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Industry Symposia
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The future of anemia of CKD: where are we going?

The latest on the underlying mechanism

Christoph Wanner, Germany

Anemia is a condition where the number of red blood cells (RBCs) is insufficient to meet the body's physiologic needs. It is diagnosed by measuring blood hemoglobin (Hb) levels. The World Health Organization (WHO) defines anemia for pregnant and non-pregnant women, and for men at <11.00 g/dL, <12.00 g/dL and <13.00 g/dL Hb respectively.[1]

Anemia of chronic kidney disease (CKD) mainly occurs in patients with a glomerular filtration rate >30ml/min/1.73 m^2. Two different pathways can lead to anemia of CKD: [2]Reduced production of erythropoietin (EPO) leading to reduced erythropoiesis; and

(i) Inflammation leading to the release of inflammatory cytokines causing excess production of hepcidin which, in turn, induces degradation of the iron exporter ferroportin and reduced iron availability.

Increased hepcidin restricts iron availability.[2] When hepcidin levels are normal, iron can be mobilized from intracellular ferritin stores through ferroportin channels. In the presence of higher levels of hepcidin, the ferroportin channels are blocked, leading to an accumulation of ferritin inside the cell. In this way, increased hepcidin levels lead to decreased iron absorption in the gut, reduced iron mobilization from intracellular stores,[2,3]and reduced iron in the circulation available for erythropoiesis,[3] resulting in low serum iron, low transferrin saturation and normal-high ferritin.[4]

Two regulatory systems maintain iron homeostasis: systemic regulation through hepcidin and the iron exporter ferroportin, and cellular regulation by iron regulatory proteins.[5]

In CKD, increased hepcidin secretion from the liver causes functional iron deficiency and reduces erythropoiesis, leading to anemia.[3]

Production and secretion of EPO, and the expression of EPO receptors are regulated by tissue oxygen supply via activation of the HIF pathway.[6] The kidneys produce EPO in response to hypoxia which in turn increases the red cell mass, thereby improving tissue oxygenation.[6]

EPO is the critical growth factor that acts on bone marrow erythroid progenitor cells to prevent them undergoing apoptosis.[6] In normal conditions, low concentration of EPO allows only a small percentage of erythroid progenitor cells to survive, while the remaining progenitors undergo apoptosis.[6]In contrast, when the concentration of EPO rises in blood (either endogenously or exogenously), many more erythroid progenitor cells escape from apoptosis and proliferate to mature into erythroblasts and, eventually, RBCs.[6]

The HIF pathway is a direct oxygen sensing system. It plays an important role in cellular response to hypoxia by controlling a broad spectrum of biological processes and is regulated by two major sets of proteins: Hypoxia Inducible Factor (HIF) and Prolyl Hydroxylase Domains (PHD).[2] HIF transcription factors are protein heterodimers composed of an oxygen-sensitive α subunit and a constitutively expressed β subunit.[2] In humans, there are three HIF-α paralogs (HIF-1α, -2α, -3α, although HIF-3α does not have a prominent role in the regulation of cellular hypoxia responses) and two HIF-β paralogs, aryl hydrocarbon receptor nuclear translocator (ARNT) and ARNT2.[7] HIF 1α and -2α facilitate oxygen delivery and cellular adaptation to hypoxia by controlling a broad spectrum of biological processes. Under hypoxia, HIF induces the expression of genes that influence both erythropoiesis and iron metabolism/utilization. Under basal normoxia, HIF-α is downregulated/degraded.[2]

PHD proteins are oxygen-sensitive enzymes that regulate activity and degradation of HIF transcription factors.[8] They are hydroxylase enzymes, which have three isoforms (PHD1, PHD2, PHD3), all of which are involved in the regulation of gene expression and activity of HIF proteins in response tissue hypoxia.[2] Under hypoxia, the rate of PHD-dependent hydroxylation and degradation of HIF-α is reduced.[2]

CKD-induced dysregulation of the HIF pathway leads to impaired cellular responses to hypoxia and reduced EPO production.[9]

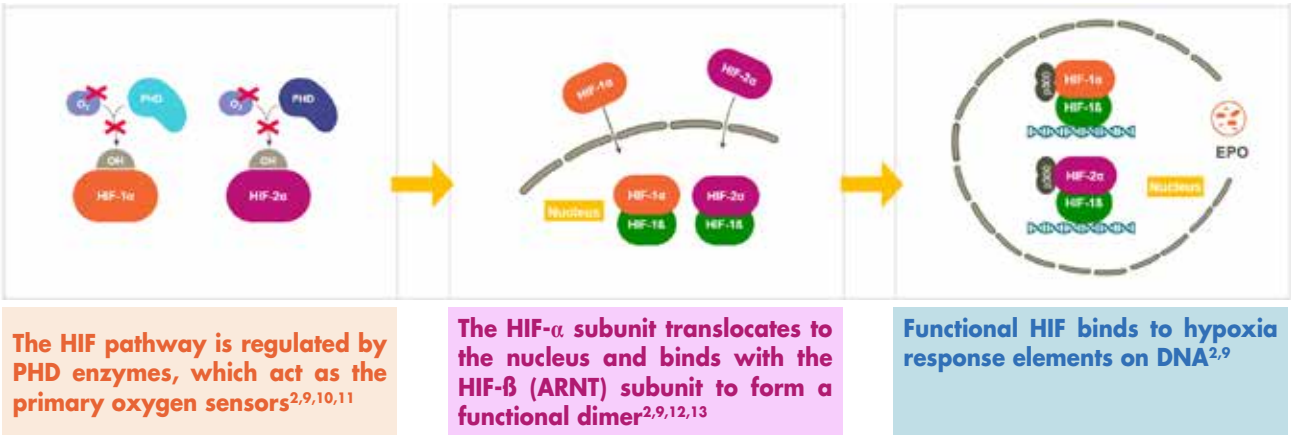

Figure 1. HIF pathway in hypoxia (in animal models). Image independently created by GSK from Ariazi JL, *et al. J Pharmacol Exp Ther* 2017;363(3):336–47 and Koury MJ, *et al. Nat Rev Nephrol* 2015;11:394–410.

In anemia, decreased oxygen transport causes tissue hypoxia, which through activation of the HIF system stimulates the production of EPO.[2] This classic hypoxia response is greatly impaired in patients with kidney failure, as the kidney is the major site of erythropoietin production under physiologic and hypoxic conditions.[2] In CKD, hypoxia-induced signaling is disrupted and anemia develops as CKD progresses.[2]

Current treatment options for anemia in the KDIGO Guidelines are:

- First line: supplemental iron,[14] oral > IV
- Second line: recombinant EPO therapy, in combination with iron supplements[14]
- Blood transfusion is a rescue therapy if other treatments for anemia fail[14]
- Kidney transplant may be curative in patients with ESRD[15]

HIF-PHIs are a novel therapeutic class for the treatment of anemia.[16] They stabilise HIF by suppressing/inhibiting PHD to mimic the physiologic response to hypoxia, stimulating erythropoiesis via endogenous EPO production and modulating iron metabolism in animal models.[16,17] As HIF-PHIs maintain a physiologic elevation of EPO production, the risk of Hb overshoots brought by erythropoiesis stimulating agents (ESAs) may be reduced.[9,18]

The HIF-PHI mechanism of action is depicted in Fig 2.

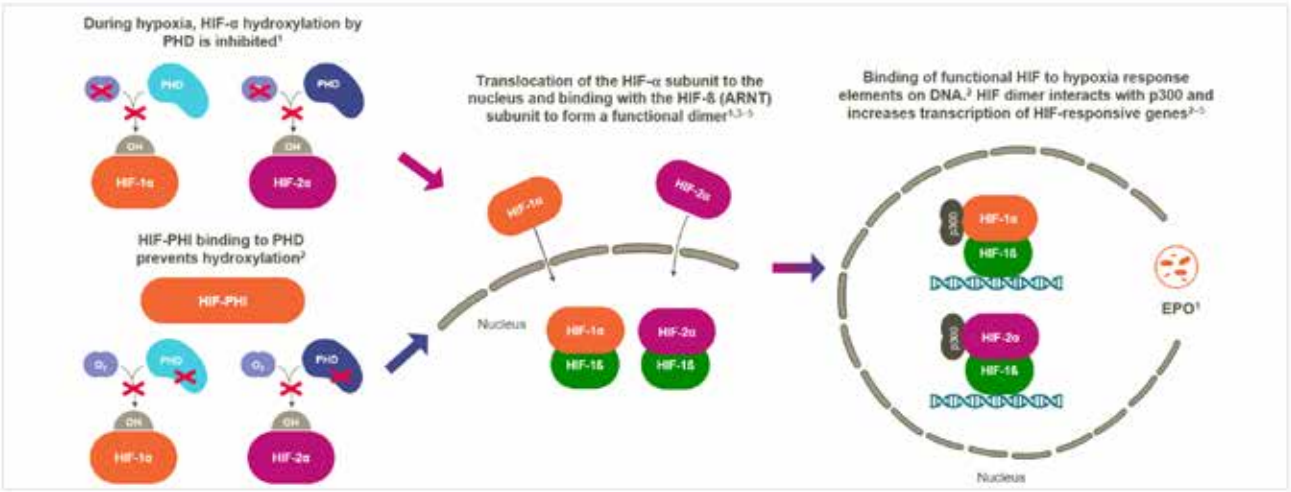

Figure 2. The HIF-PHI mechanism of action. Adapted from 1. Ariazi JL, et al. J Pharmacol Exp Ther 2017;363:336–47; 2. Koury MJ, Haase VH. Nat Rev Nephrol 2015;11:394–410; 3. Haase VH. Kidney Int Suppl 2021;11:8–25; 4. Wang GL, Semenza GL. J Biol Chem 1995;270:1230–7; 5. Ratcliffe PJ. J Clin Invest 2007;117:862–5.

HIF-PHIs have the potential to impact both absolute and functional iron deficiency directly, via the regulation of iron homeostasis proteins (e.g. transferrin, divalent metal-ion transporter 1 [DMT1], ferroportin and duodenal cytochrome B [DcytB]),[19,20] and indirectly, via suppression of hepcidin (through erythroferrone) which may increase iron availability.[19]

When to treat, why, and challenges of management

Kirsten Johansen, USA

Unfortunately, at least in the US, anemia of CKD is underdiagnosed and undertreated, due to both provider- and patient-related factors.

From the patient's perspective, there is often a failure to recognize the symptoms of anemia and to distinguish them from symptoms of CKD and other comorbid conditions.[21] On the provider side, Hb and iron stores are measured less frequently that recommended in the guidelines, particularly in non-dialysis patients. This may be due to payment issues, or time constraints and the difficulty of managing this complex condition.[21-26]

As a result, treatment is often not initiated, even when a patient's Hb is less than 10 g/dL. It may be that it is deprioritized over other topics like hypertension, especially in the non-dialysis population.[24] From the patient's perspective, polypharmacy is often an issue as multiple medications may be needed to control the sequelae of CKD, and the inconvenience of clinic visits and injections also plays a role.[25,26]

All these factors lead to undertreatment of CKD anemia. This is illustrated by the results of a large study from the Humana Research Database among 31,026 patients with non-dialysis CKD and Hb <10 g/dL who all had private health insurance. The study showed that only 39% and 50% of patients at CKD stages 4 and 5 respectively were receiving anemia treatments including oral iron, IV iron, ESA and RBC transfusion.[27] Consequently, approximately 40% of adults starting dialysis in the US have Hb <10 g/dL at the time that they start.[28]

Most of the data on the consequences of this undertreatment come from observational studies. A large systematic literature review and meta-analysis (191 studies; 2002-2018) showed that low Hb (<10 g/dL) is associated with increased all-cause mortality in both dialysis-dependent and non-dialysis-dependent CKD patients. The analysis further showed that both dialysis-dependent and non-dialysis-dependent patients with low Hb had increased cardiovascular mortality and an increased incidence of MACE (CV events including stroke, coronary heart/artery disease, heart failure, myocardial infarction and atrial fibrillation), while non-dialysis-dependent patients with low Hb were more likely to be hospitalized and to experience progression of their CKD.[29]

A more recent analysis from the DOPPS study (n=4,604 from 21 countries; 2009-2015) found that the mortality risk is higher for patients starting hemodialysis (HD) at lower Hb levels. It showed a 2-fold higher mortality for ESA experienced patients who started HD with Hb <8.0 vs ≥11.0 g/dL, despite having a similar comorbidity profile, and that every 1 g/dL Hb increase at Month 1 after starting HD, up to 11 g/dL, was associated with an 11% lower mortality during Months 4-12.[30]

Lower Hb levels are also associated with worse health-related quality of life in patients with CKD. There have been a number of studies using various quality of life instruments including:[31]

- Health status (EQ-5D-3 L): all domains showed significantly greater problems/issues among participants with lower Hb levels ($p < 0.0001$ all domains)
- Health related quality of life (HRQoL): numerically lower mean scores, indicating poorer HRQoL, were reported by patients with lower Hb levels across all CKD stages (with the exception of stage 3a) for KDQOL-36, SF-12 physical component summary, SF-12 mental component summary, symptoms and problems with kidney disease subscale, effects of kidney disease on daily life subscale, and the burden of kidney disease subscale
- Work productivity and activity impairment (WPAI): numerically higher mean percentage absenteeism, presenteeism and overall work impairment were reported by patients with lower Hb levels at CKD Stages 4 and 5 and increasing levels of total activity impairment were observed with lower Hb levels across all CKD stages (with the exception of stage 3a).

Today in the US, ESA treatment is initiated at 9.0 g/dL in dialysis-dependent patients, with the target range between 9.0-11.5 g/dL; in non-dialysis patients it is initiated at 10.0 g/dL with the target range between 10.0-11.5 g/dL.[14] These levels are well below the normal range for the non-CKD population (13-17 g/dL in men and 12-15 g/dL in women)[32] as clinicians aim to balance the increased symptoms and blood transfusions that are seen with low Hb levels against the increased risk of mortality and thrombosis seen with high Hb levels in some studies.

Current treatment options for anemia in the KDIGO Guidelines are:

- First line: supplemental oral or IV iron[14]
- Second line: recombinant EPO therapy, in combination with iron supplements[14]
- Blood transfusion is a rescue therapy if other treatments for anemia including ESAs fail, if the risk of ESAs outweigh the benefits, or when rapid correction of Hb is indicated[14]

A US study into treatment of non-dialysis patients with anemia covered by Medicare (aged 66-85 years), showed that 6.7% of patents were treated with IV or oral iron, 12.7% received ESAs and 22.2% received blood transfusions, despite their position in the guidelines as a rescue therapy.[33]

Iron supplementation is another very important treatment. There is a growing body of evidence to show that iron deficiency itself may be harmful in both heart failure and CKD patients. We also need to ensure that there is sufficient iron available for erythropoiesis. Treating iron deficiency is often enough to raise Hb levels and, especially in earlier stages of CKD, no additional treatment with ESAs may be needed. However, if ESA therapy is needed, adequate iron for erythropoiesis can improve the response to and reduce dose of ESA therapy.[14]

We have shown that the benefits of treatment for anemia of CKD include improvements in quality of life, avoidance of transfusion and how important that is for our patients, and avoidance of absenteeism and, in pediatric patients, this includes improvement in school attendance and performance.[14]

But there are challenges to the standard of care:

- Oral iron frequently causes gastrointestinal side effects – either constipation or nausea – which can lead to poor adherence which limits its use.[34]
- IV iron is associated with some toxic reactions, and there is concern about an increased risk of infection and oxidative stress[35]
- Potential limitations of ESAs include increased cardiovascular morbidity and mortality, worsening hypertension, stroke and thrombotic events and ESA hyporesponsiveness in the dialysis population[35]

But equally important as some of these risks are the difficulties and physical challenges of the burden of administration, additional clinic visits required to give injectable medication, particularly for IV iron. Even if patients are able to have these treatments at home, there is a requirement for cold storage and there are logistical challenges in getting the medication to them at home.[36]

Approximately 20% of patients with anemia of CKD are hyporesponsive to ESA therapy.[37] In general, ESA hyporesponsiveness refers to patients requiring high doses of ESAs (25-100% higher doses than recommended)[38] to increase and/or maintain their Hb levels within the acceptable range.[38] Both ESA hyporesponse and higher ESA doses are associated with poor clinical outcomes, including increased risk of cardiovascular and all-cause mortality.[14,39]

A secondary analysis of the CHOIR trial, among patients with non-dialysis-dependent CKD, looked at the association between achieved Hb and mortality and the dose of ESA required to reach that Hb. There was some association between the level of Hb and mortality, but the higher the ESA dose needed to get there was associated with a higher mortality. Average epoetin-alfa doses >10,095 U/week were associated with increased risks for CV events irrespective of the Hb achieved within the first 4 months of treatment (P=0.0074).[40]

The Nobel prize was awarded in 2019 for the discovery of the HIF pathway and the important role it plays in the physiological response to hypoxia, inducing expression of EPO in the kidney and liver; as well as influencing a wide range of hypoxia-sensitive proteins that regulate lipid metabolism, iron metabolism/utilisation, and angiogenesis.[41]

HIF-PFIs have the potential to increase EPO production, by playing an important role in the expression of EPO in both the kidney and the liver.[2] They are also involved in regulating the iron pathway and increasing iron utilization,[2] as well as downregulating hepcidin, either through erythroferrone, or by erythropoiesis itself.[2]

There have been large, clinical trial programmes for three HIF-PHI agents to date. The comprehensive study programs are in large patient populations and include both dialysis-dependent and non-dialysis-dependent patients with CKD anemia.

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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).

Reason for presentation	Road accident
Age, gender	28 years, male
BMI (kg/m^2)	31
Smoking status	Non-smoker
Hematuria (dipstick)	+
UPCR	Elevated
Kidney function	Preserved
Hypertension	+
Kidney biopsy	M0 E0 S1 T0–C0

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/1.73m^2 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.

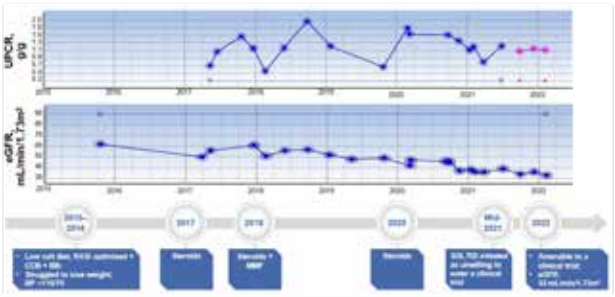

Fig 1: Patient's journey over ~6 years.
BB, beta blocker; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UPCR, urine protein-creatinine ratio
Image source Smeeta Sinha

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.[1]

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.

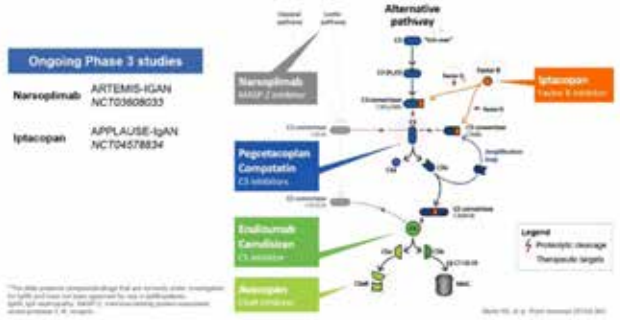

Fig 2: Complement inhibitors in development for IgAN.
This chart presents compounds/drugs that are currently under investigation for IgAN and have not been approved for use in IgAN patients - IgAN, immunoglobulin A nephropathy; MASP-2, mannose-binding protein-associated serine protease 2; R, receptor
Adapted from Merle NS, et al. *Front Immunol* 2015;6:262

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.[4] Secondly, nephrotic syndrome is more frequent in IC-MPGN (43–70%) compared with C3G (26–52%) patients.[4]

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%).[4] C3Nef, which targets the alternative complement pathway, is detected in 40–54% of IC-MPGN patients and 40–80% of those with C3G.[4] Variants in genes encoding for alternative complement pathway proteins are also detected in IC-MPGN at a similar low frequency as C3G (10–25%).[4] To date, there is no proof that the response to available treatments is different in IC-MPGN and C3G.[5]

Looking at the cause of C3G, it is systematically linked with the alternative pathway. Predominant or exclusive C3 deposits are pathological hallmarks of C3G[6,7] and acquired (autoantibodies) or constitutional (genetic variants) dysregulation of the complement system has also been reported.[7] Furthermore, animal models have linked C3G to alternative C3 convertase dysregulation.[7]

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.

Patients with C3G may present with:

- Anti-factor B antibodies which bind to an epitope in the von Willebrand type A and SP domain of Bb. They are mainly detected in children with post-infectious glomerulonephritis (90%)[8]
- Anti-factor H antibodies bind to the N-terminal portion of Factor H (SCR1-4). They are detected in 4–12% of C3G and IC-MPGN[4]
- C3 nephritic factors bind to a neo-epitope on assembled C3 convertase (C3bBb). They are detected in C3G and IC-MPGN (40–80%) and may be associated with acquired partial lipodystrophy[6,9,10]
- Anti-C3b antibodies bind to C3, C3b, iC3b, and C3c with variable affinity. They are detected in 2–3% of C3G and infection-related IC-MPGN[11]
- C5 convertase nephritic factors bind to a neoepitope on the assembled C5 convertase (C3bC3bBb-Properdin). They are detected in ~50% of C3G patients[6,9,10]

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.[12] S(C5b-9), a serological biomarker of terminal-pathway activation, significantly increased in 50% of cases.[12]

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.[12] 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 (**Figure 3**).[9,13-20]

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)

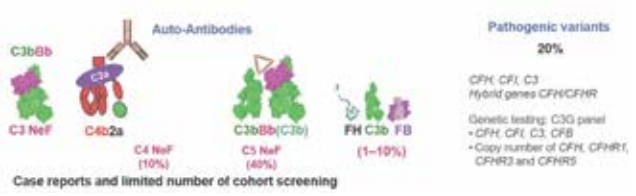

Fig 3: Cause of complement deregulation in C3G.
Adapted from Paixäo-Cavalcante D, et al. Kidney Int 2012;82(10):1084–92; Servais A, et al. Kidney Int 2012;82(4):454–64; Sethi S, et al. Kidney Int 2012;81(5):434–41; Zhang Y, et al. Clin J Am Soc Nephrol 2012;7(2):265–74; Zhang Y, et al. Clin J Am Soc Nephrol 2014;9(11):1876–82; Marinozzi M-C, et al. Kidney Int 2017;92(5):1232–41; Zhang Y, et al. Am J Kidney Dis 2017;70(6):834–43; Hauer JJ, et al. Front Immunol 2019;10:668; Smith RJH, et al. Nat Rev Nephrol 2019;15(3):129–43

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]

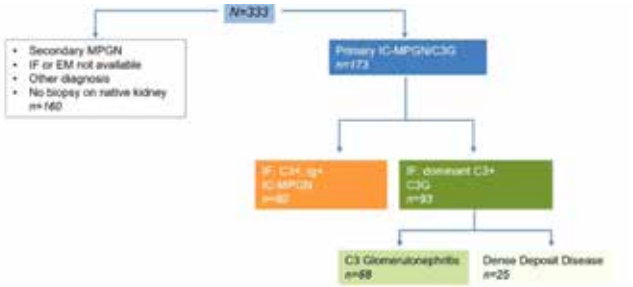

Fig 4: Selection of patients for cluster analysis.
C3G, C3 glomerulopathy; EM, electron microscopy; IC, immune-complex; IF, immunofluorescence; MPGN, membranoproliferative glomerulonephritis; N or n, number - Adapted from Iatropoulos P, et al. JASN 2018; 29(1):283–94

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

Clinical features (n=7)	Histology findings (n=17)	Complement profile (n=4)	Genetic data (n=7)
Age (onset)	Age (onset)	Serum C3	N° of AP complement gene mutations*
Familiarity for nephropathy	IgG staining on IF	Serum C4	CFH p.V621
Mico-/Gross-hematuria at onset	Intramembranous electron-dense deposits	Plasma sC5b-9	CFH p.H402Y
Proteinuria/nephrotic syndrome at onset	Subendothelial deposits	Presence of C3NeF*	CD46 c.-366A>G
Decreased GFR/ kidney failure at onset	% of sclerotic glomeruli	-	CFB p.Q/W32R
Gender	Degree of mesangial proliferation	-	C3 p.R102G
Trigger	-	-	THBD p.A473V

*** Used as a single composite variable 'N°of AP abnormalities'** - AP, alternative pathway; C3G, C3 glomerulopathy; IC, immune-complex; IF, immunofluorescence; IgG, immunoglobulin G; MPGN, membranoproliferative glomerulonephritis; n, number of patients; NeF, nephrotic factor

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]

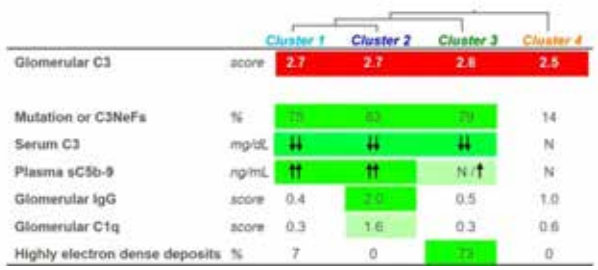

Fig 5: Cluster analysis identified four distinct groups of patients.
IgG, immunoglobulin G; N, normal
Adapted from Iatropoulos P, et al. JASN 2018; 29(1):283–94

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), SLN501 (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)

Moglie 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).[26]

Iptacopan reduced proteinuria by 45% at Day 84 compared with baseline and improved eGFR in patients with native kidneys **(Figure 6)**.[26]

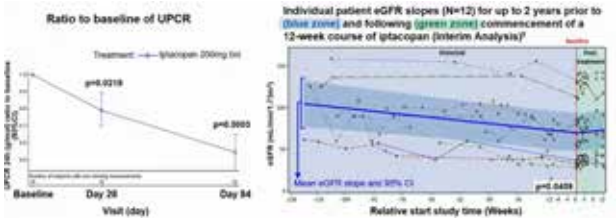

Fig 6: Iptacopan reduced proteinuria by 45% and improved eGFR in patients with native kidneys.
bid; twice a day; CI, confidence interval; eGFR, estimated glomerular filtration rate; N, total number of patients; UPCR, urine protein-creatinine ratio - Adapted from Wong EK, et al. ASN 2021 Annual Meeting: ePoster

In transplanted patients with recurrence, iptacopan significantly reduced C3 deposit scores at Day 84 compared with baseline (**Figure 7**).[26]

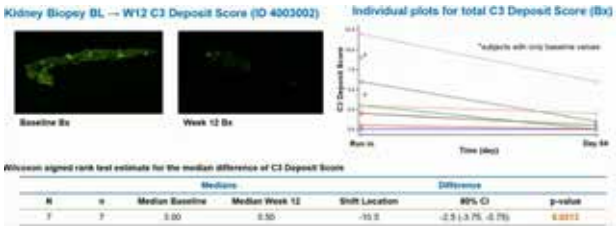

Fig 7: Iptacopan significantly reduced C3 deposit scores in patients with kidney transplant.
BL, baseline; CI, confidence interval; N, number of all subjects included in the analysis (i.e. with at least one post-baseline value of the outcome variable; n, number of subjects with non-missing measurements; W, week - Adapted from Wong EK, et al. ASN 2021 Annual Meeting: ePoster

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.[27]

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.[28]

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 200md 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

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Proteinuria in FSGS and IgA Nephropathy & The Dual Role of ET-1 and Ang II

Spotlight on IgA nephropathy – clinical significance of proteinuria

Loreto Gesualdo, Italy

The talk was framed by a case study of a 28-year-old Caucasian male with typical characteristics for IgA nephropathy:

- MEST* score(s): M1, E1, S1, T1
- Estimated glomerular filtration rate (eGFR): 67 mL/min/1.73 m^2
- Blood pressure: 140/86 mmHg
- Proteinuria: 1.5 g/d
- ACEi/ARBs*?: Yes; 3 months
- Immunosuppressive therapy (IST)?: No

**MEST, mesangial hypercellularity, endocapillary proliferation, segmental sclerosis, tubular atrophy; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.*

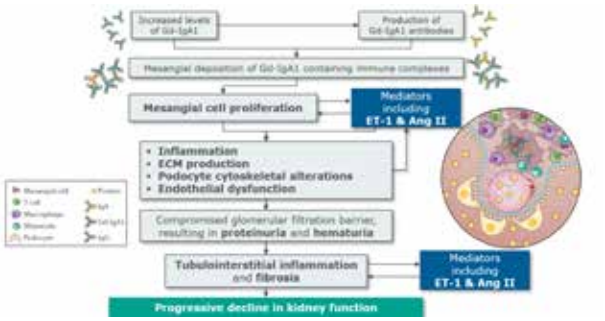


Figure 1.
IgA nephropathy is an immune complex-mediated glomerular disease. Chart based on data from Lai K, et al. Nat Rev Dis Primers 2016; 2:16001; Wyatt RJ & Julian BA. N Engl J Med 2013; 368:2402–2414; Suzuki H, et al. J Am Soc Nephrol 2011; 22:1795–1803; Kohan DE & Barton M. Kidney Int 2014; 86:896–904; Komers R & Plotkin H. Am J Physiol Regul Integr Comp Physiol 2016; 310:R877–R884; Raina R, et al. Kidney Dis 2020; 6:22–34.

IgA nephropathy is the most prevalent primary glomerulonephritis worldwide, with a global incidence of approximately 2.5 per 100,000 persons per year.[1] Patients with IgA nephropathy were found to have a 53% increased risk of all-cause mortality and 6-year reduction in life expectancy compared with matched controls.[2]

IgA nephropathy profoundly impacts patients' lives. IgA nephropathy is associated with depression and anxiety, often centered on fear of uncertainty and complications with therapy,[3] as well as reduced physical functioning, and ability to perform daily routines.[4]

IgA nephropathy is an immune complex-mediated glomerular disease (see fig 1).

Sustained proteinuria > 1 g/d has been shown to be the strongest predictor of the rate of progression of IgA nephropathy, with each incremental g/d over 1g associated with a 10- to 25-fold more rapid rate of decline in kidney function and similar differences in kidney survival. However, reduction in proteinuria can predict delay in time to kidney failure conferred by treatment effect.[5] A study presented at last year's ERA Congress showed that a 30% reduction in proteinuria at 9 months was associated with an increase in the median time to kidney failure of 10.7 years.[6] Since it plays such an important role in determining the clinical outcome, proteinuria is incorporated in risk stratification for patients with IgA nephropathy. The International IgAN Prediction Tool, recommended by the KDIGO Guidelines, incorporates clinical and histologic data to provide a prognosis at the time of biopsy to help identify patients who are at a high risk of rapid disease progression and require urgent care to protect kidney function.[7,8]

Like a substantial number of patients, the individual in the case study remained at high risk of disease progression despite first-line treatment approaches (see Fig 2), with a risk of a 50% decline in eGFR and 19.77% risk of progression to end-stage renal disease five years after renal biopsy.

Current treatment recommendations center on management of blood pressure and proteinuria. For example, the KDIGO Clinical Practice Guidelines for Glomerular Diseases state, "The goal of therapy in IgA nephropathy, is to preserve kidney function through management of blood pressure (systolic blood pressure <120 mmHg) and proteinuria (<1 g/24 hrs), which is pivotal for slowing progressive kidney disease."[8]

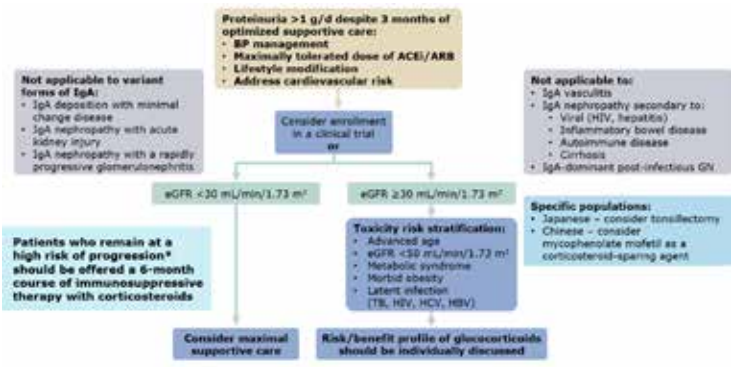
Questions[17]	Case study results
Estimated eGFR at biopsy (ml/min/1.73m^2)	67 ml/min/1.73m^2
Systolic blood pressure at biopsy (mm Hg)	140 mm Hg
Diastolic blood pressure at biopsy (mm Hg)	86 mm Hg
Proteinuria at biopsy (g/day)	1.5 g/day

Figure 2.
Application of the international IgA nephropathy prediction tool for the individual in the case study

Race (Caucasian, Chinese, Japanese, Other)	Caucasian
Use of an ACE inhibitor or ARB at the time of biopsy (yes/no)	Yes
MEST M-score (0 or 1)	1
MEST E-score (0 or 1)	1
MEST S-score (0 or 1)	1
MEST T-score (0, 1 or 2)	1
Immunosuppression use at or prior to biopsy (yes/no)	No
At how many months after renal biopsy would you like to determine risk of progression?	60 months

Looking at the management flow chart from KDIGO[8] (see fig 3) for patients with IgA nephropathy who remain at high risk of progression (defined as proteinuria >0.75–1 g/d despite 3 months of optimized supportive care), it is clear to see the next steps for the individual in the case study. As he has proteinuria > 1g/d, despite 3 month of optimized supportive care, and poorly controlled blood pressure, the first step is to increase the renin-angiotensin-system (RAS) inhibition to the maximum tolerated dose. Lifestyle modification and other steps to address cardiovascular risk must also be part of the management plan. This is a patient who might be considered either for enrollment in a clinical trial or, after stratifying the toxicity risk, for treatment with glucocorticoids.

Figure 3.
Management of patients with IgA nephropathy who remain at high risk of progression
Adapted from KDIGO 2021 Clinical practice guideline for the management of glomerular diseases. Kidney Int 2021; 100(4S):S1–S276.



There remains a high unmet clinical need in IgA nephropathy therapy:

- Approximately half of patients remain above the target proteinuria level of >0.75–1 g/d, and are at a high risk of disease progression[8]
- The use of RAS blockade with ACEis/ARBs and immunosuppression versus RAS blockade alone is still debated.[9] The ongoing low-dose TESTING Study should be very helpful to address this issue
- Corticosteroid therapy should be avoided in certain patients, and carries a significant risk of toxicity[8]

Looking to the horizon, there are a number of phase 3 trials investigating novel therapeutic approaches for the treatment of IgA nephropathy:

Trial	ClinicalTrials.gov Identifier
NEFIGARD	NCT03643965
PROTECT	NCT03762850
ARTEMIS-IgAN	NCT03608033
APPLAUSE-IgAN	NCT04578834
ALIGN	NCT04573478

Spotlight on FSGS – clinical significance of proteinuria

Sian Griffin, UK

The talk was framed by a case study of a 32-year-old Caucasian female with primary focal segmental glomerulosclerosis (FSGS):

- eGFR: 58 mL/min/1.73 m^2
- Blood pressure: 142/86 mmHg
- Proteinuria: 3.7 g/d (baseline: 8.2 g/d and nephrotic syndrome)
- ACEi/ARBs*?: Yes; 4 months
- IST?: Yes; glucocorticoids for 12 weeks

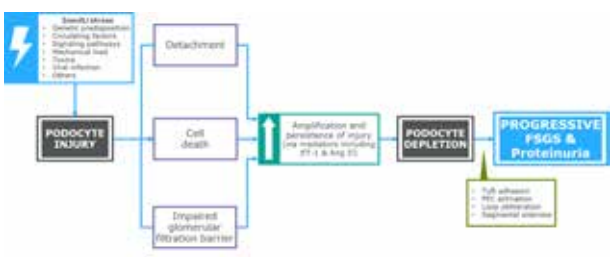


Figure 4.
FSGS is caused by sustained injury to podocytes, leading to elevated and persistent proteinuria. Chart based on data from: Abbate M, et al. Am J Pathol 2002; 161:2179–2193; Abbate M, et al. J Am Soc Nephrol 2006; 17:2974–2984; De Vriese AS, et al. J Am Soc Nephrol 2018; 29:759–774; Jefferson JA & Shankland SJ. Adv Chronic Kidney Dis 2014; 21:408–416; Kohan DE & Barton M. Kidney Int 2014; 86:896–904; Komers R & Plotkin H. Am J Physiol Regul Integr Comp Physiol 2016; 310:R877–R884.

FSGS is uncommon but is a leading glomerular cause of kidney failure. The global incidence is estimated as 0.1/100,000/year in children and 0.8/100,000/year in adults.[1] Based on analyses conducted from the Idiopathic Nephrotic Syndrome Rare Diseases Group (RaDaR-INS) in the UK, kidney failure occurs in up to 45% of adult and pediatric patients in 10 years, and is associated with an increase in mortality.[10]

FSGS is caused by sustained injury to podocytes, leading to elevated and persistent proteinuria (see fig 4), which can come from a number of different mechanisms.

The classical presentation of immune-related FSGS seems to be associated with a circulating factor, as evidenced by the potential for rapid recurrence after kidney transplantation. A number of toxins and drugs can affect the podocytes – notably bisphosphonates, MTOR inhibitors and anabolic steroids – as well as viral infections, and that which is best characterized is associated with HIV. These factors converge to cause podocyte injury.

The podocyte is a very resilient cell because it is exposed to fluctuating mechanical stress during day-to-day variations in blood pressure in response to meals, but its response to sustained injury may include detachment from the underlying glomerular basement membrane, death of

the podocyte and impairment of the glomerular filtration barrier.

There seems to be a critical threshold of podocyte loss. In early stages there can be some extension of the podocytes to cover the denuded glomerular basement membrane, but amplification and persistence of injury in the glomerular tuft, mediated by inflammatory and profibrotic mediators including endothelin-1 (ET-1) and angiotensin II (Ang II).

The podocyte is a terminally differentiated cell, so large-scale depletion of the podocytes results in large areas of bare glomerular basement membrane which then forms synechial connections to the overlying parietal epithelial cells, which can become activated. There is ongoing inflammation with obliteration of the capillary loop and segmental sclerosis. Histologically we see progressive FSGS which manifests clinically as proteinuria.

The KDIGO Guidelines were updated in 2021 to classify FSGS based on proteinuria, etiology, and histologic presentation on biopsy:[8]

- Primary FSGS: FSGS lesions, extensive foot process effacement, and nephrotic syndrome (defined as proteinuria >3.5 g/d and hypoalbuminemia (<30 g/L), often accompanied by dyslipidemia and edema). It disproportionately affects children and young adults, with a significant and often lifelong impact
- Secondary FSGS: FSGS lesions, accompanying a pathophysiologic process known to cause FSGS
- Genetic FSGS: FSGS lesions in patients who have mutations in podocyte or glomerular basement membrane proteins
- FSGS of undetermined cause: FSGS lesions with no identifiable cause and an absence of nephrotic syndrome

FSGS profoundly impacts patients' lives. Patients frequently report physical symptoms including severe edema, fatigue, and shortness of breath and often experience mental symptoms such as anxiety, depression, negative effects on sleep, and a reduced ability to socialize.[11] Pregnancy carries significant risks to both the patient and the fetus, as well as to the underlying disease.[8] This can be particularly devastating for young women and is an important issue to cover when counselling patients.

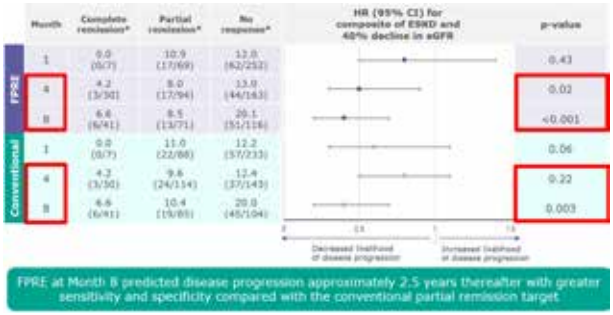


Figure 5.
FPRE for Proteinuria Predicts Kidney Survival Earlier than the Conventional Target. Adapted from Troost JP, et al. Clin J Am Soc Nephrol 2018; 13:414–421.

Persistent proteinuria in FSGS is a risk factor for progressive kidney failure and more severe proteinuria is associated with a faster time to kidney failure.[12] Less than 15% of patients with non-nephrotic proteinuria progress to kidney failure in 10 years, but 50% or more of patients with nephrotic proteinuria (>3 g/d) progress to kidney failure in 5–10 years.[12] For patients with massive proteinuria (>10–14 g/d), the average time to kidney failure is 2–3 years.[12]

Achieving partial or complete remission of proteinuria greatly improves kidney survival. An analysis of 338 adult patients with biopsy-proven FSGS (97% receiving RASi) using data from the US Department of Defense healthcare network found that complete and partial remission occurred in 26% and 25% of patients, respectively, where complete remission was defined as a reduction in proteinuria to <0.3 g/d with <25% reduction in eGFR from baseline at biopsy diagnosis. Kidney survival was significantly better with complete and partial remission than no remission at 5, 10, and 15 years.[13]

An analysis of 281 nephrotic FSGS patients from the Toronto Glomerulonephritis Registry found that relapse from partial remission was significantly associated with worse kidney outcomes in FSGS. 52% (61/117) of patients who achieved partial remission (defined as >50% reduction in peak proteinuria and to subnephrotic levels [<3.5 g/d]) relapsed after a median time of 7 months, compared to 36% (20/55) of patients from a complete remission (proteinuria value <0.3g/d) after a median time of 20 months. Relapse in the partial remission group was significantly associated with worsening kidney function (p=0.03) and a higher risk of kidney failure compared with patients who achieved

partial remission with no relapse (HR=2.90; 95% CI=1.09–7.72; p=0.03).[14]

Further stratifying those patients who have undergone a partial remission to predict those who will have either a good, or an inferior, long-term survival. Data on 466 well-characterized patients with FSGS and proteinuria were analyzed to refine proteinuria definitions. The conventional definition of partial remission is a 50% reduction in proteinuria to <3.5 g/g. The more robust FSGS data-derived partial remission endpoint (FPRE), with ≥40% reduction in proteinuria to the range 0.3-1.5 g/g, was found to be associated with better long-term outcomes and became significant as a predictor of improved long-term outcome earlier than the conventional partial remission target (see fig 5).[15] This is helpful both as an endpoint in clinical trials and when advising patients in the clinic of their likely progress.

There is significant unmet need for better treatments for these patients with a favorable safety profile. ACEis and ARBs are considered standard of care, and guidelines recommend high-dose oral glucocorticoids or Calcineurin inhibitors (CNIs), despite the lack of evidence from RCTs, as first-line IST for primary FSGS.[8] However:

- Long periods of IST are required[12]
- IST is associated with significant risk of toxicity[8]
- Relapse is common with all current therapeutic options[8]
- A substantial number of FSGS patients do not achieve proteinuria remission and remain at a high risk of progressive kidney disease[14]

There are two phase 3 trials investigating novel therapies in FSGS on the horizon:

Trial	ClinicalTrials.gov Identifier
DUPLEX	NCT03493685
ACTION3	NCT05183646

Evidence for the dual role of ET-1 and Ang II in proteinuria and CKD progression in IgA nephropathy and FSGS

Pierre-Louis Tharaux, France

ET-1 and Ang II in CKD

ET-1 and Ang II act in tandem to promote CKD progression via multiple mechanisms, including promoting inflammation, vascular dysfunction, glomerular dysfunction and tubulointerstitial injury; however, they have opposing actions on sodium homeostasis. [16–18]

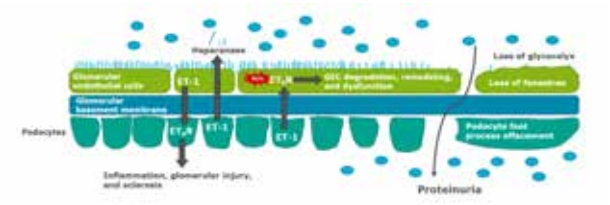


Figure 6.
Podocyte-endothelial cell interaction. Adapted from: Ebefors K, et al. Kidney Int 2019; 96:957–970; Garsen M, et al. J Am Soc Nephrol 2016; 27:3545–3551; Kohan DE & Barton M. Kidney Int 2014; 86:896–904; Mahtal N, et al. Front Med (Lausanne) 2021; 8:659013. GEC, glomerular endothelial cell; ROS, reactive oxygen species.

ET-1 and Ang II in IgA nephropathy

Several further studies suggest a role for ET-1 in IgA nephropathy:

- Elevated ET-1 in kidney biopsies from patients with IgA nephropathy correlates with proteinuria and 1-year progression[19,20]
- Specific ETAR antagonism in a murine model of IgA nephropathy reduced proteinuria and downregulated pro-inflammatory, pro-fibrotic, and pro-sclerotic pathways[21]

ET-1 and Ang II in FSGS

Expression of both ET-1 and ETAR is elevated in patients with primary FSGS. This was demonstrated by studies showing increased urinary output of ET-1 in patients with FSGS compared to healthy volunteers,[22] and increased levels of ETAR-positive glomerular endothelial cells in kidney biopsies of patients with FSGS versus controls.[23]

Experimental evidence indicates that, when stimulated by ET-1, the functional cytoskeletal dynamics of the podocyte are altered, promoting cell detachment and loss of the foot processes. When activated by ET-1, the podocyte can also produce heparanase, an enzyme that will cleave off the endothelial glycocalyx – the first layer of the glomerular filtration barrier that ensures selectivity against proteinuria in the glomerulus. The endothelial cells also react to exaggerated ET-1 signaling by triggering reactive oxygen species (ROS), opening the endothelial junctions leading to degradation of glomerular endothelial cells. This means that all layers of the glomerular filtration barrier are impaired with exaggerated ET-1 signaling (see fig 6).[16,24,25]

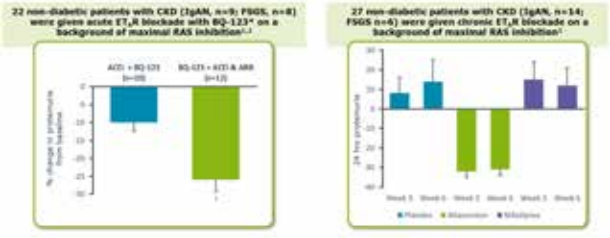


Figure 7.
Combined RAS blockade and ETAR inhibition has demonstrated a substantial anti-proteinuric effect in studies including patients with IgA nephropathy and FSGS. * BQ-123 is a selective ETAR antagonist; † p<0.01. 1. Dhaun N, et al. Hypertension 2009; 54:113–119; 2. Dhaun N, et al. Hypertension 2009; 54:e19–e20; 3. Dhaun N, et al. Hypertension 2011; 57:772–779.

Clinical evidence for dual antagonism

The RADAR study in 211 patients with diabetic nephropathy and proteinuria showed that selective ETAR antagonism with atrasentan (0.75mg or 1.25mg) on a background of stable RAS inhibition achieved a significant reduction in proteinuria.[26]

In the SONAR study, 2,684 patients with Type 2 diabetes and proteinuria were given ETAR blockade with atrasentan on a background of maximal RAS inhibition for ≥4 weeks. Atrasentan was shown to have a beneficial effect on progression of CKD, measured by a primary composite renal outcome (doubling of serum creatinine or ESKD [chronic dialysis for >90 days, kidney transplantation, eGFR <15 mL/min/1.73 m^2, or death from kidney failure]).[27]

Combined RAS blockade and ETAR inhibition has demonstrated a substantial anti-proteinuric effect in studies including patients with IgA nephropathy and FSGS (see fig 7).

Dual endothelin angiotensin receptor antagonists (DEARAs)

DEARAs such as sparsentan have regions with affinity for both ETAR and AT1R and can bind individually to either receptor to inhibit intracellular signaling.[17] Both receptors are associated with potent vasoconstrictive, proliferative, pro-inflammatory, and pro-fibrotic effects.In two separate phase 3 trials in patients with IgA nephropathy and FSGS, a dual endothelin and angiotensin receptor antagonist has been shown to be able to reduce proteinuria to a greater extent than angiotensin receptor blockade alone, with a comparable safety profile to the active comparator.[28,29]

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A shift in focus: international insights into the optimal management of CKD-MBD

How high is high enough? 25(OH)D adequacy in non-dialysis CKD-MBD patients

James Wetmore, USA and Jan Kielstein, Germany

Although a patient like Marie (see case study) may be symptom free, the five-year period when she was lost to follow up is problematic, potentially limiting both life span and the opportunity for effective clinical intervention.

Case study of Marie: a 50-year-old, white female with advancing CKD, 25(OH)D deficiency and SHPT

Lab values over time:

2011 eGFR = 52 mL/min/1.73m^2

2015 eGFR = 45 mL/min/1.73m^2⇒**referred to nephrologist**

- 25(OH)D = 36 ng/mL (90 nmol/L)
- PTH = 67 pg/mL (67 ng/L)

Lost to follow-up for nearly 5 years

2020 eGFR = 38 mL/min/1.73m^2

2020 eGFR = 38 mL/min/1.73m^2

- PTH = 97 pg/mL (97 ng/L)

2021 eGFR = 34 mL/min/1.73m^2

CKD, chronic kidney disease; 25(OH)D, 25-hydroxyvitamin D; SHPT, secondary hyperparathyroidism; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

Patient case provided by Professor Wetmore, USA.

Clinical management of Secondary hyperparathyroidism (SHPT) in the non-dialysis CKD population includes regular and early monitoring of PTH (from CKD stage 3a) and correcting vitamin D [25(OH)D] deficiency/insufficiency. However, neither the target for optimal PTH, nor the level of 25(OH)D needed to achieve sufficient reduction of PTH are well defined.[1]

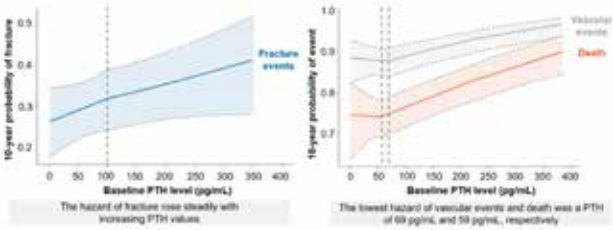

Figure 1.
PTH levels independently predict fracture, vascular events and death in Stage 3-4 CKD. Adapted from Geng S, *et al. Osteoporos Int* 2019;30:2019–25.

There is strong evidence to support early intervention. Early treatment of SHPT may interrupt the natural history of the development of gland hypertrophy, hyperplasia and autonomous function, and decrease the risk of CV and bone outcomes.[2,3] An observational study of 5,108 patients with stage 3-4 CKD show that SHPT is associated with an increased risk of facture, vascular events and death with rising PTH levels (see fig 1).[2]

As SHPT manifests early in CKD, with prevalence and severity increasing as kidney function declines, early diagnosis and treatment of SHPT is crucial.[4]

The mainstay of treatment is correcting vitamin D [25(OH)D] insufficiency.[5] Views on target vitamin D levels have changed from 20-30 ng/mL

to something closer to 100 ng/mL, or at least 50 ng/mL.[6]

Slowly increasing 25(OH)D levels with the aim of reaching >50 ng/mL[7] should allow:

- A reliable increase in 25(OH)D levels
- A minimal increase in 24,25$(OH)_2$D levels
- A physiological controlled adaption of 1,25$(OH)_2$D levels
- A physiological controlled reduction of PTH
- A minimal increase in serum Ca and P

An optimal treatment to control SHPT would increase 25(OH)D and reduce PTH with negligible effects on serum calcium, phosphate and fibroblast growth factor 23 (FGF-23),[8,9] but there are important unmet medical needs with current treatment options.

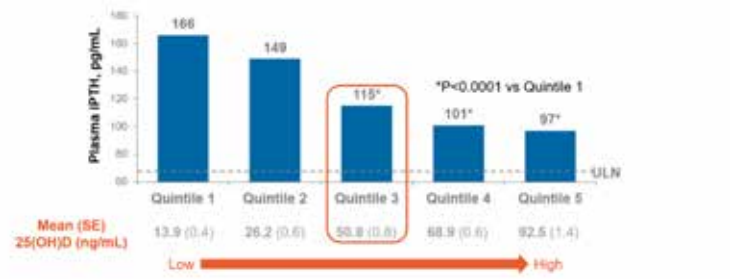

Figure 2.
Plasma PTH at weeks 20-26 as a function of post-treatment 25(OH)D quintile. Adapted from Strugnell SA, *et al. Am J Nephrol* 2019;49:284–93.

Nutritional vitamin D (cholecalciferol) and immediate release (IR) calcifediol both increase the level of 25(OH)D, but neither treatment consistently and reliably reduces PTH, and IR calcifediol also has a detrimental effect on FGF-23 levels. While active vitamin D/analogues are associated with a highly beneficial reduction in PTH, they also reduce 25(OH)D and have a highly detrimental effect on levels of calcium, phosphate and FGF-23.[9]

Extended-release calcifediol (ERC) may provide a beneficial treatment option. In phase 3 studies, it increased serum 25(OH)D levels and lowered plasma PTH consistently and steadily over time.[10,11]

At the end of the clinical trial, the investigators grouped the patient data into five quintiles of achieved level of 25(OH)D. Lower plasma PTH was observed for each quintile with increasing 25(OH)D levels (see fig 2).[7]

This represents a new paradigm in the treatment of SHPT: to raise the 25(OH)D level to the point where there is reciprocal reduction in PTH.

The favorable efficacy and safety profile of ERC has been confirmed in a real-world setting. Stage 3-4 CKD patients with SHPT and vitamin D insufficiency (n=174) were treated with ERC. Over 26-weeks of follow up, patients achieved a mean 23.7 ng/mL (P<0.001) increase in 25(OH) D and a 34.1 pg/mL (P<0.001) reduction in PTH, with no associated increase in serum calcium or phosphate levels.[12]

In the same study, 122 patients (70.1%) achieved 25(OH)D levels ≥30 ng/mL, 70 (40.2%) achieved ≥30% reduction in PTH and 53/90 patient (58.9%), whose baseline 25(OH)D was <20 ng/mL, achieved 25(OH)D ≥30 ng/mL.[12]

So, what did the results mean for the case study Marie? She commenced treatment with ERC in February 2020 and her 25(OH)D increased to about 70-75 ng/mL (175-188 nmol/L) and PTH decreased from about 90 pg/mL (70 ng/L) to about 70 pg/mL (70 ng/L) over the course of 12 months. After this there was no further reciprocal reduction in PTH, suggesting that each individual has their own physiologic 'setpoint' for PTH, and no further reduction will be seen once 25(OH)D is adequately repleted.

The PORTRAY study is a real-world evidence study led by an expert CKD-MBD steering committee from five countries. It will collect data on the use of ERC in a routine clinical setting in European patients. For more information about the PORTRAY study, contact Ingrid Gerber (Ingrid.Gerber@cernerenviza.com).

Controlling serum phosphate levels: a focus on CKD patients on dialysis

Jürgen Floege, Germany

An analysis of the European Fresenius database showed an association between serum phosphate and mortality in European hemodialysis (HD) patients, with the lowest risk of mortality (HR≤1.1) at 1.41 [1.08-1.80] mmol/L. Higher and lower phosphate levels were both associated with a higher risk of mortality.[13]

A more telling analysis from COSMOS (Current Management Of Secondary Hyperparathyroidism Study), looked not only at the relationship between phosphate and mortality, but also at what happens when you change phosphate levels. If baseline phosphate is well controlled, but either increases of decreases a few months later, mortality increases in both scenarios. Likewise, when baseline phosphate is high (>5.2 mg/dL) and then increases further, mortality increases; but importantly, when high baseline phosphate decreases, mortality also decreases to some degree.14 This is one of the first pieces of evidence that demonstrates a likely beneficial effect of phosphate control.

The source of phosphate is also important as plant phosphate cannot be digested or absorbed to the same extent as meat-based phosphate. In a highly controlled cross-over study, 9 patients with a GFR of about 30 mL/min consumed either a meat-based or a purely vegetarian diet for 7 days. Phosphate intake was similar across both groups (810 ± 27 mg/day and 795 ± 51 mg/day for the meat-based and vegetarian diets respectively), but serum phosphate increased with the meat-based diet (from 3.5 ± 0.6 to 3.7 ± 0.6 mg/dL) and decreased with the vegetarian diet (from 3.5 ± 0.6 to 3.2 ± 0.5 mg/dL) after 7 days, with a significant difference between the two groups (p=0.02). These results were reflected in FGF-23 levels: after 7 days, more FGF-23 was needed to excrete the additional phosphate for those on the meat-based diet compared to the vegetarian diet (101 ± 83 pg/mL and 61 ± 35 pg/mL respectively).[15]

A diet consisting of mainly fresh rather than processed foods is also important as phosphate additives in processed foods are readily absorbed. In a study, 10 healthy volunteers consumed a diet containing 900 mg of phosphate and no phosphate additives for the first week, followed by a diet containing the same level of calories and the same composition (% fat, protein and carbohydrates), but consisting mostly of processed foods for the second week. The additive-enhanced diet was associated with significantly higher levels of phosphate (1677 ± 167 vs 1070 ± 58 mg/day; p<0.001) and sodium (148 ± 28 vs 89 ± 28 mmol/day; p<0.05) compared to the low additive diet.[16]

High levels of phosphate have been shown to accelerate calcification. In an interventional study from Turkey, dialysis patients were given either a 1.25 or a 1.75 mmol/L calcium dialysate bath. After 2 years, coronary artery calcification was measured, and no significant difference between the two groups. When the results were stratified by phosphate (<4.7 vs ≥ 4.7 mg/dL), there was a tendency for people with higher phosphate to have more coronary artery calcification, but it was not significant. It was not until the two parameters were combined (i.e. the group that was both loaded with calcium through the dialysate and had poorly controlled phosphate) that very rapid progress of coronary artery calcification of up to 500 Agatston score points over 2 years was seen.[17]

There are many effective phosphate binders available, but there are key differences between classes in terms of pill burden, pleiotropic effects, accumulation and cost (see Fig 3).[18]

The 2017 KDIGO guidelines recommend restricting the dose of calcium-based phosphate binders in adult patients with CKD stages 3a-5D receiving phosphate-lowering treatment,[19] but it is also important to think about the patient when considering treatment to decrease phosphate levels. For example, bringing phosphate levels down, avoiding coronary artery calcification and staying healthy are much more important in a 20- or 30-year-old who is a candidate for transplant than in an 80-year-old with an average life expectancy of 1.3 years. Controlling phosphate in elderly patients is often not the priority: it is more important for them to eat, enjoy life and be active.

Sucroferric oxyhydroxide (Fe-Oxyhydroxide) is a newer phosphate binder that is effective, has a low pill burden, no pleiotropic effects and does not accumulate – the iron is not taken up. Sucroferric oxyhydroxide also dissolves more readily than lanthanum, which has to be chewed, as the tablets are starch based.[18]

In a phase 3 study, sucroferric oxyhydroxide reduced phosphate as well as sevelamer after a wash-out over 52 weeks of treatments.[20,21] Serum ferritin was increased from baseline in both the sucroferric oxyhydroxide and sevelamer groups, although the result with sevelamer was an artefact of the situation in the United States, where reimbursement switched to product bundling, leading to greater use of iv iron instead of erythropoietin. Similar results with sevelamer were not seen in the EU or other countries.[20,22]

Sucroferric oxyhydroxide gives a small increase in iron uptake, usually in those patients who are iron deficient at the outset and, unlike ferric citrate, there are no documented cases of oral iron overload induction, so it is a small but perceivable benefit.

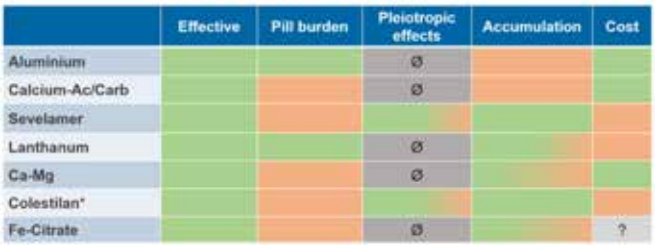

Figure 3. Overview of phosphate binders. Adapted from Floege J. *J Nephrology* 2016;29:329-40.
*Colestilan was removed from the market in the European Union. Green denotes benefit or advantage, orange potential or established disadvantage. Grey box, no known pleiotropic effects. Ac, actetate; Ca, calcium; Carb, carbonate; Fe, iron; Mg, magnesium.

The main benefit of sucroferric oxyhydroxide compared to sevelamer is the pill burden. In the first 24 weeks of the phase 3 study, average daily dose of sucroferric oxyhydroxide and sevelamer were 1.5 ± 0.6 g/day vs. 6.5 ± 2.5 g/day respectively, which translates to 3.1 pills of sucroferric oxyhydroxide and 7-8 pills of sevelamer each day.[20] There are some patients who can adapt their dose of a phosphate binder to their meal, but many are unable to do that, and it is easy for them to remember to take one tablet per meal.

In the phase 3 trial, the key adverse effect with sucroferric oxyhydroxide was diarrhea – mostly in the form of loose stools rather than watery diarrhea – and this was clustered in the very first phase.[20,21] The likely explanation for this is the adaptation of the intestinal microbiome to iron.

Dr Floege and colleagues looked at this in the oral cavity and found a different microbiome after one week of treatment with sucroferric oxyhydroxide, but that it quickly reverted to normal. It is likely that the same effect is causing the short-term incidence of diarrhea with sucroferric oxyhydroxide in the phase III study. For many patients that is a perceived benefit because they often experience constipation.
The other key adverse effect, reported by 15.4% of patients taking sucroferric oxyhydroxide, was discoloration of the feces, although it is likely that this effect was significantly under reported in the study.[20,21]

Real world data also show that, following a switch from sevelamer to sucroferric oxyhydroxide, the number of patients with well-controlled phosphate increased over 12 months, and the number with previously poorly controlled phosphate decreased markedly.[23] An interesting observation in this study is that albumin divided by phosphate increases over the 12 months following initiation of sucroferric oxyhydroxide,[23] so patients can have a little more nutritional liberty as their diet does not have to be restricted to the same extent to achieve a reduction in phosphate.

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The burden and management of symptoms in chronic kidney disease (CKD) patients on haemodialysis: an insight into CKD-associated pruritus

Exploring symptom burden in hemodialysis patients

Marc Vervloet, Netherlands

Clinicians tend to focus on hard clinical endpoints from trials, this session centers on what matters to patients.

Great achievements have been accomplished in dialysis so far. The dialysis population achieve a significantly older age, which brings more comorbidities and requires more supportive care.[Li 2017]
With a changing population, should the goals of care also change?

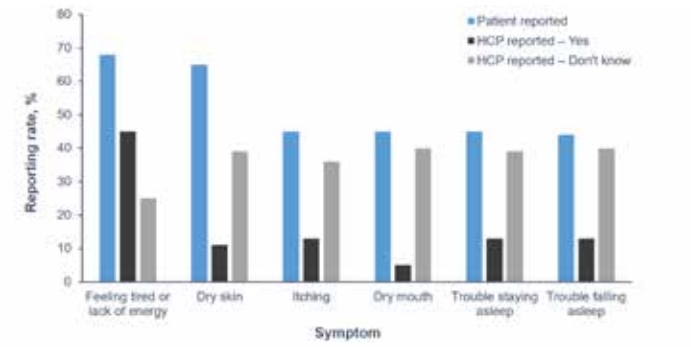

Figure 1.
Patient and HCP reports of symptoms. Adapted from Weisbord SD, et al. Clin J Am Soc Nephrol 2007;2:960–7

Many studies in nephrology looking at hard clinical endpoints fail. This includes studies on normalizing hemoglobin, aiming for higher Kt/V, dialysis modalities and blood pressure management, as well as studies investigating specific treatments. Moving away from study endpoints that focus on mortality to look more closely at symptoms and patient reported outcomes will help make physicians more aware of what is also troublesome for patients and significantly affects their daily activities and wellbeing.

A study from 2007 shows the discrepancy between symptoms reported by patients and the awareness from healthcare professionals of the number of patients experiencing these symptoms. [Weisbord 2007]
In order to bring symptom-based management to the clinic, it is necessary to identify the goals of care through shared decision-making. There are several components that contribute towards setting this goal together with patients including life expectancy, individual wishes, the burden of the disease and the burden of treatment. Quantity of life vs. quality of life can also be an important consideration when looking at goals of care. If the wish is to extend life for as long as possible, then targets like dialysis dose, laboratory results and blood pressure will be among the management goals. But if quality of life is more important, a focus on managing symptoms such as pain, sleep and anxiety will be at the core of the goals. Of course, many patients will want both quantity and quality of life, but it is still important to have the discussion about their priorities.

Physical and emotional symptoms are common in maintenance hemodialysis patients who experience a mean of 10 symptoms ranging from dry skin and itching, tiredness and bone or joint pain. The symptoms can be severe and are directly correlated with significantly impaired quality of life and depression. [Weisbord 2007]

It is often thought that optimizing dialysis will reduce the burden of these symptoms, however, a study at a recent KDIGO Controversies Conference found that the majority of factors determining patient wellbeing are not directly affected by dialysis delivery (see fig 2). [Chan 2019]

The Frail and Elderly Patient Outcomes on Dialysis (FEPOD) study has shown that frailty is a key predictor for patients at risk of a high symptom burden. [Iyasere 2016]

Uncovering the complexities of CKD-associated Pruritus

Vincent Brandenburg, Germany

Chronic pruritus is a debilitating condition that can be defined as an unpleasant sensation of the skin leading to the desire to scratch, with symptoms present for more than 6 weeks. It has a variety of underlying causes: dermatological conditions present with primary skin lesions, but these are absent when the underlying cause is psychogenic, neuropathic or systemic, as for chronic kidney disease. (Stander 2007)

CKD-associated Pruritus does not usually start with a skin lesion. The skin lesions in CKD-associated Pruritus are secondary and are often a consequence of chronic scratching. Where primary skin lesions are present, differential diagnoses should be considered as CKD-associated Pruritus is primarily a diagnosis of exclusion.

CKD-associated Pruritus is a condition with intense symptoms that markedly impair patients' quality of life. Its appearance is variable, but it is often bilateral and symmetrical. (Mathur 2010)

The estimated prevalence of CKD-associated Pruritus is approximately 70% among patients undergoing hemodialysis, (Rayner 2017) with varying degrees of severity. A large study of 68,426 patients on hemodialysis found that 39.8% were 'not at all' bothered by itching, but that 30.2%, 15.4%, 9.3% and 5.3%, respectively, reported being 'somewhat', 'moderately', 'very much', or 'extremely' bothered by itching.(Ramakrishnan 2014)

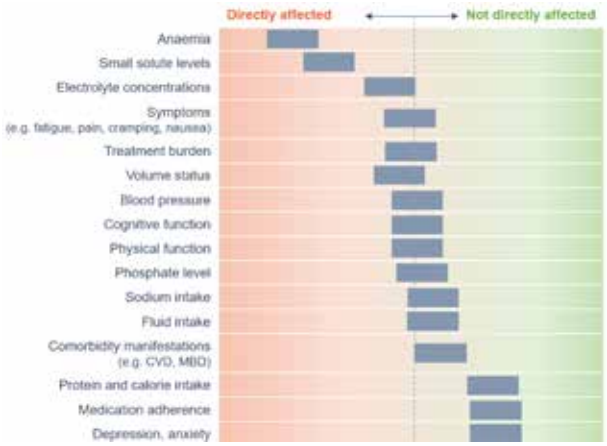

Figure 2.
Factors affected by dialysis treatment or dialysis unit care. Adapted from Chan CT, et al. Kid Int 2019;96:37–47.

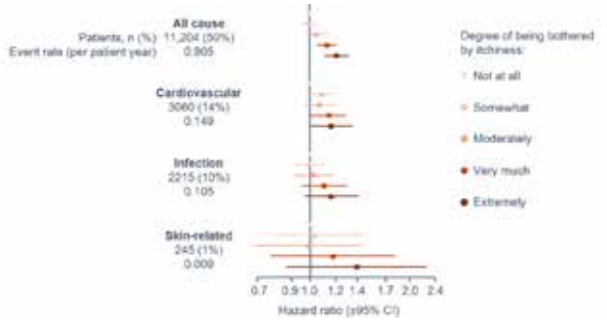

Figure 3.
Incidence of hospitalization according to CKD-associated Pruritus severity (DOPPS 2009–2018; N=23,260). Adapted from Sukul N, et al. Kidney Med 2020;3:42–53.

CKD-associated Pruritus is associated with adverse outcomes including reduced quality of life, poor sleep quality, increased healthcare costs, depression and an increased risk of mortality.(Ramakrishnan 2014, Sukul 2020)

Quality of life in hemodialysis patients deteriorates with an increase in CKD-associated Pruritus severity. Self-reported pruritus is strongly associated with both physical and mental components of health-related quality of life scores, and both progressively decrease as the severity of pruritus increases.(Sukul 2020)

The majority of patients with CKD-associated Pruritus suffer from disturbed or restless sleep, with the likelihood of experiencing restless sleep increasing as the severity of CKD-associated Pruritus increases.(Rayner 2017)

Patients with CKD-associated Pruritus are more likely to be diagnosed with depression compared with hemodialysis patients who are not bothered by pruritus. A significantly greater Beck Depression Index score was seen in patients with more severe pruritus vs. less severe/no pruritus, and the use of treatments for depression was greater among patients with more severe pruritus vs. less severe/no pruritus. (Mathur 2010)

Bacteremia and septicemia are more common in patients with severe itch vs patients without itch (Ramakrishnan 2014) and this may be due to the effect of scratching on the integrity of the skin barrier. Furthermore, patients with severe itch are more likely to be hospitalized for cardiovascular, infection and skin-related complications than those not bothered by itch (see fig 3). (Sukul 2020)

Severe CKD-associated Pruritus has been associated with an increased risk of mortality in patients undergoing hemodialysis. In a study of 1773 hemodialysis patients who were followed until death or for 24 months, severe pruritus was associated with a worse prognosis than mild or moderate pruritus (p=0.0001). Severe pruritus was also an independent predictive factor for death, even after adjusting for other factors (HR=1.595; p=0.0084).[Narita 2006]

The pathogenesis of CKD-associated Pruritus is multifactorial:[Verduzco 2020]

- Abnormalities related to uremia (implicated toxins: vitamin A, aluminum, calcium, phosphorus, magnesium)
- Peripheral neuropathy/paresthesia (abnormal nerve conduction: pattern of cutaneous innervation and nerve conduction)
- Endogenous opioid dysregulation (Imbalanced mu opioid receptor [MOR] and kappa opioid receptor [KOR] activity)
- Immune system dysregulation (pro-inflammatory state: increase in T-helper 1 (Th1) cells, C-reactive protein (CRP), IL-6, IL-2)

Uremic toxins have previously been implicated in CKD-associated Pruritus,[Hu 2019, Hiroshige 1995] but their contribution appears to be limited when managed according to current standards. No association was observed between CKD-associated Pruritus and CKD-related laboratory values in a recent, large DOPPS study. [Sukul 2020]

Dry skin (xerosis) is present in 50-85% of CKD-associated Pruritus patients and is likely to be a significant contributor to the condition, but not the only cause.[Sharizian 2017] Xerosis frequently aggravates pruritus[Coombs 2015] and predisposes patients to poor wound healing, [Sharizian 2017] although many patients with xerosis do not suffer from pruritus. [Mettang 2015] Moisturization and skin rehydration improve symptoms and should be a mainstay of therapy. [Mettang 2015]

CKD-associated pruritus may be the result of an upregulated inflammatory state. An enhanced proportion of Th1 cells and increased serum levels of IL-6 and CRP have been reported among patients with CKD-associated Pruritus compared to patients without CKD-associated Pruritus. [Mettang 2015, Kimmel 2006] IL-2 and IL-31 have also been associated with CKD-associated Pruritus. [Fallahzadeh 2011, Ko 2014]

We now know there is an imbalance between kappa opioid receptor (KOR) and mu opioid receptor (MOR) expression in CKD-associated Pruritus and that this plays a central role in the etiology and pathogenesis of CKD-associated Pruritus. In a study of MOR and KOR receptor expression, KOR expression was significantly lower in patients with CKD-associated Pruritus compared to those without,[Wieczorek 2020] although MOR expression was similar in both groups. KOR expression was negatively correlated with CKD-associated Pruritus severity. [Wieczorek 2020] Activation of KORs on peripheral sensory neurons is being investigated as a new therapeutic approach to reduce pruritic signaling.

Evolving management horizons in CKD-associated Pruritus

Kamyar Kalantar-Zadeh, USA

People with CKD frequently experience unpleasant symptoms which often occur in clusters, with one as the lead symptom and others as secondary symptoms. Uremic toxins are often considered to be the main cause of CKD-associated symptom burden, but treatment of uremia by dialysis often fails to resolve them and can engender additional symptoms. [Kalantar-Zadeh 2022]

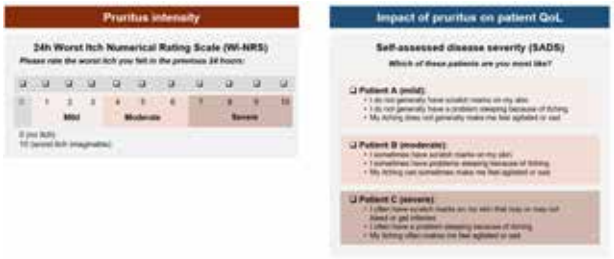

Figure 4.
Simple validated instruments to assess pruritus severity. Adapted from Mathur VS, et al. Clin J Am Soc Nephrol 2010;5:1410–19; Phan NC, et al. Acta Derm Venereol 2012;92:502–7

People with CKD, including those who depend on dialysis or transplantation, should feel actively supported in their symptom management through the identification and targeting of unpleasant symptoms via a tailored palliative care approach. Such an approach may help minimize the burden and consequences of kidney disease, and lead to improved patient outcomes, including HR-QoL and better life participation. [Kalantar-Zadeh 2022] This was the focus of the 2021 World Kidney Day campaign *Living Well with Kidney Disease.*

The relationship between CKD and pruritus is often not well understood by patients, and many fail to report it to their healthcare providers for a variety of reasons:[Aresi 2019]

- Unaware that itch is a symptom associated with CKD
- Lack of awareness around treatment options
- Acceptance of itch as inevitable
- Lack of prompting by healthcare professionals
- Time with nephrologist is too limited, and other health issues are prioritized
- Perceived trivialization of itch by nephrologists
- History of unsuccessful treatments
- Fear of additional medications

The prevalence of itch is underestimated by nephrologists: 69% of nephrologists participating in the DOPPS survey underestimated the prevalence of pruritus in their dialysis facility. (Rayner 2017)

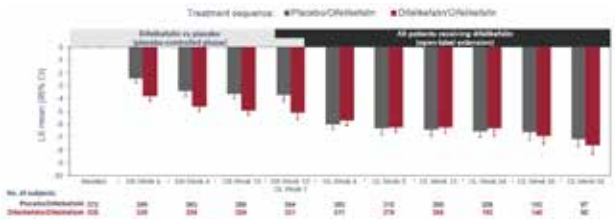

Figure 5.
Improvement in 5-D Itch response with difelikefalin. Adapted from Topf J, et al. Kidney Med 2022. doi:https://doi.org/10.1016/j.xkme.2022.100512

Alleviating the burden of CKD-associated Pruritus requires the proactive identification of patients. Simple validated instruments can then be used to assess pruritus severity: the Worst Itch Numerical Rating Scale (WI-NRS) to assess pruritus intensity and Self-Assessed Disease Severity (SADS) to determine the impact on quality of life (see figure 4).(Mathur 2010, Phan 2012)
A range of agents are used to manage itching, but with the exception of nalfurafine (available in Japan and South Korea) (Locatelli 2021) and difelikefalin (approved in the US and the EU) there are no other approved treatments for CKD-associated Pruritus. Off-label treatments may have limited evidence of efficacy and adverse effects that may be of concern for patients with CKD. (Weisshaar 2019)

An analysis from DOPPS showed that antihistamines are the most commonly used first-line treatment for patients with CKD-associated Pruritus who are not referred to a specialist,10 but this is not recommended by current guidelines. (Weisshaar 2019)
Gabapentinoids (gabapentin and pregabalin) are also used to treat CKD-associated Pruritus, however, there is a lack of evidence for their long-term use and the adverse effects associated with gabapentin – including dizziness, somnolence, weight gain, angio-edema and increased suicide risk – may limit use in CKD-associated Pruritus. (Verduzco 2020)
A number of investigational treatments, including KOR agonists and MOR antagonists are in development for CKD-associated Pruritus. Difelikefalin is the first of the KOR agonists to be approved in the US and the EU for the treatment of CKD-associated Pruritus. It is administered three times per week by intravenous bolus injection into the venous line of the dialysis circuit at the end of the hemodialysis treatment.

Difelikefalin treats CKD-associated Pruritus by activating KORs on peripheral sensory neurons and immune cells. In the peripheral nervous system, KOR activation leads to direct pruritic signal suppression and is also thought to regulate the response of C-fibers to pruritogens. Difelikefalin also reduced secretion of pro-inflammatory cytokines TNF-α, IL-1β, IL-8, and G-CSF following stimulation of primary human macrophages. (Spencer IASP 2010)

Two phase 3 double-blind, placebo-controlled multicenter trials (KALM-1 in the US; KALM-2 global) assessed the efficacy and safety of difelikefalin over 12 weeks vs placebo followed by a 52-week open label extension phase. Patients were at least 18 years of age with ESRD and moderate-to-severe pruritus. All patients had been receiving hemodialysis treatment (≥3 × per week) for at least three months prior to enrolment.(Fishbane NEJM 2020, Wooldridge ASN 2020)

Both studies showed that a significantly greater proportion of patients achieved a ≥3-point improvement from baseline in the weekly mean of the daily WI-NRS score with IV difelikefalin vs placebo,(Fishbane NEJM 2020, Wooldridge ASN 2020) and pooled data from KALM-1 and KALM-2 showed a clinically meaningful improvement in 5-D Itch and Skindex-10 total scores with difelikefalin treatment.(Topf, Kidney Med 2022) Improvement in 5-D Itch response with difelikefalin was maintained over the 52-week open-label extension of KALM-1 and KALM-2, and emerged in patients that switched from placebo (see figure 5), and the efficacy of difelikefalin was consistent among subgroups stratified according to baseline use of anti-pruritic medications.(Topf, Kidney Med 2022)

Pooled safety data from KALM-1 and KALM-2 showed that treatment-emergent adverse events were generally mild-to-moderate in the 12-

week placebo-controlled phase, with diarrhea, dizziness, nausea, gait disturbances, including falls, hyperkalemia, headache, somnolence and mental status changes being the most common.(Fishbane, Kidney Med 2022)

A multicenter, open-label study of difelikefalin in patients with moderate-to-severe CKD-associated Pruritus demonstrated an association between improvement in itch and sleep quality, providing an insight into the potential real-world effectiveness of difelikefalin in this group of patients.(Weiner ERA 2021)

Now that there is a medication that is approved for patients with moderate to severe CKD-aP, a person-centered approach to care would suggest that this should now be considered as the first line itch therapy for this group of patients, used before any off-label treatments.

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