Methotrexate May Impact Fertility in JIA Patients

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

DENVER – Chronic methotrexate therapy may harm the future fertility of girls and young women being treated for rheumatoid arthritis or juvenile idiopathic arthritis, based on preliminary findings from a prospective observational study.

"The biggest issue is that rheumatologists have become much more aggressive in their therapy for these young girls with juvenile idiopathic arthritis in the last 5-10 years. As early as 1 year of age, these girls are placed on methotrexate weekly for years and years and years. It's very common for the mothers and fathers sitting in the clinic to ask this question: Is this therapy going to affect my daughter's ability to have kids in the future?' " Dr. Amber R. Cooper said at the meeting.

The study findings suggest a need to alter how physicians counsel patients and their families on this score in light of emerging evidence that long-term cytotoxic therapy with methotrexate may threaten the oocyte pool, she said.

Thus far, 168 females aged 4-49 years have been recruited for the ongoing study from pediatric and adult rheumatology clinics. Every 3-4 months they undergo measurement of serum anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), inhibin B, and other indicators of ovarian reserve. In addition, transabdominal ultrasound is performed annually by sonographers blinded as to the patients' treatment regimen in order to assess ovarian volume and antral follicle count, explained Dr. Cooper of Washington University in St. Louis.

Among the study participants, 55% have juvenile idiopathic arthritis, formerly called juvenile rheumatoid arthritis, and 43% have rheumatoid arthritis. The rest have psoriatic arthritis or undifferentiated spondyloarthropathies. The subjects' mean age at diagnosis was 18.6 years, while at enrollment in the fertility study they averaged 25.4 years of age. Forty-three percent were on methotrexate or the related drug leflunomide, 12% were on a tumor necrosis factor (TNF) antagonist, 30% were on both, and 15% were on other agents, mainly corticosteroids, hydroxychloroquine, or sulfasalazine.

In a multifactorial analysis, patients on methotrexate/leflunomide were the only ones who showed a progressive decline in AMH with increasing time on therapy.

The primary study end point is change over time in AMH level, widely considered to be the best indicator of ovarian reserve. At enrollment, the median AMH level was 2.25 ng/mL in patients on methotrexate or leflunomide, 1.65 ng/mL in those on a TNF antagonist, 2.42 ng/mL in patients on both, and 2.54 ng/mL in patients on other agents.

In a multifactorial analysis, patients on methotrexate/leflunomide were the only ones who showed a progressive decline in AMH with increasing time on therapy. In addition, patients on methotrexate or methotrexate plus an anti-TNF biologic had significantly lower antral follicle counts than did other patients.

This preliminary finding that methotrexate may diminish ovarian reserve in patients being treated for rheumatologic diseases is biologically plausible. The drug targets rapidly dividing cells, which could include ovarian or endometrial cells, Dr. Cooper noted.

Moreover, the study findings are consistent with an earlier report by reproductive endocrinologists at Stanford (Calif.) University. The Stanford researchers found that the use of methotrexate to treat ectopic pregnancy in women being treated for infertility was associated with a significant but time-limited decline in oocytes retrieved when the patients subsequently underwent controlled ovarian stimulation. It took about 180 days following methotrex-

Continued on following page

Zyclara® [zi-clar-a]
(imiquimod) Cream
3.75%

BRIEF SUMMARY OF PRESCRIBING INFORMATION
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION
INDICATIONS AND USAGE
External Genital Warts

ZYCLARA Cream is indicated for the treatment of external genital and perianal warts (EGW)/condyloma acuminata in patients 12 years or older.

Limitations of Use

Treatment with ZYCLARA has not been studied for prevention or transmission of HPV.

Unevaluated Populations

The safety and efficacy of ZYCLARA Cream have not been established in the treatment of:
• urethral, intra-vaginal, cervical, rectal or intra-anal human papilloma viral disease.
• actinic keratosis when treated with more than one 2-cycle treatment course in the same area.
• patients with xeroderma pigmentosum.
• superficial basal cell carcinoma.
• immunosuppressed patients.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS
Local Skin Reactions

Intense local skin reactions including skin weeping or erosion can occur after a few applications of ZYCLARA Cream and may require an interruption of dosing. ZYCLARA Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease.

Administration of ZYCLARA Cream is not recommended until the skin is healed from any previous drug or surgical treatment.

Systemic Reactions

Flu-like signs and symptoms may accompany, or even precede, local skin reactions and may include fatigue, nausea, fever, myalgias, arthralgias, malaise and chills. An interruption of dosing and assessment of the patient should be considered.

Lymphadenopathy occurred in 2% of subjects with actinic keratosis treated with ZYCLARA Cream. This reaction resolved in all subjects by 4 weeks after completion of treatment.

Ultraviolet Light Exposure Risks

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of ZYCLARA Cream. Patients should be warned to use protective clothing (e.g., a hat) when using ZYCLARA Cream. Patients with sunburn should be advised not to use ZYCLARA Cream until fully recovered. Patients who may have considerable sun exposure, e.g. due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using ZYCLARA Cream.

In an animal photo-carcinogenicity study, imiquimod cream shortened the time to skin tumor formation. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid natural or artificial sunlight exposure.

Increased Risk of Adverse Reactions with Concomitant Imiquimod Use

Concomitant use of ZYCLARA and any other imiquimod products, in the same treatment area, should be avoided since they contain the same active ingredient (imiquimod) and may increase the risk for and severity of local skin reactions.

The safety of concomitant use of ZYCLARA Cream and any other imiquimod products has not been established and should be avoided since they contain the same active ingredient (imiquimod) and may increase the risk for and severity of systemic reactions.

Immune Cell Activation in Autoimmune Disease

ZYCLARA Cream should be used with caution in patients with pre-existing autoimmune conditions because imiquimod activates immune cells.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience: External Genital Warts

In two double-blind, placebo-controlled studies 602 subjects applied up to one packet of ZYCLARA Cream or vehicle daily for up to 8 weeks.

The most frequently reported adverse reactions were application site reactions and local skin reactions. Selected adverse reactions are listed in Table 1.

Table 1: Selected Adverse Reactions Occurring in ≥2% of ZYCLARA Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Trials (EGW)

Preferred Term	ZYCLARA Cream 3.75% (N=400)	Vehicle Cream (N=202)
Application site pain	28 (7%)	1 (<1%)
Application site irritation	24 (6%)	2 (1%)
Application site pruritus	11 (3%)	2 (1%)
Vaginitis bacterial*	6 (3%)	2 (2%)
Headache	6 (2%)	1 (<1%)

*Percentage based on female population of 6/216 for ZYCLARA Cream 3.75% and 2/106 for vehicle cream

Local skin reactions were recorded as adverse reactions only if they extended beyond the treatment area, if they required any medical intervention, or they resulted in patient discontinuation from the study. The incidence and severity of selected local skin reactions are shown in Table 2.

Table 2: Selected Local Skin Reactions in the Treatment Area Assessed by the Investigator (EGW)

All grades*, (%)	Severe, (%)	ZYCLARA Cream 3.75% (N=400)	Vehicle Cream (N=202)
Erythema*		70%	27%
	Severe erythema	9%	<1%
Edema*		41%	8%
	Severe edema	2%	0%
Erosion/ulceration*		36%	4%
	Severe erosion/ulceration	11%	<1%
Exudate*		34%	2%
	Severe exudate	2%	0%

*Mild, Moderate, or Severe

The frequency and severity of local skin reactions were similar in both genders, with the following exceptions: a) flaking/scaling occurred in 40% of men and in 26% of women and b) scabbing/crusting occurred in 34% of men and in 18% of women.

In the clinical trials, 32% (126/400) of subjects who used ZYCLARA Cream and 2% (4/202) of subjects who used vehicle cream discontinued treatment temporarily (required rest periods) due to adverse local skin reactions, and 1% (3/400) of subjects who used ZYCLARA Cream discontinued treatment permanently due to local skin/application site reactions.

Other adverse reactions reported in subjects treated with ZYCLARA Cream include: rash, back pain, application site rash, application site cellulitis, application site excoriation, application site bleeding, scrotal pain, scrotal erythema, scrotal ulcer, scrotal edema, sinusitis, nausea, pyrexia, and influenza-like symptoms.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of imiquimod. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Application Site Disorders: tingling at the application site.

Body as a Whole: angioedema.

Cardiovascular: capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, supraventricular tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope.

Endocrine: thyroiditis.

Gastro-Intestinal System Disorders: abdominal pain.

Hematological: decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma.

Hepatic: abnormal liver function.

Infections and Infestations: herpes simplex.

Musculo-Skeletal System Disorders: arthralgia.

Neuropsychiatric: agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide.

Respiratory: dyspnea.

Urinary System Disorders: proteinuria, urinary retention, dysuria.

Skin and Appendages: exfoliative dermatitis, erythema multiforme, hyperpigmentation, hypertrophic scar, hypopigmentation.

Vascular: Henoch-Schonlein purpura syndrome.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. ZYCLARA Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The animal multiples of human exposure calculations were based on daily dose comparisons for the reproductive toxicology studies described in this label. The animal multiples of human exposure were based on weekly dose comparisons for the carcinogenicity studies described in this label. For the animal multiple of human exposure ratios presented in this label, the Maximum Recommended Human Dose (MRHD) was set at 2 packets (500 mg cream) per treatment of actinic keratosis with ZYCLARA Cream (imiquimod 3.75%, 18.75 mg imiquimod) for BSA comparison. The maximum human AUC value obtained in the treatment of external genital and perianal warts was higher than that obtained in the treatment of actinic keratosis and was used in the calculation of animal multiples of MRHD that were based on AUC comparison.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day (163X MRHD based on AUC comparisons) included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (28X MRHD based on AUC comparisons).

Intravenous doses of 0.5, 1 and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (2.1X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (115X MRHD based on AUC comparisons).

A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (25X MRHD based on AUC comparisons), the highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (25X MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (12X MRHD based on AUC comparisons).

Nursing Mothers

It is not known whether imiquimod is excreted in human milk following use of ZYCLARA Cream. Because many drugs are excreted in human milk, caution should be exercised when ZYCLARA Cream is administered to nursing women.

Pediatric Use

Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established.

Geriatric Use

Clinical studies of ZYCLARA Cream for EGW did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Of the 400 subjects treated with ZYCLARA Cream in the EGW clinical studies, 5 subjects (1%) were 65 years or older.

OVERDOSAGE

Topical overdosing of ZYCLARA Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions.

Hypotension was reported in a clinical trial following multiple oral imiquimod doses of >200 mg (equivalent to ingestion of the imiquimod content of more than 21 packets of ZYCLARA). The hypotension resolved following oral or intravenous fluid administration.

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Obesity Is a Barrier to Mammography Compliance

BY ESTHER FRENCH

FROM THE JOURNAL OF WOMEN'S HEALTH

Younger age, obesity, more recent health plan membership, and lower family income all reduce the likelihood that a woman will complete a mammogram, reported Dr. Adrianne C. Feldstein and her associates at Kaiser Permanente Northwest in Portland, Ore.

Younger age increased the likelihood that a woman would report being "too busy" to get a mammogram and that she would have more doubts about its usefulness or accuracy. Family income was a more significant variable than was race in mammogram completion, which is "consistent with findings from other studies," they noted (J. Womens Health 2011 [doi:10.1089/jwh.2010.2195]).

The study cited 25% of the patients as reporting that a mammogram 'causes too much pain,' and in obese patients the percentage rose to 31%.

In a study of 4,708 women aged 50-69 years, investigators first evaluated a patient's likelihood of completing a mammogram during a 10-month follow-up period after patients received multiple reminders over 3-4 months. Variables included age, visits to an ob.gyn. or primary care physician, race, family income, length of health plan membership, and body mass index.

In the study's second phase, a subgroup of 340 women completed a mail-in survey that identified barriers to and facilitators for mammograms by answering yes or no to provided statements such as "I'm embarrassed about having mammogram." Their replies showed that although repeated reminders are effective, significant obstacles still remain.

Pain emerged as one of the major barriers for patients. The study cited 25% of the patients as reporting that a mammogram "causes too much pain," and in obese patients the percentage rose to 31%. The relationship between pain and obesity remains unclear and could be the subject of further investigation, Dr. Feldstein said in an interview.

Meanwhile, she recommended that mammography providers explore ways to reduce pain for all patients.

"If you have the technician do the initial compression, and then the patient verbally controls the pressure from that point on, that seems to reduce the patient's pain and still preserve the quality of the x-ray image," Dr. Feldstein said.

The study was funded by the National Cancer Institute. Dr. Feldstein and her associates said they had no relevant financial disclosures. ■

Continued from previous page

ate exposure for the drug's adverse impact upon oocyte yield to be reversed (Fertil. Steril. 2009; 92:515-9).

Of course, treatment of an ectopic pregnancy involves only a brief course of methotrexate, not the many years of exposure faced by rheumatology patients. A key question is whether these patients take an irreversible hit to the primordial oocyte pool, or if their oocyte count will eventually recover after they come off methotrexate. Dr. Cooper said she hopes to provide an answer by continuing to follow the small subgroup of participants in her study who have discontinued methotrexate, often because of intolerance. Another yet-to-be-resolved question, she said, is whether prepubertal girls are more protected from methotrexate's adverse effect upon fertility, or at greater risk.

A novel finding in her study was that hormonal contraception – used by 17% of participants – was independently associated with a decline in AMH levels over time. "This is an important observation that warrants further investigation," she said.

Her study is funded by a grant from the Society for Reproductive Endocrinology and Infertility. She reported no relevant financial disclosures. ■

Help her look forward to lighter days

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- Consistent reduction in MBL across all cycles studied —Reduced MBL as early as the first menstrual cycle
- Dosed only during menstruation, for up to 5 days

LYSTEDA™ (tranexamic acid) tablets are indicated for the treatment of cyclic heavy menstrual bleeding. Prior to prescribing LYSTEDA, exclude endometrial pathology that can be associated with heavy menstrual bleeding.

Important Safety Information

LYSTEDA is contraindicated in women with active thromboembolic disease or a history or intrinsic risk of thrombosis or thromboembolism, including retinal vein or artery occlusion; or known hypersensitivity to tranexamic acid.

The risk of thrombotic and thromboembolic events may increase further when hormonal contraceptives are administered with LYSTEDA, especially in women who are obese or smoke cigarettes. Women using hormonal contraception should use LYSTEDA only if there is a strong medical need and the benefit of treatment will outweigh the potential increased risk of a thrombotic event. Do not use LYSTEDA in women who are taking more than the approved dose of a hormonal contraceptive.

Concomitant use of LYSTEDA with Factor IX complex concentrates, anti-inhibitor coagulant concentrates or all-trans retinoic acid (oral tretinoin) may increase risk of thrombosis. Visual or ocular adverse effects may occur with LYSTEDA. Immediately discontinue use if visual or ocular symptoms occur. In case of severe allergic reaction, discontinue LYSTEDA and seek immediate medical attention. Cerebral edema and cerebral infarction may be caused by use of LYSTEDA in women with subarachnoid hemorrhage. Ligneous conjunctivitis has been reported in patients taking tranexamic acid.

The most common adverse reactions in clinical trials (≥5%, and more frequent in LYSTEDA subjects compared to placebo subjects) were: headache, sinus and nasal symptoms, back pain, abdominal pain, musculoskeletal pain, joint pain, muscle cramps, migraine, anemia, and fatigue.

LYSTEDA has not been studied in adolescents under age 18 with heavy menstrual bleeding.

Please see Brief Summary of Prescribing Information on adjacent page.

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