MOCRAVIMOD AMELIORATES CHRONIC GRAFT-VERSUS-HOST DISEASE AFTER MOUSE ALLOGENEIC HSCT

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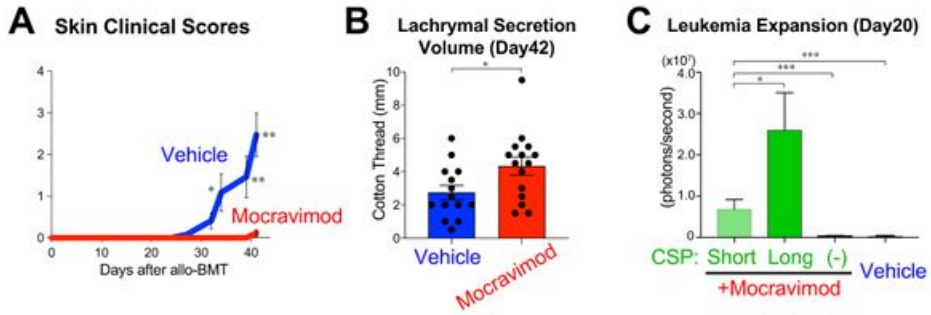
Title: **MOCRAVIMOD AMELIORATES CHRONIC GRAFT-VERSUS-HOST DISEASE AFTER MOUSE ALLOGENEIC HSCT**

Background: Sphingosine-1-phosphate receptor (S1PR) modulators are a new drug class that sequesters T cells in the lymph nodes (LNs) by downregulating S1PR1. We have previously shown that short-term administration of the S1PR1-specific modulator mocravimod (KRP203) ameliorated mouse acute graft-versus-host disease (GVHD), while significant graft-versus-leukemia (GVL) effects were maintained even after prolonged administration of mocravimod (Yokoyama, BMT 2020). In the current study, we tested whether long-term administration of mocravimod could ameliorate chronic GVHD, using a mouse model of allogeneic bone marrow transplantation (allo-BMT).

Methods: BALB/c (H-2^d) mice were irradiated (5.5 Gy) and intravenously injected with 8 × 10^6 bone marrow cells combined with 15 × 10^6 splenocytes from minor histocompatibility antigen-mismatched allogeneic B10.D2 (H-2^d) donors on day 0. Recipients were orally administered with 3 mg/kg/day mocravimod or diluent from day -1 to day +42 after allo-BMT. To evaluate graft-versus-leukemia (GVL) effects, B6D2F1 recipients were injected with luciferase-expressing P815 leukemia cells on day 0 of allo-BMT.

Results: We found chronic GVHD skin scores were significantly reduced by mocravimod, and lachrymal secretion volume was significantly preserved in mocravimod-treated recipients (Figure A, B). Pathological skin chronic GVHD scores and the fibrotic area in the liver and salivary glands were significantly decreased in mocravimod-treated recipients compared to vehicle-treated controls. Flowcytometric analysis on day +42 demonstrated that prolonged administration of mocravimod significantly reduced both $CD4^+$ and $CD8^+$ donor T cells in the mesenteric LNs, suggesting that mocravimod induced activation-induced cell death of donor T cells as expected (Hashimoto Eur J Haematol 2007, Yokoyama BMT 2019). Importantly, mocravimod significantly reduced donor $CD4^+$ T cells while sparing $CD8^+$ T cells in other organs, such as spleen, bone marrow, and liver. Mocravimod significantly increased absolute numbers of $CD62L^-PD\text{-}1^+TOX^+$ exhausted T cells in the mesenteric LNs, while it did not affect the numbers of exhausted T cells in other organs, further confirming that mocravimod strengthens donor T-cell activation specifically in the LNs. It was expected that $CD8^+$ T cells persisting after mocravimod-treatment could contribute to GVL. Thus, we evaluated GVL effects using another mouse GVHD model in which B6D2F1 recipients were transplanted from C57BL/c donors and injected with recipient-type luciferase-expressing leukemia. Leukemia-injected recipients were treated with mocravimod (day 0-42) alone or in combination with short-term (day 0-14) or long-term (day 0-42) cyclosporine (CSP). In vivo bioluminescence imaging demonstrated that leukemia was rejected in the recipients treated with vehicle or mocravimod alone. In sharp contrast, CSP significantly increased leukemia expansion, while CSP cessation on day +14 blunted leukemia growth, suggesting that mocravimod spared potent GVL effects after allo-BMT (Figure C).



Conclusions: Mocravimod primarily reduced $CD4^+$ donor T-cell expansion while sparing $CD8^+$ T cells after allo-BMT, which ameliorated chronic GVHD and contributed to persisted GVL effects after mocravimod-treatment.

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