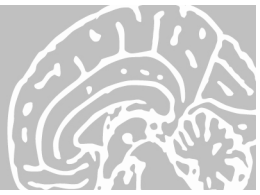
Anti-IL-6 receptor antibody therapy in neuromyelitis optica (NMO)



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Neuromyelitis optica (NMO) is an autoimmune disease affected preferentially optic nerves and the spinal cord. Anti-aquaporin-4 (AQP4) antibody plays an important role in causing the inflammatory responses to astrocytes expressing AQP4. Disease-modifying therapies for multiple sclerosis (MS) seem to be less efficacious and corticosteroids and/or immunosuppressants can be recommended as first-line therapy in Japan. However the current treatment strategy is insufficient to control the disease activity in the refractory cases of NMO.

Many studies have shown that Th17 and Th2-related cytokines in the pathogenesis of NMO. Amongst these cytokines, IL-6 is strongly associated with the disease activity of NMO. Plasmablasts (PB) preferentially produce anti-AQP4 antibody and the frequency of PB was increased in the acute exacerbation of the patient sera. IL-6 enhanced the survival of the PB. Based on these results, we proposed that IL-6 receptor blockade therapy could be effective for the treatment of NMO.

We conducted an open-label study to explore the safety and efficacy of humanized anti-IL-6 receptor monoclonal antibody tocilizumab (TCZ) in patients with refractory NMO (UMIN000005889, UMIN000007866). 11 patients were treated with monthly infusion of TCZ as add-on therapy to oral corticosteroids and/or immunosuppressants. TCZ had distinct effects on decrease of annualized relapse rate ($p<0.0001$) and EDSS ($p<0.05$). The improvement of EDSS was partly attributed to relief from severe neuropathic pain and fatigue. Immunological analysis showed that the reduction of PB frequency and anti-AQP4 antibody titers after the initiation of TCZ treatment. Meanwhile, activated regulatory T cells and $CD56^{high}$ NK cells were significantly increased by the treatment. The efficacy of tocilizumab could result from its effect on IL-6 dependent inflammatory process, involving plasmablasts, regulatory T cells, and $CD56^{high}$ NK cells.