Hydroxychloroquine and Risk of Diabetes in Patients With Rheumatoid Arthritis

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TYPE 2 DIABETES MELLITUS AFFECTS nearly 8% of US adults, and its prevalence has been increasing.1,2 Diabetes is a major cause of morbidity and mortality, with costly sequelae that include atherosclerotic disease, renal failure, and blindness. Given the importance of diabetes as a national health problem, efforts to identify treatments that can prevent this disorder have gained priority. Recent studies suggest that lifestyle modifications and medications such as ramipril, rosiglitazone, and metformin can postpone the development of diabetes mellitus.3-7 Antimalarials such as hydroxychloroquine, a long-standing safe and inexpensive treatment for autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, theoretically may improve glucose tolerance and prevent diabetes mellitus. In vitro and animal studies indicate that antimalarials improve insulin secretion and peripheral insulin sensitivity.8-11 Hypoglycemia is a rare but well recognized adverse effect of treatment with antimalarials.12 Antimalarials also have been shown to lower glycated hemoglobin levels in patients with type 2 diabetes who have suboptimal glucose control.13 In addition, the prevalence of diabetes in patients with rheumatoid arthritis is similar to that of other patients, even though patients with rheumatoid arthritis are more sedentary and often treated with corticosteroids that induce weight gain.15,16

Context Hydroxychloroquine, a commonly used antirheumatic medication, has hypoglycemic effects and may reduce the risk of diabetes mellitus.

Objective To determine the association between hydroxychloroquine use and the incidence of self-reported diabetes in a cohort of patients with rheumatoid arthritis.

Design, Setting, and Patients A prospective, multicenter observational study of 4905 adults with rheumatoid arthritis (1808 had taken hydroxychloroquine and 3097 had never taken hydroxychloroquine) and no diagnosis or treatment for diabetes in outpatient university-based and community-based rheumatology practices with 21.5 years of follow-up (January 1983 through July 2004).

Main Outcome Measures Diabetes by self-report of diagnosis or hypoglycemic medication use.

Results During the observation period, incident diabetes was reported by 54 patients who had taken hydroxychloroquine and by 171 patients who had never taken hydroxychloroquine, with incidence rates of 5.2 per 1000 patient-years of observation compared with 8.9 per 1000 patient-years of observation, respectively (P < .001). In time-varying multivariable analysis with adjustments for possible confounding factors, the hazard ratio for incident diabetes among patients who had taken hydroxychloroquine was 0.62 (95% confidence interval, 0.42-0.92) compared with those who had not taken hydroxychloroquine. In Poisson regression, the risk of incident diabetes was significantly reduced with increased duration of hydroxychloroquine use (P < .001 for trend); among those taking hydroxychloroquine for more than 4 years (n = 384), the adjusted relative risk of developing diabetes was 0.23 (95% confidence interval, 0.11-0.50; P < .001), compared with those who had never taken hydroxychloroquine.

Conclusion Among patients with rheumatoid arthritis, use of hydroxychloroquine is associated with a reduced risk of diabetes.

METHODS Participants Men and women with a diagnosis of rheumatoid arthritis established at age 16 years or older were eligible for enrollment in the Arthritis, Rheumatism, and Aging Medical Information Sys-

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tems (ARAMIS). Patients were recruited for this longitudinal observational study from 7 outpatient rheumatology practice sites across North America beginning in 1976 and ongoing through 2004. Follow-up continued at 6-month intervals into 2006. All participants fulfilled standard classification criteria for rheumatoid arthritis at enrollment,17 and those with other rheumatic diseases, except secondary Sjögren syndrome, were excluded. All sites obtained institutional review board approval prior to recruitment, and all participants provided written informed consent. Patients completed a baseline questionnaire at entry reporting health history, including any concurrent or previously diagnosed comorbid conditions such as diabetes, as well as arthritis history, including prior disease-modifying antirheumatic drug use.

For the purposes of this study, the earliest observation time (study entry) was January 1983 when data were first collected on diabetes. Of the 5743 patients with rheumatoid arthritis who enrolled in ARAMIS during the observation period, 2 subsets of patients were not included in this study. Patients were excluded from the analysis if they reported a diagnosis of diabetes or were taking hypoglycemic medications at study entry (n=211). The additional 627 patients who completed only 1 Health Assessment Questionnaire (HAQ) also were excluded from analysis because change in diabetes status could not be ascertained. Follow-up continued for each participant until diabetes onset, or censoring due to death, study withdrawal, or study end date (July 2004), whichever came first.

Variables
Health status updates were obtained by self-report in patients with rheumatoid arthritis using the HAQ. These questionnaires were mailed and returned semi-annually every January and July, with each HAQ phase assessing health status over the preceding 6 months. Entry HAQs began in 1983 when diabetes medications and diagnosis were first ascertained, and continued through 2004.

At each phase, participants reported known risk factors for diabetes and other characteristics of interest, including comorbid conditions (prevalent and incident), height, weight, medication use, and functional status summarized in the HAQ disability index (HAQ-DI). The well-validated HAQ-DI is based on responses to 20 questions about degree of difficulty (none=0, some difficulty=1, much difficulty=2, and unable to do=3) in completing activities within 8 functional categories (dressing/grooming, arising, eating, walking, personal hygiene, reaching, gripping, and doing errands and chores). The HAQ-DI score, ranging from 0 to 3 units, is an average of the scores for these 8 domains, with a score of 0 reflecting no disability and a score of 3 indicating severe disability.18,19

Body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was determined for each phase along with a maximum value. Duration of rheumatoid arthritis was ascertained at study entry. Use of hydroxychloroquine, prednisone, and methotrexate was evaluated as ever or never use, and the percentage of time taking the drug during the observation period was calculated as the number of phases taking the drug divided by the total number of phases under observation. Demographic characteristics, including age at entry, sex, race (by self-report), years of education, and practice site also were examined in conjunction with diabetes risk. Because standard rheumatoid arthritis drug therapies as well as the thresholds for diabetes diagnosis have evolved over time, year of study entry was included as a variable of interest.

Outcome
The primary outcome was incident diabetes mellitus defined by newly reported disease or new use of hypoglycemic medication(s). Diagnosis date for diabetes was assigned at the HAQ phase (6-month) midpoint. To verify newly reported diabetes without pharmacological treatment, use of hypoglycemic medications reported in subsequent phases was determined to confirm diagnosis.

Statistical Analysis
Patients with rheumatoid arthritis without diabetes were classified according to ever or never use of hydroxychloroquine during the observation period. Characteristics of the 2 groups were compared using χ² tests for categorical data and t tests for continuous variables. A Kaplan-Meier survival curve demonstrating probability of developing diabetes was constructed according to hydroxychloroquine exposure status (ever or never use). Additional Kaplan-Meier curves for diabetes were generated by duration of hydroxychloroquine use and compared with those with never use over the same periods. This approach allowed for comparison of diabetes risk by exposure, adjusting for different observation time among the groups.

To examine the risk (or hazard) of developing diabetes (adjusted for the possible confounding effects of other factors on the outcome), multivariable regression models were constructed in 2 ways. First, time-varying Cox proportional hazards regression models were examined using all of the 6-month follow-up data, thus allowing medication use and covariates to change over time. This approach also accounted for changes in standard drug therapy for rheumatoid arthritis as well as variations in the threshold for diagnosing and treating diabetes during the observation period. For example, in the Cox time-varying regression, if individuals were not taking hydroxychloroquine during certain phases of the study (possibly at study entry or if they stopped taking hydroxychloroquine before censoring or the end of the observation period), they would contribute to the estimates for patients in the never use category during those periods. Thus, the time-varying model takes all observations until censoring or dropout into account, even if a participant was not taking hydroxychloroquine at study entry or if a person stopped taking hydroxychloroquine later on.

To assess cumulative dose-related effects of hydroxychloroquine, an ordered categorical variable was established based on approximate quartiles.
of duration of use in the patients taking hydroxychloroquine. A Poisson regression model was then constructed to test the relationship between duration of drug exposure and risk of incident diabetes, providing adjusted relative risks for each category of hydroxychloroquine use compared with patients with never use. In contrast to the time-varying regression model, the observation time in the Poisson analysis for patients with hydroxychloroquine ever use began at initiation of hydroxychloroquine. Incident diabetes rates were calculated for each of the 4 groups for duration of hydroxychloroquine use and compared with patients with never use.

Results of the Poisson analysis examining duration of hydroxychloroquine use were verified using a standard Cox proportional hazards model using the same covariates and observation times.20

In both the Cox time-varying and Poisson models, potential confounding factors were addressed by adjustment and included use of prednisone and methotrexate (yes or no or percentage age time taking drug for the Poisson model), BMI, age, sex, education, race, year of entry, rheumatoid arthritis duration at entry, and HAQ-DI. Because data were collected in multiple centers, study site was used for stratification in all multivariable analyses to account for unmeasured site-related variations that may have affected outcomes.

Interactions between potentially related variables (hydroxychloroquine and prednisone, prednisone and methotrexate, hydroxychloroquine and methotrexate, prednisone and HAQ-DI, prednisone and BMI, and BMI and HAQ-DI) also were tested in the Cox time-varying model. For both regression analyses, missing values of independent variables were replaced with group means.

Statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Prevalent cases of diabetes (n = 211) who were excluded from the analysis were more likely than the included patients to be male, older at entry, nonwhite, less educated, have a higher entry HAQ-DI score, and higher maximum BMI during the observation period (P < .001 for each). Most of these factors also were associated with diabetes incidence in the follow-up study. The 627 patients excluded due to lack of longitudinal data (ie, who completed only 1 HAQ) also were more likely to be male, nonwhite, less educated (P < .001 for each), to have a higher entry HAQ-DI score (P < .01), and a lower maximum BMI (P < .05).

Of the remaining 4905 patients included in the study, 1808 (37%) reported hydroxychloroquine use at some time during the observation period. Average HAQ response rates were 89% for never users and 91% for ever users.

Patterns of Hydroxychloroquine Use

On average, hydroxychloroquine dosing was 340 mg/d over the course of follow-up; 64% of patients took 400 mg/d. Of the 1808 patients with hydroxychloroquine ever use, 1035 (57%) were taking hydroxychloroquine at study entry. The remaining 773 patients (43%) in the ever-use group started taking hydroxychloroquine during the observation period (ie, after study entry). On average, patients with hydroxychloroquine ever use were taking the drug 55% of the observation time. Discontinuation of hydroxychloroquine for at least 1 year before censoring or the end of the observation period occurred in 32% of all patients with ever use. Hydroxychloroquine was taken for an average of 3.1 years; median hydroxy-
Incidence per 1000 person-years 8.9 5.2
Years until diabetes diagnosis, mean (SD) 4.2 (4.4) 4.8 (4.6) .35
Years of observation, mean (SD) 6.2 (5.4) 5.7 (4.7)
No. of incident cases of diabetes 171 54
Total person-years of observation 19,313 10,364

Incident diagnoses of diabetes were re-
ported by 54 patients with hy-
droxychloroquine ever use compared with those with never use at each phase (TABLE 3). This finding per-
sisted with the addition to the models of demographic characteristics, known risk factors for diabetes, and rheumatoid arthritis–related covariates (hazard ratio, 0.62; 95% confidence interval [CI], 0.42-
0.92). None of the interaction terms con-
sidered, including all interactions be-
 tween hydroxychloroquine, metho-
trexate, and prednison, were signifi-
cantly associated with the outcome and did not alter the observed results regard-
ing hydroxychloroquine use.

Incident Diabetes Rates and Hydroxychloroquine
Ever Use vs Never Use
Incident diagnoses of diabetes were re-
ported by 54 patients with ever use of hy-
droxychloroquine and 171 patients with
never use (TABLE 2). Of those patients re-
porting a new diagnosis of diabetes but
not taking hypoglycemic medication, 70% of patients with never use of hy-
droxychloroquine and 48% of patients with hydroxychloroquine ever use re-
ported use of diabetes drug(s) during subsequent follow-up.

On average, patients with hydroxy-
chloroquine ever use were observed for
5.7 years until developing diabetes or
censoring by drop out, study conclu-
sion, or death compared with 6.2 years
for patients with never use. Patients
with hydroxychloroquine ever use de-
v eloped diabetes after 4.8 years of ob-
ervation on average compared with 4.2
years in the patients with never use; this
difference was not statistically signifi-
cant (P = .35). Incidence rates for dia-
betes were 8.9 per 1000 patient-years
of observation for patients with never use vs 5.2 per 1000 patient-years of ob-
ervation for patients with hydroxy-
chloroquine ever use (P < .001). Di-
betes incidence rates also varied signifi-
cantly across centers (P = .006).

The difference in probability of de-
v eloping diabetes in those with hydroxy-
chloroquine ever use compared with those
with never use was statistically significant
over time (P > .001), with those with hy-
droxychloroquine ever use being less
likely to develop diabetes throughout the
21.5-year follow-up period (FIGURE).

Hydroxychloroquine Use
and Diabetes Risk
Results of the Cox time-varying multi-
variable regression showed a signifi-
cant reduction in risk of diabetes for pa-
tients with hydroxychloroquine use
compared with those with never use at
each phase (TABLE 3). This finding per-
sisted with the addition to the models of
demographic characteristics, known risk
factors for diabetes, and rheumatoid ar-
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Hydroxychloroquine Duration
and Diabetes Risk
In Poisson regression with adjustment for
possible confounding factors, the rela-
tive risk of developing diabetes progres-
sively declined with increasing time tak-
ing hydroxychloroquine (P < .001 for
trend; TABLE 4). Patients who took hy-
droxychloroquine for more than 4 years
had a significantly lower risk of dia-
betes compared with those who had never
taken hydroxychloroquine (relative risk,
0.23; 95% CI, 0.11-0.50). In a Cox pro-
portional hazards analysis as a compari-
sion, the strength of the association of re-
duced risk of diabetes also increased with
duration of hydroxychloroquine expo-
sure; in those taking hydroxychloro-
quine for more than 4 years (n = 384), the
hazard ratio for developing diabetes was
0.22 (95% CI, 0.10-0.48; P < .001).

The observation time in patients with
never use was similar to the observation
time in all duration categories of hydroxy-
chloroquine use, except for more than 4
years of use, in which the observation time
was longer on average. Thus, it is possible
that the effect observed in the Poisson
regression for the longest duration of hy-
droxychloroquine use was an artifact of
this difference. To address this issue,
Kaplan-Meier curves based on duration
of hydroxychloroquine use were com-
pared with patients with never use over the
same observation times. Results com-
paring curves in patients with hydroxy-
chloroquine use with those with never use
showed a progressive reduction in in-
cident diabetes risk with greater duration
of hydroxychloroquine use (≤1 year, P = .52; > 1 to 2 years, P = .29; > 2 to 4
years, P = .08; and > 4 years, P < .001).
The comparison of patients who took hy-
droxychloroquine for more than 4 years
with those with never use showed signifi-
cantly lower probability of diabetes over
time in those using hydroxychloroquine
more than 4 years (Figure). Risk reduc-
tion among those with hydroxychloro-
quine use for more than 4 years ranged from 0.06 to 0.47 at specific time points
during the observation period.

COMMENT
We report herein the first evidence, to
our knowledge, suggesting that use of hy-
droxychloroquine is associated with a re-
duced risk of developing diabetes in pa-
tients with rheumatoid arthritis. This
reduction in diabetes risk persisted af-
after adjusting for diabetes risk factors and
other covariates such as BMI, func-
tional status, and corticosteroid use.
Moreover, risk reduction increased with
duration of hydroxychloroquine expo-
sure, supporting a biological action of this
drug on glucose metabolism. These re-
results show a reduction in diabetes risk of
up to 77% for patients taking hydroxy-
chloroquine for more than 4 years, a find-
ing that is comparable or superior to that
of other drugs studied in clinical trials:
rosiglitazone, combination hormone therapy, estrogen only, metformin, acarbose, and ramipril. Antimalarial agents have been reported to cause both symptomatic and asymptomatic hypoglycemia. Antimalarial agents have also been explored as an adjunct to insulin and oral hypoglycemic agents for poorly controlled type 2 diabetes. Patients with non–insulin-dependent diabetes with suboptimal disease control during an intensive outpatient intervention showed an absolute reduction in glycated hemoglobin A1c level of 3.3% when treated for 6 months with hydroxychloroquine dosed at 200 mg 3 times per day. In a trial of patients with type 2 diabetes who had poor glycemic control despite taking maximal doses of sulfonylureas, the addition of hydroxychloroquine improved glycemic control, with greatest benefit in those with baseline hemoglobin A1c levels lower than 13.5%. Petri reported a significantly lower mean glucose level among participants in the Baltimore Lupus Cohort while they were taking hydroxychloroquine, as well as a protective effect of hydroxychloroquine on abnormal glucose tolerance testing.

The present study reports 2 unique findings. First, hydroxychloroquine use was associated with reduction in risk of incident diabetes. This result is not surprising based on the changes in glucose metabolism described in patients with type 2 diabetes and in patients with lupus. Moreover, this association with reduced risk of diabetes was related to duration of hydroxychloroquine exposure. Second, those who had taken hydroxychloroquine compared with those who had never taken the drug who had prevalent disease or developed diabetes during the follow-up observation period were less likely to report use of hypoglycemic medication. Hydroxychloroquine use may modify the clinical manifestations of hyperglycemia, or it may attenuate hyperglycemia and reduce the need for hypoglycemic medications once this diagnosis is established.

Based on the age of the participants in our study and the rates of diabetes medication use after self-reported diabetes diagnosis, we speculate that the majority of patients with incident diabetes most likely have type 2 diabetes mellitus. However, the anti-inflammatory effects of rheumatoid arthritis medications may attenuate hyperglycemia and reduce the need for hypoglycemic medications once this diagnosis is established.

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tenuate both type 1 and type 2 diabetes onset, given the autoimmune nature of type 1 diabetes and the role of chronic inflammation in insulin resistance that characterizes type 2 diabetes. In addition, because those with hydroxychloroquine use also were more likely to be taking methotrexate and prednisone, they probably were more likely to have regular encounters with medical professionals and have more frequent laboratory testing, whereby asymptomatic hyperglycemia might be detected.

Substantial differences were noted in the characteristics of the rheumatoid arthritis groups that reported ever use of hydroxychloroquine vs never use during the observation period. Those with never use of hydroxychloroquine were older, had longer rheumatoid arthritis disease duration, were more disabled as indicated by their HAQ scores, and thus may have been considered less viable candidates for immunosuppressive therapy than those with hydroxychloroquine ever use, as suggested by the lower rates of use of prednisone and methotrexate in this group.

Differences between groups in year of study entry are consistent with these findings because those with never use were observed earlier when less aggressive treatment strategies were used, and fewer treatment options were available. Such factors may have resulted in less frequent “routine” encounters with health care professionals and less frequent laboratory testing. A higher likelihood of being diagnosed with diabetes or receiving hypoglycemic therapy would be expected with closer health care surveillance, which occurs during monitoring for medication toxic effects and dose adjustments. Although such an assertion bias could have resulted in higher rates of diabetes in those with hydroxychloroquine ever use, this supposition was not supported by the data. Differences in medical surveillance could have resulted in underestimation of diabetes rates in those with never use and risk reduction in the hydroxychloroquine ever use group. Despite the differences between the 2 study groups, the overall characteristics of this study cohort reflect those of a typical outpatient practice of patients with rheumatoid arthritis in North America.

We used a time-varying regression model to assess hydroxychloroquine effects on risk of incident diabetes not only because standard rheumatoid arthritis treatment has evolved over time but also because the threshold for rendering a diagnosis of diabetes has been modified. Use of the time-varying model enabled us to adjust for variations in these factors and for changes in possible confounders at each 6-month interval over the 21.5 years of observation, and allowed a more accurate reflection of total rheumatoid arthritis treatment over time.

Antimalarials have been an appealing treatment option in rheumatic diseases because decades of experience in taking these drugs provided a breadth of knowledge about their potential adverse effects. While the disease-modifying properties are not as dramatic as other current treatment options for rheumatoid arthritis, the toxicity profile of hydroxychloroquine is superior to other traditional disease-modifying antirheumatic drugs and biological therapies, leading to its use in mild to moderate disease and in combination therapy for rheumatoid arthritis. Unlike these other agents, the antimalarials confer no increased risk of infection or malignancy, and the risk of adverse effects on internal organs is minimal when dosed according to body weight. Furthermore, the drug is well tolerated, and toxicity laboratory monitoring is not routinely indicated. While retinal toxicity is rare, most physicians recommend yearly or semi-annual ophthalmologic examinations.

The mechanisms of hypoglycemia with hydroxychloroquine are inferred from studies of chloroquine, a structurally similar antimalarial with similar indications but less widespread use due to a greater risk of retinal toxicity. Chloroquine has been shown to alter insulin metabolism in humans by both increasing insulin secretion and inhibiting its clearance, leading to hypoglycemia. Animal data have shown increased insulin levels in hydroxychloroquine-treated diabetic rats. Hydroxychloroquine also has been shown to inhibit insulin metabolism in rat liver cells.

While our study showed a reduction in diabetes incidence specifically in a rheumatoid arthritis cohort taking hydroxychloroquine, these findings also may be expected to occur in patients without rheumatoid arthritis. The beneficial changes in glucose metabolism and insulin sensitivity reported among patients with lupus, patients with type 2 diabetes, and in animal models suggest that these effects are not specific to rheumatoid arthritis. The fact that antimalarials favorably affect dyslipidemia in patients with rheumatoid arthritis and lupus, independent of steroid use, suggests the possibility that hydroxychloroquine may have a role in reducing key risk factors for atherosclerosis, namely type 2 diabetes and dyslipidemia, in the general population.

Certain strengths and limitations of this study warrant mention. All data, while collected prospectively, were obtained by self-report with the limitations inherent in this approach. However, follow-up in those patients classified with incident diabetes without concomitant hypoglycemic therapy showed that hypoglycemic therapy was more often initiated in those with hydroxychloroquine never use than in those with ever use. These findings suggest that differences in self-report of diabetes by hydroxychloroquine status do not explain the observed results. Based on the age of the participants, we suspect that the majority of incident cases developed type 2 diabetes, although we cannot know this with certainty. The proportion of patients with incident diabetes not taking hypoglycemic agents during subsequent observation further substantiates this. Information on rheumatoid arthritis medications taken prior to study entry was not consistently available for all patients; thus, some patients with prior hydroxychloroquine use were classified as patients with never use; however, such misclassification would have diluted associations with hydroxychloroquine use.
While the racial homogeneity of our cohort may limit the generalizability of these findings, it is noteworthy that despite the small numbers those excluded from the present analysis due to prevalent diabetes were more likely to be non-white. Moreover, nonwhite race also was a significant risk factor for developing diabetes in our cohort. The use of this unique longitudinal database with prospectively collected data also allowed for detailed adjustment of covariates that may affect diabetes risk. Finally, these analyses accounted for variations in aspects of rheumatoid arthritis treatment as well as diabetes diagnosis and management during a long observation period, thereby minimizing the influence of these factors on our findings.

In conclusion, this study demonstrates a significant, dose-related association between hydroxychloroquine therapy and reduced risk of diabetes in adults with rheumatoid arthritis. Antimalarial drugs may have a role in treating rheumatoid arthritis not only to suppress synovitis but also to reduce the likelihood of developing glucose intolerance and dyslipidemia. As quality of life and life expectancy improve for patients with rheumatoid arthritis, and health care costs escalate, the use of inexpensive, safe therapies that have multiple beneficial effects is attractive. Further prospective studies are needed to determine whether this treatment option should be considered a standard component of rheumatoid arthritis combination therapy in the future, and to evaluate the potential role of hydroxychloroquine as a preventative agent for diabetes among high-risk individuals in the general population.

**Author Contributions:** Dr Wasko had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wasko, Hubert, Elliott, Fries, Ward. Acquisition of data: Wasko, Hubert, Lingala, Luggen, Fries. Analysis and interpretation of data: Wasko, Hubert, Lingala, Fries, Ward. Statistical analysis: Hubert, Lingala, Ward. Obtained funding: Wasko, Fries, Ward. Administrative, technical, or material support: Elliott, Fries, Ward. Study supervision: Wasko, Hubert, Fries, Ward. Financial Disclosures: Dr Wasko reported being a consultant to Centocor in cardiovascular outcomes in ongoing rheumatoid arthritis clinical trials and has been a coinvestigator in a Histogenics sponsored study of thrombomimetic markers in rheumatoid arthritis and osteoarthritis. Dr Wasko reported receiving contractual reimbursement as site principal investigator for an Aventis-sponsored clinical trial of infliximab in ankylosing spondylitis, ending in November 2002. Dr Wasko reported receiving contractual reimbursement as site principal investigator for rheumatoid arthritis clinical trials sponsored by Centocor, Roche, Human Genome Sciences, and Novartis. No other authors reported disclosures.

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**REFERENCES**