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Analysis of intensified immunosuppression response in genetically-stratified steroid resistant nephrotic syndrome (SRNS) patients predicts outcomes and suggests distinct immune mechanisms

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Introduction:
Post-transplantation disease recurrence is common in steroid resistant nephrotic syndrome (SRNS) and provides evidence for the presence of an immune-mediated plasma circulating factor. Our ability to predict disease course, treatment response and risk of recurrence for individual patients is currently limited. We previously showed that secondary steroid resistance (SSR) is the most reliable predictor of circulating factor disease that recurs post-transplantation. We aimed to further disease stratification by determining if response to intensified immunosuppression (IIS), in comprehensively genetically-screened patients, predicts disease progression and/or recurrence.

Methods:
Paediatric patients with SRNS were recruited via the United Kingdom RaDaR registry. All patients were whole genome, whole exome or SRNS-gene-panel sequenced. Complete response (CR) or partial response within six months of starting IIS was ascertained from laboratory data. Response to first-administered IIS only was analysed separately to minimise bias from the order in which clinicians chose to use medications.

Results:
Of 274 genetically-sequenced patients, 180 (93 male, median onset age 4.7 years, 26 monogenic disease, 99 focal segmental glomerulosclerosis) received IIS medications with responses available. Only 3.8% of monogenic disease patients showed CR to first IIS, compared to 25.2% of genetic-testing negative (GTN) patients (p=0.018). No monogenic disease patients recurred post-transplantation. In GTN patients, 97.4% with CR to first IIS showed no progression to end-stage renal failure (ESRF), whereas 43.2% of non-responders developed ESRF with a 73.1% recurrence rate post-transplantation. Those with SSR had a higher CR rate than primary/presumed resistance (42.5% versus 23.0%, p=0.0014) and their CR rate was highest for Rituximab (64.3%). No patients with CR to Rituximab progressed to ESRF. Biopsy findings showed no correlation with response to IIS or clinical outcome.

Discussion:
This stratifies SRNS patients into three subgroups of prognostic utility: monogenic disease patients who respond poorly to IIS but do not recur, GTN patients who respond early to IIS and have a good long-term outcome, and GTN patients who are multi-drug resistant with poor renal survival and a very high post-transplant recurrence risk. This suggests two different underlying immune mechanisms. Most of the IIS-unresponsive group are likely to have immune-mediated circulating factor disease, given the very high rate of post-transplant recurrence. Response to Rituximab gives an important clue to immune mechanism and appears to filter out a group of patients with a B-cell related mechanism that do not progress. Our data supports comprehensive genetic testing in all SRNS children. In those who test negative, calcineurin inhibitors should be used with a trial of Rituximab in patients who do not respond. If this fails, the patient

falls into the multi-drug resistant category and the chances of progression to ESRF, despite any further IIS, and post-transplant recurrence are very high.