Review

The Role of Biologics in Idiopathic Nephrotic Syndrome and Other Kidney Diseases in Children

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Review

Biologics in Pediatric Nephrotic Syndrome and Other Kidney Diseases—General Principles and Special Considerations

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Abstract: Nephrotic syndrome and other pediatric kidney diseases represent significant challenges in children due to their complex pathogenesis, often involving dysregulated immune responses and renal injury, usually leading to podocyte injury and proteinuria. The interplay of several different cytokines, chemokines and growth factors underpins the disease process. Biologic therapies, defined as targeted treatments derived from living organisms, have gained traction in managing these conditions, offering a potential shift in therapeutic paradigms. They offer a more targeted approach compared to other, usually broad-spectrum immunosuppressants such as corticosteroids and alkylating agents. The selectivity of biologics reduces systemic side effects but is often accompanied by high costs and a risk of immunodeficiency-related complications. They are usuallly integrated into therapy after failure of conventional agents. While issues remain in accessibility and safety, research into novel molecules and pathways continues to expand the therapeutic options. Some agents like rituximab and eculizumab are now established in clinical practice but novel biologics targeting various molecules are promising for future interventions. The identification of specific molecules implicated in pathogenesis has paved the way for targeted biologic therapies aimed at modulating the immune response or preserving renal integrity. This review examines the current and emerging role of biologics in treating pediatric kidney diseases, focusing on indications, contraindications, adverse effects, therapeutic positioning, and a comparison with alternative immunosuppressive treatments.

Keywords: nephrotic syndrome; dysregulated immune responses; biologic therapies; adverse effects

1. Introduction

Idiopathic nephrotic syndrome (INS), characterized by pronounced proteinuria (above 40 mg/h/m^2 in a 24-hour urine collection or 200 mg protein/mmol creatinine in an early morning spot urine),), hypoalbuminemia (with consequent hyperlipidemia) and edema is caused by several kidney diseases that increase the permeability across the glomerular filtration barrier. It is classified according to the underlying cause, such as primary NS, secondary NS, congenital and infantile NS.

Primary NS is defined as NS without systemic disease and includes various diseases, such as INS (the most common form), primary focal segmental glomerulosclerosis (FSGS, specific histologic lesion, present in some cases of INS in children), primary membranous nephropathy, membranoproliferative glomerulonephritis (it is a pattern of kidney injury, not a distinct disease entity that can be caused by several etiologies) and Immunoglobulin A (IgA) nephropathy. Secondary NS, on the other hand, is NS that is either associated with systemic disease or with another pathologic process causing glomerular injury (exposure to drugs or toxins, for example). This includes various diseases, such as membranous nephropathy (due to systemic lupus erythematosus (SLE), chronic hepatitis B or other infection or drug exposure), secondary FSGS due to hyperfiltration as a consequence of decreased nephron number (due to kidney scarring, hypoplasia or oligonephronia in children that were born preterm), postinfectious glomerulonephritis, lupus nephritis, vasculitides

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(IgA vasculitis (Henoch-Schönlein purpura, antineutrophil cytoplasmic antibody-associated vasculitis, to name just two of them) and some other causes, such as sickle cell disease (often associated with secondary FSGS), Alport syndrome, hemolytic uremic syndrome (HUS), malignancy, drugs or toxins.

Congenital NS occurs in children in the first three months of life. It can be either primary (due to a genetic mutation) or secondary (usually due to congenital or acquired infection). Infantile NS occurs after three months but before twelve months of age. Most of children with NS presenting before one year of age have a genetic cause and a poor long-term prognosis. Family history of kidney disease and presence of extrarenal features, such as dysmorphic features or developmental delay, suggest congenital NS, while symptoms and signs, such as rash, purpura, arthropathy and recent group A streptococcal infection suggest systemic disorder. Children with NS may also present with hypertension, hematuria, hypovolemia or other complications such as various infections, thromboembolism or pancreatitis [1].

INS is the most common form of childhood NS and represents over 90 % of cases between 1 and 10 years of age and 50 % in older children. INS is also classified according to steroid responsiveness, which is associated with long-term outcome. Most children with INS have histologic findings of minimal change disease (MCD) on kidney biopsy (KB), however, the latter is not necessary investigation in the diagnostic procedure in majority of children. For children with signs and syptoms of typical INS (between one and 12 years of age and without familial, extrarenal or atypical signs and syptoms suggesting a secondary cause, including genetic mutation) treatment for MCD with corticosteroids is indicated without performing genetic testing or KB. Most of these children respond to corticosteroids. However, for those children who do not respond to them, additional diagnostic procedures, such as genetic testing and/or KB is necessary. This is supported by evidence from previous studies showing that age below 12 years, normal kidney function, normal complement levels and absence of hypertension or macrohematuria were strongly associated with MCD on KB which is now not necessary in the majority of these children. For children above 12 years of age with no familial, extrarenal, or atypical signs and syptoms suggesting a secondary cause, however, KB is warranted in order to get a histologic diagnosis and to plan a treatment, but empirical treatment with corticosteroids is acceptable, especially in the presence of contraindications (that are rare) or parent's refusal of KB. Nevertheless, genetic testing and/or KB is necessary in cases of unresponsiveness to corticosteroids. Histologic examination of KB specimens reveals the underlying pathological process. Diffuse foot process effacement on electron microscopy (EM) are typical for INS while MCD, FSGS or mesangial proliferation are usually seen on light microscopy (LM). It is, however, possible that these LM patterns are a spectrum of a single disease process and not separate diseases.

INS in children primarily arises from immune dysregulation, often leading to podocyte injury and proteinuria. The interplay of several different cytokines, chemokines and growth factors underpins the disease process. The identification of specific molecules implicated in pathogenesis has paved the way for targeted biologic therapies aimed at modulating the immune response or preserving renal integrity [1].

This comprehensive review aims to provide a robust understanding of biologics in pediatric nephrology, bridging current knowledge with emerging therapeutic frontiers.

2. Biologics in Clinical Practice

2.1. Rituximab

Rituximab, a monoclonal antibody against CD20 on B cells, depletes B cells and reduces autoantibody production. Indications for its use are steroid-dependent nephrotic syndrome (SDNS), frequently relapsing nephrotic syndrome (FRNS) and refractory MCD. Contraindications are active infections, hypersensitivity to rituximab or severe immunosuppression. Most common adverse effects are infusion reactions, risk of infections and hypogammaglobulinemia. Regarding therapeutic positioning, it is increasingly used as a steroid-sparing agent, showing efficacy in reducing relapse

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rates in SDNS and FRNS compared to calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus [2].

It is, therefore, a treatment option in children with INS to achieve short- to medium-term disease remission and avoid adverse effects due to prolonged corticosteroid treatment. It is used in multidrug resistant INS and in disease recurrence after kidney transplantation (KT) as well. According to available data, the treatment response to this drug depends on several patient characteristics, dosing regimen, and the parallel use of maintenance immunosuppression. After repeated treatments, patients usually have an improved response with a longer remission period. The drug effect is unfortunately transient, with 80 % relapse rate and need for additional course of treatment. For this reason, awareness of the long-term safety with repeated treatments is of utmost importance. Although it is considered generally safe, there are issues about long-term hypogammaglobulinemia. However, there are no available biomarkers to predict treatment outcome and risk of side effects [3].

2.2. Tocilizumab

Tocilizumab is an anti-IL6 receptor monoclonal antibody that inhibits IL6-mediated inflammation. It is used in secondary forms of nephrotic syndrome (e.g., associated with autoimmune diseases) and in resistant cases of podocytopathies. Contraindications for its use are risk of severe infections and contraindication to immunosuppressive therapy. Most common adverse effects are hepatotoxicity, hyperlipidemia and gastrointestinal perforation in at-risk populations. It has therapeutic potential in cases with elevated IL6 levels, such as autoimmune-related nephropathies. A pediatric case report has been recently published with systemic onset juvenile idiopathic arthritis, presenting clinically with anasarca due to nephrotic syndrome and KB confirmed amyloidosis deposits. Treatment with tocilizumab was initiated, followed by decrease of proteinuria and normalization of kidney function [4].

2.3. Complement Inhibitors

Eculizumab is a complement C5 inhibitor, preventing the formation of the membrane attack complex. It is used for treatment of atypical hemolytic uremic syndrome (aHUS) and complement-mediated glomerulopathies. Contraindications for its use are known hypersensitivity or inadequate meningococcal vaccination status. Increased susceptibility to meningococcal infections is main adverse effect. However, there are cost implications as a limiting factor for its wider use. It is considered the first-line treatment for aHUS, often reversing renal dysfunction when administered early. In the last decade, aHUS has been shown to be a disease largely of complement dysregulation. This advance facilitated the development of new treatment options targeting terminal complement activation, such as anti-C5 antibody eculizumab [5,6].

Dysregulation of complement activation is the primary driver of disease in C3 glomerulopathy (C3G) and contributes to other complement-mediated diseases, such as IgA nephropathy, lupus nephritis and primary membranous nephropathy. No complement inhibitors are proven to halt disease progression in these diseases. However, pegcetacoplan, a targeted C3 and C3b inhibitor, may decrease complement-mediated kidney damage in C3G and other glomerular diseases where complement may have a pathogenic role. **A recent** study evaluated the efficacy and safety of pegcetacoplan for patients with complement-mediated glomerular diseases, especially in terms of proteinuria reduction and estimated glomerular filtration rate (eGFR), where **this biologic agent** have been proved useful to provide therapeutic benefit for C3G with a favorable safety profile in several glomerular diseases studied [7].

Overactivated complement is a high-risk process also in hematopoietic stem cell transplant (HSCT) recipients with transplant-associated thrombotic microangiopathy (TA-TMA) where untreated patients have bad prognosis. A recent study on 64 pediatric HSCT recipients with a high-risk TA-TMA and associated multiorgan injury evaluated treatment outcome with eculizumab. Significant survival improvement to 66 % one year post-HSCT in treated patients was observed, compared to prior reports of untreated children with same clinical features with only 16.7 % survival

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one year post-HSCT. Treatment, with a median of 11 doses of eculizumab, was continued untill TA-TMA resolved, which occured in about two months. Children with higher complement activation, assessed by increased blood terminal lytic complex (sC5b-9) at the treatment initiatian were less likely to respond, had worse prognosis and needed more doses of eculizumab, especially those with intestinal bleeding. It is of note that over 70 % of survivors had proteinuria on long-term follow-up. The best glomerular filtration rate (GFR) recovery in survivors was a median 20% lower compared to pre-HSCT GFR. According to these results, complement blockade with eculizumab is an effective therapeutic strategy for high risk TA-TMA, however, early intervention and search for additional targetable endothelial injury pathway would be useful [8].

2.4. Abatacept (B7-1 Inhibitor)

Abatacept, B7-1 Inhibitor, is indicated for use in selected cases of FSGS with podocyte expression of B7-1. Its role is in potential stabilizing podocyte function, however, its efficacy is restricted to a subset of patients which is a limitation for widespread use. Published report described successful use of abatacept that induced remission of proteinuria in patients with FSGS (most with recurrent FSGS after KT and one with primary FSGS) with B7-1 immunostaining of podocytes in KB specimens. This suggests that B7-1 could be a useful biomarker for the treatment of some glomerulopathies in patients with B7-1–positive glomerular disease, mainly by stabilizing β1-integrin activation in podocytes [9].

In addition, previous reports described the B7 expression on podocytes of patients with various kidney diseases, presenting as proteinuria, such as lupus nephritis, membranous nephropathy and diabetic nephropathy. According to them, B7 blockade seems to protect podocytes and subsequently reduce proteinuria [10]. A case report described a 19-years old boy with recurrent NS after KT and unresponsive to rituximab and plasmapheresis, who responded to abatacept and stayed in remission on immunosuppression regimen with abatacept, with a follow-up period of more than four years [11]. According to results of another pediatric study, the administration of abatacept, based on the B7-1 podocytes expression at KB specimens, was successful treatment option in 12 children (median age 12 years old) with NS recurrence after KT and unresponsive to conventional therapy with plasmapheresis and rituximab. Nine subjects responded to treatment and seven of them had KB specimen positive for B7-1 (two of them did not have biopsy), however, one of three non-responders had KB positive for B7-1. According to these results, authors proposed B7-1 podocytes staining as useful to identify patients who might respond to abatacept. However, more studies on podocyte B7-1 expression and assesing the response to abatacept in kidney diseases, presenting with proteinuria, are needed [12].

2.5. Daratumumab

Daratumumab, Anti-CD38 monoclonal antibody, has been, at research stage, combined with rituximab in clinical trials targeting comprehensive B-cell suppression. For this purpose, a study with combined treatment with rituximab (given in a single dose of 375 mg/m^2) and daratumumab (given in a single dose of 16 mg/kg) is ongoing, in order to maintain drug-free disease remission in children and young adults affected by multi-drug resistant NS (MDNS), defined as the need of two or more oral drugs, including corticosteroid, mycophenolate mofetil and calcineurin inhibitors, SRNS and post transplant NS recurrence. After the administration of the combined treatment with rituximab and daratumumab, ongoing immunosuppressive treatment is being planned to be withdrawn. As the main aim, time-free remission in MDNS will be evaluated. In patients suffering from SRNS and post transplant NS recurrence, the decrease of proteinuria will represent the first endpoint [10].

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3. Emerging Biologics in Research

3.1. Molecules Under Investigation

3.1.1. MMP12 (Macrophage Metalloelastase)

Inhibition of MMP12 may protect against podocyte injury by reducing extracellular matrix degradation. Authors of a published study investigated the mechanism of renal fibrosis, researching the expression and localization of MMP-12, whose functions in kidney diseases are not fully understood, and its regulatory molecules, in the kidneys of experimentally induced glomerulonephritis in mice. They confirmed extensive expression of MMP-12 mRNA and its protein in mice kidney, predominantly in podocytes, that progressed to NS. These results suggest that the expression of MMP-12 is involved in the progression of NS in animal models [13].

3.1.2. VEGFA (Vascular Endothelial Growth Factor A)

Anti-VEGF therapies aim to mitigate vascular endothelial damage, particularly in glomerular diseases like FSGS. VEGF plays a crucial role as a pro-angiogenic and pro-permeability factor within the kidney. Bevacizumab, a monoclonal anti-VEGF antibody, inhibits the growth of new blood vessels, which decreases blood supply and thereby prevents tumor growth. However, a study in adults in Taiwan revealed that those who received bevacizumab had a significantly, 1.35-fold higher risk of getting chronic kidney disease (CKD) compared to patients without this treatment [14]. In addition, anti-VEGF therapy-related renal side effects may present as hypertension, proteinuria and sometimes as NS and acute kidney injury. A **case** report has been published, where a 15-year-old boy developed NS and thrombotic microangiopathy about two years after treatment with anti-VEGF therapy. Treatment was discontinued after which NS remitted spontaneously within three months [15]. Additionally, VEGF has been shown previously to correlate with tumor growth and metastasis in an experimental model of Wilms' tumor. Authors of a published study confirmed that treatment with anti-VEGF antibodies can suppress both primary tumor growth and metastasis in an animal model, with a greater than 95 % reduction in tumor weight as well as prevention of formation of lung metastases. However, termination of treatment resulted in rebound tumor growth [16].

3.1.3. CSF1 (Colony-Stimulating Factor 1)

Targeting CSF1 could potentially reduce macrophage-mediated inflammation and glomerular injury. CSF1 controls the survival, proliferation, and differentiation of macrophages, which are recognized as scavengers and agents of the innate and the acquired immune system. Macrophages have many other crucial roles during development and tissue homeostasis due to their plasticity. There is evidence that CSF-1 plays an important trophic role in postnatal organ growth and kidney repair, which has been revealed by the injection of CSF-1 postnatally, increasing kidney weight, volume and number of tissue macrophages. These results show that CSF-1 is important in kidney growth, repair and resolution of inflammatory injury [17].

3.1.4. Other Molecules

Such as IL17F and IL4 (Interleukins), whose modulation showed some potential in balancing pro-inflammatory and anti-inflammatory responses [18,19] and EGF (Pro-epidermal Growth Factor) whose enhanced signaling could promote renal recovery and reduce fibrosis [20] have a potential to be therapeutic targets in the future.

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3.2. Comparison with Conventional Therapies

Biologics offer a more targeted approach compared to broad-spectrum immunosuppressants such as corticosteroids, CNIs, and alkylating agents such as cyclophosphamide (CYPH). The selectivity of biologics reduces systemic side effects but is often accompanied by high costs and a risk of immunodeficiency-related complications [1,2,5]. Table 1 highlights key differences:

Table 1. Comparison of biologics with conventional therapies.

Aspect	**Traditional Therapies**	**Biologics**
Mechanism	Broad immunosuppression & immune modulation	Target-specific pathways
Side Effects	Systemic: infections, diabetes, hypertension, nephrotoxicity	Target-specific, systemic infections, hypersensitivity
Efficacy in SRNS	Variable	Higher in certain refractory cases
Cost	Moderate	High
Administration	Oral, intravenous	Intravenous, subcutaneous

3.3. Role in Therapeutic Schemata

Biologics are typically integrated into therapy after failure of conventional agents:

- Corticosteroids: remain the cornerstone for initial treatment.
- Second-line Immunosuppressants, including calcineurin inhibitors (CNIs), mycophenolate mofetil, or alkylating agents, often combined with corticosteroids.
- Biologics: Used for resistant cases, to achieve remission or as steroid-sparing agents.

3.4. Other Diseases with Kidney Involvement

Vasculitis is defined as the presence of inflammation in blood vessels that may occur as a primary process or secondary to an underlying disease. Clinical symptoms vary widely. The various vasculitic syndromes are characterized by the type of pathologic inflammation and the type and location of the involved vessels. This determines which organs are affected as well as choice of special treatments. Quick recognition and therapy initiated as soon as possible are both very important regarding the management of these children because many of these diseases can have very severe and life threatening course without appropriate treatment [21].

Regarding treatment of children with vasculitis, it is crucial to distinguish primary vasculitis from other diseases that can mimic vasculitis, as well as from diseases causing secondary vasculitis, such as infections, pharmacological agents, malignancies, or connective tissue diseases (such as SLE and juvenile dermatomyositis), where treatment is directed to the underlying disease. In the latter, administration of immunosuppressive therapy may have very severe adverse consequences, however, they are appropriate in patients with primary vasculitis. Making an accurate diagnosis is, therefore, vital in order to begin appropriate treatment. In order to understand the management principles of childhood vasculitis, treatment is determined by various phases of disease activity as follows, as shown in Table 2 [21].

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Table 2. Treatment principles in childhood vasculitis.

Phase of disease activity	**Main characteristics**
Induction treatment	Directed at stopping the inflammatory process in a newly diagnosed patient and achieving the remission
Maintenance treatment	After achievenig remission, treatment may be continued to maintain it. In some cases, especially in diseases that are usually acute and self-limited (Kawasaki disease, for example), maintenance treatment may not be necessary, and the patient may be in remission without drugs
Relapse treatment	Treatment, required to treat a reactivation of the inflammatory process
Refractory treatment	Increased treatment requirement for patients unresponsive to standard treatment, that may include alternative or additional immunosuppressive drugs or biologic response modifiers

The benefits of a specific therapy for vasculitis and its potential adverse effects must be balanced by the consequences of allowing the vascular inflammation to follow its natural course. Treatment of the rarer types of chronic vasculitis should be conducted by clinicians with extensive knowledge of these diseases, drugs used to treat them and the effects of the disease and its treatment in a developing child. Some types of vasculitis, such as immunoglobulin A (IgA) vasculitis (Henoch-Schönlein purpura), are acute, usually self-limited and usually not nequire the use of potentially toxic drugs. Other types of vasculitis, on the other hand, such as GPA, have a chronic relapsing course with serious morbidity and mortality risk due to kidney disease and/or pulmonary involvement. In such patients, long-term immunosuppressive treatment is usually needed in order to prevent or at least minimize disease relapses and/or progression. In addition, children need special consideration regarding both short-term and long-term treatment risks and benefits. The diseases as well as their treatment affect physical, social, educational, and emotional development and can have long-term consequences which is very important to consider in a developing and growing child. Children's developing organ systems are at risk of getting a high toxic burden from various drugs. With time, the potential long-term toxicities (such as infertility, malignancy, osteoporosis, atherosclerosis) have a greater chance to manifest [21].

In children with chronic or relapsing vasculitis, immunosuppressive treatment is used to induce and maintain remission. Corticosteroids are the mainstay of treatment and may be sufficient as monotherapy in patients with mild or limited disease. But in patients with more severe disease course, additional immunosuppressive or biologic agents are generally needed. For refractory or frequently relapsing disease after standard induction therapy, rituximab is indicated in children with antineutrophil cytoplasmic antibody (ANCA) associated vasculitis. Infliximab or tocilizumab are treatment options in children with Takayasu disease [21,22].

In contrary to IgA vasculitis and Kawasaki disease, other primary systemic vasculitides (such as Takayasu arteritis, polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome) are characterized by chronic and remitting disease course. Corticosteroids, with cyclophosphamide (CYPH) for more severe disease, have been the standard of care for many types of primary chronic vasculitides. Other immunosuppressive drugs, such as methotrexate and azathioprine, as well as biologic agents, such as tumor necrosis factor [TNF] inhibitors, rituximab, and tocilizumab, have shown benefit in small studies of various systemic vasculitides in children and their use is increasing [21]. In severe systemic vasculitides, many drugs may induce disease remission, but over 50 % of patients suffer from relapses that can cause irreversible end-organ damage in long-term course with consequent significant morbidity. The cumulative toxicity from repeated courses of CYPH can cause significant morbidity as well and, therefore, alternative agents are being tested for remission

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maintenance. In this context, adult trials have confirmed rituximab (given every six months) to be successful in maintaining disease remission in ANCA-associated vasculitis (AAV), with minimal adverse effects, besides hypogammaglobulinemia [21,23].

In addition, maintenance therapy with anti-tumor necrosis factor (TNF) agents and anti-interleukin (IL) 6 monoclonal antibodies in Takayasu arteritis can provide an effective alternative to more conventional immunosuppressive agents. However, no comparable studies have been done in systemic vasculitis of childhood, although such biologic response modifiers are increasingly used to treat children with disease that is refractory to conventional treatment (corticosteroids and CYPH) or those with relapsing disease [21,24].

4. Challenges and Future Directions

- **Accessibility:** High costs of biologics limit their use, particularly in low-resource settings.
- **Long-term Safety:** Limited data on pediatric populations necessitate further research.
- **Personalized Medicine:** Advances in biomarker discovery could optimize biologic use, tailoring therapies to individual patients.

Emerging technologies such as RNA-based therapies and engineered antibodies hold promise for next-generation biologics, potentially expanding treatment options [2–5,10,11,15].

5. Conclusion

Biologics have revolutionized the landscape of pediatric nephrology, offering targeted and effective treatment options for refractory kidney diseases. While challenges remain in accessibility and safety, ongoing research into novel molecules and pathways continues to expand the therapeutic arsenal. Comparative studies with conventional therapies will further refine their role in clinical practice. While agents like rituximab and eculizumab are now established in clinical practice, emerging biologics targeting various molecules hold promise for future interventions. Ongoing research should focus on optimizing these therapies, minimizing adverse effects, and addressing cost barriers. Integration of biomarkers for patient stratification and response monitoring will further enhance the efficacy of biologics in pediatric kidney diseases.

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