Effective Health Care

Choosing Medications for RHEUMATOID ARTHRITIS

Clinician's Guide

This guide summarizes evidence comparing the effectiveness and safety of disease-modifying antirheumatic drugs (DMARDs) and corticosteroids used for rheumatoid arthritis (RA). It does not address other drugs that are no longer commonly used as first-line treatment for RA, such as azathioprine, chloroquine, cyclosporine, gold, and penicillamine. It also does not discuss analgesics, such as acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids.

Clinical Issue

For most people, the joint destruction and disability caused by RA can be slowed by long-term treatment with one or more DMARDs. These drugs are thought to work by suppressing an overactive immune system and can be classified as either synthetics or biologics. Temporary adjuvant therapy with corticosteroids can help reduce inflammation and pain.

RA treatment is generally lifelong and can require medication changes. No single DMARD is superior as an initial treatment; however, methotrexate is commonly used. Combination therapy is often used when monotherapy is no longer effective to control symptoms. Evidence is insufficient to conclude whether one combination strategy is better than another. When choosing drugs for RA, consider that DMARDs vary in their adverse events, modes of administration, and cost. The dose and price of the drugs reviewed in this guide are listed on the back page.

Clinical Bottom Line

Based on studies that compare medications for RA, we know that:

- For people with early RA (less than 3 years duration) who have not previously taken methotrexate, monotherapy with methotrexate controls symptoms as well as the biologics adalimumab or etanercept.
  LEVEL OF CONFIDENCE ● ● ○
- Combining a biologic with methotrexate brings better symptom relief than using a biologic or methotrexate alone.
  LEVEL OF CONFIDENCE ● ● ○
- Combining methotrexate and sulfasalazine does not work better than monotherapy with either drug for people with early RA.
  LEVEL OF CONFIDENCE ● ● ○
- Evidence is insufficient to determine if combining two biologics works better than using any one biologic alone.
- Methotrexate and most biologics increase the likelihood of serious infection.
  LEVEL OF CONFIDENCE ● ● ○

Source

The source material for this guide is a systematic review of 156 research publications reporting on 103 studies. The review, *Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis in Adults* (2007), was prepared by the RTI-University of North Carolina Evidence-based Practice Center. The Agency for Healthcare Research and Quality (AHRQ) funded the systematic review and this guide. The guide was developed using feedback from clinicians who reviewed preliminary drafts.

Confidence Scale

The confidence ratings in this guide are derived from a systematic review of the literature. The level of confidence is based on the overall quantity and quality of clinical evidence.

- ● ● ● **High:** There are consistent results from good quality studies. Further research is very unlikely to change the conclusions.
- ● ● ○ **Medium:** Findings are supported, but further research could change the conclusions.
- ● ○ ○ **Low:** There are very few studies, or existing studies are flawed.

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

APRIL 2008

Types of RA Drugs

DMARDs

DMARDs (synthetic or biologic) are thought to work by suppressing an overactive immune system. Although synthetic DMARDs have been available longer than biologics, their exact mechanisms of action are unknown. The biologics, however, target components of the immune system by blocking specific immune cytokines. Adalimumab, etanercept, and infliximab are all tumor necrosis factor (TNF) inhibitors. Other biologics work by blocking other cytokines or by directly suppressing lymphocytes.

Corticosteroids

Corticosteroids are used for RA because of their anti-inflammatory and immunosuppressive effects. They are commonly used as an adjunct to DMARDs, particularly early in treatment.

DRUG NAME	BRAND NAME	ROUTE
SYNTHETIC DMARDS		
Hydroxychloroquine	Plaquenil®	Oral
Leflunomide	Arava®	Oral
Methotrexate	Rheumatrex®, Trexall®	Oral
Sulfasalazine	Azulfidine®, Sulfazine®	Oral
BIOLOGIC DMARDS– TNF-INHIBITORS		
Adalimumab	Humira®	SQ
Etanercept	Enbrel®	SQ
Infliximab	Remicade®	IV
BIOLOGIC DMARDS– OTHER		
Abatacept	Orencia®	IV
Anakinra	Kineret®	SQ
Rituximab	Rituxan®	IV

IV=intravenous, SQ=subcutaneous, TNF=tumor necrosis factor.

Research Comparing Drug Effectiveness

Most research studies evaluate the effectiveness of a DMARD by measuring its ability to reduce joint swelling and tenderness, slow or limit the progression of joint damage, and improve a person's ability to function.

Some studies also evaluate RA drugs based on the 2-year radiographic appearance of joints. Evidence is insufficient to determine how well these 2-year radiographic outcomes correlate with longer term outcomes, such as severe functional disability.

Monotherapy

To reduce joint swelling and tenderness and improve function:

- Methotrexate works as well as adalimumab or etanercept (two of the TNF-inhibitors) for people with early RA who have not previously taken methotrexate. However, adalimumab and etanercept give better 2-year radiographic outcomes.
  LEVEL OF CONFIDENCE ● ● ○
- Leflunomide and sulfasalazine work as well as methotrexate. There is no difference in 2-year radiographic outcomes.
  LEVEL OF CONFIDENCE ● ● ○
- All of the TNF-inhibitors (adalimumab, etanercept, and infliximab) work equally well.
  LEVEL OF CONFIDENCE ● ● ○
- Anakinra does *not* work as well as any of the TNF-inhibitors (adalimumab, etanercept, or infliximab).
  LEVEL OF CONFIDENCE ● ● ○

Evidence is insufficient to compare:

- Hydroxychloroquine, leflunomide, and sulfasalazine with the biologics.
- Hydroxychloroquine with the other synthetic DMARDs.
- Abatacept, rituximab, or corticosteroid monotherapy with the other DMARDs.

Combination Therapy

To reduce joint swelling and tenderness and improve function:

- Combining a biologic with methotrexate works better than using either drug alone.
  LEVEL OF CONFIDENCE ● ● ○
- Combining prednisone with hydroxychloroquine, methotrexate, or sulfasalazine works better than using these synthetic DMARDs alone. It also gives better 2-year radiographic outcomes.
  LEVEL OF CONFIDENCE ● ● ○
- A triple combination of hydroxychloroquine, methotrexate, and sulfasalazine works better than a two-drug combination (methotrexate with either drug) for people previously on monotherapy.
  LEVEL OF CONFIDENCE ● ● ○
- Combining sulfasalazine with methotrexate does *not* work better than monotherapy with either drug alone for people with early RA.
  LEVEL OF CONFIDENCE ● ● ○
- Evidence is insufficient to determine whether combining two biologics works better than monotherapy with a biologic.
- Research has not addressed whether combining a corticosteroid with a biologic works better than monotherapy with a biologic.

Assessing Risks

Infection

- Most biologics and methotrexate increase the risk of serious infections that require antibiotic treatment or hospitalization.
- TNF-inhibitors increase the risk of reactivating latent tuberculosis.
- About 2 percent of people taking a biologic for 3-12 months will develop a serious infection.
- The likelihood of serious infection is greater with combinations of two biologics than with just one biologic.

  LEVEL OF CONFIDENCE ●●○

Other Serious Risks

- Methotrexate increases the risk of hepatotoxicity, including fibrosis and cirrhosis.
- Methotrexate increases the risk of interstitial lung disease and malignant lymphomas.
- Methotrexate and sulfasalazine increase the risk of bone marrow suppression.
- Corticosteroids have several well-known side effects. Long-term use of corticosteroids increases the risk of adrenal suppression, osteoporosis, obesity, diabetes, cataracts, and infection.

Injection and Infusion Reactions

- Biologics administered subcutaneously (anakinra, etanercept, and adalimumab) can cause painful injection site reactions. Reactions are more common with anakinra (67 percent) than with the TNF-inhibitors etanercept (22 percent) and adalimumab (18 percent).

  LEVEL OF CONFIDENCE ●●○

- Biologics administered intravenously (abatacept, infliximab, and rituximab) can cause infusion reactions (dizziness, nausea, or fever) in up to 50 percent of people. About 2 percent of people discontinue therapy due to these reactions.
- Biologics administered intravenously can also cause rare but life-threatening infusion reactions resembling anaphylaxis or seizures. Evidence is insufficient to determine if the risk of infusion reactions differs among these DMARDs.

Reproductive Risks for Women and Men

- Leflunomide and methotrexate should not be taken during pregnancy. Both drugs can cause congenital abnormalities, and methotrexate can also cause fetal death. Both women and men taking these drugs should be counseled about reproductive risks.
- There are not enough data to determine the reproductive risks of other DMARDs.

Selecting a DMARD

Selection of a DMARD depends on several factors, including the individual's risk of adverse events, ability to participate in frequent monitoring, preferences for the mode of administration, and cost. Nearly two-thirds of people who begin DMARD therapy change to another drug within 5 years due to ineffectiveness, side effects, or other factors. Medication adjustments typically include switching to another DMARD, combining DMARDs, or adding a corticosteroid.

Initial Drug Choice

- No single DMARD is superior as an initial treatment for RA.
- Methotrexate, the best known and one of the least costly DMARDs, slows disease progression as well as other drugs used as monotherapy.

Adjusting Medication

- Combining methotrexate with a biologic is a better strategy than combining two synthetic DMARDs or two biologics.
- When monotherapy with a synthetic DMARD isn't working well enough, consider a triple combination of hydroxychloroquine, methotrexate, and sulfasalazine. It works better than a two-drug combination (methotrexate with either drug).
- Adding prednisone to a synthetic DMARD can reduce inflammation and pain, but long-term use of prednisone can cause adverse effects.
- Combination therapy (except with two biologics) does not increase the likelihood of discontinuation due to adverse effects.

Cost

The cost of RA drugs may be a barrier. Drugs, doses, and prices are listed on the back page. Intravenous drugs incur additional expense. The oral agents are all available as generics, but biologics are not.

If your patients need help paying for RA drugs, consider a prescription assistance program. The Partnership for Prescription Assistance provides information on 475 public and private programs. Web site: www.pparx.org. Phone: 1-888-477-2669.

Dose and Price of DMARDs and Corticosteroids

Drug Name[1]	Brand Name	Dose[2]	Price per Month[3] Generic	Brand
Synthetic DMARDs— Oral				
Hydroxychloroquine	Plaquenil®	400 mg daily	$70	$125
Leflunomide	Arava®	10 mg daily	$495	$570
		20 mg daily	$495	$570
Methotrexate	Rheumatrex®, Trexall®	7.5 mg once weekly	$40	$45
		15 mg once weekly	$80	$90
		20 mg once weekly	$105	$120
Sulfasalazine	Azulfidine®, Sulfazine®	500 mg bid	$15	$30
		1,000 mg bid	$30	$60
		1,500 mg bid	$45	$85
	Azulfidine EN-tabs®	1,000 mg daily	$25	$35
		2,000 mg daily	$45	$70
		3,000 mg daily	$70	$100
Biologic DMARDs— Subcutaneous				
Adalimumab[4]	Humira®	40 mg every 2 weeks	NA	$1,585
Anakinra	Kineret®	100 mg daily	NA	$1,445
Etanercept[4]	Enbrel®	25 mg twice weekly	NA	$1,585
		50 mg once weekly	NA	$1,585
Biologic DMARDs— Intravenous				
Abatacept	Orencia®	500 mg every 4 weeks	NA	$1,080
		750 mg every 4 weeks	NA	$1,620
		1,000 mg every 4 weeks	NA	$2,160
Infliximab[4]	Remicade®	3 mg/kg every 8 weeks	NA	$730[5]
		6 mg/kg every 8 weeks	NA	$1,465[5]
		10 mg/kg every 8 weeks	NA	$2,440[5]
Rituximab	Rituxan®	1,000 mg 2 weeks apart, total of 2 doses	NA	$1,015[6]
Corticosteroids— Oral				
Prednisolone (suspension)	Various	5 mg daily	$15	$25
		7.5 mg daily	$25	$40
		10 mg daily	$30	$55
Prednisone	Various	5 mg daily	$2	$3
		7.5 mg daily	$3	$5
		10 mg daily	$3	$6

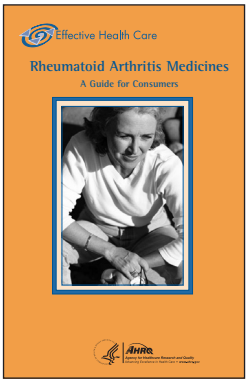
[1] These drugs were evaluated in the systematic review.
[2] Doses are representative of those used in the research studies or typical for rheumatoid arthritis.
[3] Average Wholesale Price from *Drug Topics Red Book*, 2007. Price does not include infusion-related expenses.
[4] Tumor necrosis factor (TNF) inhibitor.
[5] Price calculated for a 70-kg (154-lb) person.
[6] Price ($12,180) averaged over 12 months.
DMARDs=disease-modifying antirheumatic drugs, EN=extended release, bid=twice a day, NA=not available as generic.

AHRQ created the John M. Eisenberg Center at Oregon Health & Science University to make research useful for decisionmakers. This guide was prepared by Roger Chou, M.D., Theresa Bianco, Pharm.D., Sandra Robinson, M.S.P.H., Valerie King, M.D., Martha Schechtel, R.N., Monica Goei, M.D., Christina Dahlstrom, B.A., and David Hickam, M.D., of the Eisenberg Center.

Still Unknown

- It is not known whether the benefits or harms of DMARDs vary by age, sex, race, ethnicity, disease severity, comorbidities, or concomitant therapies.
- Because biologics are relatively new, evidence is insufficient to determine their long-term benefits and risks, including the risk of lymphoma.
- Evidence is insufficient to determine whether people with more severe RA respond better when started on a biologic or combination therapy instead of a synthetic DMARD.

Resource for Patients



Rheumatoid Arthritis Medicines: A Guide for Consumers is a companion to this Clinician's Guide. It can help people talk with their health care professional about the benefits, risks, and price of drug therapy for RA.

For More Information

For electronic copies of the consumer's guide, this clinician's guide, and the full systematic review, visit this Web site:
www.effectivehealthcare.ahrq.gov

For free print copies call:
The AHRQ Publications Clearinghouse
(800) 358-9295
Clinician's Guide,
AHRQ Pub. No. 08-EHC004-3
Consumer's Guide,
AHRQ Pub. No. 08-EHC004-2A

AHRQ Pub. No. 08-EHC004-3
APRIL 2008