# THE PRESENCE OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS IS ASSOCIATED WITH A POOR RESPONSE TO RITUXIMAB IN ADULTS WITH IDIOPATHIC MEMBRANOUS NEPHROPATHY

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## BACKGROUND

Idiopathic membranous nephropathy (IMN) is the leading cause of nephrotic syndrome in western countries. Rituximab (RTX) is a B-cell depleting anti-CD20 monoclonal antibody which has been proven to be effective for treatment of IMN resistant to conventional immunosuppressive therapy. However, whether any histological prognostic factor may help in predicting responsiveness to RTX, is, as yet, unknown. In our single-center study, we have evaluated this possibility.

## SUBJECTS AND METHODS

We report data from eight patients (3 women) from our Clinic with nephrotic syndrome secondary to IMN unresponsive to traditional immunosuppressive therapy and treated with RTX, subsequently followed-up of at least 12 months. Kidney biopsies were independently reviewed by two nephropathologists and scored with a modified Banff 1997 scoring system taking into account the extent of mononuclear cell interstitial inflammation, arteriolar hyaline thickening, interstitial fibrosis, tubular atrophy, fibrous intimal thickening, mesangial matrix increase, segmental glomerulosclerosis, and global glomerulosclerosis. Outcome endpoints were complete and partial remission, defined as 24-hours urinary protein excretion <0.5 g and <3.0 g (with at least 50% reduction versus baseline), respectively. Glomerular filtration rate (eGFR) was estimated by MDRD4 formula. RTX was administered in four weekly infusions of 375 mg/m$^2$ in 5 patients, and in a single 1000 mg infusion in 3 patients. All participants received RTX as third-line immunosuppressant therapy, and renin-angiotensin system blockers were administered throughout the study at the maximal tolerated dose. In all cases a complete depletion of CD19+ and CD20+ B cells was achieved. No other doses of RTX or immunosuppressant agents were administered throughout the 12 months follow-up. Continuous variables were compared by analysis of variance (ANOVA) for repeated measures and Bonferroni post-hoc test, categorical variables by Fisher's exact test.

## RESULTS

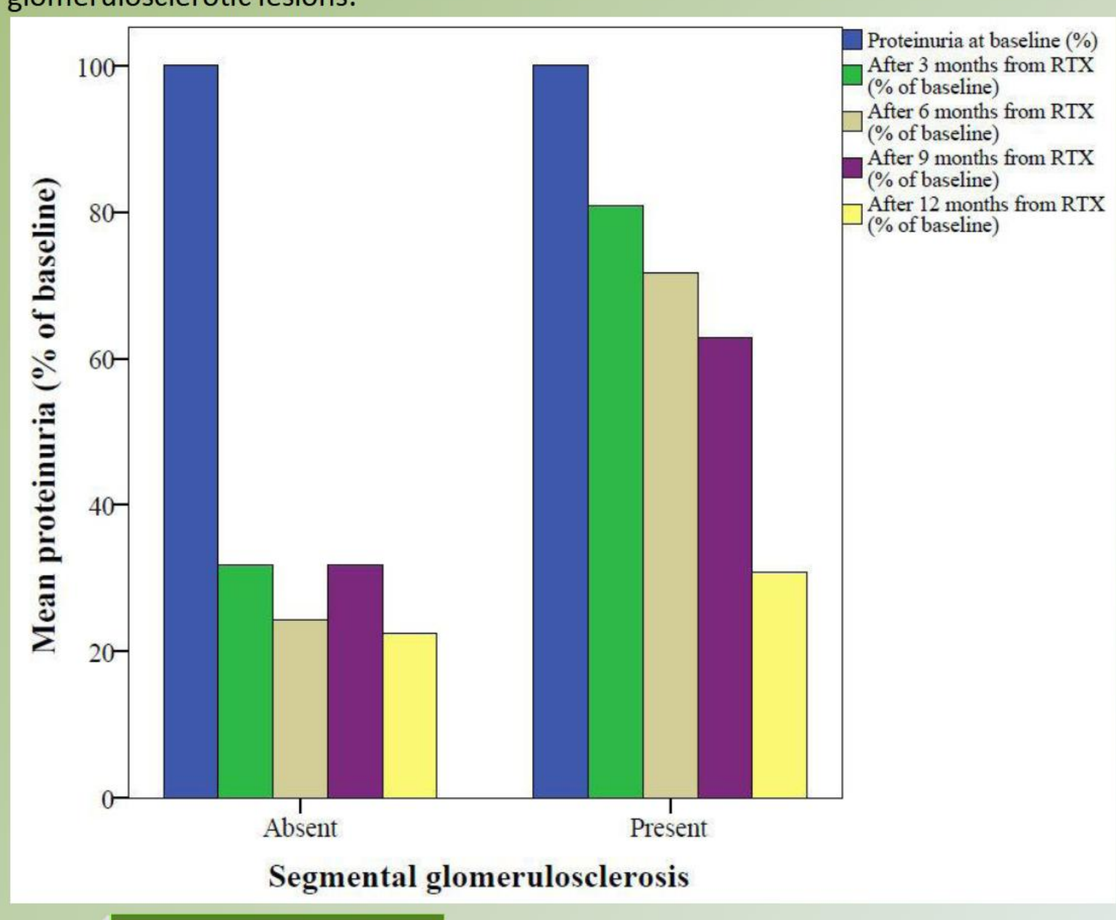
Mean age at RTX administration was 67  10 years. Partial remission was achieved by 5 patients after 3 months from RTX administration, by 6 patients after 6 months. One patient obtained a complete remission after 6 months from RTX therapy. After 12 months, the same patient maintained complete remission, and all remaining partial remission. Proteinuria significantly decreased during the follow-up (p = 0.002; Table 1), with significantly lower values after 9 and 12 months from RTX infusion as compared with baseline. Over the 12 months follow-up, 6 patients achieved partial remission and one complete remission. The components of the scoring system were found to be not associated with the in-study outcome endpoints except for segmental glomerulosclerosis (≤25% of glomeruli affected) (Figure 1), which presence was associated with the absence of partial remission after 6 and 9 months from RTX administration (Fisher's exact test: p=0.03 for both time-points). eGFR did not change throughout the study period (p=0.201; Table 1). No difference between the two different RTX regimens (four 375 mg/m$^2$ infusions or one 1000 mg infusion) and the outcome measures was observed.

**Table 1**: Proteinuria and glomerular filtration rate changes during the 12 months after rituximab administration.

| Time point | Proteinuria (g/24h) | eGFR (ml/min) |
|---|---|---|
| **Baseline (month 0)** | 8.0 ± 4.2 | 42.4 ± 16.8 |
| **3 months** | 3.3 ± 2.7<br>[2] 0.173 | 47 ± 17.7<br>[2] 0.998 |
| **6 months** | 3.0 ± 2.8<br>[2] 0.061 | 49.6 ± 15.4<br>[2] 0.565 |
| **9 months** | 3.3 ± 2.5<br>**[2] 0.026** | 51.0 ± 16.7<br>[2] 0.200 |
| **12 months** | 2.0 ± 1.4<br>**[2] 0.009** | 48.0 ± 21.5<br>[2] 0.998 |
| **Overall** | **[1] 0.002** | [1] 0.201 |

Data are depicted as mean  standard deviation. eGFR: estimated glomerular filtration rate; [1] ANOVA level of significance; [2] p vs baseline, Bonferroni post-hoc test.

**Figure 1**: mean proteinuria (% of baseline) according to the presence of segmental glomerulosclerotic lesions.




## CONCLUSIONS

In our cohort, RTX was associated with a significant decrease of proteinuria values during the follow up, without any significant reduction of eGFR. The presence of focal segmental glomerular lesions in kidney biopsies appears to be inversely correlated with the responsiveness to the drug.

## REFERENCES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