

Generic/ TRADE	Pregnancy Category	√ USES / Comments / Onset Contraindications CI	Side Effects (Common & Rare) Monitor (ACR 2002 Guidelines) M	Drug INTERACTIONS <sup>11,12</sup>	Rheumatoid Dose: <b>USUAL &amp; MAX</b>	\$/Year 🇨🇦
<b>Anakinra</b> KINERET (100mg/0.67ml syr ☞☞) ☞ -Human IL-1 antagonist	B	√ Adult Mono Tx +/- DMARDs <sup>non TNF</sup> <b>Onset:</b> 2-3 months <b>CI:</b> active infections, neutropenia	<b>Common:</b> inj site reaction ~75% esp. during 1st 4 wks, severe infection <sup>2%</sup> , headache, nausea <b>Rare:</b> neutropenia M: CBC(q1 mon x3→q3mon <sup>22</sup> )	<b>Enbrel</b> (& ? with Remicade): ↓ WBC <sup>3%</sup> , ↑ infections <sup>7%</sup>	100mg SC od (↓dose if ↓renal fx) (store in Fridge)	16,900
<b>Etanercept</b> ENBREL (25mg vial ☞☞) ☞ -recombinant soluble TNF fusion receptor protein	B	√ Mono Tx & with MTX <sup>FDA</sup> √ Psoriasis <sup>plaque, arthritis, ankylosing spondylitis</sup> <b>Onset:</b> 1-2 weeks (Up to 3 months) ↓ joint erosions, May ↓ steroid & MTX <sup>doses</sup> <b>CI:</b> MS, sepsis, HF, Dx flare if drug D/C	<b>Common:</b> headache, nausea, rhinitis, cough, burning @ inj site ~50% 1st dose → ↓ after 5 doses, antibody to drug <b>Rare:</b> pancytopenia, Lupus like, demyelination <sup>9 cases</sup> , tuberculosis <sup>reactive</sup> , optic neuritis, severe infection <sup>4.3/100 pt. yr</sup> M: CBC, tuberculin test	Anakinra & live vaccines: ↑ risk of infection	25mg SC twice/wk (50mg SC weekly <sup>FDA</sup> ) <b>Peds</b> <sup>FDA &amp; Canada (Age 4-17):</sup> 0.4 mg/kg (Max 25mg) SC twice/wk or {0.8 mg/kg (Max 50mg) SC weekly <sup>FDA</sup> }	17,400
<b>Adalimumab</b> HUMIRA <sup>avail. USA</sup>		TNF α inhibitor. 40mg SC every other Week				
<b>Hydroxychloroquine</b> PLAQUENIL (HCQ) ☞ (200mg tab)	C	√ mild RA. Lupus; Well tolerated Not slow radiologic damage <b>Onset:</b> 2-6 months (trial~ 4months) <b>CI:</b> G6PDH <sup>hemolysis</sup> , vision changes	<b>Common:</b> GI (cramps & diarrhea), rash, headache <b>Rare:</b> ocular toxicity, myopathy, skin pigment changes M: CBC; eye exam (funduscopy & visual field/yr)	digoxin: ↑ digoxin levels methotrexate: ? ↓ methotrexate levels Beta blockers: ↑ β-blocker effect	200mg po od (with food/milk) 200mg po bid, 400mg po hs (Max ≤ 6.5mg/kg/day)	230 370
<b>Infliximab</b> REMICADE (100mg VIAL ☞☞) ☞ -mouse-human anti TNF α monoclonal antibody	B	√ With MTX <sup>FDA</sup> ; ↓ joint erosions & ↑ physical functioning √ Crohn's disease <b>CI:</b> MS, sepsis, acute HF, watch for Dx flare if drug stopped <b>Onset:</b> 1-2 weeks (Up to 4 months)	<b>Common:</b> headache, nausea, lung infections, fever, urticaria, dyspnea, ↓ BP for 1st few inj. antibody reaction (10% → antinuclear & DNA antibodies) <b>Rare:</b> histoplasmosis, extrapulmonary TB, Lupus, HF, severe infection, demyelinating Dx <sup>70 cases</sup> , aplastic anemia M: CBC, tuberculin test	Anakinra & live vaccines: ↑ risk of infection	200mg <sup>3mg/kg x ~70kg</sup> IV q 8 wks 300mg <sup>5mg/kg x ~60kg</sup> IV q 8 wks (Start Week 0, 2, 6, then every 8 wks) Range: 3-10mg/kg IV q8 wk or 3-5mg/kg IV q4 wk	11,800 17,600
<b>Leflunomide</b> ARAVA ☞ (10, 20mg tab ☞☞) ☞ -pyrimidine synthesis inhibitor (prodrug)	X	√ Active/severe RA. Mono Tx <sup>FDA</sup> Slow RA progression; ↑ physical fx Drug in body up to 2yr after D/C → Questran <sup>8g TID x 11d</sup> if toxic/pregnant <b>Onset:</b> 1-3 months <b>CI:</b> obstructive biliary & hepatic Dx, viral hepatitis, impaired immune Dx	<b>Common:</b> GI (diarrhea, nausea, ↓ weight), rash, ↑ BP, alopecia <sup>8%</sup> , reversible & dose related, ↑ LFT <sup>5%</sup> , lung infection <b>Rare:</b> aplastic anemia, TENS, Stevens-Johnson <sup>12 cases</sup> , hepatotoxic (130pts BMJ <sup>2002</sup> esp if with MTX) & pancytopenia, peripheral neuropathy, interstitial lung dx M: CBC, LFT, Scr q1 mon x6 → q1-2(3 <sup>20</sup> )mon	↑ leflunomide level/toxicity by: methotrexate (2-3x ↑ of LFTs), rifampin leflunomide ↑ effects of: NSAIDs, tolbutamide, warfarin ↓ leflunomide level by: activated charcoal, cholestyramine live vaccines: ↑ risk of infection	10mg po od 20mg po od (?Loading dose= 100mg/day x 3 days but ↑ GI intolerance)	4,070 4,070
<b>Methotrexate</b> (MTX) AMETHOPTERIN/ Generics (2.5mg tab; 20 & 50mg/2ml inj x*)	X	√ Active/severe RA → ↓ radiologic progression √ Psoriasis If AST or ALT <sup>↑ 2-3x N</sup> → D/C & biopsy <b>Onset:</b> 1-2 months adding Folic acid <sup>1-5mg/d</sup> ; ↓ mouth ulcers <b>CI:</b> liver, renal & lung Dx; ↑ alcohol	<b>Common:</b> GI-nausea & diarrhea, stomatitis, rash, alopecia, pulmonary infiltrates → cough <b>Rare:</b> hypersensitivity pneumonitis <sup>&lt;2%</sup> , nephrotic, myelosuppression, hepatotoxic, hepatic & pulmonary fibrosis, phototoxicity & skin necrotizing vasculitis. M: CBC, LFT, Scr, Plt, Alb q1 mon x6 → q1-2 mon	↑ MTX level/toxicity by: Bactrim, cyclosporine, doxycycline, ethanol, leflunomide, live vaccines, NSAIDs, omeprazole, probenecid ↑ myelosuppression with: Bactrim, sulfasalazine, trimethoprim ↓ MTX levels by: cholestyramine, neomycin	7.5-10mg po weekly (↓dose if ↓renal fx) 15mg po weekly (Max 25mg/wk) 300 7.5mg IM/SC weekly (Max 25mg/wk) 840 <b>Peds:</b> 10mg/square meter per week	200-235
<b>Sulfasalazine</b> (SSZ) SALAZOPYRIN/generic (500mg tab; 500mg EC tab)	B	√ mild RA - slows radiologic progression <b>Onset:</b> 1-3 months <b>CI:</b> G6PDH, sulfa allergy, GI obstruction	<b>Common:</b> GI (nausea/abd pain), rash, photosensitivity <b>Rare:</b> leukopenia, myelosuppression, hepatitis, lupus, ↓ sperm, ↑ Scr M: CBC, LFT q2-4wk x3mon → q3mon	digoxin <sup>↓ dig level</sup> , warfarin <sup>↓ INR</sup> , azathioprine <sup>↑ toxic</sup> ↓ sulfasalazine levels by: cholestyramine, iron, phenobarb, rifampin	500mg EC po bid -start low to ↓ side effects 1000mg EC po bid (after meals) 280 1000mg EC po tid <b>Peds:</b> 30-50 mg/kg/day 360	180 280 360
<b>Azathioprine</b> IMURAN/generic (50mg tab) -purine analog immunosuppressant	D	<b>Onset:</b> 2-3 months <b>CI:</b> history of treatment with alkylating agents	<b>Common:</b> GI, flu-like illness, ↑ LFT <b>Rare:</b> myelosuppression, hepatotoxic, infection, pancreatitis M: CBC, Plt, LFT, Scr q 1-2 wk → q1-3 mon	azathioprine ↓ effect of: warfarin ↑ aza level by: allopurinol (↓ dose by ~70%) ↑ myelosuppression with: captopril	50mg po od 100mg po od (Max 150mg po od) Range: 1-2.5mg/kg/day	320 550
<b>Cyclosporine</b> NEORAL (10, 25, 50, 100mg cap; 100mg/ml liquid)	C	√ RA, Psoriasis (recalcitrant plaque) <b>Onset:</b> 2-4 months. Seldom used alone. <b>CI:</b> ↓ renal fx, uncontrolled ↑ BP	<b>Common:</b> GI, headache, paresthesia, ↑ BP <sup>dose related</sup> <b>Rare:</b> nephrotoxicity <sup>dose related</sup> , anemia, malignancy, hypertrichosis, gingival hyperplasia, tremor, ↑ LFT, ↑ K <sup>+</sup> M: Scr <sup>q2wk→q1mon if stable</sup> CBC, LFT, K <sup>+</sup> , uric acid, BP, Cp	↑ cyclo level by: allopurinol, amiodarone, danazol, diltiazem, erythromycin, flu & ketoconazole, grapefruit juice, verapamil. ↓ cyclo levels by: aluminum, carbamaz, orlistat, phenobarbital, phenytoin, rifampin, St. Johns Wort, sulfasalazine. ↑ nephrotoxicity with: aminoglycosides, amphotericin, methotrexate, NSAIDs	100mg po q12h (↓dose if ↓renal fx) 150mg po q12h (Max 4-5mg/kg/d) 2.5 mg/kg/d bid, (↑ 0.5 mg/kg/d q 2-4 wk)	4,600 6,800
<b>Tacrolimus</b> PROGRAF (0.5, 1, 5mg cap; 5mg/ml amp) 3mg po od \$3200						
<b>GOLD</b> Sodium aurothiomalate MYOCHRYSLINE (10, 25, 50 mg/ml inj);		<b>Onset:</b> 3-6 months (trial ~ 5months) <b>Oral:</b> ↓ efficacy & longer to effect than IM gold (~25% absorbed) <b>CI:</b> blood & skin Dx, lung fibrosis	<b>Common:</b> stomatitis, rash, diarrhea, edema, proteinuria <b>Rare:</b> myelosuppression, ↓ platelets, alopecia, colitis M: CBC, Plt, Scr, urine protein q1-2 wk x 20wk then when inj or every other inj. {Oral: q1-3 mon}	Aspirin: may ↑ hepatotoxicity Penicillamine: ↑ rash & suppress bone marrow	3mg po bid ⇒ Clinically often IM used 25mg IM q2-4 wks (↓dose if ↓renal fx) 50mg IM q2-4 wks ( <b>Peds:</b> 1 mg/kg) Test dose: 10mg IM → Load 50mg/wk x ~20wk	1,320 220 300
<b>Auranofin</b> RIDAURA (3mg cap)						
<b>Minocycline</b> MINOCIN (50 & 100mg cap ☞☞)	D	<b>Onset:</b> 1-3 months <b>CI:</b> children <8yr, last ½ of pregnancy	<b>Common:</b> GI upset, headache, dizziness, ↑ pigmentation, yeast infection <b>Rare:</b> vestibular dysfx, lupus, ↑ LFT, photosensitivity M: CBC, LFT	antacids, calcium, food, iron: ↓ minocycline levels, warfarin ↑ bleeding, isotretinoin ↑ BP	50mg po bid 100mg po bid	540 970
<b>Penicillamine</b> CUPRIMINE (125 & 250mg cap, 250mg tab)	D	<b>Onset:</b> 3-6 mon (Note: ↓ iron <sup>esp peds &amp; menstruating ♀</sup> ) <b>CI:</b> renal impairment, possible penicillin <sup>cross</sup> sensitivity	<b>Common:</b> GI (N/V, diarrhea), taste disorders, rash, gynecomastia <b>Rare:</b> myelosuppression, proteinuria, Goodpasture's, myasthenia <sup>gravis</sup> , neuropathy M: CBC, Scr, urinary protein q2wk → dose stable → q1-3mon	antacids, calcium, food, iron: ↓ penicillamine levels, digoxin ↓ digoxin levels, ↑ rash & ↓ bone marrow	250mg po od, 250mg bid -start low & ↑ slowly 250mg po tid before meals (Max 1-1.5g/day)	415, 750 1,070

☞=↓ dose for renal dysfx ☞=exception drug status Sask. ☞ prior NIHB ☞=NonForm. SK. ☞=not NIHB ☞ covered NIHB ☞=females /Useful for/in Alb=albumin ALT/AST=liver tests BP=blood pressure CBC=complete blood count CI=contraindication Cp=plasma level d=day Dx=disease Dysfx=dysfunction EC=enteric coated FDA=USA approved fx=function  
GI=stomach HF=heart failure inj=injection K=potassium LFT=liver function test Mon=month MS=multiple sclerosis N=normal Peds=pediatric Plt=platelet RA=Rheumatoid arthritis Ser=serum creatinine SE=side effect TB=tuberculosis TENS=toxic epidermal necrosis syndrome TNF=tissue necrosis factor Tx=treatment WK=week yr=year ☞=scored tab  
Pregnancy <sup>1-4</sup>: B=likely safe C=possible fetal risk D=fetal human risk X=teratogenic. Contraception required for most DMARDs. If possible: D/C med. ↓ dose, avoid in 1<sup>st</sup> trimester. NSAIDs: use until last 6-8 weeks of pregnancy. DMARDs: relatively safe → HCQ, prednisone, SSZ. <sup>7</sup>  
**GOAL:** Delay or prevent disability/joint damage, prevent loss of function & ↓ pain. Treat early, aggressive & often with combinations. Give patient info. Trial DMARDs for several months to ensure efficacy. Watch clinical symptoms, ↓ ESR & ↓ CRP.  
**TREAT DMARDs main tx** within 3 months; NSAIDs <sup>1st few weeks</sup>, analgesics, local steroid inj <sup>2nd/3rd</sup>, prednisone ~ <10mg/day (↑ BP, diabetes, infection, thin skin, ↑ weight, cataract, osteoporosis calcium 1500mg/d, Vit. D 800iu/d & bisphosphonates). Physio, recreation & occupational THERAPY when indicated.  
**APPROACH:** Mild Dx: HCQ or SSZ. Active Dx: MTX or Leflunomide or Combo (Common Triple=MTX,SSZ,HCQ); or Etanercept/Infliximab/Anakinra +/- MTX/Leflunomide; ... } REFER: for treatment advice (diagnosis or complications).  
**Diagnostic Criteria** <sup>22</sup>: morning stiffness; arthritis: of ≥3 joint areas, hand joints & symmetric -lasting at least 6 weeks; rheumatoid nodules, ↑ serum rheumatoid factor & radiographic changes.

## Sources:

1. **Guidelines** for the management of rheumatoid arthritis: **2002 Update**. Arthritis Rheum. 2002 Feb;46(2):328-46.
2. **Treatment Guidelines**: Drugs for Rheumatoid Arthritis. **The Medical Letter**: January, **2003**; (5) pp. 25-32.
3. Guidelines for the management of rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum. **1996** May;39(5):713-22.
4. Guidelines for monitoring drug therapy in rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum. **1996** May;39(5):723-31.
5. Drugs for Rheumatoid Arthritis. The Medical Letter July 10, 2000; (1082) pp. 57-64.
6. Lee DM, Weinblatt ME. **Rheumatoid arthritis**. Lancet. 2001 Sep 15;358(9285):903-11.
7. Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. Arch Intern Med. 2000 Mar 13;160(5):610-9.
8. Anakinra (Kineret) for Rheumatoid Arthritis. The Medical Letter: February 18, 2002; (1124) pp. 18-19.
9. Aletaha D, Kapral T, Smolen JS. Toxicity profiles of traditional disease modifying antirheumatic drugs for rheumatoid arthritis. Ann Rheum Dis. 2003 May;62(5):482-6.
10. Adalimumab (Humira) for Rheumatoid Arthritis. The Medical Letter: March 31, 2003; (1153) pp. 25-27.
11. Micromedex 2004
12. Hansten, PD and Horn JR. Drug Interactions Analysis and Management. Applied Therapeutics Incorporated. Vancouver, WA. 2004.
13. Drug Information Handbook 10th edition, 2002-2003
14. Drugs in Pregnancy & Lactation 6th edition, 2002
15. Geriatric Dosage Handbook 7<sup>th</sup> Edition, 2002
16. Handbook of Clinical Drug Data 10<sup>th</sup> edition, 2002
17. Therapeutic Choices 4<sup>th</sup> edition, 2003
18. Moreland LW, O'Dell JR. Glucocorticoids and rheumatoid arthritis: back to the future? Arthritis Rheum. 2002 Oct;46(10):2553-63.
19. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med. 2003 May 20;138(10):807-11.
20. Olsen NJ, Stein CM. **New drugs** for rheumatoid arthritis. N Engl J Med. **2004** May 20;350(21):2167-79.
- 21 . USA Food & Drug Administration: Safety update meeting on TNF blocking agents Mar 4 & 5, 2003 <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3930t1.htm> , <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3930t2.htm>
22. O'Dell, James R., Therapeutic Strategies for Rheumatoid Arthritis. N Engl J Med **2004** 350: 2591-2602.

## Clinical trials:

- Bathon JM, Martin RW, et al A comparison of **etanercept** and **methotrexate** in patients with **early** rheumatoid arthritis. (**ERA trial**) N Engl J Med. 2000 Nov 30;343(22):1586-93.
- Boers M, Verhoeven AC, et al. Randomised comparison of combined step-down **prednisolone, methotrexate and sulphasalazine** with **sulphasalazine alone** in early rheumatoid arthritis. Lancet. 1997 Aug 2;350(9074):309-18.
- Brandt J, Khariouzov A, et al. Six-month results of a double-blind, placebo-controlled trial of **etanercept** treatment in patients with active **ankylosing spondylitis**. Arthritis Rheum. 2003 Jun;48(6):1667-75.
- Braun J, Brandt J, et al. Treatment of active **ankylosing spondylitis** with **infliximab**: a randomised controlled multicentre trial. Lancet. 2002 Apr 6;359(9313):1187-93.
- Braun J, et al. Long-term efficacy & safety of **infliximab** in **ankylosing spondylitis**: an open, observational, extension study of a 3month, randomized, placebo-controlled trial. Arthritis Rheum. 2003 Aug;48(8):2224-33.
- Bresnihan B, Newmark R, Robbins S, Genant HK. Effects of **anakinra** monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. J Rheumatol. 2004 Jun;31(6):1103-11.
- Calguneri M, Pay S, et al. **Combination therapy** versus **monotherapy** for the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol. 1999 Nov-Dec;17(6):699-704.
- Chung ES, Packer M, et al. Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of **infliximab**, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive **Heart Failure** (ATTACH) trial. Circulation. 2003 Jul 1;107(25):3133-40.
- Cohen S, Cannon GW, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with **leflunomide** compared with **methotrexate**. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. (**ULTRA**) Arthritis Rheum. 2001 Sep;44(9):1984-92.
- Cohen S, Hurd E, et al. Treatment of rheumatoid arthritis with **anakinra**, a recombinant human interleukin-1 receptor antagonist, in combination with **methotrexate**: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Mar;46(3):614-24.
- Cohen SB, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ, Hanrahan PS, Kraishi MM, Patel A, Sun G, Bear MB; 990145 Study Group. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004 Sep;63(9):1062-8. Epub 2004 Apr 13.
- Fleischmann RM, et al. **Anakinra**, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003 Apr;48(4):927-34.
- Genovese MC, Bathon JM, et al. **Etanercept** versus **methotrexate** in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002 Jun;46(6):1443-50.
- Genovese MC, Cohen S, Moreland L, Liem D, Robbins S, Newmark R, Bekker P; 20000223 Study Group. **Combination** therapy with **etanercept** and **anakinra** in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum. 2004 May;50(5):1412-9.
- Gorman JD, Sack KE, et al. Treatment of **ankylosing spondylitis** by inhibition of tumor necrosis factor alpha **etanercept**. N Engl J Med. 2002 May 2;346(18):1349-56.
- Kalden JR, Schattenkirchner M, et al. The efficacy and safety of **leflunomide** in patients with active rheumatoid arthritis: a five-year followup study. Arthritis Rheum. 2003 Jun;48(6):1513-20.
- Keystone EC, Schiff MH, et al. **Once-weekly** administration of 50 mg **etanercept** in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2004 Feb;50(2):353-63.
- Klareskog Lars, van der Heijde Désirée, de Jager Julien P, et al. for the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the **combination of etanercept and methotrexate compared** with each treatment **alone** in patients with rheumatoid arthritis: double-blind randomised controlled trial. The Lancet Volume 363, Number 9410 28 February 2004.
- Kremer JM, et al. Concomitant **leflunomide** therapy in patients **with** active rheumatoid arthritis despite stable doses of **methotrexate**. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2002 Nov 5;137(9):726-33.
- Lipsky PE, van der Heijde DM, et al. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. **Infliximab and methotrexate** in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000 Nov 30;343(22):1594-602.
- Lovell DJ, Giannini EH, et al. Pediatric Rheumatology Collaborative Study Group. Long-term efficacy and safety of **etanercept** in **children** with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. Arthritis Rheum. 2003 Jan;48(1):218-26.
- Lovell DJ, Giannini EH, et al. **Etanercept** in **children** with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000 Mar 16;342(11):763-9.
- Maini R, St Clair EW, et al. **Infliximab** (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving **concomitant methotrexate**: a randomised phase III trial. **ATTRACT** Study Group. Lancet. 1999 Dec 4;354(9194):1932-9.
- Mease PJ, Goffe BS, et al. **Etanercept** in the treatment of **psoriatic arthritis** and psoriasis: a randomised trial. Lancet. 2000 Jul 29;356(9227):385-90.
- Moreland LW, Schiff MH, et al. **Etanercept** therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999 Mar 16;130(6):478-86.
- Moreland LW, Baumgartner SW, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein **etanercept**. N Engl J Med. 1997 Jul 17;337(3):141-7.
- Morgan SL, Baggott JE, et al. Supplementation with **folic acid during methotrexate** therapy for rheumatoid arthritis. A double-blind, placebo-controlled trial. Ann Intern Med. 1994 Dec 1;121(11):833-41.
- Mottonen T, Hannonen P, et al. Comparison of **combination** therapy with **single-drug** therapy in early rheumatoid arthritis: a randomised trial. **FIN-RACo trial** group. Lancet. 1999 May 8;353(9164):1568-73.

- Nuki G, Bresnihan B, et al. European Group Of Clinical Investigators. Long-term safety and maintenance of clinical improvement following treatment with **anakinra** (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2002 Nov;46(11):2838-46.
- O'Dell JR, Leff R, et al. Treatment of rheumatoid arthritis with **methotrexate and hydroxychloroquine, methotrexate and sulfasalazine**, or a **combination** of the **three** medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2002 May;46(5):1164-70.
- O'Dell JR, Haire CE, et al. Treatment of rheumatoid arthritis with **methotrexate alone, sulfasalazine and hydroxychloroquine**, or a **combination** of all **three** medications. *N Engl J Med.* 1996 May 16;334(20):1287-91.
- O'Dell JR, Blakely KW, et al. Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of **minocycline** and **hydroxychloroquine**. *Arthritis Rheum.* 2001 Oct;44(10):2235-41.
- Poor G, Strand V. Efficacy and safety of **leflunomide 10 mg versus 20 mg** once daily in patients with active rheumatoid arthritis: multinational double-blind, randomized trial. *Rheumatology (Oxford).* 2004 Mar 16 [Epub ahead of print]
- Scott DL, et al. European Leflunomide Study Group. Treatment of active rheumatoid arthritis with **leflunomide**: two year follow up of a double blind, placebo controlled trial **versus sulfasalazine**. *Ann Rheum Dis.* 2001 Oct;60(10):913-23.
- Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, Loew-Friedrich I, Oed C, Rosenburg R. Efficacy and safety of **leflunomide** compared with placebo and **sulphasalazine** in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. *Lancet.* 1999 Jan 23;353(9149):259-66.
- Strand V, Cohen S, et al. Treatment of active rheumatoid arthritis with **leflunomide** compared with placebo and **methotrexate**. Leflunomide Rheumatoid Arthritis Investigators Group. *Arch Intern Med.* 1999 Nov 22;159(21):2542-50.
- Tugwell P, Pincus T, et al. Combination therapy with **cyclosporine and methotrexate** in severe rheumatoid arthritis. The Methotrexate-Cyclosporine Combination Study Group. *N Engl J Med.* 1995 Jul 20;333(3):137-41.
- Weinblatt ME, Kremer JM, et al. A trial of **etanercept**, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis **receiving methotrexate**. *N Engl J Med.* 1999 Jan 28;340(4):253-9.