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RU486 (MIFEPRISTONE): Mechanisms of Action and Clinical Uses

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ABSTRACT

RU486 (mifepristone) has proved to be a remarkably active antiprogesterone and antiglucocorticosteroid agent in human beings. The mechanism of action involves the intracellular receptors of the antagonized hormones (progesterone and glucocorticosteroids). At the molecular level, the most important features are high binding affinity to the receptor, interaction of the phenylaminodimethyl group in the 11β-position with a specific region of the receptor binding pocket, and RU486-induced transconformation differences in the ligand-binding domain. These particularities have consequences at different steps of the receptor function as compared with agonists. However, the reasoning cannot be limited to the RU486-receptor interaction, and, for instance, there is the possibility of a switch from antagonistic property to agonist activity, depending on the intervention of other signaling pathways. It would be desirable to have derivatives with only one of the two antagonistic properties (antiprogestin, antiglucocorticosteroid) in spite of similarities between steroid structures, receptors involved, and responsive machineries in target cells. Clinically, the RU486-plus-prostaglandin method is ready to be used on a large scale and is close to being as convenient and safe as any medical method of abortion may be. The early use of RU486 as a contragestive as soon as a woman fears a pregnancy she does not want will help to defuse the abortion issue. Research should now be conducted to define an efficient and convenient contraceptive method with RU486 or other antiprogestins. The usefulness of RU486 for obstetric indications, including facilitation of difficult delivery, has to be assessed rapidly. Gynecologic trials, particularly

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in leiomyomata, should also be systematically continued. The very preliminary results obtained with tumors, including breast cancers, indicate that further studies are necessary.

INTRODUCTION

The aim of reversibly suppressing hormonal activity is as old as the hormone (from the Greek word meaning to excite) concept itself. Following the demonstration of the pivotal importance of hormone receptors in hormone action and the partial elucidation of their physicochemical structure and mechanism of action (1, 2), research into means of interrupting receptor function has come to the front line of the endocrinology field.

The interaction of a hormonal ligand with its cognate receptor leads to the simple method of antagonizing hormone-dependent action by replacing the natural ligand with an analog that precludes hormone binding to the receptor and that does not itself activate the receptor. Steroid hormones, whose structure is relatively rigid and whose many analogs can be synthesized, have been at the forefront of such antihormone research.

We previously summarized how more than 20 years of research—particularly on the synthesis of glucocorticosteroid analogs and on estrogen, antiestrogen, and steroid receptor biochemistry (3, 4)—has led to the synthesis and testing of RU486 (mifepristone) (Figure 1) and to its first human clinical use, both as an antiprogesterone in the luteal phase of the cycle and for early pregnancy interruption (5, 6), and as an antiglucocorticosteroid (6–9).

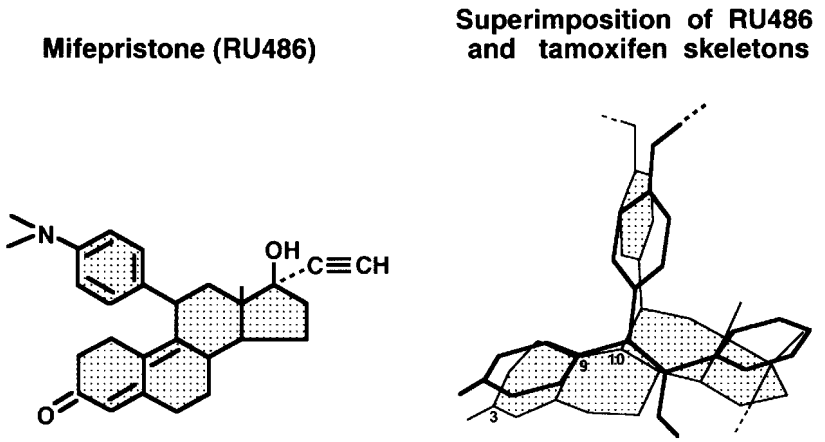

Figure 1 Formula and X-ray crystallographic structure of mifepristone (RU486): 17β-hydroxyl-11β-(4-dimethyl-aminophenyl-1)-17α-(prop-1-ynyl)-estra-4,9-diene-3-one and the antiestrogen tamoxifen (179; JP Mornon, unpublished data).

Several reviews have already treated the scientific and medical aspects of this antisteroid (6, 10–15). Here, we summarize the basic data and review some recent results related to its molecular and cellular mechanisms of action and its medical use. Not only has RU486, because of its efficacy and safety, been the first active antagonist to progesterone and glucocorticoid usable in humans, it also addresses medical and social issues of primary importance.

MOLECULAR AND CELLULAR ASPECTS OF THE STEROID ANTAGONISTIC ACTIVITY OF RU486

Basically, events that mediate antagonism of a steroid analog are dependent on the steroid structure and bioavailability, and on the appropriate receptor's ability to bind the steroid analog and to undergo a ligand-induced transconformation leading to inactivation of one or several steps of the receptor's mechanism of action.

Steroid Structure and Metabolism

The main structural characteristic of RU486 (code name and number, Roussel-Uclaf 38486; generic name, mifepristone) is the phenyl-aminodimethyl group perpendicularly grafted onto the 11β-position of the steroidal skeleton (Figure 1): All currently known antiprogestins and antiglucocorticosteroids produced by Roussel-Uclaf, Schering Berlin, Organon, and other groups have the same basic structure, which, upon binding, reversibly maintains the receptor in an inappropriate conformation.

RU486 binds with high affinity (K of dissociaton $\leq 10^{-9}$ M) to both the progesterone receptor (PR) and the glucocorticosteroid receptor (GR). There exists no pure antiprogestin compound. The antiglucocorticosteroid effect of RU486 is not useful for pregnancy termination, but conversely, this is not medically inconvenient at the usual single dose of ≤600 mg (16). Nevertheless, it does limit long-term use, so efforts have been made to find new derivatives with dissociated antagonist activities (17, 18).

A relative decrease in antiglucocorticosteroid activity has been obtained with a tetrahydrofuran ring at the C17α/β-position (RU46556, RU49295, ORG31710, and ORG31806) (19), with a modified 17β-side chain (ZK98734, lilopristone), or with a 17α-side chain (ZK97397) (20), and after inversion of the D ring upon epimerization at C13 (ZK98299, onapristone[1]) (21). Reciprocally, antiglucocorticosteroid compounds with relatively lower antiprogesterone activity than RU486 have been obtained by inversion of substituents

[1] The development of this compound has recently been stopped because it provokes signs of hepatotoxicity in human beings.

between the 17α and β position (RU40016) or by grafting the phenyl group onto the 10β-position (RU43044).

The androgen receptor (AR) has a relatively low but demonstrable affinity for RU486 (with a corresponding antiandrogen effect observed in laboratory animals), but the mineralocorticosteroid receptor (MR) has no affinity (an interesting property considering the closeness of the MR and the GR in terms of structure and steroid binding), nor does the estradiol receptor (ER).

Besides the binding of RU486 to steroid receptors and formation of a complex that directly modifies the response of the cellular machinery to the endogenous hormone, the distribution and metabolism of the steroid analog influences its efficiency. RU486 is readily absorbed by the oral route and the peak serum concentration occurs within 1 h of administration. Receptors have lower affinity for demethylated and hydroxylated (in the 17α-side chain) metabolites, which are less active than RU486, but their abundance allows them to participate in the global action of the compound. In humans and some other primates, RU486 binds to plasma orosomucoid, a particularity responsible for a long half-life, strengthening the antisteroid effect. This effect is not observed with RU40555 and onapristone. The analog RU43044 is heavily metabolized and is not active after administration to whole animals, but locally it retains its antiglucocorticosteroid efficacy.

Steroid Receptor Structure and Ligand-Induced Transconformation

The steroid hormone receptors are intracellular proteins that mediate the genomic responses to the hormones. They belong to the superfamily of nuclear receptors and are hormone-dependent transcription factors positively or negatively regulating a large set of genes. Steroid receptor molecules consist of different domains (Figure 2) (22–24): The N-terminal domain carries a transactivation function called TAF1 or t1 and is followed by the DNA binding domain (DBD), which mediates the interaction of receptors with specific DNA sequences called hormone regulatory elements (HRE), usually present in the promoter upstream of the 5′ coding region of hormone-regulated target genes. Separated from the DBD by a hinge region, the ligand binding domain (LBD) contains a second transactivation function (TAF2), the activity of which is dependent on hormone binding. The LBD is also involved in the formation of a multiprotein complex principally made up of molecular chaperons such as hsp90 and immunophilin, in which the receptor is maintained in a biologically inactive form in the absence of hormone. Nuclear localization signals and homodimerization regions of the receptor protein are also shown in Figure 2.

Upon binding, progestin and antiprogestin do not contact the same amino acids in the binding cavity of the PR. Agonist binding requires amino acids to

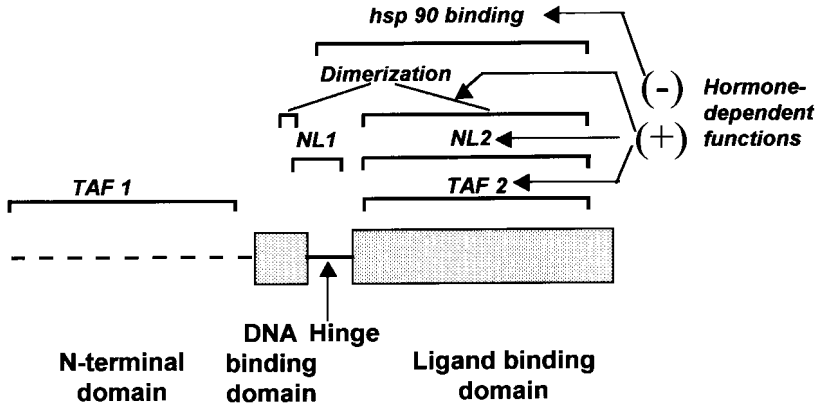

Figure 2 Functional domains in steroid hormone receptors. TAF, Transcriptional activation function; NL, nuclear localization signal.

be located at the C-terminal end of the PR, which is not required for antagonist binding: It has been proposed that this partly involves a so-called 11-b pocket, implicating amino acids in the N-terminal region of the LBD. Truncation of the 42 C-terminal amino acids of human PR (hPR) or punctual mutations in the GR C terminus give receptor mutants that no longer bind progesterone or glucocorticosteroid agonists, respectively, but that allow the antagonist to bind and function as an agonist (25, 26).

Subtle modifications in the amino acid sequence such as those observed between receptor species and between PR isoforms or due to mutations, inherited or experimentally introduced, in the receptor molecules induce variations in antagonist binding and/or activity. RU486 and several parent compounds do not bind to the chick PR (27), because of an exchange of a Gly residue (575 in the human and most mammalian PR) for a Cys in chick PR (28). Chick PR chimeras, obtained by exchanging LBD segments with corresponding hPR segments, recognize the hPR antagonists RU486 and RU39115 (without the N-dimethyl group) as partial and complete agonists, respectively (29).

Following steroid binding, receptors undergo a conformational change that is probably crucial for receptor interaction with cellular targets. Antagonist binding seems to trigger a transconformation of the hormone binding domain that differs from that observed with agonist binding. A number of physicochemical techniques such as those for determining the susceptibility to proteolytic enzymes, identifying differential antibody binding, and measuring changes of electrophoretic mobility (30–32) have been used along with mutagenetic approaches (25, 26) to demonstrate differences located at the extreme

C terminus of the protein between complexes of receptor with agonist and antagonist.

Thus, both chemical differences in the steroid and modifications of the receptor by genetic or biochemical processes can change the final response. This may be of importance for explaining different activities of a given compound, including RU486, according to the physiological status (interference by other signaling pathways) or pathological states (cancers with receptor mutations).

Antisteroid Effect at Different Steps of Hormone Action

Complexes made by the receptor and the steroid participate in a sequence of steps that are involved in the response of the target cell to the hormone. Alteration of one or several of these steps may finally impede or modify the transcriptional response of the receptor. Commencing with the binding of steroid to the ligand-free receptor, Figure 3 schematically represents four of these steps. These consist of dissociation of the initial heterooligomeric receptor complex, probably coupled to steroid-induced transconformation, receptor dimerization, receptor binding to DNA, and regulation of transcription activation functions.

HORMONE-INDUCED DISSOCIATION OF THE HETEROOLIGOMERIC COMPLEX

The GR and the PR, like other steroid hormone receptors, form an inactive, non–DNA-binding heterooligomeric, the so-called 8S complex that includes receptor-associated proteins such as the heat-shock protein hsp90 and the immunophilin FKBP59/HBI (33–35). Binding of the hormone and the resulting transconformation favors heterooligomer dissociation, and the receptor acquires DNA binding properties. In vitro, RU486 and other 11β-substituted antisteroids stabilize the hsp90-containing heterooligomeric complex formed with the GR (36–39) and rabbit PR (40), thus impeding or slowing down the formation of the activated receptor form observed after binding an agonist. Such a stabilization was not found with the human PR (41).

Consistent with stabilization of the heterooligomeric complex as a part of the antagonistic mechanism (and maintenance of the complex in the cytoplasmic compartment in some cell lines) are the observations of higher cytoplasmic concentrations of RU486-GR complexes than agonist-receptor complexes in target cells. More recently, a predominant cytoplasmic distribution was also reported for the ZK98299-PR complex (42).

HOMODIMERIZATION, HORMONE RESPONSE ELEMENT BINDING, AND CHROMATIN REMODELING

Homodimerization of PR and GR is observed upon their binding to the two halves of the same palindromic element, GRE/PRE. No

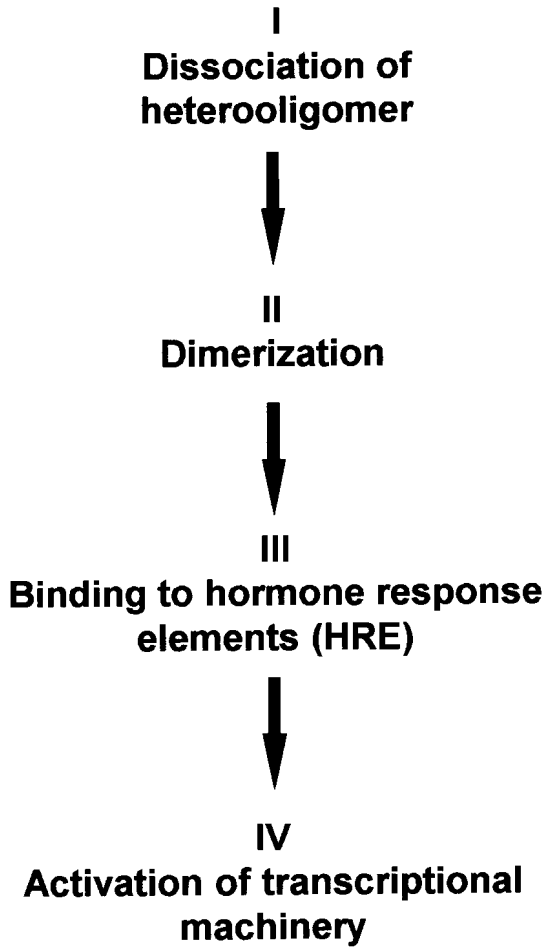

Figure 3 Main steps in the mechanism of action of steroid hormone receptors.

steroid antagonist, and this applies to RU486, has been found that precludes the dimerization in solution (in the absence of DNA) (42–46), which occurs in vitro as soon as heat-shock proteins are dissociated from the receptor.

Complexes of PR or GR with RU486 can bind to GRE/PRE (RU486-PR complex has even higher affinity than that of progesterone-PR complex), but they are unproductive and RU486 is defined as a type I antagonist. Interestingly, complexes with ZK98299 or RU43044 (GR) do not have the ability to bind to HREs (46, 47), and they are defined as type II antagonists. In competition experiments, it has been shown that these steroids inhibit the DNA bind-

ing of the PR, which is induced by progestins and type I DNA-binding antagonists.

In fact, recent data indicate the possibility of dimerization of one monomer-binding agonist and the other antagonist (or one binding RU486 and the other ZK98299) and a subsequent lack of HRE binding. This result may in part explain the strong antihormone efficacy over and above that explainable by the ligand binding affinity and the number of occupied receptor sites. The greater efficacy of RU486 over ZK98299 possibly results from the occlusion of DNA target sites by antagonist-receptor complexes so that not only are receptor molecules rendered inactive by the antagonist, there are also fewer target sites for agonist-bound receptors. Type II antisteroids may induce an alteration of the DBD structure, with a loss of DNA binding ability and of the resulting hyperphosphorylation of the receptor (46, 48). The DNA binding of RU486 and type I antagonists is consistent with an agonistic effect of RU486 observed under certain physiological conditions (see below), whereas the non–DNA-binding antisteroids (type II) never demonstrate an agonistic effect.

Analysis of the chromatin structure by in vivo footprinting of an integrated gene (an endogenous TAT or MMTV reporter gene) has indicated that progestin or glucocorticosteroid agonists can induce remodeling of the chromatin structure and, as a consequence, receptor binding to DNA and recruitment of transcription factors, whereas antagonists inhibit these effects (49, 50). Differences in the efficiency of PR and GR according to cell variants suggest a role for chromatin in providing selectivity between these two steroid receptors (51–53).

PROCESSES INVOLVED IN TRANSACTIVATION GRE/PRE are regulatory sequences often located in the promoter upstream of the coding sequence of the regulated gene. They allow the receptor dimer to be placed in an appropriate position for interaction with transcription factors that control gene transcription via RNA polymerase activity.

The activation of gene transcription is mediated by at least two transcription activation functions of the receptors (22, 54). TAF2, in the LBD, is activated by agonist binding but not by antagonists, as demonstrated with RU486, for the PR (55) (see Figure 4). When TAF2 is inhibited, TAF1, located in the N terminus of the receptor, may still operate, but its activity depends on receptor and promoter types and cell-specific factors (55, 56). It follows that the antihormone may show some agonistic activity following binding of antihormone-receptor complex to DNA (47, 55, 57). A tridimensional study of the LBD of the retinoid X hormone receptor (RXR) has indicated a particular α-helix arrangement and suggested how ligand binding may modify the C-terminal transactivation domain, allowing it to interact with an intermediary transcrip-

tion factor (58). These structural data agree with a model that proposes that only agonist can induce a functional LBD transactivation domain, possibly by relieving a repressor activity located at the C-terminal tail of the receptor (2) (Figure 4). Synergy between TAF1 and TAF2 may also be impeded by the antagonist (59).

In the repression of gene expression by glucocorticosteroid, several mechanisms have been suggested (60). H-R can bind to a particular palindromic HRE (negative HRE or nHRE) or to a half-palindromic HRE and act as a negative regulator through an altered conformation (61) or by hindering the appropriate binding of an essential transcription factor. In many cases, no GRE was found in the promoter of negatively regulated genes, and repression results from the direct binding of the GR to a transcriptional activator or intermediary factor. Such a situation was observed in the mutual transrepression observed between GR and AP1, a transcription factor involved in cell growth and made of two proteins of the *fos* and *jun* family (see below). Often, agonist-mediated repression is suppressed by antagonists, including RU486; alternatively, there are examples of partial or total agonist behavior of RU486 (61, 62; also, see below).

Additional Complexity

The existence of receptor isoforms (for instance for the PR) may add to the complexity of hormone action. Two isoforms of PR are known. The longer form (hPR_B) contains an additional N-terminal transactivation region, so it has a greater transcriptional efficacy than the hPR_A form in the presence of the agonist. The hPR_A form exhibits a transdominant negative activity, whether it is binding RU486 or an agonist, not only toward hPR_B but also toward other

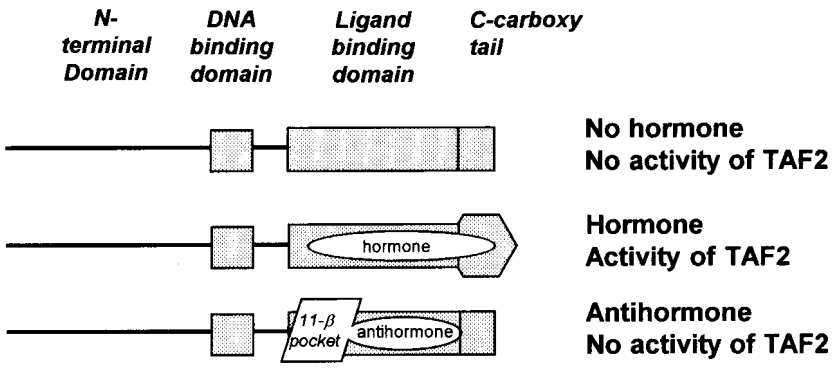

Figure 4 Schematic binding and activity of steroid hormone and antihormone.

steroid receptors (GR, MR, AR, and ER), the binding of hPR_A to PRE/GRE being not required (63, 64). This could explain some observed antiestrogen effects of RU486. The blocking of the other steroid receptor functions may involve a specific mechanism (60).

Other signaling pathways, initially unrelated to steroid action, may switch an antagonist steroid into an agonist. Each cell type has a particular signaling network involving phosphorylation cascades. Activation of protein kinase PKA (cAMP dependent) and PKC pathways often stimulates (or modulates) GR and PR activities (an effect partially inhibited by RU486). Surprisingly, activation of PKA unveils a moderate agonist activity of RU486 but not of ZK98299 and other non–DNA-binding antagonists (65), as if DNA binding were required. In the case of hPR_A, no antagonist/agonist switch was observed, suggesting that at least weak agonist activity is necessary for cAMP synergism. PKA does not increase the phosphorylation of the receptor, but the modulation of receptor activity may result from phosphorylation and activation of important transcription factor(s).

There is also the down-regulation of the corresponding steroid receptor by agonist, mainly resulting from both a decrease in the receptor protein half-life and mRNA synthesis. The receptor may repress synthesis of its own mRNA by binding to its own gene. Although poorly documented, RU486 may induce down-regulation, as observed for agonists (66, 67). In addition, whether the above events depend on the period in the cell cycle remains controversial.

If we examine cellular responses in intact animals (not only in cloned cells in culture), we must take into consideration the complex interactions that characterize the physiological state. For example, the antiprogesterone effect opens the door to an unopposed estrogen activity in estradiol receptor–containing cells, but RU486 can have an inhibitory effect on pituitary hormone glycoprotein secretion, thereby reducing steroidogenesis in the sexual glands, whereas by its antiglucocorticosteroid activity it removes inhibition of ACTH production (thus increasing the production of sex hormone precursor), and the compound may have an antiestrogen effect on endometrial growth by a non–receptor-mediated mechanism (68). For clinical use of RU486, when the health state is not primarily dependent on a single hormone, both specific cellular and physiological complexities must be taken into consideration. We have already indicated (3) how lucky we were not to know of these complex interactions before testing RU486, which worked so well on the basis of a "simple" hypothesis (5).

In summary, the mechanism of action of RU486 involves the receptors of the antagonized hormones: The most important notions are high-affinity molecular mechanisms involving interaction of the phenyl-aminodimethyl group in 11β-position with a specific region of the receptor binding pocket in LBD,

the differences between GR and PR in terms of transconformation upon RU486 binding, and a possible switch of antagonistic property to agonist function depending on receptor structure and intervention of other signaling pathways. From this complexity, it should not be surprising that RU486 administration results in different effects in some patients, particularly during long-term treatment of different kinds of cancer. Probably, as for other hormone antagonists, the effects of RU486 are only straightforward in cases where the effect of one particular hormone is preponderant (progesterone in pregnancy, cortisol in Cushing syndrome), whereas in any other cases the situation results from alterations in a number of different regulatory factors.

CLINICAL USES OF MIFEPRISTONE (RU486)

Up to now, the clinical uses of RU486 have mainly been based on its antiprogesterone activity. During the luteal phase of the nonfertile cycle and during early stages of pregnancy, progesterone activity is dominant, and its interruption rapidly provokes alteration of the endometrium/decidua alteration, which is easy to detect. The first trial, performed in Geneva in 1982 (5), indicated the actual antiprogesterone activity of RU486 in human beings, and it was followed by many clinical studies mostly in the gynecologic and obstetrical fields.

Use of RU486 for Voluntary Early Pregnancy Termination

Numerous studies have been aimed at defining the optimal dose and schedule for administration. Maximal efficiency was obtained with a single oral intake (rather than with repeated administration), at a dose of 600 mg, for pregnancies of up to 42 days of amenorrhea (beginning the first day of the last menstrual period) (69–71). Even though biologically remarkable, the results (complete eventless interruption in 80% of the cases) were not judged acceptable in view of the 95% efficacy of suction-curettage methods for pregnancies at the same age. Efficacy was greatly improved by the addition of a small dose of a prostaglandin analog, given 36 to 48 h after RU486 (see below) (72). It reached 95%, mostly because of the stimulation of myometrium activity, with coordinated contractions of augmented amplitude and frequency. In the pregnant uterus, RU486 administration leads to an increase of prostaglandin synthesis, which, in addition to a decrease of prostaglandin metabolism, accounts for the increased sensitivity of the myometrium to a small amount of prostaglandin analog (73). It was found that treatment with a single 600-mg dose of RU486 given to women pregnant for fewer than 50 days of amenorrhea, and followed 36–48 h later by a small dose of a prostaglandin analog, constitutes a medical alternative to vacuum aspiration with at least similar efficacy.

A large-scale study (74) provided accurate information on the efficacy and safety of the association of RU486 and a prostaglandin. The trial included more than 16,000 women, with amenorrhea up to 50 days in 86.4% of the patients, between 50 and 56 days in 9.3%, and more than 8 weeks in 4.3%. Of the 571 patients (3.6%) who did not receive a prostaglandin, 445 had already expelled and did not need it, as indicated in the protocol (126 women did not receive prostaglandin despite the absence of expulsion and were considered as protocol violations). Only 0.3% of the patients did not experience uterine bleeding. Overall, the median duration of bleeding was eight days. In 89.7% of the cases, bleeding lasted for 12 days or less. The uterine bleeding was significant enough to necessitate vacuum aspiration or dilatation and curettage in 0.8% of the cases. In 11 women (0.1%), a blood transfusion of 1–3 U was performed. In a few patients, bleeding lasted for significant periods of time (up to 60 days), but it was minimal. At least one adverse event each was reported in 1380 patients (8.5%), all of which were benign: uterine cramps outside the 4-h period following prostaglandin (1.6%), malaise (1.2%), fatigue (1.1%), headache (1.0%), and skin rash (0.2%). Infectious complications were rare, with vaginal discharge in 0.2%, endometritis in 0.2%, salpingitis in 0.03%, and isolated fever in 0.3%. Noticeable cardiovascular side effects were reported in four patients, consisting of three cases of severe hypotension after prostaglandin (treated by infusion by macromolecular solute) and one case of acute myocardial infarction after injection of the synthetic prostaglandin sulprostone (0.5mg) in a 38-year-old smoker.

After the drug was marketed in France and used in more than 90,000 cases, two additional myocardial infarctions occurred, after sulprostone injection, one of which was fatal. This led the French Health authorities to impose additional restrictions on the use of the method: smoking, age above 35 years, and suspicion of cardiovascular disease became contraindications to the method. Sulprostone is a PGE2 derivative, whereas gemeprost (administered in vaginal pessary), for which no cardiac complications have been reported, is a PGE1, and the route of sulprostone administration, injection, may cause a peak effect that does not occur for vaginal or oral preparations. Therefore, alternative solutions have been investigated. Misoprostol, an oral preparation of a PGE1 analog used for many years in different medical indications, was proved to be as efficient as sulprostone or gemeprost after a 600-mg RU486 administration. A large-scale trial has followed the pilot study (75), and since 1992, RU486 has been approved in France in combination with 400 μg of misoprostol or 1 mg of gemeprost (vaginal suppository). With more than 50,000 additional patients, no severe cardiac side effects have been reported so far, and the success rate is over 95%. A study was conducted by Roussel-Uclaf investigators to evaluate the influence of the age of pregnancy on the outcome

of the method. It was found that the efficacy of the RU486 plus misoprostol (400 or 600 mg) method is markedly decreased for pregnancies above 56 days of amenorrhea (Table 1) (A Ulmann, unpublished results).

Overall, based on available data on the safety of pregnancy termination by suction, it appears that if both medical and surgical methods have similar rates of severe complications (necessitating blood transfusion and/or hemostatic dilatation and curettage), the medical method gives fewer infectious and mechanical complications.

One point of interest is how the rate of persisting pregnancies can be kept as low as possible. The lowest rate is observed with the highest dose of RU486 (600 mg) for the shortest-term pregnancies. To maintain the efficacy of the method with a lower dose of RU486, for example, with the 200 mg used in the World Heath Organization–sponsored studies, it must be administered with a strong prostaglandin such as gemeprost (a suppository, which is more painful than oral misoprostol). Administration of misoprostol with 600 mg of RU486 and with 200 mg of RU486 results, respectively, in 19 and 45 pregnancies per 30,000 going to term. This is important given the potential teratogenicity of prostaglandin (76) and, by definition, the uncertainty about RU486 (77–81). In any case, it should be kept in mind that no drug schedule results in 100% termination; this is also true of suction, a fact that both patients and prescribers have to be fully aware of.

After several years of use in France, the United Kingdom, and Sweden, it can be concluded (*a*) that the actual efficacy and tolerance of RU486 followed by a prostaglandin analog, in particular misoprostol, appears comparable to suction or other surgical techniques to terminate pregnancy below 50 days of amenorrhea; (*b*) that the recommended protocol appears optimal, including

Table 1 Influence of RU 486, alone or followed by misoprostol, in the rate of persisting pregnancies.

Dose		Age (days of amenorrhea)	N	Persisting pregnancies (%)
RU486[a] (mg)	Misoprostol (μg)			
600	0	≤49	104	8.7[b]
600	400	≤49	1208	1.5[b]
600	400/600	50 to 63	621	3.1[b]
400	0	≤49	157	15.3[b]
200	0	≤49	30	26.7[b]
200	200/400	≤56	21	9.5[c]
200	600	≤56	100	3.0[d]

[a]RU486:mifepristone.
[b]Roussel-Uclaf, data on file.
[c]Ref. 156.
[d]Ref. 157.

with respect to the dose of RU486; and (*c*) that the distribution and prescription procedures recommended by the manufacturer have to be adequately followed. Administration of RU486 and prostaglandin should be medically supervised because the RU486 treatment does not affect ectopic pregnancies (82), which need to be detected as soon as possible.

Obstetrical Uses of RU486

RU486 FOR SECOND-TRIMESTER PREGNANCY TERMINATION Second-trimester pregnancy termination can be achieved through surgical means (dilatation and evacuation) or medical treatment (prostaglandin). Prostaglandins are efficient but the effective dose level causes many, sometimes severe, side effects. The report that RU486 treatment sensitizes the myometrium to the action of prostaglandin has led to trials in which RU486 prior to prostaglandin was evaluated in order to decrease the doses of administration of prostaglandin (and thus side effects) and accelerate expulsion. It was shown that RU486 significantly decreases the dose of prostaglandin needed and shortens the time to expulsion, decreasing length of hospitalization. It was even more efficient than a laminaria tent when used to prepare gemeprost-induced abortion.

RU486 FOR EXPULSION AFTER INTRAUTERINE FETAL DEATH A placebo control study, following an early pilot trial (83), indicated that expulsion takes place significantly earlier in patients given RU486 than in those given a placebo (84). RU486 is now registered in France for this indication.

CERVICAL RIPENING WITH RU486 PRIOR TO SURGICAL ABORTION Cervical maturation, as demonstrated by an increase in the cervical diameter and a decrease in cervical resistance to mechanical dilation, is favored by RU486 and includes increase of water and hyaluronic acid content and collagenase activation. In humans, data observed during first- and second-trimester pregnancy termination and expulsion after fetal death also indicated that RU486 can induce cervical maturation. Several placebo-controlled studies were performed to evaluate the efficacy of RU486 in cervical ripening prior to vacuum aspiration. Results indicated a significant effect of RU486, with an increase in cervical diameter when the compound is given 24 h prior to measurement of the cervix. The increase in cervical diameter was linearly related to the dose, up to 400mg. The duration of the subsequent vacuum aspiration was significantly inversely related to the dose. In all cases, the mechanical resistance was reduced after RU486. In comparison with gemeprost (a 1-mg pessary) given 3–4 h prior to calibration, the increase in cervical diameter induced by RU486 was the same or greater (85, 86). However, abdominal pain was significantly more frequent after gemeprost (43%) than after RU486 (10%). The antisteroid is better

tolerated, but it has to be given 36–48 h prior to surgical procedure as compared with 3–4 h for prostaglandin. Blood loss during vacuum aspiration was identical after RU486 or placebo, except in two series where blood loss was significantly lower in RU486-treated patients. Total bleeding, duration and amount, was comparable in RU486- and placebo-treated patients (85, 87–89).

RU486 FOR LABOR INDUCTION A decrease in progesterone activity occurs during parturition, but its precise role in successful delivery is unclear, particularly in primates (including humans) where it does not seem to be the primary event. In rats, RU486 can synchronize delivery, and in cattle, it is very efficient in facilitating parturition. In rhesus monkeys, it induces uterine contractions and enhances the myometrial sensitivity to oxytocin. Adrenoreceptors are unchanged in the myometrium. It is not known if RU486 increases gap junctions between myometrial cells in women as it does in rats.

RU486 crosses the placental barrier (90, 91), and therefore, it is mandatory to evaluate the possible consequences of cortisol antagonism in the newborn. Preliminary trials (92) for cases of postdate pregnancies or other medical indications for labor induction, summarized in Table 2, show that RU486 is able to induce labor and is well-tolerated by both newborn and mother. The number of hypoglycemic episodes up to 48 h after birth was identical in RU486- and placebo-treated groups. Other studies are in progress to determine the minimal dose of RU486 necessary to induce labor. Therefore, RU486

Table 2 Induction of labor with RU 486 (200 mg/d on day 1 and day 2) or a placebo[a]

Determinants	RU486 (N = 57)	Placebo (N = 55)	P
Women with spontaneous onset of labor	31 (54.4)	10 (18.2)	< 0.001
Interval between day 1 and onset of labor (hs, SD)	51.7 (26.7)	74.5 (39.5)	< 0.001
Mean (SD) total dose (IU) of oxytocin[b]	2.0 (2.2)	4.7 (3.0)	< 0.0001
Number of cesarean sections	18	18	NS
Neonatal tolerance: N(%) of infants with Apgar score below 7			
at 1 min	5 (8.8)	4 (7.3)	NS
at 5 min	0	0	
with umbilical vein pH below 7.20	4 (7.0)	3 (5.4)	NS

[a]From Ref. 92. N, Number of women (% in parenthesis); P, α probability
[b]For women delivered vaginally.

appears to be safe and efficient for inducing labor when the continuation is a risk for the fetus, mother, or both. More studies are necessary to define the optimal therapeutic schedule and to assess the consequences of neonatal exposure to RU486 on a large-scale basis. Until these results are available, the use of RU486 for convenience should be forbidden.

Contragestive and Contraceptive Uses of RU486

The use of RU486 as a contraceptive (Figure 5) and a contragestive agent has been assessed, the latter term designating all treatments operating over a period of four to five weeks postfertilization (3, 93). Six methods have been evaluated.

EMERGENCY POSTCOITAL CONTRACEPTION Two studies (94, 95) have suggested that RU486, given as a single 600-mg dose within 72 h following an unprotected intercourse, is at least as efficient as a high dose of estrogen or estro-progestative, and better tolerated. Larger trials are under way to confirm these results, to define the optimal dose of RU486, and to evaluate its consequences on menstrual cyclicity.

OCCASIONAL LATE LUTEAL-PHASE ADMINISTRATION In two studies (96, 97), it has been demonstrated that RU486 could be used as a luteal-phase occasional contraceptive, when 400 or 600 mg are given once or twice on the day of (or the day before an) expected menses in women at risk of pregnancy. The efficacy of RU486 was the same as in early pregnancy termination (approximately 80% in women with elevated beta-hCG).

MONTHLY PREMENSTRUAL (LATE LUTEAL PHASE) ADMINISTRATION Giving RU486 approximately two days before the expected day of menses over several

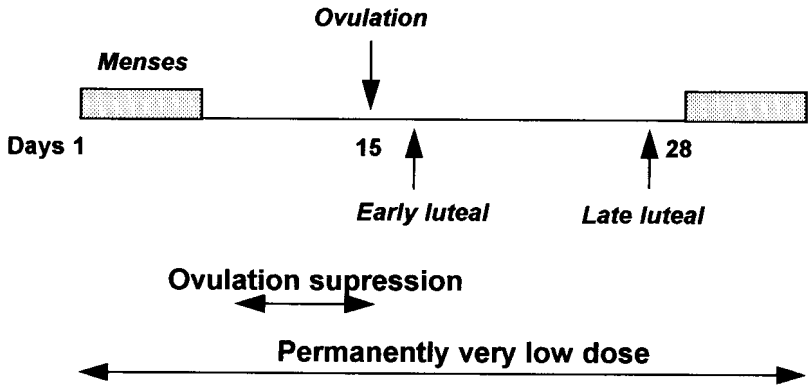

Figure 5 Contraceptive use of RU486.

months proved unsuccessful (98) because the failure rate (20%) renders the administration of RU486 alone unpracticable on a regular monthly basis, and also because, at the doses used, RU486 induced cycle irregularities with retardation of the next ovulation. The possibility that lower doses of RU486 combined with prostaglandin may circumvent these difficulties is currently under evaluation.

EARLY LUTEAL-PHASE ADMINISTRATION Progesterone acts on the endometrium to prepare for implantation, and experiments in animals have shown that endometrial receptivity and embryo implantation can be modified by antiprogestins (99–103). RU486 has been shown to induce epithelial cell apoptosis.

Treatment with twice 200 mg of RU486 was performed on women on days 2 and 3 post-luteinizing hormone surge who had had unprotected intercourse at least once during the previous three days, one day after ovulation (104). Of over 157 cycles, only one pregnancy occurred. The main drawback of such an anti-implantation method is its impracticability, necessitating the detection of ovulation. In any case, larger samples are necessary in order to have a precise quantitation of the efficacy of the method.

OVULATION SUPPRESSION A number of observations demonstrate that progesterone contributes to ovulation. The administration of RU486 during the follicular phase delays or suppresses ovulation, an effect that may be due to antiprogesterone action in ovaries, and to a suppressive effect of RU486 on gonadotropins (105–116). This may be obtained even with very low doses of RU486 (117). Thus, a new method of estrogen-free contraception could be proposed. However, such a method raises the question of a prolonged estrogen activity, since, contrary to what has been reported for monkeys, daily administration of RU486 (200 mg) for several months may be associated with endometrial hyperplasia (118). It has been suggested that this problem can be avoided by using RU486 and a progestin sequentially (119), but the contraceptive activity of such a scheme remains to be evaluated.

ENDOMETRIAL CONTRACEPTION WITH DAILY DELIVERY OF VERY LOW DOSE OF RU486 Continuous exposure to a very low dose of RU486 (i.e. ≥0.5 mg/day in women) may prevent implantation and possibly even fertilization without any change in ovulation and in estrogen and progesterone secretion pattern, as observed in the guinea pigs and in baboons (99, 120). In women, it is necessary to determine the maximal dose that does not suppress or delay ovulation but that can effect on the endometrium. Such a dose should certainly be well below 1 mg/day because this dose has been show to suppress ovulation in some women (~20%). If such a dose can be found, as preliminary data indicate (121; M

Bygdeman, personal communication), and if the contraceptive effect is proved, such administration could become a very promising estrogen-free method. The action of RU486 of interfering with sperm may be involved in this effect on fertilization (122, 123).

MALE CONTRACEPTION Progesterone increases calcium uptake by human sperm and favors the acrosome reaction (124). There is probably a membrane receptor mediating this action, as in the progesterone-induced reinitiation of meiosis in *Xenopus laevis* oocytes (125). A preliminary report of a contraceptive effect of RU486 in male monkeys with a decrease in sperm count has not yet been confirmed. Recently, a negative effect on calcium uptake by RU486, as opposed to the positive effect of progesterone, has been described with human sperm (123). It was suggested that this effect takes place at the membrane level. Whether RU486 may be useful as a novel approach to male contraception remains an open question

Other Clinical Uses of RU486 as an Antiprogestin Agent

USE OF RU486 FOR ENDOMETRIOSIS AND FIBROIDS Studies suggest that RU486 may prove useful for the treatment of endometriosis at a dose of 50 mg/day (126). Dramatic symptomatic relief was observed, although no clear-cut pathological improvement was reported. Daily administration of 50 or 25 mg of RU486 for three months induced a 50% regression of uterine leiomyomatas. The mechanism probably includes anovulation, which is constantly observed, but there are several arguments favoring a direct antiprogesterone effect on the leiomyomata cells (127, 128). Other trials are necessary to confirm efficacy of the treatment and particularly to evaluate its long-term tolerance at the endometrial level.

USE OF RU486 IN BREAST CANCERS On the basis of many pharmacological studies (129–132), it has been proposed that RU486 be used as a hormonal treatment of advanced breast cancers.

Preliminary trials (133, 134) have shown that the drug may induce partial but transient remissions, and that it could be used safely for several weeks without evidence of adrenal deficiency symptoms. Two additional studies have been performed to assess the efficacy of RU486 in patients with metastasized breast cancer (A Ulmann, unpublished data). In the first, performed under the supervision of the Canadian National Cancer Institute, RU486 was evaluated as a first-line agent. In the second, performed in Europe, the product was studied as a second-line treatment. Both studies gave disappointing results: Preliminary data analysis showed that no patient had a prolonged remission, and only a few transient remissions were noted.

USE OF RU486 IN MENINGIOMAS Meningiomas are more frequent in women, and frequently their growth is accelerated during pregnancy. Many meningiomas contain PR , often accompanied by relatively low amounts of estrogen receptor (135, 136). These facts have triggered pharmacologic studies that showed that, in some model systems (culture and transfer to nude mice) (137), RU486 slows the growth of human meningiomas. It has been proposed that RU486 be used for inoperable meningiomas (138–141). However, because meningioma growth is often extremely slow and poorly predictable, controlled studies versus a placebo are necessary to evaluate the actual efficacy of a medical treatment: Such studies are ongoing, and another year is necessary to obtain statistically meaningful results.

OTHER USES OF RU486 AS AN ANTIPROGESTIN AGENT The usefulness of RU486 in other tumors containing PR remains to be evaluated. However, use of RU486 in metastasized ovarian carcinoma appears disappointing. Recently, the prolonged remission of a (low grade) osteolytic leiomyosarcoma, a tumor containing PR, has been observed during long-term administration of RU486 (F Lioté et al, unpublished data). Treatment of premenstrual syndrome by RU486 has been considered (142), but no controlled trial has been performed. In any case, long-term administration of the compound should include the endocrine evaluation of the consequences of its predicted antisteroid activities (143, 144).

Clinical Use of RU486 as an Antiglucocorticosteroid (Cortisol Antagonistic Agent)

RU486 demonstrates antiglucocorticosteroid activity in vitro and in vivo (8, 9). Because the product eliminates the negative feedback control of cortisol on ACTH, it leads to increased ACTH and cortisol secretion (145). Blockade of peripheral effects of cortisol are evidenced by the suppression of cutaneous vasoconstriction or the decrease in circulating eosinophils induced by glucocorticosteroids (145a, 145b). The antiglucocorticosteroid effect of RU486 is dose dependent and becomes apparent for single doses of 4 mg/kg (34). Importantly, this effect can be reversed by glucocorticosteroid administration: It has been shown that 1 mg of dexamethasone antagonizes the effects of 400 mg of RU486 (152). Also, it has been demonstrated that after eight days of treament with 200 mg of RU486 per day, the adrenocortical and pituitary reserves are preserved (16). In addition, RU486 may have a weak glucocorticosteroid agonistic activity in the absence of endogenous or exogenous glucocorticosteroid (158). These effects may explain why no clinical symptom of cortisol deficiency is observed when RU486 is administered.

USE OF RU486 IN CUSHING SYNDROMES So far, the only efficient treatment using the antiglucocorticosteroid activity of RU486 is that of Cushing syndrome secondary to ectopic ACTH secretion or to adrenal carcinoma: Daily doses of 5–10 mg/kg are necessary to bring about a dramatic improvement of the symptoms (146–148). Radical surgery, impossible during hypercorticism, may become possible. On the other hand, Cushing syndrome of pituitary origin (Cushing's disease) constitutes a contraindication to the use of RU486 (stimulation of ACTH production and risk of sudden growth of a pituitary tumor) (149).

OTHER POTENTIAL USES OF RU486 AS AN ANTIGLUCOCORTICOSTEROID AGENT Theoretically, RU486 may be used in any situation where one desires to block endogenous or exogenous glucocorticoid activity (150). In practical terms, there are currently few situations where RU486 has proven useful as an antiglucocorticosteroid agent. Table 3 summarizes the various conditions where the use of RU486 has been evaluated or considered in humans.

As shown in Table 3, many uses have been considered, but in many instances, results have been negative or inconclusive. This might be due to the above-mentioned overcoming of cortisol blockade by feedback secretion of cortisol and ACTH. As a matter of fact, in a study evaluating the usefulness of RU486 for preventing cortisol-induced protein catabolism, only a transient decrease in plasma glucose was noted (151). An explanation for this apparent paradox is that the tissue blockade of cortisol by RU486 may be of short duration, whereas the secondary cortisol increase after RU486 lasts for two to three days (8, 9, 152). The use of other molecules, with longer tissue activity, or used via the intravenous route, may prove more useful. On the other hand, some pharmacologic data may look promising, but their clinical relevance must be evaluated with caution. For example, although RU486 seems to decrease the HIV replication in vitro (153), the clinical evaluation of such findings in AIDS patients must be cautious because the possible consequences of

Table 3 Potential uses of RU486 as an antiglucocorticosteroid agent

Use	References
HPA axis evaluation	7, 8, 158, 159
CNS, central depression, anxiety	160–165
Arterial hypertension, vascular reactivity, electrolyze excretion	166–169
Protein catabolism, lipid metabolism, obesity	151, 170, 171
Infection, HIV replication	153, 172
Ocular pressure, glaucoma	173, 174
Glial proliferation	175
Skin effects	176
Multidrug resistance	177, 178

cortisol blockade on the development of opportunistic infections is unknown. Moreover, antilymphoproliferative effects as well as antioxidant properties have recently been reported (154, 155).

It is probably the local use of RU486, or derivatives with preponderant antiglucocorticosteroid activity, that will develop first. For instance, an antiglucocorticosteroid could accelerate the healing of wounds and burns, particularly in stressed or aging patients.

CONCLUSIONS

RU486 has proved to be a remarkably active antiprogesterone and antiglucocorticosteroid agent in human beings. It would be desirable to have derivatives with only one of these two antagonistic activities, but considering the similarities between receptors involved and responsive machineries in target cells (for example, HREs), this may be difficult to obtain. Experimentally and clinically, it remains possible to compensate for the undesired effect by administration of the agonist. An RU486 derivative with no affinity for orosomucoid, and thus with a shorter half-life, may be useful (to test pituitary adrenal function or to obtain an antiprogesterone effect in luteal phase not interfering with the growth of the next follicle).

The RU486-plus-prostaglandin method is ready to be used at large and is close to being as convenient as any medical method of abortion may be. Studies must rapidly discern the best conditions for its distribution in parts of the world where there are problems of accessibility, including developing countries. The early use of the RU486 as a contragestive as soon as a woman fears a pregnancy that she does not want will help to defuse the abortion issue. Research should now be conducted to define a safe, convenient contraceptive method with RU486 or other antiprogestins. These are serious hopes, but the systematic studies will take several years and a great deal of money. Significant success will contribute even more to decreasing abortion as we know it. The usefulness of RU486 for obstetrical indications, including facilitation of difficult deliveries, has to be assessed rapidly. Gynecological trials, particularly in leiomyomata, should also be carefully continued. The very preliminary results obtained with tumors, including breast cancers, do indicate that further studies are necessary.

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