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Review Article

MONOCLONAL ANTIBODIES IN NEPHROLOGY

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Abstract

Monoclonal antibodies have revolutionized renal medicine by enabling targeted modulation of immune pathways involved in glomerular, vascular, and transplant-related kidney diseases. Unlike conventional immunosuppressants, monoclonal antibodies bind specific antigens with high affinity, improving efficacy while reducing off-target toxicity. Their impact has been particularly significant in autoimmune glomerulopathies, complement-mediated disorders, and antibody-mediated transplant rejection. Many renal diseases are immune-mediated, involving B-cell dysregulation, autoantibody production, immune complex deposition, complement activation, and inflammatory cytokines. Rituximab, an anti-CD20 monoclonal antibody, depletes B cells through complement-dependent and antibody-dependent cytotoxicity. It has shown strong efficacy in membranous nephropathy and anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, and although early trials in lupus nephritis were inconclusive, it remains useful in selected or refractory cases. Second-generation anti-CD20 agents, such as obinutuzumab, demonstrate enhanced cytotoxicity and promising results in lupus nephritis. Complement inhibition represents another major advance. Eculizumab, a C5 inhibitor, has dramatically improved outcomes in atypical hemolytic uremic syndrome, while ravulizumab offers extended dosing with similar efficacy. Complement blockade is also being explored in C3 glomerulopathy and transplant rejection. Emerging therapies include iptacopan, targeting factor B of the alternative pathway, and sutimlimab, inhibiting C1s in the classical pathway. Other strategies include interleukin-6 receptor blockade with tocilizumab and B-cell activating factor (BAFF) inhibition with belimumab in lupus nephritis. Despite clear benefits, monoclonal antibodies carry infection risks, infusion reactions, and high costs. Overall, they represent a cornerstone of precision-based nephrology, with ongoing research refining patient selection and long-term outcomes.

Keywords: Immune mediation; Inflammation; Monoclonal antibodies; Renal diseases; Side effects

Abbreviation

MAbs: Monoclonal Antibodies

Introduction

Monoclonal antibodies (mAbs) have fundamentally transformed the therapeutic landscape of renal medicine over the past two decades. Their development reflects advances in immunology, molecular biology, and translational nephrology, allowing targeted modulation of specific immune pathways implicated in glomerular, vascular, and transplant-related kidney diseases. Unlike traditional immunosuppressive agents such as corticosteroids or alkylating agents, mAbs are designed to bind specific antigens with high affinity, thereby reducing off-target toxicity while improving efficacy. This paradigm shift has been particularly impactful in autoimmune glomerulopathies, complement-mediated disorders, and antibody-mediated transplant rejection [1].

Renal diseases in which mAbs play a central role are largely immune-mediated. The pathogenesis of conditions such as membranous nephropathy, lupus nephritis, anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, atypical hemolytic uremic syndrome (aHUS), and C3 glomerulopathy involves dysregulated B-cell activity, autoantibody production, immune complex deposition, complement activation, and inflammatory cytokine signaling. Therapeutic targeting of these pathways using mAbs has enabled precision-based treatment strategies aligned with disease mechanisms [2].

One of the most extensively studied mAbs in nephrology is Rituximab. Rituximab is a chimeric monoclonal antibody directed against CD20, a transmembrane phosphoprotein expressed on pre-B and mature B lymphocytes. Binding to CD20 results in B-cell depletion through complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and induction of apoptosis. In membranous nephropathy, where pathogenic autoantibodies against phospholipase A2 receptor (PLA2R) are frequently implicated, B-cell depletion reduces antibody titers and promotes remission [3]. Randomized controlled trials have demonstrated that Rituximab is non-inferior or superior to cyclophosphamide-based regimens in inducing remission with fewer long-term adverse effects [4].

In lupus nephritis, B cells contribute not only through autoantibody production but also via antigen presentation and cytokine secretion. Although early randomized trials of Rituximab in lupus nephritis did not meet primary endpoints, observational data and refractory cases support its utility in selected patients [5]. Rituximab is also approved for ANCA-associated vasculitis, where it has been shown to be equivalent to cyclophosphamide for induction therapy and superior for relapsing disease [6].

Second-generation and humanized anti-CD20 antibodies such as Ofatumumab and Obinutuzumab have been investigated for patients intolerant or refractory to Rituximab. Obinutuzumab, in particular, has demonstrated enhanced antibody-dependent cellular cytotoxicity due to glycoengineering, and recent studies suggest promising results in lupus nephritis when combined with standard therapy [7].

Complement inhibition represents another major therapeutic breakthrough. The complement cascade plays a critical role in renal endothelial injury and thrombotic microangiopathy. Eculizumab is a humanized monoclonal antibody targeting complement component C5, thereby preventing cleavage into C5a and C5b and blocking formation of the membrane attack complex (C5b-9). Eculizumab has dramatically improved outcomes in atypical hemolytic uremic syndrome, a condition characterized by uncontrolled alternative pathway activation leading to microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury [8]. Early initiation of therapy is associated with improved renal recovery and reduced progression to end-stage kidney disease.

Ravulizumab, a longer-acting C5 inhibitor engineered from eculizumab, offers extended dosing intervals while maintaining efficacy. Clinical trials have demonstrated non-inferiority to eculizumab in complement-mediated disorders, providing improved convenience and potentially better adherence [9]. Complement blockade has also been explored in C3 glomerulopathy and antibody-mediated transplant rejection, although long-term efficacy data remain under evaluation.

The interleukin-6 (IL-6) pathway is increasingly recognized as an important mediator of inflammation and alloimmune responses. Tocilizumab is a humanized monoclonal antibody directed against the IL-6 receptor. In renal transplantation, chronic antibody-mediated rejection involves persistent donor-specific antibodies and microvascular inflammation. Tocilizumab has shown potential in stabilizing graft function in refractory cases [10]. In lupus nephritis, IL-6 blockade may reduce inflammatory cytokine cascades contributing to renal injury.

Targeting B-cell survival factors has also proven beneficial. Belimumab inhibits B-cell activating factor (BAFF), a cytokine critical for B-cell maturation and survival. Elevated BAFF levels are observed in systemic lupus erythematosus. Clinical trials have demonstrated that belimumab, when added to standard therapy, improves renal response rates in lupus nephritis and reduces disease flares [11]. This represents a move toward combination biologic therapy tailored to immunopathogenic mechanisms.

Although tumor necrosis factor (TNF) inhibitors such as Infliximab and Adalimumab are not primarily used for intrinsic renal disease, they may be indicated in systemic inflammatory conditions with secondary renal involvement, including vasculitis and inflammatory bowel disease-associated nephropathies. However, their use must be approached cautiously, as TNF inhibition has been associated with induction of lupus-like syndromes and rare cases of glomerulonephritis [12].

More recently, novel complement-targeting strategies have emerged. Iptacopan is an oral inhibitor of complement factor B, selectively targeting the alternative pathway. It has shown promise in C3 glomerulopathy by reducing proteinuria and complement activation markers [13]. Sutimlimab targets C1s in the classical complement pathway and is under investigation for complement-mediated renal diseases [14]. In summary the data brought up to date can be condensed as follows:

Anti-CD20 Therapy
Rituximab
Target: CD20 on B lymphocytes
Mechanism: B-cell depletion → ↓autoantibody production
Uses in renal disease:
Membranous nephropathy
Lupus nephritis
Anti-Neutrophil Cytoplasmic Antibodies-associated vasculitis
Minimal change disease (frequently relapsing)
Focal Segmental Glomerulosclerosis (selected cases)
Antibody-mediated transplant rejection
Newer anti-CD20 agents:
Ofatumumab
Obinutuzumab

Complement Inhibitors
Eculizumab
Target: C5 (blocks terminal complement pathway)
Indications:
Atypical hemolytic uremic syndrome (aHUS)
C3 glomerulopathy
Antibody-mediated transplant rejection
Paroxysmal nocturnal hemoglobinuria (non-renal primary disease)
Ravulizumab
Longer-acting C5 inhibitor
Used in Atypical hemolytic uremic syndrome (aHUS)

Anti- Interleukin-6 Pathway
Tocilizumab
Blocks Interleukin-6 receptor
Uses:
Refractory lupus nephritis
Chronic antibody-mediated rejection in transplant

B-cell Survival Factor Inhibitor
Belimumab
Inhibits BAFF (B-cell activating factor)
Approved for lupus nephritis (add-on therapy)

Anti-Tumor Necrosis Factor (TNF) Agents (Limited Role)
Examples:
Infliximab
Adalimumab
Used mainly in:
Secondary renal disease due to systemic autoimmune disorders (e.g., vasculitis, inflammatory bowel disease)
Rarely primary glomerular disease

Anti-Integrin Therapy
Natalizumab
Rarely used in renal disease
Mainly for multiple sclerosis and Crohn's disease

Emerging / Specialized Therapies
Iptacopan - oral complement inhibitor for C3 glomerulopathy
Sutimlimab - classical complement pathway inhibitor

Despite their efficacy, mAbs are associated with important risks. B-cell depletion predisposes to hypogammaglobulinemia and increased infection risk, particularly with encapsulated organisms. Complement inhibitors markedly increase susceptibility to meningococcal infections; therefore, vaccination against Neisseria meningitidis is mandatory prior to therapy initiation [8]. Infusion reactions, immunogenicity, and high cost also present practical challenges.

In conclusion, mAbs represent a cornerstone of modern nephrology, enabling mechanism-based therapy for immune-mediated renal disorders. Their integration into clinical practice reflects a broader shift toward personalized medicine, guided by immunologic profiling and molecular diagnostics. Ongoing clinical trials and biomarker-driven strategies are expected to refine patient selection and optimize long-term outcomes in renal disease [1,2].

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None.

Conflicts of interest
No conflict of interest.

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