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The mTor inhibitor rapamycin delays xenogeneic acute graft versus host disease (aGVHD) in NOD/SCID/IL2r?null mice (NSG): impact of regulatory T cells

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Background
Rapamycin (RAPA) is a potent immunosuppressive drug which induces tolerance by inhibiting activated T-cells but not regulatory (Treg) T-cells. The aim of the study was to establish a humanized model of aGVHD in NSG mice, and to assess the impact of RAPA and Treg in that model.

Methods
We first assessed the impact of the dose of PBMC infused i.v. on GVHD mortality. After 2Gy irradiation, NSG mice received either 5×105, 1×106, 2×106 or 3×106 human PBMC. We then investigated whether injection of RAPA or PBMC supplemented in Treg could mitigate aGVHD in our model. NSG mice irradiated at 2 Gy TBI were transplanted with 2×106 PBMC and i.p. PBS (control arm), or i.p. RAPA (rapa arm), or with 2×106 PBMC depleted in Treg and i.p. RAPA (Treg-depleted arm), or with 2×106 PBMC supplemented in Treg (1Treg:8PBMC) and i.p. placebo (Treg arm).

Results
NSG mice transplanted with 5×105, 1×106, 2×106 or 3×106 human PBMC died after 36±7 days, 30±6 days, 24±5 days and 16±1 days, respectively, after transplantation. At the time of death, mice presented clinical symptoms of aGVHD and showed a massive infiltration of their organs with human CD3+T-cells. Survival for mice in the rapa arm was increased compared with mice in the control arm (median survival, 96 vs. 24 days) (P<0.01), while mice in Treg-depleted arm had a survival median of 48 days (P<0.01 in comparison with the rapa arm). In contrast, mice in the Treg arm had a median survival of 71 days (P<0.01 in comparison with the control arm) (Figure 1).

Conclusions
IV injection of 2×106 PBMC into irradiated NSG mice induced a severe xenogeneic GVHD. RAPA administration increased survival but this effect was affected by Treg depletion suggesting that RAPA administration prevented death from GVHD through Treg suppression.

Figure 1.