Abstract Details

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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 (0.073mm^2 ± 0.022; p-value=0.0006) compared to control group (0.128 mm^2 ± 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, C*CND1* 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
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cell proliferation
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