Congress Review

Review of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Virtual Congress 2020

Location: ERA-EDTA Virtual Congress 2020 Review

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CAPITAL of Lombardy, one of the world's four fashion capitals, and unparalleled collector of works by Leonardo da Vinci, Michelangelo, and Caravaggio, Milan was set to offer an alluring backdrop to this year's 57th ERA-EDTA congress. The city was also home to the Italian physician Dr Carlo Urbani who discovered the severe acute respiratory syndrome (SARS) in 2003, the cause of which is a member of the coronavirus family; unwittingly, a coronavirus is the single cause of the shift to the congress' first ever virtual meeting this year.

Congregating not in Milan but in living rooms and houses all over the world, >10,000 delegates were gathered together on ERA-EDTA's virtual platform from 6th–9th June 2020. Attendees were welcomed by 200 speakers in 100 virtual sessions, alongside 1,800 e-posters and 350 virtual presentations. Prof Loreto Gesualdo, President of ERA-EDTA, greeted viewers in the Opening Plenary session, and admitted that "deciding not to give up our annual congress and to turn it into a special digital edition has been an act of courage, as well as a bet." He also paid respect to the country's healthcare workers, "who have been, and are still, in the front-line in the fight against the virus," and explained that the SARS-coronavirus-2 (CoV-2) virus has "forced us to adopt innovative and digital solutions" and "only accelerated a process that was already underway."

The pandemic has put a spotlight on nephrological expertise and highlighted its importance, as early observations have shown that the virus can cause kidney injury, albuminuria, and elevated creatinine levels. Therefore, the programme was subject to last-minute changes to accommodate for topical discussions and collaborations regarding COVID-19, including sessions on acute kidney injury and end-stage kidney disease in severe COVID-19, the particular risk of dialysis patients, and the prognosis for patients with kidney replacement therapy, as well as cytokine storm and the role of haemoperfusion.

Committed to education, science, and networking, the congress delivered an exemplary programme to aid all nephrologists in their daily practice, support and spread top quality scientific knowledge, and facilitate professional alliances. Despite holding an online meeting, ERA-EDTA's Chair of the Scientific Committee Prof Peter Blankestijn made sure this did not have an impact upon the congress' usual content, and attendees were still offered practical courses on renal molecular pathology and fistula imaging, as well as symposia, plenary sessions, and moderated poster sessions.

A great deal of attention in the scientific programme was paid to chronic kidney disease (CKD), and summaries of the Gold Plenary Sessions entitled: 'CKD: two decades of progress and challenges for the future' and 'AKI, CKD, and cancer - the costs of kidney repair', are included in our Congress Review Stories. Abstract summaries are also included in *EMJ Nephrology*, with topics such as mortality in haemodialysis patients in the Persian Gulf cooperation council countries, mepolizumab therapy in eosinophilic granulomatosis with polyangiitis, and the association between cystatin C and arterial stiffness in non-CKD patients. Congress review highlights containing summaries of the congress press releases can also be found within these pages, including updates and research on ANCA-associated vasculitis and the ADVOCATE study, specific kidney proximal tubular injury caused by SARS-CoV-2, and predictors of 5-year mortality in young dialysis patients.

Accumulatively, the 4-day congress left nephrologists with much to discuss, much knowledge gained, and an overwhelming sense of community in these unpreceded times. To turn the face-to-face congress into a successful virtual congress within a few short months was no mean feat, and, in the words of Prof Gesualdo, "I am sure this will be the starting point for change in the field of medical education."

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ERA-EDTA 2020 REVIEWED →

Add-on Belimumab Improves Long-Term Outcomes in Lupus

PROGNOSIS in systemic lupus erythematosus (SLE) is significantly impacted by renal involvement, with better outcomes seen when receiving belimumab as an add-on therapy. Addition of belimumab reduces the risk of renal deterioration or renal events associated with poorer prognosis over the long term.

The American BLISS-LN study of 448 patients with active lupus nephritis conducted a double-blind, placebo-controlled trial to assess the effect of add-on belimumab in patients treated with standard lupus treatment. The standard treatments were either mycophenolate mofetil (MMF) for both induction and maintenance (328 patients), or cyclophosphamide induction followed by azathioprine maintenance (118 patients). Belimumab is a human monoclonal antibody that blocks the activity of B lymphocyte stimulator (BLyS), which is overexpressed in SLE.

After 2 years, add-on belimumab significantly improved primary renal response (43% versus 32% with placebo; p=0.0311), where the composite endpoint was a urine protein creatinine ratio ≤0.7, and estimated glomerular filtration rate ≤20% below pre-flare value or ≥60 mL/min/1.73 m^2, with no rescue therapy required. There were also significantly more patients with a complete renal response with add-on belimumab (30% versus 19.7% with placebo; p=0.0167). The patients receiving add-on belimumab had a 50% reduction in risk of renal events associated with greater risk of poor renal prognosis, compared to placebo.

The study was presented at the ERA–EDTA Virtual Congress on 7th June 2020 congress as a late-breaking clinical trial by Dr Brad Rovin, Division of Nephrology, Ohio State University, Columbus, Ohio, USA. "MMF is already used in many patients. It has been shown to be equivalent to cyclophosphamide in the induction therapy of lupus nephritis [LN], and superior to azathioprine in the maintenance phase. Adding belimumab can further improve the treatment results."

There is a higher mortality risk for patients with renal involvement of their SLE. Improvement in renal disease significantly improves 10-year survival; ongoing study is needed, but belimumab may help to improve this longer-term survival by improving renal outcomes.

"The patients receiving add-on belimumab had a 50% reduction in risk of renal events associated with greater risk of poor renal prognosis, compared to placebo."

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Majority of Hospitalised COVID-19 Cases Have Renal Injury

PATTERNS of renal injury in patients hospitalised with COVID-19 reflect Fanconi syndrome in the majority of cases. A French study assessed patterns of renal injury and determined that the effect of the SARS-CoV-2 virus on kidney function may be a potential prognostic marker for the course of the illness. This was announced in a press release at the ERA-EDTA Virtual Congress on 8th June 2020.

Up to 80% of patients hospitalised with COVID-19 display acute kidney injury, with evidence that the virus directly affects proximal renal tubular cells. These cells express angiotensin-converting enzyme-2 (ACE-2) cell surface receptors, the avenue by which SARS-CoV-2 invades affected patients. Injury to the proximal tubules can lead to Fanconi syndrome, where impairment of their usual function to reabsorb glucose, bicarbonate, potassium, phosphate, and amino acids and proteins into the bloodstream leads to loss of these substances in the urine.

The study in Nancy, France examined data from 42 hospitalised patients with COVID-19, for a mean follow-up period of 19.7 (±12) days. 75% of the patients met criteria for Fanconi syndrome (≥2 tubular abnormalities), with a greater proportion of patients in intensive care affected (96% versus 62%). Fanconi syndrome preceded severe acute kidney injury in 88% of the patients studied. Seven of the 42 patients studied died from their illness, but for those patients who clinically improved, this improvement was matched by a reversal of the renal Fanconi syndrome.

"The proximal renal tubules seem to be a specific target of SARS-CoV-2 because of their ACE-2 receptors, and we see verification of our hypothesis that this is the cause of the tubular disorders and AKI that so many of our COVID-19 patients have developed," outlined Dr Raphaël Kormann, University of Lorraine, Vandoeuvre-lès-Nancy, France and first author of the study. "This should be subjected to further systematic investigation – with regard to the significance of Fanconi syndrome as a biomarker of tubular cell infection and as a potential predictive prognostic marker."

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The RITAZAREM Trial: ANCA-Associated Vasculitis Remission Success

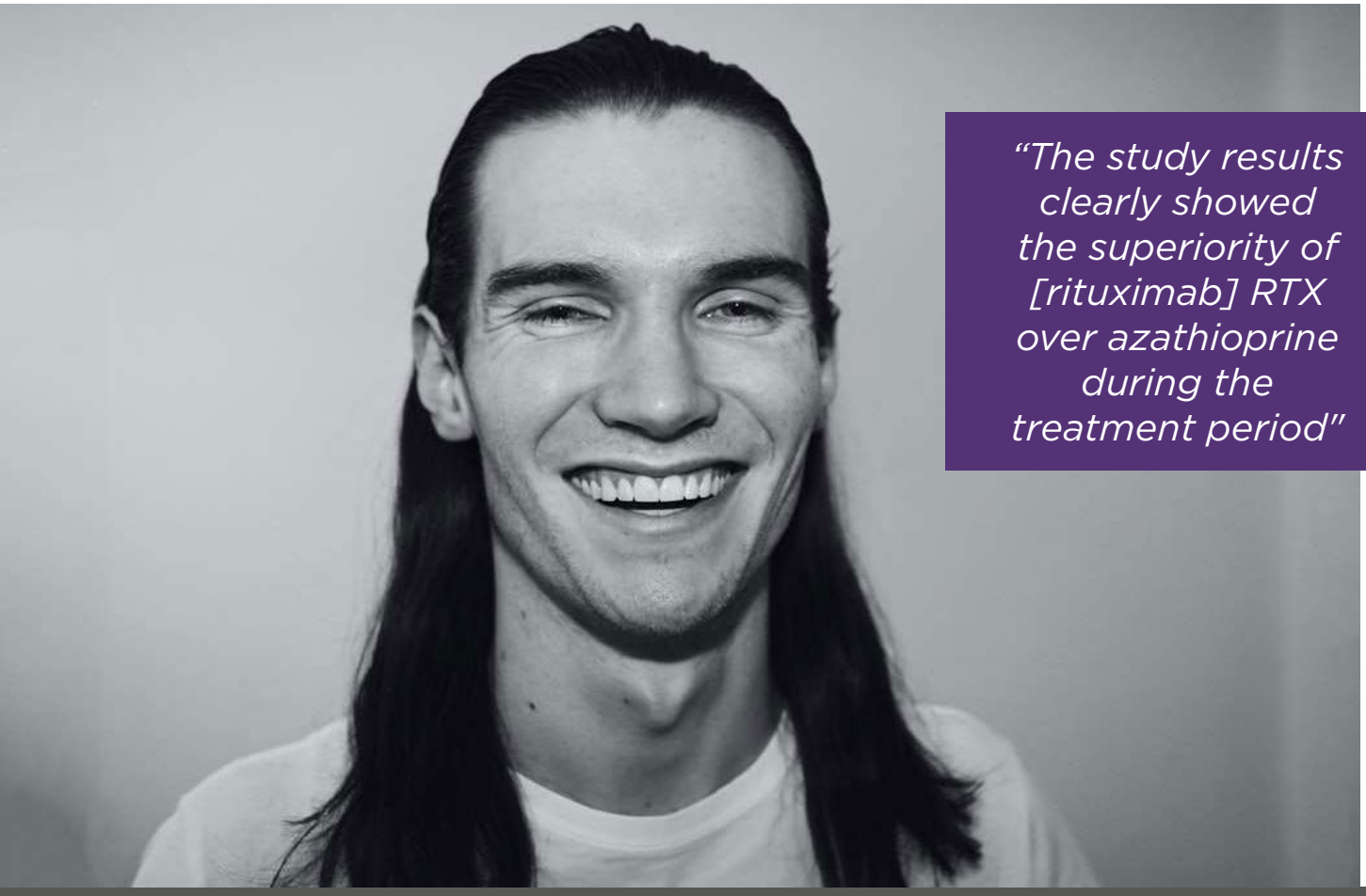
RECURRENT episodes of ANCA-associated vasculitis (AAV), an autoimmune disease involving vascular inflammation, have been successfully reduced with the treatment of the monoclonal antibody rituximab. Results from the RITAZAREM study, which trialled rituximab and glucocorticoids for preventing relapse of AAV, were announced in a press release at the ERA-EDTA virtual congress on 7th June 2020.

An international, multicentre, randomised controlled trial, the RITAZAREM study assessed relapse of AAV in patients after remission induction with fixed interval repeated rituximab or daily oral azathioprine. Patients were followed-up for at least 24 months, the median age was 59, and the median duration of disease was 5.3 years. After 4 months, 170 patients had achieved remission and these patients were randomised equally to receive either 1,000 mg of rituximab every 4 months (for a total of 5 times) or daily doses of azathioprine at 2 mg/kg.

20 months after randomisation, 11 of the 85 patients in the rituximab group had relapsed, though only two were classified as severe "major relapses." Conversely, 32 of the 85 in the azathioprine group presented with AAV relapse, of which 12 were classed as severe major relapses. Regarding severe adverse events, hypogammaglobulinaemia and infection occurred in 29% and 49% of patients in the rituximab group, respectively, compared to 25% and 48% of patients in the azathioprine group, respectively.

Dr Rona Smith from Cambridge, UK and the first author of the study, summed up the results with: "The study results clearly showed the superiority of [rituximab] RTX over azathioprine during the treatment period, without our finding any evidence that the substance has a worse risk profile – on the contrary."

AAV can be a life-threatening disease and it is therefore imperative to prevent relapses. Dr Smith hopes that the results of the study will lead to future research and guidelines being updated to indicate which patient groups would benefit most from the therapy.



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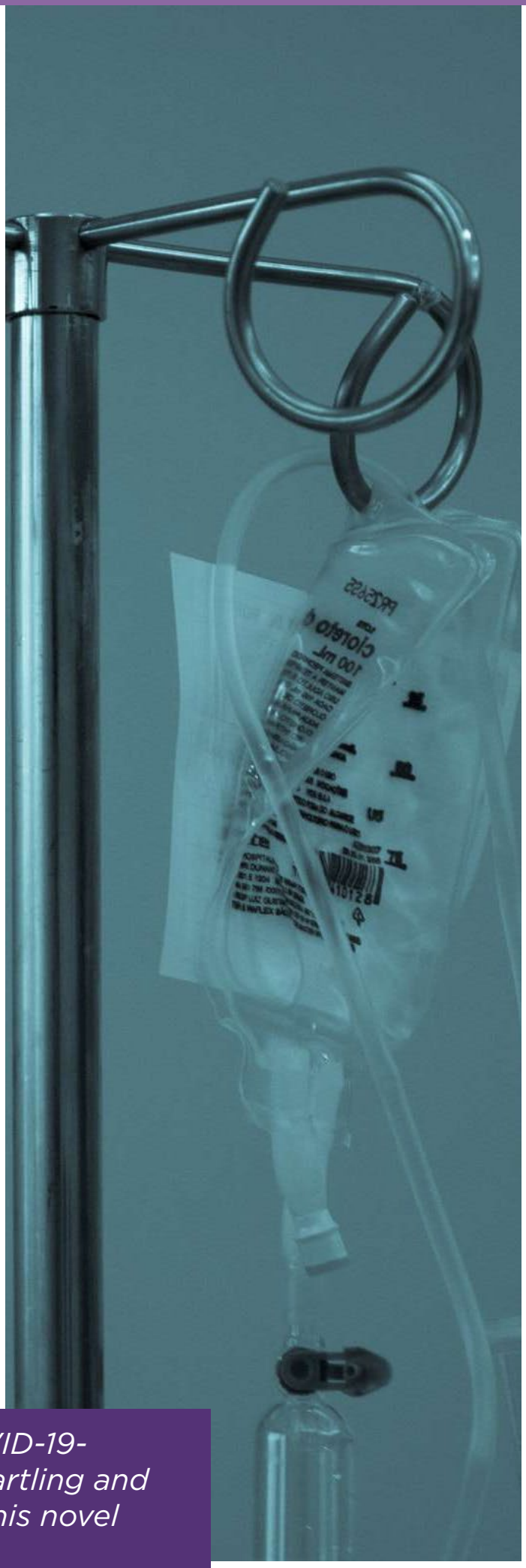
Study Finds COVID-19-Associated Acute Kidney Injury Prevalence of 80%



THE FIRST of its kind, a study characterising the occurrence of COVID-19-associated acute kidney injury (AKI) has recorded the incidence, severity, clinical presentation, and short-term outcomes in a large number of critically ill patients in France.

This was announced in a press release at the ERA-EDTA virtual congress on 8th June 2020.

71 patients with severe lung injury and COVID-19 participated in the study, which took place over 6 weeks in March and April 2020. On admission, patients presented with an average basal serum creatinine level of 69±21 µmol/L and eight patients were subsequently diagnosed with AKI, as per the Kidney Disease Improving Global Outcomes (KDIGO) criteria.

Over the course of the follow-up, which was a median of 17 days, AKI developed in 57 of the 71 patients (80%): 35% were at Stage 1, 35% at Stage 2, and 30% at Stage 3. Ten of the 57 required renal replacement therapy (dialysis) and two died within the first 72 hours. Seven days after AKI development, of the remaining 55 patients there were six patients still on dialysis and nine had serum creatinine >200 µmol/, though renal recovery had occurred in 28%. 14 days post-AKI diagnosis the renal recovery increased to 52%.

The study is in agreement with reports from China and the USA, where AKI has been diagnosed in up to 15% and 20%, respectively, of intensive care patients with COVID-19. Dr Sébastien Rubin, of Bordeaux University Hospital, Bordeaux, France and an author of the study, commented: "This high rate of COVID-19-associated AKI cases is startling and shows how renotropic this novel virus can be."

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Risk Factors for High Haemodialysis Mortality Identified

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HAEMODIALYSIS (HD) is an essential lifeline for those with severe kidney disease, but the mortality rates associated with its use are highly concerning. For the first time, an analysis into the risk factors associated with mortality in patients on chronic HD treatment since childhood has been completed. The results from this analysis were presented at ERA–EDTA 2020 and announced in a press release from the congress dated the 9th June.

Although the percentage of children and young people with severe kidney damage and requiring renal replacement therapy is low (2%), the condition is life-changing for these individuals. Without transplantation, they are dependent on dialysis, a treatment that is carried out typically three times a week for 4 hours each time, resulting in the possibility of a 'normal' childhood being reduced significantly. In addition to this diminished quality of life, the mortality risk of children on dialysis treatment is 55-fold higher when compared with healthy children. This highlights the need to characterise the risk factors associated with this staggering mortality risk, especially those that are modifiable.

In the analysis, the significance of 105 variables relating to demographics, HD treatment, and laboratory measurements as predictors of 5-year mortality were evaluated in a cohort of 363 patients who were <30 years old and had started dialysis therapy as a child (<19 years old). A flexible machine learning approach (random forest) was utilised.

The results identified two important risk factors: low albumin and elevated lactate dehydrogenase. Other factors that showed an importance in mortality risk included a reduced red blood cell count, haemoglobin level, albumin/globulin ratio, ultrafiltration rate, z-score weight for age, or inadequate dialysis dose (single pool Kt/V below target). By identifying these risk factors, a more encompassing approach to dialysis therapy can be taken to address these risk factors and reduce the mortality risk associated with it.

"The variety of retained risk factors probably highlights the importance of multimodal intervention strategies in addition to adequate HD treatment," explained corresponding author Dr Verena Gotta, University Children's Hospital Basel, Basel, Switzerland.

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Positive Results for Primary Hyperoxaluria Type 1 RNA Interference Therapy

RNA INTERFERENCE (RNAi) therapeutics tap into the natural biological gene silencing mechanism and are being utilised for treatment of a plethora of diseases, many of which are rare diseases, including lumasiran (Alnylam Pharmaceuticals Inc., Cambridge, Massachusetts, USA) for primary hyperoxaluria Type 1 (PH1). In a press release dated 7th June from ERA–EDTA 2020, the positive results from a Phase III study of lumasiran were announced.

PH1 is a rare disorder that often leaves many patients requiring dialysis from an early age. This autosomal recessive inherited disorder is caused by numerous defects in the enzyme alanine-glyoxylate aminotransferase which causes overproduction of oxalate in the liver. Oxalate is excreted in the urine, meaning that overproduction can manifest symptoms such as recurrent kidney stones, renal calcification, and kidney injury, which can lead to kidney failure. Although there are a handful of treatment approaches targeting oxalate overproduction and the associated outcomes, currently no treatment that addresses the cause of the disease is available.

In the Phase III, randomised, double-blind, placebo-controlled study, 39 patients with a confirmed PH1 diagnosis (age ≥6 years, 24-hour urinary oxalate ≥0.70 mmol/24 hour/1.73 m^2, estimated glomerular filtration rate ≥30 mL/min/1.73 m^2) either received placebo or the investigational drug lumasiran (randomised 2:1) once a month for 3 months followed by one dose every 3 months. The least square mean change from baseline after 6 months for 24 hour urinary oxalate excretion was 65.4% with lumasiran and -11.8% with placebo (p=1.7x10-14). Additionally, 84% and 52% of patients on lumasiran achieved near-normalisation or normalisation of urinary oxalate, respectively, compared with 0% of those treated with placebo. No severe or serious adverse events associated with lumasiran were reported, and the most frequent adverse event was injection-site reactions, which were mild and transient.

"Lumasiran resulted in rapid, sustained, and statistically significant reductions in urinary and plasma oxalate levels and had an encouraging safety profile," concluded lead author Dr Sander Garrelfs, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands. It was added that prevention of long-term injury to the kidneys needs to be demonstrated, which would provide evidence that this could be the long-desired treatment that would negate the need for dialysis in those with PH1.

"Lumasiran resulted in rapid, sustained, and statistically significant reductions in urinary and plasma oxalate levels and had an encouraging safety profile"

Empagliflozin Induced Estimated Glomerular Filtration Dip

EMPAGLIFLOZIN has been shown to induce an initial 'dip' in estimated glomerular filtration rate (eGFR) in patients on diuretic therapy and/or belonging to a higher Kidney Disease Improving Global Outcomes (KDIGO) risk category. These findings were presented during a press release at the ERA-EDTA Virtual Congress on 7th June 2020.

The sodium/glucose cotransporter-2 (SGLT2) inhibitor empagliflozin reduces the progression of chronic kidney disease in Type 2 diabetes mellitus patients with cardiovascular disease, by lowering intraglomerular pressure. However, the observed initial reduction in GFR after introducing an SGLT2 inhibitor has raised questions of uncertainty. Administration of empagliflozin causes an increase in tubular flow rate leading to reduced reabsorption of glucose and sodium from the glomerular filtrate. This then triggers the tubuloglomerular feedback mechanism in the kidneys which ultimately results in a decrease in GFR.

However, termination of empagliflozin stops this feedback mechanism and the GFR increases again. For this reason, Dr Bettina J. Kraus and her team at the University Hospital Würzburg, Germany, investigated whether the initial GFR dip post empagliflozin initiation was affected by baseline characteristics and/or might impact the empagliflozin induced risk reduction in kidney outcomes. Data from the EMPA-REG OUTCOME trial, a study in which Type 2 diabetes mellitus patients with cardiovascular disease had been treated (1:1:1) with empagliflozin 10 mg, 25 mg, or placebo, was analysed to identify patients who had experienced an initial eGFR dip of >10% from baseline at Week 4 after treatment initiation. Results showed that 28% of patients on empagliflozin experienced an eGFR dip and diuretic use and/or a higher KDIGO risk category at baseline correlated with an initial eGFR dip of >10% in empagliflozin, compared to placebo treatment. Furthermore, an eGFR dip >10% had no major impact on empagliflozin induced risk reduction and rates of kidney adverse events, which was consistent across the subgroups.

Prof Christoph Wanner, ERA-EDTA President-Elect, noted that these findings were more likely in those taking diuretics and/or had a more advanced stage of chronic kidney disease. However, he concluded: "For such high-risk patients, especially, any intervention is welcome that slows the progression of kidney disease and allows the need for dialysis to be postponed as long as possible."

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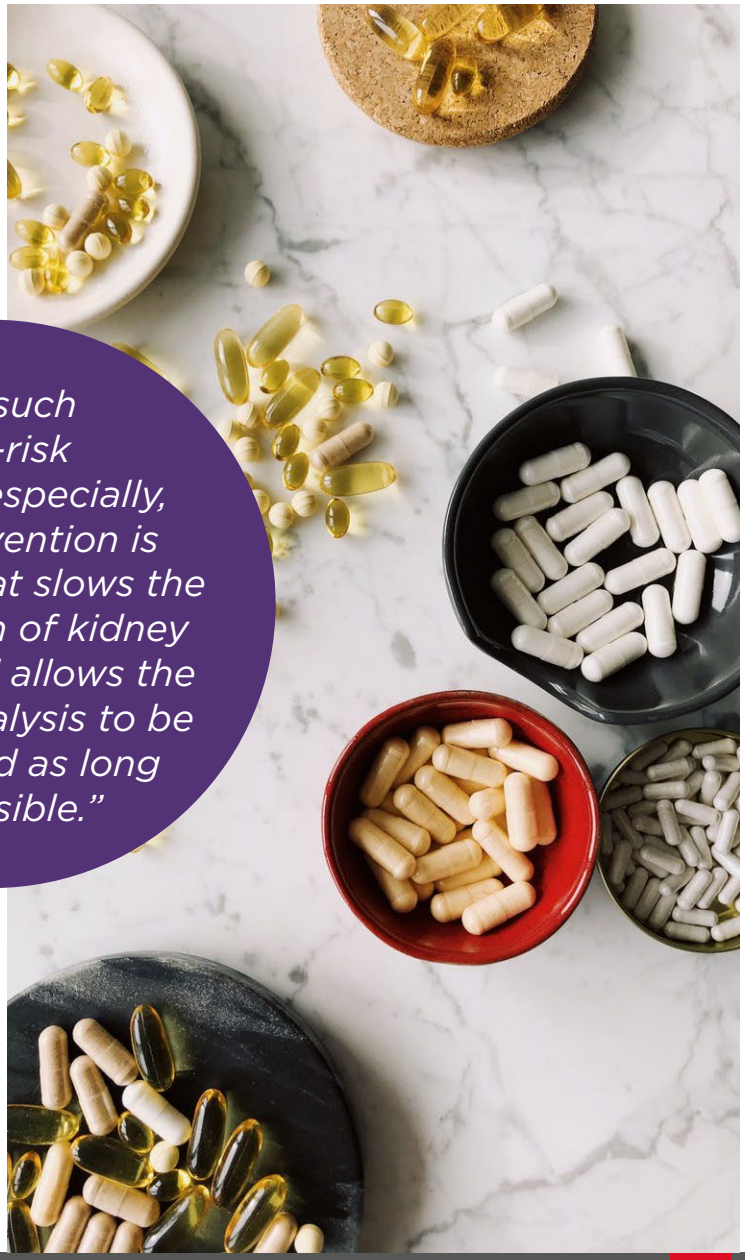

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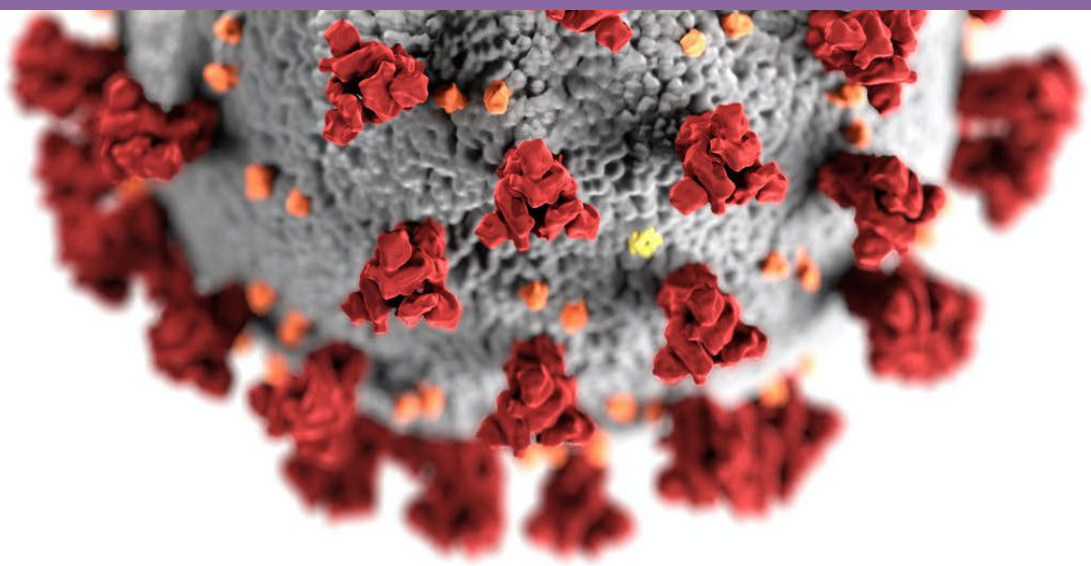

Genetic Background of Kidney Injury and SARS-CoV-2

GENETIC analysis has revealed a link to SARS-CoV-2 associated kidney injury as exemplified in findings presented during a press release at the ERA-EDTA virtual congress on 8th June 2020.

According to current studies, as many as 80% of critically ill COVID-19 patients are hospitalised with SARS-CoV-2-associated kidney injury. In half of these cases, proteinuria and haematuria are present and renal tissue examination of deceased patients revealed injury to glomeruli, podocytes, and tubular cells. In this study, two COVID-19 patients (>50 years old) presented with injury to renal structures. Both were known to have high blood pressure, and one had cardiac insufficiency while the other had hepatitis B. Kidney biopsies revealed capillary collapse in the glomeruli, podocyte swelling, glomerular deposits of immunoglobulins (IgM and complement component C3), tubule injury, partial tubule atrophy and necrosis, while inflammatory cells (monocytes, macrophages) were also present.

SARS-CoV-2 was not detected in blood, urine, or kidney tissue samples despite highly sensitive real-time PCR testing and positive virus detection from the throat swab. Molecular genetic analysis showed variants of the *APOL1* gene (homozygous G1 polymorphism and G1/G2 heterozygosity), which is associated with increased risk of kidney disease. Corresponding author Prof Ziad Massy, Hôpital Universitaire Ambroise Paré, Boulogne Billancourt, France, stated that it is probable that the injury was not caused by direct viral infection but rather by a SARS-CoV-2-induced inflammatory reaction. He added: "Particularly in the context of genetic *APOL1* risk variants, SARS-CoV-2 might have triggered the 'collapsing focal segmental glomerulosclerosis' in accordance with the 'second hit' hypothesis."

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According to Prof Alberto Ortiz, Autonomous University of Madrid, Madrid, Spain, because SARS-CoV-2 has spread across the world, SARS-CoV-2-induced kidney injury will be most prevalent in regions where the *APOL1* gene variants G1/G2 are more common. He further highlighted that because of greater rates of expression of *APOL1* risk variants in people of African-American descent, lung problems, renal complications, and associated conditions can be particularly expected in the USA, among other countries.

The ADVOCATE Study Showed the Benefits of Avacopan in Rare Autoimmune Disease

AVACOPAN is an orally administered drug which has been shown to be beneficial in achieving remission in ANCA-associated vasculitis (AAV). This is according to findings from the ADVOCATE study presented at the 57th ERA-EDTA Virtual Congress 2020 in a press release dated 7th June 2020. The ADVOCATE study was a Phase III trial spanning 52 weeks to assess the efficacy and safety of avacopan, formerly CCX168, in the treatment of AAV.

AAV is a systemic disease involving the formation of autoantibodies causing inflammation of small blood vessels and may result in severe injury of the kidneys, potentially causing harm to the lungs, upper respiratory tract, heart, skin, and nervous system, even causing death. Modern immunosuppression therapy, such as rituximab, is available and works by blocking parts of the immune system, unlike corticosteroids which work by blocking the entire immune system. This can, however, lead to infection. Prof David Jayne, Cambridge, UK, explained: "AAV must be treated with immunosuppressants. However, the side effects of these substances can be severe – especially at higher corticosteroid doses." Complement component C5a plays a role in the pathogenesis of AAV. Avacopan is a novel orally selective C5aR antagonist which has been investigated in two clinical Phase II trials to show its effect on the inhibition of activation of immune cells induced by C5a, reducing inflammation.

Patients enrolled in the trial (n=330) were randomised 1:1 to receive prednisone (n=164) or avacopan (n=166), combined with either cyclophosphamide then azathioprine, or rituximab. The patients were confirmed to have achieved sustained remission if they did not relapse between Week 26 and 52. At Week 26, remission was present in 72.3% of patients in the avacopan group compared to 70.1% in the prednisone group. At Week 52, 65.7% of patients were in remission in the avacopan group compared to 54.9% in the prednisolone group. Dr Maria Jose Soler Romeo, Chair of the Paper Selection Committee of the 2020 ERA-EDTA Congress, from Barcelona, Spain, commented on the significance of research such as this: "This is so important, because potentially life-threatening diseases such as AAV often require treatments that themselves pose risks – new immunosuppressive, specifically targeting substances are therefore urgently needed in order to improve therapies further and avoid the high dose steroids side effects."

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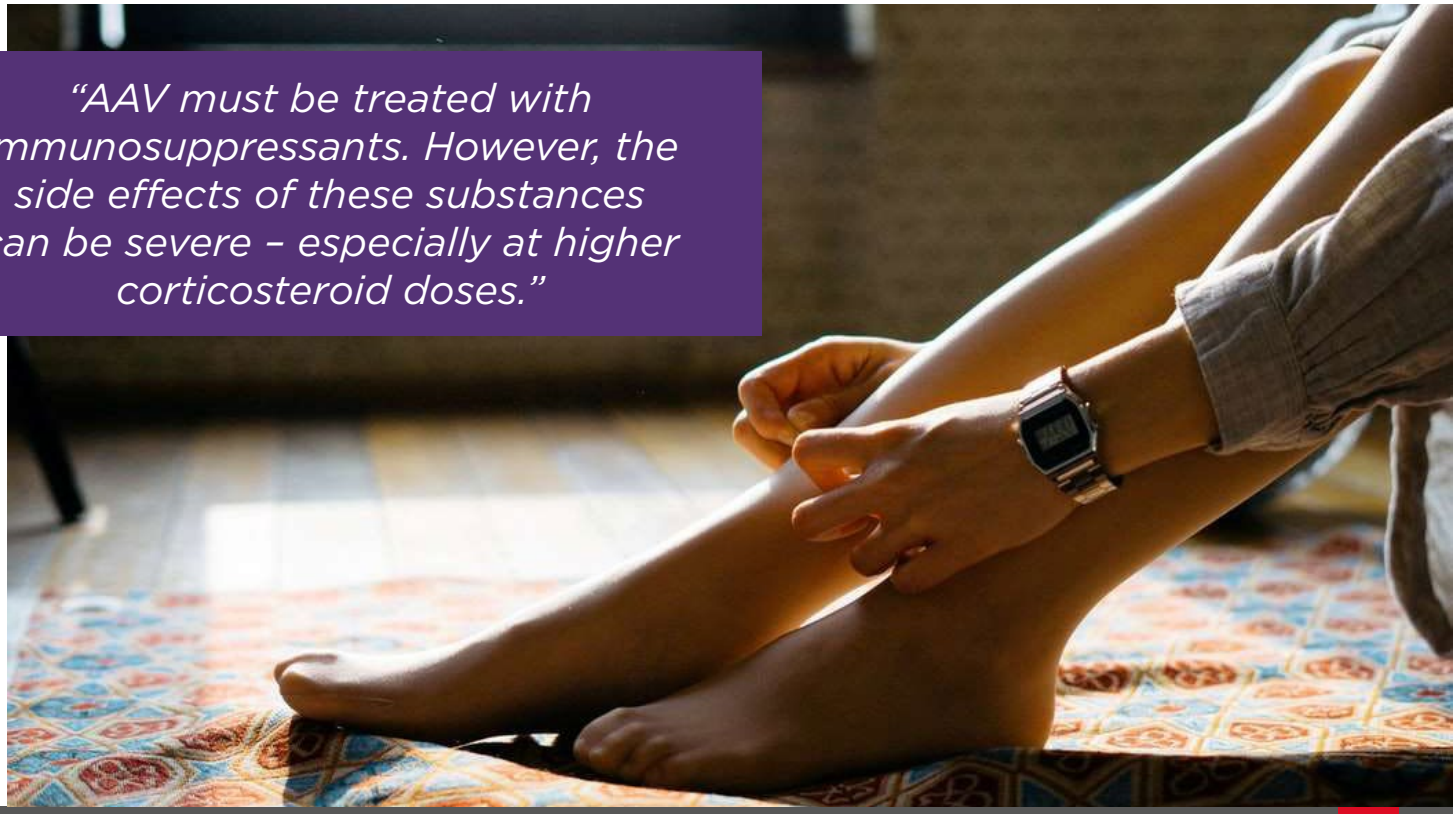

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