Dose Response and Safety Study of Meloxicam Up to 22.5 mg Daily in Rheumatoid Arthritis: A 12 Week Multicenter, Double Blind, Dose Response Study versus Placebo and Diclofenac

DANIEL E. FURST, KAREN S. KOLBA, ROY FLEISCHMANN, JOEL SILVERFIELD, MARIA GREENWALD, SANFORD ROTH, DAVID B. HALL, and PAUL J. ROSZKO for the Meloxicam Rheumatoid Arthritis Investigators

ABSTRACT. ***Objective.*** This Phase III, placebo and active controlled, multicenter trial evaluated the efficacy and safety of meloxicam 7.5, 15, and 22.5 mg daily for the treatment of rheumatoid arthritis (RA).

Methods. A 12 week, randomized, double blind, double dummy, parallel group trial compared daily oral meloxicam 7.5, 15, and 22.5 mg to placebo (negative control) and diclofenac 75 mg BID (positive control). A total of 894 patients (18 years of age with confirmed RA who flared following an NSAID-free period) were randomized to be treated. Baseline scores for all endpoints were similar among the treatment groups. Patient assessments were at 0, 2, 4, 8, and 12 weeks or early termination.

Results. All treatment groups demonstrated significant improvement from baseline ($p < 0.001$). Meloxicam 7.5 and 22.5 mg was significantly superior to placebo in all 5 primary efficacy endpoints (swollen joint count, tender joint count, patient pain, patient and physician global; all $p < 0.05$). Diclofenac 150 mg was superior to placebo for 4 of 5 primary efficacy measures (all but swollen joint count; $p < 0.05$) and meloxicam 15 mg was superior for 3 of 5 primary endpoints (patient pain and patient and physician global). AUC of patient global, patient pain, and modified Health Assessment Questionnaire demonstrated dose-response ($p < 0.04$), while AUC ACR20 showed a qualitative trend in the same direction. The rate of gastrointestinal (GI) events during the 12 week trial for all doses of meloxicam and diclofenac did not differ significantly from placebo (23.2–32.0%). GI withdrawals were comparable and not significantly different across all treatment groups (4.3–5.7%).

Conclusion. This trial demonstrated a dose response relationship for meloxicam 7.5, 15, and 22.5 mg using AUC measurement of response for the treatment of RA. All 3 doses of meloxicam, and positive control, were effective in the treatment of RA. The overall incidence rate of GI events did not differ significantly from placebo in either the meloxicam treatment groups or the positive control. (J Rheumatol 2002;29:436–46)

Key Indexing Terms:
RHEUMATOID ARTHRITIS OSTEOARTHRITIS MELOXICAM
CYCLOOXYGENASE-2 DRUG DOSE RESPONSE RELATIONSHIP

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology. The characteristic symptoms are pain, swelling, and stiffness in multiple joints[1]. Whereas disease modifying antirheumatic drugs (DMARD) are usually required for therapy of RA[2,3], nonsteroidal antiinflammatory drugs (NSAID) are added for further symptomatic pain relief and improvement of functional status.

Meloxicam [4-hydroxy-2-methyl-N(5-methyl-2-thiazolyl)-2H-1, 2-benzothiazine-3-carboxamide-1, 1-dioxide] is an NSAID of the enolic acid class that inhibits prostaglandin (cyclooxygenase, COX) synthetase. It has consistently shown a greater inhibition of COX-2 than COX-1 in all relevant pharmacological models *in vitro* as well as *ex vivo* at therapeutic doses of 7.5 and 15 mg[4-7]. Meloxicam, rofecoxib, and celecoxib interact selectively with the COX-2 site. Rofecoxib and celecoxib interact with a side pocket, while meloxicam occupies the space at the top of the COX-2 channel[8]. Additionally, meloxicam at doses up to 30 mg does not affect arachidonic acid or ADP induced

From the Virginia Mason Research Center, Seattle, Washington; Pacific Arthritis Center, Santa Maria, California; Radiant Research, Dallas, Texas; Tampa Medical Group, Tampa, Florida; Advances in Medicine, Rancho Mirage, California; Arizona Research & Education, Phoenix, Arizona; and Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, USA.

Supported by Boehringer Ingelheim Pharmaceuticals, Inc.

D.E. Furst, MD, Virginia Mason Research Center; K.S. Kolba, MD, Pacific Arthritis Center, Santa Monica, CA; R. Fleischmann, MD, Rheumatology Associate, Dallas, TX; J. Silverfield, MD, Private Practice, Tampa, FL; M. Greenwald, MD, Private Practice, Rancho Mirage, CA; S. Roth, MD, Arthritis Care and Research, Phoenix, AZ; D.B. Hall, PhD; P.J. Roszko, RPh, Boehringer Ingelheim, Ridgefield, CT.

Address reprint requests to Dr. D.E. Furst, Virginia Mason Research Center, 1201 9th Avenue, Seattle, WA 98101. E-mail: crgdef@vmmc.org

Submitted March 21, 2001; revision accepted October 17, 2001.

platelet aggregation or bleeding time, compatible with a selective effect on COX-2[9]. Meloxicam 7.5 to 15 mg once daily effectively treats the signs and symptoms of osteoarthritis in 3 week to 6 month studies[10-16]. Meloxicam is also safe and effective for ankylosing spondylitis at doses as high as 22.5 mg a day[17].

Meloxicam trials in RA show efficacy, but they are either of limited duration (3 week placebo controlled trial) or limited dosing (7.5 mg for 6 months)[18-21]. Additionally, no longterm dose-response study beyond 15 mg meloxicam has been tested in RA. An early, smaller RA trial used meloxicam doses up to 60 mg, but that dose showed no increased efficacy relative to 15 or 30 mg[22]. The 60 and 30 mg doses may have been in the flat portion of the sigmoid dose-response curve, so lower doses were chosen thereafter to examine a possible extension of the dosing regimens used to date.

Our study examines 7.5, 15, and 22.5 mg meloxicam versus placebo and 150 mg diclofenac in a 12 week, double blind, randomized, multicenter trial in patients with RA.

MATERIALS AND METHODS

Patients were required to be 18 to 80 years of age, currently using NSAID therapy for RA, and had to meet 3 or more of the following criteria: (1) at least 6 or more tender joints; (2) at least 3 swollen joints; (3) patient's assessment of pain at least 20 mm on a 100 mm visual analog scale (VAS); (4) morning stiffness lasting at least 45 minutes; (5) erythrocyte sedimentation rate (ESR) > 28 mm or C-reactive protein (CRP) > 1.2 mg/dl. Patients could be taking and continue to take DMARD that they initiated at least 3 months prior to entering the trial and/or prednisone ≤ 10 mg per day that was stable for at least one month prior to entering the trial; all were to remain stable with that dose throughout the trial. Patients were not to have any intraarticular steroids during the trial. Only one patient, in the diclofenac treatment arm, had such an injection. The data from this patient were used in the analyses without influencing efficacy endpoints. Patients were allowed diclofenac as their preceding NSAID prior to the study (about 20% of patients in each treatment group had used diclofenac).

Upon discontinuing NSAID therapy, a flare including at least 3 of the following 5 criteria had to be observed within 2 weeks: (1) worsening of at least one grade from screening on the investigator's global assessment of disease activity; (2) worsening ≥ 10 mm from screening on the 100 mm VAS patient global assessment of disease activity; (3) worsening ≥ 10 mm from screening on the 100 mm VAS patient assessment of pain; (4) at least 20% increase compared with screening visit in the number of painful or more tender joints; and (5) at least 20% increase compared with screening visit in the number of swollen joints.

Note that flare did not specifically require a change in tender or swollen joints, as flare could be designated using criteria 1 to 3 above.

Visits were scheduled at weeks 2, 4, 8, and 12. Primary endpoints included: investigator global assessment of disease activity (5 point Likert scale), patient global assessment of disease activity, patient assessment of pain (both on 100 mm VAS), number of painful or tender joints (maximum 28) and number of swollen joints (maximum 28). Other measurements included patient assessment of physical function using the modified Health Assessment Questionnaire (mHAQ) (maximum +3.0), ESR, and CRP (measured pretreatment and final visit). The use of rescue medication (acetaminophen) was allowed during the study; however, patients were prohibited from taking acetaminophen within 12 hours of a clinic visit.

While all joints were counted in the evaluation of painful or tender joints and swollen joints, the 28 core joints were the primary focus[20]. Adverse events were monitored at each trial visit. Hematology, chemistry, and urine laboratory values were performed at pretreatment and at weeks 4 and 12. Urinalysis by dipstick and creatinine clearance by 24 hour urine collection were performed pretreatment and at the final visit.

Analysis. Baseline demographics were compared using analysis of variance (ANOVA) or chi-square test of independence, as appropriate. Randomization was accomplished using a computer generated algorithm.

The mean of all on-treatment assessments (area under the curve, AUC) was used to examine change from baseline for the number of painful/tender and swollen core joints, patient 100 mm VAS for pain and global assessment of disease activity, investigator global assessment of disease activity, and the mHAQ. In addition, a modified intent to treat analysis with last observation carried forward was analyzed, with similar results. Both measures were included as primary endpoints in the protocol, requiring statistical significance in both to conclude that treatment differences were genuine. ANOVA was used to analyze changes in joint counts, mHAQ, and VAS assessments, with treatment, investigator, and DMARD as terms in the model. The initial null hypothesis of interest was that the magnitude of response between the 22.5 mg per day dose of meloxicam and placebo was the same. If this null hypothesis was rejected, then the null hypothesis was considered, in turn, for the 15 mg and then for the 7.5 mg per day doses of meloxicam. The endpoint type one error rate was maintained by initially focusing on a single comparison (22.5 mg meloxicam vs placebo). The analysis strategy described above required higher doses to be significant at the 0.05 level before testing lesser doses, thus maintaining a type one error rate of 0.05 or less and constituting a conservative strategy. Further analysis of meloxicam patients tested for linear dose-response in the dose range from 7.5 to 22.5 mg, treating dose as a continuous variable in the ANOVA model applied previously.

ESR and CRP were analyzed using baseline and patient's last visit assessments.

The proportion of patients improving by the American College of Rheumatology 20% response criteria (ACR20 response) used an AUC approach. All patients' ACR20 responses were measured at each time point. The patient either met or did not meet criteria at each time point and a line was drawn connecting all responses or nonresponses. If a patient did not complete the study, the ACR20–AUC ended at that point. The AUC of the ACR20 for each patient was then measured using simple geometry, all the AUC for patients in a given treatment group were averaged, and an ANOVA was calculated to examine differences between treatment groups. Safety analysis examined those patients who took at least one dose of medication. The assessment of safety looked at the crude incidences of adverse events over the 12 week study, mean changes in laboratory values, and marked changes in individual laboratory variables as well as mean changes in vital signs. Marked changes are defined as alkaline phosphatase ≥ 20 u/l; creatinine change ≥ 0.3 mg/dl; ALT or AST increase ≥ 10 u/l; hemoglobin decrease by ≥ 2 g/dl; or hematocrit decrease by ≥ 6%. Additional analyses used chi-square tests or Fisher's exact test when appropriate. Sample sizes (180 patients per treatment group) were based on the 2 sided, 2 sample Student t test with a significance level of 0.05 and an overall power of 80%.

RESULTS

There were no statistical differences among groups for any of the background factors or disease activity measures (Tables 1, 2). As expected, discontinuations secondary to lack of efficacy were highest in the placebo group, significantly higher than in any active treatment group (Table 3). There was a numerical but not statistically significant meloxicam dose-response for lack of efficacy (for meloxicam 7.5 mg 25.7%; 15 mg 24.5%; 22.5 mg 20.9%), while the discontinuations for lack of efficacy were least in the diclofenac group (14.4%) ($p < 0.01$ vs meloxicam 7.5

Table 1. Demographic baseline characteristics for all treated patients.

	Placebo, N = 177	Meloxicam, 7.5 mg N = 175	Meloxicam, 15 mg N = 184	Meloxicam, 22.5 mg N = 177	Diclofenac, 75 mg BID[a] N = 181
Female, %	75.1	78.9	75.5	73.4	77.9
White, %	84.7	81.1	79.9	87.0	79.6
Age, yrs					
≤ 65, %	78.0	77.7	77.7	75.1	79.0
> 65, %	22.0	22.3	22.3	24.9	21.0
Mean ± SD	56.0 ± 12.1	56.3 ± 11.5	55.6 ± 12.1	56.7 ± 11.8	54.7 ± 12.8
RA duration, yrs, mean ± SD	10.4 ± 9.1	10.3 ± 9.6	10.2 ± 9.8	9.6 ± 8.7	10.3 ± 9.8
Rheumatoid factor +, %	50.3	51.4	56.5	49.7	51.4
History of a PUB, %[b]	9.0	12.0	8.7	10.7	9.9
Using prednisone, %	36.2	32.6	35.3	26.6	29.3
Using any DMARD, %[c]	64.4	66.3	59.2	59.9	55.8
Methotrexate	44.1	46.3	35.9	44.1	39.2
Hydroxychloroquine	18.6	20.6	19.6	20.9	15.5
Sulfasalazine	8.5	10.9	9.8	6.8	3.9
Other	6.2	8.0	6.0	5.1	5.5
Prior diclofenac,%	20.9	17.1	17.9	21.5	22.7

[a]BID: twice daily administration.
[b] PUB: perforation, ulceration, or bleeding.
[c] Patients may have been taking multiple DMARD for their RA so percentage may add to > 100%

Table 2. Patient disease characteristics at flare. Values are mean (SD).

	Placebo	Meloxicam 7.5 mg	Meloxicam 15 mg	Meloxicam 22.5 mg	Diclofenac 150 mg
Tender joint count [max = 28]	17.8 (6.4)	16.9 (6.3)	17.6 (6.9)	17.4 (6.9)	17.7 (6.3)
Swollen joint count [max = 28]	14.4 (6.6)	14.5 (6.6)	14.3 (6.5)	14.5 (6.3)	14.0 (6.7)
Investigator global assessment [max = 4]	2.6 (0.62)	2.57 (0.62)	2.63 (0.70)	2.58 (0.64)	2.52 (0.63)
Patient global assessment [max = 100]	70 (17)	68 (19)	71 (19)	70 (16)	69 (18)
Patient pain assessment [max = 100]	73 (17)	70 (18)	74 (15)	72 (17)	72 (18)
MHAQ [max = 3.0]	1.12 (0.55)	1.02 (0.59)	1.06 (0.66)	1.09 (0.61)	1.02 (0.60)
ESR, mm/h	36.0 (26.5)	33.9 (21.0)	35 (23.9)	32.5 (24.3)	35.3 (23.3)
CRP, IU/ml	1.39 (1.65)	1.46 (1.73)	1.71 (1.99)	1.50 (1.70)	1.42 (1.59)

Table 3. Patient disposition. Values are number (%).

	Placebo	Meloxicam 7.5 mg	Meloxicam 15 mg	Meloxicam 22.5 mg	Diclofenac 150 mg
Treated	177	175	184	177	181
ITT population[a]	173 (97.7)	174 (99.4)	184 (100)	177 (100)	180 (99.4)
Discontinued for					
Lack of effect	61 (34.5)	45 (25.7)	45 (24.5)	37 (20.9)	26 (14.4)
Adverse event	14 (7.9)	18 (10.3)	14 (7.6)	15 (8.5)	20 (11.0)
Other	10 (5.7)	7 (4.0)	4 (2.2)	6 (3.4)	7 (3.9)

[a] Six patients had no postdose efficacy evaluations and were excluded from the intent-to-treat population. (ITT)

mg, p = 0.02 vs meloxicam 15 mg, and p = 0.13 vs meloxicam 22.5 mg). There were no statistical differences among groups (including placebo) with respect to discontinuations secondary to adverse events.

While patients were not supposed to start or increase their prednisone dose, a few patients in each group did so: placebo 5 (2.8%), diclofenac 4 (2.2%), 7.5 mg meloxicam 3 (1.7%), 15 mg meloxicam 3 (1.6%); and 22.5 mg meloxicam one patient (0.6%). These results were not statistically different among groups and were not further analyzed.

Although the ACR20 response criteria were developed to measure response to DMARD and not NSAID, these response criteria were examined during this study. The AUC of the ACR20 response criteria reveal that 7.5 mg meloxicam did not separate from placebo, while 15 and 22.5 mg meloxicam and diclofenac were significantly different from placebo. The diclofenac group was also significantly different from the 7.5 mg meloxicam group (Figure 1).

Table 4 details each variable making up the ACR response criteria separately. Both a modified intent to treat with last observation carried forward and area under the curve methodology were used for all measures but CRP and ESR (only baseline and final visit were measured for these 2 variables, so AUC was not appropriate).

All treatment groups, including placebo, showed significant improvement from baseline ($p < 0.001$). Meloxicam efficacy was evident after 2 weeks of treatment and continued to the end of trial (Figure 2). Meloxicam 7.5 and 22.5 mg were significantly superior to placebo for all primary efficacy endpoints. Diclofenac 150 mg was superior to placebo for 4 of 5 primary efficacy measures, and meloxicam 15 mg was superior to placebo for 3 of 5 primary endpoints. By the protocol-specified inference strategy, all doses of meloxicam were superior to placebo for 3 primary endpoints, with 22.5 mg also superior for the remaining 2 endpoints (the joint counts).

Neither meloxicam nor diclofenac improved CRP or ESR during this 12 week study.

Patient global assessment, mHAQ, and patient overall pain assessments were appropriate for the statistical evaluation of the dose-response relationship in this study. Figure 3 illustrates the dose responses for these 3 criteria, using an AUC analysis ($p < 0.04$ for linear dose response for all 3 variables). Investigator global assessment and ACR20–AUC did not have a significant dose-response slope ($p = 0.34$ and 0.17, respectively).

Other individual measures of response could not be analyzed for dose-response for the following reasons: (1) 15% of patients did not have sufficient change in joint tenderness counts (not required for flare per se — see above) thus confounding this variable as a measure of dose response. (2) Swollen joint count in the positive control did not separate from placebo, indicating this measure was not a sensitive response measure in this study.

Table 5 displays the overall incidence of adverse and gastrointestinal (GI) events, serious adverse events, and overall incidence of discontinuation and GI discontinuation rates due to an adverse event during the 12 week study. The rates of treatment-emergent adverse events, serious adverse events, and withdrawal from the study due to an adverse event were similar and not statistically different for meloxicam (at all doses), diclofenac, and placebo. No patient deaths were reported during the trial. Most GI withdrawals were due to nausea, diarrhea, flatulence, dyspepsia, or abdominal pain across all treatment groups (data not shown).

The incidence of upper GI perforations, ulcerations, or bleeds did not increase with the dose of meloxicam. There was no GI perforation in any patient. There were 4 meloxicam treated patients (2 in the 7.5 mg group and one each in the 15 mg and 22.5 mg groups) with treatment-emergent ulcerations or bleeds. None of these events was considered "serious" by US Food and Drug Administration

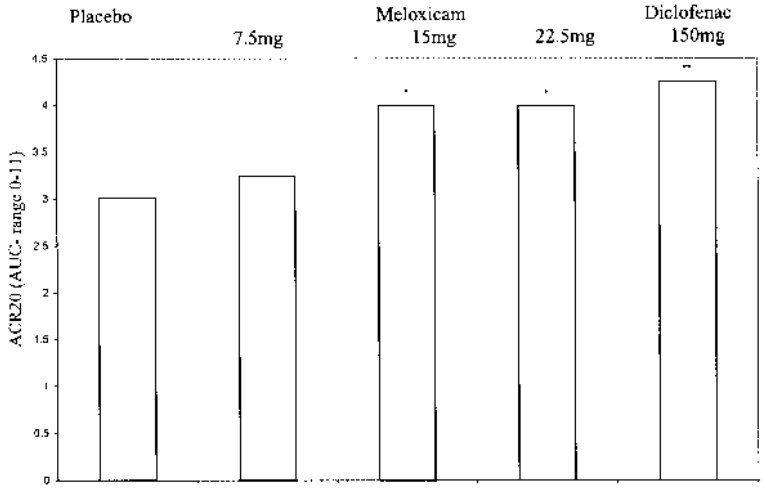

Figure 1. AUC of the ACR20 response criteria. *p ≤ 0.05; **p ≤ 0.0.

Table 4. Responses to treatment. Values are mean (SE).

	Placebo	Meloxicam 7.5 mg	Meloxicam 15 mg	Meloxicam 22.5 mg	Diclofenac 150 mg
Tender joint count					
[max = 28], LOCF	–6.1 (0.6)	–7.7 (0.6)[a]	–7.0 (0.6)	–7.7 (0.6)[a]	–8.4 (0.6)[c]
AUC	–5.8 (0.5)	–7.3 (0.5)[a]	–7.1 (0.5)	–7.7 (0.5)[b]	–8.1 (0.5)[c]
Swollen joint count					
[max = 28], LOCF	–4.3 (0.5)	–5.8 (0.5)[a]	–4.5 (0.5)	–5.7 (0.5)[a]	–5.0 (0.5)
AUC	–4.4 (0.4)	–5.6 (0.4)[a]	–4.7 (0.4)	–5.8 (0.4)[b]	–5.0 (0.5)
Investigator global					
assessment [max = 4], LOCF	–0.63 (0.07)	–0.83 (0.07)[a]	–0.86 (0.07)[b]	–0.87 (0.07)[b]	–0.86 (0.07)[b]
AUC	–0.67 (0.06)	–0.85 (0.06)[b]	–0.90 (0.06)[c]	–0.93 (0.06)[c]	–0.91 (0.06)[b]
Patient global assessment					
[max = 100], LOCF	–12.5 (2.0)	–18.7 (2.0)[a]	–21.2 (2.0)[d]	–21.6 (2.0)[d]	–22.6 (2.0)[d]
AUC	–12.7 (1.7)	–18.0 (1.7)[a]	–21.7 (1.7)[a]	–23.1 (1.7)[d]	–22.9 (1.7)[d]
Patient pain VAS					
[max = 100], LOCF	–14.4 (2.1)	–21.2 (2.1)[a]	–25.1 (2.1)[d]	–24.3 (2.1)[d]	–25.4 (2.1)[d]
AUC	–14.2 (1.8)	–20.4 (1.8)[b]	–25.6 (1.8)[d]	–26.6 (1.8)[d]	–25.6 (1.8)[d]
mHAQ [max = 3.0], LOCF	–0.24 (0.04)	–0.31 (0.04)	–0.37 (0.04)[a]	–0.38 (0.04)[b]	–0.32 (0.04)
AUC	–0.23 (0.04)	–0.31 (0.04)	–0.37 (0.04)[b]	–0.41 (0.04)[c]	–0.33 (0.04)
CRP [IU/ml], LOCF	0.19 (0.16)	0.34 (0.15)	0.08 (0.15)	0.07 (0.16)	0.50 (0.16)
ESR [mm/h], LOCF	–2.9 (1.4)	+ 2.6 (1.4)[d]	–0.0 (1.4)	+1.0 (1.4)	+ 1.7 (1.4)[b]

* Mean (SE). [a] $p < 0.05$; [b] $p < 0.025$; [c] $p < 0.005$; [d] $p < 0.0025$. LOCF: last observation carried forward. AUC: area under the curve.

definition, and none was deemed "severe" in the intensity of the event. The first case involved a 2 cm gastric ulcer in a 64-year-old female patient with a history of gastric ulcer who was taking meloxicam 7.5 mg. The investigator felt this event may have been the result of the patient's previous NSAID (indomethacin SR), but could not rule out that the study medication may also have played a part. The other 7.5 mg case involved a 74-year-old woman with a history of duodenal ulcer who experienced a moderate GI bleed and melena 42 days after initiating treatment. No endoscopy was performed to determine the site of the bleed and she was not tested for *Helicobacter pylori*. There was a very slight decrease in both hemoglobin and hematocrit from baseline levels (13.9 to 13.3 g/dl and 40.4 to 39.8%, respectively), remaining within normal range. The 15 mg case involved a 60-year-old man who experienced a moderate upper GI bleed and melena 74 days after starting treatment. No treatment was required for the events, no endoscopy was performed, and he was not tested for *H. pylori*. He was dechallenged and rechallenged with the study medication and was able to successfully complete the trial with both events resolving. The meloxicam 22.5 mg case involved a

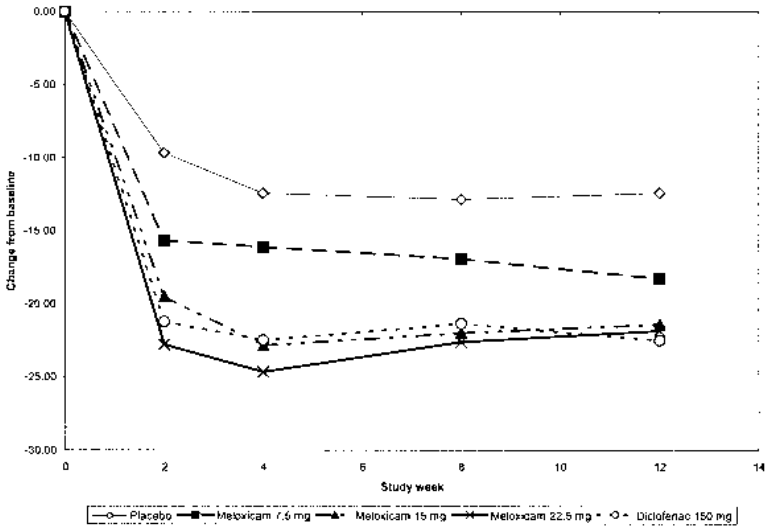

Figure 2. Patient global assessment, mean change from baseline by visit, with last observation carried forward. *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001.

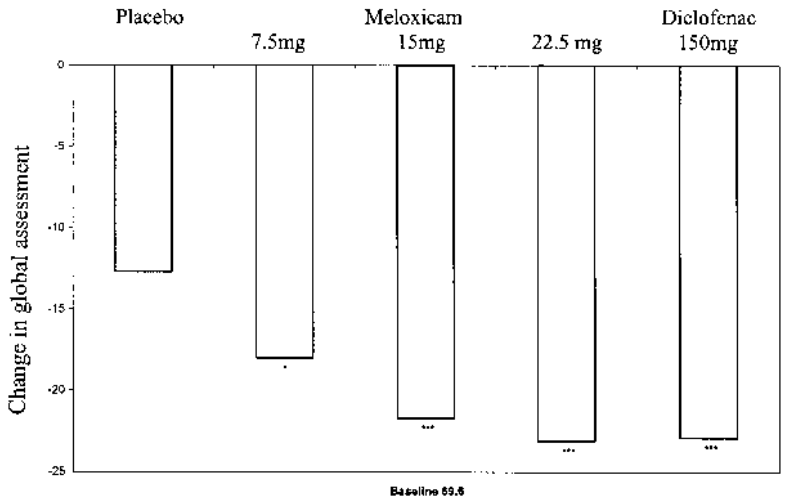

Figure 3A. Change from baseline in patient global assessment.

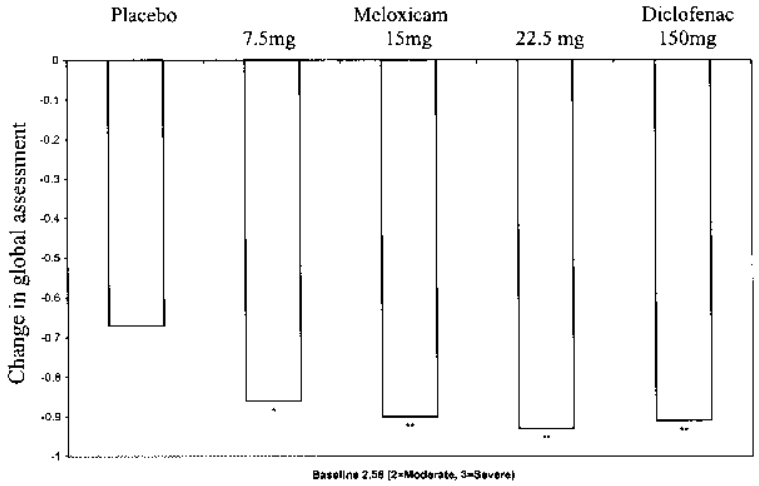

Figure 3B. Change from baseline in investigator global assessment. *p ≤ 0.05; **p ≤ 0.01.

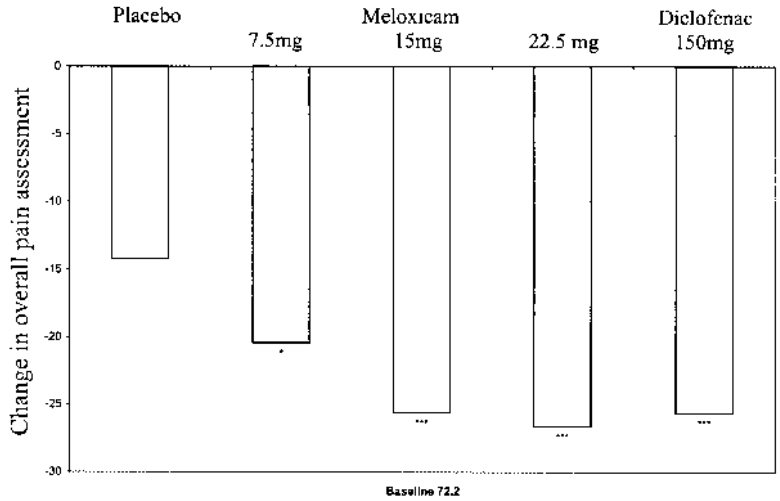

Figure 3C. Change from baseline in patient assessment of overall pain. *p ≤ 0.05; ***p ≤ 0.001.

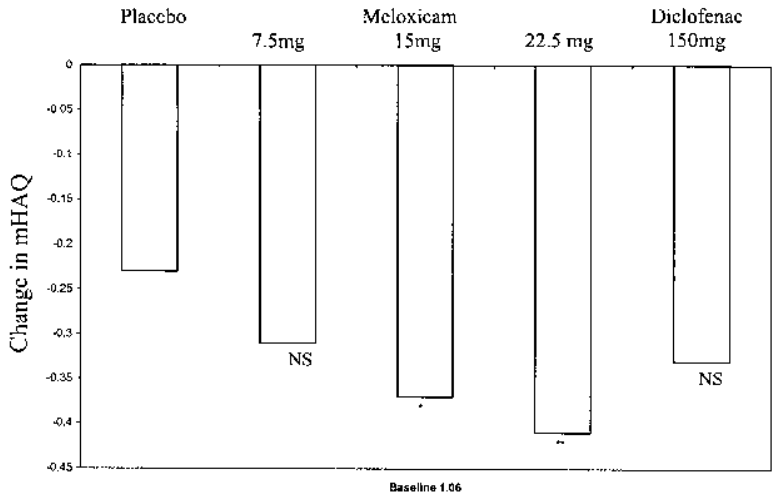

Figure 3D. Change from baseline in modified Health Assessment Questionnaire. *p ≤ 0.05; **p ≤ 0.01.

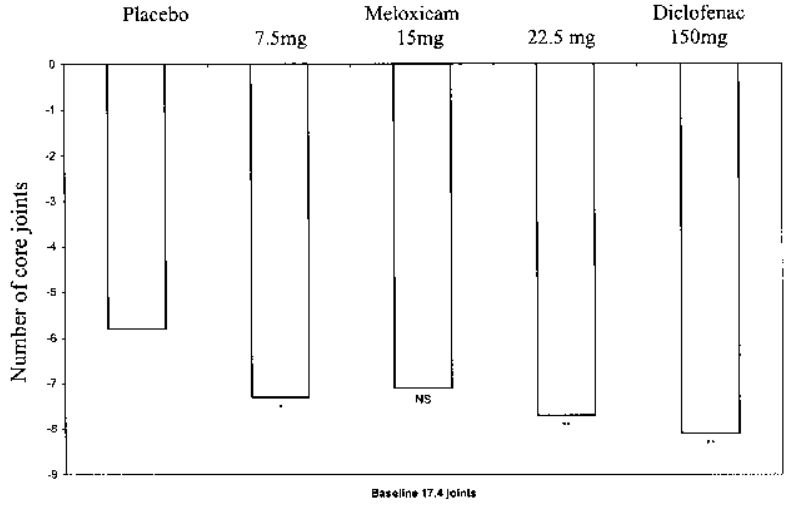

Figure 3E. Change from baseline in core tender or painful joints. *p ≤ 0.05; **p ≤ 0.01.

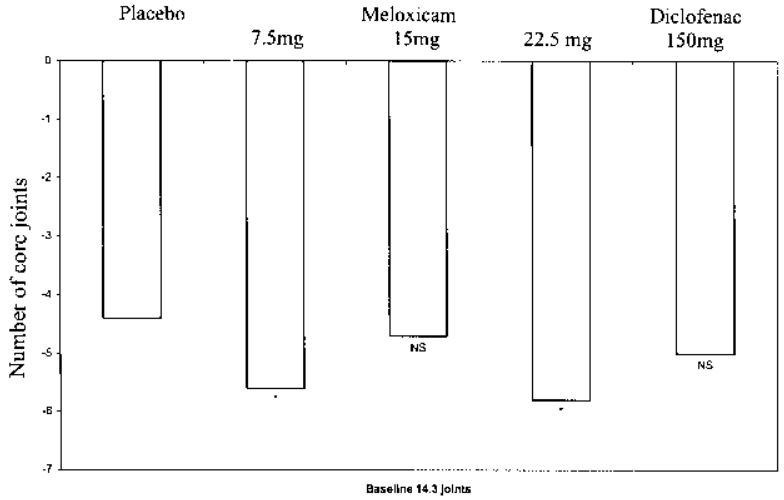

Figure 3F. Change from baseline in swollen joints. *p ≤ 0.05.

Table 5. Incidence (% of total) of adverse events (AE).

	Placebo, N = 177	Meloxicam, 7.5 mg N = 175	Meloxicam, 15 mg N = 184	Meloxicam, 22.5 mg N = 177	Diclofenac, 75 mg BID N = 181
Patients with any AE	54.8	56.0	58.2	62.1	61.9
GI AE	23.2	25.7	27.2	27.1	32.0
Upper GI PUB[a]	0	1.1	0.5	0.6	0
Patients with serious AE	2.3	2.3	0	2.8	1.7
Death	0	0	0	0	0
GI	0.6[b]	0	0	1.1[c]	0.6[d]
PUB	0	0	0	0	0
Discontinued due to AE	7.9	10.3	7.6	8.5	11.0
GI event	4.5	5.7	4.3	5.1	5.5

[a] Perforation, ulceration, or bleeding; [b] viral gastroenteritis; [c] dysphagia and diverticulitis; [d] acute appendicitis.

37-year-old woman who was diagnosed by gastroscopy with a moderate duodenal ulcer 25 days after initiating treatment after complaining of a burning sensation in her stomach after eating. She was hemoccult positive with no visible blood in the stools.

Table 6 provides the incidence of GI events occurring in ≥ 2% of patients in this 12 week study. The rate of GI adverse events was similar among all 3 doses of meloxicam (25.7, 27.2, and 27.1% for the 7.5, 15, and 22.5 mg doses, respectively). The incidence of GI hemorrhage (which includes hemorrhoidal bleeding by WHO definition) was similar among the 3 meloxicam doses (0.0 to 1.6%).

Other adverse effects not shown in tables, such as headache (9.6, 8.6, 7.6, 9.0, and 9.4%), edema (1.1, 1.1, 3.3, 2.8, and 2.2%), and hypertension (1.1, 0, 0, 0.6, and 2.2%) were not significantly different between placebo, meloxicam 7.5, 15 and 22.5 mg, and diclofenac groups, respectively.

Table 7 displays the percentage of patients with marked laboratory changes from baseline during the study. These laboratory events did not necessarily result in discontinuation. Among the marked laboratory changes, AST and ALT elevations (≥ 10 u/l) occurred more commonly among the diclofenac patients than the placebo or meloxicam patients at every dose ($p < 0.01$). Alkaline phosphatase changes (≥ 20 u/l) occurred more commonly among the diclofenac patients than the meloxicam 22.5 mg ($p < 0.05$). Serum creatinine changes (> 0.3 mg/dl) were more common for the 22.5 mg meloxicam group versus placebo ($p = 0.03$) and tended to be more common among the diclofenac treated patients versus placebo ($p < 0.06$). Statistical significance is not adjusted for multiple comparisons. No other statistical differences were found.

Between 38 and 44 patients per group were older than 65 years of age. Comparing these groups of patients to those ≤ 65 years showed no overall difference between age groups in the incidence of adverse events. However, for meloxicam 22.5 mg, the incidence of GI adverse events among those older than 65 years was 36.4% compared to 24.1% in those ≤ 65 years. For diclofenac, too, the incidence of GI adverse events in those > 65 years was 42.1%, while it was 29.4% for those ≤ 65 years. Using logistic regression on GI side effects and age as a continuous variable, no relationship was found between GI side effects and age. Although the data are suggestive, the number of patients > 65 years of age is relatively small, and it is not possible to draw clinical or

Table 6. Rate of gastrointestinal events (% of total) in ≥ 2% of treated patients.

	Placebo, N = 177	Meloxicam, 7.5 mg N = 175	Meloxicam, 15 mg N = 184	Meloxicam, 22.5 mg N = 177	Diclofenac, 75 mg BID N = 181
Patients with any GI AE	23.2	25.7	27.2	27.1	32.0
Abdominal pain	1.7	6.3	4.9	3.4	4.4
Constipation	1.7	2.3	2.2	2.8	3.9
Diarrhea	9.6	9.1	6.0	6.2	6.1
Dyspepsia	5.6	7.4	6.5	7.3	7.2
Flatulence	2.8	2.9	3.3	6.2	5.5
GI hemorrhage[a]	0.6	1.1	1.6	0	2.2
Nausea	4.0	6.9	7.6	3.4	7.7
Stomatitis	0	0.6	1.1	2.8	0.6
Vomiting	4.0	0.6	2.2	0.6	1.1

[a]Includes GI bleeding (upper and lower), rectal bleeding, and blood in stool. AE: adverse event.

Table 7. Percentage of patients with marked changes from baseline in laboratory variables.

	Placebo	Meloxicam 7.5 mg	Meloxicam 15 mg	Meloxicam 22.5 mg	Diclofenac 150 mg
Alkaline phosphatase (increased ≥ 20 u/l)	5.4	4.4	4.8	2.5[a]	9.7
Creatinine (increase ≥ 0.3 mg/dl)	3.4	6.9	3.6	9.5[b]	8.5[c]
AST (increase ≥ 10 u/l)	6.1	3.8[d]	4.2[d]	5.1[e]	15.8[f]
ALT (increase ≥ 10 u/l)	12.2	6.9[d]	8.9[d]	8.9[d]	30.9[g]
Hemoglobin (decrease by ≥ 2 g/dl)	0.7	0	1.8	1.9	1.8
Hematocrit (decrease volume by ≥ 6%)	2.0	0	1.8	1.9	2.4

[a] $p < 0.05$ vs diclofenac; [b] $p = 0.03$ vs placebo; [c] $p < 0.06$ vs placebo; [d] $p < 0.001$ vs diclofenac; [e] $p < 0.01$ vs diclofenac; [f] $p < 0.01$ vs placebo; [g] $p < 0.001$ vs placebo.

statistical conclusions as to whether the elderly using 22.5 mg meloxicam or 150 mg diclofenac may be more likely than younger patients to have GI adverse events.

Neither concomitant steroids nor concomitant DMARD caused an increase in any adverse events or GI adverse events compared to patients who did not use steroids or DMARD (data not shown).

There were no statistically significant changes in blood pressure or pulse rate between the baseline and final visit for any treatment group. Older patients showed no dose dependent trends in blood pressure or creatinine. Further, when clinically significant changes were defined as +25 mm systolic or +10 mm diastolic or +0.3 mg/dl creatinine and –20% creatinine clearance, no differences were found comparing patients < 65 years old with those older than 65.

DISCUSSION

Meloxicam 7.5, 15, and 22.5 mg daily are effective for treating rheumatoid arthritis. The 7.5 and 22.5 mg meloxicam doses were significantly better than placebo for all 5 primary endpoints, while meloxicam 15 mg and diclofenac 150 mg (the positive control) did not separate from placebo for swollen joint counts and tender joint count (for 15 mg meloxicam.) The lack of responsiveness of the positive control with respect to the swollen joint count validated the need to use a positive control in studies of RA, as it helped to explain the lack of the expected response among the meloxicam 15 mg per day group for swollen joint counts.

Diclofenac 150 mg daily was more effective than placebo for all measures except swollen joint count (see above). Diclofenac was almost as effective as 15 mg meloxicam and variably more or less effective than 22.5 mg meloxicam (no statistically significant differences — see Figures 1–3 and most tables). A small advantage for diclofenac with respect to fewer dropouts for lack of effect was offset by more dropouts for adverse events (not statistically or clinically significant, in all cases).

While both the modified intent-to-treat analysis and the AUC analysis were the primary measures in this trial, the average on-treatment measurement (an area under the curve approach) really should be the sole primary measure used, as it examines the effect of treatment over time, rather than using single point measurements. In most cases, this approach was as sensitive or more sensitive than the modified intent-to-treat (ITT) approach.

The AUC of the ACR20 response criteria (Figure 1) indicated that diclofenac, meloxicam 15 mg, and meloxicam 22.5 mg were all effective and statistically superior to placebo, despite the failure of some of the individual variables to reach statistical significance among the diclofenac and meloxicam 15 mg groups. A dose response was seen for the AUC analysis for the patient global assessment, the patient pain VAS, and the mHAQ (Table 4 and Figure 2 — AUC analysis of the data shown). A dose response was seen for the ITT analysis for tender and swollen joint counts only at 4 weeks (data not shown). Dose response was not observed in those assessments performed by the investigator rather than the patient. The lack of a dose response for the swollen and tender joint counts can, in part, be understood as related to the failure of the positive control (diclofenac) to be sensitive with respect to the swollen joint counts. An additional potential cause for the lack of dose response at endpoint using the ITT analysis can be attributed to the flare requirement. For one thing, the flare as defined in this study did not require that the swollen and tender joint counts "flared," so some patients flared without these measures changing sufficiently. This, in turn, meant that those patients could not improve, thus decreasing the sensitivity of these measures in response to the test medication, accounting in part for the lack of a dose response with respect to the tender and swollen joint counts. Additionally, there might be a more rapid response with the higher drug dose early in the study after a flare, but differences between doses would disappear if, eventually, the 7.5 mg dose resulted in a response. This would decrease the difference between doses at last observation.

A number of studies have shown meloxicam to be effective in osteoarthritis, RA, and ankylosing spondylitis (AS)[1–21], but some of them were of limited duration (3 weeks for controlled trials) or limited dose (7.5 mg for 6 months), or lacked a placebo control. This study was done

over a broader dose range and sufficient duration to more fully test the higher dose, efficacy, and longterm safety of meloxicam in patients with RA.

Although the overall incidence rate of adverse events was slightly higher with the meloxicam 22.5 mg dose (62.1%) compared with the 7.5 and 15 mg meloxicam doses (56.0 and 58.2%), respectively, this was not statistically significant. In fact, the rates of treatment-emergent adverse events, serious adverse events, and withdrawal from the study due to an adverse event were not statistically different for meloxicam (at all doses), diclofenac, and placebo (Table 5). No patient deaths were reported during the trial.

The rate of GI adverse events was similar among all 3 doses of meloxicam in this study of 12 weeks. There was no GI perforation in any patient. In addition, the incidence of ulcerations or bleeds was similar among the 3 meloxicam doses. This observation is consistent with COX-1 dependent functions, as shown by meloxicam's lack of effect on platelet aggregation or bleeding time, both COX-1 dependent measures, in healthy volunteers over 8 days with doses up to 30 mg per day[9]. However, these results may also reflect that the number of patients in this study may not have been sufficient to discern differences in such rare events. As with all NSAID, the lowest possible effective dose should be sought in order to decrease risks of side effects, regardless of the drug's COX-1 sparing effect.

The only significant pattern of abnormal laboratory tests was elevated liver enzymes observed in the diclofenac group, a side effect well known to this drug. The "marked" changes in creatinine seen in this study represented only the percentage of patients with a predefined ≥ 0.3 mg/dl change in creatinine; although statistically significant for meloxicam 22.5 mg and nearly so for diclofenac, this change was not clinically important (Table 7).

In summary, all 3 doses of meloxicam were generally effective for the treatment of RA, and there was a dose-response relationship from 7.5 mg to 15 mg to 22.5 mg, using AUC analyses, during this 12 week study. No statistically significant differences occurred comparing the efficacy of meloxicam and diclofenac.

The safety of meloxicam 22.5 mg was supported by this 12 week study. This dose of meloxicam was generally no more toxic than the doses of 7.5 and 15 mg meloxicam daily nor more toxic than diclofenac. The only difference in side effect profiles among these medications was the increase in the incidence of abnormal liver function tests in the diclofenac group and a small increase in creatinine in the 22.5 mg meloxicam and diclofenac patients.

ACKNOWLEDGMENT

Meloxicam RA Investigators: Micha Abeles, MD, Farmington, CT; John Abruzzo, MD, Philadelphia, PA; Raymond Adelizzi, DO, Stratford, NJ; Roy Altman, MD, Miami, FL; Andrew Baldassare, MD, St. Louis, MO; Richard Bath, MD, Cincinnati, OH; Scott Baumgartner, MD, Spokane, WA; Charles Birbara, MD, Worcester, MA; Bruce Blatt, MD, Philadelphia, PA; Joel Block, MD, Chicago, IL; Robert Boyd, MD, Columbia, SC; Robert Brewer, MD, Little Rock, AR; Stephen Burnstein, DO, Cherry Hill, NJ; Jacques Caldwell, MD, Gainesville, FL; Steve Carsons, MD, Mineola, NY; Walter Chase, MD, Austin, TX; Allen Chodock, MD, Mamaroneck, NY; Chris Codding, MD, Oklahoma City, OK; Julian Colton, MD, St. Petersburg, FL; Barry Cook, MD, Maitland, FL; John Cush, MD, Dallas, TX; Paul Dalgin, MD, Stamford, CT; Frederick Dietz, MD, Rockford, IL; Mary Dooley, MD, Chapel Hill, NC; Roy Fleischmann, MD, Dallas, TX; C. Michael Franklin, MD, Willow Grove, PA; Daniel Furst, MD, Seattle, WA; Larry Gilderman, DO, Pembroke Pines, FL; Edward Gillie, MD, Fort Myers, FL; Oscar Gluck, MD, Phoenix, AZ; Allan Goldman, MD, Milwaukee, WI; Gary Gordon, MD, Wynnewood, PA; Richard Gordon, MD, Mercerville, NJ; Maria Greenwald, MD, Rancho Mirage, CA; Brian Grimmett, MD, Cherry Hill, NJ; Maria Gutierrez, MD, Boynton Beach, FL; Edward Harris, MD, Whittier, CA; Scott Heatley, MD, PhD, Redwood, CA; Eric Hurd, MD, Dallas, TX; Richard Hymowitz, MD, Mt. Laurel, NJ; Christopher Jackson, MD, Salt Lake City, UT; Jeffery Jundt, MD, Temple, TX; Jeffery Kaine, MD, Sarasota, FL; Kenneth Kalunian, MD, Los Angeles, CA; Arthur Kavanaugh, MD, Dallas, TX; Alastair Kennedy, MD, Melbourne, FL; Brian Keroack, MD, Portland, ME; Daniel Kirby, MD, Melbourne, FL; Alan Kivitz, MD, Altoona, PA; Karen Kolba, MD, Santa Maria, CA; Sicy Lee, MD, New York, NY; Theodore Lefton, MD, Winter Park, FL; Jeffery Lisse, MD, Galveston, TX; Charles Ludivico, MD, Bethlehem, PA; James McKay, DO, Tulsa, OK; George McLaughlin, MD, Norristown, PA; Kenneth Miller, MD, Danbury, CT; Barry Miskin, MD, West Palm Beach, FL; Brent Mohr, MD, South Bend, IN; Larry Moreland, MD, Birmingham, AL; Carter Multz, MD, San Jose, CA; John Murray, MD; Margarita Nunez, MD, St. Petersburg, FL; Thomas O'Barr, MD, Marietta, GA; Howard Offenberg, MD, Daytona Beach, FL; Malin Prupas, MD, Reno, NV; Sanford Roth, MD, Phoenix, AZ; Eric Ruderman, MD, Chicago, IL; Joel Rutstein, MD, San Antonio, TX; Constatine Saadeh, MD, Amarillo, TX; Thomas Schnitzer, MD, PhD, Chicago, IL; Eric Sheldon, MD, Miami, FL; Yvonne Sherrer, MD, Fort Lauderdale, FL; David Silver, MD, Beverly Hills, CA; Joel Silverfield, MD, Tampa, FL; Kenneth Solinsky, MD, Babylon, NY; Roland Staud, MD, Gainesville, FL; Michael Strachan, MD, Richmond, VA; Nina Stuccio-White, MD, Marlton, NJ; Louise Taber, MD, Phoenix, AZ; Martin Throne, MD, Atlanta, GA; Elizabeth Tindall, MD, Portland, OR; Frank Vasey, MD, Tampa, FL; Daniel Wallace, MD, Los Angeles, CA; Fred Wolfe, MD, Wichita, KS; David Yocum, MD, Tucson, AZ; Muhammad Yunus, MD, Peoria, IL; Steven Zeig, MD, Ft. Lauderdale, FL, USA.

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