Reduction of Urinary Levels of Lectin Pathway Complement Components in an IgA Vasculitis Patient After MASP-2 Inhibition with Narsoplimab

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Background: A young female suffering from IgA vasculitis was treated with 4 mg/kg weekly infusions of narsoplimab (a MASP-2 inhibitor) for 12 weeks. MASP-2 is considered the key activator of the lectin pathway (LP) by cleaving C4 and C2, after the binding of LP pattern recognition molecules to its ligands. Inhibition of MASP-2 is predicted to decrease complement activation in complement-mediated kidney diseases.

Aim: In this exploratory study we measured the levels of different LP complement components to evaluate the influence of narsoplimab on complement activation.

Methods: Urine levels of complement activation markers (C4c, C3bc and soluble [s] C5b-9) and serum and urine levels of ficolin-1, -2 and -3, MBL, CL-11, MASP-2, MASP-3, MAP-1 and PTX-3 were measured using in house sandwich-ELISAs. Urine samples were subjected to LC/MS-MS. Correlations between LC/MS-MS and sandwich-ELISA were conducted using simple linear regression and Spearman's rank correlation coefficient. Significance: p value < 0.05. Urine proteins were adjusted for creatinine excretion and expressed as specific protein/creatinine ratio.

Urine C4c/creatinine ratio and C3bc/creatinine ratio levels were decreased 75% and 58% from baseline to end of treatment, respectively

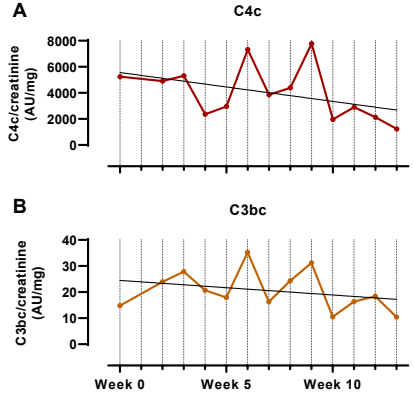

Figure 1. Complement activation markers in urine. Levels of C4c/creatinine ratio (**A**) and C3bc/creatinine ratio (**B**) in urine. Infusion with narsoplimab was not possible in week 6 and 9 as the patient was suffering from an infection. This correlates with an increase of complement markers at the specified time points.

C4 results from S-ELISA and LC/MS-MS are significantly correlated

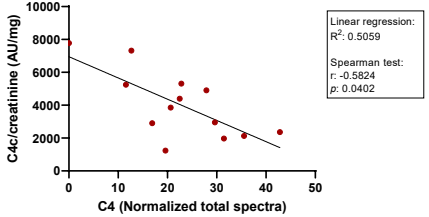

Figure 2. Correlation between C4c/creatinine (S-ELISA) C4 (LC/MS-MS). Correlation calculated by simple linear regression (R^2) and spearman's rank correlation ($p < 0.05$ was considered significant).

Urine ficolin-3/creatinine ratio levels were decreased 29% from baseline to end of treatment. MBL and CL-11 were detected but were unaltered by the treatment

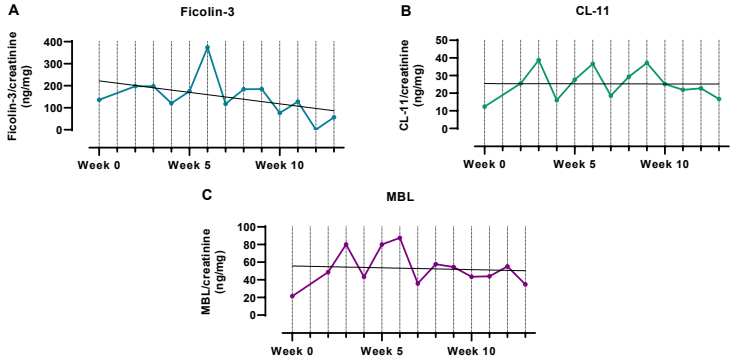

Figure 3. Pattern recognition molecules levels in urine. Ficolin-3/creatinine (**A**), CL-11/creatinine (**B**), MBL/creatinine (**C**) ratio levels in urine. Infusion with narsoplimab was not possible in week 6 and 9 as the patient was suffering from an infection. This correlates with an increase of the pattern recognition molecules at the specified time points.

- **sC5b-9, ficolin-1, ficolin-2, MASP-2, MASP-3, MAP-1 and PTX-3 were not detected in urine, indicating a specific detection of local protein and not protein leakage**
- **Serum levels of all complement components (except for PTX-3 that was undetected) were unaltered during the treatment**

Conclusion: This is the first report describing the effect of narsoplimab on urinary complement levels in a complement-mediated kidney disease. Our data suggest a decrease in local complement activation with narsoplimab treatment. Further studies are ongoing to evaluate the use of urine as a non-invasive, inexpensive and readily accessible resource to monitor responses to complement-directed treatments.

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