

Rheumatoid Arthritis: Focus on Appropriate Drug Therapy

Song Sullivan, PharmD; and Melanie Swims, PharmD, BCPS

This activity is designed for physicians, pharmacists, nurses, and general audiences.

GOAL

To understand the basic pathophysiology of rheumatoid arthritis, diagnosis, drug therapy, and monitoring.

OBJECTIVES

1. Describe the mediators thought to be involved in the pathophysiology of rheumatoid arthritis.
2. List the criteria for diagnosis of rheumatoid arthritis.
3. Understand the different drug therapy strategies used in treatment of rheumatoid arthritis.
4. Discuss the side-effect profile of drugs discussed in the following article and monitoring variables recommended.
5. List the major drug interactions for these drugs.
6. Become familiar with newer therapies under investigation for the treatment of rheumatoid arthritis.

Rheumatoid arthritis (RA) is an autoimmune disease affecting about 1% of the world's adult population and 2.5 million persons in the United States.^{1,2} The disease is primarily characterized by morning stiffness and swelling of joints, occurrences that fluctuate in intensity and duration and that can lead to progressive destruction of joints, severe functional decline, and premature mortality.^{1,3,7} Within 10 years of disease onset, 50% of patients are unable to work due to the progression of their disease.⁸ Although the number of patients affected by this disease is small, they account for more than 9 million physician visits and more than 250,000 hospitalizations per year.⁹ The annual cost of treating RA for one patient has been estimated between \$5000 and \$7000, which is an average of three times the cost of medical care for patients of the same age and sex who do not have RA.^{10,11}

To date, there is no known etiology or cure for this progressively debilitating disease. Even without a cure, the disease is always treatable and is controllable in the majority of patients. Historically, the progression of RA and the associated early mortality were clearly underestimated. RA was originally considered a benign disease, and the perceived drug toxicities of second-line therapies were thought to outweigh the benefits of early treatment. Rheumatologists now recommend earlier initiation of therapy with slow-acting antirheumatic drugs (SAARDs) and understand the toxicities associated with even the "first-line" non-steroidal anti-inflammatory agents.



CONTINUING EDUCATION CREDIT

This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council of Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-000-98-207-L-04. This course expires on June 30, 2000.

From the Veterans Affairs Medical Center, Memphis, TN (S.S. and M.S.); and the Department of Pharmacy Practice and Pharmacoeconomics, University of Tennessee, College of Pharmacy, Memphis, TN (M.S.).

Address correspondence to: Melanie Swims, PharmD, BCPS, VA Medical Center, Department of Pharmacy (119), 1030 Jefferson Avenue, Memphis, TN 38104

... PATHOPHYSIOLOGY ...

Although the cause of RA is unknown, it is thought to be an autoimmune-mediated disorder. It begins when an immunogenetically susceptible host is exposed to an endogenous or exogenous antigen that initiates an immune response within the joint.¹² Potential endogenous antigens include collagen,

glycosaminoglycans, and rheumatoid factors. Potential exogenous factors include infectious agents such as mycoplasma, mycobacterium, spirochetes, bacterial products, and viruses.^{12,13} For example, heat shock proteins found in mycobacteria have been shown to induce adjuvant arthritis in rats, and high levels of heat shock proteins are found in patients with RA.¹⁴

Epstein-Barr virus has also been investigated as a potential cause of RA. In one study,¹⁵ 80% of patients with RA were found to have circulating antibodies against Epstein-Barr virus. In another study,¹⁶ RA patients had increased B lymphocytes infected with the Epstein-Barr virus and decreased T-cell response to the virus. Whatever the etiologic factor, when the initial exposure and resulting inflammation become prolonged, it leads to the chronic inflammatory process of RA. Research continues in determining the potentially multifactorial etiology.

Genetic Factors

The major histocompatibility complex (MHC) on chromosome 6 encodes important predisposing genes.¹⁷ The majority of patients with RA have the class II MHC alleles DR1, DR4, or both. RA is six times more common in dizygotic twins and children of rheumatoid factor-positive patients.^{17,18} If one of a pair of identical twins has the disease, the other twin is 30 times more likely to develop RA.

The Synovium

The initial complaint of patients with RA is often acute joint pain. The pathologic condition of the synovial lining is critical in understanding the disease process. The earliest change observed in RA patients is damage to the vascular endothelial cells and swelling of the synovium.¹⁹ Fibrin deposition, polymorphonuclear leukocyte invasion, and hyperplasia of the lining are also seen. Soon after, T and B lymphocytes accumulate in the perivascular area. This stimulates an immune cascade resulting in a release of cytokines, products of the complement cascade, metabolites of the arachidonic acid cycle, nitric oxide, and proteolytic enzymes.¹² Cytokines act directly on endothelial cells to induce the expression of endothelial-leukocyte adhesion molecules that result in a "hyperadhesive" endothelium.²⁰ The result is chronic inflammation of the intra-articular spaces of bone and cartilage leading to joint destruction. Synovial B fibroblast cells often take on a tumorlike appearance but are not truly malignant. Many of these cells show evidence of oncogene activations and mutations associated with tumors.

Lymphocytes

Also of interest in the pathogenesis of RA is the role of lymphocytes. Once an antigen-presenting cell such as a macrophage engulfs a cell, inflammatory mediators including interleukin-1, tumor necrosis factor- α , coagulation factors, and numerous others are released. These mediators enhance the adhesiveness of endothelial cells for lymphocytes.²¹ The synovium of RA patients contain high concentrations of lymphocytes.¹⁹ As the disease progresses, the number of these cells increases. When T lymphocytes are activated, they produce cytokines, interleukins, B-cell growth factor, and B-cell differentiation factor.²² These products are directly toxic to tissues, and cytokines stimulate further inflammatory processes and attract cytotoxic cells to inflamed areas.¹⁷

T cells bearing specific T-cell receptors are selectively retained in the RA synovium. With continuous exposure to the antigen, lymphocytes accumulate and the lining of the microvasculature hypertrophies and the inflammatory process becomes chronic.²³ Drugs such as cyclosporine, which block T cells, are used today to treat RA. Because the lymphocytes play such a pivotal role, many experimental RA therapies are specifically targeting the T cells, with varied success.

Rheumatoid Factor

The role of the rheumatoid factors is also important. Rheumatoid factor is present in the serum of more than 70% of patients with RA.²³ These patients have a tendency toward more severe disease with nodules and erosions of joints. Activation of the complement cascade can be initiated by large rheumatoid factor complexes.²⁴ Local damage can occur when the superficial layers of cartilage are exposed to rheumatoid factors. This can further be exacerbated by the release of inflammatory mediators by the synovial lining cells.

The pathogenesis of RA is a complicated cascade of events involving numerous mediators, cells, and reactions. The interactions of various cell types result in progression of the disease. With additional investigation into the complex processes, we may further understand RA and may discover more specific ways to treat the disease.

... DIAGNOSIS ...

The cornerstone of RA diagnosis is a careful clinical history with an in-depth physical examination. Because there are no conclusive laboratory tests that can be used alone to diagnose the disease, all factors

must be considered equally important. The criteria²⁵ shown in Tables 1 and 2 are useful guidelines for diagnosis. These criteria were last revised in 1988 and are 91% to 94% sensitive and 89% specific for the diagnosis of RA. Other conditions can manifest similarly to RA, including systemic lupus erythematosus, psoriatic arthritis, and spondyloarthropathies.¹⁷

... THERAPEUTIC STRATEGIES ...

Drug therapy of RA has changed dramatically in this decade compared with the traditional "therapeutic pyramid" method that initiated treatment with aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Medications thought to be more toxic and more effective were added to the drug regimen later. These conservative pyramidal strategies have not improved long-term outcome.²⁶ NSAIDs, previously believed to be less toxic, were

proven to be more toxic,²⁷ while SAARDs, also known as disease-modifying antirheumatic drugs, proved to be less toxic than predicted.²⁸ Thus, the use of NSAIDs is now reserved for the few patients with a benign form of RA or as adjunctive therapy while the contemporary SAARD-based therapies have become the accepted basis for therapeutic management of RA. Because there is no "perfect" drug or cure for this disease, the goal of therapy should be effective control of the inflammatory processes of RA leading to remission. Radiographic progression is one variable often reviewed as a potential predictor of long-term disability. Evidence to date shows that SAARDs variably affect radiographic progression.²⁹ For the majority of patients, the risk of early joint destruction is high and therapy with SAARDs is necessary.

Many clinicians also use corticosteroids, particularly prednisone, in the treatment of RA. This is likely due, at least in part, to the slow onset of the SAARDs. The appropriateness of this approach is widely debated.³⁰ The efficacy of short-term steroid therapy in treatment of RA pain and inflammation is indisputable, and recent evidence has even shown a decrease in the rate of radiographic progression over a 2-year period.³¹ Long-term side effects, even at low doses, are serious and include fractures, infection, and gastrointestinal complications.³² The risk versus benefit of treating with corticosteroids is continuing to be evaluated by clinicians on a patient-by-patient basis.

Over the years, various therapeutic strategies for the optimal use of SAARDs have been explored. The "step down bridge" treatment proposed that combinations of medications should be used early to gain control of inflammation in a critical time.³³ This treatment should then be "bridged" by withdrawing drugs sequentially. The "sawtooth" strategy is based on the observation that only 5% to 15% of patients with RA who initially respond to SAARDs will continue to benefit from the same drug after 5 years.³⁴ This theory proposes that response to SAARDs only makes progression to disability irregular (like a sawtooth).³⁵ Proponents of the sawtooth strategy recommend early SAARD use, regular monitoring for disability to detect disease progression, sequential change in SAARD treatment when the patient reaches his or her disability ceiling, and use of analgesics and NSAIDs as adjunctive therapy rather than as initial therapy.

Combination SAARD therapy has been used with greater frequency than monotherapy. In one survey,³⁶ 90% of rheumatologists in the United

Table 1. Symptom List*

1. Morning stiffness in and around joint lasting at least 1 hour before maximal improvement is noted
2. Swelling of the soft tissue (arthritis) around three or more joints
3. Swelling of the proximal interphalangeal, metacarpophalangeal, or wrist joints
4. Symmetric arthritis
5. Subcutaneous nodules
6. Positive rheumatoid factor test result
7. Radiographic evidence of erosions, periarticular osteopenia, or both in the joints of the hand, wrist, or both

*Symptoms 1 through 4 must be present for at least 6 weeks; symptoms 5 through 7 may also be present in some patients

Table 2. Laboratory Findings (Useful but not Always Conclusive)

1. Nonspecific decrease of serum hemoglobin with elevated erythrocyte sedimentation rate
2. Positive rheumatoid factor
3. Increased C-reactive protein
4. Synovial fluid with greater than 2000 cells/uL that contain rheumatoid factor

States used combination therapy to treat approximately 17% of their RA patients. This approach is based on the belief that two or more drugs used in combination will be more effective than one of these drugs used alone.³⁷ One of the goals of this strategy is to enhance efficacy while keeping the level of toxicity at the same range as seen with monotherapy. Because methotrexate is the most effective SAARD monotherapy, combination therapies are recommended to include this drug.³⁸ This therapeutic strategy is still controversial, and no study to date has demonstrated conclusive long-term benefit.

... SLOW-ACTING ANTIRHEUMATIC DRUGS ...

Table 3 lists the symptoms to be monitored to assess adverse drug effects of the SAARDs discussed in the following paragraphs.

Gold Compounds—Intramuscular and Oral

Formulations include gold sodium thiomalate (Myochrysine[®]), aurothioglucose (Solganal[®]), and auranofin (Ridaura[®]).

Mechanism of Action. Gold compounds inhibit mononuclear phagocyte function, B and T lymphocyte responses, cytokines, and endothelial cell and fibroblast proliferation.⁴⁰ Onset of action is very slow.

Dose. Intramuscular (IM) Gold—The initial dose is a 10-mg test dose followed by 25-mg test dose a week later, then weekly 50-mg doses until a total of 1 g is achieved. The maintenance regimen is 50 mg every 2 weeks for 3 months or until 1.5 g total, then 50 mg every 3 weeks, then 50 mg every month. There is no evidence of additional efficacy for doses greater than 50 mg, and more frequent dosing is implemented for flares while following the maintenance regimen. Approximate time to benefit is 3 to 6 months.

Oral (PO) Gold—The initial dose is 3 mg twice daily up to 3 mg three times daily. Some recent data suggest that lower doses of 2 mg are effective if side effects will not permit normal dosing.⁴¹ Approximate time to benefit is 4 to 6 months.

Pharmacokinetics. IM Gold—Peak effect occurs in 3 to 6 hours. The effect of aurothioglucose is slower and more irregular. IM gold is distributed into deep tissue compartments in concentrations higher than

achieved with PO gold. Arthritic joints contain 2 to 2.5 times greater concentrations than other joints. Renal elimination accounts for 70% of excretion while 30% is eliminated in the feces.

PO Gold—Absorption occurs at a rate of 20% to 25%. PO gold is distributed into deep tissue compartments, and the ratio of plasma to synovial concentrations is 1.7. Half-life increases with increasing doses. The substance is 60% bound to albumin and 95% eliminated in the feces. Steady-state concentrations occur at 8 to 16 weeks.⁴²

Side Effects. IM Gold—Immediate “nitroid reaction” occurs, manifested by flushing, weakness, dizziness, sweating, and occasional hypotension and syncope. This may be circumvented by using the sesame seed oil formulation aurothioglucose, which has a slower bioavailability. Rashes account for 60% to 80% of gold toxicity, with a wide range of severity including erythema, stomatitis, and exfoliative dermatitis. Pruritus is also common and is aggravated by sun exposure. Nephropathy manifested as proteinuria occurs in 1% to 3% of patients; the drug should be discontinued if proteinuria is >1 g.⁴²⁻⁴⁴ If proteinuria is ≤1 g, a 24-hour urine specimen should be collected and cessation of the drug should be considered if the protein excretion is >500 mg/24 h. Other renal toxicities include nephrotic syndrome, which is reversible, and glomerulonephritis, which is an indication to stop therapy.

Table 3. Monitoring for Adverse Drug Effects with Each Visit

Drug	Symptom to be Monitored
IM/PO Gold	Rash, stomatitis, fever, bleeding, sore throat
Hydroxychloroquine	Changes in vision
Penicillamine	Symptoms of myelosuppression,* edema, rash
Methotrexate	Symptoms of myelosuppression, breathing difficulties, nausea, vomiting
Cyclosporine	Edema, increase in blood pressure
Azathioprine	Symptoms of myelosuppression
Sulfasalazine	Symptoms of myelosuppression, rash, photosensitivity
Cyclophosphamide	Symptoms of myelosuppression, hematuria

IM = intramuscular; PO = oral.

*Fever, easy bruising, bleeding, and symptoms of infection

Adapted from reference 39.

Hematologic effects include aplastic anemia, occurring in <1% of patients, and thrombocytopenia, which has an occurrence rate of 1% to 3%.⁴⁵ Drug therapy should be withdrawn if the white blood cell count (WBC) decreases to <3500 or if platelets decrease to <100,000. There is also a rare risk of agranulocytosis and aplastic anemia; the risk of eosinophilia, however, is relatively high (40% incidence rate).

PO Gold—Side effects are similar to IM gold but incidence of renal and hematologic toxicities are lower.⁴⁵ However, gastrointestinal side effects are higher, with a 40% incidence of diarrhea and 16% incidence of nausea, vomiting, and cramping.

Monitoring. Baseline complete blood count (CBC), urinalysis (UA), and creatinine should be obtained. CBC and UA should continue to be monitored before each weekly injection for 20 weeks, and then may be transitioned to every other injection in patients receiving therapy for more than 6 months and if prior levels have remained stable.⁴⁵

Drug Interactions. Interactions include additive toxicity with penicillamine, increased incidence of rash with hydroxychloroquine, and increased incidence of "nitroid reaction" in patients being given concurrent angiotensin-converting enzyme inhibitors.

Hydroxychloroquine (Plaquenil®)

Mechanism of Action. Hydroxychloroquine is thought to stabilize lysosomal membranes leading to diminished vesicle fusion and exocytosis of phagocytized lysosomal contents including inflammatory mediators. It also inhibits oxygen-free radicals.⁴¹

Dose. The initial dose of hydroxychloroquine (Plaquenil®) is 6.5 mg/kg of lean body weight given once or twice daily with a maximum daily dose of 400 mg. Chloroquine (Aralen®), another antimalarial agent that is less commonly used for RA, is given as 3.0 mg/kg of lean body weight given once daily, with a maximum daily dose of 250 mg. Maintenance dose should be the lowest effective dose to control symptoms. Approximate time to benefit is 2 to 4 months, and a 6-month trial should be implemented before discontinuing therapy.³⁹

Pharmacokinetics. This compound is rapidly absorbed with high tissue binding and large volume of distribution; it has a long half-life of approximately 40 days. Hydroxychloroquine is distributed into the pigmented retinal epithelium and cornea. Elimination is primarily hepatic, and 20% to 40% of the drug is excreted unchanged in the feces.⁴⁶

Side Effects. Ophthalmologic toxicities include corneal deposits, which are benign and reversible, and

macular pigmentation of the retina, which occurs in up to 5% of patients.³⁹ Mild maculopathy is reversible with discontinuation of the drug. Identified risk factors include age older than 70 years and a cumulative dose of 800 g.⁴⁷ Other side effects include reversible rash, gastrointestinal complaints, and, less frequently, insomnia, myopathy, neuropathy, skin pigment changes, and leukopenia.

Monitoring. A baseline ophthalmologic examination is not widely recommended because antimalarial retinopathy reportedly does not occur with less than 9 months of therapy.⁴⁸ If therapy is continued for longer than 6 months, an ophthalmologic examination should be performed, especially in patients older than 60 years.

In patients with normal renal function receiving hydroxychloroquine for less than 6 years, ophthalmologic examinations should be performed yearly if the dose is 6.5 mg/kg per day or less.⁴⁸ If patients have been receiving the drug for more than 7 years or are at risk for retinopathy due to higher doses or renal impairment, a monthly visual field examination with associated color vision testing should be performed.

Drug Interactions. Hydroxychloroquine can increase digoxin levels.⁴⁹

Penicillamine (Cuprimine®)

Mechanism of Action. Penicillamine dissociates immunoglobulin M rheumatoid factors and also may inhibit lysosomal enzyme release and oxygen radicals. There are also immunosuppressive effects by decreasing cell-mediated immune response.⁴⁰

Dose. Therapy is initiated at 125 to 250 mg daily and increased by 125 to 250 mg/d every 8 to 10 weeks until a maximum total daily dose of 750 mg or a response is reached. Onset of action is 3 to 6 months.

Pharmacokinetics. Absorption of the compound is good with peak effects seen in 1 hour. The half-life is 2 to 7 hours, and metabolism is primarily hepatic.

Side Effects. Bone marrow toxicities of thrombocytopenia and leukopenia occur most commonly after 6 months of therapy.⁴⁵ The drug should be discontinued if any of the following occur: platelets <100,000 or decrease by 10,000 between successive counts; WBC <4000 or decrease by 4000 between successive counts; neutrophils <2000; and monocytes increase >500. There may be a decrease in hemoglobin that precedes a serious decrease in platelets or leukocytes. Proteinuria can occur in up to 32% of patients with severity ranging from mild to severe nephrotic syndrome. Drug should be discontinued permanently if the protein excretion is >2 g/24 h.⁴⁵

Rash, stomatitis, dysgeusia, and metallic taste are common side effects. Autoimmune syndromes including systemic lupus erythematosus, Goodpasture's syndrome, and myasthenia gravis can occur in rare cases.

Monitoring. CBC and UA for proteinuria should be checked every 2 weeks until the dosage is stable, then every 1 to 3 months.⁴⁴

Drug Interactions. Because penicillamine is a chelating agent, it should be taken on an empty stomach; its absorption can be reduced by as much as 70% if taken with food, iron supplements, or aluminum- or magnesium-containing antacids.⁵⁰ For optimal absorption, penicillamine should be administered 1 hour before meals or 2 hours apart from any other drug, food, or milk.⁵¹ Patients who have a history of adverse reactions to gold salts may be predisposed to toxicities from penicillamine therapy, but the reaction may not be the same.⁵² This may possibly be because penicillamine has been shown to mobilize gold from tissues and form gold-penicillamine complexes.

Methotrexate (Rheumatrex®)

Mechanism of Action. Methotrexate is a competitive inhibitor of dihydrofolate reductase, which is responsible for the production of metabolically active tetrahydrofolate. This agent affects chemotaxis and inhibits immunoglobulin production.⁴⁰ Onset of action is faster than with other agents, but there is a plateau of effect at 6 months.

Dose. Dosing ranges from 7.5 mg to 25 mg once weekly, but doses greater than 15 mg weekly are not commonly used for treatment of RA. Approximate time to benefit is 1 to 2 months.

Pharmacokinetics. At doses of 0.1 mg/kg there is complete absorption, but at higher oral doses absorption is incomplete.⁵³ Peak effect is seen in 1 to 4 hours for oral administration and 0.5 to 2 hours for intramuscular administration. Synovial concentrations are higher in inflamed joints, and the drug is 50% bound to plasma proteins. Seventy-five percent to 80% of the drug is eliminated unchanged in the urine by glomerular filtration and active tubular secretion; dose adjustments for renal dysfunction are thus necessary. Due to methotrexate's wide distribution, it is stored in the kidneys and in the liver long after drug discontinuation.

Side Effects. The most common side effect (with an incidence rate of 20% to 70%) is gastrointestinal complaints, including nausea, vomiting, and stomatitis. These side effects may be minimized by administering folic acid 1 to 3 mg daily with no loss of methotrexate's efficacy in controlling RA.⁵⁴ If folic acid administration fails to control the side effects, leuco-

vorin 2.5 to 5 mg can be administered 24 hours after the weekly methotrexate dose.⁵⁵

One of the most serious toxicities of methotrexate therapy is hepatotoxicity, with up to one third of patients undergoing long-term therapy having elevated serum aminotransferase concentrations. Calculated risk estimates of serious hepatic complications is less than 1 case in 100,000, but another source calculates the 5-year risk as 1 in 1000, and quotes the 10-year risk as 14 in 1000.⁵⁶ Identified risk factors for liver toxicity include preexisting liver disease, alcohol abuse, diabetes, old age, obesity, and renal failure.⁵⁷

Also associated with methotrexate therapy is pulmonary toxicity, which may manifest as dyspnea, non-productive cough, shortness of breath, fever, and interstitial or alveolar infiltrates on a chest x-ray. This side effect is not dose related and occurs in 2% to 6% of patients.³⁹ The risk may be higher in males who smoke. Fatal cases have been reported and some patients may tolerate a rechallenge with the agent. The treatment of pulmonary toxicity is to discontinue the drug and initiate steroids.

Decreases in WBCs and platelets can occur with an incidence of up to 22%, and pancytopenia can occur in 1.4% of patients. Other side effects include rash (up to 20%), photosensitivity, increased nodulosis, and mood disturbance.

Pregnancy should be avoided if either partner is being treated with methotrexate because of the drug's teratogenic potential. Men should wait at least 3 months and women should wait at least 1 ovulatory cycle after stopping the drug before attempting conception.³⁹

Monitoring. A baseline CBC with differential and serum creatinine should be obtained.⁴⁵ If a patient has a history of alcohol abuse, diabetes, obesity, chronic hepatitis B or C, or abnormal baseline liver test results, a pretreatment liver biopsy should be performed. Then a monthly aspartate transaminase, alanine transaminase, albumin, and CBC should be performed. If 6 of the 12 monthly liver test results are abnormal within a year, or if albumin decreases even in a patient with well-controlled RA, a liver biopsy should be performed. A chest x-ray should also be obtained before starting therapy to determine if the patient has preexisting lung disease and for baseline images to use for future comparisons.

CBC and platelet count along with liver function tests, albumin, and serum creatinine should continue to be monitored every 4 to 8 weeks.⁴⁵

Drug Interactions. Drugs that impair renal function can impair methotrexate clearance while drugs that alter normal gastrointestinal flora (eg, antibiotics) can

alter methotrexate absorption.⁵⁸ NSAIDs and aspirin reduce the clearance of methotrexate by decreasing renal elimination of the drug through a variety of mechanisms.⁵⁹⁻⁶³ Aspirin in high doses has been shown to decrease methotrexate clearance by 20% to 35%.⁶² Several studies have reported that trimethoprim/sulfamethoxazole can increase hematologic toxicities and abnormalities.^{64,65} Three mechanisms for these interactions have been proposed: sulfamethoxazole may inhibit methotrexate's renal tubular secretion, additive pharmacologic effects, or alterations in methotrexate plasma-protein binding.⁵¹ In general, highly bound drugs may also increase free methotrexate concentrations due to displacement. Two case reports have been published about patients receiving chronic methotrexate therapy who were also treated with topical fluorouracil and developed significant skin necrosis and blistering.⁶⁶ This drug combination should be used with caution.

Cyclosporine (Sandimmune®, Neoral®)

Mechanism of Action. Cyclosporine is a fungal peptide with potent and selective immunosuppressant properties. Its exact mechanism of action is still unknown but is thought to inhibit cellular production of cytokines and to regulate T-cell activation.⁶⁷ This drug was recently approved by the US Food and Drug Administration for treatment of RA in patients who have failed one other arthritis therapy.

Dose. The standard dose is 2.5 to 3.5 mg/kg per day divided twice daily or once daily. After 4 to 8 weeks, the dose is titrated up by 0.5 to 1 mg/kg per day every 1 to 2 months. The maximum dose is 5 mg/kg per day. The dose should be tapered by 0.5 mg/kg per day after a response of 3 months to the lowest possible dose. Cyclosporine should be used for a 6-month trial and up to a 3-month trial at maximum doses before determining the drug to be ineffective.

Pharmacokinetics. The absorption of this compound is variable, requiring the presence of bile salts, and is affected by gastrointestinal motility.⁵¹ Peak blood concentrations occur 3.5 hours after oral dosing. The drug is widely distributed into the body fluids and tissues with a volume of distribution of 13 L/kg and distribution varies with renal and liver function. Cyclosporine is very lipophilic and is 90% bound to proteins. This binding is saturable and is dependent on dose and temperature. There is a first-pass hepatic metabolism, with active metabolites accounting for less than 20% of activity. The half-life of the drug is 10 to 40 hours.

Side Effects. Acute and chronic nephrotoxicity may occur in 25% to 40% of patients. Systolic hypertension can occur in a small percentage of patients who have no preexisting hypertension when treated with cyclosporine.⁶⁸ This side effect is more prevalent in patients older than 65 years. Drug labeling suggests that blood pressure should be maintained at below 140/90 mm Hg before initiating treatment with Neoral®. Other side effects include hyperkalemia, hypertrichosis, increased uric acid, hyperlipidemia, glucose intolerance, gingival hyperplasia, neurotoxicity, gastrointestinal intolerance, infectious complications, and hepatotoxicity. This agent is contraindicated in patients with a history of cancer, uncontrolled hypertension, renal dysfunction, neutropenia, immunodeficiency, decreased WBC or platelets, or liver function test results more than two times normal. It should also be used with caution in patients older than 65 years or who have hypertension or epilepsy.

Monitoring. Before initiating cyclosporine, blood pressure checks on three separate occasions, serum creatinine, liver profile, Chemistry 7 profile, magnesium, uric acid, urinary protein, and fasting lipid profile should be checked for baseline values.⁶⁷

After initiation of the drug, serum creatinine should be checked every 2 weeks for the first 3 months and then monthly if the values are stable.⁶⁷ If the dose is increased or if serum creatinine begins to rise, more frequent monitoring is recommended. If creatinine levels remain elevated at 30% over baseline for more than 1 month, the drug should be discontinued. Cyclosporine may be resumed when creatinine returns to 10% over the patient's baseline.

Blood pressure should be monitored every 2 weeks until the dosage is stable and then monthly thereafter.⁶⁷ More frequent monitoring is recommended if the dose is increased or if the serum creatinine or blood pressure increases. If the diastolic blood pressure is >105 mm Hg or sustained at greater than 95 mm Hg, calcium channel antagonists such as nifedipine or isradipine should be initiated.

CBC, potassium, and liver function tests should also be monitored periodically.⁴⁵ Symptoms to watch for include edema and increases in blood pressure.

Drug Interactions. Enzyme-inhibiting drugs such as ketoconazole, fluconazole, erythromycin, trimethoprim, oral contraceptives, verapamil, and diltiazem and others can increase cyclosporine levels.⁵¹ Enzyme-inducing drugs such as phenytoin, rifampin, carbamazepine, phenobarbital, and others can decrease cyclosporine levels. Concurrent use of vasoconstrictive and nephrotoxic agents may induce renal failure and should be avoided.

Azathioprine (Imuran®)

Mechanism of Action. Azathioprine is a cell cycle-specific antimetabolite that is metabolized to 6-mercaptopurine and further to the false purine thioinosinic acid. This results in immunosuppression, inhibition of immunoglobulins, diminished B lymphocyte proliferation, and inhibition of interleukin-2 effects.⁴⁰

Dose. If there is no response at 8 weeks, the dose may be increased by 0.5 mg/kg per day every 4 weeks to a maximum dose of 2.5 mg/kg per day. If there is no response at 12 weeks at maximum doses, then therapy should be discontinued. Maintenance doses should be tapered to the lowest effective dose. Approximate time to benefit is 2 to 3 months.

Pharmacokinetics. This compound is well absorbed after oral administration, with 30% of the drug bound to plasma proteins. Because the drug is primarily excreted by the kidneys, doses must be adjusted for renal function.

Side Effects. There is a dose-related bone marrow suppression including pancytopenia, leukopenia, macrocytic anemia, and thrombocytopenia. Other side effects include stomatitis, fever, abdominal pain, diarrhea, liver failure, and rash.

Monitoring. Baseline CBC, platelets, creatinine, and liver function tests should be checked. CBC and platelets should continue to be checked every 1 to 2 weeks until the dosage is stable or if the dosage is changed, and then these levels should be checked every 1 to 3 months.⁴⁵ Liver enzymes should also be monitored periodically, and discontinuation should be considered if jaundice develops.

Drug Interactions. Allopurinol inhibits xanthine oxidase, which metabolizes 6-mercaptopurine and can increase the toxicities associated with azathioprine therapy. When these two agents are used in combination, dose of azathioprine should be decreased by 25% to 33%.⁶⁶ Angiotensin-converting enzyme inhibitors may increase the risk of myelosuppression due to azathioprine and concomitant use should be avoided.⁷⁰

Sulfasalazine (Azulfidine®)

Mechanism of Action. Sulfasalazine is broken down by intestinal bacteria to 5-aminosalicylic acid and sulfapyridine. Unlike in ulcerative colitis, sulfapyridine is the active moiety in RA and is thought to inhibit reactive oxygen species, cytokines, and endothelial cell proliferation.⁴⁰

Dose. Doses are initiated at 500 mg daily and titrated up to 1 to 3 g divided two to three times daily. Approximate time to benefit is 1 to 2 months.

Pharmacokinetics. After oral administration, about 10% to 15% of the drug is absorbed in the small intestine unchanged. Peak concentrations occur within 1.5 to 6 hours with a mean half-life of 6 hours. The drug undergoes extensive hepatic metabolism and is then excreted renally.

Side Effects. The more common side effects are headache, unpleasant taste, gastrointestinal intolerance, rash, and mood alterations.³⁹ Hematologic effects include leukopenia in 1% to 3% of patients, rare thrombocytopenia, rare hemolysis in patients with glucose 6-phosphate dehydrogenase deficiency, and rare aplastic anemia and agranulocytosis. This drug can also cause an orange-yellow discoloration to alkaline urine and sweat.

Monitoring. CBC should be checked every 2 to 3 weeks for 3 months, then every 3 months.⁴⁵ Although there are no official recommendations, many experts recommend baseline liver enzymes should be checked in patients with known or suspected liver disease.

Drug Interactions. Sulfasalazine can chelate iron, which can result in decreased concentration of the drug. This agent also inhibits folate metabolism, which can lead to folic acid deficiency. Because antibiotics can alter the gut flora, concomitant use with sulfasalazine may alter the drug's actions.⁵³

Cyclophosphamide (Cytoxan®)

Mechanism of Action. Cyclophosphamide is an alkylating agent of the nitrogen mustard group used commonly in oncology regimens. It works by depleting both T and B lymphocytes.⁴⁰

Dose. The initial dose is 1 to 2 mg/kg per day (75 to 150 mg/d), but the minimum effective dose is 150 mg/d. Response is usually seen within 4 to 6 weeks. If no response is seen within 8 weeks, the dose can be increased up to 3 mg/d, but the drug should be discontinued if there is no response at this dose after 4 months. Once the patient is responding to the drug, the dose should be decreased 25 mg/mo to the lowest effective maintenance dose.

Pharmacokinetics. The drug is well absorbed with peak concentrations seen after 1 hour.⁵³ Bioavailability after oral administration is greater than 75%. Half-life of the drug is between 3 and 12 hours, but the parent drug and its metabolites are found in the serum for up to 72 hours. The drug exhibits wide distribution and hepatic metabolism to active alkylating metabolites. Elimination of the drug is primarily renal.

Side Effects. Hematologic toxicity, including leukopenia and rare thrombocytopenia, can be severe and dose limiting.⁵¹ A common and reversible side effect—with an occurrence rate of 33%—is alopecia, which usually begins about 3 weeks after drug initia-

tion. Sterile hemorrhagic cystitis can occur in up to 20% of patients undergoing chronic cyclophosphamide therapy. Although rare, this adverse effect is thought to be a result of accumulation of active metabolites in the urine. Dose- and duration-dependent side effects occurring in 10% to 30% of patients include azoospermia and amenorrhea. Other side effects include gastrointestinal intolerance, headache, and rare cardiotoxicity.

Cyclophosphamide has been linked to malignancy in patients using the agent as monotherapy and as combination therapy with other agents. Urinary bladder, myeloproliferative, and lymphoproliferative malignancies were the most frequently reported cases. Although the cause is unknown, this risk must be considered before starting therapy.⁵³

Monitoring. Baseline CBC, UA, creatinine, and liver function tests should be obtained.⁴⁵ CBC should continue to be monitored every 1 to 2 weeks with changes in dosage, and every 1 to 3 months after dosage is stabilized. UA and urine cytology should be obtained every 6 to 12 months after discontinuing the drug.

Drug Interactions. Because cyclophosphamide is metabolized by the liver, liver enzyme-inducing and -inhibiting drugs can affect cyclophosphamide levels.

... NEWER THERAPIES ...

As we continue to gain new insight into the immunopathology of RA, therapies targeted at specific causes are being developed. The most widely studied compounds are those that inhibit tumor necrosis factor, interleukins, and cytokines. Monoclonal antibodies and vaccines targeting T-cell receptors are also being investigated. The most promising agents in Phase III drug studies include infliximab (Avakine), a monoclonal antibody,⁷¹ and TNFR:Fc (Enbrel), a recombinant tumor necrosis factor antagonist.⁷² Oral tolerance using chicken collagen may prove to be beneficial but further studies are needed.⁷³ Results of studies show that minocycline, a macrolide antibiotic, is superior to placebo in improving the symptoms of RA and this area of research continues to be targeted.^{74,75}

... SUMMARY ...

RA is a complex disease with unknown etiology and is thought to be multifactorial. Although there is no known cure, many therapies are available to help control the symptoms of the disease. All drugs avail-

able in the treatment of RA have associated adverse drug effects that lead to monitoring variables, variables that are strongly recommended to be followed. Combination drug therapies that may affect different mechanisms of action also continue to be studied. Research continues to identify the etiology and treatments to target the causes.

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CONTINUING PHARMACY EDUCATION

This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-000-98-207-L-04. This course expires June 30, 2000.

Instructions

After reading the article "Rheumatoid Arthritis: Focus on Appropriate Drug Therapy," select the best answer to each of the following questions.

1. Rheumatoid arthritis (RA) is a disease leading to early disability in many patients. Within 10 years of onset what percentage of patients are too functionally impaired to work?

- a) 50%
- b) 25%
- c) 35%
- d) 10%

2. The postulated etiology of RA is multifactorial and may include all of the following exogenous and endogenous antigens except:

- a) mucopolysaccharides
- b) EpsteinBarr virus
- c) collagen
- d) mycobacterium

3. Predisposing factors for RA include:

- a) trauma
- b) class II MHC alleles DR1 and DR4
- c) exposure to heavy metals
- d) osteoporosis

4. Inflammatory mediators are thought to be central to the pathogenesis of RA. The synovium contains high amounts of all of the following pathogenic substances except:

- a) tumor necrosis factor
- b) interleukin1
- c) COX 2 inhibitors
- d) B lymphocytes

5. Which symptom of RA should be present for 6 weeks in order to aid in making the diagnosis?

- a) radiographic erosions
- b) osteopenia
- c) subcutaneous nodules
- d) morning stiffness of at least 1 hour

6. Suggested criteria for SAARD use include all of the following except:

- a) sufficient disease including loss of function, persistent pain, and persistent synovitis
- b) ability to tolerate a slow response
- c) correct diagnosis with an absence of contraindications
- d) use after 6-month corticosteroid failure

7. Choose the correct statement regarding SAARDs:

- a) have equivalent toxicity and efficacy in individual patients
- b) all suppress disease activity and improve serologic markers of disease
- c) consistently and uniformly retard radiographic progression
- d) should be reserved until obvious joint destruction occurs

8. The traditional pyramidal approach:

- a) is a very useful strategy for early disease
- b) has been discarded in favor of newer strategies
- c) is useful after NSAID failure
- d) emphasizes early aggressive SAARD use

9. The sawtooth strategy of RA treatment includes:

- a) sequential changes in SAARD therapies at certain disability levels
- b) combination therapies until inflammation is controlled with a step down bridge to simpler therapies
- c) avoidance of all NSAIDs
- d) aggressive use of corticosteroids

(CPE QUESTIONS CONTINUED ON FOLLOWING PAGE)

Rheumatoid Arthritis: Focus on Appropriate Drug Therapy

(PLEASE PRINT CLEARLY)

Name _____

Home Address _____

City _____

State/ZIP _____

Daytime Phone # _____

States in which CE credit is desired: _____

Social Security # _____

Please circle your answers:

- | | | | |
|------------|-------------|-------------|-------------|
| 1. a b c d | 6. a b c d | 11. a b c d | 16. a b c d |
| 2. a b c d | 7. a b c d | 12. a b c d | 17. a b c d |
| 3. a b c d | 8. a b c d | 13. a b c d | 18. a b c d |
| 4. a b c d | 9. a b c d | 14. a b c d | 19. a b c d |
| 5. a b c d | 10. a b c d | 15. a b c d | 20. a b c d |

Please complete the Program Evaluation on page 607, and send with \$15 fee, payable to University of Tennessee, to:

Glen Farr, PharmD
University of Tennessee College of Pharmacy
600 Henley Street, Suite 213
Knoxville, TN 37902

(continued from previous page)

- 10. Corticosteroids:**
 a) should always be used in the treatment of rheumatoid arthritis
 b) are perilous due to their drug interaction potential
 c) are widely used due to their proven profound decrease in mortality
 d) have long-term risks that may outweigh their benefits
- 11. Laboratory abnormalities often associated with RA include all of the following except:**
 a) positive rheumatoid factor
 b) elevated Creactive protein
 c) elevated ESR
 d) increased serum hemoglobin
- 12. Combination therapies are being more widely used than ever before. Which SAARD is almost always a component of combination therapies?**
 a) IM gold
 b) azathioprine
 c) methotrexate
 d) DPenicillamine
- 13. Contraindications to cyclosporine include all of the following except:**
 a) cancer history
 b) renal failure
 c) peripheral neuropathy
 d) uncontrolled HTN
- 14. Choose the best description of drawbacks to IM gold therapy:**
 a) pain at the injection site, leukopenia, hemolytic anemia
 b) hepatic fibrosis, pulmonary toxicity, increased salivation
 c) Goodpasture's syndrome, hematuria, diarrhea
 d) proteinuria, initial dosing frequency, rash
- 15. Methotrexate is a SAARD with many side effects. Select the side-effect profile listed below that most closely matches that of methotrexate:**
 a) leukopenia, proteinuria, dermatologic reactions
 b) hematologic toxicity, pulmonary fibrosis, hepatotoxicity
 c) gastrointestinal ulceration, nausea, cardiac arrhythmias
 d) postural hypotension, neuropathy, sore throat
- 16. Sulfasalazine's activity moiety in the treatment of RA is thought to be:**
 a) 5-aminosalicylic acid
 b) antipyrine
 c) sulfapyridine
 d) acetylsalicylic acid
- 17. Azathioprine is metabolized to the active 6-mercaptopurine. Metabolism of this is inhibited by which compound?**
 a) allopurinol
 b) aspirin
 c) phenytoin
 d) methotrexate
- 18. Select the side-effect profile of D-penicillamine listed below:**
 a) leukopenia, proteinuria, autoimmune syndromes
 b) hepatic toxicity, urticaria, onchylolysis
 c) gastrointestinal irritation, cardiac conduction disturbances, nausea
 d) pulmonary fibrosis, anemia, thrombocytopenia
- 19. Select the set of variables that accurately describe the required monitoring of methotrexate, assuming baseline monitoring has been appropriately completed:**
 a) INR, CBC, chemistry profile
 b) PTT, reticulocyte count, chest X ray
 c) CBC, liver profile, albumin
 d) hepatitis panel, thyroid studies, urinalysis
- 20. Hydroxychloroquine requires what kind of special monitoring?**
 a) ophthalmologic
 b) hematologic
 c) cardiac
 d) pulmonary function

CPE PROGRAM EVALUATION

The University of Tennessee College of Pharmacy would like to have your opinion. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your CPE test form. We thank you for your evaluation, which is most helpful.

Please circle your answers:

My pharmacy practice setting is:	Independent	Chain	Hospital	Consultant
The objectives of the lesson were achieved	Yes	No		
The quality of presentation of the material was:	Excellent	Good	Fair	Poor
The information presented will be useful to me in my practice.	Strongly agree	Mildly agree	Mildly disagree	Strongly disagree

How long did it take you to read the material and respond to the Continuing Education questions: (Please specify the number of hours.)

Please send this evaluation, along with your answer sheet and \$15 check payable to University of Tennessee, to:

Glen Farr, PharmD
 University of Tennessee College of Pharmacy
 600 Henley Street, Suite 213
 Knoxville, TN 37902