J. steroid Biochem. Vol. 27, No. 4–6, pp. 1009–1012, 1987
Printed in Great Britain

0022-4731/87 $3.00 + 0.00
Pergamon Journals Ltd

Proceedings of the VII International Congress on Hormonal Steroids (Madrid, Spain, 1986)

THE ANTIPROGESTINS: A RECENT ADVANCE IN FERTILITY REGULATION

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Summary—RU 468 (mifepristone) is the first antiprogestin available for clinical purposes. Its pharmacological properties are presented. It possesses antiprogestin and antiglucocorticoid activities. It is now in phase II–III clinical studies as a fertility control agent. The drug appears useful *per se* in four circumstances: (1) for early pregnancy (amenorrhea of less than 5 weeks' duration). Complete interruption is obtained in approximately 90% of women with a single dose of 600 mg. For this stage of pregnancy, RU 486 appears to be an interesting alternative to vacuum aspiration; (2) for late occasional luteal contraception when given as a single dose on the date of the expected period in women at risk of pregnancy; (3) for dead fetus expulsion in the 2nd or 3rd trimester of pregnancy, and (4) for cervical ripening before obstetrical procedures in pregnant women, such as D and C or vacuum aspiration. The antiglucocorticoid activity of the molecule can be demonstrated in humans by a rise in plasma cortisol, ACTH and LPH after RU 486 intake, and by blockade of some peripheral effects of cortisol. Results obtained in more than 1000 women undergoing short-term treatment with RU 486 (600 or 800 mg once) clearly indicate that the antiglucocorticoid activity of the molecule has no clinical relevance at the doses used for fertility control purposes. In conclusion, RU 486 appears to be a promising new tool for fertility control, but large-scale trials are necessary to confirm its safety and to define its optimal mode of utilization for each indication.

INTRODUCTION

In 1980, Roussel-Uclaf chemists first synthesized RU 38486 (mifepristone, RU 486) a 19-norsteroid substituted in 11β position with potent antiprogesterone activity [1]. We review here its biochemical and pharmacological properties, and give an update of current clinical trials with this compound, the first and only compound of this kind presently available for clinical use in humans.

RU 486 BINDING TO STEROID RECEPTORS

The relative affinity of RU 486 for five types of steroid receptors was evaluated [2]: it has a relative binding activity 5 times that of progesterone on rabbit uterine progestin receptors and 3 times that of dexamethasone on rat thymus glucocorticoid receptors. Its relative affinity for the rat prostate androgen receptor is a quarter that of testosterone. Its affinity for the mouse uterine estrogen and rat kidney mineralocorticoid receptors is negligible.

As would be expected from these findings, it was shown that RU 486, after single oral administration, induced a dose-dependent decrease in free cytoplasmic binding sites of both uterine progestin and thymus glucocorticoid receptors. Maximal effect was produced by 10 mg/kg: this dose did not modify free binding sites of kidney mineralocorticoid receptors and uterine estrogen receptors.

PHARMACOLOGICAL EFFECTS OF RU 486

Such data would lead to the hypothesis that this molecule has strong agonist activity. Pharmacological tests showed complete absence of such activity; in contrast, a potent antagonist activity was seen.

The effect of RU 486 on the various biological responses mediated by progesterone has been examined using models involving both exogenous and endogenous progesterone.

Effect on exogenous progesterone responses

The effect of RU 486 has been studied on the role of progesterone in endometrial transformation during the luteal phase of the menstrual cycle, the decidual reaction occurring during ovum implantation and in the maintainenance of pregnancy.

Endometrial proliferation in rabbits. A strong endometrial proliferation was induced by 0.2 mg progesterone/kg in estradiol-primed immature rabbits graded 3.2 MPU on the standard McPhail scale. Up to 100 mg RU 486/kg was totally devoid of progestomimetic activity. In combination, RU 486 produced a dose-dependent inhibition of progesterone. The inhibitory ED_{50} was about 3 mg/kg and complete inhibition occurred with 20 mg/kg.

When the two steroids were introduced simultaneously *in utero* [3], RU 486 exhibited a more potent activity. An ED_{50} was found to be about 1/3 of the dose of progesterone used (10 μg/horn).

Deciduomata formation in rats. Mechanical traumatisation or injection of various chemical agents into the uteri of rats can induce deciduomata [4]. Progesterone will induce deciduomata of similar appearance when administered to pseudopregnant rats, rats ovariectomized during estrus or ovariectomized rats pretreated with estrogen.

In our studies 10 mg progesterone/kg induced a decidual response in all rats. This effect was totally prevented by simultaneous administration of

3 mg/kg RU 486, while the compound alone at a dose of 10 mg/kg was completely devoid of any deciduogenic activity.

Maintenance of pregnancy in rats. Pregnant rats were treated for 12 days with 75 mg progesterone/kg per day subcutaneously. On day 8 they underwent laparotomy, when they were ovariectomised and the number of implantation sites were counted. Eighty-six percent of the implantation sites were maintained at day 12. When RU 486 was administered at a daily dose of 5 mg/kg per day p.o. in combination with progesterone, no conceptuses were seen at autopsy on day 12. Moreover, 75 mg RU 486/kg per day alone did not maintain pregnancy.

In addition, in a test not requiring estrogen priming but evaluating the increase in the volume/density of mitochondria localized in uterine epitherlial gland cells [5], RU 468 completely antagonized the action of the natural hormone (ED_{50} 3 mg/kg p.o.). As expected, the compound alone had no effect [6].

All the experiments described so far clearly demonstrate an antagonistic effect of RU 486 against exogenous progesterone in ovariectomized or immature animals, that is, in animals practically devoid of any sexual hormone. Moreover, these results suggest that RU 486 acts directly at the target organ level.

Effect of RU 486 on endogenous progesterone

The effect of RU 486 has also been studied on endogenous progesterone during pregnancy in rats and during the luteal phase of the menstrual cycle of monkeys, i.e. under the influence of the pituitary–ovarian axis.

Abortive effect in pregnant rodents. Ten mg RU 486/kg per day p.o. given on 3 consecutive days to gestating rats at any time during pregnancy was antinidatory and abortive. A single dose of 10 mg RU 486/kg p.o. had a totally abortive action when given on any day from the 3rd to the 18th day of pregnancy except day 15. A higher dose must be used to completely prevent implantation. In pregnant mice, the same spectrum of activity has been observed, but at doses 3 times higher [2].

Comparative histological studies of uterine tissue during abortion showed that a single oral dose of RU 486 to gestating rats acted more quickly than ovariectomy. The first histological sign of abortion is retraction of the deciduoma and its detachment from the uterine wall. This is seen 8 h after RU 486 administration, but is not visible 8 h after ovariectomy in the rat.

Under the same experimental conditions, progesterone levels are unchanged during the 8 h following RU 486 administration. This confirms that RU 486 does not inhibit progesterone biosynthesis, but rather has a direct antagonist effect at the level of the progesterone receptors [7].

Induction of menses in monkeys. The effect of RU 486 was also studied in intact monkeys with normal menstrual cycles. RU 486 was administered in doses ranging from 25 to 75 mg (8–25 mg/kg) p.o. Except for those receiving the lowest dose, all monkeys menstruated within 48 h of their last dose. Menstruation occurred before the 24th day of the cycle, whatever the treatment, and there was no modification of the length of the next cycle.

Healy *et al.*[8] found that RU 486 was active at a dose of 0.1 mg/kg intramuscularly in artificially cycled castrated monkeys. These differences in the active dose may be explained by the fact that RU 486 taken orally undergoes considerable presystemic metabolism [9] and that in the intact animal the pituitary–ovarian system may exercise compensatory activity. Moreover, results recently obtained by Germain *et al.*[10] show that a single intramuscular injection of 10 mg RU 486/kg in oily solution regularly induces menstruation in the intact monkey.

All these experiments, utilising various techniques and species, confirm the very strong antiprogesterone activity of RU 486.

Other hormonal and antihormonal activity of RU 486

From the results of *in vitro* tests on the affinity of RU 486 on steroid hormone receptors, it can be surmised that the compound will display activity at the level of glucocorticoid and androgen receptors. In the former respect it behaves as a powerful antagonist as has been shown in numerous *in vitro* and *in vivo* tests; in the latter respect, RU 486 behaves as a moderate but proven antagonist [11].

However, using dosages at which RU 486 demonstrates an antihormonal activity at progesterone, glucocorticoid and androgen receptor level, it is totally lacking in agonist or antagonist effect on estrogen and mineralocorticoid receptors. This lack of effect is fully in agreement with the results achieved in the *in vitro* binding studies [2].

CLINICAL STUDIES WITH RU 486

Results of the clinical trials with RU 486 undertaken since 1982 [12] in more than 1000 women now give a good picture of the optimal indications and of the safety of the drug.

Optimal indications of RU 486

RU 486 has been studied as an interceptive agent, for expulsion of dead fetus and for cervical ripening prior to obstetrical procedures.

RU 486 as an interceptive agent. Initially, RU 486 was used to interrupt pregnancies after 5–8 weeks of amenorrhea (WA) with various therapeutic schemes [13], involving repeated intakes of 50–200 mg/day for 3–7 days, yielding success rates of 50–70%. Later, this success rate was improved through (1) administration of large single doses and (2) careful selection of eligible patients. To date, the optimal dose appears to be 600 mg, but additional

Table 1. Administration of RU 38486 (600 mg once) until 41 days of amenorrhea: efficacy of treatment

N	Complete success	Incomplete expulsion	Ongoing pregnancy†
95*	88 (92.6%)	2 (2.1%)	5 (5.3%)

*Initial number: 104, but 9 women excluded because amenorrhea ≥ 42 days.
†Including one ectopic pregnancy.

data are necessary to confirm that this represents the minimal dose yielding the higher success rate. The age of pregnancy appears a critical factor, and higher success rates are achieved for pregnancies below or equal to 5 WA. Tables 1 and 2 illustrate these conclusions in a large series of women who received a single administration of 600 mg RU 486. One-hundred-and-four women were included in this trial: complete success rate (i.e. pregnancy interruption and expulsion without need for any additional surgical procedure) was 89.4%. However, when excluding 9 women whose amenorrhea was above 41 days, success rate was approximately 93%, a percentage comparable to that achieved with vacuum aspiration for pregnancies of identical ages [14]. In addition, the number of incomplete pregnancy interruptions was much lower than for older pregnancies. As shown in Table 2, bleeding lasted for 8 days or less in 80% of the women, but was subjectively judged abundant or very abundant in the majority of the women. Practically, the possibility of persisting pregnancies and of large bleeding implies that RU 486 must be used under adequate medical supervision and that evidence is obtained of complete pregnancy termination. Future trials will be designed to improve efficacy of RU 486 for pregnancies at a later stage. In this respect, combination treatment with oxytocic agents such as prostaglandins appears very promising [15]. Data obtained in normal non-pregnant women [16] indicate that when given during the mid-luteal phases at doses above 3 mg/kg, RU 486 exerts at least partial lutolytic action in addition to its endometrial effects. Ongoing trials are designed to study the relevance of this finding in pregnant women.

Table 2. Administration of RU 486 until 41 days of amenorrhea (600 mg once): uterine bleeding

No bleeding	2/104 (1.9%)
Date of onset (Days from RU 486 intake)	2.5 ± 1.3 (SD)
	≤3 days in 82/104 women (78.8%)
Length (days)	7.1 ± 4.2 (SD)
	≤8 days in 79/88 women (80.6%)
Abundance (subjective assessment)	
abundant or very abundant in 62/102 women (60.8%)	
more or much more abundant than usual periods in 68/95 women (71.5%)	

Use of RU 486 for dead fetus expulsion. Retention of fetus dead in utero constitutes a dangerous condition for the mother, the treatment of which remains difficult. A pilot study [17] showed that administration of 400 mg/day RU 486 for 2 days resulted in expulsion of dead fetuses (pregnancy above 16 WA at the time of fetal death) within 72 h in 9 women out of 11, without need for additional treatment such as prescription of an oxytocic agent. In contrast, a similar dose of RU 468 resulted in expulsion of only 2 out of 8 living fetus expulsion when prescribed for late therapeutic pregnancy interruption. The usefulness of RU 486 treatment for dead fetus expulsion is currently being investigated in a controlled trial vs placebo.

RU 486 for cervical ripening. In several instances [18], investigators using RU 486 for interception have noted some degree of cervical softening and dilatation which eases subsequent vacuum aspiration in case of drug failure to interrupt pregnancy. Precise evaluation of RU 468 for cervical ripening is under progress and it can be anticipated that RU 486 will be useful as a preparation for some obstetrical procedures requiring instrumental cervical dilatation such as vacuum aspiration or curettage.

Tolerance of RU 486

Data obtained so far in more than 1000 women indicate that RU 486 tolerance is very satisfactory. Mild abdominal pain, nausea/vomiting or tiredness have sometimes been reported when using RU 486 as an interceptive agent, but careful analysis of available data suggests that these symptoms are related more to pregnancy interruption that to RU 486 itself. Slight rises in liver enzymes have been noted in a few women, but here again they cannot be attributed with certainty to drug administration.

Administration of RU 486 during the mid-luteal phase in non-pregnant women does not result in post-treatment cycle impairment, except, in some cases of a slight delay in ovulation. Pregnancies have occured in women previously treated with RU 486, suggesting that drug administration does not impair subsequent fertility.

Special care has been given to the possible consequences of the antiglucogenic action of the drug. Table 3 summarizes available data. In normal volunteers, the antiglucogenic action of RU 486 is evidenced by a rise in plasma cortisol, ACTH, LPH, and also by a blockade of peripheral effects of glucocorticoids [19–21]. However, reversal of Cushing's syndrome due to ectopic ACTH production requires long-term administration of large amounts of the drug [22]. In a pilot study of the usefulness of RU 486 therapy in women with advanced breast cancer, daily intake of 200 mg RU 486 for several weeks did not result in clinical or biologi-

Table 3. RU 486 use for fertility control: relevance of antiglucogenic effects

(1)	400 mg RU 486 increase plasma cortisol, ACTH, LPH
(2)	This increase is reversed by 1 mg dexamethasone
(3)	Reversal of Cushing's syndrome requires long-term (several weeks) treatment with large doses (≥ 10 mg/kg/days) of RU 486
(4)	Long-term administration of 200 mg/day RU 486 does not induce clinical or biological functional cortisol blockade
(5)	In approximately 1,000 women, large single dose administration has never been associated with clinical or biological symptoms attributable to functional cortisol blockade
(6)	In conclusion: at the doses recommended for fertility control antiglucogenic effect of RU 486 is clinically irrelevant

cal functional cortisol deficiency. Similarly, none of the women given the drug for fertility control purposes experienced symptoms attributable to cortisol blockade. This fact is probably related to the compensatory rise in ACTH and cortisol after RU 486 intake reversing the cortisol blockade. As a matter of fact, a study in normal men (Girard *et al.*, unpublished results) indicated that when giving 1 mg dexamethasone at 2.00 a.m., 2 h after ingestion of 400 mg RU 486, no rise in plasma cortisol is observed, thus showing the reversibility of cortisol blockade.

In summary, clinical trials confirm the efficacy and safety of RU 486, the first antiprogestin available, which is likely to become soon a new tool for fertility control.

REFERENCES

1. Teutsch G.: 11 Beta-substituted 19-norsteroids: at the crossroads between hormone agonists and antagonists. In *Adrenal Steroid Antagonism* (Edited by M. K. Agarwal). Walter de Gruyter, Berlin, (1981) pp. 77–101.
2. Philibert D., Moguilewsky M., Mary I., Lecaque D., Tournemine C., Secchi J. and Deraedt R.: Pharmacological profile of RU 486 in animals. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by S. J. Segal and E. E. Baulieu). Plenum Press, New York (1985) pp. 49–68.
3. McGinty D. A., Anderson L. P. and McCullough N. B.: Effect of local application of progesterone on the rabbit uterus. *Endocrinology* **24** (1939) 829–832.
4. Tachi C. and Tachi S.: Cellular aspects of ovum implantation and decidualization in the rat. In *Physiology and Genetics of Reproduction*, Part B (Edited by E. M. Coutinho and F. Fuch). Plenum Press, New York (1974) pp. 263–286.
5. Nilsson O.: Influence of progesterone on the mitochondrial size in the uterine glands of the rat, mouse, hamster and guinea-pig. *Acta endocr., Copenh.* **78** (1975) 349–352.
6. Secchi J. and Lecaque D.: Effects of progestins and antiprogestins on mitochondria in uterine glandular cells in the rat. A quantitative investigation. *Cell Tiss. Res.* **238** (1984) 247.
7. Secchi J., Lecaque D., Tournemine C. and Philibert D.: Histopharmacology of RU 486. In *The Antiprogestin Steroid RU 486 and Human Steroid RU 486 and Human Fertility Control* (Edited by S. J. Segal and E. E. Baulieu). Plenum Press, New York (1985) pp. 79–86.
8. Healy D. L., Baulieu E. E. and Hodgen G. D.: Induction of menstruation by an anti-progesterone steroid (RU 486) in primates: site of action, dose-response relationship, and hormonal effects. *Fert. Steril.* **4** (1983) 253–257.
9. Deraedt R., Bonnat C., Busigny M., Chatelet P., Cousty C., Mouren M., Philibert D., Pottier J., and Salmon J.: Pharmacokinetics of RU 486. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by S. J. Segal and E. E. Baulieu). Plenum Press, New York (1985) pp. 103–122.
10. Germain G., Philibert D., Pottier J., Mouren M., Baulieu E. E. and Sureau C.: Effects of an antiprogesterone agent (RU 486) on the time-course of the natural cycle and gestation in intact cynomolgus monkeys (*Macaca fascicularis*). In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by S. J. Segal and E. E. Baulieu). Plenum Press, New York (1985) pp. 155–167.
11. Moguilewsky M. and Philibert D.: RU 38486: potent antiglucocorticoid activity correlated with strong binding to the cytosolic glucocorticoid receptor followed by an impaired activation. *J. steroid Biochem.* **20** 271–276.
12. Herrmann W. L., Wyss R., Riondel A., Philibert D., Teutsch, G. Sakiz, E. and Baulieu, E. E.: Effet d'un stéroïde anti-progestérone chez la femme: interruption interruption du cycle menstruel et de la grossesse au début. *C.r. hebd. Séanc. Acad. Sci. Paris* **294** (1982) 933–938.
13. Baulieu E. E. and Ulmann A.: Antiprogesterone activity of RU 486 and its contragestif and other applications. *Human Reprod.* **1** (1986) 107–110.
14. Bendel R. P., Williams P. P. and Butler J. C.: Endometrial aspiration in fertility control. A report of 500 cases. *Am. J. obstet. Gynec.* **125** (1976) 328–332.
15. Bygdeman M. and Swahn M. L.: Progesterone receptor blockage. Effect on uterine contractility and early pregnancy. *Contraception* **31** (1985) 45–51.
16. Schaison G., George M., Lestrat N., Reinberg A. and Baulieu E. E.: Effects of the antiprogesterone steroid RU 468 during mid-luteal phase in normal women. *J. clin. Endocr. Metab.* **61** (1985) 484–489.
17. Cabrol C., Bouvier d'Yvoire M., Mermet E., Cedar L., Sureau C., Baulieu E. E.: Induction of labor with mifepristone after intra-uterine fetal death. *Lancet* **2** (1985) 1019.
18. Frydman R., Taylor S., Fernandez H., Pons J. C., Forman R. G. and Ulmann A.: Obstetric indications of mifepristone (RU 486). (Submitted for publication.)
19. Gaillard R. C., Riondel A., Muller M. F., Herrmann W. and Baulieu E. E.: RU 486: a steroid with antiglucocorticosteroid activity that only disinhibits the human pituitary–adrenal system at a specific time of day. *Proc. natn. Acad. Sci. U.S.A.* **81** (1984) 3879–3882.
20. Bertagna X., Bertagna C., Luton J. P., Husson J. M. and Girard F.: The new steroid analog RU 486 inhibits glucocorticoid action in man. *J. clin. Endoc. Metab.* **59** (1984) 25–28.
21. Gaillard R. C., Poffet D., Riondel A. M. and Saurat J. H.: RU 486 inhibits peripheral effects of glucocorticoids in humans. *J. clin. Endoc. Metab.* **61** (1985) 1009–1011.
22. Nieman L. K., Chrousos G. P., Kellner C., Spitz I. M., Nisula B. C., Cutler G. B., Merriam G. R., Bardin C. W. and Loriaux D. L.: Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J. clin. Endocr. Metab.* **61** (1985) 536–540.