Considerations related DMARDS

Foroud Shahbazi

Nonbiologic DMARDs

- Methotrexate
- Mechanism of action
- Dosing
- Adverse effects
- Renal dosing

methotrexate Metoject, generics $	Initial: 7.5–25 mg weekly PO, SC or IM; increase by 2.5–5 mg Q1–4 wk Maintenance: 7.5–25 mg weekly PO, SC or IM (single dose if tolerated, or in 2 divided doses Q12H) For doses >15 mg, divided doses are better absorbed and tolerated	Nausea, malaise, flulike aches, headache, oral ulcers, transient loose stools; bone marrow and liver toxicity (rare), pneumonitis (rare), immunosuppression, malignancy (rare). Not to be used in patients with hepatitis B or C, renal insufficiency or lung disease.	Baseline CBC, LFTs, albumin, creatinine, hepatitis B and C serology, chest x-ray; monthly × 3 months, then Q1–3 months. Consider HIV screening in high-risk patients. LFTs monthly if also on leflunomide. Folic acid or folinic acid 5–7 mg/weekly or 1 mg daily given to reduce GI adverse effects, liver toxicity, mouth sores.	Alcohol restriction may minimize hepatotoxicity. Concomitant use of NSAIDs or penicillins (e.g., amoxicillin, cloxacillin, piperacillin) does not result in clinically meaningful increase in low-dose MTX serum concentrations.[100][101] [102] Avoid high-dose ASA and sulfonamides, e.g., trimethoprim/sulfamethoxazole; for prophylaxis of *Pneumocystis jiroveci* with TMP/SMX, monitor CBC, LFTs and SCr at baseline with follow-up monthly.	First-line therapy unless contraindicated. Maximum dose of MTX reduced in China (20 mg/wk) and Japan (16 mg/wk).

Toxicity and monitoring

- Gastrointestinal and Hepatic Side Effects
- Hematologic Side Effects
- Pulmonary Side Effects
- Malignancies
- Fertility
- Monitoring (CBC, LFT, Cr, HBV, HCV; vaccinate: influenza, Pneumococcus, HBV)
- Folic acid ?

leflunomide Arava, generics $$	10–20 mg daily PO	Nausea, diarrhea, anorexia, alopecia, headache, hypertension, rash. May cause hepatic toxicity, cytopenias, profound anorexia and weight loss, pulmonary fibrosis, interstitial lung disease.	Baseline CBC, LFTs, creatinine, hepatitis B and C serology; CBC, LFTs, creatinine monthly × 3 months, then Q1–3 months, LFTs monthly if also on MTX.	Alcohol restriction may minimize hepatotoxicity. Combination therapy with MTX should be used with caution due to association of higher liver and GI toxicity. Monitor liver enzymes monthly and reduce dose of leflunomide with MTX combination therapy.	Pregnancy is contraindicated while taking this medication. Washout procedure with cholestyramine 8 g TID × 11 days is recommended for serious toxicity or imminently planned pregnancy (see Choices during Pregnancy and Breastfeeding).

Leflunomide

- Mechanism of action
- Dosing metabolites
- Pregnancy
- Toxicity (GI, hepatic,
- CBC, LFT, Cr, HBV, HCV; vaccinate: influenza, Pneumococcus, HBV

Drug Class: Antimalarial Agents					
hydroxychloroquine Plaquenil, generics $	200–400 mg daily PO Maximum: 6.5 mg/kg/day based on ideal body weight The American Academy of Ophthalmology recommends 5 mg/kg/day actual body weight to reduce the risk of retinal toxicity;[97] reduce dose if <60 kg	Nausea, cramps, diarrhea, rash, nightmares, hyperpigmentation. Rarely, if dosed too high for too long, corneal and retinal deposition can occur. Rare cases of severe hypoglycemia with or without oral hypoglycemic agents have been reported.	Baseline CBC, LFTs, creatinine. Ophthalmologic exam required at baseline, i.e., optical coherence tomography (OCT) and annually after 5 years. If high risk, required annually from baseline. High risk: cumulative dose >1000 g, doses >6.5 mg/kg or 400 mg/day, treatment for greater than 5–7 years, liver or kidney disease, advanced age, obesity and pre-existing ophthalmologic disease.[98][99]	Avoid concomitant use with QTc-prolonging agents, e.g., quinine.	Used for mild to moderate RA without poor prognostic factors.

Hydroxychloroquine

- Mechanism of actin
- Dosing
- Toxicity
- Pregnancy
- Monitoring

Drug/Cost[a]	Dosage	Adverse Effects	Monitoring of Therapy	Drug Interactions	Comments
Drug Class: Aminosalicylates					
sulfasalazine Salazopyrin, generics $	Initial: 500 mg daily or BID PO, increase by 500 mg weekly to a maintenance dose of 2–3 g daily PO (in 2 divided doses)	Rash, marrow toxicity, GI intolerance.	Baseline CBC, LFTs, creatinine; CBC, LFTs Q3 months.	Sulfasalazine may decrease GI absorption of digoxin.	May cause sun sensitivity. Do not use if sulfa allergy or G6PD deficiency. Consider enteric-coated tablets to reduce adverse GI effects. May be used in pregnancy with folic acid supplementation.

Sulfasalazine

- Mechanism of actin
- Dosing
- Toxicity
- Pregnancy
- Monitoring (The ACR guidelines recommend a baseline CBC with platelets, liver enzyme monitoring (including AST, ALT, and albumin), creatinine, and consideration for G6PD)

AZATHIOPRINE — The immunosuppressive purine analog azathioprine (Imuran, and others) is sometimes used for patients with extra-articular disease such as rheumatoid vasculitis.

Drug Class: Immunomodulators					
azathioprine Imuran, generics $	Initial: 50 mg daily PO, may increase by 25–50 mg daily every 1–2 wk (maximum dose 2.5 mg/kg/day) Maintenance: lowest tolerated dose, usually 50–150 mg/day (in 1–3 divided doses)	GI disturbance (nausea, vomiting), hepatitis, drug fever, myelosuppression, immunosuppression, unconfirmed risk of malignancy.	Baseline CBC, LFTs at Q1–3 months.	Allopurinol may increase azathioprine toxicity; dosage adjustment may be necessary (one-third to one-quarter of regular dose). Avoid concomitant use of azathioprine with febuxostat or mercaptopurine. May decrease effectiveness of warfarin.	

cyclosporine Neoral, Apo-Cyclosporine, other generics $$$$$	Initial: 2.5 mg/kg/day PO in 2 divided doses, increase every 1–2 wk Maintenance: 2.5–5 mg/kg/day (in 2 divided doses)	Renal toxicity, hypertension, hypertrichosis, cytopenia, gum hyperplasia.	Blood pressure monthly, periodic CBC, LFTs, electrolytes; monitor drug blood levels.	Metabolized by CYP3A enzymes—many possible drug interactions, e.g., grapefruit, erythromycin, ketoconazole, rifampin.

Table 35-3. Other Drugs Used to Treat RA

DRUG	DOSAGE	ADVERSE EFFECTS
Traditional disease-modifying antirheumatic drugs (DMARDs)		
Hydroxychloroquine	Initially, 400 mg po once/day (eg, with breakfast or dinner) for 4-12 wk, then sometimes reduced to 200 mg once/day If improvement occurs, 200-400 mg once/day as long as effective	Usually, mild dermatitis Myopathy Generally, reversible corneal opacity Occasionally, irreversible retinal degeneration
Leflunomide	20 mg once/day or, if adverse effects occur, reduced to 10 mg once/day	Skin reactions Hepatic dysfunction
Methotrexate	Single oral dose once/wk, starting at 7.5 mg and gradually increased as needed to a maximum of 25 mg Doses > 20 mg/wk best given sc to ensure bioavailability	Liver fibrosis (dose-related, often reversible) Nausea Possibly bone marrow suppression Stomatitis Rarely, pneumonitis (potentially fatal)
Sulfasalazine*	500 mg po in the evening, increased to 500 mg in the morning and 1000 mg in the evening, then increased to 1000-1500 mg bid	Bone marrow suppression Gastric symptoms Neutropenia Hemolysis Hepatitis

Corticosteroids, systemic		
Prednisone	Not to exceed 7.5 mg po once/day (except in patients with severe systemic manifestations)	With long-term use: Weight gain Diabetes Hypertension Osteoporosis
Immunomodulatory, cytotoxic, or immunosuppressive drugs		
Azathioprine	1 mg/kg (50-100 mg) po once/day or bid, increased† by 0.5 mg/kg/day after 6-8 wk, then q 4 wk to a maximum of 2.5 mg/kg/day	Liver toxicity Bone marrow suppression Possibly increased risk of cancer With cyclosporine, impaired renal function
Cyclophosphamide	2-3 mg/kg po once/day or IV pulse therapy (may not be as effective): 0.75 g/m^2 once/mo (increased to 1 g/m^2 once/mo for 6 mo if WBC > 3000/uL), given over 30-60 min	

Biologic DMARDs

- Interleukin-1 Receptor Antagonist
- Anti–interleukin-6 Receptor Antibody
- Anti-CD20 Monoclonal Antibody

Table 3

Summary of DMARDs without and with biologic activity

Drug name	Therapeutic classification	Dosage	Adverse events	Monitoring parameters
DMARDs without biologic activity				
Hydroxychloroquine	Antimalarial agent	200-400 mg/d orally (can divide into 2 doses)	GI, dermatologic, retinal toxicity	Ophthalmic exam every 6 mo
Sulfasalazine	Anti-inflammatory agent	500-2,000 mg/d orally (can divide into 2 doses)	GI, leucopenia, hemolytic anemia	CBC with PLT at baseline, every wk for 1 mo, then every 1-2 mo
Methotrexate	Immunosuppressive agent	7.5-25 mg/wk orally (available in parental formulations)	GI, stomatitis, dermatologic, myelosuppression, hepatoxicity	CBC, BMP, LFTs at baseline and every 3 mo
Leflunomide	Dihydroorotate dehydrogenase antagonist	100 mg/d for 3 days, then 10 or 20 mg/d orally	Diarrhea, rash, alopecia, elevation in LFTs	LFTs at baseline and every 3 mo
DMARDs with biologic activity				
Etanercept	TNF antagonist	25 mg twice weekly or 50 mg weekly, subcutaneous	Infection risk, injection site reaction	Chest x-ray, PPD test
Infliximab	TNF antagonist	3 mg/kg infusion at wk 0, 2, 6, and every 8 wk (must be with methotrexate)	Similar to etanercept	Similar to etanercept
Adalimumab	TNF antagonist	40 mg every other wk, subcutaneous	Similar to etanercept	Similar to etanercept
Golimumab*	TNF antagonist	50 mg every mo, subcutaneous (must be with methotrexate)	Similar to etanercept	Similar to etanercept
Anakinra	IL-1 antagonist	100 mg/d, subcutaneous	Similar to etanercept	Similar to etanercept
Abatacept	T-cell modulator through CD80/86 signal	Weight-based infusion at wk 0, 2, 4, and every 4 wk	Similar to etanercept	Similar to etanercept
Rituximab	B-cell modulator	2-1,000 mg infusions separated by 2 wk	Infusion reaction, reactivation of HBV, decreased response to vaccinations	Similar to etanercept
Tocilizumab*	IL-6 antagonist	Weight-based infusion (4 mg or 8 mg/kg)	Thrombocytopenia, elevated LFTs, neutropenia	ANC, PLT, LFTs at baseline and after each infusion

Abbreviations: ANC, absolute neutrophil count: BMP, blood metabolic profile; CBC, complete blood count; DMARDs, disease-modifying antirheumatic drugs; GI, gastrointestinal; HBV, hepatitis B virus; LFTs, liver function tests; PLT, platelets; PPD, purified protein derivative

* These agents are not included in the updated RA guidelines due to approval in 2010.

Formulary/Source: Refs 6–8,11,12

Drug/Cost[a]	Dosage	Adverse Effects	Monitoring of Therapy	Contraindications	Comments
Drug Class: B-Cell Depletors					
rituximab Rituxan $10 000	1 g × 2 doses 2 wk apart IV; infusions are given with 100 mg of methylprednisolone Doses can be repeated after 5–6 months A lower-dose regimen of 500 mg IV × 2 doses 2 wk apart may be as effective as the standard dose[103]	Mild to severe infusion reactions (very severe reactions resulting in death have been reported rarely). Progressive multifocal leukoencephalopathy (PML) (rare).	Baseline CBC, LFTs, creatinine, hepatitis B and C serology. CD19 counts can be used to monitor B-cell levels.	Susceptibility to infection. Contraindicated in patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins, Chinese Hamster Ovary (CHO) cell proteins or to any component of the product.	Indicated in patients who have failed csDMARD and a TNFi agent. Premedicate prior to infusion with acetaminophen and an antihistamine (e.g., diphenhydramine) before infusion.

Drug Class: Tumor Necrosis Factor-alpha (TNF-alpha) Inhibitors					
adalimumab Humira $$	40 mg Q2 wk SC	Injection-site reactions; infections (including TB and opportunistic organisms); new-onset psoriasis; increased risk of lymphoma (children and adolescents), leukemia and other malignancies; autoimmune phenomena.	Baseline CBC, LFTs, creatinine, hepatitis B and C serology, PPD and chest x-ray to assess for latent TB. May consider screening for ANA.	Susceptibility to or presence of serious and/or recurrent infection; SLE, demyelinating disease and heart failure are relative contraindications.	Indicated for moderate to severe RA. Given in combination with MTX in newly diagnosed patients. May be used as monotherapy in case of MTX contraindication.

etanercept Enbrel, Brenzys[b] Erelzi[b] Enbrel: $$ Brenzys[b]: $ Erelzi[b]: $	Enbrel: 25 mg twice weekly *or* 50 mg once weekly SC Brenzys[b]: 25 mg twice weekly *or* 50 mg once weekly SC Erelzi[b]: 25 mg twice weekly *or* 50 mg once weekly SC	Injection-site reactions; infections (including TB and opportunistic organisms); new-onset psoriasis; increased risk of lymphoma (children and adolescents), leukemia and other malignancies; autoimmune phenomena.	Baseline CBC, LFTs, creatinine, hepatitis B and C serology, PPD and chest x-ray to assess for latent TB. May consider screening for ANA.	Susceptibility to or presence of serious and/or recurrent infection; SLE, demyelinating disease and heart failure are relative contraindications.	Indicated for moderate to severe RA. Given in combination with MTX in newly diagnosed patients. May be used as monotherapy in case of MTX contraindication.

infliximab Remicade, Inflectra[b] Remicade: $$ Inflectra[b]: $	Remicade: 3 mg/kg IV at 0, 2 and 6 wk, and Q8 wk thereafter For incomplete response, dose may be increased to 10 mg/kg and/or the frequency may be increased up to Q4 wk Inflectra: 3mg/kg IV at 0, 2 and 6 wk, and Q8 wk thereafter	Infections (including TB and opportunistic organisms), new-onset psoriasis, increased risk of lymphoma (children and adolescents), leukemia and other malignancies, autoimmune phenomena. Mild to severe infusion reactions (very severe reactions resulting in death have been reported rarely).	Baseline CBC, LFTs, creatinine, hepatitis B and C serology, PPD and chest x-ray to assess for latent TB. May consider screening for ANA.	Contraindicated in patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins; heart failure if using >5 mg/kg/infusion, demyelinating disease, susceptibility to or presence of serious and/or recurrent infection; SLE is a relative contraindication.	Indicated for moderate to severe RA in combination with MTX.

Table 4: Recommendations for Vaccination in Patients with Rheumatoid Arthritis

	Inactivated/Killed Vaccines			Live Attenuated Vaccines	
RA Therapy	**Influenza** (annual)	**Pneumococcal** (booster after 3–5 y)	**Hepatitis B**	**Herpes Zoster**[a]	**Other**[b]
Methotrexate[c]	Recommended	Recommended	High-risk patients[d]	>60 years[e]	Caution
Leflunomide	Recommended	Recommended	High-risk patients[d]	>60 years	Caution
Sulfasalazine	Recommended	Recommended	High-risk patients[d]	>60 years	Caution
Biologics[f]	Recommended	Recommended	High-risk patients[d]	Avoid[g] (vaccinate prior to therapy if indicated)	Avoid

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal[1]	Influenza (intramuscular)	Hepatitis B[2]	Human Papilloma	Herpes Zoster[3]
Before initiating therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓	✓	✓ *(PICO J.1)*[5]
Non-TNF biologics	✓	✓	✓	✓	✓ *(PICO J.1)*[5]
While already taking therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]
Non-TNF biologics[4]	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]