INVITED REVIEW

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MAYO CLINIC

Contemporary Monoclonal Antibody Utilization in Glomerular Diseases

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Abstract

Therapeutic monoclonal antibodies (MAbs) have been one of the fastest growing drug classes in the past 2 decades and are indicated in the treatment of cancer, autoimmune disorders, solid organ transplantation, and glomerular diseases. The Food and Drug Administration has approved 100 MAbs between 1986 and 2021, and MAbs account for 20% of Food and Drug Administration's new drug approval every year. MAbs are preferred over traditional immunosuppressive agents because of their high specificity, reduced number of drug-drug interactions, and low toxicity, which make them a prime example of personalized medicine. In this review article, we provide an overview of the taxonomy, pharmacology, and therapeutic applications of MAbs in glomerular diseases. We searched the literature through PubMed using the following search terms: *monoclonal antibodies, glomerular diseases, pharmacokinetics, pharmacodynamics, immunoglobulin, murine, chimeric, humanized, and fully human*, and limited our search to years 2018-2023. We selected peer-reviewed journal articles with an evidence-based approach, prioritizing randomized control trials in specific glomerular diseases, if available. Advances in the MAb field have resulted in a significant paradigm shift in targeted treatment of immune-mediated glomerular diseases, and multiple randomized control trials are currently being conducted. Increased recognition is critical to expand their use in experimental research and personalized medicine.

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The introduction of monoclonal antibodies (MAbs) has dramatically changed the clinical management of autoimmune diseases, cancer, and solid organ transplantation.[1] Several MAbs are seen as critical therapeutic options in diseases refractory to conventional immunosuppressive treatments, may slow disease progression and avoid severe complications compared with traditional treatment drugs, and can consequently improve patients' quality of life.

Paul Ehrlich was the first to theorize targeted immunotherapy using a monoclonal antibody.[2] Georges Köhler and César Milstein achieved fusing myeloma cell lines with B cells in 1975 to develop murine hybridoma, which are immortalized cells and can produce antigen-specific antibodies, and were awarded with the Nobel Prize in Physiology or Medicine for their discovery in 1984.[3] The first murine monoclonal antibody, muromomab-CD3/Orthoclone-OKT3 (a mouse monoclonal IgG2a antibody), was approved by the Food and Drug Administration (FDA) in 1986.[3,4] Orthoclone-OKT3 was indicated for induction and treatment of corticosteroid-resistant cell-mediated rejection in renal transplantation and was withdrawn from the market in 2010. Immunogenicity refers to the ability of a molecule to provoke an immune response. In the case of murine MAbs, such as muromomab-CD3/Orthoclone-OKT3, there was a risk of immunogenicity due to their foreign protein origin, which could lead to the development of human anti-mouse antibodies. This concern ultimately led to the FDA declining approval of new MAbs for a decade, until the approval of the first chimeric MAb, rituximab (RTX), for the treatment of B cell lymphoma. Rituximab, which is a hybrid molecule composed of both human and mouse components, was less likely to elicit an immune response and paved the way for the development of other chimeric MAbs.[5] The chimeric MAbs have been followed by humanized and then fully human MAbs, with

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adalimumab being the first fully human antibody approved for treating rheumatoid arthritis.[5]

Similar to other autoimmune diseases, the treatment of glomerular diseases has also been on the basis of immunosuppressive agents such as corticosteroids, cyclophosphamide (CP), azathioprine, calcineurin inhibitors, and mycophenolate mofetil (MMF), which have been associated with considerable toxicities.[3] Advances in the knowledge of pathophysiologic mechanisms of autoimmune glomerulopathies presented the prospect for more selective and effective and safer treatments, such as MAbs.[6] Rituximab, a chimeric MAb against the B cell–expressed type I CD20 antigen, was the first MAb used to treat glomerular disease. Although used initially for the treatment of membranous nephropathy (MN), its use swiftly spread to other glomerular diseases. This resulted in a significant paradigm shift in treating immune-mediated glomerular diseases. Since then, several monoclonal antibodies have been developed and evaluated in glomerular diseases. This review focuses on the contemporary MAbs used in glomerular diseases.

ARTICLE HIGHLIGHTS

- Therapeutic monoclonal antibodies (MAbs) have been one of the fastest growing drug classes in the past 2 decades and are indicated in the treatment of cancer, autoimmune disorders, solid organ transplantation, and glomerular diseases.
- MAbs are advantageous over traditional immunosuppressive agents because of their high specificity, reduced number of drug-drug interactions, and low toxicity.
- Recent advances in the field of MAbs have led to a significant paradigm shift in the management of immune-mediated glomerular diseases. Currently, several randomized controlled trials investigating the efficacy of MAbs in treating these diseases are underway, representing a promising future for the use of MAbs in nephrology.

Taxonomy of MAbs

There are 4 classes of MAbs[7-9]: (1) murine (manufactured by fusing murine spleen B lymphocytes with immortal myeloma cells), identified with name that ends with -omab (eg, muromomab-CD3); (2) chimeric (manufactured by using murine variable region onto human light and heavy chain; 65% human), identified with name ending with -ximab (eg, rituximab); (3) humanized (manufactured by combining the murine hypervariable regions on the top of human antibody framework; 95% human), identified with name ending with -zumab (eg, eculizumab); and (4) human (manufactured by using animals holding human transgenes, particularly hypervariable regions; 100% human), identified with name ending with -umab (eg, daratumumab).

Pharmacology and Therapeutic Applications of MAbs

Monoclonal antibodies are heterodimeric protein molecules with a molecular weight of around 150 kDa produced from a single cellular clone.[10] They consist of 2 identical light chains and heavy chains, each composed of different domains held together by disulfide bonds, forming a Y-shaped structure (Figure 1). The complementary determining region of the heavy and light variable chains regulates the antigen binding of MAbs. The constant fragment region of MAbs determines their effector function through the ability to bind Fc-γ receptors expressed on immune cells, which initiates complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.[11]

All MAbs in clinical use are the immunoglobulin G subtype and are primarily administered intravenously.[1] Their size and hydrophilicity determines the volume of distribution of MAbs. In general, MAbs have a low volume of distribution, mainly confined to plasma and extracellular fluids (usually 3-8 L). The half-life of most MAbs range from 1 to 62 days (Table 1), which allows longer intervals between dosing. These antibodies are primarily metabolized by 2 main mechanisms: (1) proteolytic catabolism, which takes place in lysosomes of cells after endocytosis of the antibody; and (2) internalization of the monoclonal antibody–target complex and intracellular degradation after target binding.[12] The proteolytic degradation of MAbs is offset when drugs bind to Fc receptors.[13] This binding recycles the drug from the endosomes to

TABLE 1. Mechanism of Action, Half-Life, and Indications of Monoclonal Antibodies Used in Glomerular Diseases[a]

Monoclonal antibody[b]	Type	Target	Half-life (d)	Indications
Rituximab	Chimeric	CD20 type I	6-62	MCD, FSGS, AAV, MN
Fresolimumab	Fully human	TGF-β receptor	14	FSGS
Obinutuzumab	Humanized	CD20 type II	26-35	Lupus nephritis
Belimumab	Fully human	BAFF	18-19	Lupus nephritis
Reslizumab	Humanized	IL5	24	AVV
Tocilizumab	Humanized	IL-6	11-19	AAV
Infliximab	Chimeric	TNF-α	7-12	AAV
Eculizumab	Humanized	C5	11-17	Atypical HUS, MPGN (dense deposit disease), C3GN
Ravulizumab	Humanized	C5	52	Atypical HUS
Narsoplimab	Fully human	Mannan-binding lectin-associated serine protease-2	Unknown	IgA nephropathy and atypical HUS
Caplacizumab	Humanized	A1-domain of vWF	1	TTP
Felzartamab	Fully human	CD38	Unknown	MN and IgA nephropathy
Isatuximab	Chimeric	CD38	Unknown	MGRS
Daratumumab	Fully human	CD38	18	MGRS

[a]AAV, antineutrophil cytoplasmic antibody—associated vasculitis; BAFF, B cell—activating factor of the tumor necrosis factor family; C, complement; CD, cluster of differentiation; FSGS, focal segmental glomerulosclerosis; HUS, hemolytic uremic syndrome; MCD, minimal change disease; MGRS, monoclonal gammopathy with renal significance; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; TGF, transforming growth factor; TNF, tumor necrosis factor; vWF, von Willebrand factor.
[b]Approved or pending approval indications by the Food and Drug Administration.

the cell surface through transcytosis, which is then released into the vascular space. This process is responsible for the prolonged half-life of these drugs. Because of the aforementioned 2 mechanisms, kidney or liver clearance of most monoclonal antibodies is not affected. Although MAbs are generally not cleared by hemodialysis or peritoneal dialysis, plasma exchange can remove them from circulation.

Regarding pharmacodynamics, MAbs have different mechanisms of action. The most used MAb in renal diseases, RTX, has a specific affinity for the B lymphocyte transmembrane protein, CD20.[14] Rituximab is a chimeric monoclonal antibody composed of a murine immunoglobulin variable region and a human immunoglobulin G1 heavy chain. It destroys circulating and tissue resident $CD20^+$ B cells but spares stem cells or plasma cells (Figure 2). The binding of the RTX antibody to the CD20 receptor leads to a formation of a complex that exposes the Fc region to effector cells such as natural killer cells, macrophages, and neutrophils. In addition, this complex formation results in the activation of the complement cascade, resulting in the formation of the membrane attack complex and subsequent cell lysis. The involved cells also undergo apoptosis, inhibition of proliferation, and cell cycle alteration. The resulting B cell depletion reduces abnormal autoreactive antibody production. It also affects T cell activation through its effects on costimulatory signal modulation, cytokines that promote T cell differentiation, and modulation of Treg and Breg cells.[11] Rituximab can also bind to sphingomyelin phosphodiesterase-acid-like-3b on the surfaces of podocytes and regulate acid-sphingomyelinase activity, preventing disruption of the actin cytoskeleton and apoptosis of the podocyte.

Although the effects of B cell depletion can persist up to a median of 4-6 months after administration of RTX in glomerular diseases, the effect on memory B cells can last for more than a year.[11] It has also been found

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that the duration of B cell depletion after a course of RTX can be affected by several factors, including the extent of proteinuria, dosing schedule, and endothelial permeability. Other receptors that are targets of MAbs include interleukins, transforming growth factor, tumor necrosis factor, CD38, B cell–activating factor, and complements (C5). The mechanism of action of other MAbs is represented in Table 1.

MAB and Renal-Specific Adverse Reactions

The discussion of MAbs and kidneys would not be complete without discussing their nephrotoxicity. Adverse effects of MAbs may occur as anaphylactic reactions, immune-related adverse events, tumor lysis syndrome, cytokine release syndrome, serum sickness, and acute kidney injury (AKI) (Table 2).[15] Other kidney-specific adverse effects include acute granulomatous and nongranulomatous interstitial nephritis, thrombotic microangiopathy (TMA), glomerular diseases such as IgA nephropathy, MN, necrotizing crescentic glomerulonephritis (GN), mesangial proliferative GN, and focal segmental glomerulosclerosis (FSGS).[16] There is no definite time interval between exposure of MAb and occurrence of AKI. This could happen even after 2 years of exposure in some cases.[17] Treatment includes discontinuation or dose reduction of MAb therapy and disease-specific treatment that may consist of corticosteroids.[18] Because of the kidney involvement associated with underlying disorders treated with MAb, it cannot be assumed that all occurrences of kidney involvement after MAb therapy are related to its use. Patients should be carefully evaluated for potential causes of AKI to make the correct diagnosis.[13] A kidney biopsy is necessary for patients exhibiting nephrotic proteinuria, progressive kidney disease, or unexplained AKI. To decrease the risk of AKI, any associated risk factors should be addressed before initiating MAb treatment. In addition, it is recommended that all patients undergo a screening kidney function test and urinalysis before beginning MAb therapy. Regular monitoring of kidney function should be continued during and after treatment because renal toxicity may occur even after treatment discontinuation.[19]

Use of MAB in Chronic Kidney Disease and End-Stage Kidney Disease

Chronic kidney disease and end-stage kidney disease (ESKD) are 2 significant comorbidities that limit use of many MAbs. Many clinical trials do not include patients with advanced chronic kidney disease and ESKD patients.[20] Pharmacokinetic properties of most MAbs suggest that they can be safely used without dose modification in these patients.[1] Most MAbs are high-molecular-weight proteins not cleared by hemodialysis membrane and, hence, do not require dose modification with hemodialysis or peritoneal dialysis.[21] However, the use of MAbs in patients with ESKD is also limited owing to a lack of data regarding efficacy and risk of drug accumulation.[20] Most clinical trials used thresholds for serum creatinine levels or creatinine clearance to exclude patients, despite the fact that these measurements are suboptimal measures of kidney function. Most of the data on the use of MAbs in such patients are on the basis of observational studies and case series.[21-24]

MAB USE IN GLOMERULAR DISEASES

Minimal Change Disease and FSGS

Minimal change disease (MCD) and FSGS are common causes of nephrotic syndrome and podocytopathies observed in adults. Although MCD is more common in children, its incidence in adults is $\geq$15%.[25,26] The term FSGS describes a histopathologic glomerular lesion that can either be detected as a rather unspecific result of a variety of underlying glomerular pathogenic processes (secondary FSGS), genetic disorders affecting podocyte integrity, or as a primary form for which an immune-mediated pathogenesis is assumed. A role for an abnormal crosstalk between B cells and autoreactive T lymphocytes has been proposed.[27] Specific treatment varies, because only primary forms and few genetic forms may benefit from immunosuppressive treatment. Approximately 63% of patients with primary FSGS have been reported to achieve remission after being treated with glucocorticoids.[27] The response rate of MCD to steroids was reported to be 75%. However, relapses are common in both FSGS and MCD.[26]

The efficacy of the second-line and third-line treatment options for corticosteroid

dependent or refractory MCD/FSGS such as calcineurin inhibitors (CNIs), MMF, and CP is acceptable; however, it is associated with significant adverse events and toxicity, which preclude long-term use. Alternatively, MAbs have a potential role in treating patients with primary podocytopathy.

Rituximab. There are still no randomized controlled trials (RCTs) to evaluate the efficacy of RTX in patients with MCD/FSGS. Tedesco et al[27] treated 31 patients with FSGS and RTX between 2009 and 2017. Rituximab was administered owing to corticosteroid dependence (58%), corticosteroid resistance (36%), or a relative contraindication to steroids (6%). The clinical response, defined as 24-hour proteinuria <3.5 g or <50% compared with baseline and a stable glomerular filtration rate (GFR), was achieved in 52% and 42% at 6 and 12 months, respectively. Patients with corticosteroid dependence reported a higher response rate (69%). For MCD, 2 small sample size studies reported that RTX, as a first-line agent, achieved a complete remission (CR, defined as proteinuria <500 mg/d) and facilitated corticosteroid withdrawal in 75%-80% of the cases.[28,29] In a recent meta-analysis of RTX use in MCD and FSGS (5 FSGS and 11 MCD observational studies with N=221) reported that the overall remission and relapse rates were 53.6% (95% CI, 15.8%-87.6%) and 47.3% (95% CI, 25.4%-70.2%) in the FSGS (n=51) studies and 80.3% (95% CI, 68.5%-88.5%) and 35.9% (95% CI, 25.1%-48.4%) in the MCD (n=170) studies, respectively.[30] Several ongoing RCTs will provide evidence-based treatment for MCD and FSGS in near future (The Use of RTX In the treatment of Nephrotic Glomerulonephritis [TURING] EudraCT; number: 2018-004611-50 and IRAS ID: 258589; and RTX From the First Episode of Idiopathic Nephrotic Syndrome [RIFIREINS]; NCT03970577).

Fresolimumab. Fresolimumab, a monoclonal anti—transforming growth factor β antibody, was studied in patient with corticosteroid-resistant FSGS (NCT01665391).[31] A total of 36 patients were enrolled in a randomized, double-blind placebo-controlled trial at 1 or 4 mg/kg dosing. The study was underpowered (originally targeted sample size of 88 patients) and did not meet the primary end points (partial, 50% reduction, or complete—urine protein-to-creatinine ratio [UPCR] < 300 mg/g—resolution of proteinuria).

The KDIGO 2021 Guideline for the Management of Glomerular Diseases still recommends high-dose glucocorticoids as a first-line therapy (grade 1D evidence) and for patients with glucocorticoid-resistant or intolerant, a trial of a CNI is recommended (grade 1C).[32]

Membranous Nephropathy

Primary MN is the second most common cause of nephrotic syndrome in adults, characterized by glomerular subepithelial IgG immune complexes depositions. Approximately, 70%-80% of patients with primary MN exhibit circulating autoantibodies to phospholipase A2 receptor (PLA2R).[33] There is an emerging evidence to support that PLA2R antibody titer correlates with disease activity.[34] Approximately 30%-40% of the patients reach ESKD in over 5-10 years after diagnosis.[35] Ruggenenti et al[36] reported that B cell depletion was associated with remission of the nephrotic syndrome in 65% of the patients with primary MN and PLA2R-Ab titer reduction preceded proteinuria response by approximately 10 months.

Rituximab. Several retrospective and prospective studies published between 2008 and 2017 revealed that that the CR and partial remission (PR) rates with RTX in MN were 60%-70% at 1 year, respectively.[37] Four RCTs were published since 2017: (1) the GEMRITUX trial,[38] RTX vs antiproteinuric treatment alone groups, reported no difference between both groups in the primary end points (CR or PR of proteinuria at 6 months). However, the rates of anti-PLA2R-Ab depletion at 6 months was 50% in the RTX group vs 12% in the antiproteinuric-alone group. Remarkably, in the extended follow-up (median, 17 months), the RTX group reached a higher remission rate of 64.9% compared with 34.3% in the antiproteinuric group; (2) the MENTOR trial[39] found significantly higher CR or PR of proteinuria at 24 months in RTX group (60%) than those of the cyclosporin group (20%) (the risk difference, 40%; 95% CI,

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25%-55%). The decline in anti-PLA2R antibody levels were greater and relapses were less in the RTX group; (3) the STARMEN trial[40] (a randomized, open-label controlled trial of 86 patients with primary MN) revealed that the primary outcome (CR or PR of nephrotic syndrome at 24 months) occurred in 83.7% in the alternating treatment with glucocorticoid and CP group and in 58.1% in the sequential treatment with tacrolimus and RTX group (relative risk, 1.44; 95% CI, 1.08-1.92). Compared with that of the tacrolimus-RTX group, the depletion of anti-PLA2R antibodies was significantly higher at 3 and 6 months in the glucocorticoid-CP group (77% and 92%, respectively); (4) the RI-CYCLO trial,[41] a randomized open-label controlled trial of 74 patients with MN and nephrotic syndrome, compared RTX (1 g on days 1 and 15) with 6-month cyclic regimen with glucocorticoid alternated with CP every other month. The primary outcome was CR of proteinuria at 12 months. The CR was lower with the RTX (6/37, 16%) group compared with the cyclic regimen (12/37, 32%) (OR, 0.4; 95% CI, 0.13 to 1.23) at 12 months. The authors concluded that no additional benefit or less harm associated with the RTX vs the cyclic glucocorticoid-CP regimen.

In summary, there is evidence supporting the use of RTX as induction treatment for treatment of MN, achieving remission in approximately 60% of all patients without the need of concomitant glucocorticoid therapy. Adding CNI to RTX does not improve efficacy of inducing CR/PR. The KDIGO 2021 Guideline for the Management of Glomerular Diseases[32] recommends risk-based treatment of MN, using rituximab or CP plus alternate month glucocorticoids for 6 months or tacrolimus-based therapy (tacrolimus and RTX) for 6 months for high-risk category and CP with glucocorticoids for patients with very high-risk category. Currently, there are ongoing clinical trials to assess the efficacy of belimumab in combination with RTX (Belimumab With RTX for Primary Membranous Nephropathy [REBOOT]; NCT03949855) and Felzartamab (anti-CD38 human antibody) (Trial to Assess Safety and Efficacy of MOR202 in Anti-PLA2R + Membranous Nephropathy [M-PLACE]; NCT04145440) for management of patients with MN.

IgA Nephropathy

There is currently no FDA-approved MAb available for treatment of IgA nephropathy. The efficacy of RTX was assessed in an open-label trial in 34 patients with IgA nephropathy.[42] At 12-months, no difference was found between RTX vs no RTX groups regarding reduction proteinuria, renal function preservation, and in serum levels of galactose-deficient-IgA_1 or IgG autoantibodies against galactose-deficient-IgA_1. However, RTX might be beneficial in IgA vasculitis nephritis.[43] There are ongoing clinical trials with Narsoplimab (a human MAb directed at Mannan-binding lectin-associated serine protease-2 (MASP-2), critical enzyme of the lectin pathway of the alternative complement system) (Study of the Safety and Efficacy of OMS721 in Patients with IgA Nephropathy; NCT03608033) and Felzartamab (Clinical Trial to Assess Efficacy and Safety of the Human Anti-CD38 Antibody Felzartamab [MOR202] in IgA Nephropathy [IGNAZ]; NCT05065970).

Systemic Lupus Erythematous

Systemic lupus erythematous is a chronic autoimmune disease with variable clinical presentation involving the skin, joints, lungs, and kidneys. Lupus nephritis (LN) occurs in 50% of affected patients with a relapsing and remitting course.[44] Current immunosuppressive options have shown incomplete efficacy (CR and PR, 40%-50%) and have been associated with substantial toxicity, low levels of adherence, and progression to ESKD in 10%-30% of the patients.[45,46] Recent evidence indicates that monoclonal antibodies, such as belimumab, RTX, and obinutuzumab, could play a crucial role in the treatment of LN.

Belimumab. Belimumab, a recombinant human IgG-1λ monoclonal antibody that inhibits B cell—activating factors (BLISS-52 and BLISS-76), was approved by the FDA for patients with active LN.[47,48] Belimumab decreases proteinuria and incidence of renal flares. The BLISS-LN, a phase III RCT (N=448), compared combined belimumab (10 mg/kg

intravenously) and standard therapy to standard therapy alone (either CP-based or MMF-based regimen) in patients with active LN (primarily classes III and IV).[49] The belimumab group reported a primary efficacy renal response (UPCR $\leq$ 0.7 g/d, preservation of renal function, or no use of rescue therapy) (43% vs 32%; odds ratio [OR], 1.6; 95% CI, 1.0-2.3) and a complete renal response (UPCR $\leq$ 0.5 g/d) (30% vs 20%; OR, 1.7; 95% CI, 1.1−2.7). A post hoc analysis of this RCT revealed that the higher rate of complete renal response with belimumab was observed in patients with UPCR<3 gr/day at baseline and Black race/ethnicity.[50]

Rituximab. LUNAR, a phase III RCT (N=144), compared standard of care (SOC) (glucocorticoids and MMF) and RTX (1 gr 4 doses on days 1, 15, 168, 182) to SOC alone in patient with class III or IV LN.[51] Despite RTX achieving significant reductions in anti-dsDNA antibody and complement 3 and 4 (C3/C4) levels, the renal response rates (CR and PR) were not different between the groups (45.8% among the SOC and 56.9% among the RTX group; *P*=.18). However, RTX has the potential to serve as a corticosteroid-sparing agent and has shown promise in treating patients with refractory LN, as found in prospective observational studies.[52-55] Nevertheless, for patients diagnosed with rapidly progressive crescentic LN and advanced renal impairment at the time of diagnosis, RTX may not be able to prevent the progression to ESKD.[56]

Obinutuzumab. Obinutuzumab is a humanized type II anti-CD20 MAb (unlike RTX and ocrelizumab, type I anti-CD20 MAb), which has a distinct mode of binding to the CD20 antigen through glycol engineered for greater affinity on effector cells. This promotes greater antibody-dependent cellular cytotoxicity.[57,58] A phase II RCT (NOBILITY trial, N=125) compared obinutuzumab (1000 mg on day 1 and weeks 2, 24, and 26) and SOC with SOC alone for primary outcome of complete renal response at 1 year.[59] CR was greater with the obinutuzumab group at 1 year (35% vs 23%; *P*=.12) and 2 years (41% vs 23%; *P*=.03). There is currently a phase III RCT (A Study to Evaluate the Efficacy and Safety of Obinutuzumab in Patients with ISN/RPS 2003 Class III or IV Lupus Nephritis [REGENCY]; NCT04221477) in progress.

Antineutrophil Cytoplasmic Antibody−Associated Vasculitis

Antineutrophil cytoplasmic antibody−associated vasculitides (AAVs) are multisystem autoimmune diseases that predominantly affect small-sized blood vessels, leading to endothelial injury and tissue damage, with a preference for the respiratory tract and kidneys.[60-62] Kidney involvement occurs in 70% of the affected patients and is generally manifested as rapidly progressive pauci-immune−necrotizing crescentic glomerulonephritis on biopsy. Granulomatosis with polyangiitis and microscopic polyangiitis (MPA) are the major subgroups of AAV. The pathogenic role of B cells in AAV provide support for the use of a B-cell−targeted therapy like RTX in this disease.[63] CP and glucocorticoids have been the standard therapy for to induce remission for more than 30 years.[62] Rituximab was shown to be noninferior to CP for inducing remission and the treatment of relapsing disease in AAV.[60,62]

Rituximab. RAVE noninferiority RCT (N=197) studied the efficacy of RTX (375 mg/m^2 for 4 weeks) against oral CP to induce remission in patients with AAV.[62] The primary outcome was remission of disease without the use of prednisone at 6 months. The RTX group achieved the primary outcome in 64% of the patients compared with 53% in the CP group (*P*<.001).

RITUXVAS, a small (N=44) 3:1 randomized European trial compared RTX with CP for the primary outcome of sustained AAV remission rates at 12 months.[60] The sustained remission (76% vs 82%; *P*=.68) and severe adverse events (42% vs 36%; *P*=.77) occurred in the RTX and CP groups, respectively. The authors concluded that the RTX was not superior to standard therapy in patient with severe AAV.

RITAZAREM trial (N=188), a large prospective observational study, evaluated the efficacy of RTX (4 × 375 mg/m^2) with a higher or lower glucocorticoid therapy to induce remission in patients with relapsing AAV (previously 79% and 36% received CP and RTX,

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respectively).[64] The trial reported that the RTX-based regimen achieved remission in 90% of the patients by 4 months.

There is also evidence (the MAINRITSAN RCT, N=115) to support the use of RTX, compared with azathioprine, as a maintenance therapy in patients with AAV.[65] The major relapse rate at 28 months was 29% in the azathioprine group compared with 5% in the RTX group (hazard ratio for relapse, 6.61; 95% CI, 1.56-27.96; $P = .002$). However, the efficacy of RTX in patients with AAV and severe kidney failure (GFR< 30 mL/min or requiring renal replacement therapy) is not clearly defined.[66]

At present, there are several RCTs in progress to assess the efficacy of RTX in patients with AAV and severe kidney failure (Exploring Durable Remission With RTX in Antineutrophil Cytoplasmic Antibody—Associated Vasculitis [ENDURRANCE-1]; NCT03942887) and role of other MAbs in AAV, such as tocilizumab (anti-interleukin [IL]-6 MAb) (Clinical trial of tocilizumab vs CP for MPA and granulomatosis with polyangiitis; WHO International Clinical Trials Registry Platform; JPRN-JMA-IIA 00325), reslizumab (anti—IL-5 MAb) (Reslizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis [EGPA] Study [RITE]; NCT02947945) and belimumab and RTX combination therapy (Rituximab and Belimumab Combination Therapy in PR3 Vasculitis [COMBIVAS]; NCT03967925).

Antiglomerular Basement Membrane Disease

Antiglomerular basement membrane (anti-GBM) disease is characterized by circulating antibodies against NC1 domain of the α-3 chain of type IV collagen (COL4A3), intrinsic to glomerular and alveolar basement membranes, resulting in rapidly progressive glomerulonephritis and alveolar hemorrhage.[67,68] The goal of treatment is to remove the circulating anti-GBM antibodies by plasmapheresis, along with prednisone and immunosuppressive medication particularly CP to minimize inflammation and new antibody formation.[69] In a French study of 119 patients with anti-GBM disease, patient survival and time to ESKD was more favorable if plasma creatinine level was <3 mg/dL at the time of diagnosis and if the initial kidney biopsy reported <30% of crescents.[70]

Rituximab. Rituximab might be helpful in the early stages of the disease to eliminate stimulated B cells and downstream production of antibodies against NC domain of Col4A3.[71] Rituximab is usually used as an adjuvant therapy to accelerate clearance of anti-GBM antibodies, during induction or maintenance in patients with severe and refractory anti-GBM disease. Rituximab, when used for refractory anti-GBM disease, reported improved patient and kidney survival.[72,73] A retrospective analysis of 14 patients with anti-GBM crescentic glomerulonephritis who received either CP or RTX for induction along with glucocorticoids and plasma exchange reported that dialysis dependency, recovery of kidney function, and patient survival was better in the RTX group.[74] The addition of RTX in anti-GBM disease and TMA could help to decrease anti-GBM antibodies, prevent recurrence, and stabilize platelet count.[75]

Monoclonal Gammopathy of Renal Significance

Monoclonal gammopathy of renal significance (MGRS) is a group of disorders, characterized by increased production of nonmalignant or premalignant B cell or plasma cell clones, which do not meet the criteria for multiple myeloma or other lymphoproliferative disorder, but cause kidney injury owing to deposition of these monoclonal proteins.[76] These monoclonal deposits in the kidney can cause a spectrum of kidney disorders from cast nephropathy, amyloidosis, monoclonal immunoglobulin (Ig) deposition diseases, immunotactoid glomerulopathy, proliferative GN with monoclonal Ig deposits (PGNMID), light-chain proximal tubulopathy, and the rare entities of crystal-storing histiocytosis and crystalglobulinemia.[77] Treatment is usually directed against the specific clone (plasma or B cell) and consists of proteosome inhibitors such as bortezomib, glucocorticoids, immunomodulatory drugs such as thalidomide, and alkylating agents such as CP.[78,79]

Rituximab. In patients who have B cell clones, RTX is successfully used to target B-cell clones.[77,80-82] In a single-center study

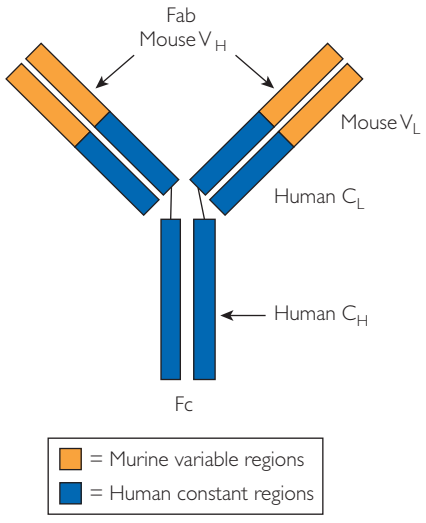

FIGURE 1. The structure of a chimeric monoclonal antibody. The variable light (VL) and variable heavy (VH) chains are the regions that recognize and bind to the antigen. The constant light (CL) and constant heavy (CH) regions provide structural stability and determine the antibody's class (eg, IgG, IgM, and IgE). The fragment antigen-binding (Fab) region is composed of the VL and VH domains and is responsible for antigen recognition and binding. The fragment crystallizable (Fc) region is composed of the CH domains and is responsible for effector functions, such as complement activation and binding to Fc receptors.

(N=20), the patients with indolent B-cell non-Hodgkin lymphomas and MGRS (biopsy-proven tubulointerstitial/glomerular involvement with or without monoclonal Ig deposition and positive for clonal B cell population in peripheral blood or bone marrow aspirate) underwent corticosteroid-sparing regimen of RTX plus bendamustine (an alkylating chemotherapy) and were able to achieve a complete renal remission in 83% of the cases.[83]

Daratumumab. Recently daratumumab, a monoclonal anti-CD38 antibody, which depletes plasma cells, is used in the treatment of MGRS with promising results with favorable safety and tolerability profile. Zand et al[84] treated 10 patients with PGNMID with daratumumab, and all patients achieved a PR (defined as >50% reduction in 24-hour proteinuria with <30% decline in eGFR) and 4 achieved CR (defined as proteinuria <500 mg/d with <15% decline in baseline eGFR) with no serious infections at 12-month outcomes. In a case review analysis assessing the safety and efficacy of daratumumab in 5 patients with PGNMID who did not respond to a bortezomib-based regimen, 3 patients achieved renal response, defined as a ≥50% decrease in proteinuria compared with baseline and an absolute proteinuria reduction of >0.5 g/d on a 24-hour urine collection in addition to a stable eGFR (<125% of baseline) at some point during the treatment.[85]

Currently, there is a phase II open-label single-arm study assessing effectiveness of isatuximab (anti-CD38 MAb) in MGRS in progress (Isatuximab in Patients with Monoclonal Gammopathy of Renal Significance; NCT04614558).

C3-Dominant Glomerulopathies (Dense Deposit Disease and C3 Glomerulonephritis)

The C3 glomerulopathies, comprising dense deposit disease and C3 glomerulonephritis (C3GN) are characterized by dysregulation of alternative complement pathway, which results in predominant C3 deposition within the glomeruli. It usually occurs owing to mutations in complement factor (C3) or regulatory proteins (CFH, CFI, and CFHR5) or antibodies to complement factors (C3, C4, and C5 nephritic factors) or complement regulatory proteins (CFH, CFI, and CFB).[32,86] Kidney biopsy reveals predominant C3 deposition with minimal or no immune complex deposits and exhibit histopathologic features of membranoproliferative GN. In dense deposit disease, there are electron-dense deposits within the GBM, and C3 glomerulonephritis (C3GN), characterized by subendothelial or mesangial deposits.[87] In the absence of underlying monoclonal proteins, treatment options are not well studied. MMF, glucocorticoids, and CP are usually given on the basis of observational studies.[88]

Eculizumab. Eculizumab, a monoclonal antibody that binds with high affinity to C5, prevents C5's cleavage, and inhibits the formation of C5a and subsequently the terminal complement complex (C5b-9), has been studied in small clinical trial and multiple

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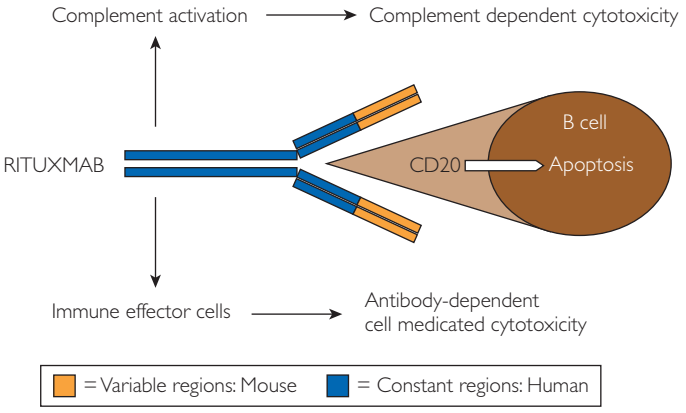

FIGURE 2. The mechanism of the action of rituximab. Rituximab is a chimeric monoclonal antibody that specifically binds to the CD20 antigen on B cells, after which CD20 triggers a series of immune responses that ultimately lead to the destruction of B cells, such as antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis (programmed cell death).

case reports. Data from these studies show that patients with crescentic GN with rapidly progressive course, more extra capillary proliferation on kidney biopsy, lower eGFR had good clinical response with eculizumab.[89-91] The response is heterogenous and warrant further studies to determine the usefulness of eculizumab in C3GNs.

Thrombotic Microangiopathy

Thrombotic microangiopathy is a pathologic lesion characterized by an endothelial injury with microvascular thrombosis and clinically presents with microangiopathic hemolytic anemia, thrombocytopenia, and AKI. These pathologic lesions can be caused by congenital mutations or autoantibodies against ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13), such as thrombotic thrombocytopenic purpura (TTP), or mutations in the alternative complement genes or autoantibodies directed against the complement proteins, namely complement-mediated TMA, or related to infections, systemic diseases, or drugs.[92] In TTP mediated by ADAMTS13 deficiency, there is an accumulation of large uncleaved thrombogenic von Willebrand factor, causing catastrophic platelet aggregation and thrombosis.[93] Congenital TTP is due to mutations in the *ADAMTS13* gene and immune-mediated TTP is due to autoantibodies against ADAMTS13. Treatment includes plasma exchange to replenish ADAMTS13, glucocorticoids, and RTX to inhibit production of autoantibodies.[94]

Caplacizumab. Caplacizumab is a MAb, which binds to the A1 domain of von Willebrand factor and inhibit platelet aggregation and has shown to reduce the time needed to improve thrombocytopenia and decrease recurrence severe thrombosis and death in patients with TTP.[95,96] In a double-blind controlled trial of 145 patients with TTP who received caplacizumab, the median time to normalization of the platelet count was shorter with caplacizumab than that with placebo (2.69 days [95% CI, 1.89-2.83] vs 2.88 days [95% CI, 2.68-3.56]; P=.01), and lower percentage of recurrence of TTP and shorter hospitalizations.[97] However, there was no significant change in all-cause mortality.

C5 Inhibitors (Eculizumab and Ravulizumab). Eculizumab, a humanized anti-C5 monoclonal antibody is widely used and approved for atypical hemolytic uremic syndrome,[98] which is a rare and life-threatening condition characterized by the abnormal activation of the complement system that can be caused by genetic mutations in complement regulatory proteins, autoantibodies that interfere with complement regulation, or acquired

TABLE 2. Monoclonal Antibody Adverse Effects and Associated Kidney Histopathologic Findings

Drug	Adverse Effects	Histopathology
Anti-VEGF (bevacizumab)	Acute kidney injury, proteinuria, hypertension	TMA
EGFR inhibitors (cetuximab, panitumumab)	Hypomagnesemia; other electrolyte disorders	No kidney histopathologic lesion
CD20 receptor blocker (Rituximab)	Acute kidney injury (through tumor lysis syndrome)	Crystalline (uric acid) nephropathy and ATN
TNF-α receptor blocker (Infliximab, adalimumab)	Acute kidney injury, proteinuria	IgA nephropathy; mesangial GN, FSGS
Immune check point inhibitors (ipilimumab, pembrolizumab, nivolumab, atezolizumab, tremelimumab)	Acute kidney injury proteinuria	ATIN, ATN, MCD, FSGS, MGN, IgA nephropathy, lupus-like nephritis, C3GN, AA amyloid, GPA, TMA

ATIN, acute tubulointerstitial nephritis; ATN, acute tubular necrosis; C3GN, C3 glomerulonephritis; EGFR, epidermal growth factor receptor; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; GPA, granulomatosis with polyangitis; MCD, minimal change disease; MN, membranous nephropathy; TMA, thrombotic microangiopathy; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

triggers that activate the complement system, such as pregnancy, infections, or medications. In an open-label single-arm phase 3 trial of the 41 patients with atypical hemolytic uremic syndrome treated with eculizumab, 73% reported complete TMA response with increase in platelet counts and improved glomerular filtration rates and 79% discontinued dialysis during eculizumab treatment.[98] There is an increased risk of TMA in patients on discontinuation of eculizumab and so treatment might be warranted for long term to decrease the risk of TMA recurrence.[99] In a study of 56 complement inhibitor-naïve adults with atypical hemolytic uremic syndrome and acute TMA, who received ravulizumab (a longer acting C5a inhibitor) achieved a complete resolution of TMA in 54% of the patients and 59% of the patients on dialysis at baseline came off dialysis by day 183.[100] In pregnant patients with complement dysregulation, ravalizumab was found to provide immediate and complete C5a inhibition, resulting in a complete response.[101]

Overall, MAbs have shown promising results in the treatment of various glomerular diseases. The future directions of MAbs in glomerular diseases include the following:

1. Development of new MAbs: The identification of new targets for MAbs in glomerular diseases is an area of active research. The development of new MAbs that target-specific pathogenic mechanisms could lead to more effective treatments for glomerular diseases.
2. Personalized medicine: The use of MAbs in glomerular diseases may be tailored to individual patients on the basis of their disease characteristics, such as the underlying etiology, disease severity, and response to therapy. This approach could optimize treatment outcomes and minimize adverse effects.
3. Combination therapy: Combination therapy with MAbs and other agents, such as immunosuppressive drugs or other biologic agents, may lead to more effective treatments for glomerular diseases. This approach may target multiple pathogenic mechanisms and improve treatment outcomes.
4. Biomarker-guided therapy: Biomarkers can be used to predict treatment response and identify patients who are more likely to benefit from MAb therapy. Biomarker-guided therapy could improve treatment outcomes and minimize adverse effects.

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5. Improved dosing and administration: The development of new dosing and administration strategies could improve the efficacy and safety of MAbs in glomerular diseases. This includes the development of long-acting MAbs and alternative routes of administration.

In conclusion, therapeutic MAbs are advantageous because of their high specificity, reduced number of drug-drug interactions, and low toxicity. Advances in the MAb field have resulted in a significant paradigm shift in managing immune-mediated glomerular diseases and several MAb RCT in the pipeline.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

Abbreviations and Acronyms: **AAV,** antineutrophil cytoplasmic antibody—associated vasculitis; **ADAMTS13,** a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; **AKI,** acute kidney injury; **GBM,** glomerular basement membrane; **CP,** cyclophosphamide; **CR,** complete remission; **ESKD,** end-stage kidney disease; **FDA,** Food and Drug Administration; **FSGS,** focal segmental glomerulosclerosis; **MAb,** monoclonal antibody; **MCD,** minimal change disease; **MMF,** mycophenolate mofetil; **MN,** membranous nephropathy; **OR,** odds ratio; **PLA2R,** phospholipase A2 receptor; **PR,** partial remission; **RCT,** randomized controlled trial; **RTX,** rituximab; **SOC,** standard of care; **TMA,** Thrombotic microangiopathy; **TTP,** thrombotic thrombocytopenic purpura

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