Targeting the alternative complement pathway in IgA nephropathy

A clinical perspective on the evolving therapeutic strategy for IgAN
Smeeta Sinha, UK (Session moderated by Jürgen Floege, Germany)

The presentation started with a case study of a patient with immunoglobulin A nephropathy (IgAN) who experienced deterioration of the disease despite treatment.

The patient presented in 2015 following a road accident. He was hypertensive, so his urine was tested by the treating physicians to assess kidney damage. Dipstick hematuria was present, so urine protein-creatinine ratio (UPCR) was evaluated and found to be elevated. Kidney function was preserved, and the kidney biopsy was relatively clean, with S1 the sole finding (Table 1).

### Table 1: Patient characteristics at presentation (2015).

<table>
<thead>
<tr>
<th>Reason for presentation</th>
<th>Road accident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, gender</td>
<td>28 years, male</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Non-smoker</td>
</tr>
<tr>
<td>Hematuria (dipstick)</td>
<td>+</td>
</tr>
<tr>
<td>UPCR</td>
<td>Elevated</td>
</tr>
<tr>
<td>Kidney function</td>
<td>Preserved</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
</tr>
<tr>
<td>Kidney biopsy</td>
<td>M0 E0 S1 T0–C0</td>
</tr>
</tbody>
</table>

BMI, body mass index; C, crescents; E, endocapillary hypercellularity; M, mesangial hypercellularity; S, segmental sclerosis; T, interstitial fibrosis/tubular atrophy; UPCR, urine protein-creatinine ratio

Between 2015 and 2016, the patient's blood pressure (BP) was reduced to <110/70 mmHg through management with optimal supportive therapy, including a low salt diet and renin-angiotensin system inhibition (RASi) optimization with the addition of a calcium channel blocker and a beta blocker. Weight loss was encouraged, although this was challenging due to compromised mobility following the accident. However, by 2017, kidney function had declined, prompting referral to the specialist clinic (Figure 1).

It was at this point that proteinuria started to rise and treatment with steroids was initiated. Proteinuria initially improved but subsequently started to increase. As the patient was young and starting to experience side effects from the steroids, a steroid-sparing regime with mycophenolate mofetil (MMF) was started in mid-2018, which was used routinely at that time for IgAN patients. The patient was therefore started on steroids and MMF. Proteinuria then decreased consistently by the end of 2019; however, as soon as that regimen was stopped, proteinuria elevated once more.
Steroids were initiated again in 2020, but they had less effect on proteinuria compared with 2017. By the middle of 2021, treatment with steroids was stopped due to limited efficacy and the onset of side effects. A sodium-glucose cotransporter-2 inhibitor was started in 2021 as the patient was unwilling to enter a clinical trial at that time.

Despite the interventions described, and associated improvements in proteinuria, there was a sustained decline in the estimated glomerular filtration rate (eGFR) which had reached 33 mL/min/1.73m² by 2022. Over the years, it has been difficult to find effective treatments to halt or reverse the decline in kidney function for this patient, but there is hope for the future, particularly since he is now willing to enter a clinical trial.

This case study illustrates that complete remission of proteinuria was not achieved at any point. If a regression line were drawn on the eGFR chart, it would be linear, demonstrating that, despite treatment in accordance with guidelines, the patient is progressing to kidney failure.

Clinicians always hope that the next treatment will make a difference, but without genuine understanding of pathophysiology, it is impossible to generate new therapies with potential in clinical trials. There has been little progress in IgAN for 20 years, but a number of investigational drugs are currently in development.

A decade ago, few nephrologists considered IgAN a complement-mediated condition, but the complement system is now becoming an integral part of nephrology (Figure 2). It now appears that factors influencing the complement alternative pathway are implicated in IgAN, including the lectin pathway and Factor B involvement. In addition to complement, there are other pathophysiological areas of interest, such as a proliferation-inducing ligand (APRIL) and B cell activation factor (BAFF) of the tumor necrosis factor family, investigating prevention of the development of dysregulated IgA.

There are also downstream opportunities for the optimization of supportive care which traditionally include BP control, weight loss, a low salt diet, and RASi. There are now trials of interest with drugs, such as sparsentan, that can reduce proteinuria, although they are not targeted. As a result, there are two potential new options for patients which may work synergistically: optimizing supportive care and disease-modifying drugs that target the cause of disease.

Data from clinical trials are becoming available. In a Phase 2 study with iptacopan, a Factor B inhibitor, in patients with IgAN, a significant, dose-dependent reduction in proteinuria was seen at 3 months (1-sided, p=0.038) and UPCR continued to decrease between Months 3 and 6.2,3 It will be important to see if this translates into an improvement in eGFR in future studies; so far, the results are promising because iptacopan targets the cause of IgAN.

Complement inhibition not only targets glomerular disease but also the fibrotic process, and there is a wealth of animal data showing that complement inhibition leads to antifibrotic effects which would not be evident from a study where the endpoint is proteinuria. However, the
endpoint of clinical trials for potential drugs to prevent kidney fibrosis would be loss of glomerular filtration rate (GFR), which would require long-term studies lasting for up to 20 years, which is unrealistic. It is therefore necessary to measure the impact of drugs on markers for the disease, and Phase 2 data with iptacopan has shown an impact on some of the complement markers, indicating that there is inhibition of the pathway leading to IgAN. Demonstrating this effect will be important for future adoption of these potentially disease-modifying treatments.

C3G in the spotlight – a clinical and therapeutic overview

Veronique Frémeaux-Bacchi, France and Moglie Le Quintrec-Donnette, France (Session moderated by Giuseppe Remuzzi, Italy)

Giuseppe Remuzzi introduced the session with a case study of a 22-year-old Caucasian with rapidly progressing C3 glomerulopathy (C3G), despite having no family history of kidney disease.

The patient was admitted to the emergency department in December 2013 due to general malaise and diffuse edema. Laboratory tests showed nephrotic syndrome, microhematuria, and low C3, although kidney function was normal at this time. Treatment with intravenous steroids and albumin was initiated, but no benefit was seen; five days after admission, there was clinical worsening with gross hematuria and rapidly progressive kidney failure. A kidney biopsy revealed a dominant C3 with immunofluorescence (IF).

Considering the severe evolution and the presence of crescent formation on kidney biopsy, a number of treatment strategies (plasma exchange, mycophenolate, eculizumab) were implemented with no success. Kidney failure developed shortly after, and hemodialysis was initiated. This continued until July 2016, when she underwent a kidney transplant. A transplant biopsy was performed that showed recurrence of C3G; treatment with iptacopan, an oral, selective inhibitor of Factor B, was started in July 2020 which led to partial remission.

Rare diseases of complement may have different contributory factors: A genetic component (associated with complement mutations, such as CFH, CFI, C3, CFB, CD46, CFHR5, CFHR-CFHR, and IQGAP1), an antibody component (associated with antibodies, such as C3NeF, C5NeF, C4NeF, anti-CFH, anti-C3b, and anti-FB), and trigger factors (including infections, drugs, tumors, and transplantation).

Veronique Frémeaux-Bacchi went on to discuss how the laboratory results guide the management of C3G.

Looking at diagnostic challenges in C3G, kidney pathology, including C3 deposits, can first be identified using kidney biopsy, but there are currently only two descriptive biomarkers to aid diagnosis and treatment decisions: serum creatinine and proteinuria. Diagnosis would be more definitive with proof of the molecular origin of disease but, in practice, if a patient has low C3, the important questions are “why is there complement activity?” and “why is it not controlled by C3 convertase in either the fluid phase or the tissue?”

Mechanistic biomarkers are needed, but this requires characterization of complement activation, either via the alternative or classical pathway; is it fluid-phase activation or tissue activation alone? The cause of the C3G is also important: Is it a hereditary disease or an acquired complement abnormality? This information should aid diagnosis of the specific type of disease and inform treatment decisions.

An optimum approach for differentiating C3G from other types of glomerulonephritis is an important consideration. Kidney biopsy, with either light or IF electron microscopy (EM), is used to differentiate membranoproliferative glomerulonephritis (MPGN) into two distinct types; where there are exclusive or predominant C3 deposits, it could be either C3G or dense-deposit disease (DDD); where both complement and immunoglobulin (Ig) deposits are present, it is referred to as immune-complex MPGN (IC-MPGN).

Are IC-MPGN and C3G distinct entities? Generally, classical pathway activation is suggested if Ig is present; the presence of C3 alone suggests activation via the alternative pathway. However, when serial kidney biopsies are performed in the same patient, diagnosis following biopsy may not be consistent because Ig deposits are variable and may disappear, while C3 deposits are present consistently.

There are few arguments supporting C3G and IC-MPGN being distinct entities. Firstly, glomerular C4d staining is positive in the majority
(80%) of primary and secondary IC-MPGN cases (although only a limited number of primary IC-MPGN cases have been studied), but only (and faintly) in a minority (13%) of C3G cases. Secondly, nephrotic syndrome is more frequent in IC-MPGN (43–70%) compared with C3G (26–52%) patients.

A different conclusion might be reached from evaluating biological aspects of the two diseases. The frequency of low serum C3 (complement alternative pathway activation) is similar in IC-MPGN (46–70%) and C3G (38–80%). C3Nef, which targets the alternative complement pathway, is detected in 40–54% of IC-MPGN patients and 40–80% of those with C3G. Variants in genes encoding for alternative complement pathway proteins are also detected in IC-MPGN at a similar low frequency as C3G (10–25%). To date, there is no proof that the response to available treatments is different in IC-MPGN and C3G.

Looking at the cause of C3G, it is systematically linked with the alternative pathway. Predominant or exclusive C3 deposits are pathological hallmarks of C3G and acquired (autoantibodies) or constitutional (genetic variants) dysregulation of the complement system has also been reported. Furthermore, animal models have linked C3G to alternative C3 convertase dysregulation.

The difference between the classical and alternative pathways is the mechanism of activation. The alternative pathway is constantly activated at a low level. There is cleavage of the C3 forming C3 convertase that cleaves C3 to the fragment C3b.

There are, therefore, consequences to activation of the alternative pathway; there is capacity to increase cleavage of C3, but activation of C5 convertase is also induced, leading to the liberation of C5a, indicative of activation of inflammation. There is also activation of C5b-9 in the tissue, which has consequences in the kidney.

C3 and C4 are routinely determined in the laboratory, and low C3 and normal C4 levels are serological biomarkers for complement activation. While low C3 (a sign of alternative pathway complement activation) is found in only 50% of cases, there are always C3 deposits on the tissue. There is, therefore, a difference between the fluid phase and tissue complement activation, suggesting that there may be a difference between the two conditions. S(C5b-9), a serological biomarker of terminal-pathway activation, significantly increased in 50% of cases.

There is, therefore, no ideal complement biomarker for the diagnosis of C3G, or to monitor complement activation within the kidney, as there is no correlation between C3 deposits and the level of complement activation. However, the question remains whether these biomarkers might have a role in evaluating clinical responses to a new therapy.

Identification of the cause of complement deregulation in C3G involves screening for antibodies and pathogenic variants.
However, there are limitations to screening: 9,13-20
- There is no consensus for detection and characterization
- It can only be carried out by specialized laboratories
- Methods are variable and technically complex (analysis of C3 breakdown products, enzyme linked immunosorbent assay, hemolytic assays)
- The results of the tests used to detect antibodies depend on laboratory procedures
- The heterogeneous nature of nephrotic factor (NeF)

Giuseppe Remuzzi explained how membranoproliferative glomerulonephritis (MPGN) has been classified into IC-MPGN (immunoglobulin positive, not C3 dominant) and complement-mediated C3G (no/few immunoglobulins, C3 dominant). EM in patients with dominant C3 can be an indicator for C3G or DDD but does not show any features that are useful to distinguish between IC-MPGN and C3G.21 IC-MPGN and C3G are ultra-rare conditions associated with complement dysregulation. There is broad inter-individual variability for both diseases, leading to classification challenges; there are currently no effective treatments.21 A cluster analysis can help in the classification of MPGN (Figure 4).22

Thirty-five histologic, biochemical, genetic, and clinical variables were used to develop this cluster analysis from 173 patients with primary IC-MPGN/C3G (Table 2) which identified four distinct clusters of patients (Figure 4). All four groups had important glomerular C3 deposits, including cluster 4, which had markedly different results for other variables.22

Table 2: Histologic, biochemical, genetic, and clinical variables in 173 patients with primary IC-MPGN/C3G

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Histology findings</th>
<th>Complement profile</th>
<th>Genetic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (onset)</td>
<td>Age (onset)</td>
<td>Serum C3</td>
<td>N° of AP complement gene mutations*</td>
</tr>
<tr>
<td>Familiarity for nephropathy</td>
<td>IgG staining on IF</td>
<td>Serum C4</td>
<td>CFH p.V621</td>
</tr>
<tr>
<td>Micro- / Gross-hematuria at onset</td>
<td>Intramembranous electron-dense deposits</td>
<td>Plasma sC5b-9</td>
<td>CFH p.H402Y</td>
</tr>
<tr>
<td>Proteinuria/ nephrotic syndrome at onset</td>
<td>Subendothelial deposits</td>
<td>Presence of C3NeF*</td>
<td>CD46 c.:366A&gt;G</td>
</tr>
<tr>
<td>Decreased GFR/ kidney failure at onset</td>
<td>% of sclerotic glomeruli</td>
<td>-</td>
<td>CFB p.Q/W32R</td>
</tr>
<tr>
<td>Gender</td>
<td>Degree of mesangial proliferation</td>
<td>-</td>
<td>C3 p.R102G</td>
</tr>
<tr>
<td>Trigger</td>
<td>-</td>
<td>-</td>
<td>THBD p.A473V</td>
</tr>
</tbody>
</table>

* Used as a single composite variable ‘N’ of AP abnormalities* - AP, alternative pathway; C3G, C3 glomerulopathy; IC, immune-complex; IF, immunofluorescence; MPGN, membranoproliferative glomerulonephritis; N or n, number - Adapted from Iatropoulos F, et al. JASN 2018; 29(1):283–94
Clusters 1, 2, and 3 had similar results for mutations or C3NeFs; serum C3 was also very low in all clusters. Plasma sC5b-9 is elevated in clusters 1 and 2, but this was rarely the case in cluster 3. Glomerular IgG and glomerular C1q are both present in cluster 2, more so than in all other clusters, and high electron-dense deposits are prominent in cluster 3, although they can also be seen but to a lesser extent in cluster 1 (Figure 5).22

This cluster analysis helps differentiation between fluid- (cluster 1, 2 and 3) and solid-phase (cluster 4) complement activation. When this is combined with other variables, clear distinctions between the clusters become evident.22

Data from 33 newly recruited patients are in agreement with observations in the cluster cohorts and this work is now a part of a European initiative to assess whether cluster classification could continue to be helpful when more patients are included and whether there is potential to move towards a precision medicine approach for C3G and IC-MPGN. This initial theoretical approach would need to be developed once compounds in Phase 2/3 development are approved for use:22

- Cluster 1: Fluid phase AP C3 and C5 convertase activation – Iptacopan (Factor B inhibitor), Avacopan (C5aR1 inhibitor), Eculizumab (anti-C5 antibody)
- Cluster 2: Fluid phase AP C3 and C5 convertase activation + classical pathway activation – Pegcetacoplan (C3 inhibitor), SUN501 (liver-targeting C3 silencing)
- Cluster 3: Fluid phase AP C3 convertase activation only – Iptacopan (Factor B inhibitor), Danicopan (Factor D inhibitor)
- Cluster 4: Solid phase AP complement activation with normal C3 and plasma C5b-9 levels and intense staining on IF – ADX-097 (anti C3dmAb-FH), GEM307 (FH potentiating Ab)

Maglie Le Quintrec-Donnette highlighted that there are currently no approved therapies for C3G. As the disease is heterogeneous, not all patients require aggressive treatment. For patients with proteinuria <1g/g and stable creatinine, the first (and sometimes only) treatment is with angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), but those with proteinuria >1g/g, nephrotic syndrome, or acute and progressive deterioration of kidney function and limited fibrosis (<30%), require more aggressive treatment.

Current therapies mainly target the inflammatory component. A study in a Spanish cohort of 60 patients found that those receiving treatment with MMF and a corticosteroid had higher remission of C3G compared with patients taking other immunosuppressive or antiproteinuric treatments. Anti-complement therapies (investigational compounds and eculizumab) provide an alternative treatment option because C3G is mediated by the dysregulation of the alternative complement pathway.

Seven years ago, an open-label, non-blind, proof-of-concept efficacy and safety study of eculizumab in patients with biopsy-proven DDD (n=3) or C3 glomerulonephritis (C3GN) (n=3) was performed. All of the patients were adults, with proteinuria >1g/g, or a decreased GFR, both of which are predictors of a poor long-term outcomes in many glomerular diseases. The patients were treated for 1 year, but no clear benefit of eculizumab was found: 2 patients had improved eGFR, 1 had decreased proteinuria, and 2 showed no effect.23 Another study of eculizumab by the same team produced similar results.

Retrospective studies in France investigating the efficacy of eculizumab enrolled 26 patients and found it to be beneficial in patients with crescentic rapidly progressive C3G, while the effect in patients with non-rapidly progressing forms was more limited.24,25

**Iptacopan: Phase 2 study in C3G**

Detailed results from a Phase 2 study on iptacopan were presented at the American Society of Nephrology (ASN) in 2021. The study enrolled two cohorts of patients aged ≥18 years with an eGFR ≥30 mL/min for patients on a maximum-recommended or maximum-tolerated dose of ACEI or ARB.26
- Cohort A: Non-transplanted patients with reduced C3 levels (<0.90 × lower limit of the lab normal range) and UPCR ≥100 mg/mmol (or ≥1g/24h total urinary protein excretion
- Cohort B: Transplanted patients (>90 days before the screening visit) with recurrent C3G and no histological, laboratory, or clinical signs of rejection

The primary objectives of the study were a reduction in proteinuria at Week 12 (Cohort A) and histopathological changes (C3 deposit score) in kidney biopsies at Week 12 (Cohort B).

Iptacopan reduced proteinuria by 45% at Day 84 compared with baseline and improved eGFR in patients with native kidneys (Figure 6).

In transplanted patients with recurrence, iptacopan significantly reduced C3 deposit scores at Day 84 compared with baseline (Figure 7).

Further clinical trials are underway in C3G for:
- C3 inhibitors:
  - Pegcetacoplan, NCT04572854 (Phase 2) and NCT05067127 (Phase 3)
- Factor D inhibitors:
  - Danicopan, NCT03369236 (Phase 2) – This trial is now discontinued and danicopan is no longer being developed in C3G
  - BCX9930, NCT05162066 (Phase 2)
- C5a receptor inhibitors:
  - Avacopan, NCT03301467 (Phase 2)

Each trial is unique in its choice of targets and presumed effects.

**Pegcetacoplan**

Pegcetacoplan binds to a pocket of C3 and inhibits activation of C3, C3b, C3, and C5 convertase. It is administered twice weekly (Days 0 and 4) by subcutaneous infusion.

The NOBLE Phase 2 study recruited 12 patients with post-transplant recurrence of C3G or IC-MPGN in the renal allograft. The primary objectives were efficacy of pegcetacoplan in reducing C3c staining on renal biopsy after 12 weeks of treatment, and the safety of pegcetacoplan and reduction of C3 on biopsy in patients with recurrence in renal allograft effects for up to 52 weeks.

The VALIANT Phase 3 study enrolled native and transplanted patients with primary C3G and IC-MPGN. The endpoint was a reduction in UPCR ≥50% at Weeks 26 and 52 compared with baseline.

**Danicopan**

Danicopan is an oral treatment that decreases Bb domain production and suppresses AP convertase formation.

In a Phase 2 proof-of-concept study, 13 patients with C3G were randomized to receive danicopan or placebo for 6 months. The starting dose...
of danicopan was 100mg three times a day (TID) for the first 2 weeks, increasing to 200mg TID for the remainder of the treatment period. The primary endpoint was change from baseline in a composite biopsy score at Week 28, which incorporated changes in the activity index, glomerular C3 staining, and glomerular macrophage infiltration at the end of six months of treatment.29

All patients who completed the double-blind treatment period were enrolled in the open-label extension period to receive danicopan 200mg TID.29 This trial is now discontinued and danicopan is no longer being developed in C3G.

**BCX9930**

The Phase 2 RENEW Basket trial with BCX9930 in 42 patients with complement-mediated kidney disease (C3G, IgAN, and primary membranous nephropathy; 14 patients each). The primary endpoint was the change in 24-hour UPCR at Week 24. Other endpoints included changes in urine protein excretion, eGFR, morphologic response to biopsy, and levels of complement biomarkers.30

**Avacopan (CCX168)**

The ACCOLADE Phase 2 study evaluated the safety and efficacy of avacopan in patients with C3G. In the initial 26-week placebo-controlled period, patients received avacopan 30 mg or a matching placebo orally twice daily. This was followed by a 26-week period when all patients received the active treatment (avacopan) and an 8-week observation period with no avacopan treatment.31 The primary objective was to evaluate the efficacy of avacopan compared with placebo, based on histologic changes in kidney biopsies after 26 weeks of treatment compared with those taken at baseline. The primary endpoint was based on the percentage change from baseline in the C3G Histologic Index for disease activity.31
Further readings

2. Barratt J, et al. Late breaking clinical trials presentation at 58th ERA-EDTA Congress, June 5–8, 2021
3. Rizk DV. Late breaking clinical trial presentation at WCN Congress, February 24–27, 2022
27. NCT04572854. ClinicalTrials.gov (accessed May 2022)
28. NCT05067127. ClinicalTrials.gov (accessed May 2022)
29. NCT03369236. ClinicalTrials.gov (accessed May 2022)
30. NCT05162066. ClinicalTrials.gov (accessed May 2022)
31. NCT03301467. ClinicalTrials.gov (accessed May 2022)