

RHEUMATOID ARTHRITIS

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Epidemiology

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Decreasing mortality in patients with rheumatoid arthritis: results from a large

population based cohort in Sweden, 1964-1995. *Journal of Rheumatology* 29:906-12, 2002.

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This cohort study assessed the impact of rheumatoid arthritis on employment status on patients with early RA followed up to 5 years treated with conventional second line drugs. Originally culled from the original ERAS study, a third of RA patients who were employed at onset were on disability at five years. High HAQ scores and manual work were predictors of disability. This provides incentive to the patient and the medical team alike that aggressive treatment of RA is needed to prevent disability.

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Functional Disability in Rheumatoid Arthritis

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Pathogenesis

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Review of current knowledge of genetic factors, T- cells, cytokines and other factors in the pathogenesis of tissue destruction in RA.

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Gives an overview of the immunopathology of the various stages of rheumatoid arthritis and defines the therapeutic measures that should be carried out for each.

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Part of a series of Immunology reviews in this journal, this review defines the role of cytokines in the pathogenesis of RA.
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Diagnostic Tests

Antibodies, Inflammatory Indices

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Radiology and other imaging modalities

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This longitudinal prospective study followed 500 patients with early RA who underwent annual radiologic assessment up to six years. Radiologic damage using the Sharp/van der Heijde method progressed at a constant rate. Feet joints especially the 5th MTP, became eroded earlier compared to hand joints.

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This prospective longitudinal study involving 256 RA patients describes the longitudinal radiographic course of the disease, and identifies and quantitates predictors of radiographic progression. Radiographic progression using Sharp scores, occurred at a constant rate over 19 years. Acute phase reactants were the strongest predictor of progression.

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Six hundred fifty films from 292 patients with RA were studied prospectively to assess progression of RA over 25 years. The average annual rate of progression of the total radiologic score, which sums erosion and joint space abnormalities and has a maximum possible score of 314, was approximately 4 units per year over the first 25 years after onset; this progression was more rapid in the earlier years of disease and slightly slower in the later years.

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Corticosteroid usage was reported to prevent radiographic damage in patient with early RA. The effect of corticosteroid use (prednisone= \leq 5mg) on radiographic progression of joint damage was assessed in 824 patients who

were participating in a 3-year prospective clinical trial comparing the efficacy of various NSAIDs. In the 197 patients who started prednisone at least 6 months before study entry, x-rays showed progressive joint damage.

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Radiographic joint space narrowing and erosions are seen in as much as 67% of patients within the first two years of disease. Correlation of XR scores with physical examination scores are highly significant for joint deformity and limited motion and modestly significant for joint swelling. Three quantitative methods, the Steinbrocker radiographic stage, modified Sharp method, and Larsen method, are highly significantly correlated and yield similar results in comparisons with other clinical measures.

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55. Ostergaard M, Szkudlarek M. Magnetic resonance imaging of soft tissue changes in rheumatoid arthritis wrist joints. *Seminars in Musculoskeletal Radiology* 5(3): 257-74, 2001.

MRI has received increasing attention for its potential in diagnosing early RA. It also offers prognostic and monitoring data. Although more thorough validation is needed, MRI is a very promising method for the assessment of both established and early RA.

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Cervical Spine Disease

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59. Halla JT, Hardin JG, Vitek JG, Alarcon GS, et al. Involvement of the cervical spine in rheumatoid arthritis. *Arthritis & Rheumatism* 32(5): 652-8, 1989.
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The above three articles are excellent reviews of the various manifestations of cervical spine disease in rheumatoid arthritis.

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Rheumatoid Foot

73. Burra G, Katchis SD. Rheumatoid arthritis of the forefoot. *Rheumatic Diseases Clinics of North America* 24:173-80, 1998.
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Extra-Articular Manifestations of Rheumatoid Arthritis

Interstitial Lung Disease

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computed tomograph, chest radiography and pulmonary function tests. *Thorax* 56:622-627, 2001.

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Pleural Disease

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Cardiovascular Disease

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This retrospective study compared the incidence of cardiovascular events in RA patients compared to the general population. Two hundred thirty-six consecutive patients with RA were assessed for the 1-year occurrence of CV-related hospitalizations and deaths. An incidence of 3.43 per 100 patient-years of CV events were noted in RA patients compared to an incidence of 0.59 per 100 person-years for the control group. The results of this study suggests that other unidentified mechanisms are responsible for the higher incidence of CV disease in RA. Clinicians treating RA patients should be aware of this increased risk and should carry out appropriate diagnostic and therapeutic measures.

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The above three studies provide evidence of cardiovascular disease in RA patients without symptoms suggestive of it. Most common echocardiographic findings were aortic root alterations, valvular abnormalities, and effusions were noted. 1mm ST depression was noted on electrocardiography.

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Felty's Syndrome

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Classic article.

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Amyloidosis

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Anemia in Rheumatoid Arthritis

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Rheumatoid Vasculitis

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Rheumatoid Nodules

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Treatment

NSAIDs, COX-2 inhibitors

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Corticosteroids

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Two-year randomized double blind placebo controlled clinical trial which assessed the clinical efficacy, disease-modifying properties and side effects of low-dose steroid therapy as monotherapy for previously untreated patients with early active RA.

MTX, SSZ, HCQ, CYC-A, Leflunomide

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Prospective study involving 29 patients that assessed the safety and efficacy of oral methotrexate for the treatment of refractory RA.

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This extended study assessed the efficacy of prednisolone-MTX-SSZ therapy vs SSZ monotherapy. Sustained suppression of the rate of radiologic progression in patients with early RA was seen.

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This large multicenter trial from the Netherlands evaluated the effectiveness of a step-down approach utilizing combination treatment in enhancing symptom resolution in 155 patients with early RA. Patients given combination therapy had a remission rate of 28% compared to 16% for the monotherapy group at 28 weeks. However, the difference in clinical response was not significant in the two groups after both steroid and methotrexate treatment were withdrawn at week 34 and 46 respectively.

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This 2-year double-blind, placebo-controlled trial assessed the efficacy of MTX+HCQ vs MTX+SSZ and MTX+HCQ+SSZ therapies in RA patients. Triple combination therapy is safe and much more efficacious compared to the other combination regimens.

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This 24-week multicenter randomized, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of leflunomide versus placebo when added to ongoing, stable-dose methotrexate therapy in patients with persistently active rheumatoid arthritis. In leflunomide recipients, there was a 46% ACR 2- response. Overall incidence of side effects and discontinuation rates were similar in both groups. Combination therapy with MTX and LEF is safe with appropriate liver enzyme and hematologic monitoring.

172. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, Fox R, Moreland L, Olsen N, Furst D, Caldwell J, Kaine J, Sharp J, Hurley F, Loew-Friedrich I. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. Archives of Internal Medicine 159(21):2542-50, 1999.

This double-blind, placebo, and active-controlled 12-month study compared the efficacy and safety of leflunomide treatment with placebo and methotrexate treatment in patients with active RA. Using ACR response and success rates, rate of radiographic progression, improvement in function and quality of life were comparable in the leflunomide and methotrexate groups and statistically were superior compared to placebo.

173. O'Dell JR, Paulsen G, Haire CE, Blakely K, Palmer W, Wees S, Eckhoff PJ, Klassen LW, Churchill M, Doud D, Weaver A, Moore GF. Treatment of early seropositive rheumatoid arthritis with minocycline: four-year followup of a double-blind, placebo-controlled trial. Arthritis & Rheumatism 42(8):1691-5, 1999.

174. O'Dell JR, Haire CE, Palmer W, et al. Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 40: 842-8, 1997.

These two trials evaluated the efficacy of minocycline versus placebo in treating 46 patients with seropositive RA treated within the first year of disease up to four years. Initially 65 of minocycline recipients achieved a 50% improvement in their Paulus score. In the four-year follow-up study, RA was in remission in 8 minocycline-treated patients whereas 10 required DMARD therapy. Both studies were limited by their small size. Radiologic evaluation was also not performed to assess the effectiveness of minocycline in preventing erosions.

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This is a larger double-blind, randomized, placebo-controlled, multicenter 48-week trial assessed the safety and efficacy of minocycline in the treatment of 219 patients rheumatoid arthritis versus placebo. Overall minocycline recipients had significant improvement in joint tenderness and swelling, laboratory parameters (Hct, platelet, ESR < RF) and physician and global assessment, HAQ scores.

176. Tugwell P, Pincus T, Yocum D, Stein M, et al. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *New England Journal of Medicine* 333:137-42, 1995.
177. Stein CM, Pincus T, Yocum D, Tugwell P, Wells G, Gluck O, Kraag G, Torley H, Tesser J, McKendry R, Brooks RH. Combination treatment of severe rheumatoid arthritis with cyclosporine and methotrexate for forty-eight weeks: an open-label extension study. The Methotrexate-Cyclosporine Combination Study Group. *Arthritis & Rheumatism* 40(10):1843-51, 1997.

Anti-Cytokine therapies

178. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of Etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *New England Journal of Medicine* 340:253-9, 1999.
179. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N England Journal of Medicine* 337(3):141-7, 1997.
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This randomized, double-blind, placebo-controlled trial assessed the benefit of prolonged and simplified dosing (25mg SQ BIW) of etanercept in a RA patients. ACR 20 and ACR 50 responses were 59% and 50% respectively at 6 months in the etanercept group. More patients in the etanercept group achieved ACR 70 response, improved quality of life, minimal disease status compared to placebo. Etanercept was also well tolerated with no dose-limiting side effects.

181. Genovese MC, Bathon JM, Martin FM, Fleischmann RM, Tesser JR, Schiff MH et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis. *Arthritis & Rheumatism* 46: 1443-50, 2002.

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183. Lipsky PE, Van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, Smolen JS, Weisman M, Emery P, Feldmann M, Harriman GR, Maini RN. 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. New England Journal of Medicine.* 343(22):1594-602, 2000.
- This extended 54-week trial assessed the clinical responses of patients receiving infliximab + methotrexate therapy. Significantly greater reduction in the signs and symptoms of RA, quality of life was noted in patients receiving infliximab and methotrexate compared to methotrexate alone. Radiographic joint damage increased in patients on MTX monotherapy but not in those receiving infliximab.*
184. Elliott MJ, Maini RN, Feldmann M, et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor α . *Arthritis & Rheumatism* 36(12):1681-90, 1993.
185. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis & Rheumatism* 41(9): 1552-63, 1998.
186. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet* 344:1105-10, 1994.
187. Bresnihan B, Alvara-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P et al: Treatment of rheumatoid arthritis with recombinant human IL-1 receptor antagonist. *Arthritis & Rheumatism* 41: 2196-204, 1998.
188. Cohen S, Hurd E, Cursh J et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate. *Arthritis & Rheumatism* 46: 614-24, 2002.
189. Nuki G, Bresnihan B, Bear MR, McCage D. Long-term safety and maintenance of clinical improvement following treatment with anakinra in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis & Rheumatism* 46(1):2838-46, 2002.

190. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, Teoh LA, Fischkoff SA, Chartash EK. Adalimumab, A. Fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis & Rheumatism* 48(1):35-45, 2003.

Proisorba Column

191. Caldwell J, Gendreau RM, Furst D, et al. A pilot study using a staph protein A column (Proisorba) to treat refractory rheumatoid arthritis. *Journal of Rheumatology* 26:1657-62, 1999.
192. Felson DT, LaValley MP, Baldassare AR, et al. The proisorba column for treatment of refractory rheumatoid arthritis. *Arthritis & Rheumatism* 42(10):2153-9, 1999.

The above two studies evaluated the safety and efficacy of of extracorporeal treatments with protein A (Proisorba) columns in the treatment of patients with severe refractory rheumatoid arthritis.

Tacrolimus, Rituximab

193. Furst DE, Saag K, Fleischmann MR, Sherrer Y, Block JA, Schnitzer T, Rutstein J, Baldassare A, Kaine J, Calabrese L, Dietz F, Sack M, Senter RG, Wiesenhutter C, Schiff M, Stein CM, Sato Y, Matsumoto A, Caldwell J, Harris RE, Moreland LW, Hurd E, Yocum D, Stamler DA. Efficacy of tacrolimus in rheumatoid arthritis patients who have been treated unsuccessfully with methotrexate: a six-month, double-blind, randomized, dose-ranging study. *Arthritis & Rheumatism* 46(8):2020-8, 2002.

This phase II, randomized, double-blind, placebo-controlled monotherapy multicenter study assessed the efficacy, safety, and optimal dose of tacrolimus monotherapy in 268 patients with rheumatoid arthritis. Tacrolimus improved disease activity in methotrexate-resistant or -intolerant patients with RA. The optimal dose of tacrolimus appears to be >1 mg but < or=3 mg daily.

194. Leandro MJ, Edwards JC, Cambridge G. Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion. *Annals of the Rheumatic Diseases* 61(10):883-8, 2002.

Twenty-two patients underwent B lymphocyte depletion as part of a trial to assess dose response, safety and efficacy of this mode of treatment for RA. Major improvement in ACR criteria and disease activity was seen with rituximab 600 mg/m² and cyclophosphamide. These observations provided a prerequisite for the design of formal trials of B cell depletion and other B cell directed treatments.

195. Vita SD, Zaja F, Sacco S, Candia AD, Fanin R, Ferraccioli G. Efficacy of selective B cell blockade in the treatment of rheumatoid arthritis: evidence for a pathogenetic role of B cells. *Arthritis & Rheumatism* 2002; 46(8):2029-33.

This study demonstrated clinical efficacy of selective B cell blockade with rituximab, an anti-CD20 chimeric monoclonal antibody, in a subset of patients. Five patients who were nonresponders to combination therapy with MTX, CYC-A and even to anti-TNF therapy (in two patients) exhibited varying responses (ACR 20-70) with decreases in CRP, RF and erosive changes on XR. This study suggests that differences in B cell commitment in RA pathobiology might have a function in the different responses observed.

Complications of Therapy

196. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *New England Journal of Medicine* 345: 1098-104, 2001.
197. Charles PJ, Smeenk RJT, de Jong J, et al. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha. *Arthritis & Rheumatism* 43(11):2383-90, 2000.
198. Mohan N et al. Demyelination occurring during anti-TNFalpha therapy for inflammatory arthritides. *Arthritis & Rheumatism* 44:2862-9, 2001.
199. Shakoor N et al. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 359: 579-80, 2002.
200. Ferraccioli G et al. Anticardiolipin antibodies in rheumatoid patients treated with etanercept or conventional combination therapy: direct and indirect evidence for a possible association with infections. *Annals of the Rheumatic Diseases* 62: 358-61, 2002.
201. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis & Rheumatism* 46(12):3151-8, 2002.
202. Lee J-H, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor α antagonists infliximab and etanercept. *Arthritis & Rheumatism* 46(10): 2565-70, 2002.

203. Moreland LW, O'Dell JR. Review: Glucocorticoids and rheumatoid arthritis: back to the future? *Arthritis & Rheumatism* 46(10):2553-63, 2002.
204. Doran MF, Crowson CS, Pond GR, O'Fallon M, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls. *Arthritis & Rheumatism* 46(9):2287-93, 2002.

Perioperative Medical Care in Rheumatoid Arthritis

205. MacKenzie CR, Sharrock NE. Perioperative medical considerations in patients with Rheumatoid arthritis. *Rheumatic Diseases Clinics of North America* 24:1-17, 1998.
206. Lyssy KJ, Escalante A. Perioperative management of rheumatoid arthritis. Areas of concern for primary care physicians. *Postgraduate Medicine* 99:191-206, 1996.
207. Grennan DM, Gray J, Loudon J, Fear S. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. *Annals of the Rheumatic Diseases* 60:214-7, 2001.

Contrary to previous reports, this prospective, randomized trial demonstrated that continued methotrexate treatment did not increase the risk of postoperative infections/surgical complications in RA patients within one year of elective orthopaedic surgery.