British Journal of Pharmacology

British Journal of Pharmacology (2018) **175** 3626–3627 3626

LETTER TO THE EDITOR

Inhibition of PI3K/AKT/mTOR pathway for the treatment of endometriosis

Correspondence Simone Ferrero, MD, PhD, Academic Unit of Obstetrics and Gynecology, Ospedale Policlinico San Martino, Largo R. Benzi 10, 16132 Genoa, Italy. E-mail: simone.ferrero@unige.it

Received 14 March 2018; **Accepted** 13 May 2018

Fabio Barra[1,2], Lorenzo Ferro Desideri[1,2] and Simone Ferrero[1,2]

[1]*Academic Unit of Obstetrics and Gynecology, Ospedale Policlinico San Martino, Genoa, Italy, and* [2]*Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genoa, Genoa, Italy*

We read with great interest the article by Matsuzaki *et al*. (2018) entitled '*In vitro* and *in vivo* effects of **MK2206** and **chloroquine** combination therapy on endometriosis: autophagy may be required for regrowth of endometriosis' recently published in the *British Journal of Pharmacology*.

The authors showed the efficacy of MK2206, an **Akt** inhibitor, in combination with chloroquine for inducing autophagy of endometriotic stromal and epithelial cells. Moreover, in their study, this double regimen succeeded in reducing the size of endometriotic implants in a xenograft mouse model of endometriosis.

The rationale of this study is based on evidence of the important role displayed by **PI3K**/Akt/**mTOR** pathway in the pathogenesis of endometriosis. In fact, it has been suggested that this pathway may significantly modulate survival, proliferation of endometriotic cells and angiogenesis in endometriotic implants and that it may also be involved in resistance to progestins. To confirm its importance, some studies reported the overexpression of this pathway in women with endometriosis (Lee and Kim, 2014).

The positive results of the study by Matsuzaki *et al*. (2018) are in line with the previous studies on **temsirolimus** and **everolimus**, two rapamycin-analogues that specifically inhibit mTORC1. In two preclinical studies on rats, these drugs were able to cause significant reduction of endometriosis implants growth (Kacan *et al.,* 2017; Lee and Kim, 2014).

Although Matsuzaki *et al*. (2018) should be congratulated for their laboratory findings, we would like to raise some concerns on the administration of PI3K/Akt/mTOR inhibitors and, in particular MK2206, in the clinical treatment of endometriosis.

Currently, in oncology, several agents inhibiting key components of this pathway are being tested, such as mTOR (e.g. **rapamycin** analogues), PI3K (e.g. **LY294002**), PI3K/mTOR (e.g. **BEZ235**; dactolisib) or Akt inhibitors (e.g. MK2206). Specifically, MK2206 is being investigated for the treatment of patients with breast, non-small lung and pancreatic cancers (Janku *et al.,* 2018).

Although, in an oncological setting, patients with specific mutations (i.e. **PIK3CA** and **PTEN**) tend to have higher benefit receiving these inhibitors, a first non-negligible problem is that there are no validated predictive biomarkers for the selection of patients and for monitoring drug efficacy (Janku *et al.,* 2018).

More importantly, as the majority of these inhibitors are in early clinical development, there is a lack of solid clinical data on their efficacy and toxicity. However, a not negligible incidence of drug-related adverse events and treatment discontinuation has been reported, in patients receiving these compounds in clinical trials for advanced cancer. Their metabolic, haematological, respiratory, renal and dermatological related toxicities may be partly due to a broad activity profile and crossover inhibition of other ubiquitous lipid and protein kinases. Although some of these adverse events, such as oral stomatitis (30–60% of patients treated) or rash (30–40%), seem to increase with the dosage of the drug, they are often idiosyncratic and unpredictable, potentially occurring from days to years after the beginning of the therapy (Janku *et al.,* 2018). Moreover, evaluating the double regimen administered in the study (Matsuzaki *et al.,* 2018), it should be stated that also chloroquine itself is not free from gastrointestinal (12%), dermatological (3%) and less frequently ophthalmological adverse events (Rainsford *et al.,* 2015).

In conclusion, the administration of MK2206, eventually combined with chloroquine, may be acceptable for cancer therapy, in which the primary endpoints are represented by disease-free survival and overall survival. By contrast, it appears less reasonable to use them in young women with endometriosis where the goal is improving the quality of life. In fact, endometriosis needs a long-term therapy combining clinical efficacy, such as prevention of implants recurrence or control of disease-related pain, with acceptable costs and, more importantly, tolerability. Given this background, it seems unlikely that in the near future, MK2206 or its

DOI:10.1111/bph.14391

combination with chloroquine may have an important role in the treatment of women with endometriosis.

Conflict of interest

The authors declare no conflicts of interest.

References

Janku F, Yap TA, Meric-Bernstam F (2018). Targeting the PI3K pathway in cancer: are we making headway? Nat Rev Clin Oncol 15: 273–291.

Kacan T, Yildiz C, Baloglu Kacan S, Seker M, Ozer H, Cetin A (2017). Everolimus as an mTOR inhibitor suppresses endometriotic implants: an experimental rat study. Geburtshilfe Frauenheilkd 77: 66–72.

Lee II, Kim JJ (2014). Influence of AKT on progesterone action in endometrial diseases. Biol Reprod 91: 63.

Matsuzaki S, Pouly J-L, Canis M (2018). *In vitro* and *in vivo* effects of MK2206 and chloroquine combination therapy on endometriosis: autophagy may be required for regrowth of endometriosis. Br J Pharmacol 175: 1637–1653.

Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF (2015). Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology 23: 231–269.