

# COX-2 Options Restricted, CAM May Gain Ground

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CHICAGO — The withdrawal of rofecoxib and valdecoxib from the market may give an even greater number of arthritis patients the impetus to try non-pharmacologic therapies, Sharon L. Kolasinski, M.D., said at a symposium sponsored by the American College of Rheumatology.

Already, roughly half of adults in the

United States have tried complementary and alternative medicines (CAM), and patients with rheumatoid arthritis (RA) are among the highest users, said Kolasinski, assistant professor of medicine and chief of clinical services at the University of Pennsylvania School of Medicine, Philadelphia.

This trend isn't all bad as some alternative therapies can help reduce pain and keep the arthritis patient active, she said.

"Nonpharmacologic therapies are an

important part of what our patients are actually choosing to use whether we suggest it or not," said Dr. Kolasinski.

"The evidence suggests that mind-body interventions can be of considerable benefit including coping with chronic pain, and perhaps we should consider them more often."

There is a substantial body of evidence-based research supporting the use of mind-body interventions such as meditation, cognitive behavioral therapy,

and biofeedback. Additionally, tai chi, yoga, and acupuncture may be appropriate adjunctive therapies in some patients.

Dr. Kolasinski said the evidence does not support the use of magnetic bracelets or mattress pads, although copper bracelets are a common sight in many rheumatologists' offices.

An intriguing study of 20 RA patients demonstrated an American College of Rheumatology (ACR) 20 response in half of the patients practicing tai chi, and no similar response in patients enrolled in a stretching and wellness education program for 12 weeks.

Dr. Kolasinski and colleagues at the university found that 8 weekly sessions of yoga significantly improved Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain and disability scores in seven women with OA.

Stiffness also improved, however, not significantly, she said.

A follow-up gait study to determine if the effects were merely due to increased personal attention, showed that walking speed increased after yoga (Osteoarthritis and Cartilage 2003;11:S44).

The results suggest that the

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regimen may be appropriate for patients with valgus knee deformities, however, it may not be for those with valgus deformities, she said.

There are few data on the value of acupuncture in RA, but a definitive study in patients with knee osteoarthritis (OA) concluded that acupuncture is a reasonable adjunctive therapy for pain relief, particularly for patients without other options.

Relative to a sham control group, significant improvements in WOMAC pain and function scores were reported in 570 knee OA patients who previously had been treated with high-dose drug therapy and who had received 23 acupuncture sessions over 26 weeks (Ann. Intern. Med. 2004;141:901-10).

In particular, WOMAC function scores were nearly 3 points better in the true acupuncture group compared with function scores in the sham group.

Differences between the groups were not significant, however, in WOMAC measures of pain or global assessment, according to the investigators who were based at the University of Maryland School of Medicine, Baltimore.

High dropout rates are common in nonpharmacologic therapy trials, suggesting that physicians may want to propose a variety of adjunctive therapies to help keep arthritis patients physically active, she said.

## BARR LABORATORIES, INC. Brief Summary (See package brochure for full prescribing information).

**Trexall™** (methotrexate tablets, USP)  
Rx only

### WARNINGS:

- METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTI-METABOLITE THERAPY. BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL), METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY. DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS. PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See PRECAUTIONS.) PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.
- Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women child-bearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate. (See CONTRAINDICATIONS.)
  - Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.
  - Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See PRECAUTIONS, Drug Interactions.)
  - Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions are not preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See PRECAUTIONS, Organ System Toxicity, Hepatic.)
  - Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5 mg/week. It is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.
  - Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.
  - Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
  - Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.
  - Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See PRECAUTIONS, Organ System Toxicity, Skin.)
  - Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.
  - Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

### INDICATIONS AND USAGE:

#### Neoplastic Diseases:

**Trexall™** (methotrexate tablets) are indicated in the treatment of gestational choriocarcinoma, choriocarcinoma destruens and hydatidiform mole.

Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides, (cutaneous T cell lymphoma), and lung cancer, particularly squamous cell and small cell types. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas.

#### Psoriasis:

**Trexall™** (methotrexate tablets) are indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis flare is not due to an undiagnosed concomitant disease affecting immune responses.

**Rheumatoid Arthritis Including Polyarticular-Course Juvenile Rheumatoid Arthritis:**

**Trexall™** (methotrexate tablets) are indicated in the management of selected adults with severe, active, rheumatoid arthritis (ARA criteria), or children with active juvenile rheumatoid arthritis, who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs). Aspirin, NSAIDs, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored (see PRECAUTIONS, Drug Interactions). Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cyclosporin agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

#### CONTRAINDICATIONS:

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (see PRECAUTIONS) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one full menstrual cycle after therapy for female patients. (See Boxed WARNINGS.)

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers. Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

#### WARNINGS: SEE BOXED WARNINGS.

#### PRECAUTIONS:

**General:** Methotrexate has the potential for serious toxicity. (See Boxed WARNINGS.) Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer. (See OVERDOSAGE.) If methotrexate therapy is reinstated, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

**Information for Patients:** Patients should be advised of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need to close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be written or refilled on a PRN basis. Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproductions should be discussed with both male and female patients taking methotrexate.

**Laboratory Tests:** Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended; hematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial or changing doses, or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated. Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See PRECAUTIONS, Organ System Toxicity, Hepatic.)

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

**Drug Interactions:** Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant methotrexate and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxic (e.g., azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate. Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by an additive antifolate effect.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal

somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which is considered completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. Benefits should be weighed against the potential risks before using methotrexate alone or in combination with other drugs, especially in pediatric patients or young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

#### Pregnancy:

Psoriasis and rheumatoid arthritis. Methotrexate is in Pregnancy Category X. See CONTRAINDICATIONS.

#### Nursing Mothers:

See CONTRAINDICATIONS.

#### Pediatric Use:

Safety and effectiveness in pediatric patients have been established, only in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis.

Published clinical studies evaluating the use of methotrexate in children and adolescents (i.e., patients 2 to 16 years of age) with JRA demonstrated safety comparable to that observed in adults with rheumatoid arthritis. (See CLINICAL PHARMACOLOGY, ADVERSE REACTIONS AND DOSAGE AND ADMINISTRATION.)

#### Organ System Toxicity:

**Gastrointestinal:** If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

**Hematologic:** Methotrexate can suppress hematopoiesis and cause anemia, aplastic anemia, leukopenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n=128), leukopenia (WBC <3000/mm<sup>3</sup>) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm<sup>3</sup>) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound neutropenia and fever should be escalated immediately and fever should require parenteral broad-spectrum antibiotic therapy.

**Hepatic:** Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is advised in patients with preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2-4 months), 2) a total cumulative dose of 1.5 grams, and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common pretherapy. Although these mild changes are usually of no consequence, if they are detected, the drug should be discontinued.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 50 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretherapy liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored as per recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

**Infection or Immunologic States:** Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

**Neurologic:** There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had cranial irradiation. Serious neurologic sequelae, including optic neuritis, have been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m<sup>2</sup>). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dosage regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, transient blindness, seizures and coma. The exact cause is unknown.

**Pulmonary:** Pulmonary symptoms (especially a dry nonproductive cough) or a nonspecific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection needs to be excluded. This lesion can occur at all dosages.

**Renal:** High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

**Skin:** Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal administration. Reactions are usually more severe in patients who are treated with high doses of methotrexate. Patients with psoriasis and non-neoplastic diseases.

**Other Precautions:** Methotrexate should be used with extreme caution in the presence of debility. Methotrexate exits slowly from third-space compartments (e.g., pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third-space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

#### ADVERSE REACTIONS:

**IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN THE PREVIOUS SECTION. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.**

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse reactions are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

**Alimentary System:** Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemes, melena, gastrointestinal ulceration and enteritis, parotitis.

**Blood and Lymphatic System Disorders:** Suppressed hematopoiesis causing anemia, aplastic anemia, leukopenia and/or thrombocytopenia. Hypogammaglobulinemia has been reported rarely.

**Cardiovascular:** Pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

**Central Nervous System Disorders:** Headache, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient sublethal cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy.

**Infection:** There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections included sepsis, necrotic, histoplasmosis, cryptococcosis, *Herpes zoster*, *H. simplex* hepatitis, and disseminated *H. simplex*.

**Musculoskeletal System:** Stiffness, fracture.

**Ophthalmic:** Conjunctivitis, serious visual changes of unknown etiology.

**Pulmonary System:** Respiratory fibrosis, respiratory failure, interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

**Skin:** Erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration, and exfoliative dermatitis.

**Urogenital System:** Severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomasia; infertility, abortion, fetal defects.

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

**Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies:** The approximate incidences of methotrexate-attributed (i.e., placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids. Hepatic histology was not examined in these short-term studies. (See PRECAUTIONS.)

**Incidence greater than 10%:** Elevated liver function tests 15%, nausea/vomiting 10%, rash/pruritus 10%, stomatitis 10%, dizziness 10%, anemia 10%, leukopenia 10%, pancytopenia 10%, thrombocytopenia 10%.

**Incidence 1% to 3%:** Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm<sup>3</sup>), pancytopenia, dizziness. Two other controlled trials of patients (n=680) with Rheumatoid Arthritis on 7.5 mg - 15 mg/wk oral doses showed an incidence of interstitial pneumonitis of 1%. (See PRECAUTIONS.)

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

**Adverse Reactions in Psoriasis:** There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969 and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3% and 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies.

**Adverse Reactions in JRA Studies:** The approximate incidences of adverse reactions reported in pediatric patients with JRA treated with oral, weekly doses of methotrexate (5 to 20 mg/m<sup>2</sup>/wk or 0.1 to 0.65 mg/kg/wk) were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14%; gastrointestinal reactions (e.g., nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 12%; alopecia, 0.5%; dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m<sup>2</sup>/wk in JRA, the published data for doses above 20 mg/m<sup>2</sup>/wk are too limited to provide reliable estimates of adverse reaction rates.

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