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TENIDAP IN RHEUMATOID ARTHRITIS

A 24-Week Double-Blind Comparison with Hydroxychloroquine-Plus-Piroxicam, and Piroxicam Alone

WARREN D. BLACKBURN, JR., H. MALIN PRUPAS, JOEL C. SILVERFIELD, JEFFREY E. POILEY, JACQUES R. CALDWELL, RONALD L. COLLINS, MICHAEL J. MILLER, DAVID H. SIKES, HERBERT KAPLAN, ROY FLEISCHMANN, CRAIG D. SCOVILLE, JOEL E. RUTSTEIN, ERIC R. HURD, JAMES S. LOUIE, ARTHUR D. BANKHURST, ARTHUR L. WEAVER, ANTHONY I. SEBBA, DANIEL J. APPELROUTH, NORMAN P. HUDSON, GARY V. GORDON, RICHARD D. GORDON, CHARLES L. LUDIVICO, MITCHELL C. AUSTIN, KAREN M. SANDERS, PATRICK T. SCHUETTE, ROBERT A. MOIDEL, ALLEN R. KRASKA, NAITEE TING, WILLIAM R. SHANAHAN, JR., and LELAND D. LOOSE

Objective. **To compare the clinical efficacy, effect on serum C-reactive protein (CRP), serum amyloid A (SAA), and plasma interleukin-6 (IL-6) levels, and safety of tenidap with a combination of hydroxychloroquine-plus-piroxicam, and piroxicam alone, in the treatment of rheumatoid arthritis (RA) patients.**

Methods. **A double-blind, randomized, multicenter study in which patients with active RA were treated with tenidap 120 mg/day, hydroxychloroquine 400 mg/day and piroxicam 20 mg/day, or piroxicam alone 20 mg/day, for 24 weeks.**

Results. **At weeks 12 and 24, tenidap produced greater improvements than piroxicam based on 5 primary efficacy parameters; this improvement showed statistical significance in 4 of the 5 measures at week 12, and in 3 of the 5 measures at week 24. Clinical improvements in the hydroxychloroquine-plus-piroxicam–treated patients were similar to those seen in patients treated with tenidap. Compared with piroxicam, tenidap was associated with significantly greater reductions in serum CRP concentrations at 4, 12, and 24 weeks, and significantly greater reductions in SAA concentrations at weeks 12 and 24. The decrease in SAA concentrations was also significantly greater at weeks 4 and 24 in the tenidap-treated group than in the hydroxychloroquine-plus-piroxicam–treated group. Significant reductions in plasma IL-6 levels were observed at weeks 4, 12, and 24 within the tenidap group, and at week 24 within the hydroxychloroquine-plus-piroxicam–treated group. The overall occurrence of side effects, including gastrointestinal side effects, was similar in all 3 treatment groups. A small proportion of tenidap-treated**

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Warren D. Blackburn, Jr., MD: Birmingham Veterans Administration Hospital and University of Alabama at Birmingham; H. Malin Prupas, MD: Reno, Nevada; Joel C. Silverfield, MD: University Community Medical Center, Tampa, Florida; Jeffrey E. Poiley, MD: Orlando, Florida; Jacques R. Caldwell, MD: Halifax Clinical Research Center, Daytona Beach, Florida; Ronald L. Collins, MD: Columbia Arthritis Center, Columbia, South Carolina; Michael J. Miller, MD: The McGuire Clinic, Richmond, Virginia; David H. Sikes, MD: East Pasco Specialty Care, Zephyrhills, Florida; Herbert Kaplan, MD: Denver Arthritis Clinic, Denver, Colorado; Roy Fleischmann, MD: Metroplex Clinical Research Center, Dallas, Texas; Craig D. Scoville, MD: Idaho Falls, Idaho; Joel E. Rutstein, MD: San Antonio, Texas; Eric R. Hurd, MD: Arthritis Centers of Texas, Dallas, Texas; James S. Louie, MD: Harbor UCLA Medical Center, Torrance, California; Arthur D. Bankhurst, MD: University of New Mexico, Albuquerque, New Mexico; Arthur L. Weaver, MD: Arthritis Center of Nebraska, Lincoln, Nebraska; Anthony I. Sebba, MD: Teaneck, New Jersey; Daniel J. Appelrouth, MD: Atlanta, Georgia; Norman P. Hudson, MD: Columbus, Ohio; Gary V. Gordon, MD: Wynnewood, Pennsylvania; Richard D. Gordon, MD: Mercerville, New Jersey; Charles L. Ludivico, MD: Bethlehem, Pennsylvania; Mitchell C. Austin, MD: Newport Beach, California; Karen M. Sanders, MD: Veterans Administration Medical Center, Richmond, Virginia; Patrick T. Schuette, MD: Chicago, Illinois; Robert A. Moidel, MD: Rheumatology Associates, Sellersville, Pennsylvania; Allen R. Kraska, PhD, Naitee Ting, PhD, William R. Shanahan, Jr., MD, Leland D. Loose, PhD: Department of Clinical Research, Central Research Division, Pfizer Inc., Groton, Connecticut.

Address reprint requests to Warren D. Blackburn, Jr., MD, Birmingham VA Hospital, 700 19th Street South, (111-F), Birmingham, AL 35233.

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patients (6.4%) manifested mild, nonprogressive, reversible proteinuria of presumed renal proximal tubular origin, and 3–4% of patients had elevated transaminase levels.

Conclusion. **In the treatment of patients with RA, tenidap is as effective as the combination of hydroxychloroquine-plus-piroxicam, and is more effective than piroxicam alone; moreover, tenidap's safety profile is comparable to that observed with piroxicam alone, and with hydroxychloroquine-plus-piroxicam. The clinical response observed in this study, as well as the prompt decreases in acute-phase protein levels of CRP and SAA, and in plasma IL-6 levels, suggest that tenidap represents a new type of antiarthritic medication, with properties similar to, but not identical to, a therapeutic combination of a nonsteroidal antiinflammatory drug with disease-modifying antirheumatic drugs.**

Tenidap is a novel therapeutic agent in the treatment of rheumatoid arthritis (RA) that produces the same effect as nonsteroidal antiinflammatory drugs (NSAIDs) in that it inhibits cyclooxygenase; however, tenidap is structurally distinct from conventional NSAIDs (1,2), and functionally distinct in its effects on inflammatory cytokines and cells (3). A number of studies have demonstrated that tenidap modulates cytokine activity in vitro. For example, it decreases the release of the proinflammatory cytokines interleukin-1 (IL-1), IL-6, and tumor necrosis factor α (TNFα), into macrophage cell culture supernatants, and may reverse some of the catabolic effects of these cytokines (4–8). Tenidap, in contrast to NSAIDs and steroids, down-regulates IL-1 receptor expression on chondrocytes, and inhibits metalloprotease production (9).

There is a large body of evidence implicating these proinflammatory cytokines in the pathogenesis of RA (10–14). IL-1, IL-6, TNFα, and other cytokines are produced in the synovium of patients with RA, and they likely play an important role in modulating the tissue injury characteristic of this disease. In addition, these cytokines stimulate the production of acute-phase proteins, and several studies have demonstrated that one of these acute-phase proteins, C-reactive protein (CRP), may be a useful clinical marker of disease activity, and may predict radiographic progression of disease (15–23). Interestingly, compounds considered disease-modifying antirheumatic drugs (DMARDs) typically decrease the circulating levels of acute-phase proteins, whereas NSAIDs generally do not alter them (24).

These observations suggest that tenidap is a potentially important new agent in the therapy of RA. Indeed, preliminary clinical studies using conventional clinical outcome measures have demonstrated that tenidap is more effective than placebo and diclofenac (an NSAID), and as effective as the combination of diclofenac and auranofin (a DMARD) in the treatment of RA (25). Just as important, tenidap has been as well tolerated as diclofenac alone, and better tolerated than the combination of diclofenac and auranofin.

The present study was designed to compare, using both standard clinical parameters and biochemical measures of disease activity, the safety and efficacy of tenidap with the combination of hydroxychloroquine-plus-piroxicam, and piroxicam alone, in patients with relatively early disease who had not been previously treated with a DMARD. The initial 24-week analysis in this 2-year study is reported herein.

PATIENTS AND METHODS

Participating clinics. All protocols were approved by the institutional review board of each participating clinic.

Study patients. Patients were eligible for inclusion in the study if they were at least 21 years of age and had RA based on the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria (26). Patients were required to have had the disease for $\geq$6 months, to be in anatomic stage $\leq$3, and to be in Steinbrocker functional class $\leq$3 (27). All patients enrolled in the study had not been previously treated with DMARDs and had, despite adequate NSAID therapy, active disease, as defined by the presence of $\geq$10 swollen joints in addition to 2 of the following: 1) $\geq$12 painful joints; 2) morning stiffness lasting $\geq$60 minutes; and 3) erythrocyte sedimentation rate (ESR) $\geq$25 mm/hour for men and $\geq$35 mm/hour for women (Westergren method).

Patients were excluded if they had a chronic or acute condition that might jeopardize their participation in the study. Other exclusion criteria included 1) a history of allergy or intolerance to any NSAID; 2) a history of peptic ulcer disease or other gastrointestinal disorder that could affect drug absorption; 3) current or prior (within a month of enrollment) use of an H_2 receptor antagonist, sucralfate, or misoprostol, or long-term antacid usage; and 4) significant predefined deviations in serum chemistry values, blood counts, or urinalysis results. Women of child-bearing potential had to have a negative pregnancy test result, and had to have practiced successful contraception for at least 3 months prior to enrollment.

Patients were required to have received a stable NSAID dosage, other than piroxicam, for at least 1 month prior to the study. Patients were excluded if they had previously received a course of DMARD; moreover, no DMARD was allowed for the first 6 months of the study, except in the hydroxychloroquine-plus-piroxicam treatment group. Patients with a history of receiving up to 14 days of

therapy with hydroxychloroquine, azathioprine, sulfasalazine, or up to 1 dose of weekly methotrexate were permitted into the study. Up to 10 mg/day of prednisone, or an equivalent drug, was permitted if the dosage was stable for at least 1 month prior to entry, and the dosage was not to be changed during the course of study. Intraarticular or intramuscular corticosteroids were not permitted. Patients were allowed to take the analgesics acetaminophen, 650 mg every 4 hours, or propoxyphene, 650 mg every 4 hours, for non–joint-related pain such as headache or muscle strains. Aspirin at a dosage of up to 325 mg daily was permitted throughout the study.

Study design. Patients were entered into the study after meeting admission criteria and signing a consent form. They were then maintained on their NSAID regimen until the day before their baseline clinic visit. At the baseline visit, patients were stratified according to the presence or absence of erosions observed in anteroposterior radiographs of the hands, and then randomized in equal numbers to double-blind treatment with either tenidap, hydroxychloroquine-plus-piroxicam, or piroxicam alone.

Drug administration. At baseline, patients were started on a regimen of either a single daily dose of tenidap (120 mg), hydroxychloroquine (400 mg/day) given as 2 equal doses plus piroxicam (20 mg) given as a single daily dose, or a single daily dose of piroxicam (20 mg). Tenidap and piroxicam capsules were identical in appearance. Patients receiving either tenidap alone or piroxicam alone also received a placebo tablet.

Evaluation of efficacy. *Clinical parameters.* Primary efficacy measures were joint tenderness, joint swelling, physician global assessment, patient assessment of pain according to a visual analog scale (VAS), and patient global assessment. Secondary efficacy parameters were grip strength, functional capacity, duration of morning stiffness, and Arthritis Impact Measurement Scales (AIMS) scores (28). These variables were assessed at screening, baseline, and at 4, 12, and 24 weeks. Physician assessments included 1) degree of tenderness on pressure and/or pain on movement in each of 68 diarthrodial joints using a 4-point scale (0 = none, 1 = mild, 2 = moderate; 3 = severe); 2) degree of swelling in 66 diarthrodial joints using a 4-point scale; 3) global assessment of overall disease activity using a 5-point scale (1 = no symptoms, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe); 4) grip strength using a JAMAR hand dynamometer (0–90 mm Hg); and 5) classification according to Steinbrocker functional capacity. Patient assessments included 1) pain assessment using a VAS; 2) global assessment of overall disease activity using the same 5-point scale used by the physician assessor; 3) duration of morning stiffness; and 4) completion of a 13-point AIMS.

Biochemical parameters. Westergren ESR, serum CRP levels by rate nephelometry (limit of detection 0.1 mg/dl), and SAA levels (29) by enzyme-linked immunosorbent assay (ELISA) (limit of detection 1.0 μg/ml) were measured at screening, baseline, and at 1, 2, 4, 12, 16, and 24 weeks. Rheumatoid factor (RF) titer levels were measured at baseline, and at 12 and 24 weeks. IL-6 plasma levels were measured at baseline, and at weeks 4 and 24 using a commercial ELISA (limit of detection 1.0 pg/ml) (R & D Systems, Minneapolis, MN).

Evaluation of safety. All adverse events spontaneously reported by patients or observed by the investigator during and up to 7 days after the completion of the study therapy were recorded and graded for severity (mild, moderate, or severe). The treating physician was asked to express an opinion regarding the association of the event to the blinded therapy. Those events considered related or probably related were deemed treatment-related side effects.

A complete blood cell count (including hemoglobin level, red blood cell count and indices, white blood cell count and differential, and platelet count), serum chemistry analyses (to evaluate levels of electrolytes, γ-glutamyl transferase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, uric acid, total bilirubin, blood urea nitrogen, creatinine, total protein, β_2-microglobulin, glucose, and lipids), and a urinalysis (which included evaluation of protein, calcium, creatinine, uric acid, electrolytes, and amino acid levels) were performed at baseline, and at 1, 2, 4, 8, 12, 16, and 24 weeks by investigators in a central laboratory. All clinically significant abnormal laboratory findings were followed up until the value had returned to normal or baseline. The urine protein:creatinine ratio, and patient's age, sex, and weight were used to estimate 24-hour protein excretion (30). A 24-hour urine specimen was collected and assayed from those patients with an estimated 24-hour urine protein excretion $\geq$250 mg, or in whom 24-hour urinary protein excretion increased by 50% above a baseline value. Creatinine clearance, and levels of urinary total protein, creatinine, and β_2-microglobulin, were determined in patients if 24-hour urine protein excretion exceeded 750 mg.

Other safety evaluations included a 12-lead electrocardiogram, and ophthalmologic examinations at baseline and at 24 weeks.

Compliance. Each patient was questioned at each visit about medication compliance and usage of concomitant medications, glucocorticoids, and analgesics. Pill counts were performed at each visit to further monitor compliance.

Statistical analysis. Based upon the variability observed in previous tenidap studies, it was estimated that a sample size of 100 in each treatment group would be sufficient to detect a mean difference between any 2 treatment groups of 5.5 painful (tender) joints, 4 swollen joints, and 0.3 in physician's global assessment, with an $\alpha \leq 0.05$ and a power of 80%.

All statistical tests were 2-tailed, and between-group differences were considered significant if $P \leq 0.05$. Intent-to-treat analyses, with the last observation carried forward to weeks 4, 12, and 24 (using the last observation obtained up to and including day 35, 104, and 225, respectively), were used to compare changes from baseline for all variables, except for discontinuation of therapy due to lack of efficacy, Steinbrocker functional capacity, serum CRP levels, and RF titers. In addition, a completer analysis was performed for primary efficacy variables, with those patients evaluated at weeks 4 (21–35 days), 12 (63–104 days), and 24 (148–225 days), and in whom the efficacy assessments were determined within 3 days of receiving the last treatment dose.

Changes from baseline in mean primary and secondary efficacy parameters, and discontinuations due to lack of efficacy, were compared among treatment groups using

analysis of covariance (ANCOVA), with adjustments for treatment, center, presence of hand erosions, and steroid use. Changes in functional capacity were analyzed using the Cochran-Mantel-Haenszel statistical test.

For the analysis of serum CRP levels, patients were categorized according to whether these levels were above or below the limits of detection at baseline (0.1 mg/dl). Within these categories, the last available measurements were ranked and analyzed using an analysis of variance (ANOVA) model. For RF titers, patients were categorized at baseline as <1:20 or ≥1:20, and the distribution of the last-observation titers was analyzed in a similar manner to CRP levels.

Changes in ESR and log-transformed SAA levels were analyzed using ANCOVA. IL-6 data were also log transformed prior to analysis, and measurements below the limits of detection by assay were assigned a value of 1.0 pg/ml prior to log transformation. A parametric ANCOVA model, with baseline log IL-6 as a covariate and the presence or absence of bone erosions, steroid use, and center as blocking factors, was employed. Since all IL-6 assays were conducted at one laboratory, a secondary analysis, excluding center as a blocking factor, was performed.

Changes from baseline in laboratory-safety test values were examined using the Kruskal-Wallis test. Changes between baseline and final values for urine protein, glucose, and red and white cells, per high power field, were cross-tabulated and examined for trends based on the effects of the study drug.

Age of patients at baseline was compared among the treatment groups using ANOVA, with adjustments for erosions and steroid use. Body weights of patients were compared, with further adjustment for sex. Race, sex, and baseline functional capacity were compared among treatment groups using Cochran-Mantel-Haenszel statistical tests, with adjustments for erosions and steroid use. Baseline primary efficacy parameters were compared using ANOVA, with adjustments for erosions and steroid use. Since the conclusion of this study is not made on the basis of multiple statistical hypothesis testing, *P* values did not need to be adjusted for multiple comparisons.

RESULTS

Patients. Of the 411 patients screened, 367 met entry criteria and were randomized to receive treatment. Of these, 125 patients received tenidap, 124 received hydroxychloroquine-plus-piroxicam, and 118 received piroxicam alone. Two patients in the tenidap group and 2 in the piroxicam group did not receive baseline evaluations, and, therefore, were excluded from subsequent evaluations. The treatment groups were similar at baseline with respect to sex, race, duration of disease, and age (Table 1). In the small subset of patients receiving steroids at baseline, the average daily dose of prednisone, or its equivalent, was 6.91 mg in the group randomized to receive tenidap, 5.68 mg in the group randomized to receive piroxicam, and 5.47 mg in the group randomized to receive hydroxychloroquine-plus-piroxicam. These differences in average daily steroid dose were not statistically significant; moreover, the small differences in the percentage of patients receiving steroids among the 3 treatment groups were not statistically significant. The impact, if any, of steroid usage on baseline clinical parameters was minimal since there was not a consistent relationship between steroid dose, percentage of patients using steroids, and clinical variables. Similarly, at baseline, primary, secondary, and biochemical measures were comparable. As a group, patients with erosions observed on hand radiographs had a longer duration of disease and were slightly older, but did not differ in other characteristics, including baseline disease activity parameters.

One tenidap-treated patient developed classic RA shortly after the eighteenth birthday, and is included in all safety and efficacy analyses. Exclusion of this 1 patient did not alter any statistical analyses.

Two-hundred forty-four patients (66%) com-

Table 1. Demographic and clinical characteristics at baseline for 367 patients with rheumatoid arthritis (RA) in a controlled study comparing tenidap with piroxicam alone and with hydroxychloroquine (HCQ)–plus-piroxicam

Parameter	Treatment group		
	Tenidap	Piroxicam	HCQ/ piroxicam
Total no. of patients	125	118	124
No. of female patients (%)	84 (67)	89 (75)	94 (76)
Age, years			
Mean ± SEM	52.5 ± 1.25	50.2 ± 1.20	53.1 ± 1.19
Range	18–81	21–78	24–77
No. of patients >65 years	27	17	26
Duration of disease, years			
Mean ± SEM	4.2 ± .54	4.8 ± .67	4.1 ± .48
Range	0.3–34.0	0.5–49.0	0.4–30.0
Functional class, no. of patients			
I	2	7	4
II	102	97	104
III	8	7	9
Not evaluated	13	7	7
No. of steroid users (%)	26 (21)	28 (24)	30 (24)
Steroid dose*	6.91	5.68	5.47
No. of patients with erosions observed on hand radiographs (%)	50 (40)	44 (37)	48 (39)
Race, no. of patients			
White	108	99	101
Black	13	13	14
Asian	0	2	1
Other	4	4	8

* Average daily dose (mg) of prednisone (or its equivalent) in steroid-treated patients.

Table 2. Reasons for discontinuation of study therapy in 123 patients with RA*

	Treatment group		
	Tenidap, no. (%)	Piroxicam, no. (%)	HCQ/piroxicam, no. (%)
Total patients	42 (33.6)	43 (36.4)	38 (30.6)
Lack of efficacy	15 (12)	17 (14.4)	15 (12)
Adverse reaction			
Side effect	9 (7.2)	8 (6.8)	9 (7.3)
Abnormal laboratory findings	7 (5.6)	3 (2.5)	3 (2.4)
Other†	11 (8.8)	15 (12.7)	11 (8.8)

* See Table 1 for definitions.
† Lack of compliance, lost to followup, withdrawal of consent.

pleted 6 months of therapy. The 123 patients who discontinued treatment included 42 of the 125 (33.6%) in the tenidap group, 38 of the 124 (30.6%) in the hydroxychloroquine-plus-piroxicam group, and 43 of the 118 (36.4%) in the piroxicam group. Rates of discontinuation, primarily due to lack of efficacy, adverse events, and abnormal laboratory findings, were not statistically different among the treatment groups (Table 2). In each group, the leading reason for discontinuation was lack of efficacy, occurring in 15 (12.0%), 15 (12.0%), and 17 (14.4%) of the patients in the tenidap, the hydroxychloroquine-plus-piroxicam, and the piroxicam groups, respectively. The number of patients with disease duration of >10 years was small (20 patients per group) and comparable among the 3 treatment groups.

Response to therapy. At week 4, the changes from baseline in the primary efficacy parameters were similar for all 3 treatment groups (Table 3). By week 12, improvements of each primary outcome measure in the tenidap and hydroxychloroquine-plus-piroxicam groups were greater than in the group treated with piroxicam alone. At weeks 12 and 24, the mean changes from baseline were numerically greater in the tenidap group than in the piroxicam group for all 5 variables, and these differences were statistically significant at both time points for the physician and patient assessment of disease activity, and for the number of swollen joints. The difference in pain was also significant at week 12. Although, in the patients randomized to receive piroxicam, 4 of the 5 baseline clinical variables were numerically the highest among the 3 treatment groups, between-group differences were not statistically significant, and, in fact, may have afforded a greater opportunity for improvement in the piroxicam-treated patients. When patients who were receiving steroids were independently evaluated, those receiving tenidap had significantly ($P < 0.05$)

Table 3. Primary and secondary outcome measures for RA patients, by study week and treatment group (intent-to-treat, last observation carried forward)*

Parameter	Group	Baseline	Week 4	Week 12	Week 24
Physician's assessment of disease activity	T	3.03 ± 0.05	2.66 ± 0.06	2.49 ± 0.06†	2.52 ± 0.07†
	P	3.10 ± 0.05	2.75 ± 0.06	2.73 ± 0.07	2.78 ± 0.07
	HCQ+P	3.03 ± 0.04	2.60 ± 0.05	2.46 ± 0.06‡	2.42 ± 0.07‡
Patient's assessment of disease activity	T	3.12 ± 0.06	2.81 ± 0.07	2.60 ± 0.07†	2.61 ± 0.07†
	P	3.27 ± 0.06	2.94 ± 0.07	2.96 ± 0.08	2.89 ± 0.08
	HCQ+P	3.21 ± 0.06	2.77 ± 0.06	2.60 ± 0.07‡	2.61 ± 0.07‡
Number of painful joints	T	26.17 ± 1.03	18.11 ± 1.35	15.58 ± 1.31	15.56 ± 1.37
	P	29.14 ± 1.14	21.57 ± 1.42	19.54 ± 1.29	19.98 ± 1.44
	HCQ+P	27.85 ± 1.17	18.71 ± 1.31	16.12 ± 1.40	16.78 ± 1.45
Number of swollen joints	T	23.91 ± 0.95	17.87 ± 1.21	15.82 ± 1.18†	15.56 ± 0.77†
	P	23.65 ± 0.93	19.27 ± 1.15	17.98 ± 1.12	18.17 ± 0.81
	HCQ+P	22.28 ± 0.92	16.31 ± 1.09	14.65 ± 1.07	13.76 ± 0.80‡
Pain (visual analog scale)	T	15.77 ± 0.60	13.19 ± 0.70	11.50 ± 0.76†	11.58 ± 1.04
	P	17.22 ± 0.66	14.41 ± 0.81	14.35 ± 0.77	13.97 ± 0.84
	HCQ+P	16.51 ± 0.65	13.11 ± 0.69	10.93 ± 0.75	11.06 ± 0.85
Average grip strength (mm Hg)	T	17.30 ± 1.00	18.22 ± 0.99	19.05 ± 1.00	19.28 ± 1.04
	P	15.65 ± 0.79	16.50 ± 0.82	16.68 ± 0.87	16.87 ± 0.84
	HCQ+P	14.60 ± 0.82	16.08 ± 0.82	17.27 ± 0.85	16.88 ± 0.85
Duration of morning stiffness (minutes)	T	171.31 ± 20	150.95 ± 24	98.10 ± 15†	111.46 ± 20
	P	199.57 ± 28	176.23 ± 27	188.19 ± 32	147.76 ± 24
	HCQ+P	208.19 ± 25	123.19 ± 19	128.42 ± 23	128.67 ± 23

* Values are the mean ± SEM. T = tenidap; P = piroxicam; HCQ = hydroxychloroquine.
† $P < 0.05$, tenidap versus piroxicam.
‡ $P < 0.05$, HCQ-plus-piroxicam versus piroxicam.

Table 4. Biochemical outcome measures for RA patients, by study week and treatment group (intent-to-treat, last observation carried forward)*

Parameter	Group	Baseline	Week 4	Week 12	Week 24
Erythrocyte sedimentation rate (mm/hour)	T	36.10 ± 2.24	34.07 ± 2.45	32.63 ± 2.43†	31.25 ± 2.40†
	P	37.23 ± 2.39	37.15 ± 2.69	37.18 ± 2.66	35.84 ± 2.55
	HCQ+P	37.80 ± 2.34	35.60 ± 2.55	31.39 ± 2.54†‡	31.11 ± 2.23†‡
Serum amyloid A (mg/dl)	T	2.10 ± 0.15	1.78 ± 0.14†§	1.78 ± 0.13†§¶	1.64 ± 0.12†§¶
	P	2.49 ± 0.16	2.31 ± 0.17	2.66 ± 0.17	2.63 ± 0.16
	HCQ+P	2.31 ± 0.15	2.55 ± 0.16†‡	2.35 ± 0.16	2.39 ± 0.16†
Interleukin-6 (pg/ml)	T	1.66 ± 0.12	1.50 ± 0.12†	1.42 ± 0.11†§	1.35 ± 0.11†#
	P	1.74 ± 0.12	1.67 ± 0.13	1.65 ± 0.13	1.69 ± 0.13
	HCQ+P	1.69 ± 0.12	1.60 ± 0.11	1.63 ± 0.11	1.16 ± 0.11†‡
C-reactive protein (mg/dl)	T	2.05 ± 0.26	1.16 ± 0.19†¶	0.99 ± 0.20†¶	0.99 ± 0.20†¶
	P	1.95 ± 0.23	1.85 ± 0.23	2.08 ± 0.25	1.86 ± 0.22
	P+HCQ	1.84 ± 0.20	1.69 ± 0.23	1.45 ± 0.21‡	1.36 ± 0.20†

* See Table 3 for definitions.
† $P < 0.05$, within-group comparison of change from baseline.
‡ $P < 0.05$, HCQ-plus-piroxicam versus piroxicam.
§ $P < 0.05$, tenidap versus HCQ-plus-piroxicam.
¶ $P < 0.05$, tenidap versus piroxicam.
# $P < 0.06$, tenidap versus piroxicam.

more improvement from baseline than those receiving piroxicam, in all 5 primary outcome measures at 12 weeks, and in patient assessment of disease activity and number of swollen joints at 24 weeks.

When evaluations were performed on patients completing 24 weeks of therapy, similar results were obtained. Patients in the tenidap or hydroxychloroquine-plus-piroxicam groups improved more than those in the group treated with piroxicam alone. The improvement of patients in the tenidap group was statistically significantly greater than in the piroxicam group, based on the physician assessment of disease activity and the number of swollen joints at 12 and 24 weeks. Patient assessment of disease activity was statistically significantly different only at 12 weeks.

Among the secondary efficacy parameters, duration of morning stiffness and functional capacity at week 12 improved significantly more in the tenidap group than in the piroxicam group. However, the difference in improvement in morning stiffness between these 2 groups was no longer apparent at 24 weeks.

There was equivalent improvement between the hydroxychloroquine-plus-piroxicam group and the tenidap group in primary and secondary parameters at all of the evaluted time points. Improvements from baseline were significantly greater in the hydroxychloroquine-plus-piroxicam group than in the piroxicam group for 2 of the 5 primary efficacy variables (physician and patient assessment) at week 12, and for 3 of the 5 primary variables (physician and patient assessment, and swollen joints) at week 24.

When analyses that separated patients with erosions present at baseline were performed, trends in observations similar to those found in the aggregate patient group were noted (i.e., no statistically significant change in response to treatment was demonstrated when comparing patients with or without erosions at baseline; data not shown).

Biochemical parameters. Effects on the biochemical parameters are shown in Table 4. Serum CRP concentrations varied little in the piroxicam group during the 24 weeks of therapy. In the tenidap-treated group, CRP levels decreased significantly; mean levels approached the lower limits of detection by assay, and were significantly less than in the piroxicam group at 4, 12, and 24 weeks. Similar observations were noted in both completer and intent-to-treat analyses. Changes in CRP levels in the hydroxychloroquine-plus-piroxicam group were intermediate, and circulating CRP levels were significantly greater than in the tenidap group at 4 and 24 weeks. When the evaluation was limited to patients with detectable CRP at baseline, the difference between the tenidap and the piroxicam groups was even more significant ($P \leq 0.002$). To investigate the changes in acute-phase proteins, plasma IL-6 levels were also determined. As shown in Table 4, only patients treated with tenidap had statistically significant decreases from baseline in plasma IL-6 levels at all time points. At week 24, patients treated with either tenidap or hydroxychloroquine-plus-piroxicam had statistically significant decreases in their plasma IL-6 levels, whereas patients treated with piroxicam never demon-

strated a significant reduction in this cytokine. Reduction in IL-6 levels was greatest in the hydroxychloroquine-plus-piroxicam group at week 24.

To explore the possibility that early decreases in CRP levels could predict a favorable clinical outcome, the median 4-week decrease in CRP levels for all patients in this study, regardless of treatment group, was determined; the clinical response of all patients with an above-the-median 4-week decrease in CRP levels was compared with those who had a decrease below the median. Patients who had an above-the-median change from baseline values at week 4 showed a statistically significantly greater improvement in the number of both painful and swollen joints.

ESR decreased statistically significantly from baseline by weeks 12 and 24 in the groups treated with tenidap or hydroxychloroquine-plus-piroxicam, but did not change significantly in the piroxicam group. There was a significantly greater decrease in ESR in the hydroxychloroquine-plus-piroxicam group than in the piroxicam group at weeks 12 and 24.

SAA levels decreased statistically significantly in the tenidap group, but increased in the hydroxychloroquine-plus-piroxicam group.

Side effects. Treatment-related side effects occurred in approximately half of the patients in each treatment group. Most were mild or moderate in severity and were not different among treatment groups (Table 5). The most common side effects were gastrointestinal. Gastrointestinal perforations, ulcers, or bleeding were experienced by 3 patients in the tenidap group, none in the piroxicam group, and 2 patients in the hydroxychloroquine-plus-piroxicam group. One of the 3 patients in the tenidap group had a perforated gastric ulcer and died from postoperative atherosclerotic complications.

Treatment was discontinued because of side effects in 9 (7.2%) of the tenidap-treated patients, 9 (7.3%) of the hydroxychloroquine-plus-piroxicam–treated patients, and in 8 (6.8%) of the piroxicam-treated patients. The reason for discontinuation was most commonly gastrointestinal problems, and these accounted for 13 of the 26 patient withdrawals from the study.

Abnormal laboratory findings. Alterations in laboratory test results occurred infrequently in all 3 treatment groups, and resulted in discontinuation of therapy for 7 (5.6%), 3 (2.4%), and 3 (2.5%) of the patients in the tenidap, hydroxychloroquine-plus-piroxicam, and piroxicam groups, respectively (Table 6).

Table 5. Occurrence of treatment-related side effects in study patients, with withdrawals from the study due to side effects*

Parameter	Treatment group		
	Tenidap, no. (%)	Piroxicam, no. (%)	HCQ/ piroxicam, no. (%)
Total no. of patients	125	118	124
Patients with side effects	64 (51)	54 (46)	63 (51)
Patients with gastrointestinal side effects	44 (35)	26 (22)	42 (34)
Patients withdrawn due to side effects	9 (7.2)	8 (6.8)	9 (7.3)
Total no. of side effects	123	85	119
Dyspepsia	17 (13.6)	8 (6.7)	13 (10.4)
Nausea	12 (9.6)	7 (5.9)	11 (8.8)
Abdominal pain	8 (6.4)	7 (5.9)	9 (7.2)
Diarrhea	8 (6.4)	4 (3.3)	5 (4)
Flatulence	8 (6.4)	2 (1.6)	7 (5.6)
Asthenia	6 (4.9)	2 (1.6)	2 (1.6)
Constipation	6 (4.8)	3 (2.5)	6 (4.8)
Headache	5 (4)	3 (2.5)	13 (10.4)
Vomiting	5 (4)	1 (0.8)	2 (1.6)
Skin disorders	5 (4)	10 (8.5)	13 (10.5)
Gastritis	4 (3.2)	0	0
Insomnia	4 (3.2)	3 (2.5)	1 (0.8)
Peripheral edema	4 (3.2)	1 (0.8)	0
Peptic ulcer/gastrointestinal bleeding	3 (2.4)	0	2 (1.6)
Duodenal	1 (0.8)	0	2 (1.6)
Gastric	1 (0.8)†	0	0
Duodenal/gastric	1 (0.8)	0	0
Hemorrhage	0	0	1 (0.8)
Anorexia	2 (1.6)	0	3 (2.4)
Ulcerative stomatitis	2 (1.6)	0	5 (4)
Dizziness	1 (0.8)	3 (2.5)	1 (0.8)
Esophageal ulcer	1 (0.8)	0	0
Tinnitus	1 (0.8)	1 (0.8)	3 (2.4)

* HCQ = hydroxychloroquine.
† Patient had a perforated gastric ulcer and subsequently died from post-surgical atherosclerotic complications.

Greater than 3-fold elevations in transaminase levels occurred in 4 tenidap-treated patients SGPT 4.0–6.1 × upper limit of normal, in none of the hydroxychloroquine-plus-piroxicam–treated patients, and in 1 patient treated with piroxicam alone (SGPT 11.4 × upper limit of normal). Liver function test abnormalities led to study drug discontinuation for 5 patients in the tenidap group and 1 patient treated with piroxicam. In each case, transaminase levels returned to normal the treatment was stopped. Other abnormal findings leading to discontinuation of treatment included decreases in hemoglobin levels (1 tenidap patient, 2 hydroxychloroquine-plus-piroxicam patient), decreased white blood cell (WBC) counts (1 hydroxychloroquine-plus-piroxicam patient, 2 piroxicam alone patients), decreased proteinuria levels (1 tenidap pa-

Table 6. Occurrence of treatment-related, clinically significant abnormal laboratory findings in 2 or more study patients within any of the 3 treatment groups*

Parameter	Treatment group		
	Tenidap, no. (%)	Piroxicam, no. (%)	HCQ/ piroxicam, no. (%)
Total no. of patients	125	118	124
Patients with abnormal laboratory findings	25 (20)	10 (8)	10 (8)
Patients withdrawn due to abnormal findings	7 (5.6)	3 (2.5)	3 (2.4)
Hemoglobin, >20% decrease	0	0	3 (2.4)
Hematocrit, >20% decrease	1 (0.8)	0	2 (1.6)
Albumin, <0.9 × LLN	2 (1.6)	0	0
SGOT, >3 × ULN	5 (4)	1 (0.8)	0
SGPT, >3 × ULN	4 (3.2)	1 (0.8)	0
Sodium, <0.95 × LLN	2 (1.6)	0	0
Uric acid, >1.2 × ULN	0	2 (1.7)	1 (0.8)
Urine hyaline casts, >1/HPF	4 (3.2)	0	5 (4)
Urine glucose, qualitative, >1+	1 (0.8)	2 (1.7)	0
Urine protein, qualitative, >1+	1 (0.8)	2 (1.6)	0
Urine protein, >500 mg/day	8 (6.4)	1 (0.8)	1 (0.8)
Urine protein, ≥750 mg/day	2 (1.6)	0	1 (0.8)
Urine protein, ≥1000 mg/day	1 (0.8)	0	1 (0.8)

* HCQ = hydroxychloroquine; LLN = lower limit of normal; SGOT = serum glutamic oxaloacetic transaminase; ULN = upper limit of normal; SGPT = serum glutamic transaminase; HPF = high power field.

tient), and increased creatinine levels (1 hydroxychloroquine-plus-piroxicam patient).

Proteinuria of >500 mg/24 hours was detected in 8 of the tenidap-treated patients and in 1 patient from each of the other 2 treatment groups (Table 6). Small increases in urinary protein excretion above the limit of the normal range (150 mg/day) were detected in the majority of tenidap-treated patients at some time during the study. Two (1.6%) of the patients in the tenidap-treated group, 1 (0.8%) in the hydroxychloroquine-plus-piroxicam group, and 0 (0%) in the piroxicam group developed proteinuria of ≥750 mg in 24 hours. Patients with proteinuria >750 mg/day were mandated by protocol to temporarily discontinue blinded therapy to assess reversibility. As mandated by protocol, 1 tenidap-treated patient discontinued treatment due to proteinuria of ≥750 mg/24 hours, which returned to normal values within 23 days. Levels of urine β_2-microglobulin (MW ~12,000) were measured as a marker of tubular proteinuria in 6 of the 8 tenidap-treated patients, and found to be elevated in all 6 patients. None of the patients with proteinuria >500 mg/24 hours in any group had concomitant elevation in either blood urea nitrogen or serum creatinine levels. None of the patients with proteinuria developed an "active" urine sediment, and there were no apparent shifts in the urine WBC counts, red blood cell counts, or glucose levels from baseline to last observation in the tenidap-treated patients.

In the tenidap-treated group, there were small but clinically significant changes from baseline to last observation in levels of median serum uric acid (−1.2 mg/dl), bicarbonate (−2.0 mg/liter), phosphorus (−0.2 mg/dl), and creatinine (+0.1 mg/dl), and in estimated 24-hour urinary protein (+90 mg). These changes were due to small increases or decreases occurring in many patients rather than to large changes occurring in a few.

DISCUSSION

The results of this study, involving 367 patients with RA who had not been previously treated with DMARDs, demonstrate that 120 mg/day of tenidap is clinically equivalent to the combination of hydroxychloroquine-plus-piroxicam, and significantly more effective than piroxicam alone. Treatment with tenidap, unlike piroxicam, was associated with rapid and marked reductions in CRP, SAA, and IL-6 levels. All 3 treatments were well tolerated, and the occurrence of side effects and discontinuations due to adverse events were similar in the 3 groups.

The superior clinical efficacy of tenidap over piroxicam was demonstrated at both 12 weeks and 24 weeks, as was the superior efficacy of the combination therapy over piroxicam alone. This equivalent efficacy of tenidap and hydroxychloroquine-plus-piroxicam was seen in the results which showed a similar magnitude of improvement in efficacy parameters at weeks 4, 12, and 24, as well as a similarity in the proportion of patients who discontinued therapy due to lack of efficacy (12% in both groups).

Tenidap was differentiated from piroxicam by the significantly greater improvements in both efficacy and biochemical parameters. In tenidap-treated patients, there was a rapid and sustained decrease in CRP and SAA levels, significant reductions occurring in both parameters at 4 weeks, and further significant reductions apparent at weeks 12 and 24. By contrast, piroxicam had a negligible effect on these parameters at all time points, and the effect of the combination therapy, hydroxychloroquine-plus-piroxicam, was delayed. One of the primary cytokines responsible for the induction of the hepatic synthesis of acute-phase proteins is IL-6 (13,31). In conjunction with the decline in CRP and SAA levels, IL-6 levels decreased

in both the tenidap and hydroxychloroquine-plus-piroxicam treatment groups, but not the piroxicam alone group.

Measurement of acute-phase protein levels and ESR has long been considered a valid method for determining disease activity in RA, and both measures have been incorporated in recent aggregate measurements (15–23). As noted above, there appears to be a dichotomy in the clinical response associated with these measures, depending on the therapy being evaluated. Patients treated with NSAIDs generally show no decline in these acute-phase responses, whereas patients treated with DMARDs generally demonstrate a decrease in these markers (24). Consistent with these observations, our patients who were treated with hydroxychloroquine-plus-piroxicam did show a decrease in CRP levels; however, this decrease was delayed in comparison with the rapid decrease observed in the tenidap group. Previous studies have shown a good correlation between disease activity and CRP levels; moreover, other studies, as well as the present data, have shown that CRP levels may predict both response to therapy and even radiographic progression of disease (15,18,20). As previously demonstrated in other clinical studies (32), the rapid and sustained decrease in acute-phase protein levels in the tenidap-treated group further supports the contention that tenidap is distinct from NSAIDs, and, in terms of the pattern of clinical response in these measures, shares properties with DMARDs.

Tenidap was well tolerated, and the number of patients experiencing side effects in this group did not differ from the other 2 treatment groups. Five tenidap-treated patients did have asymptomatic elevation of serum transaminase levels. In each case, the drug was discontinued and transaminase levels returned to normal. Compared with the other groups, there was a greater number of tenidap-treated patients who developed low-grade, tubular proteinuria, which, in 1 patient, whose treatment was discontinued due to proteinuria, was readily reversed (within 23 days). The tubular nature of the proteinuria is supported by the observed small decreases in the tenidap group in serum uric acid, bicarbonate, and phosphate levels, by the small increase in serum creatinine levels (approximately 10% of urine creatinine is secreted [33,34]), and by the absence of an "active" urine sediment. The relative enrichment of urinary protein by a low MW species (β_2-microglobulin), normally filtered by the glomerulus and reabsorbed by the tubule (35,36), is also strongly supportive of a partial inhibition of renal proximal tubular transport by tenidap. The changes in urine protein levels and in serum chemistry values observed with tenidap are not clinically significant and are reversible. In fact, some patients, now treated for up to 5 years with tenidap, have had no further evidence of progression of their proteinuria or development of renal failure (Blackburn WD: personal observation).

Hydroxychloroquine-plus-piroxicam was well tolerated, and patients treated with this regimen had no significant differences in side effects when compared with the other treatment groups. Similarly, the number of patients discontinuing therapy because of side effects when compared with the piroxicam-alone group were not different. This result is comparable to previous work indicating that hydroxychloroquine is one of the safest slow-acting agents commonly used for treatment of RA (37,38).

In summary, these results indicate that tenidap is an effective antirheumatic agent, clinically equivalent to and as well tolerated as the combination of hydroxychloroquine and piroxicam, and has properties suggestive of the ability to modify disease. Thus, tenidap is a useful addition to the therapeutic measures available for the treatment of RA.

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