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Brief review

Complement blockade: Therapeutic promises and remaining challenges in clinical practice



Bloqueo del complemento: promesas terapéuticas y retos pendientes en la práctica clínica

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ABSTRACT

Understanding of the complement system in glomerulopathies has advanced significantly, revealing that this system—beyond its role in innate immunity—is a key mediator of kidney injury across a wide spectrum of nephropathies, from those driven by immune complexes to those caused by primary dysregulation of the alternative pathway.

The introduction of complement inhibitors, such as C5 blockade with eculizumab, marked a milestone: in aHUS it significantly improved renal function and patient survival, and in paroxysmal nocturnal hemoglobinuria it reduced thrombotic complications, achieving survival rates comparable to the general population. These advances have spurred the extension of this approach to other nephropathies and the development of new anti-complement agents.

However, the heterogeneity of complement dysregulation among glomerulopathies—and even among patients with the same disease—limits the application of a uniform therapeutic strategy. This scenario calls for a more precise characterization of the underlying pathophysiological mechanisms and the identification of critical points of intervention in each clinical context.

Currently, inhibitors targeting both proximal and terminal steps of the cascade are being investigated to achieve more individualized therapies, although challenges remain, such as the lack of reliable biomarkers, uncertainty regarding optimal treatment duration, scarcity of disease-specific trials, high costs, and the integration of these agents with immunosuppressive regimens.

The aim of this review is to analyze the role of the complement system in glomerulopathies and to summarize current and future therapeutic advances, with particular emphasis on the challenges and opportunities on the path toward more personalized medicine.

RESUMEN

La comprensión del complemento en las glomerulopatías ha avanzado notablemente, mostrando que este sistema, más allá de la inmunidad innata, es un mediador clave del daño renal en un amplio espectro de nefropatías, desde las mediadas por inmunocomplejos hasta aquellas debidas a la desregulación primaria de la vía alternativa.

La introducción de inhibidores del complemento, como el bloqueo de C5 con eculizumab, marcó un hito: en el SHUa mejoró de forma significativa la función renal y la supervivencia de los pacientes, y en la hemoglobinuria paroxística nocturna redujo las complicaciones trombóticas, logrando una supervivencia comparable a la población general. Estos avances impulsaron la extensión de este enfoque a otras nefropatías y el desarrollo de nuevos fármacos anti-complemento.

Palabras clave:

Vía alternativa del complemento
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Terapia anticomplemento

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Sin embargo, la heterogeneidad en la desregulación del complemento entre glomerulopatías, e incluso entre pacientes de una misma enfermedad, limita la aplicación de una estrategia uniforme. Este escenario exige una caracterización más precisa de los mecanismos fisiopatológicos y la identificación de los puntos críticos de intervención en cada contexto clínico.

Actualmente se investigan inhibidores en fases proximales y terminales de la cascada para alcanzar terapias más individualizadas, aunque persisten desafíos como la ausencia de biomarcadores fiables, la duración óptima del tratamiento, la escasez de ensayos específicos, el elevado coste y su integración con la inmunosupresión.

El objetivo de esta revisión es analizar el papel del complemento en las glomerulopatías y revisar los avances terapéuticos actuales y futuros, con especial atención a los retos y oportunidades hacia una medicina más personalizada.

Introduction

In recent years, the understanding of the role of the complement system in the pathophysiology of glomerular diseases has experienced a substantial advance. Beyond its classical function in innate immune defense, we now know that it can act as a potent mediator of kidney injury across a broad spectrum of glomerular diseases, from its role as an effector of injury in immune complex-associated glomerulonephritis (SLE, membranous nephropathy...) to a promoter of injury in diseases predominantly mediated by dysregulation of the alternative pathway (AP), such as C3 glomerulopathy (C3G) and atypical hemolytic uremic syndrome (aHUS). This evidence has transformed the traditional view of the complement system, positioning it as a key therapeutic target.

The aim of this review is to reflect on the scientific and clinical reasons that justify considering various types of complement inhibitors in glomerular disease, to discuss the current state of therapeutic development in this field, and to highlight the challenges—both conceptual and logistical—that must be addressed to achieve a rational, equitable, and evidence-based implementation.

The development of complement inhibitors, particularly those targeting terminal component C5, has marked a milestone in the treatment of some of these diseases, offering tangible clinical benefits in contexts previously lacking effective options. The introduction of eculizumab as a terminal complement inhibitor demonstrated improvement in patient survival and quality of life in aHUS¹ and paroxysmal nocturnal hemoglobinuria (PNH).² In aHUS, C5 blockade not only achieved a rapid and sustained hematological response but also a substantial improvement in renal function, reducing the risk of end-stage kidney disease from 50–60% to 10–15%.³ This milestone triggered interest in the AP of complement in other kidney diseases and in the development of new drugs capable of blocking key points of the complement cascade.

The promising results previously described have led to the consideration of C5 inhibition as a nearly universal treatment in diseases where this pathway plays a relevant role. However, this approach has important limitations. The most significant is the heterogeneity in complement dysregulation among the different glomerular diseases, and even among patients with the same clinical entity. There is growing evidence that complement activation displays diverse patterns in each disease, with heterogeneous nuances even within each of them, which implies that a uniform strategy represents an excessive simplification with a potential negative impact in terms of both efficacy and safety.

Classification of glomerulopathies according to their relationship with complement

In recent years, new molecules targeting different critical points of the complement cascade have been developed, opening a strategic opportunity for greater therapeutic individualization. However, the current knowledge of the underlying mechanisms remains incom-

plete, and we currently lack reliable biomarkers of complement activity. In aHUS, the most extensively studied entity so far, serological or urinary markers of complement activation are elevated in only 30–50% of patients with active disease.⁴ These limitations mean that, for now, optimally personalized complement blockade remains an outstanding goal.

With the purpose of shedding light on this complexity, Fakhouri et al.⁵ propose dividing glomerular disease into 4 categories according to its relationship with complement (Fig. 1 and Table 1).

The first category would encompass those diseases in which dysregulation of the AP of complement constitutes the primary and main driver of kidney injury. This group includes C3G and aHUS. Although both entities share an alteration of the AP of complement, specifically dysregulating the C3 convertase, they are nonetheless diseases with distinct pathophysiological mechanisms, different clinical courses, and consequently, specific therapeutic strategies.

In aHUS, uncontrolled activation of the C3 convertase triggers diffuse endothelial injury mediated by the membrane attack complex (C5b-9). Current treatment with terminal inhibitors such as eculizumab or ravulizumab has been shown to reduce endothelial damage and halt the progression of microangiopathy. Nevertheless, it is worth considering whether drugs targeting more proximal levels of the AP, acting on the regulators of the C3 convertase where the primary defect originates, could achieve greater therapeutic efficacy. This hypothesis has been demonstrated through experience with pegcetacoplan in PNH,⁶ in which proximal inhibition has shown additional benefits compared to terminal blockade. It has even been suggested that a combined strategy, targeting both proximal and terminal phases of the complement cascade, could offer superior results. Clinical trials with this purpose are currently underway.⁷

C3G, for its part, is characterized by glomerular deposition of complement degradation products (mainly C3c and C3d) in different renal compartments, as a consequence of sustained hyperactivation of the C3 convertase. In recent years, several clinical trials with inhibitors targeting regulatory elements of this enzyme—such as factor B blockers (iptacopan)—⁸ and C3 blockers (pegcetacoplan)—⁹ have shown a significant reduction in proteinuria, tissue deposits, and a slowing of glomerular filtration rate (GFR) decline. In contrast, terminal pathway blockade with the C5a receptor inhibitor avacopan¹⁰ failed to modify either histological activity or proteinuria in these patients. There is accumulating evidence that the so-called idiopathic immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) share complement dysregulation as their main pathogenic mechanism. Consequently, these entities should probably be approached similarly to C3G and considered within this same nosological category.^{11,12}

The second category includes antibody-mediated glomerular diseases, among them lupus nephritis, membranous nephropathy, IgA nephropathy (IgAN), anti-glomerular basement membrane (GBM) glomerulonephritis, cryoglobulinemia, and humoral transplant rejection,¹³ among others. It is known that immune complexes, whether deposited or formed in situ, can activate the classical complement pathway and, to some extent, the lectin pathway, thereby amplifying

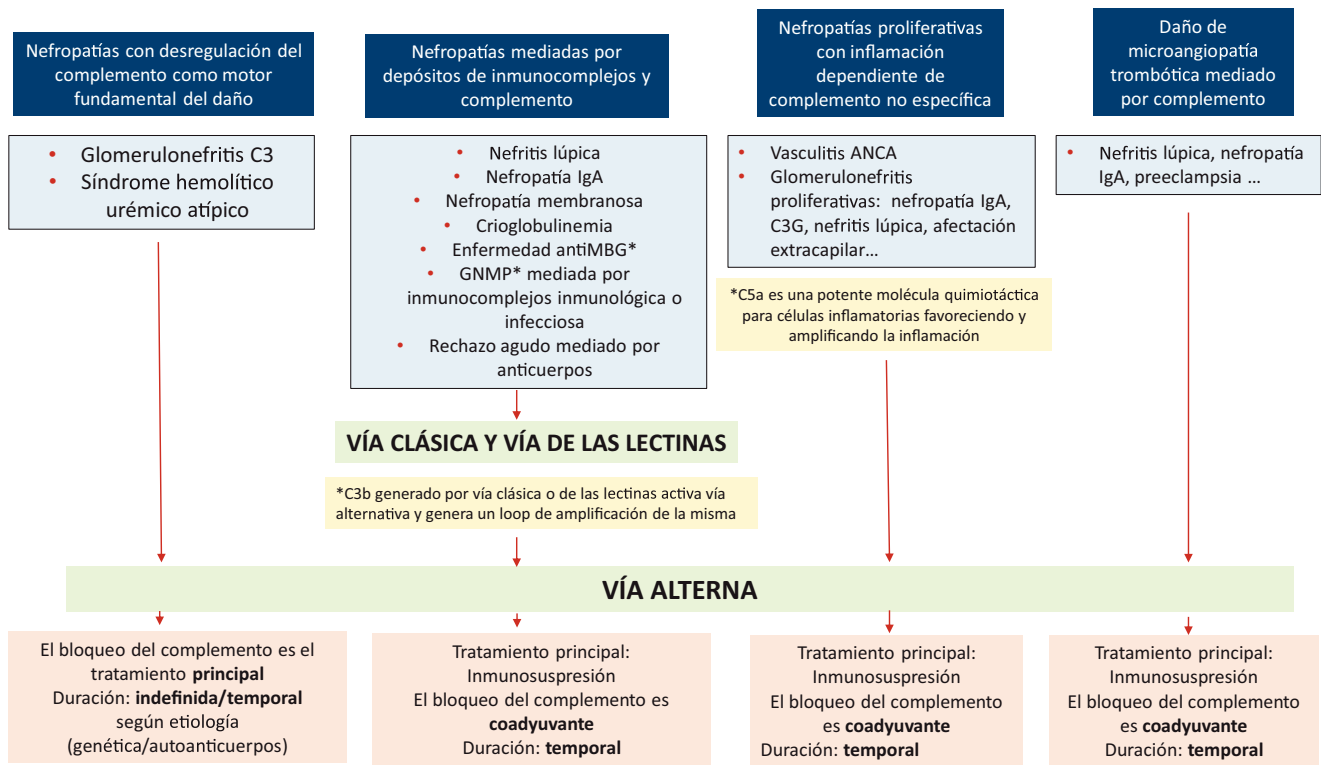


Fig. 1. Main mechanisms of complement dysregulation underlying the different forms of glomerular injury. Treatment proposal. Anti-GBM disease: anti-glomerular basement membrane antibody disease; MPGN: membranoproliferative glomerulonephritis.

cellular injury. It is known that C3b generated by activation of the classical or lectin pathways can secondarily activate the AP, amplifying complement activation within the tissue. In fact, in vitro experiments have shown that this secondary amplification through the AP accounts for the largest proportion of complement activation fragments generated by immune complexes.¹⁴ Thus, animal models deficient in AP complement activation have been shown to be protected from immune complex-mediated injury. These results support the importance of the AP in the pathogenesis of these glomerular diseases and its potential blockade as a therapeutic approach. Some clinical trials have shown encouraging results with AP complement inhibition in these diseases, such as in IgA nephropathy with iptacopan¹⁵ and ravulizumab.¹⁶

The third category would encompass those situations in which complement dysregulation, whether or not directly involved in the pathophysiology of the disease, additionally contributes to potentiating the associated inflammation. In this context, complement blockade should not be considered the primary therapeutic strategy, but rather an adjuvant and transient treatment while the true underlying pathogenic mechanism is treated and controlled.

It is known that proliferative glomerular diseases, both acute and chronic, can be accompanied by a variable degree of cellular inflammation. Such inflammatory changes can manifest as mesangial proliferation, crescent formation, fibrinoid vascular necrosis, or peritubular capillaritis, and there is evidence that they could be, at least in some cases, mediated by the C5a component, a potent chemotactic molecule for inflammatory cells.¹⁷

In this way, we can speculate that in crescentic forms of IgAN or C3G, as well as in ANCA vasculitis, C5a blockade (or blockade of its receptor) could represent an alternative to the use of high-dose steroids during the first weeks of treatment, with the goal of limiting inflammatory damage. In patients with C3G after one year of treatment with eculizumab, complement fragment deposits were not modified, but glomerular proliferation and neutrophil infiltration were reduced.¹⁸ Recently, a phase 3 clinical trial demonstrated that

C5a receptor blockade could replace the use of steroids in patients with non-severe ANCA vasculitis.¹⁹

Genetic and functional evidence in ANCA vasculitis points to proximal complement dysregulation (C3 convertase), supporting the development of therapies with more proximal blockade of the system.²⁰

Interestingly, this “anti-inflammatory” effect is not limited to glomerular disease but can also be observed in tubular injury. In a mouse model injected with cholesterol microcrystals, treatment with C5a or C5aR inhibitors prevented immunothrombosis, the decline in glomerular filtration rate, and the expected ischemic necrosis.²¹ Similarly, complement blockade prevented the development of tubular injury from rhabdomyolysis.²²

Although the application of complement-blocking therapies with this indication is very promising—as it could be useful in patients with more aggressive forms of disease to limit the inflammatory response—the current evidence is still insufficient to recommend its routine clinical use beyond ANCA vasculitis, where it has been proposed as a strategy to reduce the need for high-dose steroids.

The fourth category would include complement-mediated thrombotic microangiopathy damage concomitant with other primary glomerular lesions. Histological findings of TMA have been described in approximately 8–20% of kidney biopsies with a diagnosis of lupus nephritis²³ and in 2–53% of biopsies with a diagnosis of IgA nephropathy.²⁴ In both entities, this association correlates with a more severe clinical presentation and accelerated renal progression.²⁵ Severe arterial hypertension is frequent in this context, although TMA can also manifest in normotensive patients.

Evidence on the use of eculizumab in this category is limited to isolated clinical cases and small patient series. The KDIGO 2024 guidelines for lupus nephritis recommend considering complement inhibitors, such as eculizumab, in those cases of lupus nephritis associated with TMA that do not respond to either plasmapheresis or conventional immunosuppressive treatment.²⁶ However, optimal doses and treatment duration remain uncertain and must be

Table 1
Forms of complement dysregulation in the different glomerular diseases. Main approved and investigational treatments.

Nephropathies directly mediated by complement dysregulation			
Disease	Rationale	Approved drugs	Investigational drugs
C3 glomerulonephritis	Predominant C3 deposition. Autoantibodies or intrinsic (genetic) dysregulation of the AP in the fluid phase ³⁴	Pegcetacoplan (anti-C3) ⁹ Iptacopan (anti-factor B) ⁸	Eculizumab (anti-C5), danicopan (anti-factor D), narsoplimab (MASP-2 inhibitor)
Idiopathic immune complex-associated MPGN	Tissue immunoglobulin and complement deposition. Evidence of alternative pathway activation (and lesser classical pathway activation) described	Pegcetacoplan (anti-C3) ⁵	Pegcetacoplan (anti-C3), danicopan (anti-factor D)
Atypical hemolytic uremic syndrome	Complement dysregulation by autoantibodies or genetic AP alterations at the cell surface. Increased C5b-9 production. Endothelial injury ³⁵	Eculizumab (anti-C5) ³ Ravulizumab (anti-C5)	Avacopan (anti-C5a), iptacopan (anti-factor B), narsoplimab (MASP-2 inhibitor)
Nephropathies with immune complex and complement deposition. Immune complexes predominantly activate the classical and lectin pathways; however, the C3b generated additionally activates the alternative pathway ¹⁴			
Disease	Rationale	Approved drugs	Investigational drugs
Lupus nephritis	"Full house" pattern on biopsy. C3 and C4 hypocomplementemia. Immune complexes activate C3a and C5a, which produce inflammation and recruit C5b-9, causing tissue injury		Ravulizumab (anti-C5), pegcetacoplan (anti-C3), vemircopan (anti-factor D), narsoplimab (MASP-2 inhibitor)
IgA nephropathy	Codominance of tissue IgA and C3 along with C4, properdin, MBL, and C5b-9. Lectin pathway activation (MASP-2, C4d) ^{36,37} . Genetic variants of complement (CFH, CFHR5) or elevated FHR levels associated with worse prognosis ³⁸	Iptacopan (anti-factor B) ³⁰	Eculizumab (anti-C5), ravulizumab (anti-C5), cemdisiran (anti-C5), avacopan (anti-C5a-R), pegcetacoplan (anti-C3), narsoplimab (MASP-2 inhibitor), sefaxersen (anti-factor B)
Membranous nephropathy	C3 fragments and C5b-9 colocalize with IgG in subepithelial deposits ³⁹ . In experimental models: C3 depletion prevents proteinuria		Pegcetacoplan (anti-C3), iptacopan (anti-factor B), anti-factor D (BCX9930), narsoplimab (MASP-2 inhibitor)
Anti-GBM disease	Deposits of C1q and C3 together with IgG in a linear pattern along the GBM. MBL, C4d, factor B, C5b-9, and properdin deposits point to classical and lectin pathway activation ⁴⁰		Eculizumab (anti-C5)
Cryoglobulinemia	Tissue immunoglobulin and C3 deposits. C3 and C4 hypocomplementemia		
Acute humoral rejection Immunological or infectious IC-mediated MPGN	C4d deposits in peritubular capillaries ⁴¹ Immunoglobulin and complement deposits characterize the disease. AP activation described		Eculizumab (anti-C5)
Nephropathies with non-specific complement-dependent inflammation			
Disease	Rationale	Approved drugs	Investigational drugs
Proliferative glomerulonephritis, especially those with crescent formation: ANCA vasculitis, SLE, IgA, C3...	C5a is a potent chemotactic molecule for inflammatory cells. Elevated serum levels of C3a, C5a, and C5b-9 described ⁴² . Decreased serum C3 associated with worse prognosis ⁴³	Avacopan (anti-C5a-R) ¹⁹	Iptacopan (factor B inhibitor), vilobelimab/IFX-1 (anti-C5a)
Complement-mediated thrombotic microangiopathy damage associated with other glomerulopathies			
Disease	Rationale	Approved drugs	Investigational drugs
Lupus nephritis, IgA nephropathy, acute humoral rejection, catastrophic antiphospholipid syndrome...	8–20 % of kidney biopsies with a diagnosis of lupus nephritis and 2–53 % of biopsies with a diagnosis of IgA nephropathy		Eculizumab in case series and in KDIGO recommendations for treatment of lupus nephritis with associated thrombotic microangiopathy ²⁶

ANCA: antineutrophil cytoplasmic antibodies; anti-GBM disease: anti-glomerular basement membrane antibody disease; FHR: factor H-related proteins; MPGN: membranoproliferative glomerulonephritis; SLE: systemic lupus erythematosus; AP: alternative complement pathway.

individualized according to the clinical course of each patient, with early initiation of treatment being crucial to optimize renal recovery.

New complement-blocking drugs are in development, expanding the potential targets for inhibition within the complement cascade and offering increasingly specific therapeutic options according to the disease. However, as previously mentioned, the relationship between glomerular disease and complement is complex and not yet fully

understood. Identifying which pathways are dysregulated in each disease, and at what point they predominate throughout its course, will be essential to effectively individualize treatment.

In any case, we must not forget to approach glomerular disease from a holistic perspective, paying attention not only to complement but also to immunological, hemodynamic, genetic, and inflammatory factors present in these diseases.

Table 2
Current limitations for the routine clinical use of complement blockade in glomerular disease.

Limitation	Details
Still limited and heterogeneous clinical evidence	Few randomized trials per entity, small sample sizes, short follow-up, with intermediate outcome variables...
Non-standardized patient selection	In clinical trials, preselection based on complement activation or its absence has not been performed
Therapeutic target	Uncertainty about whether, in addition to clinical response, complement regulation should be a treatment goal
Unknown optimal timing of initiation and duration	No consensus on when to initiate (inflammatory vs. chronic phase), or how long to maintain blockade once clinical remission is achieved
Long-term safety	Increased susceptibility to infections. Scarce data on long-term immunological and oncological effects
Integration with standard immunosuppression	Lack of information on how to combine anticomplement treatment with immunosuppressive medication. Risk of cumulative toxicity
Specialized monitoring and diagnostics	Limited availability and interlaboratory variability of complement testing: functional studies, autoantibodies, genetic studies
Cost and access	Absence of pharmacoeconomic evaluations. High cost
Special populations with scarce data	Pediatrics, pregnancy, comorbid patients, or those with very advanced renal function
Inconvenient dosing for patients	Most available drugs require in-hospital administration, in intravenous or subcutaneous formulations, which requires patients to attend the hospital with high frequency

Challenges and unresolved issues

To date, treatment with complement drugs poses multiple challenges and unresolved issues (Table 2).

Need for robust biomarkers

It is crucial to have biomarkers capable of predicting complement activation, identifying the predominant activation pathway, and monitoring therapeutic response in real time. Conventional tests, such as serum C3 and C4 determination (except in the case of C3G), usually have limited sensitivity and specificity. Similarly, the quantification of other constituent proteins of the complement cascade or their fragments has not been shown to provide clinically relevant information.²⁷

The hypothesis has been raised that local complement activation at the renal level could play a determining role, which would explain why urinary biomarkers could more faithfully reflect disease activity than serum parameters. In this regard, in an analysis performed in patients included in the phase 3 clinical trial with ravulizumab in adults with atypical hemolytic uremic syndrome, the area under the curve (AUC) for predicting activity was 0.72 for urinary C5b-9 levels, compared to 0.52 for plasma levels.²⁸

In other glomerular diseases, some studies suggest that urinary detection of complement system fragments such as “Bb” in lupus nephritis²⁹ or in vasculitis³⁰ could more precisely reflect intraglomerular inflammatory activity. However, the available evidence is still limited, and further prospective and multicenter studies are needed to validate their diagnostic and prognostic utility, as well as their role in monitoring treatment response.

Optimal duration and sequence of treatment

Most available clinical trials have relatively short follow-up periods; therefore, the duration of the response and the complete profile of possible long-term adverse effects are still unknown. In chronic diseases such as C3G, characterized by flares and remissions, it is not clearly established whether treatment should be maintained indefinitely or whether controlled withdrawal periods can be defined. In the face of the temptation to prolong complement blockade chronically after achieving a clinical response, it is necessary to consider both the risk of serious infections and the high cost of these drugs. On the other hand, treatment withdrawal may carry a significant risk of relapse and disease progression.

In some entities, such as PNH, the therapeutic decision is more straightforward, given that discontinuation of terminal complement

blockade is almost invariably associated with a severe relapse. However, in most glomerular diseases, this relationship is not as well defined. In aHUS, the presence of pathogenic genetic variants constitutes the main predictive factor for relapse.³¹ Thus, in patients without pathogenic genetic variants, treatment withdrawal is relatively safe, with a relapse rate below 5%. In contrast, the decision in cases with variants of uncertain significance is more complex and requires individualized assessment.

Although sufficient evidence is not yet available, a similar scenario could be expected in the few cases of C3G of genetic origin. In immune complex-mediated forms, however, the information is scarce and there are no conclusive data to guide clinical practice.

There is also no robust evidence for those situations in which complement acts primarily as an amplifier of inflammation or as a trigger for thrombotic microangiopathy. In these contexts, it can be hypothesized that treatment should be transient, limited to a brief period—weeks or a few months—until the acute episode is controlled, avoiding unnecessary exposure to chronic therapy.

Trial design to provide clinically relevant information

The intrinsic heterogeneity of glomerular diseases, together with the rarity of some entities such as C3G, constitutes an important obstacle to the development of robust clinical trials. This methodological difficulty translates into overly broad inclusion criteria and the use of non-specific endpoints, usually focused on short-term measures, which do not capture the course of the disease or the sustainability of the response after treatment withdrawal.

The pioneering trials published recently represent a necessary advance but have limitations that affect the interpretation of their results and their applicability in real-world clinical practice. It is essential that future studies adopt more precise designs adapted to the complexity of these diseases, incorporating clinically relevant endpoints, prolonged follow-up periods, and strategies that allow patient stratification according to biomarkers or genetic characteristics. Only in this way will it be possible to generate more solid evidence to guide informed therapeutic decisions and reduce the current uncertainty in clinical management.

Cost and accessibility

These innovative therapies represent a real challenge for healthcare systems. For years, eculizumab was considered the most expensive drug on the market. The introduction of biosimilars and the development of new agents have contributed to reducing its price, although the cost remains very high and constitutes a significant

limitation for the equitable expansion of its use across all regions of the world.

The molecules in development, unlike the current ones which are predominantly antibodies, will be peptides. In general, peptides are preferred over antibodies due to their lower difficulty and cost of production, their feasibility for subcutaneous and even potentially oral administration, as well as a lower risk of immunogenicity.³²

Integration of anticomplement therapy with immunosuppression

Even in those glomerular diseases in which injury is directly mediated by complement dysregulation, the need to combine immunosuppressive treatment sometimes arises. In fact, in the 2 clinical trials with complement inhibitors in C3G, concomitant use of prednisone and mycophenolate was allowed. It is reasonable to think that elimination of antibodies that prolong the half-life of the C3 convertase (C3NEF) could exert an additional and sustained benefit in the course of the disease.³³

In the remaining glomerulopathies, in which complement dysregulation does not constitute the initial mechanism of injury, combination with immunosuppression remains essential. However, it is foreseeable that current regimens will need to be revised as complement-blocking therapies become available. The first example of this change is the use of avacopan in ANCA vasculitis, where it has demonstrated the ability to significantly reduce steroid exposure.

In conclusion, complement blockade constitutes one of the most promising strategies in current nephrology, but its rational implementation requires overcoming critical challenges that must be addressed before these therapies can be considered for widespread use. Only through a critical approach, based on solid evidence and therapeutic individualization, will it be possible to translate these advances into lasting clinical benefits for patients.

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Declaration of competing interest

GF-J declares having consultancy contracts with Alexion and having received honoraria from Sobi and Novartis for participation in scientific advisory committees.

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