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Effect of rituximab in MCNS: a role for IL-13 suppression?

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We read with great interest the article by Aditi Sinha and Arvind Bagga (Rituximab therapy in nephrotic syndrome: implications for patients' management. *Nat. Rev. Nephrol.* 9, 154–169; 2013).[1] These authors reported the beneficial effects of rituximab treatment in patients with nephrotic syndrome and speculated that rituximab might cause apoptosis via complement-dependent cytotoxicity and antibody-dependent cytotoxicity, leading to rapid depletion of B cells.[1] Furthermore, rituximab is reported to induce T-regulatory and B-regulatory cell populations, restore immune tolerance, and attenuate the downregulation of sphingomyelinase-like phosphodiesterase 3b in podocytes.[1]

We would like to add another possible mechanism that may explain the beneficial effect of rituximab on minimal-change nephrotic syndrome (MCNS). Although rare, some reports have shown that Th2 cytokines, such as interleukin (IL)-13, may play an important role in the pathogenesis of MCNS.[2–4] Yap *et al.* reported that $CD4^+$ and $CD8^+$ IL-13 mRNA expression was increased in patients with nephrotic relapse compared with those in remission, healthy individuals, and patient controls (children with viral infections, but without idiopathic nephrotic syndrome; $P < 0.008$) and that this finding was related to an increase in expression of cytoplasmic IL-13 in phorbol myristate acetate/ionomycin-activated $CD3^+$ cells ($6.66 \pm 3.39\%$) in patients with nephrotic relapse compared with expression in patients in the remission phase ($2.59 \pm 1.35\%$, $P < 0.0001$).[2] Yap *et al.* speculated that IL-13 may act on monocytes to produce vascular permeability factors involved in the pathogenesis of proteinuria in patients with relapse of nephrotic syndrome.[2] Cheung *et al.* also showed that the percentage of $CD3^+$ IL-13-producing cells was significantly increased in children with nephrotic relapse, and correlated with serum IgE levels during the active phase of the disease ($r = 0.90$, $P < 0.001$).[3]

In addition, Lai *et al.* have demonstrated that IL-13-transfected rats ($n = 41$) show a minimal-change-like nephropathy (characterized by increased proteinuria, hypoalbuminaemia and hypercholesterolaemia) compared with control rats ($n = 17$).[4] In their study, the glomeruli of rats transfected with IL-13 showed no significant histologic changes, but electron microscopy findings showed that up to 80% of podocyte foot processes showed fusion and that glomerular gene expression of *B7-1*, *IL-4Rα* and *IL-13Rα2* were upregulated, whereas those of nephrin, podocin and dystroglycan were downregulated.[4]

Although not in the setting of MCNS, another study has shown that rituximab could reduce levels of IL-13 expressing T cells.[5] Simon *et al.* showed that the numbers of cytokine-expressing $CD4^+$ and $CD8^+$ T cells were reduced with a relative decrease in the mRNA expression of IL-5 (mean 53%) and IL-13 (mean 83%) after rituximab therapy in patients with moderate to severe atopic dermatitis not responding to topical corticosteroid and/or calcineurin inhibitor therapy.[5]

So there is a possibility that rituximab might be beneficial in MCNS by suppression of IL-13, which could be involved in the development of MCNS, in addition to depletion of B cells. However, further studies are necessary to evaluate serial changes in levels of IL-13 after rituximab treatment in MCNS and to elucidate the exact role of IL-13 in the pathogenesis of MCNS.

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Competing interests
The authors declare no competing interests.

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