Dear colleagues and friends

Welcome to Istanbul and the 50th ERA-EDTA Congress!

We are honoured to host the 50th ERA-EDTA Congress in Istanbul, the most beautiful city of Turkey, and are proud to present an outstanding scientific programme that will make the 2013 ERA-EDTA Congress a unique one, worthy of the golden anniversary year of our Society.

The Scientific Committee has taken great care in preparing the high-quality programme that incorporates the latest developments and ideas in basic research, transitional and clinical science. Our agreed mission is to promote nephrological science in order to benefit patients with kidney diseases. Therefore the programme is closely linked to the advances in modern nephrology and also to the epidemiology of chronic kidney disease.

Scientific highlights

The track structure focuses on the topics of greatest importance and provides orientation in the not only attractive, but also very extensive scientific programme – more than 300 talks will be presented by international experts. On the whole, the attempt has been made to bring acute and chronic kidney failure as well as dialysis and end-stage renal disease, transplantation, hypertension, fluid and electrolyte homeostasis, glomerular diseases, paediatric nephrology and ethical issues under one roof. The congress offers many opportunities in terms of symposia, workshops, master classes and courses (e.g. “Ultrasound in Nephrology” or “Interventional Nephrology” which is held in collaboration with the American Society of Diagnostic and Interventional Nephrology to update knowledge of practical relevance and to exchange experience in face-to-face dialogue.

The topics covered by the congress include many highlights. At this point I would like to draw special attention to the highly anticipated symposium on late breaking clinical trials: The ERA-EDTA congress is again the setting for a wide range of new clinical data – more than 2400 abstracts of pioneering studies have been published in the abstract book. During the late breaking clinical trial session the results of the most path-breaking ones will be presented.

In addition, we are looking forward to the plenary lectures presented by highly renowned nephrologists: Professor Sever (Turkey) will talk about the link between disasters and nephrology. Professor Hoffmann (France) will deliver a lecture on innate immunity, Professor Remuzzi (Italy) will discuss the possibility of kidney engineering and Professor Ikizler (USA) will focus on the important question which diets could improve the outcome of our patients.

Educational opportunities

Returning attendees of the ERA-EDTA congress can expect a number of new offerings and an enhanced experience this year. New features include the “Working Groups Fair & Overview on Health Care in Nephrology, Dialysis and Transplantation in Europe”. This additional day – initiated and organised by my highly esteemed colleague Professor Rosanna Coppo – provides a platform for the presentation of the nine ERA-EDTA working groups, their projects and collaboration with international associations. There will be a joint symposium of the ERA-EDTA and the European Society of Paediatric Nephrology and another one of the ERA-EDTA’s transplantation working group and the European Society for Organ Transplantation.

The whole congress programme reflects the idea of networking. I am very glad that we have jointly organised a symposium together with the Chinese Society of Nephrology focussing on the epidemiology of...

Continued on page 2
The awareness of crush syndrome needs to be increased.

Prof. Sever: There are no studies specifically addressing the effects of the early versus late initiation of dialysis in crush-related AKI cases. Crush-related AKI differs from AKI because of the accompanying hypercatabolic state, and the rapid development and high incidence of life-threatening problems, i.e. severe hyperkalaemia, acidosis, pulmonary oedema and uraemic complications.

The recently published European Renal Best Practice (ERBP) “Crush Recommendations” therefore suggest more liberal indications for starting dialysis in crush syndrome patients in anticipation of potential complications.

What is the preferred mode of dialysis?

Prof. Sever: We recommend intermittent haemodialysis because of a high clearance rate of low molecular weight solutes, the possibility of dialysing without anticoagulation, and the possibility of treating several patients per day at the same position.
It can take days to bring trained experts or equipment to disaster areas. How can the inhabitants in these regions be trained so that they can contribute to the rescue effort? Prof. Sever: This is a vital issue. We have seen very different data about the participation of the local public in rescue activities – for example after the Southern Italian earthquake in 1980 and the Armenian earthquake in 1988. Residents living in disaster-prone regions must therefore be trained for rescue activities, especially within the first hours and days of the disaster. This can be made possible with the support of media, especially television.

Turkey is particularly prone to earthquakes. How does your country prepare to provide adequate medical help? Prof. Sever: As far as renal disaster relief preparedness is concerned, we have a central coordination system and have assigned local disaster relief coordinators to 17 sectors of the country who are responsible for applying local primary action plans. In addition, we send medical material and personnel to the disaster area from unaffected regions. These plans were very effective after the recent Ercis earthquake (in 2011). For mega-disasters we will certainly need outside help, e.g., through the RDRTF.

What are the most common mistakes made in medical logistics or support campaigns? Prof. Sever: In my opinion, some countries are not well prepared for disasters, and many of them are not even aware of such a threat. But we also face serious problems with regard to foreign support: donated material is not always effective, and inexperienced personnel sent to disaster regions can cause an additional workload for local administrations. Poorly organised relief efforts with their influx of rescuers and material only worsen the chaos, creating a secondary disaster and interfering with global rescue activities – as seen after the Haiti earthquake in 2010.

What can medical societies such as ERA-EDTA or ISN do to help in the case of an emergency, and how can they advance preparedness? Prof. Sever: In the case of an emergency these societies should organise pragmatic assistance campaigns and send medical items, as well as experienced personnel, to the affected countries to help people cope with disaster-related problems.

Founding the ISN’s RDRTF after the Armenian earthquake in 1988 proved to be a very useful initiative. Thanks to the efforts of this structure, very effective help campaigns were organised after the earthquakes in Marmara, Turkey (1999); Bam, Iran (2003); Kashmir, Pakistan (2005); and finally Haiti (2010).

With regard to the second part of your question, the societies should definitely increase awareness of the threat of renal disasters, organise CME courses in collaboration with the national societies, and suggest that members develop national disaster preparedness scenarios including the assignment of medical relief coordinators.

Dos and don’ts when giving fluid for AKI prevention in crush victims

- Do start fluids at the earliest convenience; if possible, even before extrication.
- Do infuse fluids at a rate of 1 l/hr during the first two hours of extrication and decrease the fluid administration rate by at least 50% (<500 ml/h) afterwards.
- Do prefer isotonic saline in mass disasters, while bicarbonate half-isotonic saline would be a better selection in small-scale disasters. This is a logistical rationale; it is easy to reach isotonic saline in the chaos of mass disasters, while it may be problematic to prepare bicarbonate solutions in chaotic mass disaster circumstances.
- Do individualise the type and rate of fluids in view of demography of the victim, trauma pattern, environmental conditions, time spent under the rubble and many other factors.
- Do not give disaster crush victims any solution containing even small amounts of potassium, unless you have laboratory facilities to check the biochemistry.
- Do not administer mannitol to oligoanuric patients.
- Do not prefer colloids over crystalloids in disaster crush victims.

Crush syndrome is a complicated problem, carrying a high risk of morbidity and mortality.

Presenting the treasures of European nephrology

The Working Group Fair before the official congress opening offers more than 30 CME courses.

The idea for a Working Group Fair started when we discussed how to celebrate the 50th anniversary of the ERA-EDTA congress, according to Professor Rosanna Coppo, chair of the Scientific Committee of the ERA-EDTA Congress in Istanbul. “To show the power of our scientific working groups, we decided that they should present their educational activities before the official opening of the congress.” Indeed, the number of working groups has grown to six over the last years, dealing with important questions related to immunonephrology, inherited kidney diseases, dialysis, transplantation, mineral and bone disorders in chronic kidney disease and cardiovascular medicine.

In addition, there is also EUTox, another working group endorsed by the ERA-EDTA and the ERA-EDTA Registry. Some of the CME tracks will even be organised as a joint event with other scientific societies, such as the European Society of Renal Transplantation and the European Society of Paediatric Nephrology.

Already last year in Paris, the CME courses offered by the ERA-EDTA attracted great interest – rooms were fully packed and attendees were standing because there were no more seats available. This year the CME programme was extended to about 30 pre-congress courses which is a real treasure for those attending and a very good update for a small fee only. Coppo hopes that in addition to the regular congress attendees many local doctors from Turkey and the Balkan area will enjoy this programme.

Read more about the ERA-EDTA working groups on the following pages of this issue.
Cardio-renal initiatives on the verge

EURECA-m studies help elucidating how renal dysfunction engenders cardiovascular complications.

The European Renal and Cardiovascular Medicine Working Group (EURECA-m) has seen some really exciting initiatives and developments over the previous months, according to its chairman Gerard London. The renowned nephrologist refers for example to a NDT publication, which came out in January 2013 and is based on new data derived from the EURECA-m Registry. The registry involves several centres in Europe, and one of its aims is to measure conventional echocardiographic parameters in patients with end-stage renal disease on chronic dialysis. Although echocardiography is part of the core curriculum of cardiologists, it suffers from a major limitation related to its high operator dependence and experience. The publication describes a central reading protocol that has been set up for the registry in order to give robustness to the echo studies. This standardised, core lab led approach and the link of echocardiographic parameters to the rich clinical database of the EURECA-m Registry represents a novel opportunity for European nephrologists to undertake observational and intervention studies of the highest standard.

Ultrasound also plays a central role in the LUST study, in another major EURECA-m project. The study aims at testing the use of ultrasound B-lines to measure lung water and thereby prevent death and cardiovascular events in high-risk haemodialysis patients. Lung water frequently occurs in dialysis patients and may lead to left-ventricular disorders. London hopes that “the LUST study may help to improve clinical outcomes in a category of patients where several previous clinical trials failed to show a benefit of a variety of interventions, including drug-based interventions like statins and, very recently, cinacalcet”. To organise the study, EURECA-m made an open call to all European centres and got very positive feedback: 43 European centres were interested in participation and 25 centres were eventually selected based on the validity of their local infrastructure. These centres include seven French units, five Italian units, two German, Polish, Spanish and Greek units, and one unit from the UK, Israel, Romania, Slovenia and Turkey, respectively. A special kick-off meeting was held on March 8-9, 2013, in Barcelona, Spain. The trial will last for two years.

Gerard London is also happy to report that EURECA-m’s CME activities attracted considerable interest among nephrologists: EURECA-m celebrated a successful CME course in Ankara in September 2012, organised by Gultekin Suleymanlar, and another one in April 2013, organised by Denis Fouque in Lyon. “For the Istanbul congress we set up a high-grade pre-congress CME programme which provides an excellent overview on the most interesting topics in the field of cardio-renal care,” London concludes.

New working group on CKD-MBD

Disorders of mineral metabolism and bone disease are common complications in chronic kidney disease.

Only recently, the ERA-EDTA Council approved a new working group dedicated to mineral and bone disorders (MBD) in chronic kidney disease (CKD). The term refers to a systemic disorder due to CKD which manifests itself by either one or a combination of abnormalities in calcium, phosphorus, parathyroid hormone (PTH), or vitamin D homeostasis, changes in bone turnover and vascular calcification.

Professor Cozzolino: you are the chairman of the new CKD-MBD working group. Which projects do you want to pursue in this field?

Prof. Cozzolino: Disorders of mineral metabolism and bone disease are common complications in CKD and contribute to increased morbidity and mortality and decreased quality of life in affected individuals. Importantly, there is an increasing body of convincing evidence suggesting that these disorders are associated with the increased risk for cardiovascular calcifications, morbidity and mortality of these patients. One of our first projects is related to calciphylaxis, a poorly understood and highly morbid syndrome of vascular calcification and skin necrosis that affects only 1–4% of the population with end-stage renal disease. The incidence might have increased during the last decade due to, for example, a more widespread use of parenteral vitamin D and iron dextran. An internet-based registry for this disease is already available in Germany and we are now ready to start a pan-European one, which will also be based in Aachen at the Institute of Doctor Vincent Brandenburg and Professor Jürgen Floege. This will hopefully enable us to obtain information from 500 patients in one year. We would also like to evaluate the best possible therapy for stage III or IV CKD patients, who are deficient of vitamin D, but are not on dialysis and seem to accumulate phosphates. However we do not intend to focus on one drug or one target only. Many trials in this field failed because they addressed only one single parameter, be it PTH, potassium, phosphorus, haemoglobin or blood pressure. In daily clinic practice doctors will control all these parameters. So it would be very interesting to see whether the progression of CKD and cardiovascular disease could be stopped if we integrate therapies.

Where do you see the challenges in treating CKD-MBD?

Prof. Cozzolino: It is extremely important to stimulate communication about the optimal treatment for these patients. Despite of guidelines, we observe considerable differences regarding the clinical practice among various European countries. In addition, we have to deal with a growing number of older patients. This year, we scheduled two meetings to cover the visual pathology, clinics and treatments of CKD-MBD, one on May 18 in Istanbul, where we will have the opportunity to introduce our activities, the other one will be our first workshop on December 5 in Milan. We are also in contact with other ERA-EDTA working groups such as EURECA-m.

What are the highlights of your working group session in Istanbul? Prof. Cozzolino: We are going to officially present ourselves for the first time in this session and will introduce the German calciphylaxis registry. We also invited Markus Ketteler to give a presentation about hidden phosphates, as hyperphosphataemia has become a topic in managing CKD.

ISSUE 1 / May 18, 2013

CME Track
EURECA-m Working Group
Room: Emirgan 2
Date: 18-05-2013
From: 10:00 to 13:00 and 14:00 to 17:00

CME Track
CKD-MBD Working Group
Room: Macka
Date: 18-05-2013
From: 10:00 to 13:00
Two critical decisions in treating elevated serum phosphorus:

**WHEN & HOW**

Renvela®: right from the start™ in your chronic kidney disease patients new to dialysis.

This product (or indication) is not yet registered in every country. Check the drug compendium in your country or consult our company before prescribing it.

**Product Summary:** Renvela 800 mg film-coated tablets. Renvela 2.4 g powder for oral suspension. **Active substance:** sevelamer carbonate. Subject to medical prescription. **Composition:** Each tablet contains 800 mg sevelamer carbonate. Each tablet also contains microcrystalline cellulose, sodium chloride and zinc stearate. The tablet coating contains hypromellose and diacetylated monoglycerides. The printing ink contains iron oxide black (E172), propylene glycol, isopropyl alcohol and hypromellose. Each sachet contains 2.4 g sevelamer carbonate. The powder contains propylene glycol, citric acid, sodium chloride, sucralose, ferric oxide (E172). **Therapeutic indications:** Renvela is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis. Renvela is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus > 1.78 mmol/l. Renvela should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Hypophosphataemia. Bowel obstruction. **Possible side effects:** The safety of sevelamer (as either carbonate and hydrochloride salts) has been investigated in numerous clinical trials involving a total of 969 haemodialysis patients with treatment duration of 4 to 50 weeks (724 patients treated with sevelamer hydrochloride and 245 with sevelamer carbonate), 97 peritoneal dialysis patients with treatment duration of 12 weeks (all treated with sevelamer hydrochloride) and 128 patients with CKD not on dialysis with treatment duration of 8 to 12 weeks (79 patients treatment with sevelamer hydrochloride and 49 with sevelamer carbonate). The most frequently occurring (≥5% of patients) undesirable effects possibly or probably related to sevelamer were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity. Data possibly or probably related to sevelamer from these studies are listed by frequency here next. Gastrointestinal disorders: nausea, vomiting, upper abdominal pain, constipation (very common) and diarrhoea, dyspepsia, flatulence, abdominal pain (common). The reporting rate is classified as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated. **Post-marketing experience:** During post-approval use cases of pruritus, rash, intestinal obstruction, ileus/subileus and intestinal perforation have been observed in patients during treatment with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate. **Product Licence holder:** Genzyme Europe BV, Gooimeer 10, 1411 DD Naarden, The Netherlands. **Date of revision of text:** September 2010. **Attention:** Please see full prescribing information.

©2013 sanofi-aventis LLC. A SANOFI COMPANY. All rights reserved. GL.SEV.04.13.001

To learn more, visit booth #Q11 at the European Renal Association – European Dialysis and Transplant Association Congress May 18 – May 21.
Promoting research in immunonephropathy

The Immunonephrology Working Group tracks the various aspects of immune-mediated renal damage.

Professor Rosanna Coppo draws a positive balance of what has been achieved by the Immunonephrology Working Group (IWG). Indeed, the list of IWG projects is impressive: for example, the EU-LAR/ERA-EDTA recommendation for the management of lupus nephritis has been completed last year and results will be reported in Istanbul. Moreover, VALIGA, the European Validation Study of the Oxford Classification of IgA nephropathy (IgAN), has also been completed recently and is about to be published; it includes 1,147 patients from 55 centres in 13 different countries; with a total of 150,000 records it is the largest database in Europe for glomerular disease. Rosanna Coppo will be presenting the major results of VALIGA in Istanbul. In addition, the VALIGA network has generated a number of interesting post-VALIGA investigations which will be started soon. They are planned on the basis of a genome-wide association study of IgAN done in collaboration with the Columbia University in New York and will help identify additional factors influencing the severity of IgA nephropathy at presentation and the risk of progression to end-stage renal failure, including genetic variability, complement activation, cytokine network and new urinary biomarkers.

The STAR-MEN (Sequential Therapy with Tacrolimus and Rituximab in Membranous Nephropathy) study addresses another important topic in immunonephropathy. Cyclic treatment with corticosteroids and alkylating agents is still considered to be the first choice in membranous nephropathy, but the severity of side effects is an important drawback. STAR-MEN evaluates whether sequential therapy with tacrolimus followed by a cycle of rituximab will result in a higher number of patients with complete and partial remission of nephrotic syndrome than standard treatment. Despite some initial challenges the trial, led by Manuel Praga, is active now.

In addition, the group supported the start-up of other research projects, such as KIDNEYNET CONNECT, a shared European Platform for excellence in nephrology and podocyte research, headed by Harry Holthofer and the EuroKUP initiative CKD Bio, led by Goez Spasovski. CKD Bio aims to identify surrogate markers that predict outcomes in chronic kidney disease due to glomerulonephritis through an extensive and cohesive EU clinical and research network. “We do not finance these projects, but we facilitate the start-up, for example by supporting patient enrollment,” says Coppo. The IWG is also ready to start a registry that will focus particularly on recurrent glomerulonephritis following renal transplantation. As transplant survival rates improve, recurrence of glomerulonephritis is expected to become more prevalent over the next years. “Thus, we need to know how fast the disease progresses, what its prevalence would be and which treatment can slow down progression. The project chaired by Juergen Floege and Loreto Gesualdo will help to find the answers,” says Rosanna Coppo. Another idea refers to a closer collaboration between renal biopsy registries in Europe and the United States. “We went on to discuss this idea with Agnes Fogo, who leads the American group, and after solving some economical issues we hopefully can start.”

CME Track
Immunonephrology Working Group
Room: Beyazit
Date: 18-05-2013
From: 10:00 to 13:00 and 14:00 to 17:00

Good news on haemodiafiltration

The European DIALysis Working Group aims at enhancing the quality of dialysis therapies.

There are good news for patients with end-stage renal disease – online haemodiafiltration (OL-HDF) can reduce all-cause mortality compared with standard haemodialysis, according a Catalanian group of researchers. Their data published in February 2013 suggest that switching eight patients from haemodialysis to OL-HDF may prevent one annual death. “Doseage seems to be decisive for this beneficial effect,” says Peter Blankestijn, who chairs the EUropean DIALysis (EUDIAL) Working Group of the ERA-EDTA. Obviously a minimum amount of convection volume has to be delivered in order to obtain the survival benefit from OL-HDF. “This may also explain why we didn’t see these benefits in former investigations, such as our own CONTRAST study or the Turkish OL-HDF study: in both trials, a substantial percentage of patients received low dosage while in the Catalanian study the average dosage was higher.”

However, what do these results mean for clinical practice? First, in any future study, data on the actual delivered volume should be reported and not only the target volume. Second, it is important to evaluate the factors that determine the actual achieved volume in OL-HDF. “The question arises why this dosage is achieved in some patients and not in others,” Blankestijn comments. “Therefore, one of our goals this year is to combine all data of the three studies, do a more detailed analysis and hopefully come back with some answers.” The Turkish and Catalanian study groups have already agreed to deliver all their individual data to EUDIAL for a meta-analysis. If everything goes well, results could be available by the end of this year.

Now, the time has also come to address the question which patient groups may benefit the most of OL-HDF. Growth retardation, for example is an important problem in children on dialysis, especially in those with end-stage kidney disease. Usually they receive growth hormone to catch-up growth, but preliminary data indicate that haemodiafiltration may reduce growth retardation in this particular group of patients. One of the major limitations in this field is that many of the paediatric nephrology centres treat only a low number of young patients, which is not enough to pursue renal studies. Fortunately, the ERA-EDTA, in collaboration with the European society of Paediatric Nephrology (ESPN) is running a paediatric registry, so the infrastructure is already available. “We got into contact with some paediatric nephrologists who are very enthusiastic about the idea of joining forces and learning more about the value of haemodiafiltration in this particular group of patients,” says Blankestijn. “We’ll have a first CME course in Istanbul and another one later in London to get this initiative started.”

CME Track
EUDIAL Working Group
Room: Emirgan 1
Date: 18-05-2013
From: 11:00 to 13:00 and 14:00 to 15:30
From biomarkers to uraemic toxins

EUTox unites experts in the field of uraemia and uraemic toxicity.

Starting in 1999, the European Uraemic Toxins (EUTox) Work Group was launched by its members Raymond Vanholder, Bernd G.Stegmayr and Ulrich Baumeister. During the 27th ESAO Meeting in Lauenanne in 2000, the work group convened for its first meeting and in 2010, EUTox was endorsed by the ERA-EDTA. The group aims at bringing together experts in the field of uraemia and uraemic toxicity to make progress in understanding, preventing and treating renal disease.

One of the first projects EUTox accomplished was the publication of a joint review about the main topic of interest of each member. Since then, the group’s activities have been focussed on promoting research, educational activities and the dissemination of knowledge on uraemic toxicity. EUTox actively participates in the ERA-EDTA CME programme by organising CME sessions during regular group meetings, for example in Skopje (Makedonia), Malaga (Spain), Berlin (Germany) and Naples (Italy), to quote the 2011 and 2012 events. Coordination of collaborative research resulted in more than 140 joint publications to date. Research has been orientated along three main axes: i) uraemic solutes, biological systems and biomarkers, ii) vascular diseases related to chronic kidney disease, and iii) dialysis and removal techniques. In the field of uraemic solutes, EUTox has established a list of known uraemic toxins, which has been updated in 2012 and is made available through the uraemic toxins data base (http://eutoxdb.odeessoft.com/viewtoxins.php). In its Master of Molecules programme (MoMs), the group aims at characterising the effects of uraemic toxins on various biological systems. During the Working Group Fair in Istanbul, EUTox offers a highly interesting CME programme.

References:


Angel Argilés, Chairman of EUTox, CNRS, Montpellier, France and Joachim Jankowski, Co-Chairman of EUTox, Charité University Hospital, Berlin, Germany

CME Track EUTox
Room: Beylerbeyi 2
Date: 18-05-2013
From: 10:00 to 13:00 and 14:00 to 17:00

Networks in paediatric nephrology

ESPN intensifies collaboration with ERA-EDTA and IPNA.

The founding of the European Society for Paediatric Nephrology (ESPN) in 1967 was a milestone for paediatric nephrology in Europe. Now, more than 2,000 European paediatricians in 46 European countries work in the field of paediatric nephrology, and approximately 500 of them meet regularly at the annual ESPN meetings. In 2013, the ESPN Council has launched a call for new working groups. Seven fields of interest have been identified, including transplantation, dialysis, mineral bone disorders in chronic kidney disease, congenital anomalies of the kidney and urinary tract, inherited renal disorders, nephrotic syndrome and immune-mediated renal disorders.

Rosanna Coppo, Secretary General of the ESPN, explains the rationale behind this approach: “In Europe there are several initiatives, cohort studies and registries which have been developed by active paediatric nephrologists with the aim of gathering a sufficiently large group of children with rare conditions to allow studies of genetic background, clinical data, outcome and therapeutic approaches. These initiatives are highly appreciated by the ESPN and we now want to advance this work by facilitating a comprehensive European network creating increased visibility and collaboration with the International Paediatric Nephrology Association (IPNA) and the ERA-EDTA. By doing so we hope that we can promote academic activities in areas not yet covered.”

No additional financial support can be provided at the moment. However, the ESPN will search for industry sponsorship for well-defined working group activities in future. The society can also help to improve the visibility of a working group, facilitate the dissemination of results and promote CME courses – a CME session jointly organised by the ESPN and the ERA-EDTA will take place during the ERA-EDTA congress in Istanbul. Moreover, the combined ESPN/ERA-EDTA European Registry for Children on Renal Replacement Therapy in Amsterdam provides an infrastructure, which can give optimal support and may help to enroll patients in clinical studies.

CME Track Paediatric Nephrology.
Room: Uskudar I
Date: 18-05-2012
From: 9:00 to 13:00 and 13:00 to 17:00
Approaching inherited kidney disorders

WGIKD brings together geneticists, general and paediatric nephrologists.

Dozens of inherited diseases affect the kidney; collectively, they account for at least 10% of patients with end-stage renal disease in Europe. The underlying genetic defects may compromise all aspects of kidney function and can also cause extrarenal symptoms. In terms of frequency, inherited kidney disorders vary from relatively frequent diseases, such as autosomal dominant polycystic kidney disease (ADPKD), to ‘rare’ diseases that, by definition, affect less than five persons in every 10,000. The ERA-EDTA Working Group on Inherited Kidney Disorders (WGIKD) aims at filling a gap in European nephrology and mobilizing a critical mass of expertise.

“I’m very happy to say that we succeeded in providing the first scientific grants last year. We call them ‘impulsion grants’, because they were created to boost clinical or basic projects pertinent to patients with inherited kidney disorders. One was granted for preparing a European cohort of children with autosomal dominant polycystic kidney disease (ADPKD), another one promotes research on microRNA in ADPKD, and the third one is about genetics of CKD genetics in Cyprus,” explains WGIKD Chair Olivier Devuyst. The EuroCYST project to establish a large scale pan-European cohort of adult ADPKD patients is another big objective. The study protocol is currently being finalised; if approved, the study could start with six pilot centres in the summer of 2013. Significant progress was also achieved regarding the educational mission of the working group: with 80 participants, the first CME course in Zurich in December 2012 was already a great success; the next one on polycystic kidney disease will follow in Oxford in October 2013. Moreover, the group has extended its scientific network to include Chinese colleagues interested in inherited kidney disorders. Collaboration with paediatric nephrologists is also in the focus of the WGIKD efforts, according to Devuyst. WGIKD organised several activities jointly with the European Society of Nephrology (ESPN). A joint meeting with ESPN and the International Paediatric Nephrology Organisation will take place later this year in Shanghai.

And what about the WGIKD highlights in Istanbul? The field has witnessed great developments over the last year. Thus, attendees can look forward to the pre-congress CME programme, which includes sessions about new perspectives in genetics diagnosis, tubular disorders, polycystic kidney disease, registries and policies, according to Devuyst.

Endorsing renal transplantation in Europe

The DESCARTES Working Group is committed to improve transplant rates and transplantation outcomes.

Since its launch in December 2013, the number of members of the new DESCARTES Working Group has already grown to 374 nephrologists from 55 different countries in Europe and beyond. The acronym DESCARTES stands for ‘Developing Education, Science and Care for Renal Transplantation in European States’ and summarises the working group’s ambitious goal to contribute to the improvement of renal care and especially of patients living with a kidney transplant.

DESCARTES focuses on three pillars to implement these objectives; in its educational activities the group aims at addressing general nephrologists to promote pre-emptive transplantation and stimulate living donor transplantation. Daniel Abramowicz, head of the renal transplantation programme at the Université Libre de Bruxelles in Brussels and chairman of DESCARTES, explains the group’s rationale by saying that “the improvement of pre-emptive transplantation from living donors is a crucial step to prevent organ shortage, increase transplant rates and allow for better patient outcomes. General nephrologists can direct their patients reaching terminal kidney failure towards pre-emptive living donor transplantation.” To foster discussions on this issue, the group, in collaboration with the European Society of Organ Transplantation (ESOT) will organise a symposium at the ERA-EDTA Annual Meeting. Moreover, the DESCARTES/ESOT joint pre-congress CME track in Istanbul will also deal with the question of how to improve transplant rates and outcome of transplant patients. Additional joint events will follow at the ESOT congress in September 2013.

In the field of transplant research, the DESCARTES advisory board sees the absence of clinical studies on the effect of immunosuppressive therapy in elderly transplant patients as a big challenge. DESCARTES is therefore investigating the possibility for a controlled clinical multicentre trial to optimise immunosuppression in this steadily growing patient group. New fundamental knowledge could also arise from investigating the few patients, who achieved an immunosuppression-free state (also referred to as clinical operational tolerance) after transplantation. These patients could hold the key to tolerance; therefore the DESCARTES board plans to identify European kidney transplanted patients with operational tolerance.

Cooperation and networking is finally the third focus of DESCARTES. In March, DESCARTES met with the kidney group of ESOT to find out, where the two committees could join forces to promote transplantation within the common framework of Europe and abroad, both scientifically and towards the authorities. Abramowicz concludes that “the Annual Meeting in Istanbul is an excellent opportunity to meet DESCARTES and ESOT members and exchange scientific ideas. Interested researchers and clinicians shouldn’t miss our sessions and CME courses. If you want to keep posted about DESCARTES initiatives and start networking with colleagues involved in kidney transplantation, you can become a DESCARTES member; it is fast and free on the ERA-EDTA website.”
Nobel Prize Laureate Jules A. Hoffmann is a pioneer in investigating the innate immunity of insects and more recently of the genetically tractable fruit fly Drosophila. In 2011, he, together with Bruce Beutler and Ralph Steinmann, received the Nobel Prize in Physiology or Medicine for breakthrough discoveries concerning the activation of innate immunity. The scientists have revolutionised our understanding of the immune system by revealing key principles for its activation.

The Toll pathway – crucial in microbial sensing of the fruit fly

Hoffmann’s work on the immune system of insects reaches far back into the past. While studying in Strasbourg in the 1960s he started looking at antimicrobial defence mechanisms in insects, initially of grasshoppers, a severe plague in many countries of the world at that time. Early in the 1990s he and his team at the French National Center for Scientific Research (CNRS) in Strasbourg turned towards Drosophila as a model organism and focused their research on antimicrobial peptides as effector molecules. The discovery of Toll genes by Christine Nüsslein-Volhard (awarded with the Nobel Prize in Physiology or Medicine in 1995, together with Erich Wieschaus and Edward Lewis) attracted the attention of Hoffmann’s group, and they started to work with Toll-deficient Drosophila mutants. While Nüsslein-Volhard’s findings referred to the essential involvement of Toll genes during embryogenesis, the Hoffmann lab discovered its role in the innate immune system of the fruit fly. A crucial discovery as it revealed a second vitally important Toll function: the Toll pathway being involved in microbial sensing and the stimulation of the production of antimicrobial peptides.

Two distinct pathways involved in innate immunity

However, the Toll pathway is not the only one involved in innate immunity. The second one is the immune deficiency (Imd) pathway. Hoffmann explains: “Two recognition and signalling cascades control the immune response in Drosophila. The Toll pathway is activated by Gram-positive bacteria and by fungi, whereas the Imd pathway responds to Gram-negative bacterial infection.” Toll and Imd pathways can interact synergistically and it has been shown that cross-regulation occurs.

In the signalling cascades following infection, nuclear factor kappa B (NF-κappa B) proteins play a major role as inducible transactivators. The Drosophila genome codes for three NF-κappa B family members: Dorsal and DIF (for dorsal-related immunity factor) are proteins retained in the cytoplasm by binding to the same inhibitor protein Cactus; the third family member, Relish, requires proteolytic cleavage for activation. All of these proteins function in the host defence of Drosophila to control the expression of genes encoding immune-responsive peptides and proteins. Prominent among the induced genes are those encoding peptides with direct antimicrobial activity such as drosomycin which encodes an antifungal peptide and which is often used as a readout for Toll pathway activation. But noteworthy, says Hoffmann: “During infection, the Toll and Imd pathways control the expression of hundreds of genes.”

Flies as a model for human diseases

The pioneering work of the Hoffmann laboratory, in conjunction with that of other groups in Europe and the United States, has prompted a flood of research activities on innate immunity all over the world. Other scientists were able to confirm and extend these findings in various species up to mammals including man. Evidence has been provided that molecules involved in innate immunity are of evolutionary ancient origin and highly conserved domains have been detected. Members of the NF-κappa B family, for example, are already present in sponges and cnidaria and can be found in all bilateria up to mammals.

The identification of Toll-like receptors (TLR) and other homologues in mammals is particularly interesting for medicine. It is worth mentioning in this context that the Drosophila Imd pathway exhibits stringent similarities with the mammalian Tumor Necrosis Factor Receptor (TNFR) pathway. These findings demonstrate how important flies can serve as model organisms to study certain aspects of human disease. Professor Hoffmann is sure: “While our research was done initially to answer basic questions on insect antimicrobial defences, the extensions to mammals in biomedical laboratories has resulted in applications. The development of new adjuvants working through Toll-like receptors may be a good example of the impact of such basic research. Other potential fields of application include autoimmunity and inflammation which also involve Toll-like receptors, for example in lupus nephritis.” The Nobel Prize Committee concluded in 2011: “As a consequence of their discoveries, new fields of research have opened up that hold the promise to improve vaccination and treatment against infection, cancer and inflammatory diseases.”

Plenary Lecture 1: Innate immunity: from flies to humans

Jules Hoffmann, CNRS, Strasbourg, France

Room: Harbiye
Date: 19-05-2013
From: 11:45 to 12:30

©Cold Spring Harb Perspect Biol 2009;1:a000232

ERA-EDTA

ISSUE 1 / May 18, 2013

Nobel laureate Prof. Jules Hoffmann
© CNRS Photothèque – Didier Pascal

Induction of Toll and Imd pathway in Drosophila by pathogens Gram-positive bacteria are recognized by peptidoglycan recognition proteins PGRP-SA, GNB1 and PGRP-SD. This recognition results in the activation of a proteolytic cascade culminating in the cleavage of the cytokine Spaetzle via the Spaetzele Processing Enzyme (SPE). Upon binding to the Toll receptor, dimeric cleaved Spaetzle activates the intracellular signalling cascade. Fungi are recognized by GNB3 which also activates SPE via a proteolytic cascade. Entomopathogenic fungi also activate the Toll pathway through the circulating zymogen Persephone. Gram-negative bacteria are directly detected by the transmembrane receptor PGRP-LC.

An evolutionary ancient immune defence system combats pathogenic microorganisms.
Francesco Locatelli received the ERA-EDTA Award for his outstanding scientific achievements

Francesco Locatelli began his nephrological career more than 40 years ago. “After exciting years as a young nephrologist at the Milan Polyclinic, I was offered the opportunity to build a nephrology department at the Adige and Manzoni Hospital in Lecco at the age of 31 years. I accepted with enthusiasm and had the chance to create a well-organised team,” Locatelli recalls the first years of his career. Since then, Professor Locatelli has been active in a broad range of topics from hypertension to nutrition, progression of chronic kidney disease, adequacy of dialysis, electrolyte homeostasis, IgA nephropathy and anaemia. He is a prolific writer and was involved in a large number of important clinical trials. He is also a welcome guest and speaker at many scientific meetings. In addition, he was involved intensively in guidelines where he first served as a chairman of the European Best Practice Guidelines on anaemia. He was also on the board of the National Kidney Foundation Dialysis Outcome and Quality Initiative (NKF-DQI) guidelines on anaemia. Later on, he became a member of the first Board of Directors of Kidney Disease: Improving Global Outcomes (KDIGO).

Locatelli is truly one of the giants of nephrology who was at the basis of a broad array of clinical information that has its repercussion today and will continue to impact future nephrology practice.

Professor Jorge Cannata-Andia was a young nephrologist, when he became a member of ERA-EDTA in 1982. “Coming back to Spain from the Western Infirmary Hospital in Glasgow, I realised that the Spanish nephrologists should participate more in European organisations such as the ERA-EDTA. In 1982, the ERA-EDTA congress took place in Madrid, and two of my abstracts were accepted for oral presentation. It was challenging, to do my first two international presentations in English, but it was a good experience.” Since then, Professor Cannata-Andia actively participated in the ERA-EDTA. In 1993, he was elected ordinary council member. In 2002, he became first Scientific Advisory Board in 2006, establishing ERA-EDTA Registry Courses in 2005, and lobbying for financial support for the QUEST project. Moreover, Cannata-Andia was also instrumental in the ERA-EDTA becoming part of the European Kidney Health Alliance (EKHA), which is currently very active in lobbying the European Community both for research funding and for awareness issues. Being asked about the most challenging situation of his presidency, Cannata-Andia refers to the preparation of the World Congress of Nephrology in 2009. “The ERA-EDTA and the International Society of Nephrology had decided to organise this congress as a joint meeting, but it was not clear if it would be in Milan or elsewhere. The President of the ISN, William Couser, and myself made the first steps of this big plan, choosing Milan as the venue,” Cannata-Andia recalls. Their initial efforts paid off and the WCN Congress became a big success.

The award acknowledges the merits of Professor Cannata-Andia to the ERA-EDTA. However, his enthusiasm has not only been an important factor for the achievements of the ERA-EDTA, he is also a respected and laudable scientist with particular interest in mineral bone disorders in chronic kidney disease with a large number of highly appreciated publications in high impact factor peer-review journals. “Unfortunately, I do not have as much leisure time as I would like,” he says. “However, every year I try to spend some days travelling. I enjoy photography and music – jazz, tango and flamenco are among my favourites.”

Dr. Julien Zuber receives the 2013 Stanley Shaldon Award for Young Investigators

Next to being a qualified nephrologist, Julien Zuber has also obtained master degrees in enzymatic biochemistry, medical epidemiology and biological therapeutics. Dr. Zuber, who ranked number three in the French national medical competitive examination, accomplished the largest part of his career at Necker Hospital in Paris, France. At present, however, he works as a Fullbright research fellow at the Columbia Centre of Translational Immunology in New York, because he strongly aspired to move into a more translational basic research arena in immunology. “This was the reason, why I took the opportunity to complete my post-doctoral training in the lab of Dr. Megan Sykes at Columbia, who is a leader in this field,” Dr. Zuber explains. “This is a wonderful opportunity for me to acquire the most relevant and innovative skills for monitoring the cellular alloimmune response and to gain expertise to mixed-chimerism-based tolerance induction protocols in humans.” After returning to France, Dr. Zuber aims to develop a similar programme based on his experience acquired in the United States.

When asked about the most inspiring person in his academic career, Dr. Zuber refers to Professor Christophe Legendre, Head of the department of kidney transplantation at Necker Hospital. “He has been strongly encouraging and supporting scientific audacity provided that the research attempts to eventually improve patient care. And he helped me to develop critical thinking skills,” Dr. Zuber says. Curiosity for science and critical thinking pay off – Dr. Zuber published an impressive amount of 51 original publications.

When he doesn’t work in the lab or the clinic, Dr. Zuber enjoys family life, doing sports, traveling across the country, hiking in gorgeous landscapes and visiting the amazing museums of New York. “These are great places to be,” he says.
IN aHUS, COMPLEMENT-MEDIATED TMA CAUSES SUDDEN AND PROGRESSIVE ORGAN FAILURE AND PREMATURE DEATH\textsuperscript{1,5}

<table>
<thead>
<tr>
<th>Follow-up (months)</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>12.5</td>
<td>12</td>
</tr>
<tr>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>75</td>
<td>3</td>
</tr>
</tbody>
</table>

**Cumulative fraction of patients free of events**

Modified from Caprioli et al.\textsuperscript{5,9}

\textbf{aHUS is a catastrophic disease that can result in sudden and progressive vital organ failure and premature death\textsuperscript{6,9}}

\textbf{Early and chronic intervention is critical\textsuperscript{6-11}}

- 70\% of patients with aHUS who have the most common CFIH mutation die, require dialysis, or have chronic renal insufficiency\textsuperscript{2,3,9}
- 33\% to 40\% of patients die or progress to end-stage renal disease (ESRD) with the first clinical manifestation\textsuperscript{1-11}
- 65\% of all patients die, require dialysis, or have permanent renal damage within the first year after diagnosis despite plasma exchange or plasma infusion\textsuperscript{2,3,9}

For more information, visit Alexion booth n° S11

Pregnancy in dialysis patients

The DIAPER study is collecting data on treatment and outcomes.

Because pregnancies in dialysis patients are rare, most nephrologists will encounter only one or two cases of women on dialysis getting pregnant during their time in medical practice. It is suggested that the frequency of pregnancy in young women on dialysis is rising and that the survival of infants born to these women is increasing. Nevertheless, most of the publications on pregnancies in dialysis in Europe are case reports or small case series. Those that were published may unintentionally have focused on cases with favourable outcomes and therefore suffer from publication bias.

Recently, the ERA-EDTA Registry therefore initiated the “DIAlysis and Pregnancies in EuRope (DIAPER)” study. With this study we aim to estimate the incidence of pregnancies in chronic dialysis patients between 2007 and 2011 in different European countries.

In addition, we aim to assess which treatment regimens are used in pregnant dialysis patients and are associated with the best outcomes for mother and child.

To start with, each dialysis centre in Europe is asked to complete a short questionnaire with three questions, even if the centre did not record any pregnancies in the past five years. Centres that did record one or more pregnancies between 2007 and 2011 and agree on further participation in the study, receive another more extensive questionnaire by e-mail, including questions on demographics, treatment during pregnancy, delivery, and outcomes of mother and child.

All national and regional renal registries participating in the ERA-EDTA Registry were contacted and asked to help us in collecting data for the DIAPER study by forwarding the first questionnaire to all dialysis centres in their country or region. At the moment of writing this article (first week of April 2013), the first phase of the data collection is running in 15 European countries, and at least 15 other countries will follow. So far, 17 pregnancies in 15 women treated with chronic dialysis from eight different countries were identified and more detailed information on these cases is currently being collected.

The results of this study are much needed as they may help to optimise outcomes for mother and child and could help nephrologists to advise patients who would like to become pregnant and to care for them if they get pregnant. Please, help us to obtain a response rate as high as possible.

If your centre would like to participate in the DIAPER study and was not yet invited to do so, or if you would like to know more about the study, you may contact me at m.noordzij@amc.uva.nl. More details on the study design and the first results of the DIAPER study will be presented during the ERA-EDTA Registry symposium.

mTOR inhibitors: lights and shadows

The clinical use of mTOR might be advantageous and dangerous at the same time.

The mammalian target of rapamycin (mTOR) is a key intracellular kinase that regulates cell growth and metabolism in response to intracellular and environmental inputs, including nutrients, oxygen levels, growth factors and cytokines signals (fig.). Its specific inhibitors sirolimus and everolimus are currently used in kidney transplant recipients as immunosuppressive drugs to prevent allograft rejection. Several mechanisms underlie the immunosuppressive effects of mTOR inhibitors. Indeed, they have been reported to inhibit T cell proliferation, induce anergy, modulate T cell trafficking, promote regulatory T cells, and prevent maturation of dendritic cells as well as production of type I interferon.

In the last ten years of clinical use, we learned that mTOR inhibitors may have pleiotropic and even diverging effects: they are primarily immunosuppressive drugs, but can induce immunostimulatory effects on CD8+ T cells. mTOR inhibitors have been shown to reduce the development of atherosclerotic lesions, but at the same time cause severe hyperlipidaemia and may promote inflammation. They delay the progression of interstitial fibrosis and glomerulosclerosis, but induce a significant increase in proteinuria.

mTOR inhibitors have been demonstrated to prolong lifespan, to reduce the effects of ageing and to prevent the development of neoplasia, but their use has been associated with an increase in graft recipients mortality. Moreover, mTOR inhibitors have also been shown to induce a reduction of body mass index, but are associated with the development of type II diabetes. Playing with mTOR, a central switch of cell metabolism, might be advantageous and dangerous at the same time and, even if mTOR inhibitors have been used in the clinical setting for more than ten years, we still need time to learn how to take advantage of their beneficial properties without paying an excessive fee to their “side” effects. In addition, we should consider that their clinical use might shed light on some key biological questions on the link between metabolism, immune response and ageing.

S18: Immunosuppression: when not enough, when too much?

Date: 19-05-2013
From 8:45 to 10:15
Learn more about HighVolume HDF in the Lunch Symposium “High Volume Matters in Haemodiafiltration” on May 19th, 2013 from 12.30-14.15 hrs in hall Rumeli B.

Come and talk to us about the new HighVolume HDF study:
- Significant 30% reduction of all-cause mortality
- 33% lower risk of cardiovascular mortality
- Significant 28% reduction of intradialytic hypotensive episodes
- All-cause hospitalisation lowered significantly by 22%

Interested? See you at our booth Level B5, booth no. M7 or visit www.HighVolumeHDF.com

“Because I want my patients to live longer and better.”
One marker is not enough

Prognostic accuracy in acute kidney injury can only be achieved by using a panel of biomarkers.

Acute kidney injury (AKI) is frequent especially in hospitalised patients and independently associated with increased morbidity and mortality. Currently no effective therapy of AKI is available. Therefore, efforts focus on early prevention, and potentially early initiation of renal replacement therapy to improve the outcome in AKI. The development of AKI needs to be detected as early as possible for prevention to be most effective, as only a very narrow window seems to exist.

To apply effective prevention timely, early detection of AKI has become a high clinical and research priority. The recent AKIN definitions of AKI incorporate serum creatinine and urine output as markers to diagnose AKI. However, these markers do not permit early detection of AKI. Recently, serum and urinary markers such as cystatin C, IL-18, KIM-1 and NGAL performed well in pilot trials in small, homogeneous cohorts as detection and prognostic markers of AKI. Often, these promising results could not be confirmed in larger multicentre trials. As AKI is multifactorial and heterogeneous in origin, it seems unlikely that one singular marker will enable accurate assessment. Rather, a biomarker panel will be required to detect AKI early and to predict its outcome. In 2010, our group used capillary electrophoresis-mass spectrometry to identify a panel of 20 peptides predictive of AKI. A good diagnostic performance was obtained with an area under the ROC curve of 0.91. In a subsequent study we addressed the question whether this high prognostic value can also be reached by one single peptide analyte detected by capillary electrophoresis-mass spectrometry. As shown by ROC comparison in figure 1, even with the most discriminating single peptide it was not possible to reach the same level of prognostic accuracy as with the established AKI peptide marker panel composed of 29 different peptide fragments derived from β-2-microglobulin, α-1-antitrypsin, fibrinogen α and the collagen chains α-1(I) and α-1(III). This finding further supports the hypothesis that a panel of markers is needed to accurately detect AKI several days in advance to its onset.

Lessons from experimental models

Humanised mouse models have come to the forefront of transplant immunology research.

Transplant tolerance, defined experimentally as donor-specific non-reactivity, is the holy grail of transplant immunology research. The clinical correlate is operational tolerance, i.e. long-term allograft survival with normal function in the complete absence of immunosuppression. 60 years have passed since the first report of experimental tolerance, yet the widespread attainment of clinical tolerance still remains elusive.

While the injection of neonatal recipients with donor-derived cells is not a viable clinical strategy, this method has paved the way for various techniques that employ chimerism to induce tolerance. For example, myeloablative therapy and donor-derived bone marrow transplantion have been used with some success in adults, but are only clinically acceptable in patients with haematological indications for bone marrow ablation. Mixed chimerism may be employed through non-myeloablative conditioning, producing a state where donor cells represent a proportion of the total haematopoietic pool. However, this technique does not guarantee tolerance and risks the development of graft-versus-host disease (GvHD). There is evidence that peripheral tolerance with regulatory T cells (Treg) plays an important role in maintaining the tolerant state after the induction of chimerism. Experimental work from our group and others has demonstrated that Treg may be harnessed independently through in vivo induction or ex vivo expansion and use as a cellular therapy. Other peripheral regulatory therapies under assessment include regulatory B cells, macrophages, dendritic cells and stem cells.

Both chimerism and peripheral regulatory immunotherapies have been developed in experimental animal models. However, effective immunotherapies developed in such models may have catastrophic effects in humans, as demonstrated by the TGN1412 trial. Cellular therapies are implicitely species-specific and therefore require assessment in an appropriate experimental model that accounts for differences in the immunobiology between species. Cells developed for use in rodents are significantly different in both function and phenotype to human cells, as are the methods for their production. To address this challenge, humanised mouse models have come to the forefront of transplant immunology research. These models allow the efficacy of human cellular therapies to be assessed in vivo in the context of human allografts. They also provide limited safety data which is normally only attainable at the clinical trial phase. By bridging the gap between laboratory and clinical trials, humanised mice allow accelerated translational research without incurring direct patient risk, and may contribute to the early elimination of therapies that would otherwise fail at the final hurdle of the clinical trial phase. Indeed, the use of humanised models has facilitated the first clinical trials of Treg which are now underway.

Amaya Albalat1, Jochen Metzger2, and Harald Mischak1,2
1University of Glasgow, UK
2Mosaïques diagnostics GmbH, Hannover, Germany
S10: Biomarkers for AKI
Room: Rumeli B
Date: 19-05-2013
From: 14:30 to 16:00

Fadi Issa, Transplantation Research Immunology Group, University of Oxford, UK
S7: Transplant tolerance
Room: Rumeli A
Date: 19-05-2013
From: 8:45 to 10:15
Treating end-stage renal disease in ADPKD

What can epidemiology tell us about effective renoprotection in autosomal polycystic kidney disease?

Autosomal polycystic kidney disease (ADPKD) is the most common heritable kidney disease, affecting approximately one in every 1000 subjects. Most affected subjects show progressive renal function decline and need renal replacement therapy between their 50th and 70th year of age. It is generally assumed that this patient group forms around 10% of all subjects who are dependent on dialysis or living with a kidney transplant, but differences in prevalence between regions have been suggested.

Several treatment options have become available to postpone the need for renal replacement therapy in subjects with renal disease, such as blood pressure control, inhibition of the renin-angiotensin aldosterone system (RAAS) and low protein diets. These treatment options have also been tested in ADPKD, generally with disappointing results. However, these studies should be interpreted with caution, since they were not powered to reach definitive conclusions. Furthermore, the ADPKD patients included in these studies were often in a phase of their disease where renal function is still relatively stable. In such patients it is not possible to study the renoprotective efficacy of interventions. Therefore, a conclusive answer to the question whether common renoprotective regimens are ineffective in ADPKD is lacking.

Interestingly, two epidemiological studies even suggested that the average age of onset of end-stage renal disease in ADPKD patients has increased considerably during the last two decades. These findings were interpreted as evidence for the effective use of renoprotective therapies in this patient group.

Unfortunately, these studies were underpowered, too, and should therefore be considered as hypothesis generating rather than as proof of renoprotection being obtained in this patient group. Moreover, the increase in average age at which these patient start renal replacement therapy could also be due to the fact that during the last decades the elderly have become eligible to enter programmes for renal replacement therapy.

Despite the fact that ADPKD is one of the most common causes of end-stage renal disease, it is surprising that the epidemiology of treated ESRD due to ADPKD has poorly been studied. Based on the ERA-EDTA registry data, Ron Gansevoort will be giving a comprehensive overview of the so far largest epidemiological ADPKD data set. Attention will be paid to regional differences in the prevalence of treated end-stage renal disease patients with ADPKD, to the type of renal replacement therapy received by these patients, and to method-specific mortality data. Most importantly, data will be provided on the incidence and average age at onset of treated end-stage renal disease. In particular, the author will address the question whether epidemiological data can provide information about the effectiveness of normal renoprotective regimens in ADPKD in the absence of solid data from randomised controlled trials.

Ron T. Gansevoort, Dept. Nephrology, UMC Groningen, The Netherlands

S4: ERA-EDTA Registry

Date: 19-05-2013
From 8:45 to 10:15

JOIN COMPACT RENAL
AND BE PART OF THE CKD-MBD COMMUNITY

CompAct Renal provides the latest scientific articles on hyperphosphatemia and beyond – from leading international experts, for experts.

FOLLOW US ON WWW.COMPACT-RENAL.COM
Tubular damage markers for AKI diagnosis

For AKI risk prediction, NGAL performs superior over simultaneously measured serum creatinine or urine output.

Cardiovascular risk profile in children on RRT

The ERA-EDTA Registry symposium on Sunday provides an overview of coexisting multiple cardiovascular risk factors.
Regulatory T cells in kidney transplantation

Drawing conclusions on the influence of immunosuppression on regulatory T cells is difficult.

Kidney transplantation is the most effective method of treating end-stage renal disease. However, long-term kidney allograft survival has not improved substantially, and both acute and chronic rejection have been suggested to be involved in late kidney allograft loss. Long-term immunosuppression is associated with several side effects and for many patients the triple drug regimen is unnecessary because of their weak alloreactive-ness. However, strategies of weaning these drugs off have not yet been accompanied by reliable tests which allow for monitoring changes in both alloreactivity and tolerance.

As early as in 1995, Sakaguchi et al. described CD4+CD25+FoxP3 regulatory T cells which play a critical role in the alloimmune response. According to Lopez et al., induction therapy with rabbit antithymocyte globulin (rATG) expanded the CD4+CD25+FoxP3 regulatory T cell (Treg) population in a dose-dependent manner in vitro. This type of induction depletes T cells from the periphery, allows for early repopulation of Tregs in vivo and preserves its suppressive activity. Thus, the success of this induction therapy is likely to be explained by enhanced regulation that sustains for several weeks after transplantation, in addition to T cell depletion.

The influence of maintenance immunosuppression on Tregs has been widely discussed. A regimen free of calcineurin inhibitor (CNI, tacrolimus or cyclosporine A), including belatacept, was shown to have no direct effect on the expansion of Tregs in the graft tissue. However, when using rATG induction followed by a sirolimus-based, CNI-free regimen, the recruitment of Tregs into the allograft was suggested to play a role for graft acceptance. Similarly, patients with subclinical rejection, who had no Tregs in their graft infiltrates, exhibited significantly worse graft function at three and five years after transplantation. Bedtard et al. found subclinical rejection in six-months protocol biopsies with Foxp3+ Treg infiltrates in patients who received rATG induction and sirolimus, while biopsies of patients treated with basiliximab induction and CNI-based immunosuppression exhibited no infiltrates. By contrast, another study reported elevated expression of FOXP3 in rejection which was not associated with kidney allograft outcome.

Due to inconsistencies in therapeutic regimens, firm conclusions about the proper role of circulating and infiltrating Tregs in kidney grafts cannot be drawn so far. The adoptive transfer of Tregs represents the scope of several experimental therapies under recent investigation.

NETS – the double-edged sword

Neutrophils have been linked to many aspects of immune regulation and autoimmunity, in addition to their direct antimicrobial functions. Defects in neutrophil function, either in humans or in animal models, result in immunodeficiencies with severe consequences for the host.

Neutrophils are granulocytes that acquired their name because their granules stain with neutral dyes, as first described by the pioneering work of Paul Ehrlich. Neutrophils are sometimes also referred to as polymorphonuclear cells, or PMNs, because of the unusual, multilobulated shape of their nuclei. It has long been established that neutrophils efficiently ingest microbes and encase them in a vacuole where they are exposed to high concentrations of antimicrobials and eventually killed. Phagocytosis is one of neutrophils’ main functions in the immune defence. Notably, neutrophils can also undergo a unique form of cell death, called “netosis”, which results in the release of “NETs” or neutrophil extracellular traps.

NETs are composed of modified chromatin and specific neutrophil proteins. NETs are released in response to microbial and other stimuli, and they are thought to have evolved to help fighting infections. After initial stimulation, neutrophils generate large amounts of reactive oxygen species (ROS) which are essential for neutrophils to respond to many stimuli. By mechanisms that are still not fully understood, ROS formation leads to the release of neutrophil elastase (NE), a neutrophil-specific protease, from the granules into the cytoplasm. Eventually, NE reaches the cell nucleus where it processes histones, preceding the relaxation of chromatin and the eventual release of NETs. Interestingly, NET components, such as DNA, histones and some neutrophil proteins, are also the targets of antibodies in some autoimmune diseases, such as systemic lupus erythematosus (SLE).

NETs are degraded by DNaseI, an enzyme produced by the pancreas. Notably, a hereditary form of SLE was mapped to DNaseI and one of its homologues in two independent cohorts, suggesting that inefficient NET degradation may be linked to the disease. Furthermore, it was shown that neutrophils from SLE patients are more prone to make NETs in response to several stimuli, including autoantibodies, and that NETs can stimulate other white blood cells, such as dendritic cells, to make cytokines. Taken together, it appears that the untimely or inappropriate formation or degradation of NETs is linked either to the initiation or the progression of SLE. It is interesting to speculate whether NETs play a role in other autoinflammatory or autoimmune diseases. NETs might also represent a new target for diagnosis or treatment of these diseases.

Arturo Zychlinsky, Max Planck Institute for Infection Biology, Berlin, Germany
S26: Lupus nephritis and vasculitis
Room: Harbyje
Date: 20-05-2013
From: 14:30 to 16:00

Ondrej Viklicky, Institute for Clinical and Experimental Medicine, Prague, Czech Republic
S7: Transplant tolerance
Room: Rumeli A
Date: 19-05-2013
From: 8:45 to 10:15

Induction of regulatory T cells by rabbit antithymocyte globulin (rATG).

Treating immune-mediated renal diseases
Fernando Fervenza will be presenting on anti-CD20 therapy in several glomerular disease processes.

Recent insights have shown the importance of autoantibodies in the pathophysiological mechanisms of several immune-mediated glomerular diseases. In diseases such as ANCA-associated vasculitis, membranous nephropathy and lupus nephritis, autoantibodies either have been involved in causing direct glomerular injury or correlate with disease activity for many years. It is known that B lymphocytes have been implicated in the pathogenesis of ANCA-associated vasculitis. The frequency of activated B lymphocytes is known to be associated with both disease activity and severity of ANCA-associated vasculitis. B lymphocytes were also thought to be crucial in the production of potentially pathogenic ANCA.

Several clinical studies have provided evidence that a therapy directed against B cells, such as cyclophosphamide, is effective in patients with ANCA-associated vasculitis. The same has been shown in patients with membranous nephropathy and lupus nephritis. Cyclophosphamide has striking, but nonselective effects on B cell function and suppresses the secretion of immunoglobulins. Thus, targeting B lymphocytes holds particular promise for selectively depleting B cells and therefore halting the production of immunoglobulins directed against antigen(s) present in the glomeruli, improving or even resolving the glomerular pathology and reducing proteinuria. There is evidence that this strategy is effective in the treatment of other antibody-mediated diseases such as rheumatoid arthritis.

Given this understanding, rituximab has been tested as a new therapeutic agent for the treatment of immune-mediated renal disease. Rituximab is a genetically engineered chimeric murine-human monoclonal antibody directed against CD20 antigen, which is expressed on human B cells and at low levels on a small subset of T cells, too. Initially designed for the treatment of non-Hodgkin’s B cell lymphoma in 1997, it has emerged as a potent immunosuppressant for many autoimmune diseases; thus, it was approved by the FDA for the treatment of patients with rheumatoid arthritis, and more recently for the treatment of ANCA-associated vasculitis.

Rituximab has also been used to treat patient with membranous nephropathy and heavy proteinuria. Over 150 patients have been treated so far with rituximab at a dose of 1 gram intravenously two weeks apart, 375 mg/m² for four weeks, or according to a B cell-driven protocol. The response in proteinuria has been shown to be gradual and sustained with no significant differences in the effectiveness at one year between the different dosing regimens. Total B cell counts started to recover at three months, which is faster than in patients with ANCA-associated vasculitis, rheumatoid arthritis or non-Hodgkin’s lymphoma; these findings suggest that heavy proteinuria resulted in decreased levels in rituximab, though there was no correlation between rituximab levels, degree of proteinuria or response to drug.

Remission rates of 60-80 % were similar between patients with or without previous immunosuppressive therapy. No serious adverse events were attributed to rituximab. The drug may also allow successful withdrawal in calcineurin-inhibitor dependent patients.

Pilot studies also show promise on the use of rituximab in the treatment of nephrotic syndrome in children and adults with minimal change disease and steroid-sensitive focal segmental glomerulosclerosis. Given its efficacy, tolerability and safety profile in comparison to more conventional treatment regimens, rituximab is rapidly emerging as a critical treatment modality in glomerular disease. In the presentation entitled “Anti CD20: emerging treatment strategies of immune-mediated glomerular disease”, the current state of anti-CD20 therapy in several glomerular disease processes will be reviewed.

Hutchinson–Gilford progeria syndrome
Reduction of progerin levels can be achieved through an antisense gene therapy approach.

Hutchinson–Gilford Progeria (HGPS) is an extremely severe and rare segmental premature ageing syndrome characterised by postnatal growth retardation, typical dysmorphic features, lipodystrophy/lipoatrophy and generalised amyotrophy, early skin changes such as sclerosis and thinning with hypo-/ hyperpigmented areas, reduced bone densities, and accelerated, severe atherosclerosis. The disease invariably leads to death in teens at the mean age of 13.5 years, due to myocardial infarction in most cases. No validated treatment is available to date.

In 2003, our group identified the LMNA gene, encoding the ubiquitous nuclear proteins Lamins A/C with a recurrent, de novo, heterozygous mutation causing most typical HGPS cases. This mutation activates a cryptic pre-mRNA splice site leading to the production of a truncated Lamin A precursor called “progerin”. Progerin cannot be fully post-transcriptionally processed, remains aberrantly prenylated and accumulates in cell nuclei, where it exerts several toxic effects. Progerin is produced at low levels in healthy cells during aging in culture and by fibroblast cultures of aged individuals, substantially contributing to the cellular pathological phenotypes associated with the ageing process. The presence of progerin in human tissues has further been demonstrated in the skin of aged individuals or in human smooth vascular cells. Progerin may also be involved in the closure of the ductus arteriosus (ductus botalli, due to its temporally and spatially restricted expression in its smooth vascular cells after birth.

In 2008, preclinical studies in vitro on patients’ cells and animal models of the disease, obtained in collaboration with Carlos Lopez-Otin’s group, Oviedo, provided proof-of-principle that the combined use of pravastatin, a statin, and the aminophosphonate zoledronic could improve the natural course of the disease and ameliorate several disease parameters such as growth, bone density and survival. The beneficial effects of these drugs could be ascribed to the reduction of progerin prenylation levels, as well as to their specific pharmacological activities. These data allowed our group to launch a phase II open-label, single-arm, monocentric trial conducted in La Timone Children’s Hospital, in Marseille, France, on 12 European children affected by progeria. The trial aimed to assess the safety and efficacy of a combination of pravastatin and zoledronic on several disease parameters, including growth, bone density and turnover as well as cardiovascular risk parameters. The data, issued after a two-year treatment, are under publication.

A study reporting partial beneficial effects after a two-year treatment with a farnesyl transferase inhibitor (lonafarnib) in a cohort of HGPS children has been published last year.

```markdown
<table>
<thead>
<tr>
<th>Room: Uskudar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: 19-05-2013</td>
</tr>
<tr>
<td>From:14:30 to 18:00</td>
</tr>
<tr>
<td>S9: Biological targets for treatment of glomerular diseases</td>
</tr>
</tbody>
</table>
```
More recently, again in collaboration with Carlos Lopez Otin, we developed a novel knock-in mouse line, carrying the LMNA mutation (p.G609G) equivalent to the human one causing HGPS (p.G608G). This model faithfully reproduces the molecular defects underlying the disease and its clinical features. Using these mice, we obtained the first preclinical in vivo proof of principle that the reduction of progerin levels can be achieved through an antisense gene therapy approach by intravenous delivery, with beneficial effects on several disease parameters, including lifespan. Our next goal is to translate these studies into a novel clinical trial for children affected by progeria. Given the tight link established between progeria and ageing, all results obtained in this rare disease may also have important spin-offs in the field of normal ageing.

References

Anna Chiara De Sandre-Giovannoli, La Timone Children’s Hospital, Marseille, France

S3: Progeria syndrome in chronic kidney disease/end-stage renal disease
Room: Rumeli B
Date: 19–05–2013
From: 8:45 to 10:15

Pierre Ronco, Hanna Debiec, Tenon Hospital, Paris, France
S14: Membranous nephropathy
Room: Uskudar
Date: 19–05–2013
From: 16:15 to 17:45

Insights into membranous nephropathy

When glomerulopathies serve as disease models ...

Membranous nephropathy (MN), a major cause of nephrotic syndrome and chronic renal insufficiency, is an immune-mediated disease characterised by the accumulation of immune deposits on the outer aspect of the glomerular basement membrane (GBM) containing mostly IgG4 and variable amounts of IgG1 antibodies as well as antigens that have long eluded identification. In experimental models, either podocyte antigens or circulating antigens that become “planted” in the glomerular capillary wall serve as targets for circulating antibodies which locally form immune complexes and stimulate assembly of the C5b-9 attack complex. This sequence of events actually causes proteinuria.

The glomerulus Rhesus disease

When mothers are deficient in neutral endopeptidase (NEP), an enzyme located at the podocyte membrane, neonates are born with a severe form of membranous nephropathy which usually recovers within a month simultaneously with the disappearance of maternal antibodies produced during pregnancy. Careful studies of the five families that we have identified as yet, led us to conclude that maternal anti-NEP IgG1 were responsible for the neonatal glomerular disease whereas IgG4 which fails to activate classical and alternative complement pathways did not seem to be “nephritogenic”. These observations suggest that diseases caused by maternal-fetal incompatibilities extend beyond Rheus disease and may affect the kidney and other organs as well, a matter of thought for neonatologists and paediatricians.

MN as a molecular model of auto-immunity

In the wake of these studies that provided the proof of principle that a human podocyte antigen could serve as target for circulating antibodies, Beck and colleagues identified the M-type phospholipase A2 receptor (PLA2R), another podocyte antigen associated with 70 to 80% of primary forms of membranous nephropathy in the adult. This major breakthrough has led to the development of new diagnostic tests comparable to those used in lupus (immunofluorescence and ELISA), which will induce a paradigm shift in the diagnosis and surveillance of patients with membranous nephropathy. Our recent findings in a patient with a monoclonal anti-PLA2R IgG3 kappa who developed a recurrent membranous nephropathy in the grafted kidney, suggest that these antibodies were pathogenic.

Although our genome-wide associated study (GWAS) clearly showed that the PLA2R1 gene was strongly associated with primary membranous nephropathy, we failed to identify rare variants or mutations in PLA2R1 that could account for a neo-epitope specific for patients with primary membranous nephropathy and be responsible for PLA2R antigenicity in these patients. These findings suggest that a rare combination of common polymorphisms in PLA2R and/or rare variants of intronic and regulatory sequences might be involved. It is likely that development of autoimmunity to PLA2R results from genetic variations in both immune response genes such as HLA-DQA1 identified in our GWAS and in PLA2R. Other gene variants as well as environmental hits might also be implicated in the triggering of the disease as well as in its progression or spontaneous remission.

Based on the above discoveries, MN represents an ideal disease model to decipher the mechanisms of triggering and resolution of autoimmunity.

MN as a model of food-induced disease

We recently found that in young children with so-called “idiopathic” membranous nephropathy, a cationic form of bovine serum albumin (BSA) could be the culprit. These children had both high serum titres of anti-BSA antibodies and elevated levels of circulating BSA which was detected in glomerular immune deposits without PLA2R. These findings suggest that unusual processing of BSA during preparation of infantile milk formulas, by the intestinal microbiote or in the gastrointestinal epithelium may lead to a cationic form of BSA which binds to the glomerular capillary wall and triggers the local formation of immune complexes.

These uncommon cases highlight a role for environmental factors which in combination with genetic factors, may concur to the development of membranous nephropathy.

Pierre Ronco

Progerin staining in patients’ fibroblast cell nuclei, with progressive accumulation and nuclear morphology aberrations during culture passages.
The promise of mesenchymal stromal cells

In his lecture, Ton Rabelink will discuss issues of autologous MSC infusion in renal transplantation.

Bone marrow-derived cell fractions, including multipotent mesenchymal stromal cells (MSCs) have been tested in preclinical models of kidney injury. In particular, MSC can enhance the intrinsic reparative capabilities of the kidney. Although initially considered to possess substantial plasticity and regenerative potential, it is consensus today that MSCs are multipotent only within the limits of their respective lineage, while their therapeutic effects within the kidney are caused by paracrine effects. A promising approach is the administration of MSCs in renal recipients to treat allograft rejection, as an induction treatment and as a possible strategy to minimise calcineurin.

In a recent study by Tan et al., the effect of autologous MSC infusion was studied as an alternative to anti-IL2 receptor antibody for induction therapy in adults receiving transplants from related living donors. MSC infusions were given on the day of transplantation just prior to surgery and at day 12, and were combined with triple therapy, both with standard dose calcineurin inhibition as well as with a lower dose. The rejection rate with MSC induction appeared lower (8 %) as compared to induction therapy with IL2 receptor blockade, which was relatively high at 20 %. Importantly, however, rejection rates after 12 months increased to up to 17 % in the MSC arm, which may be related to the fact that initial depleting induction therapy was withheld. Moreover, final rejection rates were substantially higher than usually observed with standard immune suppression regimes, such as for example used in the Symphony study.

Although the study points towards the feasibility of an entirely new strategy for immune suppression in organ transplantation, there are important issues to consider as well. MSCs cannot be characterised by a single surface marker and due to lack of standardisation carry a big risk of failure in clinical development. Moreover, since the bone marrow contains only 0.001-0.01 % primary MSCs, significant ex vivo amplification and cultivation is necessary to obtain sufficient cells for clinical application. Taken together, this implies substantial manufacturing risks and very high costs. Even more importantly, progenitor characteristics, as well as the immune-modulating properties of MSCs also carry inherent safety risks. This is underscored by two smaller clinical studies using MSCs in an induction setting as well as in the setting of subclinical rejection.

In the first study MSC infusion induced a protolerogenic environment characterised by lower memory/effector CD8+ T cell, expansion of CD4+Treg and reduction of donor-specific CD8+ T cell cytotoxicity. Moreover, few days after cell infusion, the MSC-treated patients developed acute renal insufficiency. It was hypothesised that the subclinical inflammatory environment of the graft in the few days post-surgery could have favoured recruitment and activation of the infused MSC promoting a pro-inflammatory milieu with eventual acute renal dysfunction (engraftment syndrome).

The second study addressed safety and feasibility in kidney allografts recipients who received expanded autologous bone marrow derived MSCs, when a protocol biopsy at four weeks or six months had shown signs of rejection and/or an increase in IFTA. Six patients received MSC infusion because the 6-month protocol biopsy showed such pathology. Five of them demonstrated a profound reduction in PBMC proliferation 12 weeks after MSC infusion upon stimulation with donor specific PBMCs. Moreover, three patients developed virus infections which are typically associated with too much immune suppression. These included BK nephropathy, CMV reactivation and primary CMV infection more than six months after discontinuing valganciclovir prophylaxis. Of note, in none of the patients receiving MSC, regular immune suppression was lowered when the MSCs were given, as they all had signs of rejection or IFTA in the biopsy. In two patients with clinical indication for a repeat biopsy after MSC infusion, resolution of tubulitis and IFTA was observed.

These first clinical observations with MSCs in the field of organ transplantation raise several important questions: What endpoints should be chosen in studies investigating this type of cell therapy and how to design these studies? How do we balance organ survival against the risk for side effects, such as opportunistic infections and development of cancer? In his lecture, Professor Ton Rabelink will discuss these issues.

How to improve quality of care?

A special symposium today is dedicated to renal healthcare systems in Europe.

Chronic kidney disease (CKD) affects approximately 7 % of all people aged 30 years and older; this translates into more than 70 million patients in developed countries worldwide. The ageing population and the growing prevalence of diabetes and other non-communicable diseases will further perpetuate the rise of CKD. Approximately 1.7 % of Europe’s total healthcare budget is spent on patients with end-stage renal disease – a disproportionate expenditure in relation to the small percentage of patients on renal replacement therapy (RRT) of approx. 0.07 %. In the light of these figures it is important to identify patients at high risk of adverse outcomes and to find the most efficient way to deliver appropriate care to them. For improvement, chronic disease management programmes may have to re-
From basic theory to hands-on workshops

ASDIN and ERA-EDTA jointly invite to the first ‘Interventional Nephrology Session’ of this Congress.

The American Society of Diagnostic and Interventional Nephrology (ASDIN) is honoured and delighted to sponsor jointly with the ERA-EDTA the first “Interventional Nephrology” session and workshop of this Congress. Interventional nephrology is a young, but rapidly growing subspecialty focused on the application of techniques relevant to the particular needs of patients with chronic kidney disease (CKD). Since its birth in the mid-1990’s, interventional nephrology has grown to become a part of mainstream nephrology care and practice. Interest and activity have grown beyond the shores of North America and many of our European nephrologists have long been performing AVF surgical creation and repair as well as peritoneal and haemodialysis catheter implantations. Other procedures of interest are solid organ and vascular ultrasound and endovascular interventional techniques such as angioplasty, thrombectomy and stent implantation.

This session is aimed at the clinical nephrologist who has not performed endovascular procedures and is interested in being exposed to basic theories and a general feeling of what is involved in these procedures. The clinician who is adept at these procedures but also wishes to learn of the nuances and subtleties of the techniques would benefit from the sessions. The three-hour session begins with an hour of didactics that stresses the clinical indications and contraindications to these procedures, the technique, complications, their prevention and management. This is followed by a hands-on workshop demonstrating both the fluoroscopic and peritoneoscopic methods of peritoneal dialysis catheter implantation, real-time ultrasonographic cannulation of the internal jugular vein with placement of a tunneled haemodialysis catheter and simulation of a vascular access angioplasty and thrombectomy. Each participant will have sufficient hands-on experience with the model and interactive time with the faculty, all of whom are active and seasoned interventionalists and thought leaders in intervention-al nephrology.

As a society, ASDIN promotes the appropriate application of new and existing procedures in order to improve the care of patients with kidney disease. With globally exploding numbers of chronic kidney disease and end-stage renal disease, the medical community is challenged to deliver optimal care with the most efficient use of limited time and resources.

New and evolving technologies or novel applications of existing technologies will have more of an important role to play as the demand for renal replacement services increases.

The challenge for the interventional nephrology community is to enhance our understanding of the biology of the disease processes and develop better treatment options which are accessible, widely applicable and which have durable results.

Aris Q. Urbanes, President of ASDIN; Grosse Pointe Park, Michigan, U.S.A

SS4: Interventional nephrology
Room: Topkapi A/B
Date: 19-05-2013
From: 8:30 to 11:30
Date: 20-05-2013
From: 14:30 to 17:45

READY TO GROW YOUR NEPHROLOGY CAREER?

Join DaVita® in Saudi Arabia

DaVita®, a leading provider of kidney care with over 2,000 centers globally, is looking for nephrologists who want to impact patient care and quality of life on a larger scale. This will include being trained as interventionalists and working in DaVita-operated vascular access centers. You will have the opportunity to oversee outcomes, patient care, quality, safety, training and policies and procedures. Join a team making a difference in kidney care!

Grow your career with DaVita in Saudi Arabia

Email DaVita at KSA@davita.com to discover the benefits of becoming a part of the DaVita team.

Visit DaVita’s booth at ERA-EDTA
Ethical considerations in RRT

A special symposium today addresses the ethical, medical and social challenges for nephrologists.

An anonymous review published in 1981 in the Lancet highlighted for the first time the ethical dilemmas that nephrologists face in day-to-day practice. Interestingly, but perhaps not surprisingly, the same stressful ethical issues were presented for discussion at an international conference, and published in 2010.

Social and cultural changes in society place unachievable demands when attempting to provide equitable treatment for patients with end-stage renal disease. Old age, treatment accessibility and financial constraints represent just some of the points of conflict, according to Richard Trompeter of the Royal Free Hospital in London, UK. “Novel and interesting ethical suggestions to improve organ donation have been published recently. The introduction of trials to evaluate potential tax incentives is just one such example,” he says.

In some countries clinical ethics committees are an integral component in the decision-making process. The value of such groups is being evaluated constantly, as is the inclusion or not of the patient. Trompeter voices encouragement for such fora for non-confrontational discussion to solve complex moral problems, at both local and international level.

“Ethics are indeed important for each and every nephrologist,” he concludes.

Multimorbidity is a key problem

Krzysztof Marczewski of the University of Zamosc, Poland, remembers the times when not everybody could be dialysed due to a shortage of places: “Age was one of the most important criteria for dialysis selection in the early 1980s.” Today, patients older than 60 years account for nearly half, and in some centres, even more than half of dialysis patients. However, with the abolition of this age limit the question arose if dialysis in the elderly provides real benefits. Marczewski refers to length and quality of life as the major therapy goals, but questions the assessment methods for the latter. He emphasises that multimorbidity rather than a patient’s chronological age is decisive for renal replacement therapy (RRT).

He would therefore recommend to test comorbidities including depression and cognitive impairment before starting dialysis and to integrate geriatric tests into periodic assessments of dialysis in the elderly. Social, economic and legal aspects may also play a role in the decision for dialysis or conservative therapies. He calls for more research in this area and stresses the necessity “to define the desired goals you want to achieve.” Marczewski concludes that each decision for dialysis versus conservative therapy in elderly patients needs individual consideration, based on the classic four principles of Beauchamp and Childress: autonomy, beneficence, non-maleficence and justice. And in case a nephrologist really does not know what to do, he should follow the bios Ethics principle: “in dubio pro vita”.

Extra training in ethics is needed

The demand of considering both prolongation and quality of life when starting renal replacement therapy is also confirmed by Drasko Pavlovic from Zagreb, Croatia: “Due to multiple comorbidities the prognosis of elderly may not be good, even with dialysis. In some countries a prognostic score has been developed to predict survival in elderly patients, which can ease the decision of the nephrologist,” Pavlovic explains. Guidelines or shared decision-making in the initiation of dialysis can be useful. “However,” argues Pavlovic, “the question is whether such guidelines can be applied in all countries because of cultural, socio-economic, and religious differences.”

When faced with RRT, older patients should promptly be informed of all treatment options, if they are conscious. Moreover, they should be made aware of the prognosis. Family members or guardians should be included in this process. Sometimes the family doctor, a psychiatrist or a priest can also be of assistance to the patient. “The decision should be a joint one and no decision should be final,” says Pavlovic. He also suggests the introduction of appropriate trainings into the education of nephrologists to be better prepared for these new challenges.

Economic and cultural challenges

“Economics forms the basis of ethics – this is apparently true when looking at dialysis from a global perspective, when the way into dialysis is too fast, for example by proactive recruitment or premature initiation, and the way out of dialysis is too long, due to restrictions to transplantation or refusal to stopping dialysis,” Keller explains. He also points out that, in addition to economics, social and cultural values form the basis of ethics. “Although it is in the best interest of the patient to be part of a community with moral and emotional principles, cultural traditions can also do harm to the patient on dialysis: The primacy of patient autonomy can result in self-destructive behaviour or irrational decisions. Giving life per se an absolute value as in some religious traditions can force the patient to stay on dialysis when further measures are completely futile.” Keller concludes.
The 4C study
A new multinational trial aims at studying the cardiovascular comorbidity in children with chronic kidney disease.

Launched by the ESCAPE Clinical Research Network in 2009, the prospective observational 4C study explores the emergence and progression of early cardiovascular abnormalities in children with chronic kidney disease (CKD). With more than 700 children and adolescents with CKD stage IIIb to V followed for at least four years in 55 centres in 12 European countries, the study is a perfect example of successful multinational investigator-driven clinical research in European nephrology.

This paediatric population is considered uniquely suited to study early cardiovascular sequelae of chronic kidney disease with high sensitivity since in children cardiac and vascular morphology and function are not yet altered secondary to diabetes, hypertension and vascular ageing.

4C is collecting extensive clinical information

In the 4C study annual cardiovascular assessments are performed which include measurements of carotid intima-media thickness and pulse wave velocity, echocardiographies and ambulatory blood pressure monitoring. All examinations are performed with uniform equipment by eight jointly trained regional coordinators visiting their study sites once a year.

Extensive clinical information is collected via online data capturing, laboratory measurements are performed centrally, and a biobank of DNA, plasma, serum and urine specimens has been established at the coordinating centre in Heidelberg. Moreover, ex vivo studies of arterial tissue are performed utilising specimens obtained at the time of fistula creation, PD catheter placement and transplantation.

An initial analysis of key cardiovascular endpoints revealed distinct arterial thickening in 60%, increased stiffness in 25%, left ventricular hypertrophy in 50% and 24-hour hypertension in 30% of the children. These abnormalities appear to progress with time as glomerular filtration rates decline.

Comprehensive panels of established and emerging biomarkers of cardiovascular disease and renal failure progression are measured to identify those biomarkers that are informative and allow individualised risk prediction. Furthermore, genome-wide association studies have been performed with the aim of identifying common genetic variants predisposing to early cardiovascular and renal disease progression.

In a collaborative effort with the North American CKiD consortium the investigators have recently finished genotyping the ESCAPE, 4C and CKiD cohorts, a population of altogether 1300 well-phenotyped children with chronic kidney disease.

Data collection is continued beyond the start of RRT

The study does not end with the start of renal replacement therapy. In the 4C-D and 4C-T ancillary studies cardiovascular assessments are continued as the children progress to dialysis and transplantation, allowing the investigators to address the impact of dialysis modalities and transplantation with or without a preceding dialysis period. In this way, the specific cardiovascular impact of treatment modalities, including the potential for cardiovascular disease regression after successful transplantation, will be addressed.

The study receives funding from the ERA-EDTA, the KfH Foundation for Preventive Medicine, the German Ministry for Education and Research, and the North-American National Institute of Health.

Franz Schaefer, Paediatric Nephrology, University Hospital Heidelberg, Germany

S34: Cardiovascular disease in children with CKD
Room: Beylerbeyi
Date: 20-05-2013
From: 16:15 to 17:45

Franz Schaefer running a half marathon in Heidelberg, Germany. Conducting the 4C Study feels like running long distances, he says.
A combination of corticosteroids and alkylating agents usually represents the standard treatment for idiopathic membranous nephropathy (MN) but further therapy options are available. Cyclosporine has been frequently prescribed as a first or second choice. Cyclosporine may obtain a significant reduction of proteinuria in 70-80% of MN patients, but most responders have a relapse of nephrotic proteinuria after the drug is withdrawn. Therefore, treatment should be prolonged. Unfortunately, little information is available about long-term results.

There is also little experience with tacrolimus. Apparently, this agent can achieve a high rate of remissions, but most patients have a relapse after tacrolimus is withdrawn. The major concern with calcineurin inhibitors remains nephrotoxicity. Careful monitoring of serum creatinine and blood pressure, low doses for maintenance, and repeated renal biopsy in those receiving long-term therapy can minimise nephrotoxic effects in patients with normal or subnormal renal function.

The experience with mycophenolate mofetil (MMF) is still limited; only small-sized randomised trials with short-term follow-up are available. It seems that MMF is not effective when administered alone, while it may favour remission in combination with moderate doses of steroids. However, relapse rates are high in responders.

Observational studies and a randomised trial showed that synthetic adrenocorticotropin (ACTH), administered by intramuscular or subcutaneous injection at a dose of 1 mg twice a week for one year, can significantly reduce proteinuria in MN patients. Similar results have been obtained in a small observational study with natural gel ACTH. The mechanism of action is probably related to the stimulation of melanocortin receptors with subsequent inhibition of immune and inflammatory response. ACTH might be a good option for patients who have contraindications or do not respond to cytotoxic therapy or calcineurin inhibitors. However, further data are needed before recommending its use in patients with MN.

Rituximab is now used by a number of centres as a primary treatment for MN. A high rate of remissions (mainly partial) has been reported by a few observational studies. Patients showing relapse of nephrotic syndrome may benefit from further administrations of rituximab. The drug seems to be well tolerated, but cases of cancer and cardiovascular events have been reported, although it is unclear if these events were actually caused by rituximab. Little information is available about the optimal doses, the number of administrations, and the long-term effects of rituximab.

In summary, there are different therapeutic options for patients with membranous nephropathy. However, well-designed prospective randomised controlled trials with adequate size and long-term follow-up are still needed to identify the treatment with the best therapeutic index in this disease.
OUR NAME HAS CHANGED.
OUR COMMITMENT TO NEPHROLOGY ENDURES.

The partner you once called Abbott is now AbbVie. Our name has changed but our commitment to join you in improving patient care has not. We stand by our promise to develop and deliver innovative medicines and work with you to elevate the standard of care in the treatment of kidney disease.

abbvie.com