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Mark Ebell, MD
Section Editor

MINOCYCLINE FOR RHEUMATOID ARTHRITIS

TITLE: Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial
AUTHORS: Tilley BC, Alarcon GS, Heyse, SP, et al
JOURNAL: *Annals of Internal Medicine*
DATE: January 15, 1995; Volume 122:81–9

Clinical question. Is minocycline safe and effective in the treatment of rheumatoid arthritis?

Submitted February 13, 1995.

Dr Ebell is from the Department of Family Medicine, Wayne State University, Detroit, Michigan. Requests for reprints should be addressed to Mark H. Ebell, MD, 4201 St Antoine, UHC-4J, Detroit, MI 48201.

Dr Shaughnessy is from the Harrisburg Hospital Family Practice Residency Program, Harrisburg, Pennsylvania, and Dr Slawson is from the University of Virginia Health Sciences Center, Charlottesville, Virginia. Requests for reprints should be addressed to David Slawson, MD, Department of Family Medicine, University of Virginia Health Sciences Center, Box 414, Charlottesville, VA 22908.

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Background. It has been proposed that chronic *Mycoplasma* infection may be responsible for rheumatoid arthritis. Although some physicians have reported that lengthy trials of tetracycline result in clinical benefit, these trials have been uncontrolled and unrandomized. A previous placebo-controlled trial did not show any benefit, but the dose of tetracycline (250 mg per day) was quite low. A recent randomized trial showed some benefit, but it was small and of limited duration.

Population studied. The study included 219 adult patients who had active rheumatoid arthritis according to the 1987 definition of the American College of Rheumatology. This definition includes nine or more tender joints and six or more swollen joints capable of assessable improvement. Disease-modifying agents such as phenylbutazone, methotrexate, and steroids were not allowed within 4 weeks of entering the trial or during the trial period. Patients who were taking nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose corticosteroids were required to remain on a regimen of stable doses of these medications during the study period. In general, the inclusion and exclusion criteria were appropriate, and the population was probably typical of patients with moderate, active rheumatoid arthritis.

Study design and validity. The study was a multicenter, randomized, double-blind, placebo-controlled trial. One half of the patients were given 100 mg minocycline twice daily, and the other one half were given a similar-looking placebo twice daily. The two groups were generally similar in disease severity, medication use, and demographics.

Outcomes measured. Two types of outcomes were measured: patient-oriented and physiologic. Patient-oriented measures included the total number of affected joints, a patient self-assessment of morning stiffness, swelling and tenderness, functional status based on eight activities of daily living, and overall disease activity on the preceding day. Physiologic outcomes included the erythrocyte sedimentation rate, IgM rheumatoid factor, and platelet count (an acute-phase reactant).

Physician raters were trained to ensure uniformity, and most patients were assessed by the same physician at each visit. Most symptom scores had been assessed for reliability and validity in previous studies. Intention-to-treat analysis was used for all outcomes, ie, results were reported for all patients, even those who did not complete the intervention. This is important, because if the intervention had been unpleasant or harmful, patients might

have dropped out early, making the treatment group's outcome look better than it actually was.

Results. More patients in the group receiving minocycline had improvement in joint swelling (54% vs 39%, $P=.023$) and joint tenderness (56% vs 41% $P=.021$). There was no difference between groups in the degree of morning stiffness. Patients in the treatment group had a greater increase in grip strength than did those in the control group as well as greater improvement in physiologic measures, such as IgM rheumatoid factor, platelet count, and erythrocyte sedimentation rate. There was no significant difference, however, between the treatment and control groups with regard to global patient-oriented outcomes of overall disease activity as assessed by the patient, overall disease activity as assessed by the physician, and functional status.

Recommendations for clinical practice. Minocycline appears to have a physiologic effect on rheumatoid arthritis, and there is evidence that it may help reduce joint swelling and tenderness in some patients. However, there is no evidence that this treatment has a significant effect on overall disease activity or functional status. Given the low toxicity of minocycline in patients who are not and do not plan to become pregnant, it seems appropriate to consider a 1-year trial of minocycline in patients with active rheumatoid arthritis. Given the variable efficacy of the therapy, it is important to assess the patient's response carefully and objectively and at regular intervals.

Mark H. Ebell, MD
Detroit, Michigan

SIMVASTATIN DECREASES MORTALITY

TITLE: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)
AUTHORS: Scandinavian Simvastatin Survival Study Group
JOURNAL: *Lancet*
DATE: November 19, 1994; Volume 344:1383–9

Clinical question. Can long-term treatment of hypercholesterolemia with simvastatin (Zocor) decrease all-cause mortality in patients with known coronary heart disease (CHD)?

Background. There is ample documentation that high serum cholesterol is associated with coronary heart disease (CHD). Evidence also suggests that lowering cholesterol decreases the risk of patients experiencing, or dying from, a coronary event. No current clinical trials have convincingly shown, however, that cholesterol-lowering strategies actually prolong life in patients with CHD.

Population studied. The study included 4444 patients aged 35 to 70 years with a history of angina pectoris or acute myocardial infarction (MI), who were recruited from 94 centers in Scandinavia. Patients were excluded from the study if they had congestive heart failure, atrial fibrillation, unstable or Prinzmetal angina, or if they had experienced an MI during the preceding 6 months.

Study design and validity. Patients with fasting cholesterol levels between 5.5 and 8.0 mmol/L (212 and 310 mg/dL) were randomized to receive simvastatin 20 mg or placebo. The dose was increased as necessary to decrease the cholesterol to <5.2 mmol/L (200 mg/dL). Double-blinding was preserved by allowing a study supervisor to monitor cholesterol determinations and provide dosing instructions to the clinician. Patients continued on therapy for a median follow-up of 5.4 years. The study was stopped earlier than scheduled when the difference between the two groups became statistically significant. In general, studies may be stopped by an external monitoring committee when treatment is proven so helpful that it would be unethical to deny it to the control group, or when an intervention is so harmful that it would be unethical to continue giving it to the treatment group. Use of such a "stopping rule" is becoming common in large trials.

Outcomes measured. The primary endpoint of the study was mortality related to any cause. Secondary endpoints included the incidence of major coronary events (coronary deaths and silent or nonfatal MI), revascularization procedures, noncoronary deaths, and hospital admissions for acute coronary events. Intention-to-treat analysis was used for all outcomes: results were reported for all patients, even those who did not complete the intervention. This is important because if the intervention had been either unpleasant or harmful, patients might have dropped out early, making the group's outcome look better than it actually was.

Results. There was a statistically significant decrease in total mortality in the treated group as compared with the placebo group (8% vs 12%, $P<.001$). Coronary-related deaths were also reduced in the simvastatin-treated group (relative risk = 0.58), and, unlike other studies of cholesterol therapy, there was no increase in the number of deaths from noncardiovascular causes. Simvastatin did not increase the number of violent deaths (suicide and trauma-related) as has been seen in some other studies.