Reducing initial duration to 2 weeks	Decreases steroid toxicity	KainthD *et al*[11]
		Decreasing relapse rate and cumulative steroid dose by increasing initial duration to 6 weeks	Decreases steroid toxicity	Schijvens AM *et al*[12]
		Use of alternate day instead of daily steroids	Decreases steroid toxicity	Bolton WK *et al*[20]
	Cyclophosphamide	Using monthly intravenous boluses instead of daily oral dose	Decrease cumulative cyclophosphamide dose and toxicity Increased compliance	Prasad N *et al*[23]
	Calcineurin inhibitors: Cyclosporine Tacrolimus	Targeting dose according to area under the curve(AUC)	Reduced dose Decreases toxicity Cost benefit	Etienne O *et al*[26]
		Using inhibitors of drug metabolism	Reduced dose Decreases toxicity Cost benefit	Kahan BD[30]
	Rituximab	Using lower initial dose of 100 mg and targeting subsequent doses based on CD19 counts	Cost benefit Lesser risk of developing Rituximab antibodies	George J *et al*[35]
Idiopathic Membranous Nephropathy	Corticosteroids Methyl prenisolone	Lowering pulse dose from 1 gram to 500 mg	Reduced toxicity Cost Benefit	RaoUR *et al*[45]
	Cyclophosphamide	Substituting for chlorambucil	Decreases Toxicity	Jha V *et al*[46]
	Rituximab	Lower initial dose and targeting booster dose according to CD19 counts	Decrease risk of infections Cost benefit	Ramachandran R *et al*[51] George J *et al*[52]
IgA Nephropathy	Corticosteroids	Restrict use to specific situations	Reduces toxicity	Hogg RJ *et al*[59] Itami S *et al*[60]
		Using targeted steroid release in ileum (Budesonide)	Reduces toxicity Cost effective	Fellstrom BC *et al*[61]
		Using non immunosuppressive agents to decrease proteinuria	Reduces toxicity Cost effective	Rovin BH *et al*[62] Wheeler DC *et al*[63]
Lupus Nephritis	Cyclophosphamide	Reduced dose and duration	Reduces toxicity Cost effective	Houssiau FA[67]
	Mycophenolate Mofetil	Substituting with Azathioprine	Cost effective	Abraham MA *et al*[69] Sahin GM *et al*[72]
	Cyclosporine	Substitution with Voclosporin	Better efficacy Less toxicity	Brad HR etal[78]
	Anti-CD19 chimeric antigen receptor (CAR-T cells)	Replacing conventional immunosuppressive agents in Lupus	Better efficacy Lesser overall immunosuppression Less toxicity	Mackensen A *et al*[79]

AUC, area under the curve; CAR-T, Chimeric Antigen Receptor T-cell therapy; CD19, Cluster of Differentiation 19; IgA, Immunoglobulin A.

Conclusions

Though immunosuppressive drugs have a role in various immune-mediated glomerular diseases, there is no clarity on the ideal choice, combinations, dose, or frequency. Table 2 offers suggestions based on the literature review of possible methods for optimizing immunosuppression. However, larger randomized controlled multicenter trials are needed to decide the ideal immunosuppression protocols to obtain the best clinical effects with the least toxicity and cost for the treatment of various glomerular diseases.

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Conflict of interest

None.

Author contributions

Contributed to study concept and design: JG, RJ; acquisition of the data: JG, RJ; assay performance and data analysis: JG; drafting of the manuscript: JG. RJ; critical revision of the manuscript: JG, RJ; supervision: JG.

Abbreviations

AUC, area under the curve; ANCAs, antineutrophil cytoplasmic antibodies; CAR-T, Chimeric Antigen Receptor T-cell therapy; CD19, Cluster of Differentiation 19; CNI, calcineurin inhibitor; FRNS, frequent relapsing nephrotic syndrome; IgA, immunoglobulin A; MCD, minimal change disease; MMF, mycophenolate mofetil; MN, membranous nephropathy; PLA2R, phospholipase A2 receptor; pIgA1, polyclonal immunoglobulin A1; PR3, Proteinase 3; SDNS, steroid-dependent nephrotic syndrome.

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