Graft-versus-host-disease (GVHD) is a severe complication of allogeneic hematopoietic cell transplantation (allo-HCT) characterized by the production of high levels of proinflammatory cytokines. Activated Janus kinases (JAKs) are required for T-effector cell responses in different inflammatory diseases, and their blockade could potently reduce acute GVHD. We observed that inhibition of JAK1/2 signaling resulted in reduced proliferation of effector T cells and suppression of proinflammatory cytokine production in response to alloantigen in mice. In vivo JAK 1/2 inhibition improved survival of mice developing acute GVHD and reduced histopathological GVHD grading, serum levels of proinflammatory cytokines, and expansion of alloreactive luc-transgenic T cells. Mechanistically, we could show that ruxolitinib impaired differentiation of CD4(+) T cells into IFN-? and IL17A-producing cells, and that both T-cell phenotypes are linked to GVHD. Conversely, ruxolitinib treatment in allo-HCT recipients increased FoxP3(+) regulatory T cells, which are linked to immunologic tolerance. Based on these results, we treated 6 patients with steroid-refractory GVHD with ruxolitinib. All patients responded with respect to clinical GVHD.
symptoms and serum levels of proinflammatory cytokines. In summary, ruxolitinib represents a novel targeted approach in GVHD by suppression of proinflammatory signaling that mediates tissue damage and by promotion of tolerogenic Treg cells.