WHAT'S HOT WHAT'S NEW - AN UPDATE FROM THE IPNA 2016 MEETING

Immune Mediated Renal Disorders

Atypical HUS

1) The first abstract describes the relation of the age of onset and renal survival, extrarenal complications in patients with aHUS. It includes global registry data which had the largest patients number to date. Association with age at first presentation and mutations, renal outcomes and frequency of ESRD in adults and children were compared

FP-S18-1 - Age at onset, renal survival and extrarenal complications in patients with aHUS: Findings of the global atypical haemolytic uraemic syndrome registry

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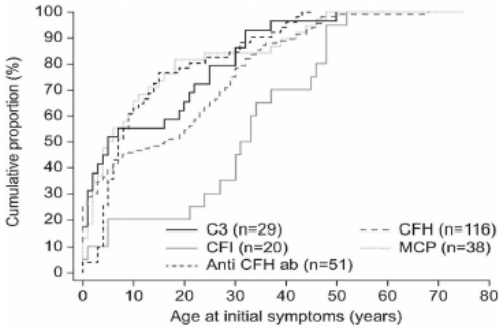
Objectives: To characterise impact of complement abnormalities on phenotypes and outcomes of patients (pts) with atypical haemolytic uraemic syndrome (aHUS) enrolled in the global aHUS registry prior to eculizumab treatment.

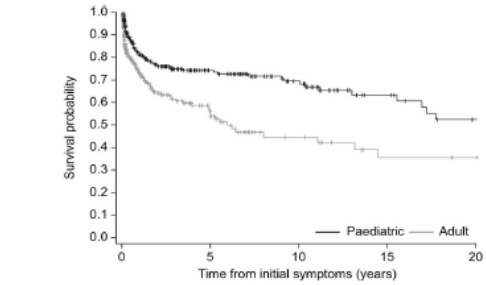
Methods: All pts with aHUS are eligible. Demographics, medical history, and treatment outcomes data are collected at enrolment and then every six months.

Results: As of November 2015, 846 pts were enrolled (384 childhood, 462 adult onset). Family history of aHUS was positive in 16%. Median age at first aHUS manifestation was 7.2, 7.7, 18.5 and 34.3 years in pts with MCP, C3, CFH and CFI mutations, respectively, and 8.4 years for pts with CFH autoantibodies (Fig 1). For pts diagnosed since 2011, renal, gastrointestinal, cardiovascular, central nervous system and pulmonary TMA manifestations occurred in the 6 months prior to baseline in 143 (68%), 80 (38%), 60 (28%), 45 (21%) and 24 (11%) paediatric pts, respectively and were least common in pts with MCP mutations. Five years after disease onset, end-stage renal disease (ESRD) had occurred in 26% of paediatric pts as compared with 46% of adults (Fig 2). Overall, incidence of ESRD was not significantly different in pts with or without any identified mutation. Five-year renal survival was 43%, 46%, 57%, 64% and 92% in pts diagnosed with CFH, CFH autoantibodies, C3, CFI and MCP mutations, respectively, and 65% in pts with no identified complement abnormality.



Differences in distribution of age at initial symptoms were analysed by Wilcoxon Rank sum test. P<0.01 for CFI vs. all other mutations.

- Figure 1. Age at first presentation (for 203 pts with a single identified complement gene mutation and 51 pts positive for CFH autoantibodies)



Paediatric	Events	61	5	4	4	8
	At risk	366	95	56	26	17
Adult	Events	100	6	3	0	1
	At risk	411	43	19	10	7

- Figure 2. Time to ESRD

Conclusions: We describe the phenotype and natural history of aHUS in the largest cohort of pts to date, which includes pts of all ages. This is the first report to show extra-renal manifestations occur in >30% of paediatric patients and that pts with CFI mutations have later onset of aHUS compared with other complement abnormalities. ESRD occurred significantly less frequently in pts with childhood compared with adult-onset. Renal outcomes were most favourable in pts with MCP mutations and least favourable in pts with CFH mutations and CFH autoantibodies.

2) The second abstract is about long term prognosis in children with aHUS. Turkish aHUS Registry results showed that age over 2 years, extrarenal involvement, nephrotic range proteinuria and CFH mutation were associated with poor renal prognosis

FP-S1O-3 - Turkish Atypical Hemolytic Uremic Syndrome Registry: Evaluation of long term prognosis

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Objectives: We aimed to evaluate the long term renal prognosis in children enrolled in Turkish aHUS registry and to determine the factors affecting the disease course.

Methods: Children with aHUS were evaluated for clinical presentation, mutations in complement genes, presence of CFH antibodies, treatment, renal replacement therapy (RRT), end stage renal disease (ESRD), eGFR, proteinuria and hypertension.

Results: There were 146 children in aHUS registry. As 3 patients died at the acute stage and 13 patients were lost to follow-up, 130 children (56.9% female, median age at onset 3.5 years) were enrolled for long term prognosis. At presentation, 35.4% were 90 in 74.6%. Proteinuria and hypertension were present in 30.2% and 39.7% of 116 patients not requiring RRT, respectively. Overall, 56.9% of patients had chronic renal disease characterized by ESRD, low eGFR, proteinuria or hypertension. ESRD risk was increased in children >2 years of age at onset, while chronic renal disease was higher in the presence of extrarenal organ involvement, nephrotic range proteinuria at onset and CFH mutation. Presence of hypocomplementemia was associated with lower risk of chronic renal disease. Interestingly, proteinuria, hypertension and overall chronic renal disease rate was higher in those treated with eculizumab.

Conclusions: More than half of the children with aHUS developed chronic renal disease. Age over 2 years at onset, extrarenal organ involvement, nephrotic range proteinuria and CFH mutation were associated with poor renal prognosis.

Complement mediated kidney injury

3) This abstract describes the importance of monitoring of eculizumab concentration using newly developed eculizumab assay in the management of treatment schedule of patients with aHUS

FP-S30-1 - Pharmacokinetics and pharmacodynamics of eculizumab in individualized treatment of atypical HUS

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Objectives: The atypical hemolytic uremic syndrome (aHUS) is a devastating renal disease, caused by complement dysregulation. Approval of monoclonal complement inhibitor eculizumab/Soliris started a new era in the treatment for this disease. However, data on pharmacokinetics and pharmacodynamics of this drug remain limited.

Methods: Eculizumab was measured by in-house ELISA method. Complement activity was analyzed using Wieslab® complement screen assay. In total, 209 samples were taken from 11 patients before the eculizumab infusion in the induction (weekly), maintenance (2-weekly) and tapering (every 3, 4, and 5 weeks) phases of therapy.

Results: Our newly-developed eculizumab assay had variation coefficients of 2.9 % (intra-assay, 352 µg/mL) and 5.2 % (inter-assay, 328 µg/mL) and detection limit of 8 µg/mL. The samples with >50 µg/mL demonstrated <6% of complement activity in classical and alternative complement pathways. The eculizumab levels had ranges of 36-459 µg/mL and 40-772 µg/mL during induction and maintenance phases, respectively, with 3 samples from 2 patients.

Conclusions: Our data demonstrate large differences in attained eculizumab concentrations among patients at all treatment stages. In induction and maintenance, the detected concentrations were up to 9-15 fold higher than required for efficient complement inhibition (50 µg/mL), although 3 samples did not reach this target value. Thus, eculizumab therapy should be adjusted to meet the needs of individual patients and monitoring of eculizumab concentration is useful to guide the treatment schemes. We have shown that target eculizumab values (>50 µg/mL) may be reached with extended intervals; extension of intervals for these patients may improve cost-effectiveness of therapy.

4) This study indicates a new mechanism that Ca dependent Von WillebrandFactor (VWF) has a repair role on endothelial cell after complement activation. Authors concluded that VWF is a new complement regulator on endothelial cells

FP-S30-3 - Role of von Willebrand Factor (VWF) in endothelial cell repair after complement activation

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Objectives: Complement dysregulation on endothelial cells causes EC activation/injury and leads to thrombotic microangiopathy. Different from previous concepts, our data demonstrate that complement dysregulation does not result in EC death. The current study focuses on EC complement evasion strategies, especially plasma membrane (PM) repair. We particularly focused on von Willebrand Factor (VWF), a protein stored in EC Weibel-Palade bodies (WPB), which we recently identified as new complement regulator on ECs.

Methods: Complement activation on ECs was induced via sensitization on blood outgrowth endothelial cells (BOECs) from healthy controls and patients with von Willebrand disease (VWD) lacking both VWF and their storage WPBs. FM1-43X dye and calcein release were used to determine PM integrity.

Results: Complement activation resulted in PM insertion of C5b-9 pores in control and VWD BOECs resulting in rapid Ca2+ influx. In response, VWF was recruited to the EC surface via WPBs merging with the PM and releasing VWF multimers within 30-60 min. Importantly, control but not VWD BOECs resealed their PM within 30 min. In control BOECs known cellular mechanisms for PM repair (endocytosis, lysosomal recruitment) were not critically involved in PM repair.

Conclusions: PM repair is a major strategy of ECs to overcome complementmediated injury. Our study indicates a new mechanism: Ca2+-dependent VWF recruitment to the EC surface resulting in complement regulation and EC PM repair via WPBs. The understanding of the detailed mechanism warrants further investigatio.

IgA nephropathy and HSP nephritis

The role of CD40/CD40L signaling pathway on IL-10 producing regulatory B cells in the pathogenesis of HSP nehritis was examined in this abstract.

FP-S26-2 - Effect of CD40/CD40L signaling on IL-10-producing regulatory B cells in Chinese children with Henoch-Schönlein purpura nephritis

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Objectives: The aim of the present study was to examine the role of interleukin-10 (IL-10)-producing regulatory B cells (B10 cells) in the pathogenesis of Henoch-Schönlein purpura nephritis (HSPN) and the possible role of CD40/CD40 ligand (CD40L) signaling on the generation of B10 cells.

Methods: We examined the percentages of B10 cells, CD19+ CD24hiCD38hiB cells, CD19+ CD24hiCD27+ B cells, Th17 cells, and T regulatory (Treg) cells within the peripheral blood mononuclear cell (PBMC) population in healthy subjects and patients with HSP and HSPN.

Results: The results showed that expression of IL-10 by B10 cells, CD19+ CD24hiCD38hi B cells and CD19+ CD24hiCD27+ B cells was significantly decreased in patients with HSPN and returned to normal levels in HSP and HSPN patients in remission.The percentages of B10 cells, CD19+ CD24hiCD38hiB cells and CD19+ CD24hiCD27+B cellsnegatively correlated with the Th17/Treg ratio. However, there was no difference in the percentage of B10pro+B10 cells, Th17 cells, Treg cells and Th17/Treg ratio between children with HSP/HSPN and healthy controls after CD40L stimulation for 48 h in vitro.

Conclusions: Whereas the level of IL-10 expressed by CD19+ CD40+ B cells was significantly decreased in HSPN patients, and the percentage of B10pro+ B10 cells and Treg cells was significantly reduced and that of Th17 cell was significantly increased in the presence ofanti-CD40L monoclonal antibody (mAb). Thus the CD40/CD40L signaling pathway plays a role in B10 cell differentiation, which may contribute to the pathogenesis of HSP and the severity of renal injury in HSPN by regulating the Th17/Treg balance.

Lupus Nephritis

This study has shown that MMF is an effective and safe immunosuppressive agent as induction and maintenance therapy in childhood lupus nephritis

FP-S34-1 - Mycophenolate Mofetil (MMF) as induction and maintenance therapy in childhood Lupus Nephritis (LN).

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Objectives: We evaluated the effectiveness and side effects of MMF as induction and maintenance therapy in childhood LN

Methods: We observed 63 children with SLE, 53 (81%) had biopsy proven LN, 41 (35 F/6 M, mean age 12,7 yrs) were treated with MMF. In 31 (75%) LN was the first sign of SLE, in 10 LN appeared after a mean time 3.8 yrs (1- 11yrs) from SLE onset. Histologic classes (Weening) were: II in 9 pts, III in 7 IV in 18, V in 5. Before MMF, Methylprednisolone i.v. pulses were administered. Hematuria was always present, proteinuria ranged from 1.7 to > 9 g/day, decreased C3 and increase in anti-dsDNA ab were present. Treatment outcome was monitored through assessment of SLEDAI score, renal function, proteinuria, serological markers and side effects. MMF was administered twice daily at mean dose 29/mg/Kg/day. Oral prednisone (P) was associated to MMF.

Results: After a mean followup 4.5 yrs (0.5-8.3) all pts had sustained remission: proteinuria was absent or < 0.5g/day in 23, 0.5-1.0g/day in 15, > 1g in 3.; all but one of 9 children with renal failure at onset normalized; C3 mormalized in 25 (61%). A steroid sparing effect (P maintenance dose 0.3 mg/Kg/alternate day in 27 pts). Until now 6 pts are off therapy from 1.7 yrs mean period (0.8-3.2) after at least 4 yrs therapy, no flares from 3yrs, proteinuria < 1 g/day, normal pCreat, inactive urinary sediment. In 10 pts a second serial renal biopsy, after 2 yrs, showed decrease of activity indexes, chronicity indexes did not change. No hematological side effects were seen; because of gastrointestinal signs in 6 pts, MMF was shifted to gastroresistant formula; one pt had Herpes Zoster infection; transient hair defluvium in 9 was observed.

Conclusions: MMF is effective in controlling LN activity and allows a significant steroid sparing effect in an age range patients very sensitive to devastating physical and psychological side effects of steroids and immunesuppressant agents. For us MMF is the first line treatment in children and adolescents with LN.