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Long-term outcome of low dose cyclophosphamide (CYC) and plasma exchange (PLEX) induction in ANCA-associated vasculitis (AAV)

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Introduction.– Adverse events to the treatment of AAV are the greatest threat for 1 year’s outcome. The use of PLEX in AAV is not commonly accepted in patients (pts.) with creatinine < 500 μmol/L. We combined low dose of CYC and PLEX in order to minimize the infection/sepsis rate, which mostly is due to the immunosuppression.

Patient.– A prospective cohort study of all AAV pts. referred between 2000–2010 was performed. All pts. had AAV based on positive ANCA and a compatible clinical syndrome. The use of PLEX was decided on severity of renal biopsy and ANCA titres. Immunosuppression consisted of prednisolone 1 mg/kg/day and a low dose of daily oral CYC (100 mg/day in pts. < 65 years and 50 mg/day in pts. > 65). AZA/MMF was given for maintenance of remission.

Results.– One hundred and thirty-two pts. were admitted and 118 followed for a mean of 5.7 years (range 0.2–12.3; 676 pts. years). Fifty-seven percent were male, 47% were MPO-ANCA positive. Thirty-six (34%) relapses occurred during the 12 years of follow up. The use of low dose CYC and PLEX for induction resulted in a low rate of complications. As the septicaemia and mortality was low, the combination of PLEX and low CYC seems to be less toxic, than the conventional AAV induction treatment regimen.

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Longitudinal ANCA measurements for predicting a relapse in patients with ANCA associated vasculitis

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Introduction.– To assess the predictive value of longitudinal anti-neutrophil associated antibody (ANCA) measurements for a relapse in a community-based cohort of patients with ANCA associated vasculitis.

Patients.– All ANCA-positive patients who visited the clinic in Maastricht between 1–1–2000 and 1–10–2011, with a diagnosis of primary ANCA associated vasculitis were evaluated. Disease severity was classified as limited or severe according to the WG1T Research group. Patients were routinely tested by indirect immunofluorescence (IIF) and first generation solid phase ANCA tests for MPO- and PR3-ANCA.

Results.– One hundred and one patients with severe disease (65 PR3-ANCA, 36 MPO-ANCA) and 52 patients with limited disease (36 PR3-ANCA, 16 MPO-ANCA) were included at first-time remission. During an average follow-up of 49.8 months (SD 31.4) and an average of 15.1 ANCA measurements (SD 13.7), 71 relapses were recorded (27 major, 44 minor). At the time of diagnosis of a relapse, all patients with major and 31 (70.5%) with minor relapses were ANCA positive, whereas 22 of 27 (81.5%) major relapses and 21 of 44 (47.7%) minor relapses were preceded by an ANCA rise. An ANCA rise is more predictive as measured by the first generation ANCA test [HR 2.712 (95%CI 1.559–4.715)] than by IIF [HR 2.280 (95%CI 1.310–3.969)]. Upon stratification in disease severity, an ANCA rise is clearly predictive in patients with severe disease [HR 4.722 (95%CI 2.364–9.432)], while non-significant in patients with limited disease.

Conclusion.– Longitudinal ANCA measurements to predict a relapse are useful in patients with severe disease but not in patients with limited disease.

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P171
Low %CD5+ B cells in patients with ANCA vasculitis portends a shorter time to relapse after rituximab

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Introduction.– We recently reported that CD5+ B cells, as a surrogate marker of B regulatory cells, are decreased in active ANCA/small vessel vasculitis (ANCA-SV) and normalize during disease remission [1]. After B cell depletion with rituximab, we found that patients who repopulated with a low or decreasing %CD5+ B cells and were on low maintenance immunosuppression had a shorter time to relapse than patients on similar levels of immunosuppression but normalized %CD5+ B cells or patients with similarly low %CD5+ B cells but on full dose maintenance immunosuppression with MMF. To avoid infections and adverse events from therapy, clinicians require improved markers of disease activity and impending relapse to guide immunosuppression strategies post-rituximab. In this study, we test our hypothesis that CD5+ B cells may serve this purpose in a larger cohort.

Methods.– We examined B cell phenotype in patients with ANCA-SV after rituximab therapy by flow cytometry. Whole blood or PBMCs were stained with antibodies to CD19, CD20, CD45 and CD5. Data from research samples was supplemented with data acquired from clinical Rituximab panels.

Results.– Without consideration of immunosuppression dose, in 31 patients, those who had <30% CD5+ B cells at the time of B cell repopulation (≥1% CD19+/CD20+/lymphocytes) relapsed sooner (14 ± 5 m) than patients who repopulated with ≥30% CD5+ B cells (26 ± 12 m; P = 0.03) after rituximab.

Discussion.– We present data that confirm the %CD5+ B cells, as a component of the human B regulatory cell phenotype, is an indicator of future relapse. Moreover, a low %CD5+ B cells correlates with a shorter time to relapse regardless of immunosuppression dose. Monitoring whether CD5+ B regulatory cells contribute to B cell repopulation...
following rituximab therapy may help guide remission maintenance therapy in these patients.

**Conclusion.**—CD5+ B cells may be a novel immunological biomarker to follow induction of remission and impending flare in patients with ANCA vasculitis before and after treatment with rituximab.

**Reference**

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**P172**

**Monocyte chemoattractant protein-1 (MCP-1) in antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis: Biomarker potential and association with polymorphisms in the MCP-1 and the CC chemokine receptor-2 (CCR2) gene**

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**Introduction.**—ANCA-associated small vessel vasculitis (AAV) morbidity and mortality have decreased over the last four decades, but there is still a need of better biomarkers for distinguishing which patients will have a more severe outcome, in order to optimize the treatment.

The aim of this study was to confirm our previous results of urinary MCP-1 (uMCP-1) as a prognostic marker, and to explore its potential as a marker of disease activity. Another part of the study was to explore the association of AAV and polymorphism in the MCP-1 gene (-2518A/G) and the CCR2 gene (V64I).

**Patients.**—One hundred and fourteen patients with AAV were followed regularly between 2002 and 2009 at Skane University Hospital. Urine samples, blood samples and clinical status were registered. uMCP-1 was analyzed by an in house ELISA. PCR-RFLP was used for the polymorphism analyses.

**Results.**—Patients with severe prognosis had significantly higher levels of uMCP-1 compared to patients with non severe prognosis and healthy controls. Patients with renal damage had higher levels compared to patients without renal damage. There was a tendency of higher uMCP-1 levels in active disease compared to remission. AA in the -2518 position of the MCP-1 gene was associated with a more severe outcome compared to the A/G or G/G genotype. The A/A genotype was associated with levels of uMCP-1. No significant associations were seen for the CCR2-V64I.

**Discussion.**—This study confirms the association of high uMCP-1 levels in patients with poor prognosis of AAV. It also suggests an association of the A/A genotype at position -2518 in the MCP-1 gene with poor prognosis.

**Conclusion.**—MCP-1 is clearly a candidate biomarker of potential clinical value. The A/A genotype association needs further evaluation.

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**Pathogenesis**

**P173**

**Abundant neutrophil extracellular traps in thrombus of patient with microscopic polyangiitis**

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**Introduction.**—Patients with MPO-AAV have an increased risk of deep vein thrombosis (DVT). However, the mechanism remains elusive. Recently, it has been reported that aberrant formation and disordered regulation of NETs could be implicated in the development of MPO-AAV. On the other hand, NETs interact with coagulation factors and can induce thrombosis. In this study, we carried out autopsy on an MPO-AAV patient complicated with DVT, and then the association of NETs and DVT was examined.

**Methods.**—NETs in the glomeruli and thrombus were examined by immunofluorescent staining. To quantify the NETs volume in the thrombus, immunohistochimistry was performed using anti-citrullinated histone 3 antibody. The area of NETs was quantified by Image J software and then standardized by the numbers of neutrophils counted in the serial sections. The amount of NETs in the thrombus was compared to other thrombi derived from a patient who died of bacterial sepsis and from one who died of post-operative pulmonary embolism.

**Results.**—NETs were detected in the glomerular crescents despite the absence of microbes in the MPO-AAV patient. Interestingly, abundant NETs were detected in the thrombus complicated with MPO-AAV, and the amount of NETs was significantly greater compared to other thrombi unrelated to MPO-AAV.

**Discussion.**—It is reported that MPO-ANCA can induce NETs, and that NETs can induce thrombosis. This study suggests the possibility that the pathogenesis of thrombosis in MPO-AAV could be critically associated with the mechanism via NETs.

**Conclusion.**—This study suggests the possibility that the pathogenesis of DVT in MPO-AAV could be critically associated with the mechanism via MPO-ANCA and NETs.

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