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TREATMENT OF EARLY RHEUMATOID ARTHRITIS WITH MINOCYCLINE OR PLACEBO

Results of a Randomized, Double-Blind, Placebo-Controlled Trial

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Objective. **To determine if minocycline is an effec-tive therapy for seropositive rheumatoid arthritis (RA) when used within the first year of disease.**

Methods. **The Rheumatoid Arthritis Investiga-tional Network enrolled 46 patients with RA of <1 year duration into a 6-month study of minocycline (100 mg twice daily) versus placebo. All patients were rheuma-toid factor positive. The primary end point of the study was successful completion of 6 months of treatment with no drug toxicity while maintaining 50% improvement in composite symptoms of arthritis.**

Results. **Eighteen of the 46 patients who were enrolled met 50% improvement criteria at 3 months, and maintained at least a 50% improvement for 6 months with no significant drug toxicity. Among them were 15 of the 23 patients (65%) treated with minocy-cline and 3 of 23 patients (13%) treated with placebo *(P* < 0.001).**

Conclusion. **In patients with early seropositive RA, therapy with minocycline is superior to placebo.**

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Rheumatoid arthritis (RA) is a common disease (1) that often has a profound impact, causing substantial morbidity in most patients (2) and premature mortality in many (2-4). Conventional therapy for RA includes administration of nonsteroidal antiinflammatory drugs (NSAIDs), followed by disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, hydroxychloro-quine, sulfasalazine, or gold in patients who have per-sistent active disease. Short-term studies (5-14) and meta-analyses (15,16) have repeatedly proved the effi-cacy of these latter drugs, but their long-term efficacy is less than optimal. Most patients are no longer taking these drugs after 2-5 years (17,18), because of either toxicity or lack of efficacy.

The use of tetracycline to treat RA is not a new idea (19-21), and was initially advocated based largely on the idea that RA was caused and/or perpetuated by an infectious agent (19,20). Until recently, the evidence to support the efficacy of tetracyclines in the treatment of RA has been largely anecdotal (19-25). Renewed interest in the use of tetracyclines to treat RA has occurred because 2 randomized, controlled, double-blind studies in patients with well-established RA have demonstrated modest degrees of improvement after treatment with a tetracycline derivative, minocycline (26,27). Exciting new information suggests several pos-sible antiarthritic effects of tetracyclines other than their antibacterial effects (28-35).

Currently, rheumatologists are emphasizing the importance of early control of RA (36), and studies have shown that patients respond best when treated early with

disease-modifying therapy (37). Because of these find-ings and the data suggesting the possible antiarthritic action of tetracyclines, we undertook the present study to determine whether minocycline was an effective ther-apy if given within the first year of disease to patients with seropositive RA.

PATIENTS AND METHODS

This study was conducted by the Rheumatoid Arthritis Investigational Network. This network brings the rheumatolo-gists at the University of Nebraska together with rheumatolo-gists in Nebraska, Iowa, South Dakota, Kansas, Minnesota, and Illinois who are interested in clinical studies in RA. All physicians participating in this network were involved not only with patient enrollment and data collection, but also in the development of the study protocols.

Patient selection. Patients followed up in the rheuma-tology clinics at the University of Nebraska Medical Center, the Omaha Veterans Administration Medical Center, or the private offices of network physicians were asked to participate if they met the criteria for the study. The protocol was approved by the Institutional Review Board at the University of Nebraska Medical Center, and all patients gave written informed consent.

The eligibility criteria were as follows: age between 19 and 70 years, RA fulfilling the American College of Rheuma-tology (formerly, the American Rheumatism Association) cri-teria (38), elevated serum rheumatoid factor (RF) titer, dura-tion of disease >6 weeks and <1 year, active disease (i.e., meeting at least 3 of the following criteria: erythrocyte sedi-mentation rate [ESR] >=28 mm/hour, morning stiffness >=45 minutes, >=8 tender joints, and >=3 swollen joints), negative results on serum tests for Lyme disease, and no elevation of serum IgM parvovirus antibody levels. Patients who had pre-viously received DMARD or steroid therapy and women of childbearing age who were not practicing contraception were not eligible.

Experimental design. Forty-six patients were enrolled in this 6-month, double-blind, randomized, controlled study. The pharmacy handled the randomization; equal numbers of cards with each group assignment were mixed, drawn, and placed in sequentially numbered envelopes that were opened as the patients were enrolled. The patients were treated with minocycline (Lederle, Pearl River, NY) or matching placebo. The dosage of minocycline was 100 mg twice per day and was constant throughout the study. Patients in both groups contin-ued their pre-study NSATD treatment at stable doses.

Three months after enrollment, physicians who were unaware of the treatment groups evaluated the patients. If at that time, patients did not meet criteria for 50% improvement, we considered their treatment ineffective and they were dropped from the blinded portion of the study. We again evaluated the patients after therapy had been given for 6 months and recorded whether they had improved by 50% over baseline; if so, we considered their treatment effective. The blinded portion of the study ended after the 6-month evalua-tion. Regardless of the response to therapy, the minocycline or placebo was stopped in all patients at 6 months. All patients were then followed up in the open portion of the study for an additional 6 months (9 months for patients who were consid-ered treatment failures at the 3-month time point). Therefore, the total duration of the study was 1 year (3-6 months in the blinded portion and 6-9 months in the open portion). During the open portion of the study, the treating physician was free to prescribe whatever therapy he or she deemed most appropri-ate. If the patient had been receiving minocycline during the blinded portion of the study and had a disease flare during the "open portion (11 patients), minocycline was restarted.

The number of patients enrolled was determined by assuming a 10% response rate in the placebo group and a 40% response rate in the treated group. To detect this magnitude of difference at the $a = 0.05$ and $b = 0.2$ levels (power of 80%), 24 patients in each group were needed.

Evaluation criteria. The major end point was whether patients had improved by 50% at 6 months, based on their fulfilling at least 3 of the following requirements (modified Paulus composite criteria [39]): morning stiffness <30 minutes or improved by 50%, joint tenderness improved by 50%, joint swelling improved by 50%, and ESR <30 mm/hour for women or <20 mm/hour for men. Treatment was considered unsuc-cessful in patients who did not have this degree of improve-ment at the 3- or 6-month evaluation.

Additional evaluation measures included an estimate of the duration of morning stiffness and a modified Ritchie Articular Index (40), in which 38 joints were scored on a 0-3 scale for tenderness (tender joint score) and for swelling (swollen joint score). Patient global status and overall pain scale (scored by the patient) and physician global assessment were scored using a visual analog scale, with 0 representing normal and 10 representing severe problems (41).

Toxicity monitoring. All patients were questioned about toxicities, including dizziness, at each followup visit. The treating physician could withdraw the patient from the study at any time due to side effects of the drug.

Concurrent therapy. During the blinded portion of the trial, patients were allowed to take concurrent NSAIDs at stable doses, but were not allowed to take systemic or intraar-ticular steroids. During the open portion of the trial, physicians could prescribe any medication, including changing NSAIDs, starting or restarting minocycline, or initiating DMARDs and/or steroids.

Statistical analysis. The primary end point was suc-cessful completion of the 6 months of the blinded portion of the protocol. Differences between groups in the numbers of patients completing the protocol and in the numbers of treatment failures were analyzed using both the chi-square test and the log rank test (42). We developed a Kaplan-Meier curve for patients completing the protocol, with all patients who did not complete counted as treatment failures. The log rank test was used to determine differences between groups (42). Cox proportional hazards regression analysis was used to adjust for differences between the groups at entry.

Differences in mean values for other outcome vari-ables were evaluated using Student's 2-tailed t-test, assuming unequal variance (42). Analysis of covariance was used to adjust for differences in disease severity between treatment groups at baseline (42). Because of expected small cell size, P values for comparison of the treatment groups at 1 year were calculated using Fisher's exact test.

Table 1. Baseline characteristics of rheumatoid arthritis patients treated with minocycline or placebo*

Characteristic	Minocycline (n = 23)	Placebo (n = 23)
Mean (range) age, years	41 (21–56)	48 (28–70)
No. female/no. male	16/7	17/6
Disease duration, months	5 ± 3	4 ± 2
% RF positive	100	100
ESR, mm/hour	26 ± 18	37 ± 23
Morning stiffness, minutes	136 ± 65	128 ± 78
Tender joint score†	24 ± 11	23 ± 15
Swollen joint score†	18 ± 9	18 ± 9
Total joint score†	42 ± 18	41 ± 20
Patient global status score, 0–10 VAS	5.3 ± 1.8	4.8 ± 2.4
Physician global assessment score, 0–10 VAS	4.8 ± 1.6	4.6 ± 1.6

* Unless otherwise indicated, values are the mean ± SD. RF = rheumatoid factor; ESR = erythrocyte sedimentation rate; VAS visual analog scale.
† Thirty-eight joints scored on a 0–3 scale.

RESULTS

Each of the 46 patients was randomly assigned to 1 of the 2 treatment groups: minocycline (n = 23) or placebo (n = 23). There were no differences between the groups at study entry (Table 1). One patient dropped out of the study because of toxicity and 27 patients because of lack of efficacy. Eighteen patients success-fully completed the 6-month blinded portion of the study, having improved by 50% at 3 months and main-tained this improvement at 6 months.

Toxicity. One patient in the placebo group stopped treatment because of a gastrointestinal bleed. None of the minocycline-treated patients withdrew due to toxicity. None of the patients reported dizziness that precluded continuation of the protocol.

Results of treatment. Eighteen patients had im-proved by 50% at 3 months and maintained this im-provement at the end of the 6-month treatment period. This included 15 of 23 patients (65%) in the minocycline group and 3 of 23 patients (13%) in the placebo group *(P* < 0.001). Efficacy (50% improvement) was not demonstrated in 8 patients in the minocycline group and 19 in the placebo group. The remaining patient in the placebo group withdrew because of toxicity.

A Kaplan-Meier curve showing the proportion of patients in each group who successfully completed the 6-month treatment period is presented in Figure 1. All

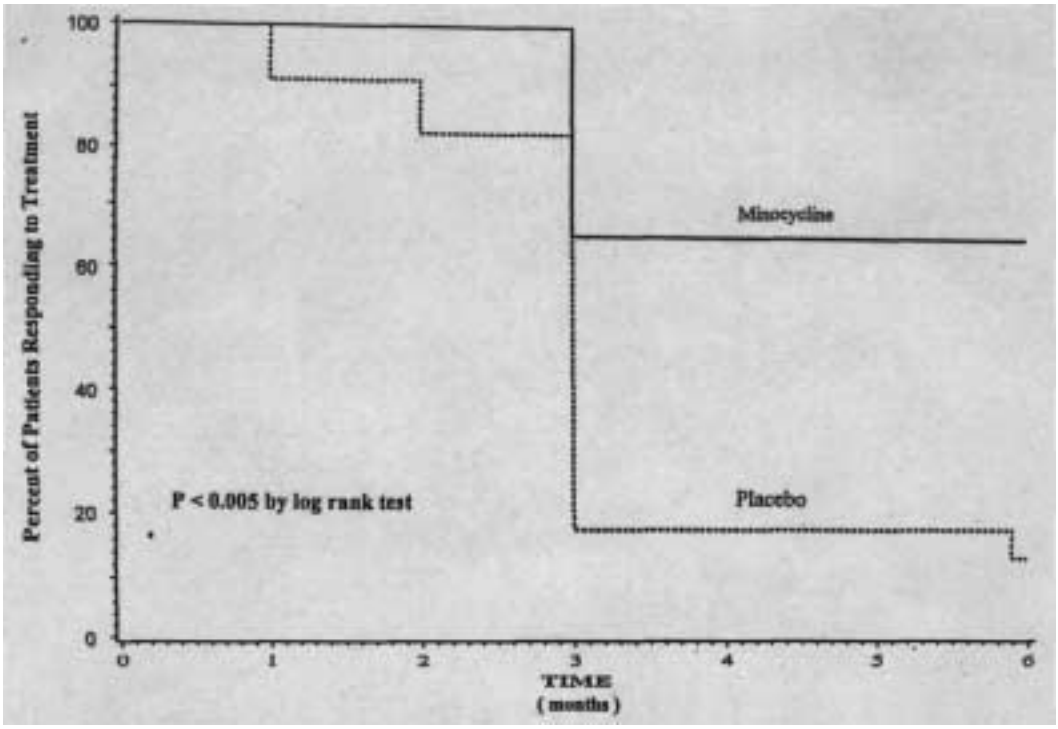

Figure 1. Kaplan-Meier plot of the proportion of patients responding to treatment with either minocycline or placebo.

Table 2. Changes in disease activity measures in rheumatoid arthritis patients treated with minocycline or placebo*

	Minocycline (n = 23)	Placebo (n = 23)	P
ESR, mm/hour			
Initial	26 ± 18	37 ± 23	0.09
Followup	15 ± 17	33 ± 29	
Change	11 ± 16	4 ± 14	0.12
Total joint score†			
Initial	42 ± 18	41 ± 20	0.88
Followup	25 ± 23	37 ± 20	
Change	16 ± 21	6 ± 19	0.09
Tender joint score†			
Initial	24 ± 11	23 ± 15	0.89
Followup	13 ± 15	20 ± 12	
Change	10 ± 11	5 ± 11	0.11
Swollen joint score†			
Initial	18 ± 9	18 ± 9	0.87
Followup	12 ± 13	17 ± 12	
Change	7 ± 12	3 ± 9	0.18
Morning stiffness, minutes			
Initial	136 ± 65	128 ± 78	0.75
Followup	65 ± 63	114 ± 85	
Change	70 ± 73	16 ± 91	0.03
Patient global status score, 0–10 VAS			
Initial	5.3 ± 1.8	4.8 ± 2.4	0.49
Followup	3.3 ± 2.6	5.5 ± 2.9	
Change	2.0 ± 2.9	0.5 ± 2.7	0.006
Physician global assessment score, 0–10 VAS			
Initial	4.8 ± 1.6	4.6 ± 1.6	0.69
Followup	3.1 ± 2.5	5 ± 2.3	
Change	1.6 ± 2.5	0.3 ± 2.6	0.01

* Values are the mean ± SD. Followup evaluations were done at 3 months or 6 months, depending on response. ESR = erythrocyte sedimentation rate; VAS = visual analog scale.
† Thirty-eight joints scored on a 0–3 scale.

patients who did not complete the study were counted as treatment failures, including the 1 patient with drug toxicity and the 27 who were efficacy failures. The difference between treatment groups was statistically significant (P = 0.005 by log rank test). To assure that this difference was not the result of a difference in severity of disease at baseline, an adjusted analysis of time to treatment failure was done using ESR, disease duration, patient global status, physician global assess-ment, and total joint count as variables. None of these variables had a statistically significant effect on the time to failure of treatment.

Other measures of efficacy. Table 2 shows the results of other clinical measures of arthritis activity at baseline and at 6 months. Patients in the minocycline group tended to have clinical improvement in all 7 efficacy measures; the degree of improvement in mom-ing stiffness, patient global status, and physician global assessment in the minocycline group reached statistical significance ($P < 0.05$) compared with the degree of improvement in the placebo group. The within-group changes between baseline and followup for all of the efficacy parameters shown in Table 2 were significant in the minocycline group ($P < 0.01$), while the placebo group reflected no statistically significant changes.

Observations during the open portion of the study. Table 3 compares the minocycline group and the placebo group at 1 year. The number of patients who had improved significantly (>50% improvement or re-mission) was greater in the minocycline group. Similarly, there were fewer minocycline-treated patients who re-quired DMARD therapy at 1 year.

DISCUSSION

With currently available DMARD therapy, complete remission of RA is disappointingly rare (43,44). This realization has fueled a surge of interest in alter-native forms of therapy for the treatment of RA, includ-ing a significant increase in the use of combination DMARD therapy (45) and of minocycline (26,27).

This double-blind, placebo-controlled study dem-onstrates the benefit of minocycline when used to treat patients with seropositive RA within the first year of disease onset. We believe that several key points about our study design are worth emphasizing: we enrolled only patients with early disease (these patients have been shown by many to have the best response to therapy [37]), we enrolled only patients who were RF positive and thus we were studying a relatively homogeneous patient population and a group of pa-tients who were destined to have a low spontaneous remission rate, and finally, we chose to define success as 50% improvement of symptoms instead of the 20% that is often used.

We believe our results are even more remarkable

Table 3. Therapy at 1 year: minocycline versus placebo

	Patients originally in minocycline group (n = 23)	Patients originally in placebo group (n = 20)	P
No. in remission	5	1	0.13
No. improved by 50%	20	9	0.004
No. receiving DMARDs*	7	17	<0.001
No. receiving minocycline	11	3	0.023
No. receiving no therapy	5	1	0.13

* DMARDs = disease-modifying antirheumatic drugs.

because our study design almost certainly decreased the chances of finding a positive effect. Since we were conducting a placebo-controlled trial, we required 50% improvement at 3 months as a criterion for continuation in the study. We did not want to continue placebo treatment for more than 3 months in patients with active RA. Data from our study and others suggest that maximum benefit of minocycline does not occur until after 1 year of therapy (28). Therefore, we almost certainly lost patients before they had a maximal re-sponse to minocycline.

The magnitude of improvement in our minocycline-treated patients was dramatic compared with the modest but statistically significant benefit in a study conducted in the Netherlands (26) and in the Minocycline in Rheumatoid Arthritis trials (27). Recon-ciliation of these seemingly disparate results requires acknowledgment that our study group consisted of an entirely different patient population. The most signifi-cant difference was the disease duration, which averaged 8.6 years and 13 years in those other trials and **<5** months in our trial. The observed difference in magni-tude of response may be explained by the fact that patients with early disease respond better to most ther-apies. Alternatively, there may be a window of opportu-nity early in RA when minocycline can produce dramatic benefit. Additionally, we observed fewer side effects in our trial compared with the Netherlands trial, especially with regard to dizziness. The reasons for this are unclear, but the young age of our patients is one possible explanation.

Minocycline has been shown to have antiinflam-matory, immunomodulatory, and chondroprotective ef-fects (28,29) in addition to its antibacterial activity. Tetracyclines, particularly minocycline and doxycycline, are potent inhibitors of metalloproteinases (30-32), including collagenase and gelatinase. Metalloprotein-ases are almost certainly active in RA joint destruction, and studies in animal models of arthritis (both RA and osteoarthritis [33-35]) have shown benefit with minocy-cline or doxycycline treatment. Modified derivatives of minocycline that retain their ability to inhibit metallo-proteinases but do not have antibacterial effects remain effective in some of these models. Finally, there has been much recent enthusiasm for, and some evidence to support the use of, agents with activity against tumor necrosis factor a in the treatment of RA (46). Interest-ingly, tetracyclines, especially minocycline and doxycy-cline, inhibit the production of tumor necrosis factor (47,48).

Early advocates for the use of tetracyclines in the treatment of RA based their choice on its antibacterial effect (19,20), believing that RA was initiated and perpetuated by an infectious agent. Two currently well-accepted DMARDs, gold and sulfasalazine, were ini-tially used for similar reasons (49,50). Recent experi-ences with Lyme disease, human immunodeficiency virus infection, and hepatitis C infection are vivid re-minders of how much we have to leam about infectious triggers of diseases with immunologic and rheumatic manifestations. In the case of Lyme disease, were it not for a group of concerned parents of children who had been recently diagnosed as having juvenile rheumatoid arthritis (51) and a relatively obvious vector, the tick, this disease would almost certainly have remained an enigma. Therefore, it is clearly possible that an infec-tious agent will be shown to play a role in the pathogen-esis of RA.

Even though there has been near unanimity of opinion of rheumatologists that RA should be treated early to prevent the occurrence of joint damage (36,45), few studies on true early treatment of RA are available. There are many reasons for this, including the difficulty of making a definitive early diagnosis of RA, the delay between onset of symptoms and presentation to a phy-sician and then referral to a subspecialist who might enroll patients in studies, and the reluctance of physi-cians and patients to be involved in studies, particularly early in the disease. The size of our clinical research network and the willingness of patients to take antibiot-ics helped us overcome these obstacles.

Our study does not address the critically impor-tant question of the mechanisms of action of minocy-cline. Based on the observed benefit in animal models of arthritis when tetracyclines are used, we postulate that part of the efficacy is due to inhibition of matrix metalloproteinases. Whether antibacterial effects are important is unknown, but we certainly cannot rule out this possibility. Interestingly, the majority of our patients who had favorable responses to minocycline had flares when this treatment was stopped. Whether this reaction is evidence in favor of one of the proposed mechanisms over another is unclear.

We believe that minocycline is an effective ther-apy for use within the first year of disease in patients with seropositive RA. Further studies are needed to define the optimal duration of treatment and the drug's mechanism or mechanisms of action, and to compare it with other disease-modifying drugs used early in the course of disease.

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REFERENCES

1. Hochberg MC: Adult and juvenile rheumatoid arthritis: current epidemiologic concepts. Epidemiol Rev 3:27-44, 1981
2. Scott DL, Symmons DPM, Coulton BL, Popert AJ: Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1:1108-1111, 1987
3. Pincus T, Brooks RH, Callahan LF: Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. Ann Intern Med 120:26-34, 1994
4. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, Spitz PW, Haga M, Kleinheksel SM, Cathey MA: The mortality of rheumatoid arthritis. Arthritis Rheum 37:481-494, 1994
5. Sigler JW, Bluhm GB, Duncan H, Sharp JT, Ensign DC, McCrum WR: Gold salts in the treatment of rheumatoid arthritis: a double-blind study. Ann Intern Med 80:21-26, 1974
6. Dixon AJ, Davies J, Dormandy TL, Hamilton EBD, Holt PSL, Mason RM, Thompson M, Weber JCP, Zutshi DW: Synthetic D(-) penicillamine in rheumatoid arthritis: double-blind con-trolled study of a high and low dosage regimen. Ann Rheum Dis 34:416-421, 1975
7. The Multicentre Trial Group: Controlled trial of D(-) penicilla-mine in severe rheumatoid arthritis. Lancet 1:275-280, 1973
8. Finals RS, Kaplan SB, Lawson JG, Hepburn B: Sulfasalazine in rheumatoid arthritis: a double-blind, placebo-controlled trial. Ar-thritis Rheum 29:1427-1434, 1986
9. Williams HJ, Ward JR, Dahl SL, Clegg DO, Willkens RF, Oglesby T, Weisman MH, Schlegel S, Michaels RM, Luggen ME, Polisson RP, Singer JZ, Kantor SM, Shiroky JB, Small RE, Gomez MI, Reading JC, Egger MJ: A controlled trial comparing sulfasalazine, gold sodium thiomalate, and placebo in rheumatoid arthritis. Arthritis Rheum 31:702-713, 1988
10. Hannonen P, Mottonen T, Hakola M, Oka M: Sulfasalazine in early rheumatoid arthritis: a 48-week double-blind, prospective, placebo-controlled study. Arthritis Rheum 36:1501-1509, 1993
11. Weinblatt ME, Coblyn JS, Fox DA, Fraser PA, Holdsworth DE, Glass DN, Trentham DE: Efficacy of low-dose methotrexate in rheumatoid arthritis. N Engi J Med 312:818-822, 1985
12. Ward JR, Williams HJ, Egger MJ, Reading JC, Boyce E, Altz-Smith M, Samuelson CO Jr, Willkens RF, Solsky MA, Haves SP, Blocka KL, Weinstein A, Meenan RF, Guttadauria M, Kaplan SB, Klippel J: Comparison of auranofin, gold sodium thiomalate, and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. Arthritis Rheum 26:1303-1315, 1983
13. Anderson PA, West SG, O'Dell JR, Via CS, Claypool RG, Kotzin BL: Weekly pulse methotrexate in rheumatoid arthritis: clinical and immunologic effects in a randomized, double-blind study. Ann Intern Med 103:489-496, 1985
14. Williams HJ, Willkens RF, Samuelson CO Jr, Alarcon GS, Gut-tadauria M, Yarboro C, Polisson RP, Weiner SR, Luggen ME, Billingsley LM, Dahl SL, Egger MJ, Reading JC, Ward JR: Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. Arthritis Rheum 28:721-730, 1985
15. Felson DT, Anderson JJ, Meenan RF: The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis: results of two metaanalyses. Arthritis Rheum 33:1449-1461, 1990
16. Felson DT, Anderson JJ, Meenan RF: Use of short-term efficacv/ toxicity tradeoffs to select second-line drugs in rheumatoid arthri-tis: a metaanalysis of published clinical trials. Arthritis Rheum 35:1117-1125, 1992
17. Wolfe F, Hawley DJ, Cathey MA: Termination of a slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospec-tive evaluation of 1017 consecutive starts. J Rheumatol 17:994-1002, 1990
18. Morand EF, McCIoud PI, Littlejohn GO: Life table analysis of 879 treatment episodes with slow acting antirheumatic drugs in com-munity rheumatology practice. J Rheumatol 19:704-708, 1992
19. Sanchez I: As tetraciclinas no tratamento da artrite reumatoid e doencas reumaticas inflamatorias [Tetracycline treatment in rheu-matoid arthritis and other rheumatic diseases]. Brasil Med 82:22-31, 1968
20. Brown TM, dark HW, Bailey JS, Gray CW: A mechanistic approach to treatment of rheumatoid type arthritis naturally occurring in a gorilla. Trans Am Clin Climatol Assoc 82:227-247, 1970
21. Skinner M, Cathcart ES, Mills JA, Finals RS: Tetracycline in the treatment of rheumatoid arthritis: a double blind controlled study. Arthritis Rheum 14:727-732, 1971
22. Brown TM, Bailey JS, Iden KI, Clark HW: Antimycoplasma approach to the mechanism and control of rheumatoid disease. In, Inflammatory Diseases and Copper. Edited by JRJ Sorenson. Clifton, NJ, Humana Press, Inc., 1982
23. Brown TM, Hochberg MC, Hicks JT, Clark HW: Antibiotic therapy of rheumatoid arthritis: a retrospective cohort study of 98 patients with 451 patient-years of follow-up. Int Congress Rheu-matol S8:5, 1985
24. Breedveld FC, Dijkmans BAC, Mattie H: Minocycline treatment for rheumatoid arthritis: an open dose finding study. J Rheumatol 17:43-46, 1990
25. Langevitz P, Bank I, Zemer D, Book M, Pras M: Treatment of resistant rheumatoid arthritis with minocycline: an open study. J Rheumatol 19:1502-1504, 1992
26. Kloppenburg M, Breedveld FC, Terwiel JP, Mallee C, Dijkmans BAC: Minocycline in active rheumatoid arthritis: a double-blind, placebo-controlled trial. Arthritis Rheum 37:629-636, 1994
27. Tilley BC, Alarcon GS, Heyse SP, Trentham DE, Neuner R, Kaplan DA, Clegg DO, Leisen JCC, Buckley L, Cooper SM, Duncan H, Pillemer SR, Tuttleman M, Fowler SE, for the MIRA Trial Group: Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial. Ann Intern Med 122:81-89, 1995
28. Alarcon GS: Tetracyclines in the treatment of rheumatoid arthri-tis: they work, but we do not know the reason(s). J Clin Rheumatol 1:190-193, 1995
29. Greenwald RA: Tetracyclines may be therapeutically beneficial in rheumatoid arthritis, but not for the reasons that you might think. J Clin Rheumatol 1:185-189, 1995
30. Greenwald RA: Treatment of destructive arthritic disorders with MMP inhibitors: potential role of tetracyclines. Ann N Y Acad Sci 732:181-198, 1994
31. Nip LH, Uitto V-J, Golub LM: Inhibition of epithelial cell matrix metalloproteinases by tetracyclines. J Periodontal Res 28:379-385, 1993
32. Golub LM, Ciancio S, Ramamurthy NS, Leung M, McNamara TF: Low dose doxycycline therapy: effect on gingival and crevicular fluid collagenase activity in humans. J Periodontal Res 25:321-330, 1990
33. Greenwald RA, Moak SA, Ramamurthy NS, Golub LM: Tetracy-clines suppress matrix metalloproteinase activity in adjuvant ar-thritis and in combination with flurbiprofen ameliorate bone damage. J Rheumatol 19:927-938, 1992

34. Ganu V, Doughty J, Spirito S, Goldberg R: Elevation of urinary pyridinoline in adjuvant arthritic rats and its inhibition by doxycy-cline. Ann N Y Acad Sci 732:416-418, 1994
35. Yu LP, Smith GN Jr, Brandt KD, Myers SL, O'Connor BL, Brandt DA: Reduction of the severity of canine osteoarthritis by prophy-lactic treatment with oral doxycycline. Arthritis Rheum 35:1150-1159,1992
36. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines: Guidelines for the management of rheuma-toid arthritis. Arthritis Rheum 39:713-722, 1996
37. Van der Hei.de A, Jacobs JWG, Bijisma JWJ, Heurkens AHM, van Booma-Frankfort C, van der Veen MJ, Haanen HCM, Hofman DM: The effectiveness of early treatment with "second-line" antirheumatic drugs: a randomized, controlled trial. Ann Intern Med 124:699-707, 1996
38. Amett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, Medsger TA Jr, Mitchell DM, Neustadt DH, Pinals RS, Schaller JG, Sharp JT, Wilder RL, Hunder GG: The American Rheuma-tism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31:315-324, 1988
39. Paulus HE, Egger MJ, Ward JR, Williams HJ, and the Coopera-tive Systematic Studies of Rheumatic Diseases Group: Analysis of improvement in individual rheumatoid arthritis patients treated with disease-modifying antirheumatic drugs, based on the findings in patients treated with placebo. Arthritis Rheum 33:477-484, 1990
40. Egger MJ, Huth DA, Ward JR, Reading JC, Williams HJ: Reduced joint count indices in the evaluation of rheumatoid arthritis. Arthritis Rheum 28:613-619, 1985
41. Felson DT, Anderson JJ, Boers M, Bombardier C, Chemoff M, Fried B, Furst D, Goldsmith C, Kieszak S, Lightfoot R, Paulus H, Tugwell P, Weinblatt M, Widmark R, Williams HJ, Wolfe F: The American College of Rheumatology preliminary core set of dis-ease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 36:729-740, 1993
42. Zar JH: Biostatistical Analysis. Second edition. Englewood Cliffs, NJ, Prentice-Hall, 1984

43. Pinals RS, Masi AT, Larsen RA, and the Subcommittee for Criteria of Remission in Rheumatoid Arthritis of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee: Preliminary criteria for clinical remission in rheuma-toid arthritis. Arthritis Rheum 24:1308-1315, 1981
44. Alarcon GS, Blackburn WD Jr, Calvo A, Castaneda 0: Evaluation of the American Rheumatism Association preliminary criteria for remission in rheumatoid arthritis: a prospective study. J Rheuma-tol 14:93-96, 1987
45. O'Dell J, Case L: The treatment of rheumatoid arthritis in 1995: results of a survey (abstract). Arthritis Rheum 38 (suppi 9):S366, 1995
46. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, Leeb B, Breedveld FC, Macfarlane JD, Biji H, Woody JN: Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 344:1105-1110, 1994
47. Gearing AJH, Beckett P, Christodoulou M, Churchill M, Clem-ents J, Davidson AH, Drummond AH, Galloway WA, Gilbert R, Gordan JL, Leber TM, Mangan M, Miller K, Nayee P, Owen K, Patel S, Thomas W, Wells G, Wood LM, Woolley K: Processing of tumour necrosis factor-a precursor by metalloproteinases. Nature 370:555-557, 1994
48. McGeehan GM, Becherer JD, Bast RC, Boyer CM, Champion B, Connolly KM, Conway JG, Furdon P, Karp S, Kidao S, McElroy AB, Nichols J, Pryzwansky KM, Schoenen F, Sekut L, Truesdale A, Verghese M, Wamer J, Ways JP: Regulation of tumour necrosis factor-os processing by a metalloproteinase inhibitor. Nature 370:558-561, 1994
49. Forestier J: Rheumatoid arthritis and its treatment by gold salts. J Lab Clin Med 20:827-840, 1935
50. Svartz N: Salazopyrin, a new sulfanilamide preparation. Acta Med Scand 110:577-598, 1942
51. Steere AC, Malawista SE, Snydman DR, Shope RE, Andiman WA, Ross MR, Steele FM: Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis Rheum 20:7-17, 1977