Inhibition of KIF20A reduces endometriosis implants in a randomized xenograft mouse model

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Study question:
To assess effects of KIF20A inhibition by BKS0349, a high-affinity new inhibitor derived from Paprotrain, in endometriotic lesions generated in an endometriosis xenograft mouse model.

Summary answer:
KIF20A inhibition by BKS0349 decrease cell proliferation, induces cell cycle arrest and promotes apoptosis of endometriotic lesions, reducing their size in a xenograft mouse model.

What is known already:
Several studies have reported that ovarian endometriotic may be the origin of ovarian carcinoma or ovarian endometrioid cancer types, suggesting a possible etiological association between endometriosis and ovarian cancer. In this regard, accumulating evidence has shown that ectopic KIF20A overexpression might confer malignant phenotype to ovarian tumors by promoting cell proliferation and inhibiting apoptosis. In addition, it has been reported that KIF20A downregulation inhibits cell proliferation, induces cell cycle arrest in G0/G1 phase, and promotes apoptosis, proposing KIF20A as a therapeutic target for numerous tumors. However, to date, no data about the role of KIF20A in endometriosis has been described.

Study design, size, duration:
This is a prospective study in which human endometrial biopsies (n=4) were transfected by mCherry adenovirus and intraperitoneally implanted in mice, generating a xenograft mouse model of endometriosis. Female mice were divided in Vehicle group (n=8), BKS0349 group (n=8) and Cabergoline (positive control) group (n=8). Vehicle and BKS0349 were administrated once a week and Cabergoline was orally administrated every day for 21 days. Mice were sacrificed 72 hours after last administration.

Participants/materials, setting, methods:
Human endometrial tissue was obtained from egg donor women at the time of oocyte retrieval procedure. mCherry adenovirus was used to label endometrial tissue. mCherry-labeled endometriotic lesions were introduced in 6-week-old athymic nude female mice and monitored over time using IVIS Spectrum Preclinical in vivo Imaging System. Cellular proliferation was assessed by immunohistochemistry for Ki67 and apoptosis was evaluated with TUNEL staining. CCND1 gene expression was measured by qRT-PCR using StepOnePlus System.

Main results and the role of chance:
A significant reduction in fluorescent signal was observed 72 hours after treatment end (D24) for BKS0349 group (p-value=0.0313) and from D14 for Cb2 group (p-value=0.0313 on D14-21; p-value=0.0156 on D24) compared to D0, while this reduction was not highly pronounced in control group. In addition, fluorescent signal on D24 showed a significant decrease in BKS0349 group compared to control group (40% ± 19.3 vs. 81% ± 30.7; p-value=0.0303), according with significant size reduction of endometriotic lesions observed in BKS0349 group (0.073mm² ± 0.022; p-value=0.0006) compared to control group (0.128 mm² ± 0.019) at the end of the experiment. Functional studies showed significant reduction of proliferating cells in BKS0349
group compared to control group (3.5% ± 3.4 vs 9.2% ± 3.8; p-value=0.0082), which was even more pronounced than our positive control group (Cb2) (5.7% ± 5.8). In addition, CCND1 expression was decreased in BKS0349 group compared to control group (Fold Change=0.259; p-value=0.049). Finally, while endometriotic lesions in control group were practically absent of apoptotic cells (25.48% ± 13.3), an increase of apoptotic cells in endometriotic lesions from BKS0349 (39.73% ± 22.95) and Cb2 (37.7% ± 24.87) group was observed, being statistically significant in animals treated with the KIF20A inhibitor, BKS0349 (p-value=0.0317).

**Limitations, reasons for caution:**
Results obtained in this mouse model of endometriosis could not be directly assumed in humans due to the phylogenetic distance with mouse.

**Wider implications of the findings:**
KIF20A inhibition by BKS0349 induces apoptosis and inhibits cell proliferation by cell cycle arrest in G0/G1 phase and consequently reduces endometriotic lesions size. This suggest that KIF20A could be used as a novel therapeutic treatment for endometriosis due to its important role in cell cycle regulation and apoptosis.

**Trial registration number:**
NA

**Keywords:**
endometriosis
KIF20A
cell proliferation
apoptosis
cell cycle arrest