

# Teratogen Update: Reproductive Risks of Leflunomide (Arava™); A Pyrimidine Synthesis Inhibitor: Counseling Women Taking Leflunomide Before or During Pregnancy and Men Taking Leflunomide Who Are Contemplating Fathering a Child

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Arava™ (leflunomide) is a pyrimidine synthesis inhibitor used in the treatment of active rheumatoid arthritis (RA). The chemical name for leflunomide is N-(4'-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide. Because the drug has been successful in the treatment of rheumatoid arthritis, it is being widely prescribed. In spite of the clear warning that the drug should not be prescribed for pregnant women, approximately 30 women have become pregnant while taking leflunomide as of December 1999. This commentary was prepared to aid teratology counselors and genetic counselors who might be contacted by physicians or patients about the risk of leflunomide exposure during pregnancy. Before the subject of risk is discussed, it is important to understand the results of preclinical testing, pharmacokinetic studies, and clinical studies that are available.

## BACKGROUND INFORMATION

Preclinical and clinical studies pertaining to the reproductive risks of preconception and postconception exposures to leflunomide, a new drug, marketed by Aventis became available for analysis and interpretation. Using the basic science principles of teratology and the preclinical reproductive toxicology studies, an attempt was made to estimate the reproductive risks of leflunomide. All the preclinical and clinical data prepared for submission to the Food and Drug Administration (FDA) were available for analysis.

The scientists and clinicians of Aventis concluded that Arava should not be administered to pregnant women. The drug was marketed as a category X drug according to the present FDA classification. The actual wording in the product label with regard to reproductive warnings is as follows: Pregnancy must be excluded before the start of treatment with Arava™. Arava™ is contraindicated in pregnant women or in women of childbearing potential who are not using reliable methods of contraception. Pregnancy must be

avoided during Arava™ treatment or prior to the completion of the drug elimination procedure after Arava™ treatment.

### Use in women of childbearing potential.

There are no adequate and well-controlled studies evaluating Arava™ in pregnant women. However, based on animal studies, leflunomide may increase the risk of fetal death or teratogenic effects when administered to a pregnant woman. Women of childbearing potential must not be started on Arava™ until pregnancy is excluded and it has been confirmed that they are using reliable contraception. The patient must be advised that if there is a delay in the onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing, and if positive, the physician and the patient must discuss the risk of pregnancy. It is possible that rapidly lowering the blood level of the active metabolite, by instituting the drug elimination procedure described below, at the first delay of menses, may decrease the risk to the fetus from Arava™.

Upon discontinuing Arava™, it is recommended that all women of childbearing potential undergo the drug elimination procedure described below. Women receiving Arava™ treatment who wish to become pregnant must discontinue Arava™ and undergo the drug elimination procedure described below, which includes verification of M1 metabolite plasma levels less than 0.02 mg/L (0.02 µg/ml). Human plasma levels of the active metabolite (M1) less than 0.02 mg/L (0.02 µg/ml) are expected to have minimal risk, based on available animal data.

**Drug elimination procedure.** The following drug elimination procedure is recommended to achieve nondetectable plasma levels of <0.02 mg/L (0.02 µg/ml) after stopping drug treatment with Arava™:

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Received 7 January 2000; Accepted 19 April 2000

1. Administer cholestyramine 8 g three times daily for 11 days. (The 11 days do not have to be consecutive, unless there is a need to lower the plasma levels rapidly.)
2. Verify plasma levels of less than 0.02 mg/L (0.02 µg/ml) by separate tests, spaced at least 14 days apart. If plasma levels are higher than 0.02 mg/L (0.02 µg/ml), additional cholestyramine treatment should be considered.

Without the drug elimination procedure, it may take up to two years to reach plasma M1 metabolite levels less than 0.02 mg/L (0.02 µg/ml) due to individual variation in drug clearance.

**Nursing Mothers.** Arava™ should not be used by nursing mothers. It is not known whether Arava™ is excreted in human milk. Many drugs are excreted in human milk, and there is a potential for serious adverse reactions in nursing infants on Arava™. Therefore a decision should be made whether to proceed with nursing or to initiate treatment with Arava™, taking into account the importance of the drug to the mother.

**Use in Males.** Available information does not suggest that Arava™ would be associated with an increased risk of male-mediated fetal toxicity. However, animal studies to evaluate this specific risk have not been conducted. To minimize any possible risk, men wishing to father a child should consider discontinuing the use of Arava™ and taking cholestyramine 8 g, 3 times daily for 11 days.

**Mechanism of action (Davis et al., '96; Silva et al., '98; Hermann et al., '97):**

Leflunomide is a novel isoxazole immunomodulatory agent that inhibits de novo pyrimidine synthesis and has antiproliferative activity. After oral administration, it is rapidly metabolized to an active metabolite (A77 1726), which is presumed to be the active drug in vivo. Leflunomide has demonstrated prophylactic and therapeutic effects in animal models of autoimmune disease. In preclinical models of chronic graft-versus-host disease (GvHD) and solid-organ graft rejection, it has prolonged the time to rejection and/or reversed ongoing rejection. In addition, leflunomide has exhibited mild antiinflammatory and weak analgesic and antipyretic activity. In a model of experimental septicemia, leflunomide did not alter the resistance of mice to bacterial pathogens.

In vitro, after mitogen stimulation, the active metabolite of leflunomide, inhibits T-cell proliferation, DNA synthesis, and expression of certain cell surface and nuclear antigens directly involved in T-cell activation and proliferation. It inhibits mitogen-stimulated proliferation of human peripheral blood mononuclear cells (PBMC) and proliferation in transformed murine and human cell lines, in a dose-dependent fashion. This antiproliferative activity is reversed by the addition of uridine to the cell culture, indicating that the active metabolite acts at the level of de novo pyrimidine biosynthesis. Leflunomide inhibition of GvHD (graft ver-

sus host disease) in vivo is also reversed by feeding uridine, further indicating that the active metabolite acts at the level of the de novo pyrimidine biosynthesis pathway.

It has been demonstrated that the active metabolite binds to, and is a potent inhibitor of, dihydroorotate dehydrogenase (DHO-DH), an enzyme in the de novo pyrimidine synthesis pathway that is important for DNA synthesis. In vitro, incubation of PHA/IL-2 stimulated human peripheral T cells with the active metabolite of leflunomide, triggered cell cycle arrest at the G1 phase or, in those cells undergoing DNA synthesis, at the S phase.

Together, these data suggest that, at concentrations achievable in patients, leflunomide inhibits de novo pyrimidine synthesis in activated lymphocytes and other rapidly dividing cell populations resulting in reversible cell cycle arrest.

**Pharmacokinetics in humans**

The pharmacokinetics of leflunomide, based on plasma concentrations of the active metabolite, have been studied in healthy subjects and in patients with rheumatoid arthritis.

After oral administration, leflunomide is rapidly converted to the active metabolite (A77 1726). Animal studies suggest that conversion takes place during passage through both the gut wall and the liver. After oral administration of a 100-mg dose of <sup>14</sup>C-leflunomide to healthy volunteers, leflunomide was not detectable in plasma over the plasma sampling period (0.5 hr to 37 days). Plasma concentrations of total radioactivity and the active metabolite were superimposable, demonstrating extensive conversion to the active metabolite during the absorption process. The minor metabolite, 4-trifluoromethylaniline (TFMA) has been detected in the plasma of animals and humans, but at much lower concentrations (ng/ml) than those of the active metabolite (µg/ml). Urinary and fecal recovery of <sup>14</sup>C over 28 days accounted for 43% and 48% of total radioactivity, respectively. The slow but nearly complete recovery of radioactivity as metabolites indicated nearly complete absorption of leflunomide in humans. Unchanged leflunomide was not detected in urine or feces. The urinary metabolites were primarily glucuronide conjugates of leflunomide and an oxanilic acid derivative of the active metabolite, while the active metabolite was the primary metabolite in the feces. The metabolic biotransformation of the active metabolite is not controlled by a single enzyme and has been shown to occur in microsomal and cytosolic cellular fractions. The active metabolite is cleared by slow excretion in feces, probably by biliary elimination, and slow metabolism to the oxanilic acid metabolite excreted in urine. After independent intravenous administration of the active metabolite, clearance averaged 31 ml/hr, steady-state volume of distribution of 11L, and elimination half-life of 10 days. A similar clearance estimate (29 ± 17 ml/hr)

was obtained from population pharmacokinetic analysis of rheumatoid arthritis patients enrolled in pivotal safety and efficacy studies.

After single doses of leflunomide to healthy subjects, peak plasma concentrations of the active metabolite were reached between 6–12 hrs. Plasma concentrations then declined monoexponentially, with a half-life of approximately 8 days. Based on determination of the active metabolite, the bioavailability of leflunomide from a tablet formulation relative to an oral solution was 80%. Arava administered with a high fat/high carbohydrate meal was bioequivalent to administration under fasting conditions. Arava can therefore be taken without regard to meals.

In a 24-week study in patients with rheumatoid arthritis, steady-state was reached at 7–8 weeks. Mean plasma concentrations of the active metabolite, 24 hr after a 100-mg loading dose (8.5  $\mu\text{g/ml}$ ), were twice those after a 50-mg loading dose (4.0  $\mu\text{g/ml}$ ). Pre-dose plasma concentrations after 24 weeks of dosing were linearly related to the maintenance dose (9, 18, and 63  $\mu\text{g/ml}$  after 5, 10, or 24 mg/day, respectively) and the elimination half-life averaged 14–18 days. The pharmacokinetics of the active metabolite are therefore linear over the range of loading and maintenance doses to be used clinically.

Based on the half-life in this patient population and the recommended dosing interval (24 hr), a loading dose is needed to yield steady-state concentrations more rapidly. It is recommended that a 300-mg loading dose be administered as a single 100-mg dose per day for 3 days.

In studies with plasma samples obtained from healthy subjects, the active metabolite was extensively bound to protein (albumin). The unbound fraction was 0.62%. Binding of the active metabolite was linear up to 573  $\mu\text{g/ml}$ . Compared with healthy subjects, the unbound fraction was slightly increased in plasma from patients with rheumatoid arthritis and was approximately doubled in patients with chronic renal insufficiency, but in healthy subjects, patients with rheumatoid arthritis and patients with renal insufficiency, the unbound active metabolite represented less than 2% of the total serum concentration. The extensive protein binding of the active metabolite is consistent with its low volume of distribution.

Oral administration of activated charcoal or cholestyramine is effective in enhancing the elimination of the active metabolite. During oral administration of activated charcoal, 50 g 4 times per day (qid), or cholestyramine, 8 g 3 times per day (tid), the half-life of the active metabolite decreased to approximately 24 hr. Although the mechanism for the enhanced elimination is unknown, it may be related to interruption of enterohepatic recycling and/or dialysis across the gastrointestinal mucosa.

When subjects with end-stage renal disease were administered a single 100-mg dose of leflunomide orally, plasma concentrations of the active metabolite, both before and after dialysis (chronic ambulatory peri-

toneal dialysis [CAPD]) or hemodialysis), were comparable to those of healthy volunteers administered the same dose. Because of its high protein binding, the active metabolite is not removed significantly by dialysis.

### Preclinical reproductive studies

In oral embryotoxicity and teratogenicity studies in rats and in rabbits, leflunomide was embryotoxic (growth retardation, embryoletality) and teratogenic (in rats, malformations of the head, rump, vertebral column, ribs, and limbs; in rabbits, malformations of the head and bilateral dysplasia of the spine of the scapula). The no-effect level for embryotoxicity and teratogenicity in rats and rabbits was 1 mg/kg body weight, which is equivalent to 18.32 and 52.5  $\mu\text{g/ml}$ , respectively.

A blood level of 0.03  $\mu\text{g/ml}$  and an AUC of 0.72  $\mu\text{gh/ml}$  are regarded as safe based on the following considerations:

1. Compared with the  $C_{\text{max}}$  levels in rats and rabbits, which did not cause embryotoxicity or teratogenicity, the level of 0.03  $\mu\text{g/ml}$  is 123 times (compared with rat) and 136 times (compared with rabbit) lower than the blood level in the rat and rabbit which has been determined as the no-effect level.
2. Compared with AUC in rats and rabbits, the level of 0.72  $\mu\text{gh/ml}$  is 25 times (compared with rat) and 72 times (compared with rabbit) lower than the blood level in the rat and rabbit which has been determined as the no-effect AUC level.

Scientifically, these safety margins are sufficient. It is highly probable that the safety margins are even higher. It has been shown that the pharmacodynamic effects of leflunomide, namely dihydroorotate dehydrogenase (DHO-DH) inhibition and anti-proliferative activity, considered to be responsible for the embryotoxic and teratogenic effects, are species-specific and significantly different. The inhibitory effect of leflunomide on DHO-DH activity is 40 times, and its antiproliferative effect on cell cultures is 300 times stronger in rat than in man. However, since it cannot be determined whether the human embryo or fetus is more sensitive than the adult, these species differences and possible consequences on safety margins cannot be considered for estimating the reproductive risks of leflunomide in humans.

The average steady-state plasma level of the active metabolite of leflunomide in Phase III studies was 30–40  $\mu\text{g/ml}$ . This is derived from the average clearance of 24 ml/h, which is given in the population kinetics report:  $C_{\text{ss}} = (\text{dose}/\text{time})/\text{CL} = (20/24)/24 = 35 \text{ mg/L}$ . The safe human level is 0.03 mg/L, i.e., a factor of 1,000 or approximately 10 half-lives. Thus, if a woman treated with leflunomide wants to become pregnant, the medication has to be stopped and cholestyramine or charcoal has to be administered repeatedly to decrease the blood levels rapidly to a level that is

considered not to cause an increased teratogenic or reproductive risk, i.e.,  $<0.03 \mu\text{g/ml}$ . This is an extremely conservative approach. This approach was suggested by the FDA, namely, to get the blood level down to undetectable levels. High-performance liquid chromatography (HPLC) cannot determine leflunomide levels of  $<0.02 \mu\text{g/ml}$  and 11 days of cholestyramine therapy will accomplish this goal. Cholestyramine, 8 g tid, reduces the half-life of the active metabolite to approximately one day. Therefore, an eleven day regimen of cholestyramine, 8 g tid, is recommended.

Without cholestyramine, half-lives of up to 96 days have been found (population kinetics analysis). Thus, it may take up to 2 years to reach plasma active metabolite levels of  $<0.02 \mu\text{g/ml}$  due to individual variations in drug clearance.

### **Carcinogenesis, mutagenesis, and impairment of fertility from leflunomide exposure**

Two-year carcinogenicity studies in mice and rats were conducted including exposures in mice that were above those used clinically. Results in the mouse carcinogenicity study showed increased incidences of malignant lymphomas (males, high dose 15 mg/kg/day) and lung adenoma/carcinoma (females). The incidence for the latter, however, was within the spontaneous range known for the mouse strain (CD-1). Results from the rat carcinogenicity study did not indicate a carcinogenic potential of leflunomide (6 mg/kg/day). These results are very difficult to interpret because the rat enzyme, DHO-DH, is 40 times more sensitive to leflunomide and the mouse is also more sensitive.

Leflunomide did not show mutagenic/genotoxic effects in vitro (Ames test, HGPRT test, UDS test) or in vivo (mouse micronucleus test, Chinese hamster chromosomal aberration test). A minor metabolite of leflunomide, 4-trifluoromethylaniline (TFMA), has been detected sporadically in low levels in patients receiving leflunomide. In 268 of 491 patients, plasma concentrations of TFMA were determined. In 66 patients (25%) the TFMA concentrations were low ( $8.1 \pm 3.0 \text{ ng/ml}$ ). TFMA concentrations did not increase over time, indicating that it did not accumulate. TFMA was mutagenic in the Ames test, the HGPRT and in vitro cytogenetics tests. It was not mutagenic in the unscheduled DNA synthesis test in hepatocytes, in the mouse micronucleus test, and in the in vivo cytogenetics tests in Chinese hamster ovaries (CHO). Treatment of patients with leflunomide is not believed to result in unacceptable risks due to the very low amounts of TFMA formed in humans at the selected daily dose of 20 mg.

### **EVALUATION OF REPRODUCTIVE EFFECTS OF LEFLUNOMIDE**

The following questions that pertain to the reproductive risks of leflunomide are addressed.

1. *Are there teratogenic risks to pregnant women taking leflunomide during pregnancy?* What would be a reasonable safety factor, based on the fact that we have

pharmacokinetic data for the no-effect level for teratogenicity in an animal model (Brent, '86, '87, '99; Brent et al., '86; Beckman and Brent, '99; Brent and Beckman, '99).

No epidemiological studies have been completed with regard to the teratogenicity of leflunomide, since the drug was introduced in 1998. Of the few women who have been exposed during pregnancy, most have decided to interrupt their pregnancies. The pharmacokinetic level of the active metabolite of leflunomide reached clinically in humans is in the range of exposure that results in teratogenesis in the rat and rabbit. It is evident that leflunomide effects vary with species and it appears that the rat and rabbit are more sensitive to leflunomide's inhibition of pyrimidine synthesis. But it is difficult to translate that metabolic difference into differences in teratogenic potential, because there are no data on leflunomide's effect on the human embryo. Therefore, the conservative approach is to be concerned that therapeutic blood levels of the active metabolite of leflunomide represent a teratogenic risk.

Based on the no-effect level of leflunomide for teratogenicity and other reproductive effects as determined from in vivo animal studies and the fact that reproductive effects from intrauterine exposures are deterministic (threshold) effects, there should be no teratogenic risk at blood levels that are 10-fold lower than the no-effect blood level of leflunomide. A 100-fold reduction in blood level would present no teratogenic risk and would be an extremely conservative level that should provide an environment for embryonic and fetal development that does not have a measurably increased risk. Therefore, if the blood level of the active metabolite is lowered to  $<0.02 \mu\text{g/ml}$ , there is no likelihood of a teratogenic risk. This is based on the FDA recommendation that the cholestyramine washout attain nonmeasurable levels of leflunomide as determined by HPLC, and this level is  $<0.02 \mu\text{g/ml}$ . This can be readily accomplished with the 11-day cholestyramine washout. It should be pointed out that 100-fold reduction below the no-effect level is an extremely conservative approach. A 10-fold reduction below the no-effect level is also likely to represent no measurable teratogenic risk. This may be important in evaluating inadvertent exposures in unintended pregnancies.

2. *Is there a teratogenic risk due to the presence of 4-trifluoromethylaniline (TFMA), a minor metabolic product of leflunomide?* TFMA (4-trifluoromethylaniline) represented less than 5% of the metabolic products of leflunomide and was present in nanogram quantities in human pharmacokinetic studies. Therefore, the concentrations of TFMA attained after therapeutic administration of leflunomide are too low to represent a teratogenic risk.

3. *What are the reproductive risks for men who father a child when receiving leflunomide therapy?* In particular, what is the risk of fathering a child with congenital malformations or other harmful effects on the fetus due to exposure to leflunomide, its active metabolite or 4-trifluoromethylaniline (TFMA) (Brent, '94, '99)?

The review of the reproductive effects of mutagenic agents consistently indicates the low risk of these agents for reproductive effects in the  $F_1$  generation. Leflunomide and its main metabolic product interfere with pyrimidine synthesis but do not have the mutagenic potential that has been demonstrated for proven mutagenic agents. The reproductive risks for men taking leflunomide are related to the properties of the drug, which are primarily related to the interference with DNA synthesis. Even with the potential reduction in DNA synthesis the risks of infertility are remote, unless the individual already has an infertility problem before starting the medication. Since leflunomide does not have mutagenic potential and the minor metabolite, TFMA is in such low concentration, there should be no measurable increase in the risk of genetic disease in the offspring. TFMA, a minor metabolite of leflunomide, accounts for less than 5% of the metabolic products. In a large series of patients receiving leflunomide in therapeutic doses, 25% of the patients had undetectable levels of TFMA. In the remaining 202 patients, plasma concentrations were very low ( $8.1 \pm 3.0$  ng/ml). While TFMA at high concentrations was mutagenic in the Ames test, the HGPRT and cytogenetics tests, it was not positive in an in vivo cytogenetics test, unscheduled DNA synthesis, and the mouse micronucleus test. Thus, the mutagenicity testing of leflunomide and the pharmacokinetics would indicate that preconception exposures would represent no measurable genetic risk in exposed populations and a theoretical risk of reducing gonadal cell populations, but not to the extent of affecting fertility at therapeutic exposure levels in humans.

## CLINICAL EVALUATIONS AND RECOMMENDATIONS

### Planning a pregnancy

For men or women who are taking Arava for the treatment of rheumatoid arthritis who are planning a pregnancy, they can eliminate the drug to safe levels with an 11-day regimen of cholestyramine. Cholestyramine, 8 g tid, reduces the active metabolite half-life to approximately 1 day. After 11 days of the washout, the blood level would be 100-fold lower than the no-effect level of 3  $\mu$ g/ml. Without cholestyramine, half-lives of up to 96 days have been found (population kinetics analysis). Thus, 11 half-lives are approximately 2 years in the worst case situation. Therefore, common sense would dictate that men or women planning a pregnancy should initiate the 11-day cholestyramine washout.

While the reproductive risks of preconception exposure to leflunomide are minuscule, the most conservative approach would be to have a woman wait for three menstrual cycles after the washout before conceiving, and a man should wait for at least one spermatogenesis cycle after the washout before considering impregnating his wife. This recommendation for men is described in the package insert (Although available information

does not suggest that Arava would be associated with an increase in male-mediated fetal toxicity, to minimize any possible risk, men wishing to father a child should consider discontinuing the use of Arava and take cholestyramine, 8 g tid, for 11 days.)

### Unplanned pregnancy by mothers and fathers taking leflunomide

Women who become pregnant while taking leflunomide are at risk of reproductive effects, based on the theoretical extrapolation of the reproductive studies in rats and rabbits. Even if the woman informs her physician that she has missed her menstrual period and the pregnancy test is positive, it would be unlikely that a cholestyramine washout could be completed before organogenesis begins. Even with the most conscientious patient and doctor, it has not been possible to avoid exposure during early organogenesis, in most instances. Nevertheless, it is theoretically possible to lower the leflunomide level substantially before organogenesis begins, if pregnancy is diagnosed at the time of the first missed menstrual period and the washout is begun immediately. Therefore, in most instances, the mother has to be told that there is a theoretical risk that the fetus may have been affected, based on animal studies.

The sensitive period for the interference with neuronal cell migration and proliferation is between the 8th and 15th weeks of pregnancy. Washouts that begin in the third week post conception, would prevent the risk of microcephaly and mental retardation but would not prevent effects during early organogenesis.

Men taking leflunomide who inseminate their partner have a much different situation. Leflunomide and its main metabolites do not have mutagenic potential and TFMA is a weak mutagen and is present in extremely low concentrations. Therefore, the theoretical risk of a chromosomal abnormality or a point mutation at the molecular level is extremely small. This is also true for women who have a washout before they get pregnant.

When enough human experience with inadvertent exposure to men fathering children while on leflunomide is accumulated, we may conclude that men taking leflunomide need not consider stopping the medication if they contemplate having children, because leflunomide and its main metabolites do not have mutagenic potential and TFMA is a weak mutagen and is present in extremely low concentrations.

### Breast feeding

The package insert indicates that mothers who are taking leflunomide should not breast-feed their infants. Pharmacokinetic data concerning the level of leflunomide in breast milk is not available in order to determine the leflunomide exposure to a breast-feeding infant. It is possible that the exposure might be insignificant. Without the pharmacokinetic data, it would not be advisable for a mother to breast-feed while taking leflunomide.

### Counseling

Approximately 30 women have become pregnant on leflunomide who have been brought to my attention by referrals from rheumatologists and counselors at Hoechst-Marion-Roussell (now called Avantis). In spite of the efforts to initiate the cholestyramine washout as soon as pregnancy was diagnosed, in all but one instance, there was exposure to therapeutic levels of leflunomide during early organogenesis. It is theoretically possible to diagnose pregnancy at the time of the first missed menstrual period and have two to three days of cholestyramine washout before organogenesis begins. Therefore, the predominant risk during this period would be pregnancy loss. Malformations are at a much lower risk with teratogenic exposures during the period before organogenesis begins (the "all-or-none period") (Wilson and Brent, '53). After discussions with the physicians and patients, all but three of the pregnant women have elected to interrupt their pregnancies.

The three women who have elected to maintain their pregnancies have been advised about their risks. They have been advised to be followed by a perinatologist, with level 2 ultrasounds and serum alpha fetoproteins. Amniocentesis will be offered because of the patient's age or recommendations of the perinatologist. An increase risk of chromosomal abnormalities is not to be expected because of leflunomide exposure. It is possible that these three pregnancies are not at an increased risk of congenital malformations and therefore it is possible that the offspring may be unaffected. This suggestion is derived from the animal data which indicates that the rodent is more sensitive than the human to some of the effects of leflunomide, which may indicate that leflunomide has less of a teratogenic risk in the human at serum concentrations that are present in the rodent that result in teratogenicity. Regardless of this theoretical possibility, the conservative approach is to assume that therapeutic doses of leflunomide have teratogenic potential in the human.

Most of the women who became pregnant were ostensibly using contraception. But apparently, there were contraceptive failures. In a number of instances, the women had considered themselves infertile and had been suffering from rheumatoid arthritis for many years. The dramatic improvement in their clinical condition was concomitantly associated with a return to fertility. It is difficult to determine the prevalence of this phenomenon. If it is prevalent, the rheumatologists who prescribe leflunomide, will have to reinforce the importance of contraception in women who may consider themselves to be infertile.

### Clinical presentations

It should be pointed out that in every consultation with pregnant women taking Arava, the physician had counseled the patient to use contraception and that pregnancy represented a teratogenic risk. In every instance cholestyramine therapy had been initiated on

the day of the positive pregnancy test or within a few days after the diagnosis of pregnancy. No one could have been aware of the fact that a number of women with severe rheumatoid arthritis considered themselves infertile and may not have been concerned about their need for contraception. It may be that oral contraceptives plus a condom may be a more appropriate method of contraception. From the counseling standpoint, most rheumatologists would call with a meager knowledge of the pregnancy, i.e., not having available the last menstrual period (LMP), date of conception, family size, patient's name, and age. In many instances, contact was made with the obstetrician, or family to gather important information for the purpose of counseling the mother and family.

1. In typical cases of unplanned pregnancy, the mothers suspected that they were pregnant or a pregnancy test was positive some time during the week after the missed menstrual period (cholestyramine being initiated from the 18th to the 30th postconception day). That means that all these mothers had significant leflunomide exposure during early organogenesis. These mothers were told that the embryo was exposed to leflunomide during early organogenesis, and there was a theoretical risk of malformations to several organ systems, based on animal studies. Without human data, we cannot be certain of the magnitude of this risk, or even whether a risk exists. Since neuronal proliferation and migration occurs later in development, if the embryo was not affected during organogenesis, an increased risk of microcephaly and mental retardation would be unlikely. All but three of these mothers elected to terminate their pregnancies. Better counseling could be provided if a leflunomide level were obtained on the day pregnancy was diagnosed, 2 days into the cholestyramine washout and at the end of the washout.
2. One mother had her pregnancy test at the time of the missed menstrual period and also was aware of the day of conception. Cholestyramine was initiated on the 16th day postconception and, therefore, there is a possibility that the embryo was exposed to much lower levels of leflunomide than were all the other mothers. She elected to continue her pregnancy because of ethical considerations, not because of the lower exposure to her embryo. The three pregnancies that are continuing have not as yet come to term.
3. A woman of reproductive age who was on Arava called to ask about the risk of pregnancy because of the fact that her ova were exposed to leflunomide. Could leflunomide result in damage to her ova and result in damage to future pregnancies? If the women underwent cholestyramine washout and waited for three ovulatory cycles before becoming pregnant, there would not be a measurable genetic risk from the preconception exposure to leflunomide.
4. Men who are planning parenthood and are being

treated with leflunomide should undertake cholestyramine washout and wait for at least one and possibly three spermatogenic cycles before inseminating their spouse.

5. Men who inseminate their spouse while taking leflunomide are not at increased risk of parenting a child with birth defects or genetic disease, since leflunomide and its metabolites are not mutagenic or cytotoxic. The very small quantity of TFMA, which has mutagenic potential, is present in such small quantities that it can be disregarded. While it would have been less anxiety-provoking for the family if cholestyramine washout had been performed, this nonmeasurable risk would not warrant an interruption of a wanted pregnancy.

### EPILOGUE

Since September 1998, when the drug was approved, pregnant women exposed to Arava have been referred for counseling to the Clinical and Environmental Laboratories at the duPont Hospital for Children. As of January 2000, a *Rheumatoid Arthritis and Arava in Pregnancy Study* has been established by the Organization of Teratology Information Services (OTIS) in order to provide counseling as well as postmarketing surveillance relative to the teratogenicity of Arava in human pregnancy. The study, which is sponsored by the drug manufacturer (Aventis Corporation, Bridgewater, NJ), is a multicenter prospective cohort study. A group of women with first-trimester prenatal exposure to Arava will be ascertained through the 21 participating OTIS member services located throughout North America and will be followed in order to document pregnancy outcome with respect to the presence or absence of a pattern of malformation in liveborn infants. Secondary endpoints to be evaluated include the rate of spontaneous abortion or stillbirth, pre- or postnatal growth deficiency, and premature delivery. For information and patient referral, the toll-free number is 1-(877)-311-8972.

### ACKNOWLEDGMENTS

Basic science data, animal studies, and pharmacokinetic studies performed and presented by scientists from Hoechst-Marion-Roussel (Aventis) at the August

1998 FDA hearing have been used for preparing portions of this commentary. The author was a consultant to Hoechst-Marion-Roussel (renamed Aventis because of a merger) to evaluate the reproductive and teratogenic risks of leflunomide and assist in preparing the package labeling.

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