JOURNAL OF FERTILITY AND REPRODUCTIVE HEALTH
Oct-Dec 2023, VOL. 1, ISSUE 1, pp. 1-2
https://doi.org/10.61577/jfrh.2023.100001

RESEAPRO JOURNALS

EDITORIAL

OPEN ACCESS

News about progesterone receptor modulators

Michael Oettel

Endocrino-Pharmacology Advice, Jena/Germany and Evestra Onkologia, Lodz, Poland

ARTICLE HISTORY

Received 01 June 2023; Revised 23 June 2023; Accepted 30 June 2023

The role of natural progesterone as a progesterone receptor modulator and its chemical analogues, the progestins cannot be overestimated in human and animal reproduction and beyond. Our knowledge is based on molecular biological basics, physiological and endocrinological findings, clinical observations through drug development, commercialization, and ecological aspects. The most important applications are mainly in Reproductive Health (female and male contraception, pregnancy maintenance, miscarriage, hormone replacement therapy, endometrial hyperplasia, endometriosis, and adenomyosis, uterine fibroids, abnormal uterine bleeding, including heavy menstrual bleeding, and preterm labor). Progestins also play a role in oncology by regulating cell proliferation, apoptosis, and metastasis in gynecological and brain cancers. The non-classical effects include immunomodulation and neuroprotection but are also involved in increased risks for breast cancer and decreased mood. Progesterone is mainly used in assisted reproduction using a different application, delivery forms, and structural analogues [1]. For the newest progestin-only pills with Drospirenone or Levonorgestrel [2,3], an over-the-counter-distribution (self-administration) is in discussion [4].

The design and development of progestins followed, until now, the "classical" methodology. That means stepwise structure/activity optimization via focussed chemical synthesis based on interactions with the nuclear PR in vitro as well as in vivo. In addition, the interactions with other steroid receptors like ERα and β, AR, MR, and GR were evaluated. Many clinically used steroidal compounds with different endocrine-pharmacological profiles suggest that "A progestin isn't a progestin." In the last few years, we learned more about the importance of the role of the nuclear PR-isoforms A and B and their physiological and clinical significance [5]. A great step forward has been generated by investigating the non-genomic membrane receptors (induce cellular cascades in minutes/hours), which can be divided into the adipoQ receptors (mainly expressed in the reproductive organs) and the PR-components (PGRM 1 +2) found in the forebrain structures. The third non-genomic PR is the mitochondrial receptor (PR-M) that regulates cellular energy [6,7]. Examples of known non-genomic effects of the progestin dienogest (STS 557) are inhibition of PGE2, reduction of COX-2 and stromal cell-derived factor 1 (SDF-1), inhibition of aromatase, down-regulation of VEGF, NF- B inactivation (see pathogenesis of osteoporosis), and GABA4-receptor modulation [8]. It is easy to imagine the significance of these non-genomic progestin effects when the associated membrane receptors are used as an additional pharmacological target for finding new types of progestins, e.g., higher anti-proliferative or mood-enhancing effects. On the other hand, pure antagonists of membrane PRs have not yet been found.

Coming now to the anti-progestins, including the so-called Selective Progesterone- Receptor-Modulators (SPRMs), the story started with Mifepristone (RU 486) in the 1970s of the last centuries [9]. Since then, several SPRMs have been in development, with two currently in clinical practice: Mifepristone and Ulipristal acetate for emergency contraception and for managing abnormal uterine bleeding (AUB) in women with uterine leiomyomas or uterine fibroids [10]. Both compounds also show shrinking of endometriotic lesions and fibroid volume. Depending from the chosen compound, further PR-antagonists (the so-called "pure" antagonists like Vilaprisan [11]) were found. Unfortunately , due to Sponsors considerations about preclinical toxicological findings, the development of Vilaprisan (BAY 1002670) was terminated despite very good clinical results for the treatment of uterine fibroids [12]. The next step in developing SPRMs was the successful clinical examination of Asoprisnil (J 867) for treating endometriosis and uterine fibroids [13]. This compound shows more PR-agonistic than PR-antagonistic activities. Therefore, the definition "Mesoprogestin" was introduced in the literature. Unfortunately, the typical endometrial changes under SPRM therapy the so-called progesterone receptor modulator associated with benign endometrial changes (PAEC) were misinterpreted and resulted in a stopping the development of Asoprisnil [12]. However, Asoprisnil inspired a further structure/activity optimization of the relation between PR-agonistic and PR-antagonistic effects. As a result, EC 313 was selected by Evestra Onkologia for further development. EC 313 is 21,21-difluoro-11β-[4'-(3'-furanyl)phenyl]-17,23-epoxy-19, 24-dinor-17α-chola-4,9,20-triene. The chemical structure differs very clearly from that of the other known SPRMs [14].

In an in vivo xenograft model of human uterine fibroids (UF) in immunodeficient NOD-SCID mice, the treatment with EC 313 resulted in a statistically significant and dose-dependent reduction in fibroid xenograft-weights inhibition of the estradiol-induced proliferation, reduction of ER and PR-concentrations in the xenografts, and no signs of unopposed estrogenicity. UF-related desmin and collagen were markedly reduced. All the endpoints were significantly better when compared to Ulipristal acetate, used as a control [15]. The data indicate that the mixed agonistic/antagonistic target-specific feature of EC313 is the consequence of a

***Correspondence:** Michael Oettel, Endocrino-Pharmacology Advice, Jena/Germany and Evestra Onkologia, Lodz, Poland, e-mail: michel.oettel@gmx.de

super-additive synergism based on a bifunctional principle of this mixed PR-agonist/antagonist. This short comment about the trends in the research and development of PR modulators demonstrates the possibilities for optimizing pharmacological approaches and future clinical changes.

Disclosure statement

No potential conflict of interest was reported by the author.

References

1. Labarta E, Rodríguez C. Progesterone use in assisted reproductive technology. Best Pract Res Clin Obstet Gynaecol. 2020;69:74-84.
2. Regidor PA, Mueller A, Mayr M. Pharmacological and metabolic effects of drospirenone as a progestin-only pill compared to combined formulations with estrogen. Womens Health. 2023;19:17455057221147388.
3. Duijkers IJ, Klipping C, Rautenberg T, Schug BS, Kochhar PS, Osterwald H, et al. Effect on ovarian activity and ovulation inhibition of different oral dosages of levonorgestrel. Contraception. 2022;110:6-15.
4. Guillard H, Laurora I, Sober S, Karapet A, Brass EP, Glasier A. Modeling the potential benefit of an over-the-counter progestin-only pill in preventing unintended pregnancies in the US. Contraception. 2023;117:7-12.
5. Azeez JM, Susmi TR, Remadevi V, Ravindran V, Sujatha AS, Sreeja S. New insights into the functions of progesterone receptor (PR) isoforms and progesterone signaling. Am J Cancer Res. 2021;11(11):5214.
6. Fedotcheva TA. Clinical use of progestins and their mechanisms of action: present and future. Mod Technol Med. 2021;13(1):93-106.
7. Thomas P. Membrane progesterone receptors (mPRs, PAQRs): review of structural and signaling characteristics. Cells. 2022;11(11):1785.
8. Oettel M, Zentel HJ, Nickisch K. A progestin isn'ta progestin: dienogest for endometriosis as a blueprint for future research–Review as a contribution for discussion. Horm Mol Biol Clin Investig. 2020;42(2):133-142.
9. Philibert D. RU 38486: An original multifaceted anti-hormone in vivo. Adrenal Steroid Antagonism. 1985;23(3):247-251.
10. Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update. 2016;22(6):665-686.
11. Wagenfeld A, Bone W, Schwede W, Fritsch M, Fischer OM, Moeller C. BAY 1002670: a novel, highly potent and selective progesterone receptor modulator for gynaecological therapies. Hum Reprod. 2013;28(8):2253-2264.
12. Shi J, Tan X, Feng G, Zhuo Y, Jiang Z, Banda S, et al. Research advances in drug therapy of endometriosis. Front Pharmacol. 2023;14.
13. Elger W, Bartley J, Schneider B, Kaufmann G, Schubert G, Chwalisz K. Endocrine pharmacological characterization of progesterone antagonists and progesterone receptor modulators with respect to PR-agonistic and antagonistic activity. Steroids. 2000;65(10-11):713-723.
14. Błaszczak-Świątkiewicz K, Krupa A, Mnich E, Elger W, Oettel M, Nair H, et al. Next step in the development of mesoprogestins: the preclinical profile of EC313. Front Endocrinol. 2023;14.
15. Nair HB, Santhamma B, Dileep KV, Binkley P, Acosta K, Zhang KY, et al. EC313-a tissue selective SPRM reduces the growth and proliferation of uterine fibroids in a human uterine fibroid tissue xenograft model. Sci Rep. 2019;9(1):17279.

https://doi.org/10.61577/jfrh.2023.100001