Choosing Medications for Adults with Rheumatoid Arthritis: Clinician Summary Guide

Introduction

This guide summarizes evidence comparing the effectiveness and safety of disease-modifying antirheumatic drugs (DMARDs) and corticosteroids used to treat 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.

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.

Clinical Bottom Line

Based on studies that compare medications for RA (see "Confidence Scale"), 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: ● ● ○

Types of RA Drugs

DMARDs

DMARDs (synthetic or biologic; Table 1) 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.

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.

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.

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

Table 1. DMARDS

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

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 2-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 2 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% of people taking a biologic for 3 to 12 months will develop a serious infection.
- The likelihood of serious infection is greater with combinations of 2 biologics than with just 1 biologic.
  Level of confidence: ● ● ○

Other Serious Risks

- Methotrexate increases the risk of hepatotoxicity, including fibrosis and cirrhosis, interstitial lung disease, and malignant lymphomas.
- Methotrexate and sulfasalazine increase the risk of bone marrow suppression.
- 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

Table 2.
Dose and Price of DMARDs and Corticosteroids

			Cost per Month[3]	
Generic[1]	**Brand**	**Dose[2]**	**Generic**	**Brand**
Hydroxychloroquine	Plaquenil	400 mg/d	$70	$125
Leflunomide	Arava	10 mg/d	$495	$570
		20 mg/d	$495	$570
Methotrexate	Rheumatrex, Trexall	7.5 mg/wk	$40	$45
		15 mg/wk	$80	$90
		20 mg/wk	$105	$120
Sulfasalazine	Azulfidine, Sulfazine	500 mg bid	$15	$30
		1000 mg bid	$30	$60
		1500 mg bid	$45	$85
	Azulfidine EN-tabs	1000 mg/d	$25	$35
		2000 mg/d	$45	$70
		3000 mg/d	$70	$100
Adalimumab[4]	Humira	40 mg/2 wk	NA	$1585
Anakinra	Kineret	100 mg/d	NA	$1445
Etanercept[4]	Enbrel	25 mg/wk	NA	$1585
		50 mg/wk	NA	$1585
Abatacept	Orencia	500 mg/4 wk	NA	$1080
		750 mg/4 wk	NA	$1620
		1000 mg/4 wk	NA	$2160
Infliximab[4]	Remicade	3 mg/kg/8 wk	NA	$730[5]
		6 mg/kg/8 wk	NA	$1465[5]
		10 mg/kg/8 wk	NA	$2440[5]
Rituximab	Rituxan	1000 mg 2 wk apart, total 2 doses	NA	$1015[6]
Prednisolone (suspension)	Various	5 mg/d	$15	$25
		7.5 mg/d	$25	$40
		10 mg/d	$30	$55
Prednisone	Various	5 mg/d	$2	$3
		7.5 md/d	$3	$5
		10 mg/d	$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.

with anakinra (67%) than with the TNF-inhibitors etanercept (22%) and adalimumab (18%).

Level of confidence: ● ● ○

- Biologics administered intravenously (abatacept, infliximab, and rituximab) can cause infusion reactions (dizziness, nausea, or fever) in up to 50% of people. About 2% of people discontinue therapy because of 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

- 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 the drug's 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.

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The letter stressed that residents are often pressured to accept the first bed available and oftentimes do not have an opportunity to assess the care provided at that facility or to consider other options. The letter also points out that there have been cases in which arbitration agreements signed by illiterate residents were enforced. Proponents of the legislation also point to the vast number of LTC arbitration agreements that are challenged in court—more than 100 cases have been filed in the past 5 years challenging arbitration agreement—as evidence of their fundamental unfairness.[3]

Opponents of the proposed legislation have also begun their own lobbying effort aimed at defeating the legislation. Twenty organizations signed a letter urging members of Congress to oppose the Fairness in Nursing Home Arbitration Act.[4] In this letter, groups such as the National Center for Assisted Living (NCAL), the American Health Care Association (AHCA), and the US Chamber of Commerce highlighted the positive points of mandatory arbitration. They noted that studies have shown that consumers prevail more than 70% of the time in arbitration and that these disputes are resolved on average in less than 100 days, significantly less than the average 2-year litigation process.

At this point, the future of the Fairness in Nursing Home Arbitration Act of 2008 is unclear. Passage of the Act would drastically cut the number of LTC disputes that are resolved through arbitration. If the Act is defeated, state courts will have to continue to examine the enforceability of arbitration agreements on a case-by-case basis. Either way, this is an important issue for the LTC industry to follow closely going forward. ALC

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References

1. Martinez and Kohl Introduce Fairness in Nursing Home Act. Mel Martinez US Senator Florida Web site. http://martinez.senate.gov/public/index.cfm?FuseAction=NewsReleases.View&ContentRecord_id=8F239FEC-1DFC-4CD5-9DB2-1532DD585808&IsTextOnly=False. April 9, 2008. Accessed July 1, 2008.

2. Letter to US Senators. National Association of Consumer Advocates Web site. http://naca.net/_assets/shared/633475012313078750.doc. May 22, 2008. Accessed July 1, 2008.

3. Freking K. Patients signing away right to sue nursing homes. *USA-Today* Web site. www.usatoday.com/news/washington/2008-06-17-250882710_x.htm. June 17, 2008. Accessed July 1, 2008.

4. US Chamber of Commerce. Multi-industry letter opposing the onslaught of anti-arbitration bills and provisions that have been introduced in this Congress. US Chamber of Commerce Web site. www.uschamber.com/issues/letters/2008/080501_anti_arbitration.htm. May 1, 2008. Accessed July 1, 2008.

Clinical Practice Guidelines

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Adjusting Medication

- Combining methotrexate with a biologic is a better strategy than combining 2 synthetic DMARDs or 2 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 2-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 2 biologics) does not increase the likelihood of discontinuation due to adverse effects.

Cost

The cost of RA drugs may be a barrier (Table 2). 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. (See www.pparx.org or call 1-888-477-2669.)

Resource for Patients

Rheumatoid Arthritis Medicines: A Guide for Consumers is a companion to this Clinician's Guide.

Still Unknown

- It is not known whether the benefits or harms of DMARDs vary by a person's age, gender, 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. ALC

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. 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