
Early rheumatoid arthritis in African-Americans: The CLEAR Registry

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ABSTRACT

African-Americans have been under-represented in genetic studies of rheumatoid arthritis (RA) susceptibility and severity. Genetic and non-genetic factors influencing the radiographic severity of RA and its response to treatment are poorly understood, particularly in African-Americans. The Consortium for the Longitudinal Evaluation of African-Americans with early RA (CLEAR) Registry, a collaborative effort among four institutions in the southeast USA, will hopefully provide a useful resource to study these issues.

Introduction

The cause of rheumatoid arthritis (RA) is unknown, but there is evidence to support a role for both genetic and non-genetic influences. The same factors that increase susceptibility may also influence disease severity and treatment outcomes. For a variety of reasons, the vast majority of clinical research in RA has been performed on Caucasian populations. Many studies have originated in the United Kingdom or other parts of Europe that often include small

populations of African descent. Historically, African-Americans have been more reluctant than Caucasians to participate in clinical research (1). Thus, African-Americans have been under-represented in established RA cohorts. There are many unanswered questions about RA in African-Americans, which mandates their inclusion in future clinical research (see Table I). In addition, African-American populations represent an ideal population for genetic analyses aimed at identifying novel genes associated with RA susceptibility and severity, particularly because the recent admixture of Caucasian and African genomes may provide greater power in the context of admixture mapping (2, 3).

It is important to point out that race and ethnicity are defined by a complex set of social, political, biological, and economic aspects, which are unique to each society; therefore, purely biological criteria are inadequate (4). Thus, there is intrinsic complexity and controversy regarding the validity of utilizing racial/ethnic categories in genetic research. In fact, the validity of racial/-

Table I. Questions about RA in African-Americans (A-A).

- * What are the effects of RA on quality of life, functional status and work status in A-A?
 - * What is the prevalence of adverse events, such as glucocorticoid-induced osteoporosis, among A-A with RA?
 - * Does the major histocompatibility complex class II shared epitope influence the likelihood of joint erosions in A-A with RA? What other HLA or non-HLA genes influence disease severity or outcome?
 - * What are the effects of medical co-morbidities on mortality in A-A with RA?
 - * Does socioeconomic status (SES) affect disease severity and outcome in A-A with RA? What are the relative contributions of SES and genetic polymorphisms on outcome?
 - * Do A-A have patterns of response to current therapies that are different from Caucasians?
 - * Are there associations between health behaviors, i.e. smoking, exercise, diet, obesity and outcomes in A-A with RA?
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ethnic categories for and genetic research on human disease has recently been challenged. Some researchers propose that a race-neutral approach should be adopted, with the focus on genetic clustering rather than on self-identified ethnicity for human genetic categorization (5,6), while others claim that there is no biological basis for race (7). However, Risch *et al.* have provided an epidemiological perspective on the issue of human categorization in biomedical and genetic research that strongly supports the continued use of self-identified race and ethnicity (8). The goal of any study analyzing genetic variations and disease is to identify clinically relevant alleles (6), but this does not negate the validity of the biology of race.

Genetic differences between African-Americans and Caucasians with RA

Although the prevalence of RA is approximately 0.5-1% in both Caucasians and African-Americans, there may be significant differences in the genetic factors influencing susceptibility, severity, or outcome. Major histocompatibility complex (MHC) DRB1 alleles containing the shared epitope are associated with RA susceptibility and severity in Caucasians, but are present in less than one-third of African-Americans with RA (9). Moreover, a high RA prevalence has been reported in Native American populations, while a low prevalence has been reported in certain Asian populations (10).

Recent genome-wide scans using an affected sibling-pair approach have identified genetic regions outside the MHC locus that may be important in susceptibility to RA (11-14). A number of non-HLA susceptibility loci were identified on chromosomes 1, 4, 12, 16, and 17 in the North American Rheumatoid Arthritis Consortium (NARAC) families (13). Approximately 90% of the families in NARAC were Caucasian; the remaining subgroups were Hispanic (5%), African-American (3.5%), Asian (0.8%), and Native American (0.8%) (13). A stratification of the family data by race/ethnicity showed that there were disproportionate contributions to

Table II. IL-6 SNP allele and haplotype frequencies in Caucasians and A-A normals and RA patients. * AA vs. Caucasian RA ($P = 0.0002$, c^2). † A-A vs. Caucasian controls ($P = 0.0001$, c^2).

IL-6 Allele	A-A RA (n = 216)	A-A Nml (n = 126)	Cauc RA (n = 20)	Cauc Nml (n = 20)
-598 G	205 (0.95)	120 (0.95)	13 (0.65)	14 (0.68)
-598 A	11 (0.05)	6 (0.05)	7 (0.35)	6 (0.32)
-573 G	195 (0.90)	114 (0.91)	20 (1.00)	19 (0.98)
-573 C	21 (0.10)	12 (0.10)	0 (0)	1 (0.02)
-174 G	202 (0.94)	121 (0.96)	13 (0.65)	14 (0.68)
-174 C	14 (0.06)	5 (0.04)	7 (0.35)	6 (0.32)
IL-6 Haplotype	A-A RA*	A-A Nml†	Cauc RA	Cauc Nml
A (GGG)	181 (0.84)	106 (0.84)	13 (0.65)	13 (0.650)
B (GCG)	21 (0.10)	12 (0.10)	0	1 (0.050)
C (AGC)	11 (0.05)	3 (0.02)	7 (0.35)	6 (0.300)
D (GGC)	3 (0.01)	2 (0.02)	0	0
E (AGG)	0	3 (0.02)	0	0

allele-sharing at some loci. For example, when the Caucasian subset was analyzed separately, several markers showed increased statistical significance over the data set that included families of all races/ethnicities. This suggests that the non-Caucasian families (predominantly African-American) contributed to the significance level of the markers that lost statistical significance in the analysis of the Caucasian subset. Unfortunately, there were insufficient numbers of African-American families in the NARAC to analyze these regions more fully. Thus, genes in the HLA complex play a major role in RA susceptibility, but several other regions may also contribute significantly to overall genetic risk, and these regions may vary by race/ethnicity.

The emergence of the post-genome era and the resulting extensive and growing databases of single nucleotide polymorphisms (SNPs) provide opportunities for understanding genetic influences on chronic diseases in ways that were unimaginable only a generation ago. SNPs are common, stably inherited variations that may influence gene transcription, RNA stability, or protein function. Although SNPs in genes that are important in the immune system have been proposed as markers of RA disease severity, data are incomplete and studies have typically involved predominantly Caucasian populations.

Although all humans share > 99% nucleotide sequence homology in their genome, there are potentially important racial/ethnic differences in SNP allele and haplotype frequencies in genes relevant to RA. Interleukin-6 (IL-6) is an important mediator in RA, as it is expressed at high levels in lymphocytes, fibroblasts, and type B synoviocytes in RA synovium (15) and is present in high concentrations in RA sera and synovial fluid (16-19). The concentration of IL-6 in RA synovial fluid appears to correlate with chronic synovitis (20) and radiographic joint destruction (17). Human IL-6 and soluble IL-6 receptor can induce osteoclast-like cell formation, further suggesting that IL-6 in RA synovial fluid contributes to joint destruction (17, 21). Clinical improvement in RA patients treated with anti-IL-6 antibody has been reported (22). A randomized, double-blind, placebo-controlled, dose-escalation trial of an anti-IL-6 antibody demonstrated a significant American College of Rheumatology 20% improvement response (ACR 20) (23). Notably, erythrocyte sedimentation rates and C-reactive protein levels fell significantly in treated groups. An IL-6 G/C polymorphism at position -174 has been reported to influence IL-6 expression levels and susceptibility to systemic onset juvenile RA (JRA) in Caucasians (24). We identified a novel IL-6 promoter SNP at position -573 re-

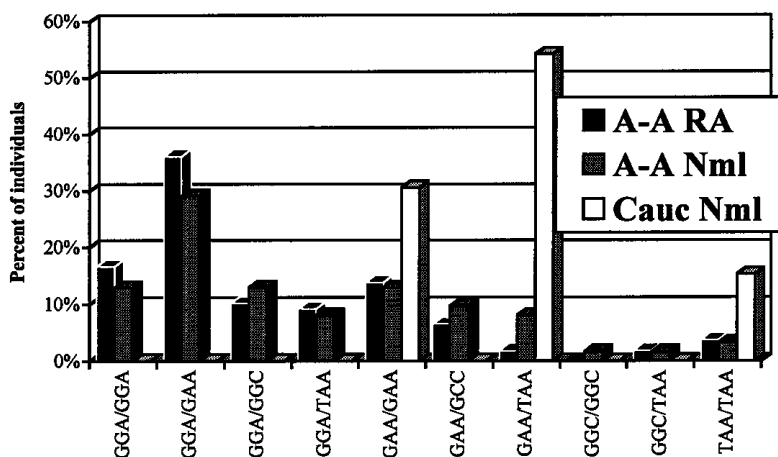


Fig. 1. Distribution of TNFR1 haplotypes among A-A subjects with RA, A-A controls, and Caucasian controls. The difference in haplotype combinations between A-A controls and Caucasian controls was highly significant ($P = 0.000001$, χ^2). Reprinted from ref. 28 with permission from John Wiley & Sons, Inc. © 2002 American College of Rheumatology.

lative to the IL-6 gene start site. This SNP, together with previously identified SNPs at -598 and -174, allows the identification of 5 novel haplotypes (25). We characterized SNP genotypes and haplotypes in patients in the Grady African-American RA cohort and in African-American controls, as well as in Caucasian RA patients and controls. Although there were no differences in allele or haplotype frequencies between RA patients and controls of either race/ethnicity, we found significant racial/ethnic differences in allele and haplotype frequencies (Table II). IL-6 may play a more important pathogenic role in individuals of different race/ethnicity, but this question has not been addressed directly.

We and others have also found racial/ethnic differences in allele frequencies of known SNPs in tumor necrosis factor receptor (TNFR) genes (*TNFRSF1A* and *TNFRSF1B*). The frequency of the *TNFRSF1B* 196G allele that influences susceptibility to familial RA in Caucasians (26, 27) was similar to that observed in African-American RA patients and African-American controls, but differed between African-American controls and Caucasian controls (28). Three SNPs in the 5' flanking region of the *TNFRSF1A* gene (-609G/T; -580A/G; -383A/C) were genotyped. There were no significant differences in *TNFRSF1A* allele frequen-

cies between African-American RA patients and African-American controls. Allele frequencies were strikingly different, however, between African-American controls and Caucasian controls: -609T (0.13 vs 0.42), -580G (0.49 vs 0), -383C (0.14 vs 0). We characterized 4 novel haplotypes defined by the 3 *TNFRSF1A* SNPs, which again were markedly different in their distribution among Caucasian controls and African-American controls (Fig. 1). While we found no associations of known TNFR SNPs or haplotypes with RA, significant racial/ethnic differences were observed at both loci (28). Comparison of these data with other published racial *TNFRSF1A* and *TNFRSF1B* genotype frequencies suggests that African-American, Caucasian, and Asian populations differ significantly in their distributions. These striking racial/ethnic differences in TNFR SNP frequencies may influence the likelihood of familial RA, severe disease, or response to TNF inhibitors, and have important evolutionary implications.

Admixture analyses in African-Americans with RA as a means of identifying novel susceptibility alleles

The progress in finding genes for complex traits such as RA has been complicated by genetic admixture of the popu-

lations under study. In the context of genetic linkage studies, unidentified subpopulations reduce statistical power and complicate the possibility of finding genetic loci which influence complex traits. The genetic structure of a population could therefore have a significant impact on the interpretation of association data, especially when comparing populations with different Caucasian (or other) admixture levels. It is important to note that admixture, while a confounder in some approaches, such as affected sibling-pair analysis, may provide important information on susceptibility loci.

The African-American population can best be described genetically as an admixed population formed by the gene flow between 2 or more genetically distinct populations [Reviewed in (29)]. This complicated admixture process began more than 250 years ago when the first African slaves arrived in the US. Because of the nature of the slave trade, it is difficult to determine the precise ethnic origins of slaves who migrated from Africa, but the most important regions are west and west central Africa, including Gambia and Senegal (the region formerly referred to as Senegambia), Sierra Leone, the Ivory Coast (formerly Windward Coast), Ghana (formerly Gold Coast), Nigeria (formerly Bight of Benin and Bight of Biafra), and Angola. After their forced migration to the US, this African population underwent admixture with other ethnic groups, namely Europeans and Native Americans (30).

African-Americans are a resident population that has special value in genetic studies due to both the high levels of genetic diversity and admixture (30). Previous studies have reported a 3-26% admixture of Caucasian genes in African-Americans, with a higher proportion found in the Northern states than in Southern states (31, 32). In a more recent study, it was shown that the admixture process varies widely even within geographic regions. For example, Charleston, South Carolina was estimated to have an admixture rate of 11.6%, while the African-American population in New Orleans had an estimated 22.5% Caucasian component

(30). A study of HLA phenotyping data among African-American populations in Alabama, Maryland, and North Carolina found differences in the HLA phenotypes in the Alabama population compared to those in Maryland and North Carolina (33). According to results from the donor registry of the 1995 National Marrow Donor Program (consisting of over 1.35 million HLA-typed healthy volunteers), there are significant differences in allele and haplotype frequencies between the 5 major racial groups in the US (Caucasians, African-Americans, Asian-Americans, Hispanic Americans, and Native Americans) (34). In this study, there were a fairly large number of HLA haplotypes that were relatively specific to African-Americans. Furthermore, there were differences in HLA-DR4 allele frequencies between healthy African-Americans (5.7%) and healthy Caucasians (16.8%), which may have important implications in RA. In summary, these studies show that genetic diversity exists between racial/ethnic populations.

Because of the history and nature of admixture, African-American populations are especially suitable for linkage disequilibrium studies. African-American populations offer the advantage that linkage disequilibrium has been created recently (5-20 generations) due to the admixture process; because the linkage disequilibrium is recent, it can extend over large chromosomal regions. There have now been at least 3 independent groups reporting that in admixed populations, strong allelic association is observed between linked markers spaced at substantial distances (5, 30, 35-37). These extended areas of linkage disequilibrium can make analysis of the population quite powerful (2, 3, 38).

One promising approach is mapping by admixture linkage disequilibrium or simply admixture mapping (2, 3, 38-41). Admixture generates allelic associations between all marker loci where allele frequencies are different between the parental populations (42). These associations will decay with time in a way that depends on the genetic distance between them. Thus, disease risk

alleles that are different between the parental populations can be mapped in admixed populations using special panels of genetic markers showing high frequency differences between the parental populations. These markers, which are termed ancestry informative markers (AIMs), also called ethnicity difference markers, are characterized by having particular alleles that are more common in one group of populations than in other populations. The *TNFRSF1A* -609G, *TNFRSF1A* -580G, IL-6 -598G, and -174G alleles described above, all of which are much more common in African-Americans than in Caucasians, may serve as useful AIMs in admixture studies. If any disease-susceptibility alleles or disease-protective alleles are present in sufficiently different frequencies in the parental populations, then the admixture mapping method can be used to pinpoint the susceptibility or protective gene in the admixed population.

Racial/ethnic differences in treatment response in diseases other than RA

Although there are no definitive markers of treatment response in RA, and the issue of race/ethnicity in treatment response has not been specifically examined, there are several relevant studies of other chronic diseases showing that treatment responses may vary by race/ethnicity. In a large study of patients with advanced heart failure, Beta-Blocker Evaluation of Survival Trial, treatment with the beta-blocker bucindolol resulted in a significant survival benefit for non-African-Americans, an effect that was not seen among African-Americans patients (43). Exner *et al.* reported an analysis of pooled data from the Studies of Left Ventricular Dysfunction prevention and treatment trials, two large, randomized trials comparing enalapril with placebo in patients with left ventricular dysfunction (44). In their analysis, African-American patients had higher rates of death from any cause and more hospitalizations for heart failure despite similar doses of drug in the two groups. At 1 year, enalapril therapy was associated with significant reductions from

baseline in blood pressure among white patients, but not among African-American patients (44).

Treatment of chronic hepatitis C virus (HCV) infection provides another prominent example in which racial differences are associated with treatment outcome. Although the likelihood of a sustained response to a course of interferon alpha-2b depends on several clinical and viral factors, including age, viral genotype, and initial serum levels of HCV RNA, racial factors are also a significant determinant of treatment response. In a large randomized, controlled trial using either consensus interferon or interferon alpha-2b, the rates of end-of-treatment and sustained virological responses were lower among the 40 African-American patients (5% and 2%) than among the 380 white patients (33% and 12%) ($P=0.04$ and 0.07) (45). In another trial, the end-of-treatment response was significantly higher in Caucasians (14/49, 31%) than in African-Americans (5/61, 8%) ($P < 0.05$), especially in patients with HCV genotype 1 (46). The reasons for differences in treatment responses among individuals of different race/ethnicity remain to be delineated and will likely involve both genetic and non-genetic factors. Frequencies of SNP alleles with biologic effects in genes relevant to the disease pathway may vary widely between African-Americans and Caucasians, and may be one factor that contributes to discrepancies in treatment response rates.

Socioeconomic factors in health care of African-Americans

Numerous studies have shown that African-Americans have poorer health status than Caucasians in the US. Low socioeconomic status has been associated with higher levels of obesity in African-American women, increased risk for cardiovascular disease, increased severity of rheumatoid arthritis, and increased overall mortality (47-50). Multiple approaches have been used to try to dissect how much the poorer health status of African-Americans can be accounted for by low socioeconomic status. Among the individual components of socioeconomic sta-

tus are occupation, educational level, and income. Studies analysing these components have found significant associations between lower educational levels and cardiovascular disease, self-reported arthritis, and severity of rheumatoid arthritis (49-51).

There are substantial differences in health care delivery between different racial/ethnic groups in the US (52). For example, a recent study of Medicare outpatient claims found that only one-third of elderly patients with RA and only 42% of elderly patients with systemic lupus erythematosus saw a rheumatologist over a one-year period (53). More importantly, there were fewer visits to rheumatologists among African-Americans than among Caucasians, particularly women. There are marked racial/ethnic disparities in the utilization of joint replacement for end-stage osteoarthritis of the knee or hip (54). African-American patients appear to be less willing than Caucasian patients to consider joint replacement. This difference appeared to be explained by between-group differences in expectations of hospital course, pain, and function following replacement surgery (55). Although glucocorticoid induced osteoporosis is a major problem for patients with RA, African-American patients who are chronic glucocorticoid users are substantially less likely than Caucasians to undergo bone mineral density testing or receive prescription osteoporosis medications even after adjusting for other osteoporosis risk factors (56). These and other studies have underscored the importance of studying ethnic disparities in health care and health status (57, 58).

Health-related racial/ethnic disparities have lead to the creation of a number of national programs, such as the Office of Research on Minority Health started by the National Institutes of Health in 1990, and The Healthy People 2010 Initiative developed in 1979. The goal of these programs is to eliminate racial/ethnic disparities in healthcare, in large part by improving access to healthcare. Despite these efforts, however, a recent analysis has shown there has been no decrease in black-white disparities in age-adjusted mortality or

life expectancy since 1945 (59). Thus, access to health care may be less important than cultural issues (for example, willingness to seek medical care, expectations of visits to physicians, etc.) with regard to racial/ethnic disparities in health. Current opinion suggests that a fundamental change in the focus of minority healthcare towards disease prevention, rather than treatment, will be necessary to equalize the existing racial disparities (59, 60).

Need for early treatment of RA

Several studies have now shown that early treatment of patients with RA provides better outcomes than delayed treatment (61-64). Published data have documented that RA patients with aggressive synovitis develop radiographically evident joint damage within the first 2 years of disease, with 50% of total radiographic damage within the first 6 years. Approximately one-fourth of RA patients become work disabled at ~ 6 years after diagnosis and one-half at 20 years after diagnosis (65). Early control of inflammation appears critical to prevent significant disease-related morbidity and mortality. We concur with the conclusion of others that both patients and physicians should regard early RA as an urgent medical problem (66, 67).

Some of the unresolved questions surrounding treatment of early RA in African-Americans are similar to those in other populations, such as the identification of a subset of patients who might have a poorer outcome and should therefore be treated earlier with potent immunosuppressive drugs. An important issue in the treatment of all patients with early RA is prompt referral to rheumatologists who are experienced with state-of-the-art treatments. Many institutions, including our own, have started clinics specifically designed to evaluate and treat early arthritis in as expeditious a manner as possible. Such clinics are now commonplace in many parts of Europe, where nationalized health care is common; investigators at many of these institutions have helped to establish guidelines for prompt referral of patients with suspected RA (68).

Another important factor in outcome of RA is the use of disease modifying anti-rheumatic drugs (DMARDs). At present, reimbursement issues may often influence the use of specific therapies. Some medications, including self-administered drugs such as etanercept or adalimumab (TNF antagonists), are not covered by Medicare. Identification of pharmacogenetic markers of clinical response and toxicity may help reduce expenses related to treatment by optimizing the initial choice of agents, reducing the costs of laboratory monitoring, and minimizing adverse effects. With the sequencing of the human genome, increasing knowledge of genetic polymorphisms, and the burgeoning field of pharmacogenetics, the era of personalized medicine (prescription of drugs based on genetic predictors of clinical response) may soon be realized (69, 70).

In many chronic illnesses (e.g., cardiovascular disease), premature death serves as a benchmark for disease severity and provides rationale for aggressive therapy (e.g. treating hypertension and hyperlipidemia). The concept of premature mortality in RA has only recently been widely recognized. Cardiovascular mortality, the leading cause of excess death in RA, has been found to be approximately 2-fold that of controls for patients from Caucasian RA cohorts, and aggressive DMARD therapy has been shown to substantially reduce cardiovascular mortality for these patients (71). Comorbid illnesses may disproportionately affect the survival of African-Americans with RA. Additionally, stroke and hypertension are much more common in African-Americans from Southern states than among Caucasians from the same geographic areas (72). Thus, the effects of comorbid conditions on the outcomes of RA must be considered among African-American patients.

The CLEAR Registry

In 2000, the National Institutes of Health (NIH) released a Request for Proposals (RFP) entitled, "New Research Registries for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)". In res-

ponse investigators at four academic institutions formed the Consortium for the Longitudinal Evaluation of African-Americans with RA (CLEAR). The University of Alabama at Birmingham is the CLEAR Coordinating Site, and collaborators include investigators at Emory University, the University of North Carolina, and the Medical University of South Carolina. These sites were chosen on the basis of their being located in the southern part of the United States, and having developed their own unique and workable methods of recruiting African-American patients for clinical studies. The CLEAR registry and DNA repository has the goal of identifying 500 African-American patients with early RA (disease duration less than 2 years) to allow analysis of genetic and non-genetic factors associated with disease severity.

Comprehensive demographic, medical, and socioeconomic data will be collected at baseline. Disease activity will be assessed at baseline, and at 3 and at 5 years using the number of swollen and painful joints, patient and physician global assessments, the Health Assessment Questionnaire, and pain as measured on a visual analog scale. Data on functional status will be captured using the SF-36, a validated instrument that provides a self-perceived measure of mental and physical functioning. Medications will be documented at baseline and at 6-month intervals, including at 3 and 5 years of disease duration. Medications for other medical conditions will be recorded. Comorbidities such as diabetes, thyroid disease, coronary artery disease, hypertension, and lung disease will be recorded. The 5-item helplessness subscale of the Rheumatology Attitudes Index will be used to measure the patient's helplessness. Fatigue will be assessed using a 10 cm horizontal visual analog scale.

For each patient, at the time of entry blood will be obtained for the isolation of DNA and serum and the establishment of Epstein-Barr virus transformed cell lines. Dual-energy x-ray absorptiometry scan of one hip and the lumbar spine will be obtained at baseline (< 2 years of disease) and at 5 years of disease duration, and data will be normal-

ized to account for the variation between specifications of machines made by different manufacturers. Radiographs of the hands, wrists and feet will be obtained at baseline and at 3 and 5 years of disease duration.

To date, 169 subjects (135 women, 34 men) have been enrolled in CLEAR. The mean age is 51.5 years and the mean disease duration at enrollment is 13.6 months. Enrollment of an additional 331 subjects is planned. Preliminary data from the CLEAR registry suggest that a large percentage of African-Americans with early RA (< 2 years of disease) have joint erosions on hand and foot radiographs, and a surprisingly high number of subjects have decreased bone mineral density at the time of enrollment. The CLEAR registry and DNA repository represents a pivotal resource for the study of genetic and non-genetic influences on disease severity and outcome of early RA in African-Americans.

Appendix

The Consortium for the Longitudinal Evaluation of African-Americans with Early Rheumatoid Arthritis: Coordinating Center, University of Alabama at Birmingham, Birmingham, AL: Larry W. Moreland, MD, Director; S. Louis Bridges, Jr., MD, PhD, Co-Director; George Howard, DrPH, Investigator; Graciela Alarcón, MD, MPH, Investigator; Prerna Gala, MSPH, Research Manager; Rosemary Snead, MSHA, Administrative Officer; Paula McKenzie, RN, Site Coordinator; Eugene Oliver, BS, Data Coordinator; Andrew O. Westfall, MS, Biostatistician; Jeroan Allison, MD, MSEpi; Michael Holland, MCSA, Systems Manager. University of Nebraska Medical Center and Omaha VA Medical Center: Ted R. Mikuls, MD, MSPH. Grady Hospital and Emory University, Atlanta, GA: Doyt Conn, MD, Investigator; Janet McNicholl, MB, MD, Investigator; Joyce Carlone, MN, RN, Site Coordinator; Karla Caylor, BS, RN, Site Coordinator. University of North Carolina, Chapel Hill, NC: Beth Jonas, MD, Investigator; Leigh Callahan, PhD, Investigator; Chris Summers-Bean, MSN, RN, Site Coordinator. Me-

dical University of South Carolina, Charleston, SC: Edwin Smith, MD, Investigator; Gary Gilkeson, MD, Investigator; Evette Robinson, BS, Site Coordinator.

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