Contemporary Clinical Trials 50 (2016) 238–244

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

The effects of urate lowering therapy on inflammation, endothelial function, and blood pressure (SURPHER) study design and rationale

Michael B. Saddekni [a], Kenneth G. Saag [a], Tanja Dudenbostel [b], Suzanne Oparil [b], David A. Calhoun [b], Sebastian E. Sattui [c], Daniel I. Feig [d], Paul Muntner [e], David T. Redden [f], Phillip J. Foster [a], Elizabeth J. Rahn [a], Stephanie R. Biggers [a], Peng Li [f], Angelo L. Gaffo [a,*]

[a] Department of Medicine, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, AL 35294, USA
[b] Department of Medicine, Division of Cardiovascular Disease, University of Alabama at Birmingham, AL, 35294, USA
[c] Department of Medicine, University of Alabama at Birmingham, AL 35294, USA
[d] Department of Pediatrics, Division of Nephrology, University of Alabama at Birmingham, AL 35294, USA
[e] Department of Epidemiology, University of Alabama at Birmingham, AL 35294, USA
[f] Department of Biostatistics, University of Alabama at Birmingham, AL 35294, USA

ARTICLE INFO

Article history:
Received 1 June 2016
Received in revised form 22 August 2016
Accepted 28 August 2016
Available online 30 August 2016

Keywords:
Hyperuricemia
Prehypertension
Urate lowering therapy (ULT)
Uric acid
Serum urate
Hypertension
Blood pressure
Allopurinol
Endothelial function

ABSTRACT

Background: The association between hyperuricemia and hypertension is controversial. Animal models, epidemiological data, and small clinical trials have favored a causative role for hyperuricemia in hypertension but more studies are necessary to elucidate putative mechanisms, population susceptibility, and potential for urate-lowering therapies (ULT) to decrease blood pressure (BP).
Purpose: To describe the background and design of the Serum Urate Reduction to Prevent Hypertension (SURPHER) study.
Methods: SURPHER is a single center, double-blinded, crossover trial in which participants are randomly assigned to allopurinol (300 mg) or placebo. Enrollment focused on adults 18–40 years old with baseline systolic blood pressure ≥ 120 and <160 mm Hg or diastolic blood pressure ≥ 80 and <100 mm Hg, and serum urate ≥5.0 mg/dL or ≥4.0 mg/dL for men or women, respectively. SURPHER recruitment targets participants without chronic kidney disease (estimated glomerular filtration rate > 60 mL/min/1.73 m2), and without prior diagnosis of gout or use of ULT to treat gout. The primary outcome is change from baseline in blood pressure assessed by 24 hour ambulatory blood pressure monitoring and mechanistic outcomes include changes in endothelial function as measured by flow-mediated dilation, as well as C-reactive protein levels.
Results: Since June 16, 2014 until present, SURPHER is recruiting participants in the city of Birmingham, Alabama.
Limitations: The study aims to enroll otherwise healthy young adults for a pharmacological intervention study with multiple study-related procedures. Challenges related to recruitment are anticipated and multiple strategies for increasing recruitment and retention are planned if necessary.

1. Introduction, background, and rationale

High serum urate concentration is a well-established causative factor for the development of gouty arthritis. There is growing interest in a role for serum urate as contributing factor for the development or worsening of vascular, cardiac, and renal disease. The association between serum urate levels and blood pressure (BP) has been described for many decades [1–13]. Evidence from animal studies provides strong support for this association [14]. The contribution of serum urate to hypertension is further supported by evidence from small clinical trials demonstrating antihypertensive benefit of urate lowering therapy (ULT) in adolescence [15,16]. Mechanisms involved in the development of hypertension include the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and endothelin-nitric oxide system. It is of particular note that transport of serum urate into human

Abbreviations: AAs, African Americans; ABPM, ambulatory blood pressure monitoring; AEs, adverse events; AHS, allopurinol hypersensitivity syndrome; BP, blood pressure; CoRT, Center of Research Translation in Gout and Hyperuricemia; CRP, C-reactive protein; CV, cardiovascular; DBP, diastolic blood pressure; DSMB, Data Safety and Monitoring Board; FMD, flow-mediated dilation; GCP, Good Clinical Practice; GRF, glomerular filtration rate; hsCRP, high sensitivity C-reactive protein; IRB, Institutional Review Board; NIAMS, National Institute of Arthritis and Musculoskeletal and skin Diseases; PI, Principal Investigator; RAAS, renin-angiotensin-aldosterone system; REDCap, Research Electronic Data Capture; SAEs, serious adverse events; SBP, systolic blood pressure; SURPHER, Serum Urate Reduction to Prevent Hypertension; UAB, University of Alabama at Birmingham; ULT, urate lowering therapy; URAT-1, urate anion transporter-1.

* Corresponding author at: Department of Medicine, Division of Clinical Immunology and Rheumatology, Shelby Building 306, 1825 University Blvd, University of Alabama at Birmingham, Birmingham, AL 35233, USA.
E-mail address: agaffo@uabmc.edu (A.L. Gaffo).

http://dx.doi.org/10.1016/j.cct.2016.08.016
1551-7144/

endothelial cells via the urate anion transporter-1 (URAT-1) results in reduced nitric oxide levels in endothelial cells and concurrent activation of the RAAS [17,18–20]. The resultant endothelial dysfunction is an independent risk factor for cardiovascular events via promotion of both atherosclerosis and hypertension [21–23]. endothelial dysfunction and increased plasma renin activity have been associated with increases in serum urate [19,20]. Administration of allopurinol, a first-line ULT, to treat hyperuricemia has been shown to improve endothelial function in both animal and human studies [19,24–26]. Moreover, higher serum urate concentrations are positively associated with increased levels of inflammatory markers, such as C-reactive protein (CRP). Improvements in endothelial function and BP control have been associated with decreases in C-reactive protein levels, suggesting another potential vasoprotective mechanism for ULT [27,28]. Our previous double-blinded, crossover trial demonstrated that administration of allopurinol (200 mg daily) for one month significantly reduced clinic and ambulatory BP among adolescents with hypertension and hyperuricemia when compared with placebo [15]. We also showed that the uricosuric drug probenecid reduced BP in both children and adolescents, thus supporting the hypothesis that reduction of serum urate levels by mechanisms other than xanthine-oxidase inhibition is associated with BP reduction [29]. Our group also described an increased risk for incident hypertension among young adults with serum urate level ≥ 5.0 mg/dL for men, and ≥4.0 mg/dL for women followed over 20 years [30]. Finally, it is well established that hypertension disproportionately affects African-Americans (AAs) [31] and that African-Americans have differential responses to hypertension therapies [32]. The main objective of the Serum Urate Reduction to Prevent Hypertension (SURPHER) study is to determine if ULT is associated with reductions in BP in young adults, paying special attention to ethnic and gender differences in the response. Mechanisms mediating this effect, particularly endothelial dysfunction and markers of inflammation, will be examined. We hypothesize that BP in AAs is more sensitive to variations in serum urate and that this may be an additional mechanism to explain the higher prevalence of hypertension among young AAs. We further hypothesize that any relationship between inflammatory marker levels, serum urate, and BP would be optimally tested in a younger population with a lower prevalence of vascular damage [33,34].

2. Methods

2.1. Study organization

The SURPHER organizational structures and responsibilities are similar to many previous single center clinical trials. The study is sponsored by National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) as part of the funded University of Alabama at Birmingham (UAB) Center of Research Translation in Gout and Hyperuricemia (CoRT) (P50AR060772). SURPHER is registered at clinicaltrials.gov (https://clinicaltrials.gov/show/NCT02038179) and the study has been approved by the UAB Institutional Review Board (IRB).

2.2. Study design decisions

2.2.1. Overall study design

SURPHER is a single center, double-blinded, crossover trial in which participants are randomly assigned to 300 mg of allopurinol as ULT or placebo (Fig. 1). Change from baseline in BP assessed by 24 hour ambulatory blood pressure monitoring (ABPM) is the primary study outcome. We plan to recruit and randomize 112 participants from the Birmingham, Alabama, USA metro area into the study. The sample will include 56 African-Americans and 56 participants of other races/ethnicities.

2.2.2. Eligibility, recruitment, retention, and adherence

The SURPHER inclusion/exclusion criteria are presented in (Table 1). Three major inclusion criteria include 1) pre-hypertension or stage I hypertension defined as the following after the mean of two clinic measurements: systolic blood pressure (SBP) ≥ 120 and <160 mm Hg or; diastolic blood pressure (DBP) ≥ 80 and <100 mm Hg; 2) a serum urate ≥5.0 mg/dL for men or ≥4.0 mg/dL for women; and 3) are between 18 and 40 years old. Two major exclusion criteria include 1) any current pharmacological treatment for hypertension excluding calcium channel blockers; 2) prior diagnosis of gout or past use of ULT for gout. Patient recruitment began on July 14th 2014 and is ongoing. Recruitment efforts include posting of flyers in university, metro, and community areas frequented by our target demographic of young adults. Announcements and profiles for the study have also been placed on the websites researchmatch.com, craigslist.com, and facebook.com. Other recruitment efforts include direct mailing advertisement through databases of individuals interested in research studies, advertisements in local area newspapers, and radio stations. Participants are also being recruited directly from outpatient care facilities.

Attention to adherence and retention planning began before enrollment commenced. During screening and an initial placebo run-in phase, individuals who demonstrate a significant risk for non-adherence to study medication or for completing study visits are excluded from trial participation. Once participants enroll, a baseline assessment of adherence using standardized, valid adherence measures in conjunction with assessment of behavioral "red flags" by clinic staff allows for early identification of potential problems so that study resources could be devoted to improving adherence and retention for these individuals. Throughout the study, participants are called at 2 weeks intervals to

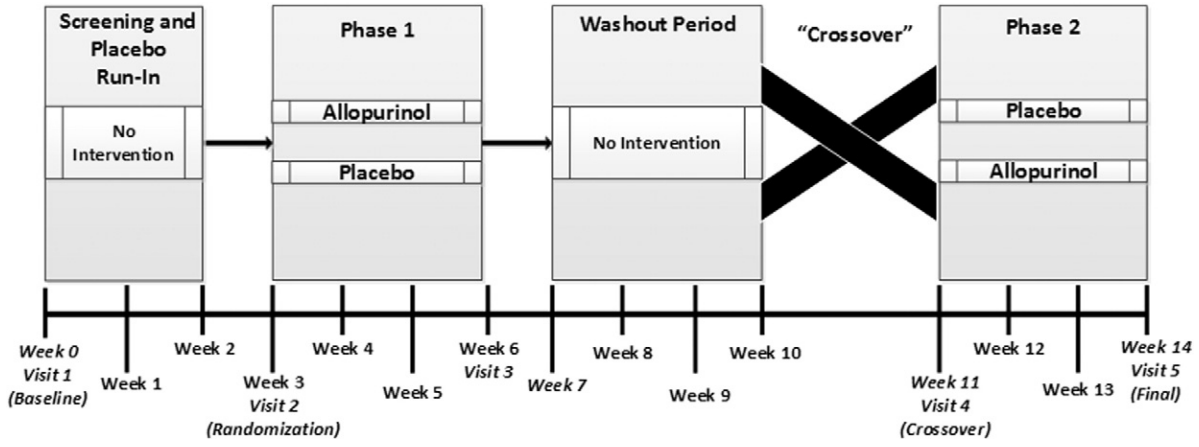

Figure 1. Study Design Diagram Participants are screened for eligibility and then begin a 2 week run-in period. Upon completion of run-in, participants are randomized in Phase 1 to allopurinol, 300 mg or placebo for 4 weeks. This is followed by a 4-week washout period and then crossover to Phase 2 (i.e. participants who previously received allopurinol receive placebo, and vice versa) for 4 weeks.