FROM THE DEPARTMENT OF

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MIFEPRISTONE FOR PREOPERATIVE TREATMENT OF UTERINE LEIOMYOMA

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ABSTRACT

AIM: To explore the clinical impact and its molecular regulation on uterine leiomyomas in preoperative treatment with mifepristone, a progesterone receptor modulator (PRM).
BACKGROUND: Uterine leiomyomas are highly prevalent in fertile women, increasing with age up to 35-50 % in a population approaching the age of 50. These most often benign tumors, frequently cause menorrhagia, and may interfere with fertility and the outcome of pregnancy. Progesterone and estrogen have a role in leiomyoma growth regulation, as well as in endometrial and breast cell proliferation and the development of endometrial and breast cancer. The objective of the current project was to study the effect of mifepristone on leiomyoma growth, as well as on cell proliferation in human endometrial and breast tissue in premenopausal women.
METHODS: Thirty premenopausal women scheduled for surgical treatment due to uterine leiomyoma were randomized to either 50 mg mifepristone or non active treatment every other day, for 12 weeks before surgical intervention. Uterine and leiomyoma blood flow and leiomyoma volume were measured once a month until surgery. Endometrial biopsies were obtained and analyzed before and at end of treatment. Breast biopsies were assessed at baseline and at the end of the study for the expression of Ki-67 by immunocytochemical analysis in order to evaluate mammary epithelial cell proliferation. On surgery biopsies were collected from the periphery of the dominant leiomyoma. In order to investigate the gene expression leading to volume change in myoma, microarray analysis followed by Real time PCR analysis was performed. The degree of apoptosis was studied by TUNEL. Functional studies using primary cell cultures from fresh and untreated leiomyoma biopsies were performed to investigate the antiglucocorticoid response of mifepristone in the Integrin pathway.
RESULTS: There was a significant difference in percentual volume regression of the dominant leiomyoma between the treatment groups ($p=0.014$). The controls ($N=15$) had a percentual n.s. increase in volume of mean (± 95% Confidence interval), +8% (-10%, +26%) over time. The mifepristone group ($N=12$) had a significant volume regression of -27% (-47%, -8%), $p=0.028$ within the mifepristone group and between the treatment groups at the end of study ($p=0.014$). Mifepristone treatment significantly reduced the number of bleeding days ($p<0.001$) and increased blood haemoglobin values ($p=0.046$). The breast Ki-67-index was significantly reduced by mifepristone treatment ($p=0.012$). Breast symptoms, like soreness ($p=0.035$), swelling ($p=0.028$) and the score for sense of increased volume ($p=0.043$), were reduced within the mifepristone treated group. The incidence of hot flushes was more frequent in the mifepristone treated group ($p=0.012$). Endometrial morphology showed no hyperplasia or atypia. Microarray displayed 17 pathways significantly changed by mifepristone exposure, among which Integrin, EGF, NRF-2 mediated Oxidative Stress response and Ephrine pathways were the top 4 most significant. In a subgroup analysis of good ($N=4$) versus poor ($N=4$) responders, with regard to the effect of mifepristone in induction of volume regression, the Glutathione pathway was the second most significant. Among good responders GSTM1 was expressed, while it was not detectable by Real time PCR in non responders. In primary cell cultures, the genes PIK3R1 and PAK3 proved to respond to the antiglucocorticoid effect of mifepristone.
CONCLUSION: Mifepristone may offer an effective, well tolerated preoperative treatment option for women with uterine leiomyoma and the associated uterovaginal bleeding. Our results also show an antiproliferative effect of mifepristone in normal premenopausal breast epithelium, implicating a possible protective effect. It is suggested that GSTM1 may be of importance for the response in leiomyoma volume regression as induced by mifepristone, and could have a role as a biomarker for tailoring of the medical treatment of uterine leiomyomas.

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