CLINICAL RESEARCH STUDY

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Randomized Controlled Trial of Sildenafil for Preventing Recurrent Ischemic Priapism in Sickle Cell Disease

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ABSTRACT

BACKGROUND: Successful preventive therapy for ischemic priapism, a disorder of penile erection with major physical and psychologic consequences, is limited. We conducted a randomized, double-blind, placebo-controlled clinical trial to assess the efficacy and safety of sildenafil by a systematic dosing protocol to prevent recurrent ischemic priapism associated with sickle cell disease.

METHODS: Thirteen patients with sickle cell disease reporting priapism recurrences at least twice weekly were randomized to receive sildenafil 50 mg or placebo daily, unassociated with sleep or sexual activity, for 8 weeks, followed by open-label use of this sildenafil regimen for an additional 8 weeks.

RESULTS: Priapism frequency reduction by 50% did not differ between sildenafil and placebo groups by intention-to-treat or per protocol analyses ($P = 1.0$). However, during open-label assessment, 5 of 8 patients (62.5%) by intention-to-treat analysis and 2 of 3 patients (66.7%) by per protocol analysis met this primary efficacy outcome. No significant differences were found between study groups in rates of adverse effects, although major priapism episodes were decreased 4-fold in patients monitored "on-treatment."

CONCLUSIONS: Sildenafil use by systematic dosing may offer a strategy to prevent recurrent ischemic priapism in patients with sickle cell disease.

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KEYWORDS: Erection; Erectile dysfunction; Nitric oxide; Phosphodiesterase type 5

Priapism is a clinical disorder characterized by prolonged penile erection in the absence of sexual arousal or desire.[1,2] Its ischemic form, presenting as a single, major episode, or recurrence, is associated with penile pain, erectile tissue destruction and loss, and permanent erectile inability.[2,3] Ischemic priapism occurs in several population groups, most notably in individuals with sickle cell disease, among whom as many as 40% are affected.[4-6]

Treatments for this disorder are lacking, in large part because the disorder is clinically misunderstood and ideal medical interventions are undeveloped.[7] Major scientific progress in this field in recent years has advanced understanding of the pathophysiology, in particular derangements in molecular effector pathways mediating penile erection.[8] On the basis of evidence that aberrant activity of the nitric oxide (nitrergic) signal transduction pathway is a molecular mechanism for this disorder,[9,10] nitrergic-regulatory phosphodiesterase type 5 inhibitors have been preliminarily investigated in uncontrolled pilot studies suggesting feasibility and potential efficacy to prevent priapism.[11,12] We conducted a randomized, controlled trial to evaluate the benefit of the phosphodiesterase type 5 inhibitor sildenafil

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Conflict of Interest: JFC has received an honorarium and travel expenses in the past; presently receives salary support through Johns Hopkins for providing consultative advice to Mast Pharmaceuticals (previously Adventrx Pharmaceuticals) regarding a proposed clinical trial of an agent for treating vaso-occlusive crisis in sickle cell disease; and is an inventor and a named party on a patent and licensing agreement to ImmunArray for a panel of brain biomarkers for the detection of brain injury.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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via an investigational protocol to prevent recurrent ischemic priapism in patients with sickle cell disease.

METHODS

Patients

Patients with sickle cell disease (confirmed SS or SC hemoglobinopathy), aged 14 to 45 years, were recruited from regional hematology and urology clinics. Inclusion criteria were occurrences of at least 2 self-reported priapism episodes per week and ability to provide written informed consent or assent. Exclusion criteria were estimated glomerular filtration rate <50 mL/min, clinical cirrhosis, pulmonary hypertension based on echocardiography, alcohol use exceeding 2 standard drinks daily, or formal contraindications for using phosphodiesterase type 5 inhibitor therapy.[13] The study was approved by the Institutional Review Board (#NA_00017554) and the Food and Drug Administration (IND 075673) and registered at www.ClinicalTrials.gov as NCT00940901.

CLINICAL SIGNIFICANCE

- Adherence to a sildenafil dosing regimen is critical because 66.7% of adherent patients demonstrated a 50% reduction in priapism episode frequency during the open-label phase.
- Four-fold fewer priapism-related hospital visits occurred among patients adherent to therapy than those who were nonadherent or receiving placebo, suggesting a potential benefit in reducing the occurrence of major episodes.
- No significant differences regarding adverse effects of sildenafil therapy were found between the sildenafil and placebo groups.

Study Design

This was a single-center, 2-phase, double-blind, placebo-controlled, parallel-group study conducted prospectively from June 2008 to November 2012. After baseline evaluation, consisting of clinical history, physical examination, routine serologic testing, and completion of study-specific instruments (Priapism/Sexual Activity Log and Priapism Questionnaire), patients were randomized in a 1:1 allocation to enter an 8-week double-blind phase (phase 1) consisting of daily sildenafil 50 mg or placebo (Pfizer Inc, New York, NY). The subsequent 8-week open-label phase (phase 2) of sildenafil 50 mg once daily was offered to all participants. Participants were instructed to take the medication in the morning a few hours after awakening and without sexual stimulation.[11,12] Patients were monitored by biweekly nurse coordinator phone calls (to record progress and medication changes and to document adverse event occurrences and adherence to study drug) and by in-clinic evaluations every 4 weeks (which included repeat administration of study instruments). A Data Safety and Monitoring Board performed quarterly reviews with assessments of trial progress, clinical outcomes, and occurrence of adverse events.

Outcomes and Statistical Analysis

The primary efficacy outcome was a 50% reduction (1-tier decrease) in priapism episodes biweekly from the baseline of each respective trial phase. Secondary outcomes included subjective improvements in episode frequency and duration and decrease in the median number of biweekly episodes of priapism in each phase. A simple tiered scoring system was devised, with the assignment of a numeric value to a priapism recurrence range as follows: 0 = no episodes, 1 = 1 to 2 episodes, 2 = 3 to 4 episodes, 3 = 5 to 8 episodes, 4 = 9 to 16 episodes, 5 = >16 episodes.

An a priori sample size of 24 patients in each group was calculated on the basis of a 50% reduction from a baseline mean frequency of 5.9 ± 5.0 priapism episodes per individual (Johns Hopkins Hospital historical data), considering a statistical power of 80% and an alpha error of 0.05. Last observation carried forward was used to determine the final priapism episode range at the completion of each study phase. Identical methods were applied for both intention-to-treat and per protocol analyses. We defined protocol adherence as 60% of expected drug-regimen use.

Baseline scores were compared between treatment groups using the Wilcoxon rank-sum test. Repeated evaluations for each patient were analyzed using a linear mixed model. Categorical outcomes were compared using the Fisher exact test. Data were analyzed using SAS version 9.2 (SAS Institute, Inc, Cary, NC). A P value <.05 was considered statistically significant.

RESULTS

Among 110 patients with sickle cell disease evaluated with recurrent ischemic priapism, 13 were enrolled and entered in phase 1. Baseline demographic and clinical characteristics are shown in **Table 1**. No significant differences

Table 1 Baseline Characteristics

	Placebo (n = 7)	Sildenafil (n = 6)	P Value
Age, y ± SD	23.0 ± 8.7	21.7 ± 5.3	.75
Hypertension, no. (%)	1 (14.3)	2 (33.3)	.56
Stroke, no. (%)	3 (42.9)	1 (16.7)	.56
Avascular necrosis, no. (%)	1 (14.3)	0 (0)	1.00
Acute chest syndrome, no. (%)	1 (14.3)	2 (33.3)	.56
Asthma, no. (%)	2 (28.6)	2 (33.3)	1.00
Smoker, no. (%)	1 (14.3)	2 (33.3)	.56
Alcohol use, no. (%)	3 (42.9)	3 (50)	1.00

no = number; SD = Standard Deviation.