TREATMENT OF EARLY SEROPOSITIVE RHEUMATOID ARTHRITIS WITH MINOCYCLINE

Four-Year Followup of a Double-Blind, Placebo-Controlled Trial

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Objective. **Rheumatoid arthritis (RA) causes substantial morbidity and mortality, and current treatments are suboptimal. Recent studies have demonstrated the short-term efficacy of minocycline in the treatment of patients with early RA. This study was undertaken to compare patients treated with conventional therapy in the early phase of their RA and those treated with minocycline, after 4 years of followup.**

Methods. **Forty-six patients with seropositive RA of <1 year's duration had been enrolled in a double-blind study of minocycline (100 mg twice daily) versus placebo. After the blinded portion of the study (3-6 months, depending upon response), all patients were" treated with conventional therapy.   This report com-pares those patients randomized to receive placebo for 3 months and then conventional therapy for the duration of 4 years versus those originally randomized to receive minocycline.**

Results. **Twenty of the 23 original minocycline-treated patients and 18 of the 23 original placebo-treated patients were available for followup (mean 4 years). At followup, RA was in remission (American College of Rheumatology criteria) without disease-modifying antirheumatic drug (DMARD) or steroid therapy in 8 of the patients originally treated with minocycline compared with 1 patient in the placebo group (P = 0.02). Ten patients in the minocycline group versus 16 in the original placebo group currently re-quire DMARD therapy (P =0.02).**

Conclusion. **Among patients with seropositive RA, remissions are more frequent and the need for DMARD therapy is less in those treated early in the disease course with minocycline compared with those treated with conventional therapy delayed by an average of only 3 months. Minocycline appears to be an effective ther-apy for early RA; further investigation into its mecha-nism of action is needed.**

Rheumatoid arthritis (RA) is a common disease affecting 1% of adults; it often has a profound impact, causing substantial morbidity in most patients and pre-mature mortality in many. Conventional therapy for RA includes administration of nonsteroidal antiinflamma-tory drugs (NSAIDs) followed by disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, hydroxychloroquine, sulfasalazine, or gold in patients who have persistent active disease. The use of tetra-cycline to treat RA is not new; it was initially advocated based largely on the idea that RA was caused and/or perpetuated by an infectious agent. Until recently, the evidence to support the efficacy of tetracyclines in the treatment of RA has been largely anecdotal (1-4). Renewed interest in 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, mino-cycline (5,6). Exciting new information suggests several possible antiarthritic effects of tetracyclines other than their antibacterial effects (for review, see refs. 7 and 8).

Currently, rheumatologists are emphasizing the importance of early control of RA, and studies have shown that patients respond best when treated early with disease-modifying therapy (9). In a double-blind, con-trolled trial of minocycline compared with placebo in patients with early seropositive RA (10), we have previ-ously shown that the minocycline-treated patients were significantly better at 6 months and continued to show excellent responses after 1 year. In this communication, we extend those observations and report superior (and in some cases dramatic) results, after a median followup of 4 years, in the minocycline-treated patients compared with controls treated in a conventional manner.

PATIENTS AND METHODS

Patient selection. The eligibility criteria for the original protocol have been reported in detail (10); briefly they were as follows: age 19-70 years, RA fulfilling the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria (11), an elevated serum rheumatoid fac-tor titer, disease duration >6 weeks and <1 year, active disease based on meeting at least 3 of 4 criteria (erythrocyte sedimen-tation rate [ESR] >=28 mm/hour, morning stiffness >=45 min-utes, >=8 tender joints; >=3 swollen joints), negative results of serologic studies for Lyme disease, and no elevation of serum IgM parvovirus antibodies. Patients who had received previous DMARD or steroid therapy and women of childbearing age not practicing contraception were not eligible.

The original study compared active drug with placebo in a double-blind, controlled trial. This report is based on patients who were available for followup and compares those originally randomized to the minocycline group with those randomized to the placebo group. The patients randomized to the placebo group were treated with conventional therapy after completion of the placebo arm of the original study.

Experimental design. We enrolled 46 patients in the original 6-month, double-blind, controlled study. Twenty-three of the patients were randomized to receive minocycline (100 mg twice daily) and 23 to receive placebo. Three months after enrollment, patients were evaluated; if a patient did not meet 50% improvement criteria (see below), he or she was with-drawn from the blinded portion of the study. All patients remaining in the blinded portion were again evaluated for 50% improvement after a further 3 months of therapy. The blinded portion of the study ended after the 6-month evaluation, and the ninocycline or placebo was stopped. Once the blinded portion ended and the data were recorded, the physician was informed of the randomization and was then free to prescribe whatever therapy he or she deemed most appropriate, including DMARDs alone or in combination, prednisone, and minocycline. If the patient had been receiving minocycline

during the blinded portion of the study and had a good response (15 patients) but had a disese flare during the open portion (all 15 patients), minocycline was restarted in most case.

Evaluation criteria. The major end point of the origi-nal double-blind study was 50% improvement at 6 months, based on fulfilling 3 of the following criteria (modified Paulus composite criteria [12]): 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. In patients who did not have this degree of improvement at the 3- or 6-month evaluation, treatment was considered a failure. Additional evaluation measures included an estimate of the duration of morning stiffhess and a modified Ritchie Articular Index (13) (38 joints scored 0-3 for tenderness and for swelling). Patient global status and overall pain (scored by the patient) and physician global assessment were also recorded.

For the open followup phase of the study, major end points were as follows: the number of patients fulfilling ACR remission criteria (14) with and without DMARD therapy, and the number of patients requiring steroid or DMARD therapy. For the purpose of these analyses, minocycline was not con-sidered a DMARD.

Concurrent therapy. During the open portion of the study, physicians could prescribe any medication, includ-ing changing NSAIDs, starting or restarting minocycline, using DMARDs alone or in combination, and/or initiating steroids.

Statistical analysis. Differences between groups in the numbers of patients meeting the end points described above were analyzed by chi-square test. Because of expected small cell size, P values for Table 1 were calculated using Fisher's exact test.

RESULTS

In the original protocol we randomly assigned each of the 46 patients to 1 of the 2 treatment groups (23 patients in each). There were no significant differ-ences between the groups at entry (10). Results of the blinded portion of the study have been published previ-ously (10); 65% of the minocycline-treated group and 13% of the placebo-treated group met 50% improve-ment criteria at the end of the blinded portion of the study $(P = 0.005)$.

Toxicity. None of the minocydine-treated pa-tients withdrew due to toxicity during the blinded por-tion of the. .study. One patient in the placebo group withdrew because of a gastrointestinal bleed. Subse-quent to the blinded phase, 3 of the minocycline-treated patients discontinued minocycline because of hyperpigmenta-mentation and 1 patient reggrted_mild hyperpigmeota^ tion but elected to continue therapy. This occurred at 1, 2.5, 3, and 3.5 years of therapy. In the 3 patients who stopped minocycline, the hyperpigmentation decreased

Table 1. Long-term results in patients with early rheumatoid arthri-tis treated with minocycline versus placebo

	Original treatment group		
	Minocycline	Placebo	P
No. of patients available for followup	20	18	
Years of followup, mean (range)	3.8 (1.5–6.3)	4 (2.0–6.1)	
Remissions, no. (%)*	8 (40)	3 (17)†	0.16
Remissions without DMARDS, no. (%)‡	8 (40)	1 (6)	0.02
ACR 75% response, no. (%)§	13 (65)	4 (22)¶	0.01
DMARD therapy, no. (%)	10 (50)	16 (89)	0.02
Prednisone therapy, no. (%)	9 (45)	11 (65)	0.35
Current minocycline therapy, no. (%)	11 (55)	4 (24)	0.05

* Remissions according to American College of Rheumatology (ACR) criteria, but measured at only a single time point.
† One of these 3 patients was treated with minocycline during the open phase.
‡ Minocycline is not considered a disease-modifying antirheumatic drug (DMARD) in this analysis.
§ All patients with >75% response, including those in remission.
¶ Two of these 4 patients were treated with minocycline during the open phase.

Figure 1. Response to minocycline: time course. Total joint counts for the 15 responders to minocycline are plotted against the number of months from initiation of minocycline therapy. Values are the mean ± SEM.

slowly over time. None of the patients reported dizziness that precluded continuation of the treatment.

Results of long-term treatment with minocycline. Of the 23 patients who were originally treated with minocycline, 20 have had followup past 1 year (median 4.25 years, mean 3.8 years), as have 18 of the 23 placebo-treated patients. The current status of these patients is shown in Table 1. The difference between the number of patients in the minocycline group and the number in the placebo group whose RA was in remission without DMARDs (minocycline not considered a DMARD) or steroids was significant (1 of 18 [6%] in the placebo group versus 8 of 20 [40%] in the minocycline group; $P = 0.02$), as was the number of patients requiring DMARD therapy (16 of 18 [89%] of the placebo-treated patients compared with 10 of 20 [50%] of the minocycline-treated patients; $P = 0.02$). One of the 3 patients originally in the placebo group whose RA was in remission at followup was receiving minocycline at the time of the followup evaluation. Importantly, 50%. (10 of 20) of the patients originally treated with mino-cycline never riequired treatment with DMARDs or steroids, and 40% (8 of 20) fulfilled remission criteria without DMARDs or steroids

. **Time course of response to minocycline.** Figure 1 plots the total joint counts (sum of tender and swollen joints) versus months of minocycline treatment for the 15 patients who were responders to minocycline. Al-
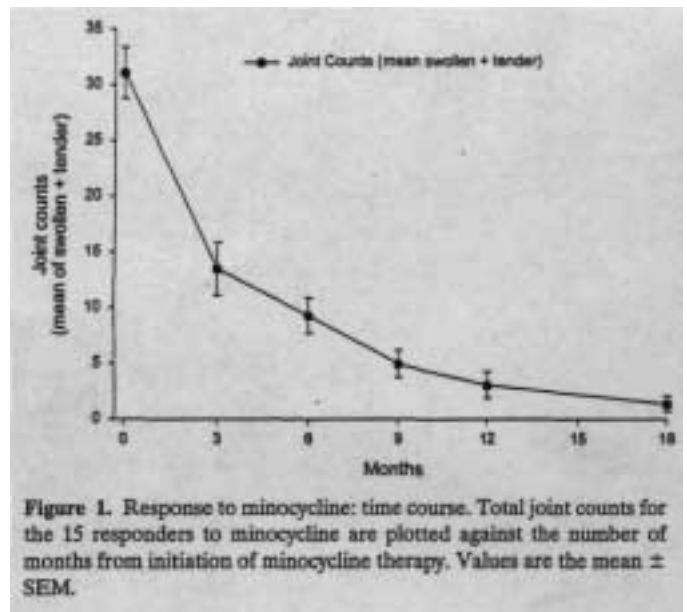
though significant response had been seen by 3 months (at which time the mean total joint count of 31.1 had decreased to 13.5), maximal response did not occur until at least 9 months.

DISCUSSION

With currently available DMARD therapy, com-plete remissions of RA are disappointingly rare (15). This realization has fueled a surge of interest in alter-nate forms of therapy for RA, including a significant increase in the use of combination DMARD therapy (16) and of minocycline (16). Our double-blind, placebo-controlled study has demonstrated the benefit of mino-cycline when used to treat patients with seropositive RA within the first year of disease (10), and the present report confirms that these patients continue to do well for up to 4 years (mean followup). We believe that several key points about our study design are worth emphasizing: all of the patients studied had early disease (these patients have been shown by many to be most responsive to therapy) (9); all were rheumatoid factor positive (and thus we studied a relatively homogeneous patient population and a group of patients who were destined to have a low rate of spontaneous remission and who could be predicted to have ongoing, aggressive disease); and, finally, we chose to define success as a 50% improvement in composite criteria instead of the 20% that is often used.

Our findings and those of other investigators suggest that the maximum benefit of minocycline does

not occur until after 1 year of therapy (7). Therefore, the results of the original study are even more remarkable. We did not want to continue placebo treatment for more than 3 months in patients with active RA; therefore, the double-blind portion of the trial was continued for only 6 months, and some patients may have been dropped from the minocycline treatment arm before they had an opportunity to have a maximal response.

The magnitude of improvement in our minocycline-treated patients was dramatic compared with the modest but statistically significant benefit in the Netherlands (5) and Minocycline in Rheumatoid Arthritis (6) trials. Reconciliation of these seemingly disparate results requires acknowledgment that our study used an entirely different patient population. The most significant 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 magnitude of response may be explained by the fact that patients with early disease respond better to most therapies. Alternatively, there may be a window of opportunity early in RA, in which minocycline can produce dramatic benefit. Additionally, we observed fewer side effects, especially dizziness, in our trial compared with the Netherlands trial. The reasons for this are unclear, but the young age of our patients is one possible explanation. Like all other treatments for RA, minocycline may need to be continued indefinitely to remain effective; therefore, the localized hyperpigmentation that appears to increase with duration of minocycline therapy is problematic. Recently, we have switched some of our patients to doxy-cycline, which is similar to minocycline in most of its known activities, but appears to be associated with less hyperpigmentation.

Tetracyclines, particularly minocycline and doxy-cycline, are inhibitors of metalloproteinases (17), including collagenase and gelatinase. Metalloproteinases are almost certainly active in RA joint destruction, and studies in animal models of arthritis (both RA and osteoarthritis) (18,19) have shown benefit with minocycline 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. In patients with RA, minocycline or doxycycline treatment has been shown to result in decreased synovial collagenase production (20), decreased levels of metalloproteinase breakdown products in the urine (21), and decreased collagenase activity in the saliva (22). In this latter open-label study, clinical features of RA also improved significantly (22).

Early advocates for the use of tetracyclines in the treatment of RA based their choice on the antibacterial effect (1,2), believing that RA was initiated and perpetuated by an infectious agent. Two currently well-accepted disease-modifying drugs, gold and sulfasala-zine, were initially used for similar reasons. Recent experiences with Lyme disease, human immunodeficiency virus, and hepatitis C are vivid reminders of how much we have to learn about infectious triggers of diseases with immunologic and rheumatic manifestations. Therefore, it is clearly possible that an infectious agent will be shown to play a role in the pathogenesis of RA. Recent data on evidence of organisms demonstrated by polymerase chain reaction in the joints of some RA patients (23,24), differences in the bowel flora of RA patients with and those without erosive disease (25), and the ability of one of the most commonly used and effective DMARDs, sulfasalazine, to alter bowel flora (26,27) are intriguing.

In addition to their antimicrobial and antimetal-loproteinase effects, the tetracyclines have been shown to have antiinflammatory effects, immunomodulating effects, and the ability to inhibit angiogenesis (7,8). With regard to the immunomodulating effects of tetracyclines, the recent reports of apparent drug-induced lupus in acne patients treated with minocycline are of interest (28). Finally, there has been much recent enthusiasm for, and some evidence to support the use of, agents with activity against tumor necrosis factor a (TNFa) in the treatment of RA. Metalloproteinases are involved in the processing of TNF and may be affected by matrix metalloproteinase inhibitors (29,30).

Our study does not address the critically important question of the mechanisms of action of minocycline. 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. We believe that metalloproteinase inhibition will be a key part of combination therapy for the future treatment of RA. Whether antibacterial effects are important is unclear, but we certainly cannot rule out this possibility. Interestingly, in the majority of our patients who had favorable responses to minocycline, the RA flared when this treatment was stopped. Whether this reaction favors one of the proposed mechanisms over another is unclear.

We believe that minocycline is effective for treating seropositive RA within the first year of disease. Further studies are needed to define thoJDptimaldura-tion of treatmefit, mJechaaism{s)_ofactiQu, and to compare minocycline with other DMARDs given alone and in combination early in the disease.

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