

Table 17.2 Disease-Modifying Antirheumatic Drugs Used to Treat Rheumatic Disease

Medication	Indications and mechanism of action	Dosing	Side effects affecting rehab	Other side effects or considerations
Nonbiological DMARD				
Methotrexate	DMARD used in treatment of rheumatic disease. Antifolate.	Adults: 7.5-15 mg once/wk by oral, SC, or intramuscular administration. Children: 10-25 mg/m ² /wk by oral, SC, or intramuscular administration as a single dose or divided into 2 doses weekly; may increase dose (maximum dose of 30 mg/m ² , approximately equivalent to 1 mg/kg). Administer with folic acid (1-2 mg by mouth/day) or folinic acid (2.5-5 mg by mouth/wk).	Cog: 0 S: 0 A: 0 Motor: 0 D: ++ Com: 0 F: 0	Stomatitis in 3%-10%; diarrhea, nausea, and vomiting in up to 10%; thrombocytopenia in 1%-3%; elevated liver function tests (LFTs) in up to 15%; discontinue if elevated LFT levels are sustained at more than 2 times normal. Rarer toxicities are leukopenia, pulmonary fibrosis, and pneumonitis. Teratogenic. DMARD of choice for initiation. Onset is 6-8 wk; patient should be supplemented with folic acid. Obtain baseline UA, CBC, and liver-function tests (AST/ALT, bilirubin, albumin); hepatitis B and C testing; repeat CBC, AST, and albumin every 1-2 mo to monitor for possible hepatotoxic side effects.
Leflunomide (Arava)	DMARD used in treatment of rheumatic disease. Pyrimidine synthesis inhibitor.	100 mg/day for 3 days, then 20 mg/day. Due to high incidence of gastrointestinal side effects and diarrhea, some practitioners do not use a loading dose and may decrease daily dose to 10 mg to reduce these side effects.	Cog: 0 S: 0 A: 0 Motor: 0 D: ++ Com: 0 F: 0	Liver toxicity; contraindicated in patients with liver impairment. Teratogenic; takes months to clear but cholestyramine can enhance clearance. High incidence of gastrointestinal side effects. Onset of response in 1-2 mo; half-life is 14-16 days. Obtain baseline ALT and then repeat monthly to monitor for hepatotoxic side effects.
Hydroxychloroquine (Plaquenil)	DMARD used in treatment of rheumatic disease. Antimalarial.	200-300 mg twice/day; after 1-2 mo, decrease dose to 200 mg 1-2 times/day.	Cog: 0 S: 0 A: 0 Motor: ++ D: ++ Com: 0 F: ++	Taking with food can reduce nausea, vomiting, and diarrhea. Ocular toxicity (accommodation defects, corneal deposits, blurred vision, scotomas, night blindness); patient should contact physician immediately if visual changes occur. Dermatologic rash, alopecia, increased skin pigmentation, mild neurologic side effects of headache, vertigo, and insomnia. Metabolized by liver and excreted by kidneys. Onset of effects is 2-4 mo; if no response occurs by 6 mo, drug should be discontinued. Baseline ophthalmologic exam and repeat every 9-12 mo. Conduct Amsler grid testing at home every 2 wk.

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				Can be used in combination with methotrexate and sulfasalazine.
Sulfasalazine (Azulfidine)	DMARD used in treatment of rheumatic disease. Salicylate.	Adults: 500 mg twice/day, then increase to 1000 mg twice/day. Children <6 yr: Not established. Children ≥6 yr: Typical dose range is 30-50 mg/kg/d. To lessen gastrointestinal irritation, start at one half to one third of maintenance dose and increase dose weekly. Maximum dose of 2 g/d.	Cog: 0 S: 0 A: 0 Motor: 0 D: +++ Com: 0 F: 0	Nausea, vomiting, diarrhea, and anorexia are minimized with low dose initiation and slow titration. Rash, urticaria, and serum sickness reactions can be treated with antihistamines or steroids. Hypersensitivity reactions require discontinuance. Leukopenia, alopecia, stomatitis, elevated liver enzymes, yellow-orange skin discoloration; may cause photosensitivity. Baseline CBC, then repeat weekly for 1 mo and recheck every 1-2 mo. Onset is 6 wk-3 mo. Can be combined with methotrexate and hydroxychloroquine as triple therapy.
Nonbiological DMARD that are cytotoxic agents				
Azathioprine (Imuran)	Nonbiological DMARD used in treatment of rheumatic disease that is a cytotoxic agent. Purine synthesis inhibitor.	50-150 mg/day; reduce dose by 25% for creatinine clearance of 10-50 ml/min and by 50% for creatinine clearance of <10 ml/min.	Cog: 0 S: 0 A: 0 Motor: 0 D: +++ Com: 0 F: 0	Reversible dose-related bone marrow suppression (leukopenia, macrocytic anemia, pancytopenia, thrombocytopenia), gastrointestinal intolerance, stomatitis, infection, drug fever, hepatotoxicity, hypertension, increased risk of infection, hyperglycemia, nephrotoxicity, tremor, hirsutism, gingival hyperplasia; may cause malignancies. Hypertension and nephrotoxicity are reversed upon discontinuance. Baseline CBC and AST; repeat every 2 wk for first 2 mo, then every 1-2 mo. Eliminated by kidneys; adjust dose for renal insufficiency. If given with allopurinol, must reduce dose to 25% of original dose.
Cyclosporine (Neoral, Sandimmune)	Nonbiological DMARD used in treatment of rheumatic disease that is a cytotoxic agent. Calcineurin inhibitor.	2.5 mg/kg/day.	Cog: 0 S: 0 A: 0 Motor: + D: +++ Com: 0 F: 0	Hypertension, increased risk for infection, hyperglycemia, nephrotoxicity, tremor, gastrointestinal intolerances, hirsutism, gingival hyperplasia. Hypertension and nephrotoxicity are reversed upon discontinuance. Measure serum creatinine and blood pressure at baseline and monthly. Onset of activity is 1-3 mo. Metabolized by liver (active metabolites) and excreted in bile. Interacts with anticonvulsants, ketoconazole, fluconazole, trimethoprim, erythromycin, verapamil, diltiazem, nonsteroidal anti-inflammatory drugs,

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				and cyclophosphamide. Reserved for patients who fail more conventional therapies.
Cyclophosphamide (Cytoxan)	Nonbiological DMARD used in treatment of rheumatic disease that is a cytotoxic agent. Alkylating agent.	1-2 mg/kg/day.	Cog: 0 S: 0 A: 0 Motor: 0 D: + Com: 0 F: 0	Bone marrow suppression, hemorrhagic cystitis, premature ovarian failure, infection, secondary malignancy (particularly an increased risk of bladder cancer). Measure baseline UA and CBC; repeat weekly for first month, then repeat every 2-4 wk.
Penicillamine (Cuprimine)	DMARD used in treatment of rheumatic disease. Agent that chelates heavy metal.	125-250 mg/day; may increase by 125-250 mg every 1-2 mo to maximum dose of 750 mg/day.	Cog: 0 S: 0 A: 0 Motor: +++ D: +++ Com: 0 F: 0	Hypogeusia (lasts 2-3 mo and then resolves), stomatitis, nausea, vomiting, anorexia. Autoimmune complications that require discontinuance include glomerular nephritis with symptoms of proteinuria and hematuria, polymyositis, Goodpasture's syndrome, myasthenia gravis, systemic lupus erythematosus, and pemphigus. Dyspepsia improves by decreasing dose. Rash of metallic taste occurring after 6 mo of therapy requires decrease in dose. Food, antacids, and iron decrease absorption. Measure baseline UA with CBC and repeat weekly for 1 mo and then monthly, or after 2 wk if dose is adjusted.
Nonbiological DMARD that are gold salts				
Auranofin	DMARD used in treatment of rheumatic disease. Gold compound.	3 mg by mouth 1-2 times/day.	Cog: 0 S: 0 A: 0 Motor: 0 D: +++ Com: 0 F: 0	Metallic taste, proteinuria, hematuria, anemia, leukopenia, thrombocytopenia; gastrointestinal side effects of nausea, vomiting, or diarrhea resolve with time; skin rash or stomatitis require discontinuance. Onset delayed for 4-6 mo. Baseline UA and CBC every 1-2 mo. 35% of patients have side effects that require discontinuance. Reserved for patients who fail other therapies.
Aurothioglucose or gold sodium thiomalate (Solganal, Myochrysine) Injection	DMARD used in treatment of rheumatic disease. Gold compound.	Start at 10 mg intramuscularly, then 25 mg the second week, then 50 mg weekly until a response occurs or until a total of 1 g has been administered. If a favorable response occurs, therapy is tapered to 50 mg every 2 wk for 3 mo, then	Cog: 0 S: 0 A: 0 Motor: ++ D: ++ Com: 0 F: 0	Same side effects as oral gold; flushing, palpitations, hypotension, headache, and blurred vision can occur with injectable gold. Severe postinjection flare with increased joint symptoms requires discontinuance.

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		every 3 wk for 3 mo, and finally to a monthly maintenance dose. No response after a total of 1 g is a treatment failure. Monthly gold should be continued indefinitely.		
Biological DMARD				
Adalimumab (Humira)	Biological DMARD used in treatment of rheumatic disease. Tumor necrosis factor antagonist.	Adults: 40 mg SC injection every other week. If response to dose is inadequate, may increase frequency of injections to weekly. Children <4 yr: Not established. Children ≥4 yr and 15-30 kg: 20 mg SC every 2 wk. Children ≥4 yr and >30 kg: 40 mg SC every 2 wk.	Cog: 0 S: 0 A: 0 Motor: + D: ++ Com: 0 F: 0	Reactions at injection site, increased upper respiratory tract infections, bronchitis, urinary tract infection. Positive antinuclear antibody titers with lupus-like disease. Usual time to effect is 1-4 wk. Half-life is approximately 2 wk (ranging 10-20 days) after a standard 40 mg dose. Can reactivate latent infections such as tuberculosis or hepatitis B. Not recommended for patients with concurrent demyelinating disease or congestive heart failure.
Etanercept (Enbrel)	Biological DMARD used in treatment of rheumatic disease. Tumor necrosis factor antagonist.	Adults and children >17 yr: 50 mg SC once/wk or 25 mg twice/wk. Children <2 yr: Not established. Children 2-17 yr: 0.4 mg/kg SC twice/ wk (administered at least 72-96 h apart); maximum dose of 25 mg.	Cog: 0 S: 0 A: 0 Motor: + D: ++ Com: 0 F: 0	Increased risk of infection, respiratory infection, positive antinuclear antibodies with lupus-like symptoms, transient neutropenia, mild reactions at injection site. 1% of patients develop anti-etanercept antibodies. May increase risk of lymphoma. Onset of action is 1-4 wk; additional improvements seen over 3-6 mo. Half-life of 70 h after 25 mg dose. Can reactivate latent infections such as tuberculosis or hepatitis B. Not recommended for patients with concurrent demyelinating disease or congestive heart failure.
Golimumab (Simponi)	Biological DMARD used in treatment of rheumatic disease. Tumor necrosis factor antagonist.	50 mg SC once/mo.	Cog: 0 S: 0 A: 0 Motor: 0 D: + Com: 0 F: 0	Headache, rash, cough, abdominal pain, nasopharyngitis, urinary tract infection, upper respiratory tract infection. Onset is days to weeks. Can reactivate latent infections such as tuberculosis or hepatitis B.
Infliximab (Remicade)	Biological DMARD used in treatment of rheumatic disease.	Adults: Start at 3 mg/kg, then repeat at 2 and 6 wk and then every 8 wk for inadequate response; can titrate to	Cog: 0 S: 0 A: 0 Motor: ++ D: ++	Infusion reaction with fever, chills, body aches, headache. Symptoms can be reduced by slowing the infusion rate and administering diphenhydramine, acetaminophen, and

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	Immunoglobulin G; antitumor necrosis factor.	10 mg/kg administered every 4-6 wk. Children: Not established. Doses of 5-10 mg/kg intravenously have been reported as effective in treating recalcitrant pediatric uveitis with juvenile rheumatoid arthritis.	Com: 0 F: 0	sometimes corticosteroids before infusion. Anti-infliximab antibodies occur in 10%-30% of patients; clinical systemic lupus erythematosus-like syndromes. Onset is days to weeks. Can reactivate latent infections such as tuberculosis or hepatitis B. Not recommended for patients with concurrent demyelinating disease or congestive heart failure. Should be given in combination with methotrexate.
Certolizumab (Cimzia)	Biological DMARD used in treatment of rheumatic disease. Tumor necrosis factor antagonist.	400 mg by SC injection at week 0, 2, and 4, then 400 mg every 4 wk.	Cog: 0 S: 0 A: 0 Motor: ++ D: ++ Com: 0 F: 0	Headache, rash, cough, abdominal pain, nasopharyngitis, urinary tract infection, upper respiratory tract infection. Can reactivate latent infections such as tuberculosis or hepatitis B.
Abatacept (Orencia)	Biological DMARD used in treatment of rheumatic disease. T-cell costimulation inhibitor.	Patients <60 kg: 500 mg. Patients 60-100 kg: 750 mg. Patients >100 kg: 1000 mg infused over 30-60 min to start, at 2 wk, and at 4 wk, then monthly.	Cog: 0 S: 0 A: 0 Motor: + D: + Com: 0 F: 0	Increased risk of infection. Respiratory infections, including pneumonia, especially in patients with chronic obstructive pulmonary disease. May increase risk of malignancy. Response occurs within 3 mo. Can reactivate latent infections such as tuberculosis or hepatitis B.
Rituximab (Rituxan)	Biological DMARD used in treatment of rheumatic disease. Antibody for CD20 (cytotoxic for B-cells).	2 infusions of 1000 mg administered 2 wk apart; leads to a rapid and sustained depletion of B-lymphocytes in the peripheral blood. This effect is sustained for 6 mo-1 yr or longer.	Cog: 0 S: 0 A: 0 Motor: + D: + Com: 0 F: 0	Infusion reactions with hives, itching, swelling, difficulty breathing, fever, chills, and changes in blood pressure are most common with the first infusion; symptoms are decreased with slowing the rate of the infusion. Increased infection risk. Can reactivate viral infections such as hepatitis B. Complete immunizations before starting therapy with rituximab; avoid live virus vaccinations. Effects are not seen for up to 3 mo after an infusion; however, effects may last 6 mo and up to 2 yr after a single infusion course.
Anakinra (Kineret)	Biological DMARD used in treatment of rheumatic disease. Interleukin-1 receptor antagonist.	100 mg/day SC injection. Should be administered at approximately the same time each day.	Cog: 0 S: 0 A: 0 Motor: + D: + Com: 0 F: 0	Reactions at injection site (erythema, itching, and discomfort) occur in 66% and resolve in 1-2 mo. Increased risk of serious infection. Opportunistic infections, including tuberculosis, are less common than with tumor necrosis factor antagonists. Neutropenia.

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				Time to effect is 2-4 wk. Do not combine with tumor necrosis factor inhibitors.

Cog = cognition; S = sedation; A = agitation or mania; Motor = discoordination; D = dysphagia; Com = communication; F = falls; DMARD = disease-modifying antirheumatic drug; SC = subcutaneously; UA = urinalysis; CBC = complete blood count; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

The likelihood rating scale for encountering the side effects is as follows: 0 = Almost no probability of encountering side effects. + = Little likelihood of encountering side effects. +/++ = Low probability of encountering side effects; however, probability increases with increased dosage. ++ = Medium likelihood of encountering side effects. +++ = High likelihood of encountering side effects, particularly with high doses. ++++ = Highest likelihood of encountering side effects; best to avoid in at-risk patients.