

[4364] "Cross Lineage" Effects of darbepoetin alfa in Normal Mice: A Comparison with Recombinant Human Erythropoietin, darbepoetin alfa and Pegylated-darbepoetin alfa. Session Type: Publication Only

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Darbepoetin alfa is a long-acting hematopoietic cytokine that has known dose-response effects upon the erythropoietic lineage in normal BALB/c mice. The intent of this study was to evaluate the non-erythroid effects of darbepoetin alfa. Darbepoetin alfa transiently induced cross-lineage effects in peripheral white blood cells (WBC) and caused a reversible increase in spleen megakaryocyte numbers. This was evident if administered at doses ≥ 10 mg/kg. In an initial dose-response study, the kinetic changes in hematological parameters between days 1 and 7 after single intraperitoneal (IP) bolus injections of darbepoetin alfa at the doses of 1, 3, 10, 30 or 50 mg/kg or sterile saline were evaluated. On days 1, 2 and 3 after injection, darbepoetin alfa induced a transient increase in WBC counts in a dose-dependent fashion. This was due to a transient lymphocytosis and a mild monocytosis. Additionally, a single IP bolus injection of darbepoetin alfa at doses ≥ 10 mg/kg caused a mild but statistically significant splenomegaly in a dose-dependent manner after 5 days. Concurrently, megakaryocyte numbers were increased in spleen sections. A single IP bolus injection of darbepoetin alfa at doses ≥ 1 mg/kg and up to 10 mg/kg failed to induce any significant changes from day 1 through 7 in the peripheral blood platelet counts when compared with the controls. An additional study was performed in normal BALB/c mice comparing the kinetics of splenomegaly and the numbers of megakaryocytes in von Willebrand factor (vWF) immunostained spleen sections after single IP bolus injections of either rHu-EPO, darbepoetin alfa or PEG-darb. The change in reticulocyte counts was consistent with the different pharmacokinetics of these erythropoietic molecules. However the reticulocytosis was more marked, sustained and right-shifted in the PEG-darb treated groups of mice. There was a positive correlation between the degree of reticulocytosis in the blood and the degree of splenomegaly after single bolus injections of either rHu-EPO, darbepoetin alfa or PEG-darb. Unexpectedly a mild thrombocytopenia was observed in the PEG-darb-treated mice between days 8 and 14 after injection. There was a direct correlation between the degree of reticulocytosis and splenic mass. The non-erythroid effects of the rHuEPO, darbepoetin alfa and PEG-darb proteins are consistent with each other and with an increased potency of the longer-lasting forms.

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