ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

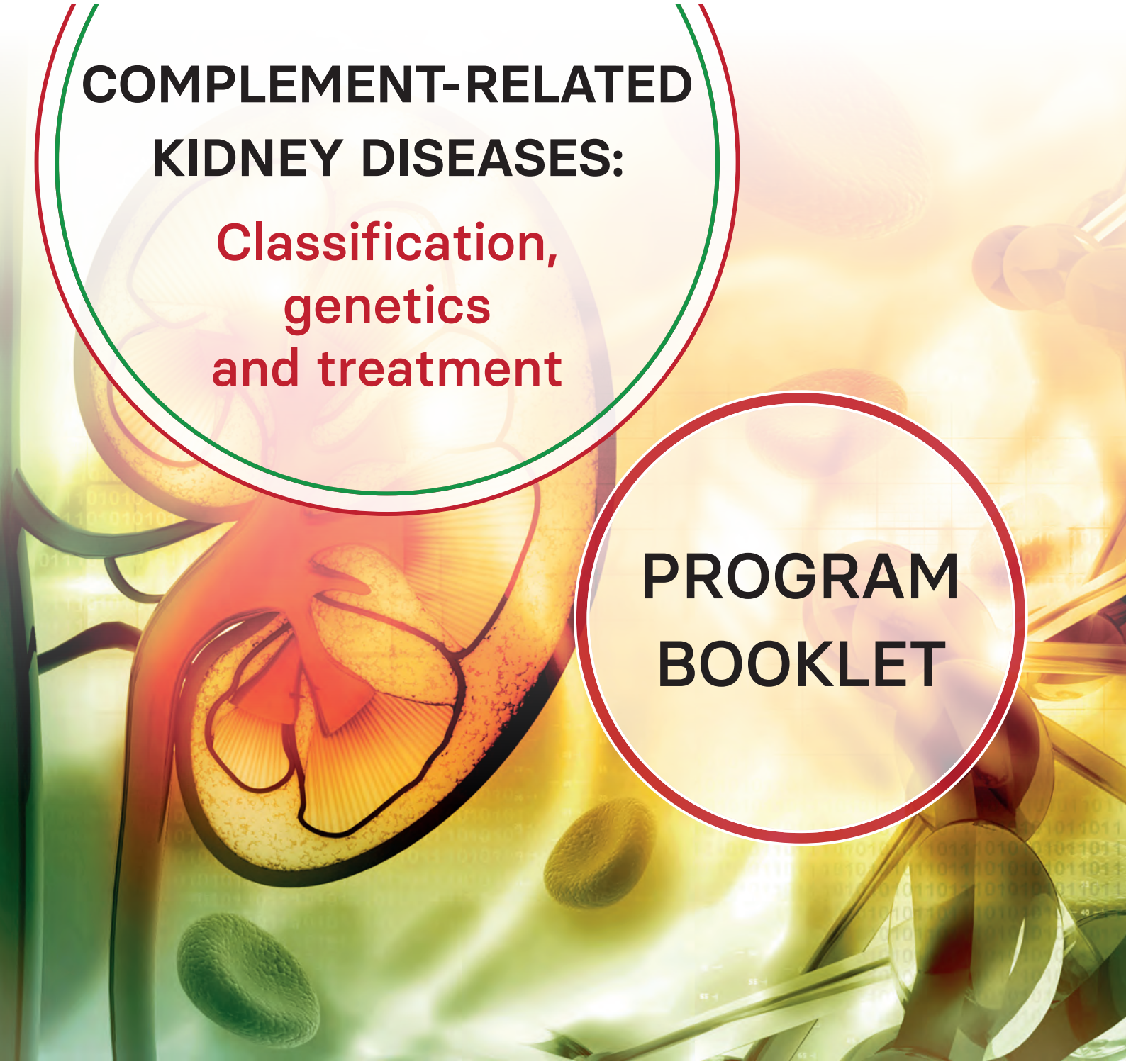
ISN International Society of Nephrology

FRONTIERS MEETINGS

JUNE 23-25, 2022 | BERGAMO, ITALY

COMPLEMENT-RELATED KIDNEY DISEASES:

Classification, genetics and treatment



PROGRAM BOOKLET

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WELCOME TO BERGAMO

With great pleasure, we welcome you to Bergamo, Italy, for the ISN Frontiers Meeting on 'Complement-Related Kidney Diseases: Classification, Genetics and Treatment.'

The meeting focuses on the two rare and severe prototypical complement-mediated kidney diseases, Atypical hemolytic uremic syndrome (aHUS), and C3 Glomerulopathies/Membranoproliferative Glomerulonephritis (C3G/MPGN).

Despite currently available treatments, key diagnosis and genetic assessment issues remain a challenge. An analysis of knowledge advancement is urgently required to identify key issues for optimal management of these two diseases. A research agenda to resolve outstanding controversial issues is also vital.

Clinicians, scientists, academics, and general practitioners will hear from a global panel of clinical and scientific experts on the latest developments in differential diagnosis, disease classification, genetics, knowledge gaps and unmet treatment requirements.

There is an urgent clinical need to precisely characterize the underlying pathogenetic mechanisms in each patient to identify the target molecule within the complex complement cascade (such as C3, factor B, factor D, C5, C5a and C5aR) and the suitable inhibitor among those in the clinical pipeline.

By bringing together and fostering connections between different experts in rare complement-mediated kidney diseases, the meeting will help strengthen existing collaborations and establish new ones that will enhance skills and expertise in the field and offer evidence-based suggestions for future research.

Yours sincerely,

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ISN Frontiers Scientific Working Group Chairs

Giuseppe Remuzzi

Marina Noris

Raja Ramachandran

ABOUT THE FRONTIERS MEETING

WELCOME AND REGISTRATION DESK

Located in the reception area on the ground floor.

Registered delegates may pick up their badges at the registration desk as of 8:30 on June 23. The registration desk will then be open as follows:

Opening Hours

- Thursday, June 23 - 8:30 - 18:00
- Friday, June 24 - 8:00 - 18:00
- Saturday, June 25 - 8:00 - 13:00

POSTERS

Posters of accepted abstracts are located in the 'Hall Bar' and the 'Sala Bianca'. Posters are mounted for the duration of the meeting and are viewable during all lunches and coffee breaks. Poster presenters will be present at the posterboards during the afternoon coffee breaks.

Hall Bar: POS-001 - POS-029

- Atypical Hemolytic Uremic Syndrome: Advances in Pathophysiology
- Atypical Hemolytic Uremic Syndrome: Diagnosis and Classification
- IC-MPGN/C3G: Advances in Pathophysiology
- IC-MPGN/C3G: Diagnosis and Classification

Sala Bianca: POS-030 - POS-056

- Late Breaking Abstracts
- Therapy of Complement-Mediated Rare Nephropathies

Set-up & Dismantle Time for Poster Presenters

- Set-up: Thursday June 23 between 9:00 - 11:00
- Dismantle: Saturday June 25 between 13:10 - 13:40
  Posters that are not removed by 13:30 will be removed by the organizers and can, unfortunately, not be recovered.

SPEAKER PREVIEW ROOM

Invited speakers are required to upload their presentation at least 2 hours before the start of their session, in the Speakers Preview Room 'Sala VIP'. The Speakers Preview Room is located on the ground floor next to the Reception Room. Speakers presenting in early morning session are requested to upload their presentation the day before their session.

NAME BADGE

Delegates are required to wear their name badges at all times for identification purposes and admission to the scientific and social programs. Should you lose your badge, you may ask for a replacement at the Registration Desk.

ISN FRONTIERS SCIENTIFIC WORKING GROUP CHAIRS

- Giuseppe Remuzzi (Italy) - Co-Chair
- Marina Noris (Italy) - Co-Chair
- Raja Ramachandran (India) - Co-Chair

OFFICIAL LANGUAGE

The official language of the ISN Frontiers Meeting is English, no translation will be provided.

COVID-19 MEASURES ONSITE

To access the congress center it is no longer mandatory, but strongly recommended to wear a FFP2 Mask. It is mandatory to promptly report the onset of flu symptoms should they occur during the stay in the structure. It is recommended to wash your hands regularly for at least 20 seconds using soap or gel.

INTERNET ACCESS

Entire Venue (excluding Sala Oggioni):

- Network: WCC
- Password: congress01

Sala Oggioni:

- Network: salaoggioni
- Password: salaoggioni

CATERING SERVICES

Coffees and lunch breaks are organized at the Hall Bar (Ground Floor) and Sala Bianca (First Floor). To comply with COVID-19 measures, and maintain a safe distance, we kindly ask the delegates to distribute on the two floors. Registration to the meeting includes buffet lunch on June 23 and June 24, as well as Coffee Breaks on June 23, 24, and 25 (morning only). A Welcome Cocktail is organized for all participants on June 23 from 18:00. No further evening activities are planned during the meeting.

DISCLAIMER

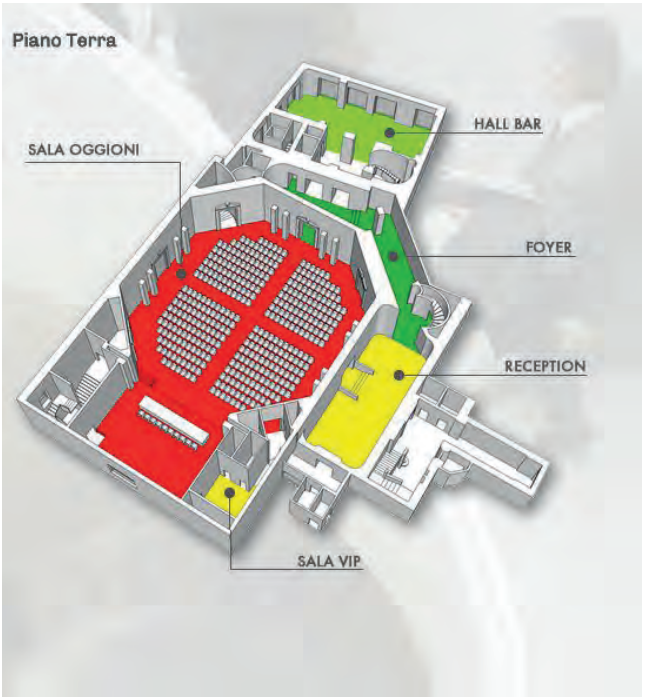
The ISN will not be liable for personal injury or safety of any participant, or loss of or damage to private property of the registered participants during the meeting.

CME ACCREDITATION & CERTIFICATE OF ATTENDANCE

The ISN 2022 Frontiers Meeting 'Complement-related kidney diseases: classification, genetics and treatment', Bergamo, Italy, 23/06/2022-25/06/2022 has been accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) with 17 European CME credits (ECMEC®s). Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity. Certificates can be printed via the registration portal. Please note you will ONLY get CME points for the days in which you have scanned your badge at the 'CME accreditation badge scanning zone'.

FLOOR PLAN

Ground floor



First floor

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PROGRAM

THURSDAY, JUNE 23, 2022

Welcome and Opening Plenary Lecture

Session Moderators: Agnes Fogo, United States; Ariela Benigni, Italy

11:00 - 11:10 Welcome from the ISN

Agnes Fogo, United States

11:10 - 11:15 Welcome from the 2022 ISN Frontiers Meeting Chairs

Giuseppe Remuzzi, Italy

Marina Noris, Italy

Raja Ramachandran, India

11:15 - 11:50 Opening Plenary Lecture: Rare Renal Diseases of Complement Dysregulation: Open a Window on the Future of Medicine

Giuseppe Remuzzi, Italy

11:50 - 12:00 Q&A

IMMUNE COMPLEX ASSOCIATED MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS AND C3 GLOMERULOPATHY

Session 1: What Have We Learnt from Animal Models?

Session Moderators: Matthew Pickering, United Kingdom; Simona Buelli, Italy

12:00 - 12:20 The Complement System and the Kidney in Humans and Rodents

Richard Quigg, United States

12:20 - 12:40 Mouse Models of C3G: Role of C3 and C5 Activation Products

Matthew Pickering, United Kingdom

12:40 - 13:00 Q&A

Lunch and Poster Viewing 13:00 - 13:50

Session 2: Advances in Pathophysiology

Session Moderators: Roberta Donadelli, Italy; Veronique Fremeaux-Bacchi, France

14:00 - 14:20 Genetic Basis: CFHR Hybrids

Peter Zipfel, Germany

14:20 - 14:40 Genetic Basis: The Role of Rare and Common Complement Gene Variants

Rossella Piras, Italy

14:40 - 15:00 Nephritic Factors and Anti-complement Futoantibodies

Sophie Chauvet, France

14:50 - 15:00 Oral Presentation from Abstract Selection: The Three C-Terminal Domains of FHR1 Influence Complement Activation and FHR1 Cooperation With Other Complement Regulators

Luce Perie, Germany

15:00 - 15:20 Q&A

Coffee Break and Poster Viewing 15:20 - 15:50

Session 3: Clinical: Unanswered Questions

Session Moderators: Anna Caroli, Italy; Camillo Carrara, Italy

15:50 - 16:10 The Variable Expression of C3G/IC-MPGN: Complement, Post-infectious, Paraproteins

Moglie Le Quintrec-Donnette, France

16:10 - 16:30 Maths Helps Clinicians with Making a Diagnosis and Predicting Outcomes

Marina Noris, Italy

16:30 - 16:40 Oral Presentation from Abstract Selection: Artificial Intelligence Assisted Quantification of Complement Convertases in Glomerulonephritis

Luce Perie, Germany

16:40 - 16:50 Oral Presentation from Abstract Selection: Outcome Of Kidney Grafts Transplanted for C3 Glomerulopathy And Membranoproliferative Glomerulonephritis

Matthieu Halfon, Switzerland

16:50 - 17:10 Q&A

17:10 - 17:20 Young Nephrologist Award Ceremony for The Best Clinical Abstract

Keynote Lecture

Session Moderators: Giuseppe Remuzzi, Italy; Matthew Pickering, United Kingdom

17:20 - 17:45 C3G/IC-MPGN in 2022

Richard Smith, United States

17:45 - 18:00 Q&A

Welcome Reception 18:00

FRIDAY, JUNE 24, 2022

ATYPICAL HEMOLYTIC UREMIC SYNDROME

Session 4: What Have We Learnt from Animal Models?

Session Moderators: Marina Morigi, Italy; Wenchao Song, United States

8:30 - 8:50 Modeling aHUS in Genetic Mouse Models
Wenchao Song, United States

8:50 - 9:10 Role of Complement in the Pathophysiology of STEC-HUS: Evidence from a Mouse Model
Carlamaria Zoja, Italy

9:10 - 9:30 Q&A

Session 5: Advances in Pathophysiology

Session Moderators: Veronique Fremeaux-Bacchi, France

9:30 - 9:50 Genetic Basis of aHUS
David Kavanagh, United Kingdom

9:50 - 10:10 Common Genetic Susceptibility Factors in aHUS
Elena Goicoechea de Jorges, Spain

10:10 - 10:30 Anti-FH Antibodies Associated HUS
Arvind Bagga, India

10:30 - 10:50 aHUS: Why the Kidney?
Lubka Roumenina, France

10:50 - 11:10 Q&A

Coffee Break and Poster Viewing 11:10 - 11:40

Session 6: Clinical: Unanswered Questions

Session Moderators: Elena Bresin, Italy; Raja Ramachandran, India

11:40 - 12:00 Primary and Secondary aHUS. Still Worth Discussing?
Giovanni Montini, Italy

12:00 - 12:20 Postpartum Renal Cortical Necrosis and aHUS
Raja Ramachandran, India

12:20 - 12:40 Monitoring Complement Dysregulation in aHUS
Miriam Galbusera, Italy

12:40 - 13:10 Q&A

Lunch and Poster Viewing 13:10 - 14:00

THERAPY

Session 7: When and How to Inhibit C5 in Complement-mediated Rare Nephropathies

Session Moderators: Christophe Legendre, France; David Kavanagh, United Kingdom

14:00 - 14:20 Eculizumab in Primary and Secondary aHUS: Who, When, and How Long?
Sjoerd Timmermans, Netherlands

14:20 - 14:40 Eculizumab in Primary and Secondary aHUS: Who, When and, How Long?
Giuseppe Remuzzi, Italy

14:40 - 15:00 Impact of C5 Blockade on Post-transplant Outcomes and Renal Epidemiology of aHUS
Christophe Legendre, France

15:00 - 15:10 Oral Presentation from Abstract Selection: Atypical Renal Recovery from Atypical Hemolytic Uremic Syndrome
Bianca Covella, Italy

15:10 - 15:30 Q&A

Coffee Break and Poster Viewing 15:30 - 16:00

Session 8: When and How to Inhibit C3 in Complement-mediated Rare Nephropathies

Session Moderators: Ariela Benigni, Italy; Richard Smith, United States

16:00 - 16:20 Manipulating the Early Steps of Complement Cascade: Emerging Drugs, Potential Risks, and Benefits
Joshua Thurman, United States

16:20 - 16:40 Lessons from Studies in Mouse Models of C3G
Ariela Benigni, Italy

16:40 - 17:00 Targeting C3, CFD, or CFB in C3G, Preliminary Results of Clinical Trials in Patients with C3G/IC-MPGN
Erica Daina, Italy

17:00 - 17:10 Oral Presentation from Abstract Selection: BCX9930, An Oral Factor D Inhibitor, Suppresses Complement Alternative Pathway Activity in Patients With Complement 3 Glomerulopathy
Xilin Chen, United States

17:10 - 17:30 Q&A

Keynote Lecture

Session Moderators: Marina Noris, Italy; Raja Ramachandran, India

17:30 - 17:55 HUS in 2022
Fadi Fakhouri, Switzerland

17:55 - 18:05 Q&A

SATURDAY, JUNE 25, 2022

PATIENT DAY

Part 1: HUS

Moderator: Giuseppe Remuzzi, Italy

8:30 - 8:40 aHUS: News and Therapeutic Perspectives
Giuseppe Remuzzi, Italy

8:40 8:50 aHUS Alliance
Len Woodward, United Kingdom

8:50 - 10:30 The Patients Meet the Doctors
Giuseppe Remuzzi, Italy
Fadi Fakhouri, Switzerland
Giovanni Montini, Italy

Coffee Break and Poster Viewing 10:30 - 11:00

Part 2: C3G/IC-MPGN

Moderator: Giuseppe Remuzzi, Italy

11:00 - 11:10 Fighting C3G: Progetto DDD Onlus
Fabrizio Spoleti, Italy

11:10 - 11:20 C3G/IC-MPGN: News and Therapeutic Perspectives
Erica Daina, Italy

11:20 - 13:10 The Patients Meet the Doctors
Richard Smith, United States
Erica Daina, Italy
Giovanni Montini, Italy

Closing Remarks

13:10 13:20 Closing
Giuseppe Remuzzi, Italy
Raja Ramachandran, India
Marina Noris, Italy

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SPEAKER BIOGRAPHIES

ARVIND BAGGA

Graduated from the All India Institute of Medical Sciences, New Delhi. He is on the faculty of AIIMS since 1991 and currently is Professor of Pediatrics, Division of Nephrology. The division is recognized for initiatives in education and enhancing training opportunities in pediatric nephrology. His research interests focus on multiple areas of pediatric nephrology, with focus on clinical trials, hemolytic uremic syndrome and nephrotic syndrome.

ARIELA BENIGNI

Ariela Benigni is Scientific Secretary of the Mario Negri Institute for Pharmacological Research and Research Coordinator at Bergamo sites. She got the Biological Science Degree at the University of Milan and the Ph.D. at the Unviversity of Maastricht. She has held distinguished positions internationally, including Consultant World Health Organization. Her team identified vasoactive and inflammatory mediators of renal damage in experimental and human progressive renal diseases. Recent interest of Benigni's group focuses on the regenerative medicine and the protective role of mesenchymal stromal cells in acute and chronic renal diseases. Her latest research is devoted to deepen the role of mitochondrial Sirtuin 3 in aging and renal diseases and the identification of mitochondria-protective agents. She acted as Associate and Academic Editor of several journals including Kidney International and is currently the Editor-in-Chief of Nephron. Ariela Benigni has published more than 338 peer-reviewed articles and is among the Top Italian Scientists.

SOPHIE CHAUVET

MD in nephrology PhD in immunologytopic of research: complement mediated kidney diseases.

ERICA DAINA

Dr. Erica Daina is a senior representative member of the Clinical Research Centre for Rare Diseases (CRCRD) established in 1992 in Italy, as part of the Mario Negri Institute. She got her degree in Medicine at the University of Milan in 1987 and the specialisation in Medical Nephrology in 1990. She performed her training at the II° Medical Division - San Raffaele Hospital - Milan, and at the Division of Nephrology and Dialysis - Riuniti Hospital - Bergamo. In 1991 started her collaboration with the Mario Negri Institute and got the specialization in Pharmacological Research. Professional positions:1996 – 2009: Head, Information Center for Rare DiseasesJanuary 2002 – present: Representative of Coordinating Centre - Regional Network for Rare DiseasesJune 2009 - present: Head, Laboratory of Rare Diseases Documentation and ResearchShe is involved in national and international collaborations in the field of public health issues in rare diseases. Clinical research activities mainly concern kidney genetic and complement meditated diseases.

FADI FAKHOURI

Fadi Fakhouri is an adult nephrologist and a clinical researcher. He has a long-standing interest in autoimmune renal diseases, particularly complement-mediated nephropathies. He has conducted several clinical and experimental studies in the field of thrombotic microangiopathies, C3 glomerulopathy and other membrano-proliferative glomerulonephritis.

AGNES FOGO

Professor Agnes Borge Fogo completed medical and pathology training at Vanderbilt University, Nashville, TN, USA. Her main research interests are progression and potential regression of chronic kidney disease, and crosstalk of tubules and glomeruli. She is also dedicated to diagnostic renal pathology, and has created an online Atlas of Renal Pathology with the American Journal of Kidney Disease and NKF. She received the Robert G. Narins award from the ASN and the Roscoe R. Robinson award from the ISN for her contributions in teaching. She has been a councilor of the ISN, served as Chair of its Renal Pathology Committee, with focus on developing educational tools related to kidney biopsy interpretation, and is President-Elect of the ISN. She is Associate Editor for Kidney International and Laboratory Investigation. She is currently the John L. Shapiro Professor of Pathology, Microbiology and Immunology, Professor of Medicine and Pediatrics and director of the Renal/Electron Microscopy Laboratory, at Vanderbilt University Medical Center.

MIRIAM GALBUSERA

She received her Biol.Sci.D. at the University of Milan. She was working from 1985 at the Mario Negri Institute for Pharmacological Research. After a fellowship in the Laboratory of Thrombosis and Hemostasis at Scripps Clinic and Research Foundation (La Jolla, CA) she returned at the Mario Negri Institute were she is currently head of the Unit of Platelet-Endotelial Cell Interaction.She was involved in studies aimed at clarify the mechanisms that favor thrombosis in HUS and TTP. These studies provided evidence that complement activation at the endothelial level has a key role in triggering thrombus formation. She developed the test with microvascular endothelial cells used for the determination of complement activation. In a model of STEC-HUS she provided evidence that Shigatoxin induced alternative complement activation leading to microvascular thrombosis in STEC-HUS. Her fields of interest include VWF and ADAMTS13 biochemistry, complement dysregulation, platelet-endothelial cell interaction and platelet pathophysiology in uremia.

ELENA GOICOECHEA DE JORGES

Dr. Elena Goicoechea de Jorge is a scientist and lecturer at Department of Immunology at the Faculty of Medicine at University Complutense of Madrid (Spain), and she is currently a member of the European Complement Network. Dr. Goicoechea de Jorge is a biochemist with a keen interest in the complement pathway and have dedicated more than 20 years to its study and understanding its involvement in various diseases. With her interest and dedication, along with her extensive background in complement genetics, biochemistry, and animal models of complement dysregulation, Dr. Goicoechea de Jorge has made important contributions to the understanding of the pathogenesis of complement-mediated diseases such as atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy. Her work has influenced and supported the implementation of complement inhibition therapy that has changed the natural history of aHUS.

DAVID KAVANAGH

David Kavanagh is the Professor of Complement Therapeutics at the National Renal Complement Therapeutics Centre (NRCTC). The NRCTC oversees the management of the complement mediated renal diseases, atypical haemolytic uraemic syndrome (aHUS) and C3 glomerulopathy in England David moved to Newcastle to start his own lab in 2008 with a Wellcome Trust Fellowship following a Kidney Research UK Fellowship at the University of Edinburgh. He was previously a Fellow at Washington University School of Medicine, St. Louis. He graduated in Medicine and Immunology from the University of Glasgow in 1998 and obtained his PhD from Newcastle University in 2006. For his work defining the role of complement in aHUS, he was awarded the Renal Association's Young Investigator award. David is also academic founder of Gyroscope Therapeutics which is using gene therapy to treat Age Related Macular Degeneration, the commonest cause of blindness in the develped world. This therapy is based on his finding of the causative role of complement factor I haploinsufficiency in disease pathogenesis.

MOGLIE LE QUINTREC-DONNETTE

Head of nephrology and transplantation department

CHRISTOPHE LEGENDRE

Christophe Legendre, MD, is professor of Nephrology at Paris Descartes University and Head of the Adult Nephrology and Transplantation Unit at Necker Hospital in Paris.

He trained at the University of Montpellier, France, and spent 3 years as a postdoctoral fellow in the Immunogenetics Laboratory (Dr. Ronald Guttmann) at McGill University, Montreal, Canada. Dr. Legendre is Consulting Editor of the American Journal of Transplantation, Deputy Editor of Transplantation and Associate Editor of Kidney International.

Dr. Legendre's main research interests include clinical evaluation of new immunosuppressants, viral infection after transplantation (hepatitis, CMV, HHV8), transplantation in high-risk recipients (immunological risk, dual transplantations, and marginal kidneys), screening kidney biopsies, and recurrence of disease post transplantation. He has published approximately 580 papers in English peer-reviewed journals.

GIOVANNI MONTINI

Prof. Giovanni Montini is the holder of the Giuliana and Bernardo Caprotti Chair in Pediatrics at the University of Milan and Director of the Pediatric Nephrology, Dialysis and Transplant Unit of the Foundation IRCCS Ca' Granda Research Institute, Milan. His main areas of clinical expertise include urinary tract infections, paediatric renal transplantation, chronic and acute kidney failure, CAKUT, nephrotic syndrome and renal involvement in mitochondrial diseases. He is an accomplished researcher and lecturer in the field of paediatric nephrology and has published over 220 peer-reviewed articles. Since 2010, he has been part of an international cooperation network project for pediatric nephrology set up in Nicaragua to help underprivileged children with kidney disease gain access to medical care, dialysis, and transplantation. In 2018, took over as director of the project.

MARINA NORIS

Qualifications: 1986: degree in Pharmaceutical chemistry and technology (University of Rome "La Sapienza")2006: PhD in Genetics (University of Maastricht) Current appointment: Head of the Laboratory of Immunology and Genetic of Rare Diseases, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Ranica, Bergamo, Italy 2020-: Member of the of the Editorial Board of JASN 2020-:member of the Editorial Board of Kidney International2016-:Member of the Research Club "Top Italian Women Scientists" promoted by ONDA.H-index: 71Main work and research experience Marina Noris has an in-depth expertise in rare genetic renal diseases particularly in rare complement related kidney diseases. In this field she contributed to discover the genetic causes of aHUS, describing mutations in genes encoding complement regulatory proteins, and their functional consequences. Her research also clarified that the specific genetic defect has a great impact on the clinical course of this disease and on the risk of disease recurrence after kidney transplantation and contributed to the achievement of a specific cure with the anti-C5 antibody eculizumab. Her group also discovered the genetic cause of very rare renal disease, the glomerulopathy with fibronectin deposits and a new genetic form of childhood onset familial FSGS associated with mutation in the myosin 1E gene. MN has been invited to hold lectures at several of National and International congresses and is author and co-author of more than 200 scientific articles in high impact journals such as Lancet, Blood, the Journal of the American Society of Nephrology and the New England Journal of Medicine.

MATTHEW PICKERING

Prof. Pickering is an established international expert on the complement system and its role in health and disease. He is a Wellcome Trust Senior Fellow in Clinical Science and his research program has been funded by the Wellcome Trust since 2003. His clinical expertise includes systemic lupus erythematous and complement deficiency states. He is a Professor of Rheumatology at Imperial College and Academic Director of the Imperial Lupus Centre. He was Head of Specialty, Rheumatology, Imperial Healthcare NHS Trust between 2014 and 2019. His research has achieved international recognition for elucidating the relationship between uncontrolled complement activation and renal disease. His research program has utilized genetic characterization of families with complement-mediated renal disease, the in vitro studies of complement regulatory proteins and the generation of unique murine models of complement-mediated kidney disease. He is a member of both the International Complement Society and the European Complement Network.

ROSSELLA PIRAS

Rossella Piras was born in Cagliari, in 1982. In 2008 she graduated in Chemistry and Pharmaceutical Technology at the University of Cagliari. In the same year, she started her research experience as a research fellow at Mario Negri Institute, in the Laboratory of Immunology and Genetic of Rare Diseases working with Marina Noris on complement related diseases like hemolytic uremic syndrome and membranoproliferative glomerulonephritis. In 2018, in collaboration with the Open University, she obtained her PhD with a thesis on acquired and genetic abnormalities in C3G and IC-MPGN. In these years Rossella has been working as a senior researcher on the identification of genetic abnormalities in aHUS, C3G and IC-MPGN by Next Generation Sequencing (NGS). She currently studies copy number variations in the genomic region of CFH-CFHRs and she is working on the molecular characterization of FHR abnormalities identified in patients with C3G and IC-MPGN.

RICHARD QUIGG

I am a clinical nephrologist with a concentration on autoimmune renal diseases. My research concentrates on understanding mechanisms that underlie kidney disease, including the role of the complement system, a major factor in the body's immune response.

RAJA RAMACHANDRAN

Dr Raja Ramachandran is a specialist in Renal Medicine at the Post Graduate Institute of Medical Education and Research, Chandigarh, India. His primary field of interest is glomerular diseases, the economics of renal transplantation and pregnancy related-AKI. Dr Ramachandran was awarded Clinical Research Programme award for his project titled 'A prospective Study of clinico-epidemiology, outcome and catastrophic out-of-pocket Expenditure associated with obstetrical-AKI' by the International Society of Nephrology (July 2015). In addition, Dr Ramachandran is currently evaluating the role of complement and genetics in pregnancy-related AKI.

GIUSEPPE REMUZZI

Giuseppe Remuzzi, MD – Bergamo, Italy. Director of the Mario Negri Institute for Pharmacological Research and "Chiara Fama" Professor of Nephrology, University of Milan.His main research interests include the causes of glomerulonephritis and the mechanisms of progression of kidney diseases. He has also conducted many studies in the field of transplant rejection. He was President of the International Society of Nephrology (ISN) for the biennium 2013-2015. In recognition of his achievements, he received many national and international awards, among them the John P. Peters Award (American Society of Nephrology 2007, San Francisco) the ISN AMGEN Award (World Congress of Nephrology: WCN 2011, Vancouver), the International Award «Luis Hernando» (Iñigo Alvarez de Toledo Renal Foundation (FRIAT): Madrid, Spain) and the "Lennox K. Black International Prize for Excellence in Medicine" (Thomas Jefferson University, Philadelphia). Prof. Remuzzi is the author of over 1450 publications in international medical journals and has written 17 books.

LUBKA ROUMENINA

Lubka Roumenina is a senior scientist in Inserm, France, leading a group studying the innate immune complement system in physiology and pathology, with a focus on diseases affecting the kidney. She explores the mechanisms of activation and regulation of the complement cascade in the blood as well as the intracellular complement proteins. Lubka is among the pioneers exploring complement in heme-mediated diseases affecting the kidney such as sickle cell anemia and rhabdomyolysis-induced acute kidney injury as well as in renal cancer. She received the Young researchers award of the International Complement Society and the award for students supervision and excellence in research of Inserm in 2018 for her discoveries linking heme and complement to the pathological process in sickle cell anemia and atypical hemolytic uremic syndrome. Lubka is a passionate complementologist and a caring mentor with a mission to inspire young researchers to become the next generation of Complementologists.

RICHARD SMITH

Dr Smith directs the Molecular Otolaryngology and Renal Research Laboratories (MORL), an internationally recognized center of expertise in ultra-rare complement-mediated renal diseases and genetic hearing loss. In the area of complement-mediated renal diseases, scientists in the MORL have identified new genetic causes of atypical hemolytic uremic syndrome and defined the complex role of genetics in the pathogenesis of the C3 glomerulopathies. To follow disease course, they have developed and validated biomarker profiling as an index of ongoing complement activity. The MORL sponsors annual conferences for families with C3 glomerulopathies and aHUS. As a reflection of his contributions to science, Smith has been elected to the National Academy of Medicine and the Association of American Physicians.

WENCHAO SONG

Dr. Wenchao Song is Professor of Pharmacology in the Department of Systems Pharmacology and Translational Therapeutics at the Perelman School of Medicine of the University of Pennsylvania and a faculty member of both the pharmacology and immunology graduate groups. Dr. Song is an internationally renowned expert on complement biology. His research group pioneered studies of mouse models of complement-mediated diseases. Their work has helped reveal fundamental knowledge of how complement is regulated in vivo, with translational relevance to anti-complement therapeutics. He has been recognized as an Established Investigator of the American Heart Association and is a recipient of the Lady Barbra Colyton Prize in Autoimmune Disease Research. He chaired the organizing committee of the XXI International Complement Workshop and was elected and served both as a Councilor and Treasurer of the International Complement Society.

FABRIZIO SPOLETI

Manager with extensive experience in business process improvement and information systems based projects, gained at various consulting companies. Professor at the Trento University and at the Lausanne University in Management of Information Systems Planning and Installation Projects. Father of a C3G patient. Founder and president of the Italian PAO dedicated to C3G nephropathies.

JOSHUA THURMAN

Joshua M. Thurman, MD is the Temple Hoyne Buell Professor of Medicine in the Division of Nephrology and Hypertension at the University of Colorado, where he is the director of the Glomerulonephritis Program. His laboratory studies the underlying causes of auto-immunity and inflammation of the kidney, and his lab has developed several novel anti-inflammatory therapeutic agents. Projects are also underway that explore the link between inflammation and cancer. Dr. Thurman's laboratory has also developed novel radiologic probes to detect and monitor renal inflammation by magnetic resonance imaging (MRI) and positron emission tomography (PET). Dr. Thurman oversees the Glomerulonephritis Clinic at the University of Colorado Hospital. The Glomerulonephritis Clinic cares for patients with all forms of inflammatory kidney disease, and also participates in clinical trials of new therapies and diagnostic tools for treating these diseases.

SJOERD TIMMERMANS

Dr. Timmermans is a physician and clinical scientist at the department of nephrology and clinical immunology, Maastricht UMC, and Limburg Renal Registry (Maastricht, The Netherlands). His research focuses on immune-mediated kidney diseases and, in particular, the thrombotic microangiopathies and small vessel vasculitides.

LEN WOODWARD

An aHUS patient advocate for 11 years. At national level , trustee of aHUSUK, leader of Answers for aHUS (Kidney Research UK) and internationally, founding affiliate of the aHUS alliance, and Director of aHUS alliance Global Action. Currently lead partner for the Global aHUS Partnership and the Global aHUS Community Advisory Board. Participated in six HTAs for eculizumab/ravulizumab in England and Scotland. Represented alliance on aHUS Registry SAB, and a member UK Rare Renal aHUS Group.Published author and contributor to aHUS Global Action's website. Retired professionally qualified accountant.

PETER ZIPFEL

Peter F. Zipfel, is University-Professor at Friedrich Schiller University, Jena and Department Head at the Leibniz Institute for Natural Product Research and Infection Biology - e in Jena Germany. His research focuses on complement in health and disease, the role of the complement system in HUS and C3 Glomerulopathy, and as target for human pathogenic microbes. Dr. Zipfel has a deep interest in complement factor H, and in Factor H related proteins. Dr. Zipfel received his PhD from the University of Bremen. He was a postdoctoral fellow in the Laboratory for Immunoregulation, National Institutes of Health in Bethesda, Maryland USA headed by Dr. Anthony Fauci. Dr. Zipfel was then Group -eader at Bernhard Nocht Institute for Tropical Medicine Hamburg and Professor at the University of Hamburg. He has organized in 2013 the 14th European Meeting on Complement in Human Diseases and the 28th International Complement workshop in the year 2021.

CARLAMARIA ZOJA

Carlamaria Zoja is head of the Department of Molecular Medicine at Mario Negri Institute for Pharmacological Research, Bergamo, Italy. She obtained her degree in Biological Science from the University of Milano and the Ph.D. from the University of Maastricht. She has been involved for many years in experimental models of kidney diseases, investigating mechanisms and mediators of disease progression with focus on the role of proteinuria, complement and pathways of inflammation and fibrosis relevant to identifying strategies to halt progressive kidney injury. She applied multi-drug approaches to models of either nondiabetic or diabetic nephropathies. Another research activity regards the role of Shigatoxin in the pathogenesis of endothelial dysfunction and microvascular thrombosis in Hemolytic Uremic Syndrome. Using in vitro and in vivo models she studied the role of glomerular complement activation in promoting microvascular thrombosis and podocyte injury in response to Shigatoxin.Carlamaria Zoja is an author in over 190 scientific publications. She belongs to the Top Italian Women Scientists group.

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SPEAKER ABSTRACTS

OPENING PLENARY LECTURE

11:15-12:00

Rare Renal Diseases of Complement Dysregulation: Open a Window on the Future of Medicine

Giuseppe Remuzzi, Italy

Complement is part of the innate immune system and plays a fundamental role in the defense against pathogens and the clearance of immune complexes and cell debris. However, complement activation is a double-edged sword and has the potential to damage self-tissues. In order to avoid self-damage, there is an absolute need for strict control by fluid-phase and membrane-bound regulatory proteins. Thus, an underperforming regulatory system can shift the balance between regulation and activation toward the latter and lead to tissue injury in response to otherwise innocuous stimuli. Deposition of both activated complement fragments from plasma in glomeruli and complement locally produced and activated in the kidney may contribute to many kidney disorders.

Interest in the complement system has been boosted in the past 20 years by the discovery that rare devastating kidney diseases, including atypical hemolytic uremic syndrome (aHUS) and membranoproliferative glomerulonephritis (MPGN), are disorders of complement regulation. aHUS-associated complement gene abnormalities mainly result in complement dysregulation restricted to the cell surface, whereas complement activation in the fluid phase prevails in most, but not all, cases of MPGN.

Based on immunofluorescence findings, MPGN has been classified into complement-mediated C3 glomerulopathy (C3G), and immune complex-mediated MPGN (IC-MPGN). However, this classification leaves a number of issues unresolved. The finding of genetic and acquired complement abnormalities in both C3G and IC-MPGN indicates that they represent a heterogeneous spectrum rather than distinct diseases. An unsupervised hierarchical clustering in a cohort of patients with primary C3G and IC-MPGN identified 4 distinct pathogenetic patterns, characterised by specific histologic and clinical features and genetic and acquired complement abnormalities. These results provide the groundwork for a more accurate diagnosis and the development of targeted therapies.

The advent of eculizumab, a monoclonal antibody that blocks terminal complement activation, has markedly improved outcome and quality of life in patients with aHUS. Eculizumab has been also used occasionally in single cases or small series. However, only a few patients have achieved remission. This heterogeneous response could be related to the extent of terminal complement activation, which may vary substantially from patient to patient. Several drugs that target the complement system at different levels are under investigation for C3G and IC-MPGN. However, clinical trials to test new therapeutics will be challenging and heavily influenced by the heterogeneity of these diseases. This creates the need to characterise each patient to match the specific complement abnormality with the type of intervention

WHAT HAVE WE LEARNT FROM ANIMAL MODELS?

12:00-13:10

The Complement System and the Kidney in Humans and Rodents

Richard Quigg, United States

Experimental renal diseases in rodents have shaped our understanding of pathophysiology and altered how we treat the human diseases they model. For example, the Heymann nephritis model of membranous nephropathy first showed autoantibodies to the glomerular podocyte were pathologic, which was confirmed decades later. Treatment of lupus nephritis with steroids, cytotoxic agents, and anti-B cell therapies were first shown effective in mouse models. Mouse models in which complement has been manipulated have provided considerable insights into human diseases. Genetic deletions of relevant complement proteins, such as factor H and C3, have provided insights into human diseases. Since then, a number of increasingly clever modifications have been made in the mouse complement system that have been illuminating and often provocative. Therapies directed towards complement proteins, and in particular those targeting C3 and C5 were first developed and studied in the mouse. Arguably, the mother of all these is the anti-mouse C5 monoclonal antibody (mAb) BB5.1 developed 35 years ago which stimulated the development of the anti-human C5 mAb marketed twenty years ago as eculizumab. Now, the pipeline of anti-complement therapeutics is quite large, and have been supported by animal studies; yet, the clinical applicability still has lagged.

The questions I would like to address are:

1. How close is the mouse complement system to humans;
2. How accurate are the mouse models of renal disease to those that occur in human; and,
3. Does manipulation of the complement system in rodents translate to what can be expected in human renal disease?

These topics will be further discussed by Drs. Pickering, Song and Zoja in this symposium.

Mouse Models of C3G: Role of C3 and C5 Activation Products

Matthew Pickering, United Kingdom

In this talk I will overview the lessons that we have learnt from modelling complement dysregulation in mice. These models have been termed mouse models of C3 glomerulopathy. They have helped us to understand the importance of the complement factor H protein family in maintaining C3 regulation. It remains a remarkable observation that disrupting factor H function in mice (performed over 20 years ago) is sufficient to result in the spontaneous (that is no trigger is needed) accumulation of C3 and C5 within glomeruli. The availability of complement knockout strains, recombinant complement regulatory proteins and novel complement regulators have enabled us to unravel the mechanisms driving these changes. The similarity between the rodent and human alternative complement pathway means that many of the observations have informed the development of treatments for C3 glomerulopathy. We are now in a very exciting era of complement therapeutics with multiple trials in progress. It is time for the models to take a back seat as we enter an age where we will have disease-modifying treatments for C3 glomerulopathy and other complement-associated renal diseases.

ADVANCES IN PATHOPHYSIOLOGY

14:00-15:20

Genetic Basis: CFHR Hybrids

Peter Zipfel, Germany

Complement is a major defense system of innate immunity and aimed to destroy microbes ad protect intact self. Each of the five FHR proteins together with the regulator Factor H are central in maintaining intact self. Sequence and copy number variations in the human FHR-Factor H gene cluster comprising the complement genes FHR1, FHR2, FHR3, FHR4, FHR5, and Factor H are linked to the human kidney diseases atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy. Distinct genetic and chromosomal alterations, deletions, or duplications generate hybrid as well as mutant FHR genes, as well as hybrid FHR-Factor H genes, and alter the FHR and Factor H plasma repertoire. A clear association between the genetic modifications and the pathologic outcome is emerging: FHR1, FHR3, and Factor H gene alterations in context with intact FHR2, FHR4, and FHR5 genes are reported in atypical hemolytic uremic syndrome. For the autoimmune form of HUS homozygous deficiency of FHR1 and FHR3 is frequent and in some cases compound scenarios with FHR1-FHR3 combined with FHR1-FHR4 deletion on the second allele are reported. In addition, alterations in each of the five FHR genes in the context of an intact Factor H gene are described in C3 glomerulopathy. These genetic modifications result in hybrid or mutant proteins which can deregulate complement, in addition they alter FHR and Factor H plasma levels, influence complement function and the interplay of the five FHR proteins with each other and with Factor H. Understanding how mutant or hybrid FHR proteins, Factor H::FHR hybrid proteins, and altered Factor H, FHR plasma profiles cause pathology in the two different disorders is of high interest for diagnosis and targting complement mediated therapy.

Genetic Basis: The Role of Rare and Common Complement Gene Variants

Rossella Piras, Italy

Immune complex-Mediated Membranoproliferative Glomerulonephritis (IC-MPGN) and C3 Glomerulopathy (C3G) are a group of kidney diseases characterized by complement C3 deposition in glomeruli. Clinical presentation and course are variable and range from asymptomatic hematuria and/or proteinuria, hypertension to nephritic or nephrotic syndrome and renal impairment. There is no universally effective treatment although several clinical trials are testing new anti-complement molecules in IC-MPGN and C3G. The diagnosis needs kidney biopsy and, immunofluorescence (IF) microscopy distinguishes IC-MPGN from C3G.

The current classification is founded on the assumption that IC-MPGN is linked to the activation of the complement classical pathway (CP) while C3G is linked to the activation of the complement alternative pathway (AP). However, studies of the last years showed comparable percentage of complement AP abnormalities in C3G and IC-MPGN. Indeed, about 20% of patients with IC-MPGN/C3G had pathogenic variants in complement regulators genes, such as CFH, CFI,

CD46 and THBD or in complement components like C3 and CFB; around 2% and 5% of patients carried uncommon CFH-CFHR genomic rearrangements in IC-MPGN and C3G, respectively. Finally, acquired defects, like autoantibodies stabilizing the AP C3 or C5 convertases, called C3NeFs or C5NeFs, or against FH, FB and C3b were identified in about 50% of patients with IC-MPGN/C3G. In addition, literature data refer an increase of the risk to develop IC-MPGN and or C3G in presence of common variants in CFH, CD46 and THBD. Genetic variants in CFHR genes have been described in C3G, often in combined with other complement abnormalities, although functional studies are required to understand their role in the disease pathogenesis.

These findings indicate that dysregulation of the complement AP may underlie the pathogenesis of both C3G and IC-MPGN which is not consistent with the current IC-MPGN/C3G classification. To address this discrepancy, a recent unsupervised hierarchical cluster analysis based on histologic, biochemical, genetic and clinical data of 173 patients was applied. The analysis provided four homogeneous groups of IC-MPGN/C3G patients characterized by specific pathophysiologic mechanisms. Of interest, it identified a group of patients without known complement abnormalities despite intense glomerular C3 deposition, spurring further research on the identification of new biochemical and genetic factors, an important goal for a more accurate diagnosis and the development of targeted therapies.

Nephritic Factors and Anti-complement Futoantibodies

Sophie Chauvet, France

Autoantibodies targeting complement proteins are heterogeneous and associated with rare complement kidney diseases such as C3 glomerulopathy, immune complex associated membranoproliferative glomerulonephritis (IC-MPGN), post infectious glomerulonephritis, atypical Hemolytic uremic syndrome (aHUS) or lupus nephritis. In C3G and IC-MPGN, targeted complement proteins are mainly C3b and factor B, both component of AP C3/C5convertases. Less frequently, autoantibodies target complement regulatory proteins such as factor H. Such acquired complement abnormalities remain rare, mainly affect children or young adults. The most frequent auto antibody, found in 50-80% of patient is C3 nephritic factor, C3NeF that binds a neoepitope of the alternative complement pathway C3 convertase, C3bBb. Its binding on C3bBb results in stabilization of the enzyme and increasing cleavage of C3 in C3b that exceed capacity of regulation. Another nephritic factor, C5NeF, is able to bind the AP C5 convertase. It is less frequent than C3NeF, sometimes associated with C3Nef and drive profile of complement biomarkers and phenotype of the disease. Indeed, patients with C5Nef most frequently have C3 glomerulonephritis phenotype and not Dense deposit disease, with elevated soluble C5b-9 level in plasma. Isolated anti C3b or anti factor B antibodies, without capacity of C3 convertase stabilization are very rare in C3G or IC-MPGN. Transient anti factor B or anti C3b antibodies are the hallmark of post infectious glomerulonephritis. Finally, antibodies targeting regulatory proteins such as factor H or CR1, are less frequent. Biological characteristic of anti FH antibodies identified in C3G are different that those identified in atypical HUS. Titers of antibodies are mainly low, without detectable circulant complex Ig-FH. Moreover, they are not associated with the typical deletion of CFHR1., found in 90% of acquired aHUS. They preferentially bind the N terminal part of factor H resulting in alteration of co factor activity of FH. In patients aged over 50, presence of anti Factor H antibodies requires research of monoclonal gammopathy. Therapeutic strategy based on auto anti complement protein antibody depletion (i.e plasma exchange or B cell depleting chemotherapy) has not demonstrated efficiency.

CLINICAL: UNANSWERED QUESTIONS

15:50-17:20

The Variable Expression of C3G/IC-MPGN: Complement, Post-infectious, Paraproteins

Moglie Le Quintrec-Donnette, France

Unavailable at time of print.

Maths Helps Clinicians with Making a Diagnosis and Predicting Outcomes

Maria Noris, Italy

Primary Membranoproliferative Glomerulonephritis (MPGN) includes a heterogeneous group of rare kidney disorders associated with complement activation. MPGN has been classified into C3 glomerulopathy (C3G) and immune-complex-mediated MPGN (IC-MPGN). C3G is further divided into dense-deposit disease (DDD), with highly electron-dense deposits in the glomerular basement membrane, and C3 glomerulonephritis (C3GN), with mesangial, intramembranous, subendothelial and subepithelial deposits. This classification is based on the composition of the glomerular deposits as observed through immunofluorescence and on the assumption that C3G arises from hyperactivation of the complement

alternative pathway (AP), whereas IC-MPGN derives from the deposition of immune-complexes that trigger the classical pathway. However, AP gene mutations and/or the C3 nephritic factors (C3NeFs) -autoantibodies that bind and stabilize the C3 convertase complex- have been found as frequently in patients with IC-MPGN as in those with C3G. There is no effective therapy for C3G or IC-MPGN. The success of the anti-C5 antibody eculizumab in other complement-mediated diseases has boosted interest from the pharmaceutical industry in the development of inhibitors that target different molecules of the complement cascade. However, the pathogenesis of C3G/IC-MPGN is complex, different patients have activation at varying levels of the complement system, and it is not known which patients would benefit from anti-C5 and which need a more proximal blockade. In a recent study, we did unsupervised hierarchical clustering on 173 C3G/IC-MPGN patients using histologic, genetic and serum/plasma complement parameters and clinical features. Through this approach we divided patients into 4 clusters characterized by specific pathophysiological mechanisms. Clusters 1 and 2 include patients with fluid-phase AP activation at both the C3 and C5 level, as shown by low serum C3 and high plasma SC5b-9. Cluster 2 shows the additional activation of the classical pathway with glomerular deposits of IgG and C1q. Patients in cluster 3 have fluid phase activation of the AP mainly at the C3 level. Finally, cluster 4 is characterized by solid-phase restricted complement activation with intense glomerular C3 deposits, with a normal complement profile in the blood. AP gene mutations and/or acquired abnormalities were identified frequently in clusters 1-3 and rarely in cluster 4. Based on data that patients in clusters 1 and 2 have signs of C5 activation and could potentially benefit from eculizumab, we evaluated the effectwe evaluated the effect of this drug in 10 of these patients in the Eagle trial.Three patients (from cluster 1) achieved a partial remission of the proteinuria, while the other 7 did not significantly benefit from the treatment. Thus, further studies are required to clarify the complex patterns of disease-predisposing factors and to provide additional parameters useful for a more precise cluster stratification of patients.

KEYNOTE LECTURE

17:20-17:50

C3G/IC-MPGN in 2022

Richard Smith, United States

"Immune Complex-Mediated Glomerulonephritis and C3 Glomerulopathy in 2022 – State of the Art

Immune Complex-Mediated Glomerulonephritis (ICGN) and C3 Glomerulopathy (C3G) describe pathologic patterns of injury diagnosed by renal biopsy. The former is characterized by glomerular deposition of polyclonal immune complexes and the third component of complement (C3) while in the latter, deposition of the third component of complement (C3) predominates. Hepatitis B and C viral infections are amongst the most common inciting causes of ICGN although it is also associated with autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis, with secondary complement activation. In C3G, in contrast, the underlying pathophysiology is driven by dysregulation of the alternative pathway of complement in the fluid-phase and in the glomerular microenvironment. C3G is poorly understood and this talk will focus primarily on this disease. In affected patients, the most commonly detected drivers of complement dysregulation are autoantibodies to the C3 and C5 convertases of complement, although genetic mutations in complement genes can also be identified that lead to overactivity of the complement system. Approximately half of patients progress to end stage renal disease within 10 years of diagnosis, and, while transplantation is a viable option, there is high risk for disease recurrence and allograft failure. This poor outcome reflects the lack of disease-specific therapy for C3G, relegating patients to symptomatic treatment to minimize proteinuria and suppress renal inflammation. Fortunately, the future is bright as several anti-complement drugs are currently in clinical trials. "

WHAT HAVE WE LEARNT FROM ANIMAL MODELS?

08:30-09:30

Modeling aHUS in Genetic Mouse Models

Wenchao Song, United States

Atypical hemolytic uremic syndrome (aHUS) is a disease caused by dysregulated alternative pathway complement activation. It is characterized by the clinical triad of thrombocytopenia, hemolytic anemia and renal failure. The anti-complement C5 mAb Eculizumab has been approved for the treatment of aHUS but how complement effectors derived from C5 activation contributed to disease pathogenesis and manifestation has not been easily studied in human patients. In this presentation, I will describe a mouse model of aHUS generated by genetically introducing a point mutation to the FH gene, the same point mutation found in some aHUS patient families. I will also discuss data from studying this mouse

model that shed mechanistic insight and understanding on the pathogenesis of aHUS and proof of concept of some novel anti-complement therapies for aHUS and related diseases.

Role of Complement in the Pathophysiology of STEC-HUS: Evidence from a Mouse Model

Carlamaria Zoja, Italy

"Shiga toxin (Stx)-producing E. coli (STEC) is a food- or waterborne pathogen responsible for global outbreaks of hemorrhagic colitis, complicated by diarrhea-associated HUS, a disorder involving thrombocytopenia, microangiopathic hemolytic anemia and acute kidney failure, mainly in early childhood. Outcomes for STEC-HUS have improved recently, but over 25% of patients who do not recover completely from the acute disease report long-term renal sequelae. The toxic effects of Stx primarily target the glomerular endothelium. After binding to its specific receptor, Stx activates a cascade of signals that cause vascular dysfunction, leukocyte recruitment, and thrombus formation. In vitro, Stx induces the expression of P-selectin on microvascular endothelial cell surface. P-selectin binds and activates C3 via the alternative pathway, leading to thrombus formation under flow. Excessive C3 activation in response to Stx generates more C3a, which potentiates endothelial P-selectin expression, thrombomodulin loss and thrombus formation. Animal models provide valuable information on complement activation in the thrombotic process that leads to kidney dysfunction in STEC-HUS. In a murine model of HUS obtained by coinjecting Stx2/LPS and characterized by thrombocytopenia and renal dysfunction, the upregulation of glomerular endothelial P-selectin was associated with C3 and fibrin(ogen) deposition, platelet clumps and reduced thrombomodulin expression. Treatment with anti-P-selectin antibody limited glomerular C3 accumulation. Factor B-deficient mice injected with Stx2/LPS were protected against glomerular abnormalities and renal dysfunction, indicating the alternative pathway was involved. The role of C3a in potentiating microvascular thrombosis is highlighted by data showing a reduction in fibrin(ogen) and in thrombomodulin loss in the glomeruli of Stx2/LPS mice treated with a C3a receptor (C3aR) antagonist. These results show that Stx-induced complement activation via P-selectin is a key mechanism of C3a-dependent microvascular thrombosis in STEC-HUS.

Another important target for Stx-induced complement activation is the podocyte, a cell population that participates in maintaining the glomerular filtration barrier. In Stx2/LPS mice, glomerular complement deposition was accompanied by podocyte dysfunction and loss, which may explain long-term renal sequelae in patients with STEC-HUS. Glomerular complement activation induced podocyte upregulation of integrin-linked kinase, a signal for podocyte adhesion/migration, and the activation of the transcription factor Snail, responsible for nephrin downregulation. Alpha actinin-4, a protein involved in maintaining podocyte organization, was lower in Stx2/LPS mice. Factor B deficiency protected mice against STx2/LPS-induced podocyte dysregulation, indicating that the activation of complement via the alternative pathway promotes podocyte dysfunction. Treatment with a C3aR antagonist limited podocyte dysfunction and loss and improved renal function, highlighting that C3a is a key factor in podocyte damage. The activation of the C3a/C3aR axis in podocytes of Stx2/LPS mice was associated with alterations in mitochondrial structure, mass and energy production, which were limited by C3aR blockade. Experimental evidence from STx2/LPS mice suggests that C3a/C3aR may be an important, novel target in STEC-HUS."

ADVANCES IN PATHOPHYSIOLOGY

09:30-11:10

Genetic Basis of aHUS

David Kavanagh, United Kingdom

"Haemolytic uraemic syndrome is a thrombotic microangiopathy (TMA) characterised by the clinical triad of thrombocytopenia, microangiopathic haemolytic anaemia, & acute renal failure. The most common form of HUS is associated with a preceding diarrheal illness caused by verocytotoxin-producing bacteria, typically Escherichia coli O157:H7.

Those not preceded by this infection are classified as atypical HUS (aHUS) (OMIM 235400). The role of complement in aHUS was first described in the late 1990s with ~50% of cases carrying mutations in the complement regulatory genes [factor H (CFH); membrane cofactor protein (MCP; CD46) or factor I (CFI)] and the complement component genes [factor B (CFB) & C3]. Genotype phenotype correlations were established with CD46 mutations having the best outcome for native disease and after renal transplantation. The identification of complement mutations provided a rationale for the use of complement inhibitors with successful clinical trials of eculizumab revolutionising outcomes.

With the introduction of Eculizumab into clinical practice it has become apparent that there is a small group of patients that do not respond to complement inhibition. This allowed the identification of non-complement genes associated with aHUS. Today next generation sequencing allows rapid identification of underlying genetic drivers of disease to personalise management of aHUS."

Common Genetic Susceptibility Factors in aHUS

Elena Goicoechea de Jorges, Spain

"The complement system is a major component of the innate immunity. Upon activation through any of its three activation pathways (classical, lectin or alternative), the complement system displays various effector functions that mediate inflammation and cell damage. Complement is tightly regulated to avoid the unnecessary consumption of its components and to prevent direct damage to host tissues and an excessive inflammation. Under certain circumstances, this regulation may fail or may be overwhelmed resulting in a pathological condition.

Rare and common genetic variants in complement genes leading to dysregulation of the alternative pathway (AP) are associated with a wide range of pathological conditions, including atypical hemolytic uremic syndrome (aHUS). Notably, common gene variants in CFH, MCP and the CFHRs have been repeatedly associated with increased susceptibility or protection for developing aHUS in independent cohorts. Interestingly, these associations illustrate the existence of genotype-phenotype correlations, as certain common variants or polymorphisms are associated with aHUS but not with other diseases such as C3 glomerulopathy.

It is well-known that some common variants in complement components and regulators have a functional impact in the molecules. Although this effect is more subtle compared to the impact that rare variants may cause, the additive effect of several common variants may have a relevant impact and define the balance between complement activation/regulation. The combination of these set of functional polymorphisms that is inherited by an individual is defined as the complotype and may determine disease susceptibility.

Although polymorphisms alone are not pathogenic, in combination with other genetic or environmental aHUS risk factors they significantly increase the penetrance of the disease. Indeed, in familial cases of aHUS the presence of aHUS-associated polymorphisms explains why some carriers of complement mutations develop the disease, while other carriers do not. In addition, some aHUS-associated polymorphisms have also been shown to favor a worse prognosis of renal function at the time of HUS onset. During the talk, the impact of the different common complement gene variants that are relevant to aHUS will be discussed."

Anti-FH Antibodies Associated HUS

Arvind Bagga, India

Unavailable at time of print.

aHUS: Why the Kidney?

Lubka Roumenina, France

"Atypical hemolytic uremic syndrome (aHUS) is a severe disease characterized by microvascular endothelial cell (EC) lesions leading to thrombi formation, mechanical hemolysis and organ failure, which affects predominantly the kidney. Complement system overactivation is a hallmark of aHUS. Despite gained knowledge and successful therapy, it is still poorly understood why the kidney is particularly affected in this disease, when the mutated complement proteins are most often in the circulation and all organs are equally exposed to them.

Several factors could contribute to this susceptibility. Unlike other capillary ECs, glomerular EC (GEC) are exposed to a high blood pressure and high blood flow, which drives the glomerular filtration process and exposes these cells to substantial shear stress. scRNAseq revealed that EC from different organs express complement factors and regulators, but at resting state this expression is low, with little difference between vascular beds. Moreover, we did not observe difference an ex-vivo complement activation for GEC and HUVEC at resting state or after cytokines activation. Little difference was reported for the expression of complement and coagulation regulators between GEC and HUVEC, at resting state or after inflammatory challenge.

aHUS is associated to deficiency of FH. Strikingly, FH knockdown in GEC disturbed cytoskeletal architecture, monolayer integrity, proliferation control, metabolism, and inflammatory signaling regulation, while in HUVEC had no effect. Therefore, endothelial-intrinsic FH exerts intracellular functions, important for the cell homeostasis.

aHUS is characterized by intrarenal hemolysis and release of heme, which is a potent DAMP. After prolonged exposure to heme, we found higher C3 deposits on glomerular EC compared with other EC in culture and in mice organs. This could be explained by a weaker binding of FH and inefficient upregulation of thrombomodulin (TM). GEC also failed to upregulate the cytoprotective heme-degrading enzyme HO-1, normally induced by hemolysis. Only HUVEC developed adaptation to heme, which was lost after inhibition of HO-1 activity. Interestingly, the expression of KLF2 and KLF4—known transcription factors of TM, also described as possible transcription modulators of HO-1- was weaker in GEC compared to HUVEC under hemolytic conditions. Strikingly, recent study reported that Klf4ΔEC mice exhibit increased pro-thrombotic and pro-inflammatory transcripts, as well as increased complement factors C3 and C5b-9 deposition, decreased CD55 and histologic features consistent with subacute thrombotic microangiopathy. Therefore, endothelial Klf4 is likely necessary

for the maintenance of a quiescent glomerular endothelial phenotype and its loss increases susceptibility to complement activation and induction of prothrombotic and pro-inflammatory pathways.

Together these results suggest that the GEC relay on intracellular FH for maintenance of their physiological phenotype, rendering them susceptible to FH abnormalities. Also, they fail to adapt to the stress imposed by hemolysis and acquire a pro-coagulant and complement-activating phenotype. The vulnerability of GEC to complement variants and to hemolysis are among the factors, promoting and amplifying complement overactivation and thrombotic microangiopathic lesions on the glomerular endothelium in aHUS."

CLINICAL: UNANSWERED QUESTIONS

11:40-13:00

Primary and Secondary aHUS. Still Worth Discussing?

Giovanni Montini, Italy

"Valentina Capone1, Gianluigi Ardissino1, Luigi Porcaro2, Donata Cresseri3, Giovanni Montini1,4.

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4. Department of Clinical Sciences and Community Health, University of Milan, Italy

Atypical Hemolytic Uremic Syndrome (aHUS) is secondary to complement abnormalities (genetic or acquired) in 50-60% of cases. Some of the remaining cases may be related to the involvement of unknown genes but may be also due to coexisting complement over-activating conditions playing the role of triggers in the development of aHUS.

Based on the presence/absence of complement abnormalities and of specific triggers, 3 distinct groups of patients can be identified: 1. Primary (with complement abnormality), 2. Secondary (trigger only), 3. Idiopathic (no complement abnormality and no manifest trigger). This approach to aHUS classification may have some important drawbacks in the management of patients particularly regarding C5 inhibition (C5i) as to treatment initiation, response rate and treatment discontinuation.

The case series of aHUS treated or referred to our Center between 2000 and 2021 was analyzed according to the mentioned classification criteria. Outcomes (response rate, case-fatality rate, frequency of ESKD and relapse rate) were compared between C5i and conventional treatment. Out of 241 patients, 144 (59.8%) had Primary aHUS, 57 (23.6%) Secondary aHUS and 40 (16.6%) Idiopathic aHUS. In patients treated with C5i (n:142) the response rate (RR) was higher compared to conventional treatment both for Primary (83.0% vs 37%) and Secondary aHUS (76.6% vs 40%), while no difference was observed for Idiopathic aHUS (64.0% vs 62%).

The frequency of ESKD was lower after C5i compared to conventional treatment both in Primary (15.7 vs 59.6%) and Secondary aHUS (14.8 vs 40.4%), while no difference was noted for the Idiopathic form (36.0 vs 40.0%). Similarly, the case-fatality rate was lower with C5i in all groups compared with conventional treatment (Primary 5.7 vs 9.5%; Secondary 8.5 vs 20.0%; Idiopathic 4.0 vs 13.0). Among patients who discontinued C5i the relapse rate was significantly higher in patients with complement dysregulation compared to patients without identified complement abnormalities.

Based on our results, C5i should be promptly started in any patient meeting the criteria for aHUS, while the distinction of aHUS in three groups of patients maintains its usefulness as regards treatment response, long term outcome and relapse rate. When complement dysregulation workup is available, patients can be better stratified and managed accordingly as fa as treatment discontinuation is concerned. "

Postpartum Renal Cortical Necrosis and aHUS

Raja Ramachandran, India

Renal cortical necrosis (RCN) is an alarming complication of AKI. Conventionally thought of as a consequence of severe renal ischemia secondary to haemorrhage, microvascular injury, or thrombosis. RCN encountered in the limited-resource countries is primarily due to pregnancy-related complications. The exact pathogenesis of RCN in the obstetric setting remains unsettled. Traditionally, nephrologists attribute RCN to haemorrhage in a limited-resource setting. However, recently we reported thrombotic microangiopathy (TMA) in all patients with RCN, and infections and haemorrhages may be the trigger for the TMA. In the premise of TMA in all patients with RCN, genetic evaluation is critical to understanding the disease entity. We evaluated for genetic defects (MLPA) in complement genes in patients with pregnancy-related

RCN; three-fourths of the patients had duplication in complement genes, mainly CFHR 1-3. So, we may conclude that the haemorrhage and infections were the second or third hit for HUS in a genetically predisposed individual.

Monitoring Complement Dysregulation in aHUS

Miriam Galbusera, Italy

"Hemolytic uremic syndrome (HUS) is a rare syndrome encompassing microangiopathic hemolysis, thrombocytopenia, and kidney failure. Most childhood cases are caused by Shiga-like toxin–producing bacteria (STEC-HUS) or neuroaminidase-producing Streptococcus pneumoniae. Primary atypical HUS (aHUS) defines cases associated with dysregulation of the alternative complement pathway. Secondary aHUS may occur as a complication of autoimmune diseases, pregnancy, malignant hypertension, and transplantation. About 60% of patients with aHUS carry genetic abnormalities affecting complement factor H, membrane cofactor protein, CFI, C3, CFB, and thrombomodulin or have anti-CFH autoantibodies. Complement gene abnormalities reported in a fraction of patients with secondary aHUS suggest that genetic predispositions to complement activation also have a role in these cases. aHUS-associated complement abnormalities result in dysregulation of the alternative pathway mainly restricted to cell surfaces, resulting in endothelial injury and microvascular thrombosis. In contrast, patients with aHUS effectively control complement in the fluid phase, so the circulating complement profile is of limited prognostic significance: about half of all patients have normal serum C3 levels and normal plasma levels of the terminal complement complex sC5b-9, even during an acute episode.

In search of biomarkers of cell surface-restricted complement activation in aHUS, we developed an ex-vivo assay based on serum-induced complement deposits on cultured human microvascular endothelial cells.

In a large case series of patients the test on ADP-activated endothelial cells demonstrated elevated C5b-9 deposits in all untreated aHUS patients, independently of disease activity, while the test on unstimulated endothelium was positive only in active disease. Thus, the test on unstimulated cells could be useful for picking up active disease. Similar results were obtained in secondary aHUS, which supports a pathogenetic role of complement.

The complement inhibitor eculizumab effectively induces disease remission, but the need for chronic treatment (every 2 weeks), the high cost and the risk of infections create the need to optimize the regimen for each patient. The ex-vivo test was used for assessing the effectiveness of eculizumab in blocking the complement terminal pathway on endothelium, and for monitoring the degree of C5 activity at the endothelial cell level and possibly highlighting relapses during eculizumab tapering and treatment discontinuation. Serum-induced C5b-9 deposits on activated and unstimulated endothelium normalized during eculizumab treatment. Ninety-six % of patients receiving eculizumab at extended 3- or 4-week intervals retained normal C5b-9 deposits on activated endothelium, despite most patients exhibiting serum CH50Eq >20 UEq/mL, indicating that adequate complement control was achieved even with incomplete blockade of circulating C5. During eculizumab tapering/discontinuation, all patients experiencing relapses, versus only 6% of those in stable remission, had elevated C5b-9 deposits on unstimulated endothelium. Thus, the ex-vivo endothelial assay could be an advance toward personalized eculizumab therapy in aHUS.

Comparison with other tests available for detecting complement hyperactivation will be addressed and limitations of the ex-vivo tests will be discussed."

WHEN AND HOW TO INHIBIT C5 IN COMPLEMENT-MEDIATED RARE NEPHROPATHIES

14:00-15:30

Eculizumab in Primary and Secondary aHUS: Who, When, and How Long?

Sjoerd Timmermans, Netherlands

The syndromes of thrombotic microangiopathy (TMA) are rare and potentially life-threatening caused by a heterogeneous group of diseases, often affecting the brain and kidneys. TMAs should be classified according to etiology to indicate targets for treatment. Deregulated complement is an important cause of TMA that defines cases not related to coexisting conditions, that is, primary atypical hemolytic uremic syndrome (aHUS). Ever since the approval of therapeutic complement inhibition, the approach of TMA has focused on the recognition of primary aHUS. Recent advances, however, demonstrated the pivotal role of deregulated complement in so-called secondary aHUS and, in particular, patients presenting with coexisting hypertensive emergency, pregnancy, or kidney transplantation, shifting the paradigm of disease. The presentation “Eculizumab in primary and secondary aHUS: who, when, and how long?” will focus on the recognition of deregulated complement in patients with secondary aHUS to commence targeted treatment in the earliest possible stage, having major impact on treatment and prognosis.

Eculizumab in Primary and Secondary aHUS: Who, When and, How Long?

Giuseppe Remuzzi, Italy

Several studies on atypical hemolytic uremic syndrome (aHUS), a rare disease characterized by the extensive formation of thrombi in the microcirculation of the kidney and other organs due to genetically determined dysregulation of the complement alternative pathway, have contributed to highlighting the role of complement activation products in microvascular thrombosis. By using an ex vivo test in which microvascular endothelial cells were incubated with serum from patients with aHUS, we documented that aHUS serum, but not control serum, induced intense membrane attack complex C5b-9 The diagnosis of aHUS is based on clinical parameters (haematologic abnormalities and acute renal failure), after ruling out Shiga toxin–producing E. coli (STEC)-HUS, thrombotic thrombocytopenic purpura (TTP) (severe ADAMTS13 deficiency with <10% protease activity) and secondary forms (autoimmune diseases, drugs, cancer and human immunodeficiency syndrome). HUS is an acute, devastating disease; specific complement inhibitor therapy is lifesaving and should be started without delay to prevent irreversible injury to the kidney and other organs

The role of C5 activation products in aHUS has been confirmed by clinical success of the anti-C5 monoclonal antibody eculizumab, which radically improved the prognosis of aHUS by inducing and maintaining disease remission. The identification of genetic and/or acquired complement abnormalities is of clinical relevance, both to confirm the diagnosis and to optimize patient management. Terminal complement blockade at the level of C5 is effective in the vast majority of aHUS patients.

Impact of C5 Blockade on Post-transplant Outcomes and Renal Epidemiology of aHUS

Christophe Legendre, France

Atypical Hemolytic and Uremic Syndrome (aHUS) is a very rare disease that will often recur after kidney transplantation with a very severe prognosis. Eculizumab, an anti-C5 monoclonal antibody has revolutionized the course of this disease and its prognosis. During this presentation, we will show data regarding the use of eculizumab in kidney transplantation, the way this drug did modified the epidemiology of the disease, data on long-lasting use of a new formula, but also the pathology of microangiopathies.

WHEN AND HOW TO INHIBIT C3 IN COMPLEMENT-MEDIATED RARE NEPHROPATHIES

16:00-17:30

Manipulating the Early Steps of Complement Cascade: Emerging Drugs, Potential Risks, and Benefits

Joshua Thurman, United States

The complement cascade plays an important role in the pathogenesis of a wide range of kidney diseases, including glomerulonephritis, thrombotic microangiopathy, transplant rejection, and tubulointerstitial injury. Many new anti-complement drugs are in clinical development, including agents that target specific activation steps or the C3 protein (the central protein of the complement cascade). These drugs are advantageous in that they block generation of all pathogenic activation fragments (C3a, C3b, C5a, and C5b-9), but they also increase patients' susceptibility to infection. These drugs may also block important homeostatic functions of the complement system. This presentation will review the opportunities and risks of blocking early steps in complement activation in patients with kidney disease.

Lessons from Studies in Mouse Models of C3G

Ariela Benigni, Italy

Alternative pathway complement dysregulation with abnormal glomerular C3 deposits and glomerular damage is a key mechanism of pathology in C3 glomerulopathy (C3G). No disease-specific treatments are currently available for C3G. Therapeutics inhibiting complement are emerging as a potential strategy for the treatment of C3G. In this study, we investigated the effects of N-acetylgalactosamine (GalNAc)–conjugated small interfering RNA (siRNA) targeting the C3 component of complement that inhibits liver C3 expression in the C3G model of mice with heterozygous deficiency of factor H (Cfh+/– mice). We showed a duration of action for GalNAc-conjugated C3 siRNA in reducing the liver C3 gene expression in Cfh+/– mice that were dosed s.c. once a month for up to 7 mo. C3 siRNA limited fluid-phase alternative pathway activation, reducing circulating C3 fragmentation and activation of factor B. Treatment with GalNAc-conjugated

C3 siRNA reduced glomerular C3d deposits in Cfh+/– mice to levels similar to those of wild-type mice. Ultrastructural analysis further revealed the efficacy of the C3 siRNA in slowing the formation of mesangial and subendothelial electron-dense deposits. The present data indicate that RNA interference–mediated C3 silencing in the liver may be a relevant therapeutic strategy for treating patients with C3G associated with the haploinsufficiency of complement factor H.

Targeting C3, CFD, or CFB in C3G, Preliminary Results of Clinical Trials in Patients with C3G/IC-MPGN

Erica Daina, Italy

Primary C3G and IC-MPGN represent a disease spectrum that is heterogeneous in terms of pathophysiology and clinical course. The optimal treatment for these conditions has not been established yet. The recent success of anti-C5 monoclonal antibody for the treatment of other complement-mediated rare diseases, such as paroxysmal nocturnal haemoglobinuria and atypical haemolytic uremic syndrome, has boosted the interest of pharmaceutical industries in the clinical development of inhibitors that target different molecules of the complement cascade. Anti-C5 monoclonal antibody and C5aR1 antagonist have been employed in small series of C3G and IC-MPGN patients. However, terminal pathway inhibitors do not affect complement activation upstream of C5 and do not prevent the formation of C3 activation fragments and their accumulation in glomerular immune deposits. Drugs that target complement upstream C5 are thus being tested and preliminary results will be presented. Altogether, the evidence indicates that the response to complement inhibition may vary greatly in C3G and IC-MPGN patients, probably depending on the degree and level of complement pathway dysregulation. In addition, because each drug may act only in specific subgroups of patients, its effect in the overall C3G and IC-MPGN population will likely be diluted. Specific evaluation of complement activity should be performed in patients before and during treatment to establish whether they may benefit from the different drugs and to establish the effective dose.

KEYNOTE LECTURE

17:30-18:00

HUS in 2022

Fadi Fakhouri, Switzerland

"Atypical haemolytic uremic syndrome (HUS) is a devastating form of thrombotic microangiopathy (TMA) affecting predominantly the kidney. Untreated, it carries a high risk of end-stage renal disease: 2/3 of adult and half of affected children progress to end-stage kidney disease, at the first episode of atypical HUS or following one or several relapses. A significant body of clinical, experimental and genetic data have helped unravel the pathogenic mechanisms underlying atypical HUS, namely an overactivation of the complement alternative pathway. This breakthrough in our understanding of the pathogenesis of atypical HUS helped designing a specific treatment. C5 blockade, with the first anti-C5 monoclonal antibody, eculizumab, has dramatically changed the perspective in the management and prognosis of atypical HUS. It is currently estimated that C5 blockade reduces the risk of end-stage kidney disease in atypical HUS adult patients from 50-60% to around 10-15%. Thus, an accurate and rapid diagnosis followed by an early treatment initiation have become crucial for the optimal management of atypical HUS patients. Nevertheless, there is to date no reliable diagnostic test for atypical HUS and the latter remains a diagnosis by exclusion. Furthermore, long-treatment with C5 blockers carries a risk of infectious complications and the burden of repeated infusions. The availability of the long-acting C5 blocker, ravulizumab, allows extending the interval between infusions from 2 weeks to 2 months.

Finally, a life-long treatment with a C5 blocker is no more a paradigm that applies to all patients with atypical HUS. In patients with no detected complement gene variants, C5 blockade discontinuation is feasible and safe. In carriers of complement gene rare and pathogenic variants, C5 blocker discontinuation has to be discussed on a case-by-case basis."

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Vivekanand Jha
India
Climate Change, Changing Biodiversity and Infections - Impact on Kidney Health

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