Dottorato di ricerca in Scienze Veterinarie XXXVI CICLO - CICLO - Anno di corso: 3°
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The CXCR1/CXCR2 inhibitor Reparixin Alters the Development of Myelofibrosis in the *Gata1*^{low} Mice

Objective: To test the effects of treatment with the CXCR1/R2 inhibitor Reparixin in the *Gata1*^{low} mice on myelofibrosis phenotype expressed by this model.

M&M: 16 *Gata1*^{low} mice were treated either with vehicle or with Reparixin for either 20 or 37 days. The drug was administered by minipumps implanted subcutaneously in the dorsal region set to deliver 7.5mg of drug/hr/kg of body weight. (***Fig. 1a***). Bone marrow (BM) and spleen fibrosis was assessed by quantification of reticulin fibers using ImageJ program. TGF-β1, CXCL1, CXCR1 and CXCR2 expression was evaluated by immunohistochemistry (IHC) and quantified using ImageJ.

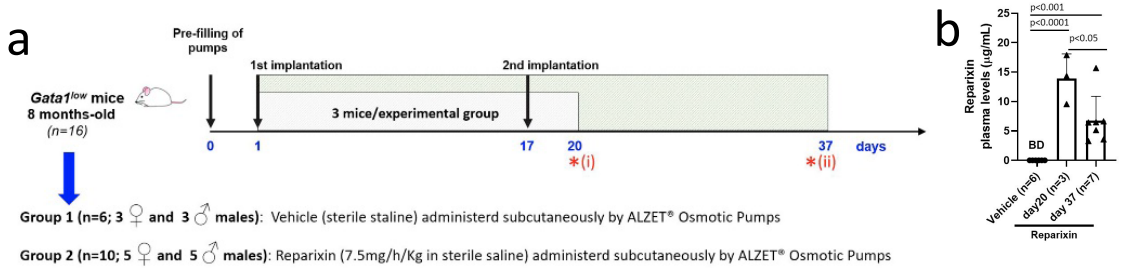

Figure 1. **(a)** Scheme of the treatment of *Gata1*^{low} mice with either vehicle or Reparixin for 20 or 37 days. Red asterisks indicate the timing of the first (i) and second (ii) end point. **(b)** Plasma levels (µg/mL) of Reparixin detected at days 20 and 37.

Conclusions: In *Gata1*^{low} mice, Reparixin reduces fibrosis by reducing TGF-β1 expression. Our results provide a preclinical rationale for further evaluation of this drug for the treatment of patients with myelofibrosis.

Results: The efficiency of drug delivery decreased over time (***Fig. 1b***). Great reductions in the fibrosis of the BM and spleen was observed in mice that had been treated with Reparixin compared to vehicle which were statistically significant by day 20. The levels of reticulin fibrosis detected at day 20 and 37 in individual mice were inversely correlated with the plasma levels of Reparixin ($p<0.05$). The BM from the Reparixin-treated group contained levels of TGF-β significantly lower than that contained in the BM from vehicle while the levels of CXCL1, CXCR1 and CXCR2 contained in the Reparixin-treated BM are similar to those of the vehicle BM (***Fig. 2***).

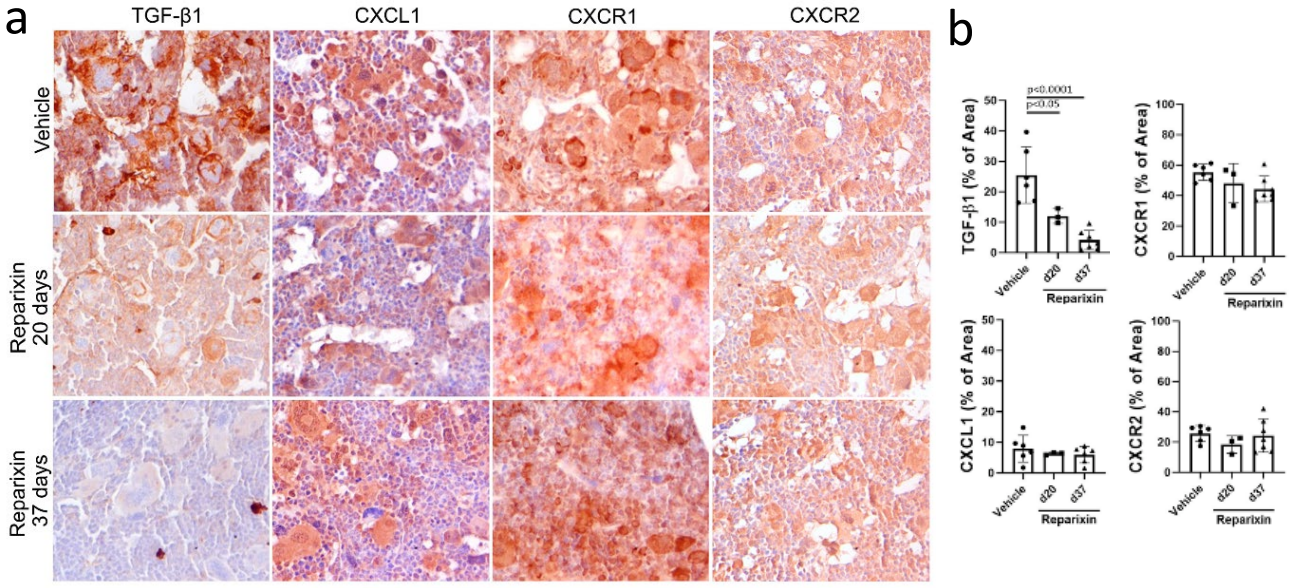

Figure 2. Treatment with Reparixin decreases the TGF-β1 content of the BM from *Gata1*^{low} mice. **(a)** IHC for TGF-β1, CXCL1, CXCR1, and CXCR2 of BM sections from representative *Gata1*^{low} mice treated either with vehicle or Reparixin for 20 or 37d. 400X. **(b)** Quantification of the TGF-β1, CXCL1, CXCR1 and CXCR2 content in the BM.