Pilot Clinical Trial of Intravenous Doxycycline Versus Placebo for Rheumatoid Arthritis

STANLEY PILLEMER, PERCIO GULKO, SOPHIE LIGIER, CHERYL YARBORO, MARK GOURLEY, RAPHAELA GOLDBACH-MANSKY, RICHARD SIEGEL, ROSEMARIE HIRSCH, FRANK PUCINO, BARBARA TILLEY, and RONALD L. WILDER

ABSTRACT. ***Objective.*** To screen for potential efficacy and assess the feasibility of intravenous (IV) doxycycline as a treatment for rheumatoid arthritis (RA).

Methods. The study was a (stratified, block) randomized, double blind, 12 week, pilot trial of IV doxycycline 300 mg/day versus identical appearing IV placebo given over 2 h for 14 days. The primary comparison was to a hypothesized placebo rate of 20% as described by Paulus. If a total of 14 consecutive subjects receiving doxycycline treatment did not respond, it would be considered futile to proceed to a Phase III trial. We planned a placebo group of 14 subjects to verify the placebo response rate and estimate sample size required for a definitive Phase III trial, if such a trial was warranted based on the pilot study. American College of Rheumatology (ACR) RA response criteria were used. After 23 subjects entered, the study was closed due to recruitment difficulties.

Results. At baseline, mean (SD) tender joint count was 37 (11.9), swollen joint count 30 (9.6), morning stiffness 317 (319) min, and erythrocyte sedimentation rate 72 mm/h (27.5). Randomization resulted in 10 subjects receiving doxycycline and 13 receiving placebo. Treatment was stopped in 8 subjects: in 6, treatment was ineffective (one taking doxycycline, 5 placebo), and in 2, rashes occurred (one taking doxycycline, one placebo). Only one subject met ACR response criteria in the doxycycline group and none in the placebo group. Having no responders in the placebo group was consistent with placebo response rate of 20% or less. Several patients required peripherally inserted central catheters for venous access.

Conclusion. The efficacy of IV doxycycline as a treatment for RA could not be ruled out. However, as the proportion of responders was small, it is unlikely that potential efficacy of IV doxycycline would outweigh potential disadvantages of IV administration. (J Rheumatol 2003;30:41–3)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DOXYCYCLINE CLINICAL TRIAL

Tetracyclines were advocated for treatment of rheumatoid arthritis (RA) with the hypothesis that bacteria are etiologic agents[1]. Although little evidence supported use of tetracyclines as antibiotics to treat RA, and an initial clinical trial of tetracycline was inconclusive[2], antiinflammatory effects of tetracyclines came to the fore[3]. Subsequently, trials showed efficacy of minocycline in RA[4-7].

Doxycycline treatment has been investigated for RA[8,9]. Doxycycline may interfere with matrix metalloproteinases[10] and expression of nitric oxide synthases[11] (iNOS), mediators of inflammation and tissue damage in RA.

We conducted a pilot trial to assess feasibility and safety of intravenous (IV) doxycycline as a treatment for RA, and to screen for potential efficacy.

MATERIALS AND METHODS

Study design. We conducted a randomized, double blind, 12 week, pilot trial of IV doxycycline 300 mg/day versus IV placebo (multivitamin solution) given once daily over 2 h for 14 days. We chose this dose and duration because it is the maximum approved for IV doxycycline. Patients were stratified by use of first or second-line therapies and randomized in blocks to balance numbers in both study arms.

Study participants had to fulfil the following inclusion criteria: (1) RA onset after age 16 yrs and age ≥ 18 yrs; (2) RA by American Rheumatism Association 1987 revised classification criteria[12]; (3) stable doses of second-line therapies such as methotrexate were allowed; (4) no requirement for failed second-line therapies; (5) no antibiotic therapy for ≥ 1 month; (6) patients who had discontinued second-line medications were required to be off them for ≥ 4 weeks before trial entry; (7) active disease as determined by all 3 of the following: ≥ 6 swollen joints, ≥ 9 joints tender on pressure, and

From the National Institute of Dental and Craniofacial Research, the National Institute of Arthritis, Musculoskeletal and Skin Diseases, the Clinical Center, and the National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland; the North Shore-Long Island Jewish Research Institute, Manhasset, New York; Washington Hospital Center, Washington, DC; and the Division of Biometry and Epidemiology, Institution, Medical University of South Carolina, Charleston, South Carolina, USA.

S. Pillemer, MD, National Institutes of Dental and Craniofacial Research; P.S. Gulko, MD, North Shore-Long Island Jewish Research Institute; S. Ligier, MD, National Institute of Mental Health; C. Yarboro, RN; R. Goldbach-Mansky, MD; R. Siegel, MD, National Institutes of Arthritis, Musculoskeletal and Skin Diseases; M. Gourley, MD, Washington Hospital Center; F. Pucino, PharmD, Clinical Center; B. Tilley, PhD, Medical University of South Carolina; R.L. Wilder, MD, PhD, MedImmune, Gaithersburg, MD.

Address reprint requests to Dr. S.R. Pillemer, Gene Therapy and Therapeutics Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, 10 Center Drive, Room 1N113, MSC 1190, Bethesda, MD 20892, USA.

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Westergren erythrocyte sedimentation rate (ESR) ≥ 30 mm/h or C-reactive protein > 0.8 mg/dl.

The exclusion criteria were (1) active infections requiring antimicrobial therapy; (2) pregnancy or inadequate contraception; (3) seronegative spondyloarthropathy, systemic lupus erythematosus, or psoriasis; (4) history or presence of pseudomembranous colitis or chronic inflammatory bowel disease; (5) tetracycline hypersensitivity; (6) chronic dermatologic disease except benign disorders, such as acne; (7) chronic antacid or iron use; (8) anticoagulants or anticonvulsants; (9) poor venous access; and (10) history of either Lyme disease or positive *Borrelia burgdorferi* serology.

Study protocol. Clinical assessments of disease activity were performed at study entry and at 2, 6, and 12 weeks. Each patient had the same examiner throughout the study. Evaluations were standardized through training sessions. Data were collected on joint tenderness, joint swelling, physician's global assessment, patient's global assessment, modified Health Assessment Questionnaire (M-HAQ), ESR, patient's pain assessment, Steinbrocker functional class, and duration of morning stiffness as described[5].

We used an approach described by Paulus[13], and based on Gehan's multistage screening strategy for identifying new cancer therapies in open label studies[14], with probability of response set at 20%. Paulus found that the placebo response rate in RA trials was about 20%[15]. Assuming a 20% (placebo) probability of success, if no successes are observed in 14 consecutive subjects, no further investigation would be warranted[13]. For one or more responses, 16 more patients would be treated, and for 3 more responses, the treatment would be tested further in a Phase III trial. A placebo group of 14 subjects was planned to verify placebo response rate and estimate the sample size required for a Phase III trial.

American College of Rheumatology (ACR) RA response criteria were used as the primary outcome measure[16]. Analysis of data for ACR RA response criteria using 50% improvement (ACR50) was performed. Data were also analyzed by Paulus criteria[15]. Under intent-to-treat analysis, patient dropouts were considered treatment failures.

Statistical analysis. Baseline comparisons of doxycycline and placebo groups were performed using t tests or Fisher's exact tests. Fisher's exact tests were also used to compare efficacy for dropouts.

RESULTS

Baseline demographic and clinical data in Table 1 showed no significant differences between groups (all p values > 0.1). After 23 subjects had been entered, the study was closed due to recruitment difficulties including decreasing referrals, competing intra-institutional studies of newer agents, discomfort and disruption of work schedule associated with 14 days of IV treatments, and the perception that antibiotic therapy was unlikely to be as effective as biologics.

One doxycycline subject met ACR response criteria at the final visit, and none met the criteria in the placebo group (Table 2), consistent with the assumed placebo response rate of 20% or less. No patients met the ACR50 criteria. There were no significant treatment group differences at the final visit by the ACR20 (p = 0.43, Fisher's exact test) or the Paulus criteria (p = 0.17, Fisher's exact test).

Treatment was stopped in 8 subjects: in 6, treatment was ineffective (one taking doxycycline, 5 placebo); no significant difference was detected between the treatment groups (p = 0.18, Fisher's exact test). In 2 subjects, pruritic maculoerythematous rashes occurred (one taking doxycycline, one placebo), but resolved without problems. No other significant adverse events occurred. Two patients in each group required peripherally inserted central catheter (PICC) lines to maintain venous access for the treatment.

Table 1. Demographic and clinical characteristics of study participants at baseline.

Variable	Doxycycline Group, n = 10	Placebo Group, n = 13
Mean age (yrs; SD)	53 (14.2)	51 (14.2)
Women (%)	8 (80)	10 (76.9)
Ethnicity (%)		
White	5 (50.0)	9 (69.2)
African-American	4 (40.0)	2 (15.4)
Hispanic	1 (10.0)	0 (0.0)
Asian	0 (0.0)	2 (15.4)
Disease duration, yrs (SD)	13 (8.0)	8 (7.5)
Joint counts: swelling (SD)	29.1 (10.9)	30.3 (8.9)
Joint scores: swelling (SD)	42.2 (17.5)	45.9 (15.5)
Joint counts: tenderness (SD)	35.8 (13.8)	37.4 (10.7)
Joint scores: tenderness (SD)	65.4 (35.8)	71.0 (30.33)
Subcutaneous nodules (%)	3 (30)	3 (39)
MHAQ disability score (SD)	1.5 (0.35)	1.6 (0.53)
Functional class		
Class II (%)	7 (70)	7 (54)
Class III (%)	3 (30)	6 (46)
IgM rheumatoid factor positive (%)	10 (100)	12 (92)
Erosions on hand or wrist radiographs (%)	10 (100)	9 (69)

MHAQ: Modified Health Assessment Questionnaire.

Table 2. Number of subjects improved using ACR and Paulus criteria.

Outcome	Doxycycline Group, n = 10	Placebo Group, n = 13	
ACR criteria			
2 weeks	2	1	
6 weeks	2	1	
12 weeks	1	0	(p = 0.43)
Paulus criteria			
2 weeks	4	3	
6 weeks	4	4	
12 weeks	5	2	(p = 0.17)

Imputing worst result for patients discontinuing study medication. p values are for Fisher's exact test.

Mean percentage changes in outcome variables over the trial are shown in Table 3. There were no significant differences between groups in the mean percentage change for any of the variables (all p values > 0.1).

Based on study data, a sample size of at least 236 subjects for a Phase III placebo controlled study of IV doxycycline would be required, ignoring dropouts, and assuming a 2 sided test with 90% power and $\alpha = 0.05$.

DISCUSSION

The efficacy of doxycycline cannot be rejected with 95% confidence at this stage, because one patient taking doxycycline responded, and we should have enrolled an additional 16 patients or a total of 30 subjects (or until we had 3 responders,

Table 3. Mean percentage change in outcome measures over the trial.

Outcome Measure	Doxycycline, n = 10	Placebo, n = 13
Joint counts: swelling	–1.5 (36.5)	–4.6 (22.9)
Joint scores: swelling	–1.4 (50.1)	–6.5 (33.5)
Joint counts: tenderness	–28.9 (44.3)	–9.7 (32.0)
Joint scores: tenderness	–29.3 (55.4)	–18.8 (32.1)
Patient global assessment	–14 (29.9)	–3.1 (21.4)
Physician global assessment	–4.0 (20.6)	–6.2 (19.0)
MHAQ disability score	–22.2 (32.7)	8.3 (74.3)
Patient assessment of pain	–22.6 (45.7)	8.3 (42.9)
Erythrocyte sedimentation rate*	–7.8 (34.2)	4.8 (29.4)

Data are expressed as percentage change (SD) calculated as (baseline minus followup)/baseline. All p values were > 0.1. * No significant differences were noted for mean percentage chnages in C-reactive protein.

whichever came first). More patients in the placebo group than the doxycycline group dropped out because of lack of efficacy. Although not significant, more patients in the doxycycline than the placebo group showed improvement by Paulus criteria at the final visit. The treatment phase was short, and may not have allowed sufficient time for response. Thus, a beneficial effect for IV doxycycline over placebo cannot be ruled out.

Since new highly effective agents with acceptable safety, such as etanercept, infliximab, or leflunomide, are currently available, the potential small benefit of doxycycline is less appealing[17-19]. A Phase III study would require at least as many subjects as the multicenter Minocycline in RA (MIRA) study[5]. No significant differences were detected between the doxycycline and placebo groups for core outcome measures. Other studies suggest that doxycycline is unlikely to be a useful treatment for RA[8,9,20]. Disadvantages of IV administration, reflected by requirement of PICC lines in 4 patients and recruitment difficulties, appear to outweigh the potential efficacy of IV doxycycline.

The Phase II pilot study design proposed by Paulus appears useful both in assessing futility and the trial processes before launching a large Phase III trial. However, newer Phase II study designs would allow more flexibility in the hypothesized placebo response rate[21].

We conclude further trials of IV doxycycline are not currently warranted. While the efficacy question has not been fully answered, difficulties in patient enrollment suggest that IV administration of doxycycline is not a practical approach. If the agent is efficacious, the benefits are likely to be modest at best and may not be comparable with available new agents.

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