MOTHERISK UPDATE

Leflunomide: new antirheumatic drug

Effect on pregnancy outcomes

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abstract

QUESTION I am treating a 34-year-old woman with rheumatoid arthritis. She began taking the new drug leflunomide (Arava®) 6 months ago and had good clinical response. She is now planning her first pregnancy. What should she do?

ANSWER Leflunomide is a new and effective disease-modifying antirheumatic drug. Animal studies have shown an increased rate of malformations and fetal death in various species, but there are no data on pregnancy outcomes in humans treated with leflunomide. Since the drug has a prolonged and unpredictable elimination half-life, it should be stopped during pregnancy. The manufacturer recommends that patients who wish to become pregnant be treated with cholestyramine, which enhances elimination.

résumé

QUESTION Je soigne une femme de 34 ans atteinte d'arthrite rhumatoïde. Elle a commencé, il y a six mois, à prendre le nouveau médicament, le leflunomide (Arava®), et la réponse clinique au traitement est favorable. Elle planifie actuellement sa première grossesse. Que devrait-elle faire?

RÉPONSE Le leflunomide est un nouvel agent antirhumatismal efficace modificateur de la maladie. Les études effectuées sur les animaux ont démontré une augmentation du taux de malformations et de mort fœtale chez diverses espèces, mais il n'existe pas de données sur les issues de la grossesse chez les humains traités au leflunomide. Étant donné que le médicament a une demi-vie prolongée et une élimination imprévisible, il faudrait cesser son usage durant la grossesse. Le fabricant recommande de traiter les patientes qui souhaitent devenir enceintes à la cholestyramine qui en favorise l'élimination.

Leflunomide is a new disease-modifying antirheumatic drug. Its immunosuppressive effects are mediated by inhibition of de novo pyrimidine synthesis.[1] Pyrimidines (cytosine and thymine) and purines (adenine and guanine) are the nucleotide bases of DNA. Other mechanisms of action of leflunomide are inhibition of the activity of protein tyrosine kinases,[2] inhibition of cyclooxygenase-2 (COX-2),[3] inhibition of lymphocyte adhesion to endothelial cells,[4] and modulation of cytokine activity.[5,6]

Pharmacokinetics

The bioavailability of oral leflunomide is almost 100%. Leflunomide is a prodrug. It undergoes conversion to the active metabolite (A77-1726) by a nonenzymatic reaction in the intestinal mucosa. Rat studies showed A77-1726 to be the active metabolite.[7] The mean plasma half-life of A77-1726 in humans is 15 days (range 5 to 40 days).[8] This prolonged half-life is partially attributable to its extensive protein binding. More than 99% of the active metabolite is bound to plasma proteins (mainly albumin).[1] The prolonged half-life is also the result of entrohepatic circulation and reabsorption (once the drug is extracted into the bile, it is then reabsorbed into the gut).

The usual regimen for treating rheumatoid arthritis (RA) starts with a loading dose of 100 mg/d for 3 days, followed by a maintenance dose of 20 mg/d. The most common adverse effects associated with leflunomide treatment are diarrhea (17%), nausea (10%), alopecia (8%), and rash (10%).[9]

Do you have questions about the safety of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at (416) 813-7562; they will be addressed in future Motherisk Updates. Published Motherisk Updates are available on the College of Family Physicians of Canada website (www.cfpc.ca). Some articles are published in *The Motherisk Newsletter* and on the Motherisk website (www.motherisk.org) also.

Therapeutic use

Leflunomide is mainly used to treat RA. Several multicentre, large-scale studies compared leflunomide with other disease-modifying

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drugs.[9-11] Response and success rates for patients receiving leflunomide and methotrexate treatment were significantly higher than rates for patients receiving placebo. Leflunomide was as effective as methotrexate and sulfasalazine in delaying joint damage, as assessed by radiography.[12]

Because leflunomide and methotrexate have different mechanisms of action, researchers postulated that combining the two drugs would result in better outcomes.[13] This approach, tested in an open-label study, had promising results with no serious interactions between the drugs.[14]

Use during pregnancy

Rheumatoid arthritis frequently affects women of child-bearing age. The effect of new drugs for RA on pregnancy outcomes is relevant to both patients and physicians. Leflunomide's mechanism of action and the findings in animal studies that the drug is a potential teratogen have led to great caution. To date, no human studies of pregnancy outcomes after exposure to leflunomide have been published, and there have been very few reports of outcomes after inadvertent exposure during pregnancy.

Animal studies provide the only available information on in utero exposure to leflunomide. Offspring of rats treated with leflunomide 15 mg/kg daily during embryogenesis had increased risk of malformations of the head (notably anophthalmia, microphthalmia, and internal hydrocephalus), rump, vertebral column, ribs, and limbs. There was also an increased rate of fetal loss, reduced maternal weight, and reduced birth weight of surviving pups. In rabbits, oral treatment with 10 mg/kg daily resulted in fused dysplastic sternebrae. For both rats and rabbits, the no-effect dose for embryotoxicity and teratogenicity (ie, the highest dose that does not cause malformations or fetal loss) was 1 mg/kg daily. No-effect plasma level was 3.6 µg/mL.

Although A77-1726 inhibition of pyrimidine synthesis is species-specific and is higher in rats than in humans, the rule of thumb is that, in the absence of data on humans, the no-effect level (NOEL) should not exceed 1% of the NOEL found in the most sensitive animal model.

Steady-state plasma levels of 63 µg/mL were found in humans treated with 25 mg/d of leflunomide. These levels exceed the NOEL in animal models. Women taking leflunomide should use reliable contraception.[15] If such women wish to become pregnant or have conceived while taking the drug, the drug should be discontinued and a drug-elimination procedure begun.[16] To enhance elimination, patients can be treated with either 8 g of cholestyramine three times daily or 50 g of activated charcoal four times daily for 11 days. Two separate measurements should verify plasma concentrations below 0.02 µg/mL.[15]

If levels remain high, more cholestyramine can be given. The rationale for this is based on the pharmacokinetic properties of leflunomide, which has an extensive entrohepatic circulation. A similar procedure is suggested for men wishing to father children.

Conclusion

Based on its mechanism of action and its teratogenic effects in animals, leflunomide should not be used by women who are planning pregnancy or already pregnant. If women treated with leflunomide wish to become pregnant, they should stop the drug and take cholestyramine to enhance drug elimination.

Motherisk participates in the Arava Follow-up Program. Please contact us if a patient becomes pregnant while taking the drug.

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