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ABSTRACTS

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OP-1 EFFICACY OF IMMUNOGLOBULIN IMMUNOADSORPTION IN THE TREATMENT OF MULTIDRUG RESISTANT IDIOPATHIC NEPHROTIC SYNDROME

Stephanie Bonneric, Theresa Kwon, Elodie Nattes,Claire Dossier, Julien Hogan
Pediatric Nephrology Department, Robert Debré Hospital

Introduction: Idiopathic nephrotic syndrome is mostly a chronic disease, which can lead to end-stage renal disease in case of cortico-resistance and multidrug resistance. The aim of this study was to analyze the evolution of pediatric patients with multidrug resistant nephrotic syndrome treated by immunoglobulin immunoadsorptions (IA) associated with intravenous immunoglobulins (IvIg).
Material and methods: In this monocentric retrospective study, 23 patients with steroid and multidrug resistant nephrotic syndrome were treated with an association of IA and IvIg, followed by B cell depletion when in remission. The primary outcome was the remission of proteinuria (uPCR<0,05g/mmol).
Results: A remission was obtained in 17 patients. 14 patients responded during the first cycle of treatment (10 daily sessions of IA), and 3 after a more prolonged treatment (up to 3 months). Anti-CD20 monoclonal antibodies were administered to maintain depletion in patients in remission. 10 patients relapsed after the first cycle of IA, and 6 developed a dependency to IA to remain in remission. Only 6 patients did not respond to IA therapy and 2 progressed towards end-stage renal disease. Out of 18 patients with long-term follow-up data (median 22,5 months), 10 patients were in remission (7 of them with no immunosuppressive therapies).
Conclusions: IA therapy is effective in inducing remission in children with steroid and multidrug resistant nephrotic syndrome. However, more than 50% of the patients relapse despite B cell depletion and a significant number of these patients become dependent on IA to maintain remission. Newer treatment strategies are needed to maintain remission and allow IA discontinuation in children with steroid and multidrug resistant nephrotic syndrome.

OP-2 SAFETY AND EFFICACY OF OFATUMUMAB IN REFRACTORY PEDIATRIC NEPHROTIC SYNDROME. AN STUDY COHORT

Yolanda Calzada Baños; Elena Codina Sampera, Pedro Arango Sancho, Víctor López-Báez, Ana Vinuesa Jaca, Lina Catherine Hernández Zúñiga, Álvaro Madrid Aris
Hospital Sant Joan De Déu

Introduction: Ofatumumab (OFA) is an anti-CD-20 monoclonal antibody used in nephrotic syndrome (NS) refractory to conventional treatments and rituximab (RTX). Our objective is to evaluate the safety and efficacy of Ofatumumab in our cohort.
Material and methods: Prospective descriptive study of 2yr follow-up (2017-2019) in children with NS refractory to first-line therapies, with anti-CD20 monoclonal antibodies indication. We divided the cohort in: steroid-dependent NS (SDNS) without response or with adverse effects related to first-line treatment (Group 1); steroid-resistant SN (SRNS) (Group 2) and SN with post-transplant recurrence (Group 3). Safety and remission rate were evaluated.
Results: 33 patients (21 SDNS, 11 SRNS, 1 recurrence) were included and administered anti-CD20. The male/female ratio was 2: 1. Mean age at diagnosis was 5.2 years. 100% of the children (33) received RTX and 18.2% (6) OFA. RTX achieved complete remission in 87.9% (29) and 48.3% of these did not relapsed. 100% of Group 1 presented complete remission after RTX, although 52.4% (11) presented at least 1 relapse after 22.9 months (mean 2.5 relapses). In group 2, 72.72% (8) remitted and 27.2% (3) presented partial remission. 36.4% (4) relapsed after 17 months of treatment (mean 1 relapse). Of the 6 who received OFA, 83.3% presented complete remission (1 SRNS and 4 SDNS) and 1 patient (SDNS) presented relapse at 24 months (mean follow-up 1 year). The other case, a 13-year-old girl with recurrence of focal segmental glomerulosclerosis (FSGS) in kidney transplantation, presented partial remission in association with immunoadsorption sessions. Adverse reactions occurred in 6% (2): allergic reaction with 2nd dose of RTX and cytokine release syndrome with 1st dose of OFA.
Conclusions: Ofatumumab in our series has proven to be safe and effective therapy in refractory NS, achieving complete remission in 5 patients who had not previously responded to Rituximab

OP-3 EVALUATION OF THE GENETICAL FEATURES AFFECTING RENAL OUTCOME IN CHILDREN WITH STEROID RESISTANT NEPHROTIC SYNDROME

Elif Comak [1], Asli Toylu [2], Ugur Bilge [3], Gulsah Kaya Aksoy [1], Mustafa Koyun [1], Sema Akman [1]
[1] Akdeniz University Medical Faculty, Pediatric Nephrology, Antalya, Turkey, [2] Akdeniz University Medical Faculty, Medical Genetics, Antalya, Turkey, [3] Akdeniz University Medical Faculty, Biostatistics And Medical Informatics, Antalya, Turkey

Introduction: Although several studies in children with steroid-resistant nephrotic syndrome (SRNS) have shown that mutations in genes encoding proteins in the podocyte skeleton may be responsible for the etiology in only one-third of cases, the genetic features related with renal prognosis and responde to immunosuppressive are not fully recognized. The aim of this study was to investigate the genetic alterations associate

with renal prognosis and resistance to immunosuppression in children with SRNS.

Material and methods: The children with SRNS were enrolled in this study. Custom genetic panel was designed for next-generation sequencing analysis of 205 SNPs in 33 target genes.

Results: A total of 25 children, 16 boys (64%), median age at last visit of 17.5 years (13-18 years), median age at diagnosis of 7.5 years (2-15), median follow-up of 9.58±4.54 years, were included in the study. All patients was diagnosed focal segmental glomerulosclerosis on renal biopsy. 13 patients had normal renal function, while the remaning 12 had end stage renal disease (ESRD) after a median of 4.5 years (2-11 years) follow up period with a median age at ESRD diagnosis of 13.5 years (6-17 years). In study group, patients were treated five different immunosuppressive medications. All patients received steroids and cyclosporin A; 10 patients mycophenolate mofetil, 10 patients tacrolimus, 1 patient cyclophosphamide, 4 patients rituximab. The genetic analysis revealed significant differences in SNP genotype frequencies between groups of ESRD and normal renal function. Genetic alterations in several genes involved in the drug metabolism (CYP3A5, CYP2C19, GSTP1, MPDH2, SLCO1B1), immune response regulation (FCGR3A, FKBP5, CXCL12), glucocorticoid receptor gene (NR3C1) and uromodulin (UMOD) were significantly associated with the lack of response to immunosuppressive treatments and renal function ($p<0.05$).

Conclusions: Our results suggest that heterogeneous genetic alterations in children with SRNS associate with resistance to different immunosuppressive treatments and renal function.

OP-4 IN VITRO ASSAYS TO DEMONSTRATE THE PRESENCE OF PLASMA-DERIVED CIRCULATING PERMEABILITY FACTORS IN THE PATHOGENESIS OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Susan Veissi [1], Bart Smeets [2], Joanna Van Wijk [3], Floor Veltkamp [5], Rene Classens [1], Thea Van Der Velden [1], Annelies Jeronimus-klaasen [1], William Morello [4], Giovanni Montini [4], Antonia Bouts [5], Lambertus P. W. J. Van Den Heuvel [1], Michiel Schreuder [1]

[1] Department Of Pediatric Nephrology, Amalia Childrens Hospital, Radboud University Medical Center, Radboud Institute For Molecular Life Sciences, Nijmegen, The Netherlands,[2] Department Of Pathology, Radboud University Medical Center, Radboud Institute For Molecular Life Sciences, Nijmegen, The Netherlands,[3] Department Of Pediatric Nephrology, Amsterdam University Medical Center, Amsterdam, The Netherlands,[4] Department Of Pediatric Nephrology, Dialysis And Transplant Unit, Foundation Irccs Cà Granda, Irccs Ospedale Maggiore Policlinico, Milan, Italy,[5] Department Of Pediatric Nephrology, Amsterdam Umc, University Of Amsterdam, Amsterdam, The Netherlands

Introduction: Circulating permeability factors (CPFs) involved in the pathogenesis of idiopathic focal segmental glomerulosclerosis (FSGS) can lead to early recurrence of FSGS and kidney failure after transplantation. Identification of FSGS patients with CPFs is clinically important as it can predict treatment response and prognosis. Currently, kidney biopsy is the gold standard diagnosis. Therefore, there is an increased demand for diagnostic assays to determine the presence of CPFs in the sera of FSGS patients. Using conditionally immortalized human podocytes as a substrate, we aim to demonstrate the presence of plasma-derived CPFs using series of *in vitro* assays.

Material and methods: Podocytes and primary glomerular endothelial cells (GMVECs) were incubated with plasma from biopsy proven FSGS patients in relapse and remission as well as from steroid-resistant nephrotic syndrome (SRNS), minimal change NS (MCNS), membranous nephropathy (MN), a non-renal control patient, and healthy controls. Cell viability, podocyte actin cytoskeleton architecture, and reactive oxygen species (ROS) formation in the presence or absence of ROS scavenger, dimethylthiourea, were investigated by CCK-8 assay, immunofluorescence staining, and CM-H2DCFDA probing, respectively.

Results: We show that plasma of patients with FSGS causes a series of events in podocytes but not in endothelial cells. These events include actin cytoskeleton rearrangement, excessive formation of ROS, and eventually also cell death. These effects were solely observed in response to plasma of relapse FSGS patients, but not in response to plasma of kidney patients with SRNS, MCNS, MN and healthy controls. The co-presence of dimethylthiourea, abolished these effects.

Conclusions: Altogether, we provide a panel of assays to measure podocyte injury and predict the presence of CPFs in FSGS plasma, providing a new framework for monitoring CPF activity that can be used for diagnostics or disease monitoring purposes. Moreover, our findings suggest that the inhibition of ROS formation or facilitating rapid ROS scavenging may exert beneficial effects in FSGS patients.

OP-5 KIDNEYNETWORK: USING KIDNEY-DERIVED GENE EXPRESSION DATA TO PREDICT AND PRIORITIZE NOVEL GENES INVOLVED IN KIDNEY DISEASE

Floranne Boulogne [1], Laura R Claus [2], Henry Wiersma [1], Roy Oelen [1], Floor Schukking [1], Niek De Klein [1], Shuang Li [1], Harm-Jan Westra [1], Bert Van Der Zwaag [2], Franka Van Reekum [3], Dana Sierks [4], Ria SchÖnauer [4], Jan Halbritter [4], Nine V.a.m. Knoers [1], Genomics England Research Consortium [5], Patrick Deelen [2], Lude Franke [1], Albertien M Van Eerde [2]

[1] Department Of Genetics, University Medical Center Groningen, University Of Groningen, Groningen, The Netherlands,[2] Department Of Genetics, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands,[3] Department Of Nephrology, University Medical Center Utrecht, Utrecht, The Netherlands,[4] Medical Department Iii - Endocrinology, Nephrology, Rheumatology Department Of Internal Medicine, Division Of Nephrology, University Of Leipzig Medical Center, Leipzig, Germany,[5] Genomics England, London, UK

Introduction: Genetic testing in patients with suspected hereditary kidney disease does not always reveal the genetic cause for the patients disorder. Potentially pathogenic variants can reside in genes that are not known to be involved in kidney disease, which makes it difficult to prioritize and interpret the relevance of variants in these genes. To help identify candidate genes for kidney disease we have developed KidneyNetwork, in which tissue-specific expression is utilized to predict kidney-specific gene functions.

Material and methods: KidneyNetwork is a co-expression network built upon a combination of 878 kidney RNA-sequencing samples and a multi-tissue dataset of 31,499 samples. It uses expression patterns to predict which genes have a kidney-related function and which phenotypes might result from mutations in these genes. As proof of principle, we applied KidneyNetwork to prioritize rare variants in exome-sequencing data from 13 kidney disease patients.

Results: We assessed the prediction performance of KidneyNetwork by comparing it to GeneNetwork, a multi-tissue co-expression network we previously developed. In KidneyNetwork, we observe a significantly improved prediction accuracy of kidney-related HPO-terms, as well as an increase in the total number of significantly predicted kidney-related HPO-terms (figure 1). Applying KidneyNetwork to exome-sequencing data of kidney disease patients allowed us to identify *ALG6* as promising candidate gene for kidney and liver cysts.