Apreaglutide Decreases Severity of Intestinal Damage from Gastrointestinal (GI) Acute Graft Versus Host Disease (GvHD) Following Allogeneic Transplantation Without Impacting Engraftment

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INTRODUCTION

• The GI tract is the key target tissue system damaged by acute GvHD resulting in the observed morbidity and mortality associated with acute GvHD.1,2
• Glucagon-like peptide-2 (GLP-2) is an essential endocrine hormone naturally secreted in the intestine to maintain GI integrity and nutrient/ fluid absorption.2
• The physiological actions of GLP-2 include increase enterocyte proliferation, increase intestinal barrier function, increase intestinal blood profusion, decrease epithelial damage, and decrease GI motility.2
• The L cells in the intestine that secrete GLP-2 are the key cells directly impacted by conditioning regimens and acute GvHD.3
• Apraglutide, a novel, long-acting synthetic GLP-2 analog, represents a potential protective and regenerative approach to GI acute GvHD prevention and treatment.
• The objective of these studies are to assess the effects of apraglutide on engraftment and GI protection following total body irradiation (TBI) and allogeneic transplantation in murine models.

METHODS

Engraftment model (study 1)
• Total-body-irradiated immunodeficient (NOG) mice (Day 0) were injected with human peripheral blood mononuclear cell (HPBMC; Day 2) and treated with apraglutide or vehicle (Days 4 to 16).
• Engraftment rate of HPBMC was determined by measuring the percentage of animals reconstituted (% animals).

Irradiation / transplantation model (study 2)
• On Day-1, BALB/cJ mice underwent TBI followed by allogeneic transplantation from C57BL/6 strain (Day 0). Mice were treated with apraglutide or vehicle on Days -9, -7, -5, -3, -1, +1, +3, +5 and +7.
• Intestinal damage indicative of GvHD (histological changes, length, hemorrhage, inflammation), body weight, and survival were assessed.
• Preconditioning and Transplantation of 100 million bone marrow and 1.5 million T cells from C57BL/6 mice were performed, separated and transplantation was done in the mice.

RESULTS

Study 1
• Apreaglutide administered before and after TBI and HPBMC injection had no impact on successful engraftment of HPBMC in immunodeficient mice.
• This was demonstrated by the lack of difference between apraglutide vs. vehicle in hCD45+ cell infiltration in blood, spleen, and bone marrow.

Engraftment Rate in Blood, Spleen, and Bone Marrow on Day 20 was Not Affected by Apreaglutide

Study 2
• Apreaglutide administered before and after TBI and allogeneic transplantation protected BALB/cJ mice from acute GvHD induced intestinal damage.
• Post-mortem histological examination revealed less mucosal degenerative-inflammatory changes (villous atrophy, mononuclear/neutrophilic cell infiltrate in the lamina propria/intra-cryptal epithelium, crypt necrosis) in apraglutide-treated mice vs. vehicle.
• Mean colon length in the apraglutide group (8.6±0.35 cm) was comparable to mice that did not undergo TBI or transplantation (9.6±0.33 cm), whereas a significant reduction was apparent in the vehicle group (7.19±0.10 cm; p<0.05).
• Weight loss and median survival were similar in both treatment groups, but apraglutide-treated mice had significantly higher overall survival vs. vehicle on Day +9 (40% vs. 0%, respectively; p=0.0134).

Apreaglutide Reduced Villi Atrophy and Decreased Colon Shortening from Total Body Irradiation

CONCLUSION

• Total body irradiation is often part of allogeneic HSCT conditioning regimen and is associated with mucosal barrier breakdown and mucositis.
• Apreaglutide showed a significant protective effect in TBI- and allogeneic-transplant-induced acute GvHD with reduced villus atrophy, decreased colon shortening, and a survival advantage.
• These results demonstrated that apraglutide treatment before and after allogeneic transplantation in immunodeficient mice does not affect engraftment.
• These findings support further exploration of GLP-2 as a novel regenerative approach for the prevention and treatment of acute GvHD.

REFERENCES

DISCLOSURES
The study was sponsored by Vectibio and conducted in collaboration with Centre de recherche de l’Hôpital Maisonneuve-Rosemont Hospital, Montreal. 1-6: Dimitriadou received fees for service as a consultant.

Poster presented at The European Society for Blood & Marrow Transplantation (EBMT) Annual Meeting, March 10-23, 2022, Prague, Czech Republic. www.ebmt.org