Abstract Type : Oral
Abstract Submission No. : 1779

Combined use of tocilizumab (IL-6 receptor blocking antibody) and mesenchymal stem cells attenuate the development of anti-HLA-A2.1 antibody in highly sensitized mice model

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Objectives: Sensitization to human leukocyte antibody (HLA) is an important obstacle to overcome for favorable long-term post-transplant allograft survival. Several desensitization protocols, such as the use of plasmapheresis, rituximab, intravenous immune globulin (IVIg), and bortezomib, are being used in these patients. However, donor-specific antibody (DSA) generation and antibody-mediated allograft injury still remains an unresolved problem awaiting better therapies. Meanwhile, tocilizumab (TCZ), IL-6 receptor blocking antibody has been used as therapeutics for chronic antibody mediated rejection, and clinical trial to use mesenchymal stem cells (MSCs) as anti-rejection therapy has been attempted. In this research, we proposed to observe the synergistic effects of TCZ and MSCs on the humoral immune responses of an allosensitized mouse model developed using HLA.A2 transgenic mice.

Methods: Wild-type C57BL/6 mice were sensitized with skin allografts from C57BL/6-Tg (HLA-A2.1)1Enge/J mice and were treated with either TCZ or MSC or both TCZ and MSC.

Results: HLA.A2-specific IgG was reduced in all of TCZ, MSC and TCZ + MSC in comparison with allo-sensitized control group, and it was the most significant in TCZ + MSC group. Combined use of TCZ and MSC also resulted in the increased pre-pro and immature B-cell proportions and decreased mature B-cells in the bone marrow ($p<0.05$ vs. control) than other groups. In the spleen, an increase in transitional B-cells was observed with a significant decrease in marginal and follicular B-cells ($p<0.05$ vs. control) in TCZ + MSC group. There was no significant difference in proportions of long-lived plasma and memory B-cells.

Conclusions:

In conclusion, combined use of TCZ and MSC inhibit B cell differentiation and maturation in spleen and bone marrow and finally resulting in the reduction of HLA.A2-specific IgG in highly sensitized mice model. Our data suggests that combined use of TCZ and MSC may serve as a useful future strategy for desensitization therapy.