Single-Blind Randomized Trial of Combination Antibiotic Therapy in Rheumatoid Arthritis

LUKE L. GOMPELS, ANGELA SMITH, PETER J. CHARLES, WENDY ROGERS, JOANNE SOON-SHIONG, ADAM MITCHELL, CAROLINE DORÉ, PETER W. TAYLOR, and CHARLES G. MACKWORTH-YOUNG

ABSTRACT. ***Objective.*** To determine the potential clinical efficacy of combination antibiotic therapy in treating rheumatoid arthritis (RA).

Methods. Twenty-one patients with active RA despite second-line treatment were randomized to receive either combination antibiotic therapy (treatment group, n = 11) or no additional therapy (control group, n = 10). Antibiotic therapy was given for 12 months and comprised oral tetracycline 250 mg twice daily, 3 times per week, and intravenous clindamycin infused on 5 consecutive days (300, 300, 600, 600, and 900 mg) followed by weekly infusions of 900 mg for 3 weeks and then fortnightly infusions for the remainder of the 12 months. The primary outcome measure was the American College of Rheumatology 20% (ACR20) response at the end of the initial treatment period of 12 months.

Results. Five patients in the treatment group (45%) achieved an ACR20 response at 1 year compared to none in the control group (p = 0.04). Eight patients in the treatment group and 1 in the control group had a greater than 20% improvement in tender joint count (p = 0.008). There were also significant differences between the groups in physician and patient global assessments. Nine patients in the treatment group completed the 6 months' followup; of these, 3 sustained the ACR20 response.

Conclusion. Combined antibiotic therapy with intravenous clindamycin and oral tetracycline may be useful in the management of active RA. A double-blind, placebo-controlled trial of therapy is justified. (J Rheumatol 2006;33:224–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ANTIBIOTIC THERAPY

There are many pharmacological treatments for patients with rheumatoid arthritis (RA). Conventional second-line agents and the newer biological agents may alter disease activity but are associated with significant drawbacks and limitations to their use[1-4].

There has been sustained interest in the use of antibiotics for the treatment of RA. Tetracycline antibiotics were originally used by Brown, *et al* in uncontrolled studies of patients with RA[5]. The rationale for their use was the hypothesis that RA might be caused by infection with *Mycoplasma* or similar organisms[6]. Although this theory has never been substantiated, uncontrolled reports of the success of tetracycline in treating RA have been encouraging. An early placebo-controlled trial showed no benefit of tetracycline[7]. However, 3 subsequent double-blind trials of minocycline in active RA demonstrated its efficacy compared with placebo[8-10]; one study has shown it to be more effective than hydroxychloroquine[11]. Minocycline is an antibiotic in the tetracycline class closely related to tetracycline itself. One drawback to the use of minocycline in the short to medium term is the frequency of hyperpigmentation[12]. Tetracycline causes this side effect only rarely, but has a spectrum of activity similar to minocycline.

The mechanism of action of antibiotics in RA is unclear. An antirheumatic effect could be due to immunomodulatory and antiinflammatory properties. Minocycline has been shown to (1) interfere with the production of prostaglandins and leukotrienes[13-15]; (2) scavenge oxygen free radicals[16]; and (3) interfere with the expression of nitric oxide synthetase[17]. Tetracyclines are also potent inhibitors of matrix metalloproteinase (MMP) activity[18] and have been shown in particular to decrease levels of interstitial collagenase (MMP-1), gelatinase (MMP-2), and macrophage elastase (MMP-12)[19].

Anecdotal evidence has suggested that clindamycin also gives benefit to patients with RA. Recently a combination of oral tetracycline and intravenous clindamycin has been used. Clindamycin was chosen because, in addition to a broad range of antibacterial activity, it may have antiinflammatory actions[20]. A retrospective review of 20 consecutive patients showed a marked improvement in pain, joint swelling, and function in 14 individuals (Hornett G, written

From the Kennedy Institute of Rheumatology; Charing Cross Hospital; and Other Disease Group Statistics, MRC Clinical Trials Unit, London, England.

Supported by a grant from the Peacock Charitable Trust. Dr. Doré is funded by the Arthritis Research Campaign.

L.L. Gompels, MRCP, Charing Cross Hospital; A. Smith, BSc, Kennedy Institute of Rheumatology; P.J. Charles, CSci FIBMS; W. Rogers, BSc; J. Soon-Shiong, MSc; A. Mitchell, FRCR, Charing Cross Hospital; C. Doré, BSc, Other Disease Group Statistics; P.W. Taylor, PhD, Charing Cross Hospital; C.G. Mackworth-Young, MD, Kennedy Institute of Rheumatology and Charing Cross Hospital.

Address reprint requests to Dr. C.G. Mackworth-Young, Charing Cross Hospital, Fulham Palace Road, London, W6 8RF, England.
E-mail: c.mackworth-young@imperial.ac.uk

Accepted for publication October 19, 2005.

communication). This improvement was generally sustained for the duration of therapy, which lasted between 6 months and 2 years.

We conducted a single-blind randomized open trial comparing the effect of intravenous clindamycin plus oral tetracycline in addition to conventional treatment with the effect of conventional treatment alone. Our objective was to determine if a double-blind, placebo-controlled trial would be justified.

MATERIALS AND METHODS

Patients. Twenty-one patients with classical RA[21] were recruited after informed consent had been obtained. All patients were under the care of the Rheumatology Department, Charing Cross Hospital. The inclusion and exclusion criteria are summarized in Table 1. Patients had continuous active disease despite stable second-line treatment (methotrexate and/or sulfasalazine and/or low dose prednisolone) for at least 3 months.

Study design. Patients were randomized to receive either combination antibiotic therapy (treatment group, n = 11) or no additional therapy (control group, n = 10). The antibiotic therapy was chosen on the basis of uncontrolled retrospective data on 14 patients (Hornett G, written communication), and consisted of the same regimen. It comprised oral tetracycline 250 mg twice daily 3 times per week as well as intravenous clindamycin: this consisted of 5 infusions on consecutive days (300, 300, 600, 600, and 900 mg) followed by weekly infusions of 900 mg for 3 weeks and then fortnightly infusions of 900 mg for the remainder of the 12 months (Table 2). In both groups the existing second-line treatment was continued unchanged. After the initial year, antibiotic therapy was stopped and both groups were followed for another 6 months. Patients were allowed to continue taking nonsteroidal antiinflammatory drugs and/or simple analgesics (e.g., paracetamol, coproxamol, or codeine).

Ethical review. This trial was approved by the Riverside Research Ethics Committee, London. A single-blind design was chosen for this study, since it was felt unethical to administer blinded intravenous placebo for a prolonged period in patients with active RA in a pilot study of this kind.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria
Age 18–80 yrs
Classical rheumatoid arthritis
Erosions on joint radiographs
Rheumatoid factor positive (titer ≥ 1:320)
Disease duration > 6 mo
Active disease: 6 or more inflamed joints
Active synovitis in the hands
Methotrexate dose ≥ 7.5 mg/wk
Sulfasalazine dose (if taken) up to 3,000 mg/day and unchanged for 3 mo
Prednisolone dose (if taken) ≤ 7.5 mg/day and unchanged for 3 mo
Exclusion Criteria
Severe disease (Steinbrocker grade IV)
Chronic/recurrent infection (e.g., chronic bronchitis, recurrent sinusitis)
Other infections
Immunodeficiency
Malignancy
Inflammatory bowel disease
Other diarrheal states
Other major illnesses
History of adverse reactions to tetracycline, clindamycin, or similar antibiotics
Other immunosuppressive medication
Pregnancy or lactation

Table 2. Summary of trial therapy for treatment group.

Day/Period	Clindamycin, mg	Tetracycline, mg/bid
Day 1	300	250
Day 2	300	250
Day 3	600	250
Day 4	600	250
Day 5	900	250
Weeks 2–4	900 weekly	250 × 3/wk
Months 2–12	900 fortnightly	250 × 3/wk
Months 13–18	None	None

Clinical evaluation. Clinical response was defined according to the American College of Rheumatology (ACR) definition of a 20% improvement (ACR20)[22] at the end of the 12-month period. This indicates a decrease in at least 20% of the number of swollen and tender joints, associated with a 20% improvement in 3 of the following: patient's global assessment of disease status, patient's assessment of pain, a Health Assessment Questionnaire (HAQ) estimating disability, and the assessor's global assessment of disease activity, all of which were measured with the use of visual analog scales (VAS), and the erythrocyte sedimentation rate (ESR)[22]. Patients who did not complete the 12-month period were judged not to have achieved a 20% response. The assessor was blinded to the randomized treatment.

Biochemical and radiographic evaluation. Serum MMP-1 and MMP-3 levels (R&D Systems, Minneapolis, MN, USA) and collagen breakdown products (procollagen II, aggrecan, and collagen types I and II cleavage products) (Ibex Technologies, Montreal, PQ, Canada) were measured in a blinded fashion retrospectively pretreatment and at Months 12 and 18 by ELISA.

The effect of treatment on articular damage was assessed on the basis of evaluation of radiographs of the hands and feet for both erosions and joint space narrowing using the modified Sharp scoring system[23] at the outset and at Months 12 and 18. One reader scored radiographs with no knowledge of their order, the patients' treatment assignment, or their clinical response.

Statistical analysis. The primary outcome measure was the proportion of patients in each group who achieved an ACR20 response, at the end of treatment (Week 51). Fisher's exact test was used to compare the proportion of patients with an ACR20 response in the 2 treatment groups. Secondary outcome measures included number of patients completing the first 12 months of the study, individual components of the ACR20 score, and biochemical tests.

RESULTS

Patient characteristics. Patients were predominantly Caucasian women with significant disease activity and moderate joint damage documented at baseline (Table 3).

Clinical outcomes. Nine patients in the treatment group (82%) and 3 patients in the control group (30%) completed the first 12 months of the study (p = 0.03). Two patients in the treatment group and 6 in the control group withdrew due to lack of efficacy manifested by continued or worsening disease activity. Five patients in the treatment group (45%) achieved an ACR20 response at 1 year, while none of the control group did (p = 0.04). Eight patients in the treatment group and 1 in the control group had a greater than 20% improvement in tender joint count (p = 0.008). Six patients

Table 3. Baseline characteristics for treatment and control groups. Results are expressed as mean (standard deviation) unless otherwise defined. The Health Assessment Questionnaire (HAQ) scores ranged from 0 (no difficulty) to 3 (unable to perform the activity). The physician and patient global assessment and pain scores were assessed using a visual analog scale (VAS; ranging from 0 to 100 mm) with higher scores indicating poorer status or more severe pain. Twenty-eight joints were assessed for swelling and tenderness.

Characteristic	Treatment Group (n = 11)	Control Group (n = 10)
Female, %	91	90
Positive RF, %	73	80
Age, yrs	58 (15)	60 (12)
Disease duration, yrs	9 (8)	7 (3)
HAQ scores	2.0 (0.7)	2.3 (0.6)
Physician global assessment	50 (23)	47 (23)
Patient pain score	55 (17)	50 (16)
Patient global assessment	47 (18)	56 (27)
Serum CRP, mg/l	8 (6)	15 (15)
ESR, mm/h	29 (19)	35 (18)
Tender joints, n	13 (8)	16 (9)
Swollen joints, n	13 (6)	11 (7)

RF: rheumatoid factor, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

in the treatment group and 1 in the control group had a greater than 20% improvement in the swollen joint count ($p = 0.06$). Nine patients in the treatment group completed 6 months' followup: of these, 3 sustained the ACR20 response (Table 4). There were also significant differences between the groups in physician and patient global assessments. There were no withdrawals in the treatment group due to side effects.

Biochemical and radiographic outcomes. Levels of MMP-1 and MMP-3, procollagen II, aggrecan, and collagen cleavage products were measured in serum samples at baseline, 12 months, and 18 months. Baseline levels were similarly abnormal in the treatment and control groups. There was no significant change in mean levels of any of the measures at 12 and 18 months compared with baseline for the treatment group as a whole, nor for the 5 patients who showed an ACR20 response at 12 months (results not shown). There were no significant changes over the course of the study among the controls.

Among the treatment group, there was no significant change in the mean radiological Sharp score at 12 and 18 months compared with baseline (Table 5). This also applied to the subgroup that showed an ACR20 response at 12 months. There were insufficient radiographs from the control group to allow comparison with the treatment group.

DISCUSSION

This randomized single-blind study of combination antibiotic therapy in active RA showed a significant difference between the treatment and control groups in terms of ACR20 response at 1 year, and at completion of the study. There were also significant differences in tender and swollen joint counts and in physician and patient global assessments of disease activity.

Table 4. Comparison of patients achieving a 20% or greater improvement in clinical variables at 2 timepoints.

(a) Week 0 and 51 Variable	Treatment (n = 11) n (%)	Control (n = 10) n (%)	p
ACR response*	5 (45)	0 (0)	0.04
Completed	9 (82)	3 (30)	0.03
HAQ	4 (36)	0 (0)	0.09
Physician global assessment	7 (64)	1 (10)	0.02
Patient pain score	5 (45)	2 (20)	0.4
Patient global assessment	5 (45)	0 (0)	0.04
CRP	0 (0)	1 (10)	0.5
ESR	5 (45)	1 (10)	0.15
Tender joint count	8 (73)	1 (10)	0.008
Swollen joint count	6 (55)	1 (10)	0.06

(b) Weeks 0 and 71 Variable	Treatment (n = 11) n (%)	Control (n = 10) n (%)	p
ACR response*	3 (27)	0 (0)	0.2
Completed	9 (82)	2 (20)	0.009
HAQ	3 (27)	1 (10)	0.6
Physician global assessment	7 (64)	1 (10)	0.02
Patient pain score	5 (45)	0 (0)	0.04
Patient global assessment	5 (45)	1 (10)	0.15
CRP	1 (9)	1 (10)	1.0
ESR	5 (45)	0 (0)	0.04
Tender joint count	9 (82)	1 (10)	0.002
Swollen joint count	6 (55)	0 (0)	0.01

* As defined in Materials and Methods.

Comparisons of changes during treatment (Table 4) show that the most appreciable improvements were achieved in tender and swollen joint counts as well as physician and patient pain scores. There was a trend towards greater frequency of ESR20 (20% reduction in ESR) in the treatment group, but this was not significant. Further analysis up to Weeks 71 (6 months after the discontinuation of treatment) showed that while the ACR20 response was lost in 2 out of 5 patients, there was still a significant difference in the tender joint count. Patient well-being and lack of toxicity of these medications were evidenced by a very low withdrawal rate in the treatment arm compared with placebo.

The fact that 2 patients in the treatment group lost their ACR20 response by 18 months (i.e., 6 months after withdrawal of antibiotic therapy) further supports the contention that the antibiotic treatment was contributing to control of disease activity.

Several mechanisms have been proposed to explain the effect of tetracycline and other antibiotics on RA. These

Table 5. Radiological Sharp scores at Weeks 0, 51, and 71 for treatment group. There were insufficient radiographs at Weeks 51 and 71 in the control group to allow comparison. Δ Weeks 0–51:change in score between Weeks 0 and 51.

	Week 0	Week 51	Week 71	Δ Weeks 0–51	Δ Weeks 51–71
Range	2–245	1–243	1–246	–6 – +27	–8 – +9
Mean	95.3	98.5	100.9	+3.3	+2.3
Median	61	63	66	–1	+3

include a modulation of metalloproteinase activity, alteration of bowel flora, and possible effects on lymphocyte function[24,25].

While there were no significant changes in markers of bone, cartilage turnover, or MMP levels between treatment and control groups, this does not exclude the possibility that the effect of antibiotics in the treatment group could have been due to other local tissue changes not detectable by the serum assays used in our study. For instance, alteration in bowel flora might result in clinical improvements without altering metalloproteinase activity. The absence of change in serum MMP-1 and MMP-3 levels is in keeping with the lack of significant change in C-reactive protein levels. Due to high withdrawal in the control group, inadequate data were available to determine whether there was a difference in radiographic progression of erosive joint disease between the groups.

Our study was limited by its single-blind design. Intravenous therapy of the kind used in this trial could be expected to have a substantial placebo effect. Some measures that were significantly different between the groups (e.g., patient's perception of pain and tender joint count) were subjective. However, others such as tender joint count scores were objective. Another limitation was the length of study, which was probably too short to detect significant changes in radiological Sharp scores.

Overall, our results suggested that combined antibiotic therapy with intravenous clindamycin and oral tetracycline may be useful in the management of active RA. Further study of this therapy, including a double-blind, placebo-controlled trial, is justified.

REFERENCES

1. Brooks PM. Treatment of rheumatoid arthritis: from symptomatic relief to potential cure. Br J Rheumatol 1998;37:1265-71.
2. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. N Engl J Med 2004;350:2591-602.
3. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. N Engl J Med 2004;350:2167-79.
4. Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.
5. Brown TM, Bush SW, Felts WR. Management of the chronically ill patient. In: Wohe MG, editor. Long term illness. Philadelphia: WB Saunders; 1959.
6. Ford DK. The microbiological causes of rheumatoid arthritis. J Rheumatol 1991;18:1441-2.
7. Skinner M, Cathcart ES, Mills JA, Pinals RS. Tetracycline in the treatment of rheumatoid arthritis. Arthritis Rheum 1971;14:727-32.
8. Kloppenburg M, Breedveld FC, Terwiel JP, Mallee C, Dijkmans BA. Minocycline in active rheumatoid arthritis. A double-blind, placebo controlled trial. Arthritis Rheum 1994;37:629-36.
9. Tilley BC, Alarcon GS, Heyse SP, et al. Minocycline in rheumatoid arthritis. A 48 week, double blind, placebo controlled trial. MIRA Trial group. Ann Intern Med 1995;122:81-9.
10. 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 1997;40:794-6.
11. O'Dell JR, Blakely KW, Mallek JA, et al. Treatment of early seropositive rheumatoid arthritis: a two year, double blind comparison of minocycline and hydroxychloroquine. Arthritis Rheum 2001;44:2235-41.
12. Basler RS. Minocycline-related hyperpigmentation. Arch Dermatol 1985;121:606-8.
13. Pruzanski W, Greenwald RA, Street IP, et al. Inhibition of enzymatic activity of phospholipase A2 by minocycline and doxycycline. Biochem Pharmacol 1992;44:1165-70.
14. ElAttar TM, Lin HS, Shultz R. Effect of minocycline on prostaglandin formation in gingival fibroblasts. J Periodontal Res 1988;23:285-6.
15. Golub LM, McNamara TF, D'Angelo G, et al. A non antibacterial chemically modified tetracycline inhibits mammalian collagenase activity. J Dent Res 1987;66:1310-4.
16. Van Barr HM, van de Kerkhof PC, Mier PD, Happle R. Tetracyclines are potent scavengers of the superoxide radical [letter]. Br J Dermatol 1987;117:131-2.
17. Amin AR, Attur MG, Thakker GD, et al. A novel mechanism of action of tetracylines: effect on nitric oxide synthetases. Proc Natl Acad Sci USA 1996;93:14014-9.
18. Gabler WL, Creamer HR. Suppression of human neutrophil functions by tetracyclines. J Peridontal Res 1991;26:52–8.
19. Vincenti MP, Clark IM, Brinckerhoff CE. Using inhibitors of metalloproteinase to treat arthritis. Arthritis Rheum 1994;37:1115-26.
20. Warner GT, Plosker GL. Clindamycin/benzoyl peroxide gel: a review of its use in the management of acne. Am J Clin Dermatol 2002;3:349-60.
21. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
22. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
23. Van der Heijde D. Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. Baillieres Clin Rheumatol 1996;10:435-53.
24. Kloppenburg M, Verweij CL, Miltenburg AM. The influence of tetracyclines on T cell activation. Clin Exp Immunol 1995;102:635-41.
25. Gaston JSH. The involvement of the gut in pathogenesis of inflammatory synovitis. Br J Rheumatol 1998;41:1548-51.