NEPHROLOGY EDUCATION PORTAL

Industry Symposia

Summary Reports

58TH ERA-EDTA CONGRESS FULLY VIRTUAL JUNE 5-8, 2021

Special Edition

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RENAL DENERVATION - A DIFFERENT TOOL FOR HYPERTENSION CARE

Medtronic
Further, Together

Endovascular renal sympathetic denervation (RDN) was first proposed as a treatment method for resistant hypertension a decade ago. The treatment methodology and clinical evidence have advanced significantly since that time. Several renowned experts in the field of RDN presented the latest evidence on the procedure, its applicability in practice, and possibilities that this method is offering to chronic kidney disease (CKD) patients at a symposium held during the 58th ERA-EDTA Congress (only virtual).

Latest Evidence on Renal Denervation

Konstantinos Tsioufis, Greece

RDN appears to be a promising alternative for blood pressure (BP) control, and the procedure has demonstrated safety in multiple clinical trials. RDN requires a complete treatment of the distal main renal artery, branches, and accessory arteries. Renal nerves generally originate from proximal ganglia and converge on the renal artery, but accessory arteries are also common and always innervated and can contribute to the development of hypertension.

The application of radiofrequency (RF) RDN relies on extensive clinical experience with RF ablation on more than 6,700 patients and 12,000 patient years of follow-up. The multi-electrode RDN Symplicity Spyral catheter is able to position electrodes to generate 360 degrees of ablation and also treat the renal branches and accessory arteries to maximize the probability of complete denervation. The efficacy of this technique in the absence of antihypertensive medications was evaluated in the SPYRAL HTN-OFF MED Pivotal trial, a prospective, randomised, sham-controlled trial. The investigation randomly assigned 331 patients with office systolic blood pressure between 150 and 180mmHg, and diastolic BP≥90mmHg to either RDN (166 patients) or sham procedure (165 patients). Recently published results revealed that RDN showed superiority in achieving the baseline-adjusted change in 24-h systolic BP and baseline-adjusted change in office systolic BP from baseline to 3 months after the procedure with a favourable safety profile. The BP-lowering effect was consistent regardless of the time of the day, thus precluding the traditionally increased early morning risks for stroke and cardiovascular events. Similar results were obtained in the SPYRAL HTN-ON MED trial in which RDN in the main renal arteries and branches combined with medications significantly reduced BP compared to antihypertensive therapy alone. Also, evaluation of hourly changes in 24-h systolic blood pressure and diastolic blood pressure showed blood pressure reduction throughout 24-h period for the renal denervation group.

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The largest and longest investigation of long-term safety and efficacy of RDN in real-world patients was undertaken based on the data from the Global SYMPLICITY Registry. This prospective, open-label registry conducted worldwide followed office and 24-h ambulatory systolic BP three years after RDN with Symplicity Flex or Spyral in 2,590 patients demonstrating significant and sustained office and ambulatory BP reductions with no long-term safety concerns. These results were corroborated in a recently published meta-analysis by Ahmad et al. suggesting that should the observed effect of RDN on BP continue long term, this procedure might provide a life-long 10% relative risk reduction in major cardiac events and 7.5% relative risk reduction in all-cause mortality.

Renal Denervation in Practice

Roland E. Schmieder, Germany

The initial promising results of RDN prompted the introduction of this method into practice providing an insight into specific situations where the procedure could be of particular value. Some of these cases are presented in this symposium.

Case 1 underlines the importance of recognizing apparent resistant hypertension which is, in fact, a result of poor adherence to drug treatment. It presents a 50-year-old hypertensive female with a positive history of CV disease and variable adherence to the prescribed medication therapy which included an angiotensin II antagonist and a calcium channel blocker. She is overweight, with office BP 159/93mmHg and 24-h ambulatory BP 149/82mmHg. The serum creatinine level, eGFR, and HbA1c are within a normal range, but LDL is borderline high. This is a typical case identifying nonadherence to antihypertensive treatment as a critical contributor to suboptimal BP control. Studies have identified that each increase in the number of antihypertensive medications led to a substantial increase in nonadherence, especially when converting from two to three medication classes. Poor adherence is associated with increased all-cause and cerebrovascular mortality risk. The major barriers to medication adherence include economic, physiological, and social issues, such as side effects, perceived lack of efficacy, lack of visible symptoms, poor understanding of the illness and its risks, cost concerns, and cultural beliefs. Therefore, RDN might be a convenient option for nonadherent patients to decrease mortality and improve quality of life.

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Case 2 presents a 70-year-old male with a 10-year history of hypertension, type 2 diabetes, left ventricular hypertrophy, and CKD. Despite good adherence to a four antihypertensive medication treatment protocol, office BP is 176/95mmHg, and 24-h ambulatory BP is 154/91mmHg. Large-scale studies have found RDN to be effective and durable in high-risk populations with various comorbidities including diabetes, CKD, resistant hypertension, and atrial fibrillation. The procedure reduced Office systolic BP at three years by -16.4 mmHg in patients with diabetes, -11.6 mmHg in CKD, -23.5 mmHg for resistant hypertension, and -17.6 mmHg in atrial fibrillation. In patients aged ≥65 years, the observed reduction was -18.4 mmHg. These results were associated with a 26% relative risk reduction in major cardiovascular events over three years.

Case 3 represents a typical example of the onset of a hypertensive disease continuum. It presents a 40-year-old male with a sedentary profession, sleep apnoea, obesity, dyslipidaemia, well-controlled type 2 diabetes, smoking habit, and a newly diagnosed hypertension with an office BP of 160/110mmHg and 24-h ambulatory BP of 150/103mmHg. Being young, the patient is concerned about the lifelong medication treatment and is exploring other options to effectively and persistently control hypertension. While in current practice referring physicians and proceduralists are more likely to recommend RDN procedure to patients with higher BP and a greater number of antihypertensive medications, patient preference for renal denervation is unrelated to their baseline blood pressure or medication status. The rationale for this premise is substantiated by the fact that hypertensive patients often regard the choice of RDN to lower BP differently from physicians and a considerable proportion of them, especially those not taking medications, might prefer a device-based approach to reduce their BP.

Should Renal Denervation be an Option for CKD Patients?

José Antonio García Donaire, Spain

It is a well-known fact that CKD is associated with an increased sympathetic activity which contributes to the progression of the disease and is associated with adverse cardiovascular outcomes. End-stage renal disease (ESRD) is associated with an even higher increase in plasma norepinephrine than hypertension alone. The RDN procedure was first introduced as an option to reduce sympathetic nerve activity and BP in patients with resistant hypertension and preserved renal function rendering promising results.

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Later on, concerns arose whether the technique would be safe and effective in hypertensive patients with CKD. Initial studies performed nearly a decade ago suggested a favourable short-term safety profile and beneficial BP effects of renal nerve ablation in patients with CKD stages 3-4 and resistant hypertension. Later research even underlined the role of RDN in further mitigation or even cessation of renal function decline, irrespective of BP-lowering effects in CKD patients, an effect that lasted well over 6 months after the procedure. The most recent recognition of these results originates from the Global SYMPLICITY Registry which supported previous findings.

Even with these promising results, ESRD patients on haemodialysis (HD) still represent a challenge, even though this population often suffers from resistant hypertension despite the administration of many antihypertensive drugs. Ott et al. were the first to report performing the procedure in HD patients corroborating the data on renal safety of RDN even in small arteries. More recently, Scalise et al. supported these findings concluding that the BP reduction in HD patients persisted over a one-year follow-up.

Kidney transplant patients represent yet another population in which sympathetic activity is frequently observed and post-transplant hypertension is a major contributing factor to graft failure and cardiovascular morbidity. This process is maintained by the preservation of sympathetic afferent activity from the native non-functional kidneys, in the absence of efferent feedback to the renal transplant, which would otherwise modulate neurohumoral activity. A small study by Schneider et al. found that RDN is feasible and safe in this population as well, with a significant reduction in office BP persisting 6 months after the procedure.

Upcoming larger prospective trials should focus on the identification of patients with uncontrolled hypertension with all levels of CKD who may derive a substantial benefit from RDN.

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Further reading

Persu A, Maes F, Renkin J, Pathak A. Renal Denervation in Hypertensive Patients: Back to Anatomy? Hypertension. 2020;76(4):1084-1086. doi: 10.1161/HYPERTENSIONAHA.120.15834.

Sato Y, Kawakami R, Jinnouchi H, et al. Comprehensive Assessment of Human Accessory Renal Artery Periarterial Renal Sympathetic Nerve Distribution. JACC Cardiovasc Interv. 2021;14(3):304-315. doi: 10.1016/j.jcin.2020.09.043.

Böhm M, Kario K, Kandzari DE; SPYRAL HTN-OFF MED Pivotal Investigators. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. Lancet. 2020;395(10234):1444-1451. doi: 10.1016/S0140-6736(20)30554-7.

Kandzari DE, Böhm M, Mahfoud F; SPYRAL HTN-ON MED Trial Investigators. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet. 2018;391(10137):2346-2355. doi: 10.1016/S0140-6736(18)30951-6.

Mahfoud F, Böhm M, Schmieder R, et al. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. Eur Heart J. 2019;40(42):3474-3482. doi: 10.1093/eurheartj/ehz118.

Ahmad Y, Kane C, Arnold AD, et al. Randomized blinded placebo-controlled trials of renal sympathetic denervation for hypertension: A meta-analysis. Cardiovasc Revasc Med. 2021:S1553-8389(21)00082-8. doi: 10.1016/j.carrev.2021.01.031.

Gupta P, Patel P, Štrauch B, et al. Risk Factors for Nonadherence to Antihypertensive Treatment. Hypertension. 2017;69(6):1113-1120. doi: 10.1161/HYPERTENSIONAHA.116.08729.

Mahfoud F, Mancia G, Schmieder R, et al. Renal Denervation in High-Risk Patients With Hypertension. J Am Coll Cardiol. 2020;75(23):2879-2888. doi: 10.1016/j.jacc.2020.04.036.

Schmieder RE, Kandzari DE, Wang TD, Lee YH, Lazarus G, Pathak A. Differences in patient and physician perspectives on pharmaceutical therapy and renal denervation for the management of hypertension. J Hypertens. 2021;39(1):162-168. doi: 10.1097/HJH.0000000000002592.

Hering D, Mahfoud F, Walton AS, et al. Renal denervation in moderate to severe CKD. J Am Soc Nephrol. 2012;23(7):1250-7. doi: 10.1681/ASN.2011111062.

Hering D, Marusic P, Duval J, et al. Effect of renal denervation on kidney function in patients with chronic kidney disease. Int J Cardiol. 2017;232:93-97. doi: 10.1016/j.ijcard.2017.01.047.

Ott C, Schmid A, Ditting T, Veelken R, Uder M, Schmieder RE. Effects of renal denervation on blood pressure in hypertensive patients with end-stage renal disease: a single centre experience. Clin Exp Nephrol. 2019;23(6):749-755. doi: 10.1007/s10157-019-01697-7.

Scalise F, Sole A, Singh G, et al. Renal denervation in patients with end-stage renal disease and resistant hypertension on long-term haemodialysis. J Hypertens. 2020;38(5):936-942. doi: 10.1097/HJH.0000000000002358.

Schneider S, Promny D, Sinnecker D, et al. Impact of sympathetic renal denervation: a randomized study in patients after renal transplantation (ISAR-denerve). Nephrol Dial Transplant. 2015;30(11):1928-36. doi: 10.1093/ndt/gfv311.

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A NEW PERSPECTIVE IN THE MANAGEMENT OF ATTP: THE NEPHROLOGIST APPROACH

SANOFI GENZYME

Welcome & Introduction

Paul Brinkkötter, Germany

Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare blood disorder with an incidence of 2-13 cases per million/year. It presents with features of thrombotic microangiopathy (TMA), including widespread platelet consumption into microthrombi, microangiopathic haemolytic anaemia , and ultimately ischemia and end-organ complications. At a virtual satellite symposium held during the fully virtual ERA-EDTA 2021 congress, Dr Ralph Wendt, Professor François Provôt and Professor Paul Brinkkötter discussed the challenges of diagnosing aTTP, the acute treatment of this life-threatening disorder, and how experience through learning is improving patient care and reducing mortality.

Diagnosing aTTP and its challenges

Ralph Wendt, Germany

TTP is caused by innate or acquired deficiency of ADAMTS13 (A Disintegrin-like And Metalloproteinase with ThromboSpondin type 1 motif, member 13), a protease that cleaves von Willebrand factor (VWF) multimers. aTTP, also known as immune-mediated TTP (iTTP), results from autoantibodies against ADAMTS13. Signs and symptoms of an acute aTTP flare include petechiae and purpura, headache and/or confusion or stroke-like symptoms, fatigue, dyspnoea due to anaemia, cardiac and gastrointestinal symptoms.

Dr Wendt advised that any clinical suspicion of TMA should prompt urgent testing of ADAMTS13 activity. If ADAMTS13 activity is <10%, the patient has TTP. A positive test for the antibody to ADAMTS13 means that the diagnosis is aTTP, while a persistent negative antibody result suggests congenital TTP (cTTP) associated with ADAMTS13 gene mutation. He added that severe ADAMTS13 deficiency alone without signs of TMA and especially organ involvement does not represent an acute TTP flare, relapse or exacerbation, and is no reason to start treatment. It could, however, eventually lead to a TTP flare, which may be unpredictable and be the result of minor triggers or even no identifiable triggers.

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Since aTTP is a dangerous disorder that is associated with high mortality when untreated, rapid diagnosis and initiation of treatment are critical. The two standard methods of diagnosing severe ADAMTS13 deficiency are fluorescence resonance energy transfer (FRET) and classic chromogenic enzyme linked immunosorbent assay (ELISA). Both are time consuming, require considerable technical skill, and may not be immediately available. Rapid testing for ADAMTS13 activity is now available, but compared with gold-standard ELISA, it is associated with 20% overdiagnosis of severe ADAMTS13 deficiency, as well as the more concerning false exclusion of patients with TTP.

In clinical practice, rapid identification of TMA patients who most likely have aTTP, and who will benefit most from emergency treatment, often depends on clinical judgement and can be ascertained by clinical scores, such as the PLASMIC and French scores. A PLASMIC score of ≥6 or a French score of ≥2 indicates a high probability for TTP. Dr Wendt concluded that, in clinical practice, it is possible to combine rapid testing with a clinical scoring system, but clinicians should be aware of possible misdiagnosis. Waiting for results of ADAMTS13 activity should not, however, delay treatment; if clinical scoring indicates a high probability of TTP, treatment should be initiated immediately to reduce the high mortality seen in untreated patients.

Acute aTTP treatment: where do we stand in 2021?

François Provôt, France

Despite treatment with therapeutic plasma exchange (TPE) and immunosuppression with steroids and rituximab, aTTP has acute mortality rate of up to 20%. In addition, refractory disease occurs in up to 42% of patients and may lead to poor outcomes. There is therefore a need for targeted, rapid-acting treatment to reduce early mortality and morbidity.

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Caplacizumab is a nanobody (a single variable domain immunoglobulin) that specifically targets microthrombi formation by inhibiting the interaction between the A1 domain of VWF and the platelet GP1b receptor. In 2018, caplacizumab was approved in Europe for the treatment of aTTP based on data from two clinical trials: the phase 2 TITAN trial and the phase 3 HERCULES trial. The two studies included a total of 220 adults with acute aTTP diagnosed by clinical presentation, who were randomized to either caplacizumab or placebo plus TPE and immunosuppression during TPE treatment, and after TPE cessation for 30 days in TITAN and 30-58 days in HERCULES.

Professor Provôt reported that in an integrated analysis of TITAN and HERCULES, compared with placebo, caplacizumab significantly reduced the number of deaths (0 vs 4; $p<0.05$) and the incidence of refractory TTP (0 vs 8; $p<0.05$) during the treatment period. Treatment with caplacizumab also resulted in a faster time to platelet count response (HR 1.65; $p<0.001$); a 72.6% reduction in the proportion of patients with the composite endpoint of TTP-related death, TTP exacerbation or occurrence of at least one treatment-emergent major thromboembolic event during treatment (13.0% vs 47.3%; $p<0.001$); and a 33.3% reduction in the median number of TPE days (5.0 vs 7.5 days). No new safety concerns were highlighted, with mild mucocutaneous bleeding being the main adverse effect.

According to Professor Provôt, this integrated analysis is the first publication in which no aTTP-related deaths have been reported in randomized trials. He added that, because of its rapid onset of action, caplacizumab might act as 'bridge' until rituximab efficacy is achieved. The faster time to platelet recovery also raises the possibility of reducing the number of TPE days and time in hospital, especially in critical care.

Outcomes in clinical trials are reflected in real-world experience with caplacizumab. The French experience began in September 2018 and includes 90 patients with acute aTTP, who all received the same regimen as in HERCULES. The percentage of patients with the composite primary outcome of refractoriness and death within 30 days of diagnosis was 2.2% vs 12.2% in historical controls ($p=0.01$). Compared with controls, patients receiving caplacizumab also had fewer exacerbations (3.4% vs 44%, $p<0.01$), recovered durable platelet count 1.8 times faster (95% CI 1.41-2.36; $p<0.01$) with fewer TPE sessions and lower plasma volumes ($p<0.01$ both). As in the randomized trials, there were no unexpected adverse events.

Professor Provôt concluded that standard of care for acute aTTP is now TPE, immunosuppression with corticosteroids and rituximab, and caplacizumab. However, despite improved treatment, it is likely that many patients die before TTP is diagnosed and it remains essential to raise awareness of the diagnosis among clinicians.

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Experience through learning: clinical pearls

Paul Brinkkötter, Germany

A 46-year-old white male presented to the emergency department in late summer 2018 with generalized weakness, low platelets, petechial hemorrhages of the skin, high LDH, schistocytes and anemia. He had acute kidney injury with a creatinine of 5.31 mg/dl. His PLASMIC score was 5, reflecting a moderate risk of ADAMTS13 activity <10%—a diagnosis confirmed by laboratory testing showing ADAMTS13 activity of ≤0.3%, below the limit of detection.

The patient responded well after receiving high-dose glucocorticoids and TPE within a few hours of admission. Platelet count normalized within two days but fell after the two-day weekend break in treatment. Despite restarting TPE and initiating rituximab, disease activity could not be controlled. Following a compassionate use agreement on 1st September 2018, caplacizumab was started. The patient responded rapidly, and disease activity remains under control. However, very low ADAMTS13 levels continued, and caplacizumab treatment was extended for a total of 58 days according to the HERCULES study protocol.

Professor Brinkkötter reported that during treatment, the patient showed a highly dynamic platelet response, most likely reflecting the bone marrow response, and considered that this phenomenon can easily be misinterpreted as an exacerbation or early relapse, especially when caplacizumab is discontinued. It is therefore critical to monitor clinical symptoms and LDH levels and other markers for hemolysis. This patient's LDH levels remained within the normal range, and experience was similar in the first 60 German patients treated with caplacizumab in 2018-19.

Median time to ADAMTS13 >10% in the German cohort was 21 days after the last TPE. 11 patients, whose ADAMTS13 activity was <10% when stopping caplacizumab, experienced disease exacerbation or relapse.

Professor Brinkkötter commented that these data indicate that ADAMTS13 activity can serve as a biomarker to guide therapy and assess relapse risk. If activity remains suppressed, there is a 50% risk of relapse, especially within the first month. Reflecting other published data, all relapses in the German cohort occurred within two weeks of stopping caplacizumab at a mean of 6.9 (3.9-9.9) days.

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There is an ongoing debate whether early use of rituximab can shorten time to ADAMTS13 normalization. There was no clear effect on ADAMTS13 normalization in 48 of 60 patients in the German cohort, who were receiving rituximab front line. However, Professor Brinkkötter regarded these data as inconclusive since physicians tended to withhold rituximab in milder cases or give it primarily in refractory disease or exacerbations. He also considered the pathophysiology concept supporting use of rituximab in acute aTTP to be convincing.

Caplacizumab is now recommended as first-line therapy in current guidelines, and Professor Brinkkötter concluded that German and French data confirm its real-world effectiveness in acute episodes of aTTP. Treatment of aTTP has become success story and the disorder has lost much of the fear it held since it was first described in 1924.

Further reading

Diagnosing aTTP and its challenges

Brocklebank V, et al. Thrombotic microangiopathy and the kidney. Clin J Am Soc Nephrol 2018;13(2):300-317

Mackie I et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of ADAMTS13. Int J Lab Hematol 2020;42(6):685-696

Coppo P, et al. Thrombotic thrombocytopenic purpura: Toward targeted therapy and precision medicine. Res Pract Thromb Hemost 2019;3(1):26–37

Sukamer S, et al. Thrombotic thrombocytopenic purpura: pathophysiology, diagnosis, and management. J Clin Med 2021;10(3):536

Acute aTTP treatment in 2021

Joly BS, et al. Understanding therapeutic targets in thrombotic thrombocytopenic purpura. Intensive Care Med 2017;43(9):1398-1400

Peyvandi F, et al. Caplacizumab prevents refractoriness and mortality in acquired thrombotic thrombocytopenic purpura: integrated analysis. Blood Adv 2021

Coppo P, et al. A regimen with caplacizumab, immunosuppression, and plasma exchange prevents unfavorable outcomes in immune-mediated TTP. Blood 2021;137(6):733-742

A new perspective in the management of aTTP

Volker LA, et al. ADAMTS13 and VWF activities guide individualized caplacizumab treatment in patients with aTTP. Blood Adv 2020;4(13):3092-3101

Zheng XL, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost 2020;18(10):2496-2502

FRONTIERS IN THE MANAGEMENT OF AHUS

Atypical haemolytic uremic syndrome (aHUS) is a rare, life-threatening disease caused by complement dysregulation and presenting as thrombotic microangiopathy (TMA). Approval of the complement protein C5 inhibitor eculizumab in 2011 revolutionized treatment of aHUS, but clinical challenges remain. How do the extent and intricacies of complement involvement in aHUS pathophysiology influence diagnosis? How does clinical trial data translate into real-world use of a C5 inhibitor? And how should clinicians manage the complexities of aHUS in a kidney transplant setting? These challenges were discussed by Professor Hermann Haller, Dr Anja Gäckler and Dr Yahsou Delmas at a virtual symposium held during the 2021 ERA-EDTA fully virtual congress.

Complement C5 at the heart of aHUS

Hermann Haller, Germany

TMA is difficult to diagnose since it is a systemic disease, affecting multiple organs and systems. The first clinical symptoms include thrombocytopenia, microangiopathic haemolysis and fever. Up to 48% of aHUS cases also have central nervous system (CNS) findings, while up to 80% have impaired renal function. Patients may present with other conditions such as pregnancy or malignant hypertension, symptoms may occur at any age, and onset may be acute or more chronic with relapses.

Professor Haller emphasized that differential diagnosis of aHUS must include both predisposing or genetic molecular mechanisms and precipitating factors or external triggers. In some patients, genetic factors are so strong that it requires only a minor external trigger like a viral infection to precipitate aHUS, while a severe trigger in which the complement cascade is highly activated is required when there is only a minor genetic polymorphism.

Genetic analysis can provide important diagnostic clues, but Professor Haller considered the clinical diagnosis of aHUS to be more important and he advised against waiting for a genetic diagnosis before initiating treatment. This is because, the earlier C5 inhibition is started, the more likely it is that further damage from microangiopathy will be prevented and organ function will be preserved.

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Professor Haller advised that discontinuation of the C5 inhibitor can only be considered if it is medically justified. Discontinuation is not recommended for patients who have lost a previous allograft. In other patients, discontinuation should be on a case-by-case basis, considering: the severity of the disease, whether there has been prolonged period of organ function normalization or stabilization; biopsy results; and TMA activity. Family history and genetic analysis are important, as is the risk of recurrence of conditions that amplify complement. Finally, if treatment is discontinued, close monitoring is essential and patient compliance should be checked and education regularly reinforced.

C5 inhibition in aHUS, from clinical trials to practical use

Anja Gäckler, Germany

Although highly effective in treating aHUS, eculizumab requires a standard regimen of intravenous infusions every two weeks in patients with a body weight of ≥10 kg. Ravulizumab is a long-acting, humanized monoclonal antibody that has been engineered from eculizumab to enable increased elimination half-life and allow an extended dosing interval from two to eight weeks, without sacrificing immediate and complete C5 inhibition.

Dr Gäckler outlined the results of the phase III trial of ravulizumab in adults, a multicentre, open, single-arm trial that included 56 complement-inhibitor naïve patients (aged ≥ 18 years, body weight ≥ 40 kg) who fulfilled diagnostic criteria for aHUS. Patients received meningococcal vaccination before or at the time of treatment; if vaccine was received less than two weeks before start of treatment, appropriate prophylactic antibiotics were given until two weeks after vaccination.

On the primary endpoint, complete TMA response was achieved in 30/56 patients (53.6%) during the initial evaluation period, with a median response time of 86.0 days. On hematologic endpoints, during the initial evaluation period 47 (83.9%) patients achieved platelet count normalization and lactate dehydrogenase (LDH) normalization was reached in 43 (76.8%) patients; further, a 25% improvement from baseline in serum creatinine was achieved by 33 patients (58.9%).

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Renal function (eGFR) substantially improved from baseline, with a median increase of 29.0 (–13 to +108) ml/min) to day 183, increasing substantially by day 15. Dialysis was discontinued in 17/29 patients (59%) who were on dialysis at baseline. Of 27 patients not on dialysis at baseline, 21 (78%) remained off dialysis at the last available follow-up (which may have occurred after day 183). 95.8% (45/47) of patients showed improvement or preservation in renal function with regard to CKD stage, with 68% improving.

Dr Gäckler added that there were no unexpected adverse events (AEs), and most occurred within the first 26 weeks. Through all available follow-up, 20 patients (34.5%) experienced treatment-related AEs, most commonly headache, diarrhea, and vomiting. Serious AEs occurred in 33 patients (56.9%), most commonly hypertension and pneumonia. Three patients (5.2%) discontinued treatment and withdrew from the study because of an SAE (autoimmune haemolytic anaemia, intracranial haemorrhage, and immune thrombocytopenic purpura). No meningococcal infections or deaths related to the study drug occurred.

On the basis of the phase III trial, ravulizumab was approved in Europe in patients with aHUS and body weight ≥10 kg, who are complement inhibitor treatment-naïve, or have received eculizumab for at least three months with evidence of response. Originally presented in a 10mg/ml formulation, ravulizumab is now available in a 100mg/ml formulation, reducing the number of vials and infusion time required for dosing.

Complement inhibitor treatment is associated with an increased risk of infection with encapsulated bacteria. Dr Gäckler recommended that to minimize this risk, patients should be given information about Neisseria gonorrhoeae prevention, and vaccinated against meningococcal infection. Vaccination against Haemophilus influenzae and pneumococci should be given to patients aged <18 years and considered in those ≥18. Patients should always carry a safety card, and they should be educated about the signs of serious infection, especially meningitis.

Dr Gäckler has switched 12 patients with aHUS, including five kidney transplant patients, from eculizumab to ravulizumab. In general, patients were pleased with the reduced burden of treatment, and the medical staff report that administration of ravulizumab was simple and convenient.

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aHUS and kidney transplant, a particular challenge

Yahsou Delmas, France

TMA is a complicated differential diagnosis in the setting of kidney transplantation. Dr Delmas explained that TMA aetiology may be cumulative, and may be related to medication (such as calcineurin (CNI) or mTOR inhibitors) and malignant hypertension. Transplant patients are at risk of infections, including Shiga toxin, which results in diarrhea in 30% of aHUS patients. Finally, the presentation of vitamin B9 and/or vitamin B12 deficiency can resemble that of TMA. She added that these aetiologies can act as triggers for complement-mediated aHUS, and a normal C5 does not rule out complement activation in transplant patients.

Prophylactic eculizumab improves post-kidney transplant outcomes in aHUS patients. Timing of initiation is important, as optimum survival is seen when eculizumab is introduced within one week of aHUS recurrence post-transplantation. Since patients with early recurrence post-kidney transplant have a very high risk of recurrence within two years of the next transplant, risk stratification is essential.

KDIGO proposes risk stratification based on the patient history and type of variant, with the highest risk seen in patients with a previous early recurrence, a pathogenic mutation and a gain-of-function mutation. In these patients, KDIGO recommends prophylactic eculizumab started on the day of surgery and continued after kidney transplantation. Prophylactic eculizumab or plasma exchange is recommended in moderate-risk patients without an unrelated mutation or persistent low anti-FH antibody. No prophylaxis is recommended in low-risk patients (<10% risk of recurrence) with an isolated MCP mutation and persistently negative FH antibodies.

Licensed dosing of eculizumab in kidney transplantation is 900mg/weekly for four weeks in the initial phase, followed by maintenance dosing of 1200mg every other week. Dr Delmas recommended monitoring residual complement blockade at the beginning of treatment or if there is insufficient response. Kidney transplant patients receiving a C5 inhibitor should receive the recommended vaccinations, education about infections, and a personalized card to ensure prompt medical attention in an emergency.

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KDIGO recommends against discontinuing eculizumab in kidney transplant patients with aHUS except during intercurrent illness with an encapsulated organism. Eculizumab is first-line therapy if aHUS is diagnosed post-transplant. If acute renal failure necessitates dialysis restart, KDIGO recommends waiting six months before the next kidney transplant, as there may be late recovery with eculizumab. If clinicians do consider discontinuing eculizumab post transplantation, no hematologic TMA features should be present and extrarenal manifestations must be resolved.

In conclusion, early diagnosis of aHUS recurrence post-transplant is essential, as early prophylactic C5 inhibition gives the best outcomes. Patients with aHUS should be stratified for post-transplant risk of recurrence. Genetic background should be assessed, and patients should be protected by a living-donor transplant, if possible, a low dose of CNI and strict target blood pressure. Dr Delmas concluded that anti-C5 therapy has opened the door to good outcomes of kidney transplantation for aHUS patients, and we are in the era of personalized therapeutic strategies.

Further reading

Diagnosis of TMA

Campistol JM, et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. Nefrologia 2015;35:421-47

Norris M, Remuzzi G. Atypical hemolytic–uremic syndrome. N Engl J Med 2009; 361:1676-1687

Legendre CM, et al. Terminal complement inhibitor eculizumab in atypical hemolytic–uremic syndrome. N Engl J Med 2013;368:2169-81

From clinical trials to practical use

Sheridan S, et al. Design and preclinical characterization of ALXN1210: A novel anti-C5 antibody with extended duration of action. PLoS One 2018;13(4):e0195909.

Rondeau E, et al. The long-acting C5 inhibitor, ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment. Kidney Int 202097:1287-1296

aHUS and kidney transplantation

Le Quintrec M, et al. Complement genes strongly predict recurrence and graft outcome in adult renal transplant recipients with atypical hemolytic and uremic syndrome. Am J Transplant 2013;13:663-75

Goodship TH, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int 2017;91:539-551.

Zuber J, et al. Use of highly individualized complement blockade has revolutionized clinical outcomes after kidney transplantation and renal epidemiology of atypical hemolytic uremic syndrome. J Am Soc Nephrol 2019;30:2449-246

NONSTEROIDAL MRAS TO IMPROVE OUTCOMES IN PATIENTS WITH CKD AND T2D

Welcome & Introduction

María José Soler, Spain

As symposium chairwoman Maria José Soler pointed out in her introduction, the prevalence of type 2 diabetes (T2D) is high and keeps growing. This threatens kidney health, because T2D is the leading cause of kidney diseases. Renin–angiotensin–aldosterone system inhibition can slow the process of diabetic nephropathy but cannot effectively stop it. A high percentage of patients will still progress and require renal replacement therapy. Maria Soler emphasized that nonsteroidal mineralocorticoid receptor (MR) antagonists (MRAs) might be a new and promising treatment option in these patients.

Inflammation and fibrosis: An overlooked driver of CKD progression in T2D?

Katherine Tuttle, United States of America

Katherine Tuttle provided some details regarding the pathogenesis of diabetic nephropathy. As she pointed out, chronic kidney disease (CKD) progression in T2D is driven by the combined effects of metabolic, hemodynamic, inflammatory and fibrotic factors. One of the hemodynamic factors is elevated blood pressure, often seen in patients with T2D, and among the metabolic factors is poor glycaemic control; both factors are well known, but the key significance of inflammation and fibrosis was not recognized until a few years ago. It is known that diabetes is associated with chronic inflammation leading to an influx of macrophage lineage cells in patients with CKD and diabetes, which then promotes fibrosis. It is also known that the degree of interstitial fibrosis on biopsy can predict progression to kidney failure. The degree of fibrosis correlates with estimated glomerular filtration rate (eGFR) category and time to dialysis. The higher the degree of fibrosis, the shorter the time until replacement therapy is needed.

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Fibrosis biomarkers in blood and urine are upregulated in patients with CKD and T2D and can be used as progression markers. It has been shown that transforming growth factor beta (TGF β) levels correlate directly with albuminuria severity in patients with T2D. Inflammation is a common attendant symptom of fibrosis, so a robust "Kidney Risk Inflammatory Signature" (KRIS) is also associated with an increased risk of kidney failure and is elevated in patients with diabetes.

We know that aldosterone has many important effects on the kidneys and that local aldosterone is a driver of inflammation in diabetes. It has been shown that local renal aldosterone production induces inflammation and fibrosis in a streptozotocin-induced diabetic rat model – a process that could be inhibited by inhibiting aldosterone production, thus resulting in a reduction of albuminuria.

So how can hemodynamic and metabolic factors be addressed in patients with CKD and T2D? To control hemodynamic factors, we have angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs), endothelin receptor antagonists – and, more recently, sodium-glucose co-transporter-2 (SGLT-2) inhibitors. To control metabolic risk factors, there are glucagon-like peptide-1 receptor agonists (GLP-1RAs), metformin, and other antihyperglycemic agents. There are no therapeutic options available at present for targeting fibrosis. However, when we come to think about treatment targets for addressing fibrosis, the first that comes to mind is the MR, because among many other functions, the MR regulates inflammation and fibrosis, as well as fluid and electrolyte homeostasis, via differential gene expression.

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The FIDELIO-DKD trial: New insights on the benefits of MR antagonism

Rajiv Agarwal, United States of America

That the observed effects in preclinical trials translate into better outcomes for patients has now been demonstrated in a large phase 3 study that Rajiv Agarwal presented at the symposium. It investigated the efficacy and safety of finerenone in comparison with placebo in addition to standard of care for the reduction of kidney failure and kidney disease progression in patients with CKD and T2D. The "FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease" (FIGARO-DKD) trial was a double-blind, randomized, placebo-controlled trial in which 13,911 patients from more than 1000 sites across 47 countries worldwide were enrolled. During a run-in phase of 4–16 weeks, the ACEi/ARB therapy of the patients was optimized, as the maximum tolerated dose of ACEi or ARB for ≥4 weeks was one of the inclusion criteria. This was not tolerated by all, as Rajiv Agarwal pointed out: in the end, 5734 patients were randomized to receive either finerenone 10 mg or 20 mg orally once daily or placebo when added to standard of care, including blood glucose-lowering therapies and maximum tolerated dose of renin–angiotensin system (RAS)-blocking therapy such as ACEis or ARBs. At baseline, patients had advanced CKD, with a mean eGFR of 44 ml/min/1.73 m2 and a median urine albumin-to-creatinine ratio (UACR) of 852 mg/g. The primary endpoint was a composite renal endpoint comprising kidney failure, sustained ≥40% decrease in eGFR from baseline, or death from renal causes, whereas the secondary endpoint was the composite risk of cardiovascular (CV) death or nonfatal CV events (myocardial infarction, stroke, or heart failure hospitalization), assessed in a time to event analysis.

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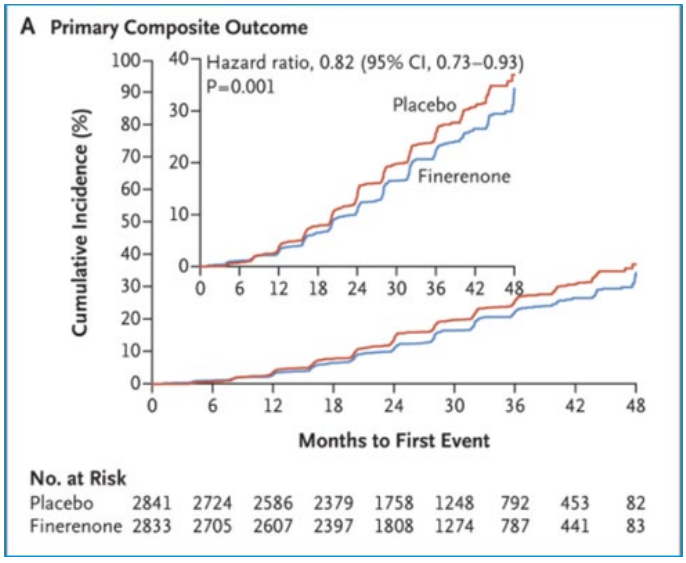
The study showed that, when added to maximum tolerated RAS therapy, finerenone significantly reduced the primary kidney outcome by 18% (p=0.001). The key CV outcomes assessed in the secondary endpoints were reduced by 14%. It was shown that these effects were not due to stricter blood pressure or blood glucose control but were effects of the agent: finerenone had modest effects on blood pressure and did not affect blood glucose compared with placebo; the difference in mean systemic blood pressure (SBP) between groups was –2.9 mmHg at month 1 and –3.0 mmHg at month 12. No safety signals were observed, and there were 75 serious adverse events leading to permanent treatment discontinuation in the treatment group and 78 in the placebo group. Although the rate of hyperkalaemia was higher in the group of patients treated with finerenone, its clinical impact was minimal. The incidences of permanent treatment discontinuation or hospitalization due to hyperkalaemia were low in both the treatment and placebo groups (2.3% vs 0.9% and 1.4% vs 0.3%, respectively).



CI, confidence interval

A subgroup analysis showed that younger age and female sex were associated with higher risk of hyperkalaemia, as well as higher baseline [K+], lower eGFR, and higher UACR. It is important to note that kidney benefits of finerenone were also maintained in the patient subgroups at highest risk of hyperkalaemia, and that elevations in [K+] are predictable and manageable through routine monitoring.

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Rajiv Agarwal concluded that finerenone showed long-term kidney and CV benefits in patients with CKD and T2D. Further studies must now investigate whether this effect can already be seen in patients in very early stages of CKD. These trials will address the question of whether the use of finerenone can prevent renal and CV disease in these patients.

From the trial to the clinic: Applying the evidence to everyday practice

Pantelis Sarafidis, Greece

An important question answered by Pantelis Sarafidis in his talk was "what types of patient with CKD and T2D could be considered candidates for treatment with finerenone?" In the FIGARO-DKD study,3 patients with eGFR 25–75 ml/min/1.73 m2 and UACR >30 mg/g were enrolled, all of them patients with "common" comorbidities. As Sarafidis pointed out, it is well known that patients with CKD and T2D are at high risk of CKD progression as well as at increased risk of death from CV-related causes – and the risk of CV mortality increases with albuminuria and decreasing eGFR. "We are seeing patients at very high risk, and we have to ask ourselves: are we doing our best in the management of patients with CKD and T2D?"

Pantelis Sarafidis pointed out that ACEi/ARBs, considered standard care, reduce renal risk but do not reduce mortality in patients with CKD and T2D. Despite best standard of care with ACEIs or ARBs, patients with CKD and T2D are at high risk of CKD progression. Sarafidis pointed out that finerenone had consistent beneficial effects on kidney outcomes, regardless of eGFR or UACR at screening and baseline blood pressure or glycated haemoglobin in the FIGARO-DKD study. "The main result was: finerenone gives you an additional 18% reduction in the risk of CKD progression. Furthermore, it offers important cardio protection in this population."

Pantelis Sarafidis pointed out that the diagnosis of CKD in patients with T2D is often too late and the treatment is often inappropriate. New treatment options such as SGLT-2 inhibitors and MRAs have opened up new avenues to CV protection in this heavily burdened population.

NONSTEROIDAL MRAS TO IMPROVE OUTCOMES IN PATIENTS WITH CKD AND T2D

Further reading

Chen YL, Qiao YC, Xu Y, et al. Serum TNF-α concentrations in type 2 diabetes mellitus patients and diabetic nephropathy patients: a systematic review and meta-analysis. Medicine (Baltimore) 2017;96:e6563

Siragy HM & Xue C. Local renal aldosterone production induces inflammation and matrix formation in kidneys of diabetic rats. Exp Physiol 2008; 93:817–824

Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020; 383:2219–2229

Agarwal R. Presented at: ISN Virtual World Congress of Nephrology 2021 (WCN'21); April 15–19, 2021; abstract WCN21-0607

NEPHROLOGY EDUCATION PORTAL

A NEW APPROACH FOR GLOMERULONEPHRITIS: TARGETING THE ALTERNATIVE COMPLEMENT PATHWAY

NOVARTIS

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Welcome and introduction

David Kavanagh, United Kingdom

Dysregulation of the complement alternative pathway (AP) appears to be a common pathophysiological background of several immune-mediated kidney diseases such as glomerulonephritis (GN) that are still classified based on clinical presentation, course of the disease, or biopsy appearance. Recent studies even accumulated clinical, genetic, and biochemical evidence that complement plays a significant role in the pathogenesis of IgA nephropathy (IgAN), the most common form of primary glomerulonephritis (GN). The accurate identification of the underlying pathogenic mechanisms in complement-driven renal diseases (CDRD) is the key to devise adequate therapeutic protocols and predict the response to interventions. A panel of experts summarized the role of the complement system in certain glomerulonephritis entities, presented emerging therapeutic approaches and future directions at a symposium held during the 58th ERA-EDTA Congress (only virtual).

The role of complement in glomerulonephritis

Peter Zipfel, Germany

Under physiological conditions, the complement system contributes substantially to homeostasis by coordinating the removal of apoptotic debris and infectious microbes, orchestrating immune responses, and generating and sending "danger" signals. The complement cascade has three activation routes, the classical and the lectin pathways on cell surfaces, and the alternative pathway, AP acting in the fluid phase and on surfaces. Following the three different initial triggers that activate a particular route, the common point of all three paths is the activation of the C3 component, cleaving it into a large fragment C3b, that acts as an opsonin, and a small fragment C3a that promotes inflammation. Activated C3 can triggers a second route of inflammatory via C5a and activates the lytic pathway, damaging the plasma membranes of cells and infectous microbes including bacteria. C5a, which is produced by this process, attracts macrophages and neutrophils and also activates mast cells.

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When not properly controlled, the complement can take action against healthy cells, thus catalyzing a plethora of glomerular diseases. The classical/lectin pathway is associated with ANCA vasculitis, IgAN vasculitis, and antibody-mediated transplant rejection, whereas C3 glomerulopathy (C3G), hemolytic uremic syndrome (HUS), FHR1-FHR3 deficient and antibody-positive HUS, hematopoietic stem-cell associated thrombotic microangiopathy, and IgAN are predominantly related to the derangements in AP. The specific activation pathways and regulatory mechanisms of complement that are disturbed in these conditions provide the targets to act upon by therapeutic agents. The major challenge in this process is to understand complement regulation, define the roles and relationships between the many regulators, understand which inhibitor acts at which site, and how and when the absence or defect of a single regulator disturbs the cascade. This should ultimately allow designing precisely acting therapeutic agents selectively targeting particular complement activation pathways to modulate these complement-driven diseases.

Towards a targeted therapy in complement-driven renal disease: a program overview

Matthias Meier, Switzerland

The benefits of anti-complement therapy have been explored for several decades in various preclinical disease models. Despite the long history, only few anti-complement drugs have entered clinical trials until recently. Nevertheless, the growing list of renal diseases implicating complement has sparked new interest in this topic, thus triggering the development of numerous clinical anti-complement drugs for the complement-driven renal diseases (CDRD). Iptacopan (LNP023) is a first-in-class, orally-administered, potent, and highly selective factor B inhibitor that directly blocks C3 convertase thus reducing the activation of the complement AP. Multiple positive phase 2 readouts and favorable safety and tolerability profile permitted rapid transition of this agent into phase 3 trials. It is currently being evaluated for the treatment of C3 glomerulonephritis (C3GN) in the APPEAR study, IgAN in the APPLAUSE study, atypical hemolytic uremic syndrome in the APPELHUS study, as well as paroxysmal nocturnal hemoglobinuria (PNH) in the APPLY as well as APPOINT studies.

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The APPEAR-C3G trial is a multicenter double-blind, parallel group study evaluating the efficacy and safety of iptacopan compared to placebo and Standard of Care (SoC) in patients with C3G in native kidneys (patients with C3G recurrence in transplanted kidney allografts were excluded). The study is expected to enroll 68 adult participants with biopsy-confirmed C3G and urine protein to creatinine ratio (UPCR) ≥1g/g. Patients will be initially randomized to receive iptacopan 200mg bid or placebo for a period of 6 months, followed by another six months of open-label treatment with iptacopan in all participants. The primary objective for double-blind treatment is to demonstrate the superiority of iptacopan compared to placebo in reducing proteinuria, while the primary goal of the open-label treatment is to evaluate the effects of iptacopan on proteinuria at 12 months. The study is expected to initiate soon and last till August 2023.

The APPLAUSE trial is designed as a double-blind, parallel-group study expected to enroll approximately 430 adult participants with IgAN and proteinuria ≥1g/day despite optimal stable RAS blockade. Participants will be randomly assigned in a 1:1 ratio to receive iptacopan 200mg bid or placebo. The primary objectives shall be to evaluate the effect of the study drug on UPCR at 9 months (interim analysis), and to evaluate its effect on slowing renal function decline by measuring the annualized total slope of estimated glomerular filtration rate over 24 months. The study is expected to finalize in January 2025.

C3 glomerulopathy: new treatment perspectives

Manuel Praga, Spain

C3 glomerulopathies (C3G) are a group of an ultra-rare kidney diseases occurring at an incidence of 1-3 cases per million only. The fundamental underlying pathogenetic mechanism of C3G is the dysregulation of the complement AP. This is generally driven by acquired factors, namely autoantibodies that target C3 or C5 convertases, which increase the half-life of these enzymes thus prolonging their activity. A less frequent cause for complement AP overactivation in C3G is genetic variation in complement-related genes.

The disease mainly affects children and younger adults, manifesting with nephrotic or nephritic syndrome, or asymptomatic urine abnormalities. The majority of C3G patients present with low serum C3 levels pointing to complement AP dysfunction.

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The diagnosis relies on identifying exclusive or predominant glomerular C3 deposits to confirm the two major subgroups of C3G - C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). These have overlapping clinical and pathological features, with C3GN primarily manifesting with amorphous mesangial, paramesangial, subendothelial and subepithelial deposits, while DDD is distinguished by the presence of dense osmiophilic intramembranous deposits on electron microscopy. In the majority of cases, C3G follows a chronic, indolent course with a 10-year renal survival of approximately 50% only. Nevertheless, cases presenting with rapidly progressive glomerulonephritis have also been described. The major predictors of renal function loss are tubular atrophy and interstitial fibrosis, baseline eGFR, and 24-h proteinuria.

There are currently no available disease-specific treatments for C3G and the upcoming KDIGO practice guideline on glomerular diseases relies on expert opinion when proposing common supportive measures in mild cases and immunosuppression in moderate to severe disease (based on biopsy finding and proteinuria level). In the absence of monoclonal gammopathy, moderate to severe C3G should be treated initially with mycophenolates (MMF or MPS), and in nonresponsive cases with eculizumab. The superiority of corticosteroids plus MMF over other immunosuppressives or eculizumab in the treatment of C3G has been substantiated in a recent study by the Spanish Group for the Study of Glomerular Diseases GLOSEN. In this cohort, relapses occurred after treatment discontinuation in one-third of the patients who had achieved remission with corticosteroids plus MMF, and a shorter treatment length of MMF was associated with a higher risk of relapse. Different case studies reported the effectiveness of eculizumab which appears to be beneficial in crescentic rapidly progressive forms of C3G, but its effect in milder forms of the disease seems to be limited. Kidney transplantation is a suitable option in C3G, although there is a high risk of recurrence in the allograft ranging from 60 to 85%. Further studies are warranted to bridge current knowledge gaps in understanding the genotype-phenotype correlations and ultimately provide a better classification and natural clinical course of the disease allowing innovative and more targeted therapies.

IgA nephropathy: novel therapeutic approaches

Jonathan Barratt, United Kingdom

IgA nephropathy is the most common form of primary glomerulonephritis worldwide with variable geographic distribution. It appears to be more frequent in Asians than in Caucasian populations.

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While the disease commonly presents with an indolent course, 50% of the patients eventually develop end-stage kidney disease requiring dialysis. Even though kidney transplantation is the preferred treatment option, a large proportion of patients develop recurrent disease-causing graft loss.

Despite advances in the understanding of the pathogenesis of IgAN, little progress has been made in its treatment with no targeted therapies approved so far. The soon-to-be-published KDIGO practice guideline on glomerular diseases advocates optimized goal-directed supportive care as the foundation of disease management in the majority of IgAN cases. This approach relies on data from the STOP-IgAN trial which did not observe significant improvement in the outcomes of patients with IgAN with the addition of immunosuppressive therapy to supportive care. Nevertheless, given the risk of progression to ESRD, the 2021 KDIGO guideline suggest that high-risk patients should either be offered enrollment in clinical trials (if available) or considered for systemic corticosteroid treatment provided that the risk/benefit profile is acceptable. According to these guidelines, the key priority for future research in this field is the evaluation of therapeutic strategies that minimize or avoid systemic corticosteroid exposure. KDIGO also recommends further investigation of the value of mycophenolate mofetil and hydroxychloroquine in different racial groups with IgAN and clinical disease severity.

Several new therapeutic approaches for IgAN are currently being evaluated in ongoing clinical trials with results expected in the coming years. Endothelin receptor antagonists sparsentan and atrasentan are being assessed in the PROTECT and ALIGN studies respectively, while the DAPA-CKD trial recently demonstrated that inhibition of sodium-glucose transporter-2 with dapagliflozin attenuates the risk of progression of chronic kidney disease in patients with IgAN. Other drugs currently being evaluated include a targeted-release corticosteroid formulation of budesonide (TRF-budesonide) and complement inhibitors. The topline results from the NeflgArd study demonstrated significant proteinuria reduction after 9 months of treatment with TRF-budesonide compared to placebo. Complement inhibitors under investigation are directed at the lectin or alternative pathway, which are predominantly involved in the pathogenesis of IgAN. Recently published results of a phase 2 study suggests that narsoplimab, a human monoclonal antibody against mannan-associated lectin-binding serine protease-2 (MASP-2), is safe, well-tolerated, and results in a clinically meaningful reduction in proteinuria and stability of eGFR in high-risk patients with advanced IgAN. Finally, a phase 2, proof of concept dose-ranging study evaluating iptacopan in IgAN has recently completed showing a significant dose-dependent reduction in proteinuria and a trend to eGFR stabilization compared to placebo at 12 weeks. Results from this study provided the foundation for the initiation of the currently recruiting APPLAUSE-IgAN trial. The future will hopefully deliver a number of novel therapeutics that may make it possible to stop the use of systemic corticosteroids. and thereby avoid the associated side effects, in IgAN and other complement-associated renal diseases.

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Further reading

Zipfel PF, Wiech T, Rudnick R, Afonso S, Person F, Skerka C. Complement Inhibitors in Clinical Trials for Glomerular Diseases. Front Immunol. 2019;10:2166. doi: 10.3389/fimmu.2019.02166.

Hou J, Markowitz GS, Bomback AS, et al. Toward a working definition of C3 glomerulopathy by immunofluorescence. Kidney Int. 2014;85(2):450-6. doi: 10.1038/ki.2013.340.

Sethi S, Fervenza FC, Zhang Y, et al. C3 glomerulonephritis: clinicopathological findings, complement abnormalities, glomerular proteomic profile, treatment, and follow-up. Kidney Int. 2012 Aug;82(4):465-73. doi: 10.1038/ki.2012.212

Fakhouri F, Le Quintrec M, Frémeaux-Bacchi V. Practical management of C3 glomerulopathy and Ig-mediated MPGN: facts and uncertainties. Kidney Int. 2020;98(5):1135-1148. doi: 10.1016/j.kint.2020.05.053.

Caravaca-Fontán F, Díaz-Encarnación MM, Lucientes L; Spanish Group for the Study of Glomerular Diseases GLOSEN. Mycophenolate Mofetil in C3 Glomerulopathy and Pathogenic Drivers of the Disease. Clin J Am Soc Nephrol. 2020;15(9):1287-1298. doi: 10.2215/CJN.15241219.

Caravaca-Fontán F, Trujillo H, Alonso M; C3G Study Group of the Spanish Group for the Study of Glomerular Diseases (GLOSEN). Validation of a Histologic Scoring Index for C3 Glomerulopathy. Am J Kidney Dis. 2021;77(5):684-695.e1. doi: 10.1053/j.ajkd.2020.11.011.

Ruggenenti P, Daina E, Gennarini A; EAGLE Study Group. C5 Convertase Blockade in Membranoproliferative Glomerulonephritis: A Single-Arm Clinical Trial. Am J Kidney Dis. 2019;74(2):224-238. doi: 10.1053/j.ajkd.2018.12.046.

Caravaca-Fontán F, Lucientes L, Cavero T, Praga M. Update on C3 Glomerulopathy: A Complement-Mediated Disease. Nephron. 2020;144(6):272-280. doi: 10.1159/000507254.

Rauen T, Eitner F, Fitzner C; STOP-IgAN Investigators. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. N Engl J Med. 2015;373(23):2225-36. doi: 10.1056/NEJMoa1415463. PMID: 26630142.

Anders HJ, Peired AJ, Romagnani P. SGLT2 inhibition requires reconsideration of fundamental paradigms in chronic kidney disease, 'diabetic nephropathy', IgA nephropathy and podocytopathies with FSGS lesions. Nephrol Dial Transplant. 2020:gfaa329. doi: 10.1093/ndt/gfaa329.

Barratt J, Rovin B, Diva U; PROTECT Study Design Group. Implementing the Kidney Health Initiative Surrogate Efficacy Endpoint in Patients With IgA Nephropathy (the PROTECT Trial). Kidney Int Rep. 2019;4(11):1633-1637. doi: 10.1016/j.ekir.2019.08.007.

Lafayette RA, Rovin BH, Reich HN, Tumlin JA, Floege J, Barratt J. Safety, Tolerability and Efficacy of Narsoplimab, a Novel MASP-2 Inhibitor for the Treatment of IgA Nephropathy. Kidney Int Rep. 2020;5(11):2032-2041. doi: 10.1016/j.ekir.2020.08.003.

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NEPHROLOGY EDUCATION PORTAL

ADVANCES IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: IMPROVING PATIENT CARE TO SLOW DISEASE PROGRESSION

SANOFI GENZYME

Welcome

Thomas Benzing, Germany

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease (~1/1000 births), and accounts for 5-10% of cases of end-stage kidney disease (ESKD). There is an urgent need to identify patients at high risk of rapid progression to ESKD, as they may be suitable for disease-modifying therapy. At a virtual satellite symposium held during the 2021 ERA-EDTA fully virtual congress, Professor York Pei and Professor Thomas Weimbs discussed recent research in genetics, kidney imaging, and dietary modifications, and provided insight into how these advances can be implemented to improve care for patients with ADPKD.

Clinical practice update and case presentations in ADPKD

York Pei, Canada

Diagnosis of ADPKD is typically through kidney imaging in the presence of a positive family history. Ultrasound is the most widely used technique using criteria derived from specific age ranges and the number of cysts detected. Magnetic resonance imaging (MRI) may be more appropriate for younger patients (age 16-40) and when more diagnostic certainty is needed—for example, when assessing family members as living kidney donors.

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ADVANCES IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: IMPROVING PATIENT CARE TO SLOW DISEASE PROGRESSION

SANOFI GENZYME

ADPKD is caused by mutations in the PKD1 (70-85% of cases) and in the PKD2 genes (15-35% cases). Professor Pei explained that mutations of the genes affect the protein structure in two ways. There may be a truncated protein product, which includes premature stop codon mutations and frameshift splice site mutations and can be considered as inactivating mutations. The second class of mutation are "non-truncating" with regard to the protein product and include single amino acid changes resulting in a nonsynonymous change of a highly conserved amino acid, as well as inframe insertion or deletions ("indels"). The resulting product may be dysfunctional rather than non-functional.

In the Toronto Genetic Epidemiology Study, about 40% of cases were due to protein-truncating PKD1 mutations, which were the most severe with about half of patients requiring renal replacement therapy by age 50. Of remaining mutations, 31% were PKD2 (the least severe prognosis), and 27% non-protein-truncating PKD1 mutations. PKD1 inframe indels accounted for 4%. However, the accuracy of mutation class-based prognosis is limited when applied to individuals, because extreme kidney disease discordance can occur even in affected relative pairs harboring the same ADPKD mutation. In one study, for example, extreme discordance was found in at least 12% of 307 ADKPD families regardless of the underlying mutated gene or mutation class.

Current clinical indications for genetic testing are lack of apparent family history, equivocal diagnostic imaging, syndromic forms of PKD, disease exclusion in young at-risk subjects (<25 years), living-related donor exclusion, application for life insurance, and prenatal/preimplantation diagnosis. According to Professor Pei, evolving indications may include early onset of severe disease, atypical imaging patterns suggestive of somatic mosaicism, marked within-family variability of disease severity suggesting a possible genetic modifier effect, and disease discordance between imaging and GFR. In the future, by using next generation sequencing (NGS) technology, with a gene panel containing both PKD1 and PKD2, as well as rare cystic disease genes and potential modifiers, it should be possible to advance our understanding of the clinical variability for ADPKD. Turning to kidney imaging-based prognostication, Professor Pei noted that in most patients with ADKPD, eGFR remains stable and within the normal range for three to four decades, yet total kidney volume (TKV) increases on average at 5% a year in adults. After eight years, TKV explained about 42% of the variance in eGFR decline. TKV appears to capture and serve as the best currently available prognosticator of eventual eGFR decline.

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ADVANCES IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: IMPROVING PATIENT CARE TO SLOW DISEASE PROGRESSION

SANOFI GENZYME

The Mayo Clinic Imaging Classification uses age and height-adjusted TKV to classify patients with ADPKD into five at-risk groups based on predicted TKV growth and kidney function decline. Individuals in Classes 1A and 1B have slower kdiney function decline, while Classes 1C, 1D and 1E are associated with more rapid decline in eGFR. When using this classification, it is important to exclude the atypical Class 2 imaging patterns that are present in about 9% of patients. In Class 2, Group A, one or more parts of the kidney are completely spared of the cystic process and the cyst-affected area is unilateral, asymmetric, segmental, or lobsided. In Class 2, Group B, while cysts may be present, decline in eGFR is predominantly caused by loss of kidney mass due to atrophy. It also important to bear in mind that it is possible for patients with ADPKD to have another, superimposed kidney disease (e.g. diabetic nephropathy).

When treating ADPKD, general recommendations are increased water and lower sodium intake, good blood pressure control, and dialysis and kidney transplantation after progression to kidney failure. Patients with rapidly progressive ADPKD may be considered for entry into a clinical trial or for disease-modifying therapy.

Dietary interventions in autosomal-dominant polycystic kidney disease

Thomas Weimbs, United States of America

ADPKD kidneys are exposed to the threat of microcrystals that can precipitate during the concentration of the primary urinary filtrate. In humans, the most significant are calcium oxalate, calcium phosphate, and uric acid crystals. These crystals can damage the epithelium, occlude urine flow, and eventually lead to microscopic kidney stone formation.

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ADVANCES IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: IMPROVING PATIENT CARE TO SLOW DISEASE PROGRESSION

SANOFI GENZYME

Professor Weimbs reported that in rat models when microcrystals lodge in kidney tubules, they activate signalling pathways such as mTOR. This leads to tubule dilation to facilitate the excretion of the crystals into the urine. In healthy rodent models, signalling switches off when crystals are eliminated and normal tubule diameter and flow are re-established. However, when PKD rats are challenged with either hydroxyproline or glyoxylate (both metabolic precursors of oxalate) in the drinking water, or with a high phosphate diet, the results are calcium oxalate and calcium phosphate precipitation, respectively, in the urine and more rapid cyst growth secondary to persistent mTOR activation.

These data suggest that it might be possible to ameliorate PKD disease progression by suppressing crystal formation in the kidneys. Citrate is a natural antagonist of calcium crystal precipitation, and can chelate and prevent calcium oxalate and calcium phosphate precipitation. In pre-clinical studies, when PKD rats are treated with increasing amounts of citrate in the drinking water, there is a dose-dependent and very significant improvement in cyst size and density.

Patients with ADPKD frequently have hypocitraturia and low urine pH. Kidney stones are also common, and their presence increases the rate of disease progression. Hyperuricemia and gout are also common, and are correlated with faster ADPKD progression. Preventive approaches might include control of dietary intake of oxalate, phosphate and uric acid (from purines). Other possibilities are administration of calcium/magnesium with food to reduce absorption of oxalate and phosphate, and supplementation with alkaline citrate to raise urine pH and urine citrate level.

Ketosis may be another promising dietary approach. In a PKD rat model, time-restricted feeding (an eight-hour feeding window) without calorie reduction has been shown to be highly effective in inhibiting mTOR signalling, proliferation, and fibrosis, with reductions in kidney-body weight ratio and cystic area. Similarly, compared with a normal diet, a five-week ad libitum ketogenic diet (high fat, normal protein, and very low carbohydrate) had a dramatic effect in regressing the renal cyst burden. During ketosis, the body changes metabolism from glucose consumption to using fat reserves, in particular fatty acids and the ketones produced by the liver. Supplementation of PKD rats' drinking water with the ketone beta-hydroxybutyrate (BHB) strongly inhibits disease progression even when the rats are allowed their usual high carbohydrate ad libitum diet.

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These animal models suggest that ketosis, achieved by a time-restricted diet, intermittent fasting, or a ketogenic diet, or supplementation with BHB, might offer adjunctive approaches in patients with ADPKD. In responses to a questionnaire of patients with ADPKD, most of the 131 respondents not only reported significant improvements in body weight, but also in PKD-related health issues, such as blood pressure.

Professor Weimbs commented that these results are surprising when considered in the context of a relentlessly progressive disease. He added that, while this self-selected group reported few or no problems in adherence to the dietary pattern, this is unlikely to apply to less motivated patients. KETO-ADKPD (NCT04680780) is a prospective study that will randomize participants to either control (no diet), a classical ketogenic diet, or intermittent fasting. The study is designed to investigate the feasibility, safety and efficacy of dietary interventions on ADPKD, and to determine which of the two diets is the optimal approach.

A second clinical trial is investigating Ren.Nu, Keto-Adaptive Nutrition for Polycystic Kidney Disease (https://ren-nu.org). This dietary program has been devised specially for PKD patients by Professor Weimbs' group in collaboration with registered dietitians, and is a 12-week remote training program involving a plant-dominant ketogenic diet, and dietary supplementation with a medical food combining BHB and citrate. The clinical trial is a prospective, 52-week, longitudinal controlled study, and its results will contribute to the growing body of evidence for dietary interventions in ADKPKD.

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Further reading

Clinical practice update in ADPKD

Pei Y & Watnick T. Diagnosis and screening of autosomal dominant polycystic kidney disease. Adv Chronic Kidney Dis 2010;17(2):140-52

Pei Y, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2015;26(3):746-53.

Gansevoort RT, et al. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. Nephrol Dial Transplant 2016;31(3):337-48.

Lanktree MB, et al. Evolving role of genetic testing for the clinical management of autosomal dominant polycystic kidney disease. Nephrol Dial Transplant 2019;34(9):1453-1460.

Irazabal MV, et al. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. J Am Soc Nephrol 2015;26(1):160-72

Dietary interventions in ADPKD

Torres JA, et al. Crystal deposition triggers tubule dilation that accelerates cystogenesis in polycystic kidney disease. J Clin Invest 2019;129(10):4506-4522

Torres JA, et al. Ketosis Ameliorates Renal Cyst Growth in Polycystic Kidney Disease. Cell Metab 2019;30(6):1007-1023.e5

Kipp KR, et al. A mild reduction in food intake slows disease progression in an orthologous mouse model of polycystic kidney disease. Am J Physiol Renal Physiol

2016;310(8):F726-F731

Warner G. Food Restriction Ameliorates the Development of Polycystic Kidney Disease. J Am Soc Nephrol 2016;27(5):1437-47

NEPHROLOGY EDUCATION PORTAL

WHEN DELAYS COULD LEAD TO ESKD. IDENTIFYING AND MANAGING PRIMARY HYPEROXALURIA IN CLINICAL PRACTICE

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Welcome & Introduction

Felix Knauf, Germany

Primary hyperoxaluria (PH) is a group of rare metabolic disorders caused by recessive gene mutations. There are three main types, PH1, PH2 and PH3, all characterized by oxalate overproduction in the liver. PH1 is the most severe form and the most frequent, accounting for 70% of cases. Delayed diagnosis is common, and there may be five years between presentation and diagnosis. At a virtual symposium held during the 2021 ERA-EDTA 2021 fully virtual congress, Professor Felix Knauf, Professor Rezan Topaloglu, and Professor Daniel Fuster discussed the importance of early diagnosis, current approaches to management, and new therapeutic innovations designed to improve outcomes in PH1.

The clock is ticking: When and how to evaluate a referral for potential hyperoxaluria

Rezan Topaloglu, Turkey

In North America and Europe, estimated diagnosed prevalence of PH1 is 1-3 per million population, though it is likely underdiagnosed due to its heterogeneous clinical presentation, and it accounts for about 1% of paediatric end-stage kidney disease (ESKD) in registries in Europe, USA and Japan. Prevalence is higher in areas of Middle East, North Africa and other countries where consanguineous marriages are common.

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Professor Topaloglu reported that nephrocalcinosis and ESKD occur most frequently in PH1 compared to PH2 and PH3. Adults with PH1 present with recurrent kidney stones, while children present with recurrent kidney stones and progressive chronic kidney disease (CKD). Infantile oxalosis has the worst prognosis: 50% have ESKD at diagnosis and 80% progress within three years.

According to OxalEurope recommendations, PH1 should be considered in any child with a first kidney stone, in adults with recurrent stone disease, and in any patient with nephrocalcinosis, particularly when associated with decreased GFR. Investigation for PH is also recommended if there are oxalate crystals (calcium oxalate monohydrate) in any biological fluid or tissue. Screening is recommended in relatives of index cases, but not in the general population. Genetic testing is recommended in subjects with phenotypic characteristics of PH1, with mutation analysis extended to siblings and parents. Prenatal diagnosis using mutation analysis should be offered to parents of an affected child.

In biochemical and enzymological assessment, OxalEurope recommends measuring 24-hour urine oxalate, creatinine and glycolate in any patient with a possible diagnosis of PH1 and preserved renal function. Plasma oxalate (POx) should be measured in CKD patients. If genetic testing is inconclusive, measurement of AGT enzyme activity is recommended.

According to Professor Topaloglu, diagnostic delay is a key challenge in PH1, and is due to a low index of suspicion because of the condition's rarity and nonspecific clinical presentation, and variability in age of onset and severity. There is also limited access to urinary metabolic and genetic screening in some countries. Diagnosis may also appear less urgent in adults, because symptoms are not as overt as in infant and paediatric patients. Adults may have a sudden and rapid progression if PH1 is not addressed adequately. Diagnostic delay—and its consequences for patients—may be avoided by greater awareness of the signs and symptoms of PH1 and by facilitating testing of appropriate patients.

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Reducing oxalate to reduce the risk of ESKD

Felix Knauf, Germany

Professor Knauf agreed that early diagnosis of PH1 is essential, as delay increases the risk of oxalos-related complications, including urolithiasis with/without nephrocalcinosis and its recurrence post-renal transplantation. Even before there is substantial loss of kidney function (CKD stages 1-3a), there is a significant inverse correlation between eGFR and POx in patients with PH. Rate of disease progression is variable, but almost all patients experience kidney failure by age 60. At eGFR <45 ml/min/1.732 urinary excretion of oxalate cannot match the rate of oxalate production, and oxalate accumulates in the plasma and tissues, resulting in systemic effects on major organs, skin, blood vessels, nerves, muscles, bones and eyes.

PH1 patients require lifelong surveillance. At eGFR > 60 ml/min/1.732, kidney function should be tested at least annually, together with renal ultrasound, fundoscopy and urinalysis to identify urinary oxalate (UOx). These investigations, plus POx, are recommended annually or more frequently when eGFR is 30-60 ml/min/1.732. At <30 ml/min/1.732, patients require frequent monitoring of POx and kidney function, together with X-ray of long bones, electrocardiogram, echocardiogram, haemoglobin, physical examination, and thyroid function testing.

Professor Knauf noted that most current management approaches do not target the cause of PH1. Dietary restrictions aim to minimize oxalate absorption but have limited impact. Non-surgical management includes hyperhydration targeted at preventing urinary calcium oxalate (CaOx) supersaturation, minimizing CaOx crystallization and stone formation in the kidney, with alkali citrate to reduce UOx saturation to inhibit crystallization. Pyridoxine can reduce hepatic oxalate production in patients with some mutations, normalizing oxalate production in a small subset of such patients.

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Patients with kidney failure need frequent, intensive dialysis, initially haemodialysis (HD) 6-7 hours daily. If this is insufficient, patients may need 6-8 hours daily six times per week plus continuous daily peritoneal dialysis, or nocturnal dialysis 8-10 hours daily. Combined liver-kidney transplant (LKTx), preferably simultaneously, is the optimal treatment for patients on dialysis, and results in better graft survival compared to kidney-alone transplantation (KTx). Pre-emptive LTx normalizes oxalate production before advanced CKD, but short- and long-term complications must be considered. Although it restores renal function, isolated KTx does not address the underlying metabolic defect, though it may be an option when there is a full response to pyridoxine.

Professor Knauf concluded that the complications, fear of disease progression, and burdens of intensive monitoring and treatment can have a psychological and emotional impact on patients with PH1 and their family and caregivers and causes considerable medical and financial burdens for families. Fortunately, a therapeutic revolution is underway. Innovative drugs are being tested in clinical trials, with preliminary data showing impressive efficacy in reducing hepatic overproduction of oxalate.

RNAi Therapeutics: A new approach to managing primary hyperoxaluria

Daniel Fuster, Switzerland

Lumasiran (approved by the European medicines Agency in November 2020) and Nedosiran (still in clinical development) are two new PH treatments that use a new approach: RNA interference (RNAi). Professor Fuster explained that RNAi is a natural pathway regulating the level of gene production by interfering with messenger RNA (mRNA), which carries the instructions for making new protein. The process is post-transcriptional but pre-translational, so there is no change at the genome level, and it differs from other therapeutic approaches that generally target proteins.

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The RNAi pathway can be exploited pharmaceutically by delivering small interfering RNAs (siRNAs) to cells to target and degrade specific mRNA in, for example, liver cells. Lumasiran is a subcutaneously delivered, double-stranded siRNAI, that inhibits glycolate oxidase (GO) production by targeting HAO1 RNA. Reducing hepatic GO levels lowers the levels of glyoxylate, so decreasing oxalate production.

The phase III, double-blind, placebo-controlled ILLUMINATE-A study included 39 adults and children aged ≥ 6 years with PH1 and eGFR ≥ 30 ml/min/1.732. Patients were randomized to either Lumasiran (3 mg/kg body weight) given once monthly for three doses, followed by maintenance doses given once every three months beginning one month after the last loading dose, or matching placebo. During the 54-month extension period, all patients received Lumasiran 3.0 mg every six months.

Professor Fuster reported that on the primary endpoint of percentage change in 24-hour UOx secretion from baseline, the least-squares mean difference (Lumasiran minus placebo) was -53.5 percentage points ($p<0.001$), with a reduction in the Lumasiran group of 65.4%, an effect seen as early as Month 1. Between-group differences for all tested secondary endpoints were also significant. The difference in the percent change in the POx level (Lumasiran minus placebo) was -39.5 percentage points ($p<0.001$). In the Lumasiran group, 84% of patients had 24-hour urinary oxalate excretion no higher than 1.5 times the upper limit of the normal range at Month 6, compared with 0% of the placebo group ($p<0.001$).

At 6 months, nephrocalcinosis grade improved in 3 of 22 patients in the Lumasiran group as compared with 0 of 12 in the placebo group. Kidney stone event rates decreased during the treatment period in the Lumasiran arm, while remained stable in the placebo group.

All adverse events (AE) were mild or moderate, most commonly mild and transient injection site reactions. There was 1 discontinuation not drug related (fatigue and disturbance in attention), no adverse event leading to withdrawal from the trial, no clinically relevant changes in laboratory measures, vital signs or ECG, or deaths related to Lumasiran.

Based on the results ILLUMINATE A and B trials, Lumasiran has been granted European marketing authorization for the treatment of PH1 in all age groups. Nedosiran is the second RNAi agent in development. It targets mRNA encoding the enzyme LDH, the last step in hepatic oxalate production, and has the potential to treat PH2 and PH3 in addition to PH1. In the PHYOX1 phase 1 study, Nedosiran was well tolerated and associated with approximately reduction of 70% in UOx. Clinical trials PHYOX2 and PHYO3 are ongoing.

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Further reading

Early diagnosis and diagnostic delay

Cochat P & Rumsby G. Primary hyperoxaluria. N Engl J Med 2013;369(7):649-58

Hopp K, et al. Phenotype-Genotype Correlations and Estimated Carrier Frequencies of Primary Hyperoxaluria. J Am Soc Nephrol 2015;26(10):2559-70

Lieske JC, et al. International registry for primary hyperoxaluria. Am J Nephrol 2005;25(3):290-6

Cochat P, et al. Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant 2012;27(5):1729-36

Reducing oxalate: current treatment

Milliner DS, et al. Plasma oxalate and eGFR are correlated in primary hyperoxaluria patients with maintained kidney function-data from three placebo-controlled studies. Pediatr Nephrol 2021;36(7):1785-1793

Sas DJ, et al. Recent advances in the identification and management of inherited hyperoxalurias. Urolithiasis 2019;47(1):79–89

Lawrence JE & Wattenberg DJ. Primary Hyperoxaluria: The Patient and Caregiver Perspective. Clin J Am Soc Nephrol 2020;15(7):909–911

Metry EL, et al. Transplantation outcomes in patients with primary hyperoxaluria: a systematic review. Pediatr Nephrol 2021 Apr 8. Online ahead of print

A new approach: RNAi therapeutics

Liebow et al. An Investigational RNAi Therapeutic Targeting Glycolate Oxidase Reduces Oxalate Production in Models of Primary Hyperoxaluria, J Am Soc Nephrol 2017;28(2):494-503

Garrelfs SF, et al. Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1 N Engl J Med 2021;384(13):1216-1226

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NEPHROLOGY EDUCATION PORTAL

TARGETING CKD PATIENTS' QUALITY OF LIFE

FRESENIUS KABI
caring for life

Welcome and introduction

Giorgina Piccoli, France

Quality of life is closely linked to nutrition – "because we are, what we eat", explained symposium chairwoman Prof. Giorgina Piccoli. Being on a diet is not necessarily painful, she was keen to emphasize – it is about changing lifestyle and can also be fun! There is more to quality of life (QoL) than just nutrition, however.

Living well with kidney disease - Importance of patients' empowerment

Kamyar Kalantar-Zadeh, United States of America

Prof. Kalantar-Zadeh focused on patients' empowerment as another important aspect of QoL, which was also the theme of World Kidney Day 2021. Living with chronic kidney disease (CKD) is not always easy, however CKD is associated with unpleasant symptoms which affect patients and their families. It is therefore important to address patients' priorities, values and goals to enable them to decide on the appropriate choices for their health, including diet. One important question is: when to start renal replacement therapy? The process can be arduous and burdensome; therefore, many patients opt instead for supportive treatment and conventional care without dialysis. "*We have tools for conservative and preventive management and can offer a gradual transition to dialysis*." Prof. Kalantar-Zadeh pointed out that empowering patients, brings them hope. "*The key word here is choice. If I give my patients more than one option, my patient will be more hopeful*." Furthermore, the approach of making a gradual transition to dialysis prolongs dialysis-free time and thus achieves better survival and quality of life by effective management of renal and non-renal comorbidities, such as cardiovascular events.

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Diet is an important factor in this context: A low dietary protein intake decreases intracapillary pressure and thus preserves kidney function. The MDRD study showed that people who were randomized to a lower protein intake initially had a loss of Glomerular Filtration Rate (GFR), but in the long term the decrease was very slow. On the other hand, there are concerns about malnutrition, of course. Prof. Kalantar-Zadeh pointed out that 0.46 g of protein per kilogram body weight per day is really all a normal healthy adult requires if essential amino acids are provided, whereas the current recommended dietary allowance is 0.8 g. He emphasized that 50% of the protein intake should be plant-based, "*vegan proteins have an adequate biological value – and potassium should not be a problem, especially since potassium binders can be used*". Prof. Kalantar-Zadeh´s plea was to fight the dogma of avoiding fruits and vegetables in CKD.

He also recommended that adding keto-analogues of amino acids (AA) should be considered. "*These allow us to go as low as 0.3-0.4 g/kg/day and ensure that the patients have an adequate supply of all nine essential amino acids.*" In one study, 56 elderly uremic patients were randomized to a low protein diet plus keto-analogues of AA versus dialysis initiation. The result showed that the diet group had slightly better survival, although the study failed to show superiority.

Prof. Kalantar-Zadeh noted that, when dialysis is needed, incremental dialysis transition (once to twice per week) is the goal, which can be reached with continued restricted protein diet on dialysis-free days, potentially supplemented with keto-analogues, in order to preserve residual kidney function longer. "*This expands patients' choices, empowers the patients and brings hope*", he concluded.

Tailored nutritional approach to improve adherence and QoL in CKD patients

Giorgina Piccoli, France

One conclusion drawn in Prof. Giorgina Piccoli's talk was that low-protein diets are feasible in many patients, including the elderly and those with comorbidities. However, there is no '*one diet for all*', and experience from practice shows that the success rate of 'prescribing a diet' is rather low. Prof. Piccoli explained the concepts of compliance, adherence and concordance, and remarked that this last one is about offering choices and setting up the right goals. Its guiding principle is that patient and healthcare providers must work together to find the best possible solution for the patient's condition.

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The MDRD trial produced some conflicting results and was unable to prove the effect of a low-protein diet. As Prof. Piccoli pointed out, this might have been due to a lack of compliance. When the results were analyzed on the basis of the amount of protein actually consumed, one benefit became obvious: Each 0.2 g less protein/kg/day was associated with a 29% slower rate of GFR loss (<0.001). But how can more patients adhere to a lower protein intake? Deferring dialysis initiation might be a powerful incentive, but in one study, only 15% of the patients could be randomized, because they were able to adapt to the diet. The rest could not, and they also knew about the possible benefits.

What lessons can be learned? First, the right target must be set, and the patient needs motivation. It is then important to adapt to local habits and rediscover traditions, because the quantity of protein in our normal diets has increased only in the two last generations. Individual habits and preferences must also be reflected. "*Diet is a system, and we have to offer different choices – the key is an individual approach, because different patients follow different diets*", said Prof. Piccoli. She highlighted a multiple step approach: (1) assess the habit, (2) normalize the protein intake, (3) then reduce the protein intake further, (4) implement keto-analogues of AA, if needed, and (5) reduce further, if possible. The results of this flexible and stepwise approach aiming at progressive reduction were shown to be very good in terms of compliance. Furthermore, new studies have shown that patients on a protein-restricted diet report a good QoL.

KDOQI guideline 2020 recommendations for nutrition in CKD - Practical considerations

Denis Fouque, France

Prof. Denis Fouque summarized the key aspects of the 2020 update of the KDOQI Clinical Practice Guideline on Nutrition in CKD, concentrating thereby on protein and energy recommendations and some practical considerations.

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TARGETING CKD PATIENTS' QUALITY OF LIFE

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He pointed out that, in adults with CKD, who are metabolically stable, an energy intake of 25-35 kcal/kg ideal body weight is recommended. Whether intake should be 25 or 35 is dependent on many factors, among them age, gender, level of physical activity, body composition, and CKD status. One should be aware that a frail elderly patient needs less energy than a young active person. However, all patients should be routinely monitored if dietary energy intake is adequate or the diet should be modified accordingly if it is not. It is important to educate patients and motivate them.

Counselling is also an important factor with regard to protein intake. In non-diabetic, non-dialysis CKD patients, the guidelines recommend protein restriction with or without keto-analogues of AA under clinical supervision in order to reduce risk of end stage renal disease and death – and improve QoL. The protein intake should be 0.55 to 0.6 g dietary protein per kg ideal body weight per day. Alternatively, the guidelines recommend a very low-protein diet providing 0.28 to 0.43 g dietary protein per kg ideal body weight per day, provided that keto-analogues of AA are given to meet protein requirements. This recommendation is based on a high level of evidence, as Prof. Fouque pointed out. For diabetics, the guideline recommends an intake of 0.6 to 0.8 dietary protein per kg ideal body weight per day to maintain a stable nutritional status and optimize glycemic control. This recommendation mirrors expert opinion, as some data are missing.

Like Prof. Piccoli before, Prof. Fouque pointed out that a stepwise approach to reduced protein intake (from an omnivorous to a mainly vegan diet) has proven more successful, but this requires progressive personal care – and more renal dieticians are needed. He emphasized that the key to success is **individualization**.

2020 Award winning research project presentation: Effects of Keto-Analogues supplementation on Quality of Life in Palliative Care of ESKD Patients

Paramat Thimachai, Thailand

Dr. Paramat Thimachai briefly summarized his study project on the effects of keto-analogues supplementation on QoL in palliative care of end-stage kidney disease patients, which won the **2020 Keto-Analogues Research Award**.

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It is known that keto-analogues of AA in combination with a reduced protein diet can improve uremic symptoms, slow down the decline in GFR and delay time to dialysis and consequently, improve the QoL. This was the basic hypothesis of the study project that Dr. Thimachai and colleagues from Phramongkutklao Hospital and College of Medicine in Bangkok, Thailand will initiate.

The plan is to include CKD stage 5 patients who are not on dialysis, and to compare the effect of a very low-protein diet **plus** keto analogues with the effects of a low-protein diet in terms of QoL (primary endpoint). Further endpoints are changes of metabolic profile, nutritional status, time to initiate dialysis and mortality. After a four-week run-in phase under standard care, the patients will be randomized (n=72 in each group). After six months, QoL will be assessed with the 'KDQOL-36' questionnaire, which has been proved to have good validity and reliability in Thai CKD patients.

Further reading

Levey AS, Greene T, Beck GJ et al. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. J Am Soc Nephrol 1999; 10 (11): 2426-39

Kalantar-Zadeh K, Wightman A, Liao S et al. Ensuring Choice for People with Kidney Failure — Dialysis, Supportive Care, and Hope. N Engl J Med 2020; 383:99-101

Brunori G, Viola BF, Parrinello G et al. Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly: a prospective randomized multicenter controlled study. Am J Kidney Dis 2007; 49 (5): 569-80

Garneata L, Stancu A, Dragomir D et al. Ketoanalogue-Supplemented Vegetarian Very Low-Protein Diet and CKD Progression. J Am Soc Nephrol 2016; 27 (7): 2164-76

Fois A, Chatrenet A, Cataldo E et al. Moderate Protein Restriction in Advanced CKD: A Feasible Option in An Elderly, High-Comorbidity Population. A Stepwise Multiple-Choice System Approach. Nutrients 2018; 11 (1): 36

Piccoli GB, Di Iorio BR, Chatrenet A et al. Dietary satisfaction and quality of life in chronic kidney disease patients on low-protein diets: a multicentre study with long-term outcome data (TOrino-Pisa study). Nephrol Dial Transplant 2020; 35 (5): 790-802

Fois A, Torreggiani M, Trabace T et al. Quality of Life in CKD Patients on Low-Protein Diets in a Multiple-Choice Diet System. Comparison between a French and an Italian Experience. Nutrients 2021; 13(4): 1354

Ikizler TA, Burrowes JD, Byham-Gray LD et al. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. Am J Kidney Dis. 2020;76 (3 Suppl 1): S1-S107

NEPHROLOGY EDUCATION PORTAL

GLYCATED ALBUMIN: A TOOL AT CLINICIANS' HAND IN MANAGING DIABETIC NEPHROPATHY

Werfen
Diagnostic Solutions for Life

Welcome & Introduction

Loreto Gesualdo, Italy

As Barry I. Freedman pointed out, assessing glycaemic control in patients with advanced CKD/ESRD is complex due to changes in glucose homeostasis, potential effects of kidney disease on glycemia assays, and altered pharmacokinetics of diabetic medications. But assuming that glycaemic control is important for outcomes of the patients, we believe the ideal assay should predict risk for cardiovascular events, survival and hospitalization. Although HbA1c has been the gold standard in patients with normal kidney function, it has been greatly questioned in patients with advanced nephropathy, particularly end-stage kidney disease (ESKD) patients on dialysis and those with a eGFR below 30 ml/min/1.73 m2. The reason is that HbA1c is determined by an interaction between haemoglobin in red cells and glucose, but in ESKD there is severely shortened red blood cell survival, ESKD patients suffer from erythropoietin, blood loss due to the dialysis, sometimes they even require blood transfusions. All this has an impact and can lower the HbA1c.

Current clinical practice in the management of Diabetic Kidney Disease

Barry I. Freedman, United States of America

Like HbA1c, glycated albumin (GA) is a glycated protein that reflects the status of blood glucose control more rapidly than HbA1c. It was therefore suggested, in a 2007 paper by Inaba et al., that GA is a far better indicator than HbA1c in haemodialysis patients with diabetes. It was shown that, in patients with no kidney disease, HbA1c was above 8%, and above 6% in dialysis patients, even though both groups had the same blood sugar levels. GA, on the other hand, was similar in both groups and obviously not impacted by kidney disease. The study group also analysed the percentage of haemodialysis patients with very good and with poor glycaemic control.

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GLYCATED ALBUMIN: A TOOL AT CLINICIANS' HAND IN MANAGING DIABETIC NEPHROPATHY

When analysis was based on HbA1c, 57.1% of the patients seemed to have excellent blood sugar control, whereas it was only 28.3% when GA was used. The difference was even more striking in those with poor glycaemic control. According to HbA1c levels, only 7.1% had poor control, whereas the figure was 36.4% when GA levels were analysed. "Nephrologists are given a false sense of security when they use HbA1c only, due to its false reduction in ESKD patients", warned Barry I. Freedman.

Nor does higher HbA1c appear to have any reliable prognostic value in this patient group. In one study, higher unadjusted HbA1c was associated with improved survival in ESKD, due to better nutrition, but when adjusted for 20 additional co-variants, higher HbA1c was associated with poorer survival in ESKD. GA, on the other hand, was an accurate predictor of patient survival and rates of hospitalization in ESKD, with minimal or no adjustment. In one published metanalysis, it appears that HbA1c > 8.5% in ESKD patients is associated with a high risk of mortality, but it has to be kept in mind that HbA1c would probably be about 10.5% in diabetes patients without kidney disease and the same blood glucose levels. "We therefore believe that GA is a much more accurate measure of glycaemic control in patients with severe nephropathy", Freedman concluded.

Importance of Best Practice Guidelines for Dialysis therapy as a tool for improving care of Diabetic Nephropathy patients

Masanori Abe, Japan

Masanori Abe emphasized again the importance of reliable glycaemic control in patients with diabetes and pointed out that HbA1c underestimates glycaemic status in patients on dialysis, whereas GA allows a more reliable assessment.

In an observational cohort of 178 haemodialysis patients with diabetes, the relationship between GA and all-cause mortality in patients with (n = 70) and without (n = 108) cardiovascular disease (CVD) were analysed. The subjects were divided into three categories based on the GA value at the start of the study. During the four-year follow-up, 24 of 108 (23.3%) patients without CVD and 30 of 70 (42.8%) patients with CVD died. GA, in addition to logCRP and age, was independently associated with mortality in all patients. Kaplan-Meier analysis showed lower GA levels less than 20% to be a significant predictor of lower mortality in the group without cardiovascular disease, but not in the CVD group.

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In the Japanese Best Practice Guidelines, GA is therefore recommended as an index of glycaemic control in patients on haemodialysis. The target level is <20%, but in patients with CVD or those who have a tendency towards hypoglycaemia, <24% is recommended as a tentative target level. At the beginning of the haemodialysis session, postprandial plasma glucose should also be measured, the target level stated in the guidelines being <180-200 mg/dl.

Masanori Abe spoke about the phenomenon of burnout diabetes, which describes the fact that some patients have lower HbA1c levels (<6%) and glucose levels after having to start dialysis treatment. According to data from the U.S., the incidence of burnout diabetes was about 40% in a cohort of 56,000 patients, and Japanese data showed a similar incidence. To study this phenomenon, Masanori Abe and colleagues conducted a study with patients with diabetes on HD whose HbA1c levels were measured and whose antidiabetic therapy was recorded. In the HbA1cone cohort, HbA1c levels were measured, whereas HbA1c and GA levels were measured in the GA cohort. The incidence of burnout diabetes (defined as HbA1c <6% or HbA1c <6% and GA <16%) was significantly different in both groups: 18.7% in the HbA1c group, but only 5.4% in the group in which GA was also considered. "The rate is extremely low", many patients with diabetes might not experience burn-out diabetes even when they have progressed to ESKD and required dialysis Masanori Abe concluded.

Personalized Medicine approaches in Diabetic Kidney Disease

Paola Pontrelli, Italy

Paola Prontrelli emphasized the importance of precision medicine, which is also being applied increasingly in the field of nephrology. Its goals are (1) to define specific molecular mechanisms driving the patient's disease, (2) to characterize and identify those patients who are at high risk and (3) to identify patients who respond (or do not respond) to a specific treatment.

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In the context of diabetes, precision medicine represents both an opportunity and a challenge. Diabetes exemplifies the problem of imprecise phenotype – the illness can affect the function of different organs, such as pancreas, liver, muscles, brain, and the kidneys. In 2020, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) launched the "Precision Medicine in Diabetes" initiative, with the aim of developing precision diagnosis tools and precision therapeutics. Various consortia and projects play an important role within this initiative, among them the "BEAt DKD" project which wants to pave the way for precision medicine in the field of diabetic nephropathy. The biggest challenge is the fact that DKD is a clinical diagnosis with rather imprecise diagnostic criteria so far, the main markers being GFR and albuminuria.

However, these markers do not indicate the specific defect which causes the impairment of kidney function in the patient and, consequently, which is the best treatment for that patient. It is important, rather, to know more about the underlying histopathological characteristics of the damage, which have been divided into three different classes characterized by: the presence of diabetic glomerulosclerosis (class 1), prevailing vascular (arteriosclerotic) and ischemic glomerular changes (class 2), other glomerulonephritides superimposed on diabetic glomerulosclerosis (class 3a), or glomerulonephritides without the presence of diabetic glomerulosclerosis (class 3b). More than 45% of the patients are affected by class 3 – which means they are affected by glomerular disease, not by diabetic glomerulosclerosis.

As Paola Prontrelli pointed out, it is therefore essential to develop novel and more specific clinical and molecular markers in diabetes patients, specifically calibrated for histopathology, in order to better sub-classify the patients and estimate prognosis and treatment. As she explained, GA is an important tool that meets these requirements. It is not only more precise in monitoring glucose control, but can also identify real diabetic nephropathy and has predictive value, in that it reflects renal tubulopathy in subjects with T2DM with normo-albuminuria and normal eGFR and can therefore predict kidney tissue damage in diabetic patients.

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GLYCATED ALBUMIN: A TOOL AT CLINICIANS' HAND IN MANAGING DIABETIC NEPHROPATHY

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Further reading

Inaba M, Okuno S, Kumeda Y et al. Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: effect of anemia and erythropoietin injection. J Am Soc Nephrol 2007; 18 (3): 896-903

Kalantar-Zadeh K, Kopple JD, Regidor DL et al. A1C and survival in maintenance hemodialysis patients. Diabetes Care 2007; 30 (5): 1049-55

Freedman BI, Andries L, Shihabi ZK et al. Glycated albumin and risk of death and hospitalizations in diabetic dialysis patients. Clin J Am Soc Nephrol 2011; 6 (7): 1635-43

Hill CJ, Maxwell AP, Cardwell CR, et al. Glycated hemoglobin and risk of death in diabetic patients treated with hemodialysis: a meta-analysis. Am J Kidney Dis. 2014; 63(1): 84-94.

Inaba M, Maekawa K, Okuno S et al. Impact of atherosclerosis on the relationship of glycemic control and mortality in diabetic patients on hemodialysis. Clin Nephrol 2012; 78 (4): 273-80.

Nakao T, Inaba M, Abe M et al. Best practice for diabetic patients on hemodialysis 2012. Ther Apher Dial 2015; 19 Suppl 1: 40-6

Ricks J, Molnar MZ, Kovesdy CP et al. Glycemic control and cardiovascular mortality in hemodialysis patients with diabetes: a 6-year cohort study. Diabetes. 2012; 61 (3): 708-15

Abe M, Hamanoac T, Hoshino J et al. Is there a "burnt-out diabetes" phenomenon in patients on hemodialysis? Diabetes Research and Clinical Practice 2017; 130: 211-220

Chung WK, Erion K, Florez JC et al. Precision Medicine in Diabetes: A Consensus Report From the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020 Jul;43(7):1617-1635

Mazzucco G, Bertani T, Fortunato M et al. Different patterns of renal damage in type 2 diabetes mellitus: a multicentric study on 393 biopsies. Am J Kidney Dis 2002; 39 (4): 713-20

Huh JH, Lee M, Park SY et al. Glycated Albumin Is a More Useful Glycation Index than HbA1c for Reflecting Renal Tubulopathy in Subjects with Early Diabetic Kidney Disease. Diabetes Metab J 2018; 42(3): 215–223

Summary Reports

NEPHROLOGY EDUCATION PORTAL

ADDRESSING GAPS IN PATIENT CARE IN RARE INHERITED DISORDERS: THE ROLE OF THE NEPHROLOGIST

Chiesi Global Rare Diseases

Transition from paediatric to adult care

David Cassiman, Belgium

Over the last 15 years, a steady increase in the number of children and adults with metabolic diseases has been observed. As David Cassiman, Leuven, Belgium, pointed out at a symposium organized by Chiesi Farmaceutici S.p.A. at the 2021 ERA-EDTA Congress, there are two types of adult patients: Former paediatric patients who have grown up with such diseases, and adults newly diagnosed with inborn errors of metabolism in adulthood. The first group is growing in size due to better pre- and post-natal diagnosis and better symptomatic or specific treatments. Many orphan drugs have been developed, and there are many patients who have been transplanted in childhood (e.g. bone marrow transplantation, liver transplantation, kidney or heart transplantation). They survive childhood, outgrow paediatric care and are transferred to the care of internists.

"A challenge we face when treating these patients that have outgrown paediatric care is the fact that there is a lack of scientific data on long-term outcomes and survival", commented Cassiman. "They might be cured for one aspect of the disease, but previously unknown features of the disease occur later on." Furthermore, these patients also develop "normal" aging issues and comorbidities such as hypertension, cancers, prostrate problems, diabetes, cardiac diseases, etc., or drug-related issues such as alcohol and smoking.

New problems also arise on reaching adulthood: these can involve social, financial and professional aspects, as well as sexuality, fertility and family planning. Many patients are lower-skilled or only partly skilled or have received a lower level of education compared to the general population in the same region, thus giving rise to specific economical and social issues.

"Our population has its own specific social and professional issues", explained David Cassiman, "but what we see on the adult care side is that there is often a lack of structure and a lack of 'dedicated' specialists. According to this expert in the field, there is liable to be a discontinuity in care provision, especially after a patient outgrows paediatric care, which unfortunately is around the very vulnerable period when patients are supposed to develop autonomy. "To bridge this gap, we need to take action!"

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A special transition program for cystinosis patients has been initiated in Leuven: If the patient is 12 or 13 years of age, a metabolic internist joins the paediatric nephrologist every three months. The patient is seen jointly, and a metabolic team takes over after he or she has grown out of paediatric care. Apart from doctors, the team also consists of dieticians, psychologists and social assistants and can provide the patient with holistic support. The nephrologist plays an important role in this team – cystinosis patients are liable to develop many complications in adulthood, some due to the cystinosis itself, but patients also suffer from the 'common' complications of transplantation, immunosuppressive treatment and kidney disease.

Managing multidisciplinary care in adult cystinosis patients

Aude Servais, France

As Aude Servais, Paris, France, pointed out, 55% of patients living with cystinosis are adults nowadays. Disease progression leads to kidney failure, diabetes, myopathy, hypothyroidism, hypogonadism, and central nervous system deterioration. In the study conducted by Brodin-Sartorius and colleagues, the first complication was ESRD at a mean age of 11.1. Hypothyroidism and diabetes usually develop after that, with neuromuscular disorders and strokes occurring in the second decade.

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But there is hope: The same study group showed that 5% of patients, with a median age of 20.9 years (15.7–27.2), all treated before 2.5 years of age, had not developed any complications at all. Registry data have shown that cysteamine given before the age of five reduces the incidence of long-term renal and extra-renal complications – this is why the continuation of cysteamine treatment also in patients treated by dialysis or transplantation is strongly recommended.

However, adherence also plays a powerful role, of course. Only 50% of the adult patients take their medication strictly according to the prescription, which is a problem, because adherence is directly associated with renal survival. Compliant patients reach ESKD significantly later than the non-compliant. It has been shown that, for each year of good cystine depletion, one year of preserved renal function is gained.

Early treatment pays off in many respects: Starting treatment before the age of five is associated with a significant delay in the occurrence of hypothyroidism. Even the incidence of diabetes can be suspended with consequent and early treatment. Cystine accumulates in the beta cells of the islets of Langerhans, with massive crystal deposits in the pancreas and complete architectural disorganisation, and treatment clearly slows this pathogenesis.

As Aude Servais emphasized, it is important to monitor cystinosis patients regularly for diabetes mellitus, especially in transplant patients, and for hypothyroidism. Annual laboratory tests for adults include thyroid function tests as well as fasting blood glucose. Haemoglobin A1c (HbA1c) tests are also recommended.

Cystine deposition in muscles may also cause progressive distal myopathy – and here again, it has been shown that starting therapy early, before the patient is five years of age, is associated with a significant delay in the occurrence of neuromuscular disorders.

Central neurological complications may also develop. These can be of two types: On the one hand, there is 'cystinosis encephalopathy' with cerebellar signs and/or motor difficulties, decrease of oral expression and motor coordination difficulties. On the other hand, stroke-like episodes involving coma, hemiplegia or milder symptoms can be observed. Patients may also develop mild neurocognitive abnormalities, e.g. specific impairments in the processing of visual information, relative weakness in visual motor, visual spatial and visual memory skills, which might be the reason why the disease is often associated with academic difficulties, primarily in arithmetic. Aude Servais pointed out the importance of conducting a Micro-Randomized Trial (MRT) and involving neurology colleagues if there are any complaints of headache, symptoms of bradykinesia, stroke or potential dementia.

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The illness also has a socio-psychological dimension: Male patients suffer from primary hypogonadism, which often is a psychological burden and has impacts on quality of life. Testosterone treatment allows puberty but does not prevent infertility. Pregnancy in women with cystinosis involves many challenges. Pre-pregnancy planning and treatment in a renal obstetric clinic with expertise in complex pregnancies is essential.

Aude Servais concluded that the spectrum of the disease has extended from a renal disease of childhood to a multisystem adult disease. The Clinical Decision Support Programme (CDSP) was set up for that reason in order to provide guidance to specialist and non-specialist clinicians in their daily clinical practice when treating adolescent and adult patients with cystinosis. The aim is to extend existing guidance with practical advice and strategies that address the requirements and management of adolescents and adults living with multi-organ effects of cystinosis.

The role of the nephrologist in Fabry care: from early diagnosis to therapeutic goals

Christine Kurschat, Germany

Fabry disease is a lysosomal storage disease and an X-linked inherited disorder. It is a mutation in the GLA gene, which codes for the α-galactosidase A enzyme, and results in translation of a malfunctioning protein and the accumulation of sphingolipids in all cells of the human body. The disease is often characterized by angiokeratoma. The disease affects other organ systems as well: The GI tract (diarrhoea, cramps), the ear and eye (hearing loss, cornea verticillate), the cardio-vascular system (cardiac arrhythmia, LVH), the central nervous system (early strokes) and the kidneys (renal insufficiency, dialysis). Nowadays, with therapies available, patients die mainly from cardiovascular complications. The delay in diagnosis is significant. Studies have shown that the time between the onset of symptoms and diagnosis is 13.7 years in male patients and as much as 16.3 years in females.

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What role do nephrologists play when kidneys are involved? Their job should primarily be to diagnose the disease at an early stage. Proteinuria and/or albuminuria are one of the earliest signs of organ damage in Fabry patients. They are signs of podocyte damage because sphingolipids accumulate in such cells. As Christine Kuscheid pointed out, the process of accumulation starts very early on in the disease. The next important step is early therapy. Christine Kuscheid referred to a European consensus paper that summarizes the current state of the art.

In classically affected males, therapy is at least recommended as soon as there are early clinical signs of kidney, heart or brain involvement, but therapy may be considered in patients aged 16 or more without organ involvement and classical mutations. This is because the disease will lead to organ damage, so a preventive strategy can be considered. A different strategy is recommended for women. As they have two X-chromosomes, one never knows whether the healthy chromosome may compensate for the diseased chromosome. In classically affected females, treatment should therefore be started when organ involvement has been diagnosed, but not before.

Another important message Christine Kurscheid emphasized was that treatment should always be continued on dialysis or after renal transplantation. As she pointed out, Fabry disease is a systemic disease, and the therapy also protects the vessels and the heart, even if the patient is on renal replacement therapy.

Two types of treatment are currently available: Enzyme replacement (available since 2001, must be infused every other week) and Chaperone therapy (an oral therapy available since 2016). It has been shown that enzyme replacement therapy significantly decreases pathogenic Gb3 deposition in the kidney, but clearance is never complete and not all patients respond very well. “In most patients we can slow the decline of renal function, but we cannot stop it.” Chaperone therapy also significantly decreases Gb3 deposition in podocytes and slows progression, but it cannot halt it completely. Moreover, it works in only about a third of patients, with success depending strongly on amenable mutations.

“There are still unmet needs in our patients”, Christine Kurscheid concluded. “It is very important to develop new therapies that can cure the patients and that can help patients who do not respond well to the therapies we have.”

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Further reading

Brodin-Sartorius A et al. Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults Kidney Int 2012;81:179-189

Gahl WA et al. Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. Ann Intern Med 2007;147(4):242-250

Ariceta G et al. Cysteamine (Cystagon®) adherence in patients with cystinosis in Spain: successful in children and a challenge in adolescents and adults. Nephrol Dial Transplant 2015; 30:457-480

Biegstraaten M et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. Orphanet J Rare Dis 2015; 10: 36

Germain et al. Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. J Am Soc Nephrol 2007; 18(5): 1547-57

NEPHROLOGY EDUCATION PORTAL

GLP-1 RECEPTOR AGONISTS AND THE KIDNEY

Summary Reports

Brief introduction to symposium, objectives, sessions and speakers

Peter Rossing, Denmark

Diabetes is the leading cause of chronic kidney disease (CKD) worldwide, with estimates that as many as 40% of patients with diabetes will develop CKD. GLP-1 receptor agonists (GLP-1 RAs) are a potent class of glucose-lowering agents. Data from recent clinical trials indicates that GLP-1 RAs may also confer renal benefits in patients with type 2 diabetes (T2D). At a virtual satellite symposium, held during the 2021 ERA-ERA fully virtual congress, Professor Roland Schmieder, Professor Ofri Mosenzon and Professor Hiddo Lambers Heerspink discussed current understanding of CKD in T2D, renal outcome data with GLP-1 RAs in T2D, and GLP-1 RAs' potential mechanism of action on the kidney.

Chronic Kidney Disease in Type 2 Diabetes: what do we know?

Roland Schmieder, Germany

Elevated blood glucose levels are often seen as defining diabetes, but it is more than a metabolic disease. Diabetes also affects the cardiovascular and vascular systems, and the kidneys. Consequently, effective management of T2D must address not only hyperglycaemia, but also the cardiovascular and renal complications of diabetes. Professor Schmieder reported that this holistic, multidisciplinary approach is reflected in the latest KDIGO guidelines on diabetes management in CKD.

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KDIGO's first step is the combination of lifestyle measures, with glycaemic and blood pressure (BP) control. It is clear that high blood glucose levels must be lowered—at a minimum to <8%—in T2D. However, while strict glycaemic control improves renal and cardiovascular prognosis in type 1 diabetes, the evidence is less clear for T2D: it seems to reduce albuminuria but its effects on serum creatinine are variable.

The randomized, controlled, open-label SPRINT trial assigned participants either to standard treatment to achieve systolic BP <140 mmHg or intensive treatment to achieve systolic BP <120 mmHg. In people with CKD at baseline but without diabetes, there was no significant between-group difference in the composite outcome of decrease in eGFR ≥ 50% or development of end-stage kidney disease (ESKD). Professor Schmieder commented that SPRINT used a very specific technique: unattended automatic office BP measurement (AOBP). This is not generally used in clinical practice and its results are approximately 10 mmHg lower than office measurement. He therefore advised that, while BP should be controlled to <140/80 mmHg (and in some patients <130/80 mmHg), lowering BP to <120 mmHg is not recommended as it increases risk of adverse effects.

KDIGO's second step is a combination of a sodium-glucose transport protein 2 inhibitor (SGLT2i) and renin-angiotensin-aldosterone system inhibitor (RAASi) to reduce risk of CKD and cardiovascular disease. In large studies, RAAS blockade resulted in a relative risk reduction in renal outcomes of approximately 40%, but a significant residual risk remains. Finerenone, a selective mineralocorticoid receptor antagonist (MRA), has been shown to reduce the risk of CKD progression and cardiovascular events in people with T2D, and in combination with a RAASi offers a new option for additional risk reduction of CKD.

Turning to antihyperglycemic therapies, Professor Schmieder noted that, after lifestyle management, KDIGO recommends the second-line combination of metformin and SGLT2i, followed by GLP-1 RAs as third line in preference to other glucose-lowering therapies. He concluded that, while there is currently insufficient data to recommend GLP-1 RAs as second-line, this evidence may become available in future.

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Kidney Outcomes with GLP1-RAs: what evidence have we seen so far?

Ofri Mosenzon, Israel

According to Professor Mosenzon, cardiovascular outcome trials provide important clues to the potential renal benefits of GLP-1 RAs. For example, in a meta-analysis of seven placebo-controlled trials including a total of 56,004 T2D patients, GLP-1 RAs showed consistent benefit on composite renal outcomes, mainly due to reduction in albuminuria. Furthermore, although composite renal outcomes differed in REWIND (dulaglutide), LEADER (liraglutide) and SUSTAIN 6 (semaglutide), renal risk was reduced in each trial.

A post hoc pooled analysis of renal outcomes in LEADER and SUSTAIN 6 found that, compared to placebo, treatment with liraglutide and semaglutide decreased the risk of an annual 30%, 40%, 50% or 57% reduction in eGFR in patients with eGFR 30-59 ml/min/1.73m2 and micro/macroalbuminuria. Similarly, in a pooled analysis of SUSTAIN 6 (subcutaneous [s.c.] semaglutide once weekly) and PIONEER 6 (oral semaglutide once daily), annual change in eGFR was slower in both active treatment arm than in the placebo group (overall estimated treatment difference [ETD] 0.60mL/min/1.73m2/year (95% CI 0.31-0.90; p<0.0001 at year 2). Patients with baseline eGFR 30-59 ml/min/1.73m2 appeared to benefit most, though the ETD was not statistically significant when considering p-value for interaction.

FLOW (NCT03819153) is an ongoing renal outcomes trial, in which 3508 T2D patients (HbA1c ≤10%) have been randomized to either 1mg semaglutide s.c. once weekly plus standard of care or placebo plus standard of care, including RAASi. The trial includes two groups of patients: eGFR ≤75 to ≥50 ml/min/1.732 plus urine albumin to creatinine ratio (UACR) >300 to <5000 mg/g, and eGFR <50 to ≤25 ml/min/1.732 plus UACR >200 to <5000 mg/g. The primary composite endpoint is the important clinical outcome of persistent ≥50% reduction in eGFR (CKD-EPI) compared to baseline, or onset of persistent eGFR <15, or renal replacement therapy, or cardiovascular or renal death.

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GLP-1 RECEPTOR AGONISTS AND THE KIDNEY

Professor Mosenzon noted that, when available, the results of the FLOW trial will fit with other renal outcome trials because the study has randomized a similar population to that in renal outcomes trials with SGLT2is and the MRA finerenone. She concluded that, depending on the results of the FLOW trial, GLP-1 RAs could represent the next frontier in the treatment of diabetic kidney disease.

GLP-1RAs and the Kidney: what might the mechanism(s) of action be?

Hiddo Lambers Heerspink, Netherlands

Professor Heerspink considered that GLP-1 RAs may mediate renal outcomes, not only through indirect effects in terms of improved glycaemic control, reduction in BP and weight loss, but also directly through natriuresis, hemodynamic, endothelial function, anti-inflammatory effects and reduced oxidative stress, or inhibition of the RAAS.

An acute infusion of exenatide increased sodium excretion and urinary pH in a study including both healthy overweight males and T2D patients. This pattern of effect suggests that exenatide blocks the sodium hydrogen exchange transporter in the proximal tubule. This increases natriuresis and decreases proton excretion thereby increasing urinary pH, and may have favourable direct effects on the kidney, as well as by reducing BP and body weight.

SGLT2i produce an acute decline in eGFR that is associated with long-term kidney protection. In contrast, in SAFEGUARD, which included T2D patients without CKD, there was no difference after 12 weeks in the acute effects of liraglutide, sitagliptin or placebo on both estimated and inulin-measured GFR. This suggests that GLP-1 RAs do not have an acute hemodynamic effect on the kidney

In contrast, GLP-1 RAs appear to improve endothelial function. In a randomized controlled trial including participants with T2D, exenatide increased the resistance hyperemia index compared to placebo. This effect was, however, abolished when exenatide was given in combination with the GLPR-1 antagonist exendin 9, indicating that exenatide has a direct effect on endothelial function that may translate into long-term kidney protection.

GLP-1 RECEPTOR AGONISTS AND THE KIDNEY

Studies have also shown that GLP-1 RAs have anti-inflammatory effects. C-reactive protein (CRP) was assessed as a measure of systemic inflammation in both PIONEER 1 (oral semaglutide versus placebo) and PIONEER 2 (oral semaglutide versus empagliflozin). There was a somewhat dose-dependent reduction in CRP in PIONEER 1 that was greater with the 7 mg and 14 mg doses than with the 3 mg dose. Additionally, in PIONEER 2, reduction in CRP was greater with semaglutide 14 mg than with empagliflozin 5 mg. The results suggest that semaglutide reduced systemic inflammation, which may translate into not only kidney protection, but also cardiovascular protection.

Finally, the effects of GLP-1 RA on RAAS remain uncertain. Several acute studies indicate that GLP-1 RAs reduce plasma renin concentration and activity, decrease angiotensin II and lower angiotensinogen concentration in the urine. These effects may also block the RAAS in the kidney, but studies have not replicated these effects during long-term intervention.

Overall, there appear to be multiple pathways by which GLP-1 RAs protect the kidney, but most mechanistic studies conducted to date are relatively small. REMODEL—Renal mode of action with semaglutide (NCT04865770) is a mechanistic, multinational, randomized controlled trial including 105 patients with T2D, HbA1 ≤ 9%, eGFR ≥40 to <75 ml/min/1.732, and UACR ≥30 to ≤5000 mg/g. All patients will be treated with maximum tolerated doses of a RAASi.

Patients will be randomized to semaglutide s.c.1 mg once weekly plus standard of care or placebo plus standard of care for 52 weeks, and will be followed up for five weeks at the end of treatment. The main endpoints include clinical, hemodynamic, inflammatory and oxidative parameters. Investigators will also collect kidney biopsies, perform MRI scans, measure GFR and urinary protein excretion, and biomarkers in blood and urine.

Professor Lambers Heerspink concluded that emerging data indicate a kidney protective role for GLP-1 RAs in patients with T2D and CKD. The mechanism of kidney protection remains incompletely understood, but it is likely to involve multiple pathways, both direct and indirect. The results of prospective clinical trials like FLOW and REMODEL will be needed to confirm the renoprotective effects of GLP-1 RAs.

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GLP-1 RECEPTOR AGONISTS AND THE KIDNEY

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Further reading

CKD in diabetes

International Diabetes Federation. IDF Atlas. 9th edition 2019

KDIGO 2020 Clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2020;98(4S):S1-S115

The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. New Engl J Med 2015; 373:2103-2116

Kidney outcomes with GLP-1 RAs

Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019;7(10):776-785.

Gerstein HC, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet 2019;394(10193):131-138

Mann JFE, et al. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med

2017;377(9):839-848

Marso SP, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375(19):1834-1844.

GLP-1 RAs and the kidney: mechanism(s) of action

Muskiet MHA, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. Nat Rev Nephrol 2017;13(10):605-628.

Tonneijck L, et al. Renal effects of DPP-4 inhibitor sitagliptin or GLP-1 receptor agonist liraglutide in overweight patients with type 2 diabetes: a 12-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2016;39(11):2042-2050

Koska J, et al. Exenatide protects against glucose- and lipid-induced endothelial dysfunction: evidence for direct vasodilation effect of GLP-1 receptor agonists in humans. Diabetes 2015;64(7):2624-35

Summary Reports

NEPHROLOGY EDUCATION PORTAL

20 YEARS OF REAL-WORLD EVIDENCE DATA FOR FABRY DISEASE

SANOFI GENZYME

Welcome

Sima Canaan-Kühl, Germany

2021 marks the twentieth anniversary of the approval of agalsidase-beta as a treatment for Fabry disease, as pointed out in her introduction by Sima Canaan-Kühl, Charité Berlin, who chaired the symposium. Over the last twenty years, considerable insights into the disease's variability have been gained, and recommendations and guidelines have been published. However, there are still some burning questions, such as how to further optimize treatments and outcomes, or how to improve the diagnosis of patients at an early age.

Optimization of fabry disease patients management after more than 20 years of clinical experience

Camilla Tøndel, Norway

As Camilla Tøndel, Bergen, Norway, pointed out in her talk, many achievements have been made, indeed. Before 2001, there was no effective Fabry treatment at all, which meant that many affected families had no hope. She reported on two brothers (13 and 14 years of age) who were her first Fabry patients back in 2001, whom she treated with enzyme replacement therapy with great success. Over a period of weeks, not only did their Gb3 levels drop significantly, but also their clinical conditions improved, especially their GI problems and pain. In 2008, Tøndel and colleagues published a kidney biopsy study that included the two brothers. Both biopsies showed significant pathology, but although the patients had normal albuminuria levels at the beginning of the study, both patients developed microalbuminuria after two years.

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The doctors doubled the dose of agalsidase alfa, which resulted in substantial clearance of podocyte inclusions. After seven years of treatment (five years after the baseline biopsy), the younger brother had been switched to full-dose agalsidase beta due to sinus arrest and his need for a pacemaker, whereas the older one stayed on double-dose agalsidase alfa. After 14 years. a dose-dependant effect on kidney histology was seen between the brothers, although it still did not translate into functional parameters. The younger brother underwent another biopsy 17 years after treatment initiation, and it showed no fibrosis, but healthy kidney tissue.

In a study presented at the ERA-EDTA Congress, Camilla Tøndel showed for six classical male Fabry patients that the initiation of ERT at a relatively young age may clear long-lived kidney cells of Gb3 and protect the kidneys from significant functional loss over a very long period. Another important insight was that the reduction of Gb3 in podocytes is higher on a high dose compared to a low dose of agalsidase. In a study of 55 males (mean age 27 years) with classic Fabry disease genotype and/or phenotype, unbiased quantitative morphometric electron microscopic studies were performed on biopsied kidney samples from patients and seven living transplant donors (serving as controls). Here again, it was found that GL3 accumulation was associated with podocyte injury and loss. The study indicates that podocyte injury and loss play an important role in the progression of Fabry nephropathy. As Camilla Tøndel concluded, it is therefore very important to start therapy early enough in the process.

However, this requires early diagnosis, which is increasingly achieved nowadays, compared to 20 years ago, when patients were often not diagnosed with Fabry disease until severe symptoms developed – although there are still exceptions.

Asked about the main biomarkers for monitoring patients, Camilla Tøndel pointed out that renal biopsy is an invasive procedure, but provides important insights and should be performed in patients every few years. In the intervals between biopsies, she recommended that attention be paid to three non-invasive biomarkers, in particular. Firstly, the albumin-creatinin-ratio as a general biomarker. Secondly, she emphasised that GFR should be measured from time to time, because in contrast to eGFR it is a biomarker that is independent of muscle mass. She pointed out that eGFR may be misleading in children in puberty. The third biomarker she recommended was lyso-GL3: “We see podocytes in the urine and we see a reduction of podocytes in the urine after treatment. That is very interesting as a biomarker, but many centres do not have that yet.”

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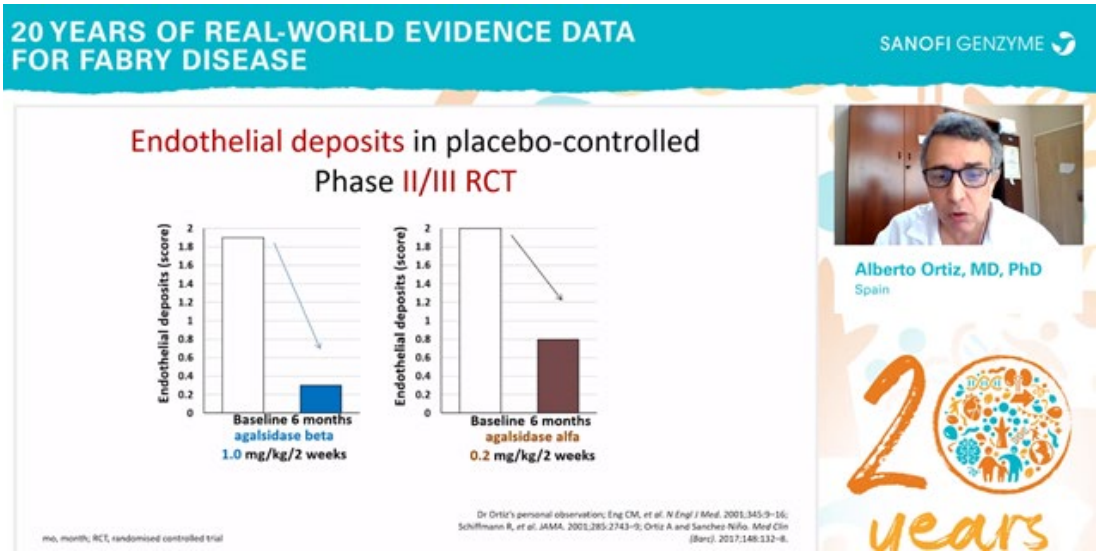
Lessons learned after two decades of fabry disease treatment

Alberto Ortiz, Spain

Before Alberto Ortiz, Madrid, Spain, gave an overview of treatment options, he reminded the audience that Fabry disease affects many more men than women, and that one has to differentiate between classic Fabry disease, in which the endothelium is full of glycolipids, and late-onset Fabry disease, in which there are no glycolipids in the endothelium. The conclusions Alberto Ortiz drew were that (1) the female population may not be best for assessing glycolipid deposits and (2) that patients with late-onset disease may not be best for assessing endothelial deposits.

Alberto Ortiz pointed out that there are phase 2 and phase 3 studies on agalsidase alfa and phase 3 studies on agalsidase beta, as well as a 5-year extension study and a 10 year follow-up, which assessed endothelial Gb3 deposits and/or pain as primary endpoints, and a phase 4 study which studied the event rate as the primary endpoint. In all these trials, most of the patients were males. Furthermore, it was shown that agalsidase beta was more effective in reducing endothelial Gb3 deposits in phase 2/3 studies, although Alberto Ortiz acknowledged that the endothelial findings may not apply to podocytes.



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The Canadian Fabry Disease Initiative (CFDI) conducted a head-to-head comparison between agalsidase alfa (0.2 mg /kg EOW) and agalsidase beta (1 mg /kg EOW) with a follow-up of ten years and thus assessed the long-term impact of enzyme replacement therapy (ERT). The primary endpoints were renal, cardiac and neurological events. Unfortunately, the study was underpowered (132 patients were enrolled, 600 had been planned for enrolment) and therefore was unable to show any statistically valid significance. However, the most common events were renal events (renal replacement therapy, doubling of serum creatinine, and proteinuria > 3.5 g/day) in males – and in this subgroup a highly significant effect became obvious. Agalsidase beta was more effective in reducing renal events (p=0.006). As Ortiz pointed out, this result is quite plausible from the biological perspective as well, because agalsidase beta had a greater impact in terms of reducing endothelial deposits than agalsidase alfa in placebo-controlled trials. It also has an effect on lyso-Gb3, which is also known to be pathogenic.

For migalastat, in contrast, there have only been two phase 3 trials with renal endpoints so far, but no long-term data or head-to-head comparisons. Moreover, most of the patients in these studies were female, and interpreting data on female patients is known to be difficult when it comes to Fabry disease. Although some women may progress to the point where they need dialysis, they are simply not the majority of female patients, so it is more difficult to identify the effects of treatment.

Alberto Ortiz then presented real-world data showing that more than 50% of male patients with classic disease are treated with agalsidase beta.

An analysis of Fabry Registry data from 2016 provided further information on the incidence of severe clinical events over time for adult patients treated with agalsidase beta. It was shown that the incidence rate for severe clinical events decreases after the first 6 months of treatment, although the median age at which agalsidase beta therapy was started was 40 years, which was quite late. Alberto Ortiz pointed out that even older patients benefit from the treatment, although the treatment is more effective when started earlier.

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Further reading

Trondel C et al. CLEARED PODOCYTES AND NORMAL KIDNEY FUNCTION IN CLASSICAL FABRY MALES 15 YEARS AFTER START OF ENZYME REPLACEMENT THERAPY AT YOUNG AGE. Abstract MO 127. ERA-EDTA Congress 2021.

Najafian B et al. Accumulation of Globotriaosylceramide in Podocytes in Fabry Nephropathy Is Associated with Progressive Podocyte Loss.J ASN April 2020, 31 (4) 865-875

Schiffmann R et al. Enzyme Replacement Therapy in Fabry Disease. A Randomized Controlled Trial. JAMA. 2001;285(21):2743-2749

Ortiz A et al. Diagnosis and treatment of Fabry disease. Med Clin (Barc) 2017 Feb 9; 148(3):132-138.

Sirrs SM, Bichet DG, Casey R, Clarke JT, Lemoine K, Doucette S, West ML. CFDI investigators. Outcomes of patients treated through the Canadian Fabry disease initiative. Mol Genet Metab 2014;111:499–506.

Arends M et al. Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: an international cohort study. J Med Genet 2018; 55: 351-8

Ortiz A et al. Time to treatment benefit for adult patients with Fabry disease receiving agalsidase β: data from the Fabry Registry. J Med Genet 2016; 53: 495-502

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