Thieme

mTor Inhibitors for the Treatment of Endometriosis

mTOR-Inhibitoren zur Behandlung von Endometriose

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Bibliography
DOI https://doi.org/10.1055/s-0043-124518
Geburtsh Frauenheilk 2018; 78: 283–284 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0016-5751

We read with great interest the article of Kacan et al. entitled "Everolimus as an mTOR Inhibitor Suppresses Endometriotic Implants: an Experimental Rat Study" [1] published in your journal.

The authors surgically induced endometriosis by the autotransplantation of uterine tissue in the peritoneal cavity of 24 rats. The animals were randomized in three groups, receiving oral everolimus, oral anastrozole, or intravenous saline solution for 14 days. Histological evaluation was done by the endometriosis score (according to Keenan et al. [2]) and immunohistochemical examination was performed by using antibodies against vascular endothelial growth factor (VEGF), CD117 and BAX. The post-treatment analysis of endometriotic implants revealed that anastrozole and everolimus succeeded in significantly decreasing their growth and size with no difference in histological and immunohistochemical results between the two drugs. The authors noted at histology that the number of ovarian follicles was not negatively altered by everolimus, differently from anastrozole that, as evidenced in literature, tends to decrease it [3].

The rational of the study is based on the evidence of the pivotal role of mTOR in angiogenesis and growth of endometriotic implants [4]. The results of the therapy are in line with a previous study performed on the animal model [5], in which Leconte et al. found that also the administration of temsirolimus (intraperitoneal 3 mg/kg), another mTor inhibitor, for 2 weeks led to significant decreases in endometriosis implants growth.

Although the authors should be congratulated for their laboratory findings, we would like to raise some concerns on the administration of mTor inhibitors, and in particular everolimus, in the clinical treatment of endometriosis. Everolimus is approved by Food and Drug Administration (FDA) for the treatment of advanced tumors, such as advanced kidney cancer, progressive or metastatic pancreatic or gastrointestinal neuroendocrine tumors, and it is currently being also evaluated in gynecological cancers. Moreover, its use is indicated for immunosuppression after solid organ transplant [6].

Although in oncologic setting it has been reported that patients with specific mutations (i.e. PIK3A, PTEN) tend to have higher benefit receiving mTor pathway inhibitors, a first non-negligible problem is that there are no validated predictive biomarkers for patients' selection and for monitoring drug efficacy [7]. A second concern is related to the fact that in the experiment endometriotic implants were surgically induced only in peritoneum of rats, and not in other localizations. Thus, it appears unlikely that drugs acting on angiogenesis-related pathways, such as mTor, may treat the symptoms caused by large nodules of deep infiltrating endometriosis (DIE), which are mainly composed of fibromuscular tissue, and may have already been present for some years.

More importantly, drugs targeting mTor pathway may cause adverse effects [8], including a large variety of metabolic, hematological, respiratory, renal and dermatological toxicities. These sometime serious side effects explain the notable rate of drug discontinuation in clinical trials for advanced cancer. Although some of them, such as oral stomatitis (30–60% of patients) or pneumonitis, seem to increase with the dosage of the drug, the majority are idiosyncratic and unpredictable, and may also occur from days to years after the beginning of the therapy. These adverse effects

may be tolerable in oncological therapy, where the primary endpoints are disease-free survival and overall survival, but it appears difficult to accept them in young women with endometriosis where the goal is improving the quality of life. In fact, endometriosis is a chronic benign disease that requires a long-term therapy combining clinical efficacy (preventing recurrence, controlling pain symptoms) with acceptable costs and toxicity. Given this background, it seems unlikely that everolimus may have a relevant role in the future treatment of women with endometriosis.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Kacan T, Yildiz C, Baloglu Kacan S et al. Everolimus as an mTOR inhibitor suppresses endometriotic implants: an experimental rat study. Geburtsh Frauenheilk 2017; 77: 66–72

[2] Keenan JA, Williams-Boyce PK, Massey PJ et al. Regression of endometrial explants in a rat model of endometriosis treated with the immune modulators loxoribine and levamisole. Fertil Steril 1999; 72: 135–141

[3] Oral E, Demir B, Inceboz U. Endometriosis and ovarian reserve. Womens Health (Lond) 2015; 11: 671–675

[4] Cinar O, Seval Y, Uz YH et al. Differential regulation of Akt phosphorylation in endometriosis. Reprod Biomed Online 2009; 19: 864–871

[5] Leconte M, Nicco C, Ngo C et al. The mTOR/AKT inhibitor temsirolimus prevents deep infiltrating endometriosis in mice. Am J Pathol 2011; 179: 880–889

[6] Wesolowski R, Abdel-Rasoul M, Lustberg M et al. Treatment-related mortality with everolimus in cancer patients. Oncologist 2014; 19: 661–668

[7] Gajate P, Alonso-Gordoa T, Martinez-Saez O et al. Prognostic and predictive role of the PI3K-AKT-mTOR pathway in neuroendocrine neoplasms. Clin Transl Oncol 2017. doi:10.1007/s12094-017-1758-3

[8] Pallet N, Legendre C. Adverse events associated with mTOR inhibitors. Expert Opin Drug Saf 2013; 12: 177–186