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Combination Therapy in Lupus Nephritis: Efficacy and Molecular Basis

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Chronic kidney diseases (CKD) is a heavy health burden, especially glomerulonephritis, it is the leading cause of end stage kidney disease in China. Lupus nephritis (LN) is the most common disease among secondary glomerulonephritis, renal involvement is a major cause of patient dead of SLE and the 20 years renal survival rate is 68.3% in Chinese patients.

Despite the availability of many new immunosuppressive drugs, treatment of lupus nephritis (LN) remains a major challenge. We used the combination therapy to improve complete remission rate in LN. The therapy consist of steroid, mycophenolate mofetil (MMF) and tacrolimus (FK), the rational of the therapy is the multiple drugs targeting different aspects of the immune response would be more effective than a single agent and, further, that lower doses of multiple drugs may maximize efficacy and minimize adverse effects.

The combination therapy for induction treatment of LN showed that compared to intravenous cyclophosphamide (IVCY), The incidence of complete remission improved 20% in combination therapy group, median time to overall response was 8.9 weeks in the combination group and 13.0 weeks in the IVCY group and without increasing the incidence of the adverse events.

To explore the underlying molecular basis of increased efficacy of the combination therapy, we conducted a mouse model of lupus nephritis in MRL/lpr mice, and treated them with monotherapies of prednisone, mycophenolate mofetil, or tacrolimus, or with their combination. Transcriptomic analysis of their kidneys was performed in the study. The validation studies were performed both in mice model and the kidney samples from patients who received the combination therapy.

We found that the top downregulated genes in all drug treatments were involved in both T and B cell receptors and in type II interferon signaling pathways. Pathway analysis suggested that the immune-related terms were highly enriched in combination therapy, suggesting a potential additive effect in improving the status of immune disorder and kidney injury in the LN mice. In addition, suppression of TLR7 expression was found uniquely in the combination therapy, reduction in both IL-6 expression and STAT3 activation was confirmed only in the combination therapy and pathways regulating the actin cytoskeleton are highly enriched in combination therapy, FK506 as well as MMF. The combination therapy use multiple drugs targeting different aspects of the immune response would be more effective than a single agent. Transcriptomic analysis of their kidneys revealed distinct molecular pathways that were differentially regulated. Combination therapy not only provided additive immunosuppressive effects, but also induced gene expression and molecular pathways to confer enhanced renoprotection.