Btk inhibitor Ibrutinib limits endometriosis progression in mice

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Introduction: Endometriosis is a gynecological disorder characterized by the presence and growth of endometrial tissue outside the uterine cavity. It affects about 5-15% of women in reproductive age, causing chronic pelvic pain and infertility. The immune system plays a key role in the pathophysiology of endometriosis, but some aspects are not completely understood. A polyclonal activation of B cells and the presence of anti-endometrial autoantibodies have been described in women with endometriosis though its exact role in the disease mechanisms remains unclear. Thus, in this report, we hypothesized that B cell depletion with anti-CD20 antibody or inactivation with Btk inhibitor Ibrutinib interfere on endometriosis progression. We have tested this hypothesis in a relevant mouse model to better characterize the role of B cells on this disease. Materials and Methods: BALB/c female mice (10 animals in each group for each experiment) were submitted to the previously described protocol of surgically-induced endometriosis and randomized in three groups. Ibrutinib Group received 15mg/kg/day of Ibrutinib by oral gavage for 21 days; Anti-CD20 Group received a single intraperitoneal dose of 100µg of anti-CD20 antibody and Control Group received only vehicle by oral gavage for 21 days. Ultrasound to evaluate implants volume was performed in Day 7 and Day 20 after the surgery. The animals were sacrificed after three weeks and blood, peritoneal fluid, spleen and endometriotic implants were collected. Volume, weight and histology of the implants were evaluated. Flow cytometry was performed in the spleen and peritoneal fluid to evaluate B lymphocytes, macrophages and T lymphocytes subtypes. RT-qPCR was performed in the implants to evaluate inflammatory, fibrotic and immune cells markers genes expression. Cytokines in the serum and peritoneal fluid were assessed by ELISA. Results: Btk inhibitor Ibrutinib prevented lesion growth, reduced mRNA expression of COX-2, αSMA and Type I collagen in the lesions and skewed activated B cells towards regulatory B cells in the spleen and peritoneal cavity of mice with endometriosis. In addition, the number of M2 macrophages decreased in the peritoneal cavity of Ibrutinib-treated mice compared to anti-CD20 and control mice. Depletion of B cells using an anti-CD20 antibody had no effect on activity and growth of endometriotic lesions and neither on the macrophages, compared to control mice. T lymphocytes were not affected by the treatments. Conclusion: We conclude that Btk inhibitor Ibrutinib controlled endometriosis progression in mice, while total B cell depletion using an anti-CD20 antibody had no effect on the course of the disease. In addition, our findings suggest that B regulatory cells might help blocking the development of endometriotic lesions, as these cells were depleted by anti-CD20 antibody and preserved by Ibrutinib. The use of this FDA approved drug to skew activated B cells towards regulatory B cells and increase the M1/M2 ratio into the peritoneal cavity opens new perspectives to better understand endometriosis and to develop new therapeutic strategies.

Keywords : B lymphocytes; endometriosis; mice; Ibrutinib; Btk inhibitor; anti-CD20; regulatory B cells; macrophages.

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