AJKD
Original Investigation

Automated Reminders and Physician Notification to Promote Immunosuppression Adherence Among Kidney Transplant Recipients: A Randomized Trial

Peter P. Reese, MD, MSCE,[1,2,3,4] Roy D. Bloom, MD,[1] Jennifer Trofe-Clark, PharmD,[1,5] Adam Mussell, MA,[3] Daniel Leidy, BA,[3] Simona Levsky, BS,[6] Jingsan Zhu, MS, MBA,[4] Lin Yang, MS,[4] Wenli Wang, MS,[4] Andrea Troxel, ScD,[2,3,4] Harold I. Feldman, MD, MSCE,[1,2,3] and Kevin Volpp, MD, PhD[4,7,8,9]

Background: Immunosuppression nonadherence increases the risk for kidney transplant loss after transplantation. Wireless-enabled pill bottles have created the opportunity to monitor medication adherence in real time. Reminders may help patients with poor memory or organization. Provision of adherence data to providers may motivate patients to improve adherence and help providers identify adherence barriers.

Study Design: Randomized controlled trial.

Setting & Participants: Kidney transplant recipients (n = 120) at a single center.

Intervention: Participants were provided wireless pill bottles to store tacrolimus and record bottle openings. Participants were randomly assigned 1:1:1 to adherence monitoring with customized reminders (including alarms, texts, telephone calls, and/or e-mails), monitoring with customized reminders plus provider notification (every 2 weeks, providers received notification if adherence decreased to <90% during that period), or wireless pill bottle use alone (control).

Outcomes: The main outcome was bottle-measured tacrolimus adherence during the last 90 days of the 180-day trial. A secondary outcome was tacrolimus whole-blood concentrations at routine clinical visits.

Measurements: Adherence for the primary outcome was assessed via wireless pill bottle openings.

Results: Mean participant age was 50 years; 60% were men, and 40% were black. Mean adherence was 78%, 88%, and 55% in the reminders, reminders-plus-notification, and control arms ($P < 0.001$ for comparison of each intervention to control). Mean tacrolimus levels were not significantly different between groups.

Limitations: The study did not assess clinical end points. Participants and study coordinators were not blinded to intervention arm.

Conclusions: Provider notification and customized reminders appear promising in helping patients achieve better medication adherence, but these strategies require evaluation in trials powered to detect differences in clinical outcomes.

Am J Kidney Dis. 69(3):400-409.

INDEX WORDS: Kidney transplantation; kidney transplant recipient (KTR); immunosuppression; tacrolimus; behavior change; adherence; compliance; automated reminder; medication reminder; wireless pill bottle; polypharmacy; end-stage renal disease (ESRD); tacrolimus trough level; allograft loss; randomized controlled trial.

Kidney transplant recipients are often nonadherent to immunosuppression medications, which can cause rejection and transplant loss.[1-3] Organ transplant recipients generally face a high barrier to adherence in the first posttransplantation year because they take multiple new medications with diverse adverse effects and frequent dose changes.[1,4] Immunosuppression nonadherence can be intentional or unintentional. Lower immunosuppression adherence is associated with younger age and further time from transplant. It is driven by nonmodifiable and modifiable factors such as medication beliefs, forgetfulness, confusion about complex regimens, competing priorities, concerns about adverse effects,

From the [1]Renal-Electrolyte and Hypertension Division, [2]Department of Biostatistics and Epidemiology, and [3]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania; [4]Leonard Davis Institute Center for Health Incentives and Behavioral Economics, University of Pennsylvania; [5]Department of Pharmacy Services, Hospital of the University of Pennsylvania; [6]School of Arts and Sciences, University of Pennsylvania; [7]Department of Medicine and Medical Ethics and Health Policy, Perelman School of Medicine; [8]Department of Health Care Management, Wharton School, University of Pennsylvania; and [9]Center for Health Equity Research and Promotion, Cresencz Philadelphia Veterans Affairs Medical Center, Philadelphia, PA.

Received March 27, 2016. Accepted in revised form October 10, 2016. Originally published online December 7, 2016.

Trial registration: www.ClinicalTrials.gov; study number: NCT01541384.

Address correspondence to Peter P. Reese, MD, MSCE, 917 Blockley Hall, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, 423 Guardian Dr, Philadelphia, PA 19104. E-mail: peter.reese@uphs.upenn.edu

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2016.10.017

or costs.[1,5-8] Taken together, these findings demonstrate the need to develop and test scalable strategies to improve adherence.[7,9-11] Given the interdisciplinary nature of transplant care, such strategies might involve physicians and other team members, such as pharmacists or clinical coordinators.[12,13]

Insights from studies of adherence and behavioral economic theory suggest new methods to overcome adherence barriers in transplantation.[14-16] First, sustaining behaviors such as medication adherence often requires repeated concrete feedback to help the patient stay engaged.[17] Unfortunately, adherence to immunosuppression creates adverse effects, but does not make patients feel better because early rejection does not usually lead to symptoms. Reminders or repeated incentives may be effective in keeping patients focused on the importance of immunosuppression adherence to future health. Second, physicians often overestimate their patients' medication adherence.[18-20] Early notification to the health care team about nonadherence might enable providers to overcome patients' concerns about adverse effects or clarify misunderstandings about dosing. Providers can also schedule appointments at shorter intervals, refer patients to specialists such as a pharmacist, or direct patients to social support when financial barriers exist. Third, social forces may influence individual behavior.[21-23] Specifically, patients may desire to avoid disapproval from their physicians related to medication nonadherence. In transplantation, immunosuppression nonadherence can be stigmatized by health care staff and even patients' families because kidney transplant recipients are stewards of a precious gift—the organ.[24,25] Therefore, real-time monitoring of medication adherence by physicians and other transplantation providers may create a "social incentive" for patients to comply with their immunosuppression regimens.[15]

Wireless technology has created opportunities to estimate pill-taking behavior in real time, supplemented by customizable visual and audible alarms, texts, telephone calls, and e-mails when a dose is due. To our knowledge, real-time provider notification of low adherence using wireless pill bottles has not previously been tested. However, directly observed therapy—either in person or using video—has been widely implemented in tuberculosis and human immunodeficiency virus (HIV) treatment, with some successful trials, particularly when there is flexibility about who receives the adherence report.[26-28] Additionally, interventions that alert physicians when patients do not refill prescriptions have also been tested.[29]

Wireless pill bottles also introduce challenges, such as requiring patients to master a new technology and clinical teams to respond to a continuous data stream. However, the transplantation setting usually features a clinical coordinator assigned to each patient who is responsible for helping with many aspects of care. If wireless pill bottles were implemented in the future, these transplantation coordinators could feasibly monitor output from pill bottles and help devise solutions.

We conducted a randomized controlled trial among new kidney transplant recipients provided with wireless pill bottles to determine whether automated reminders alone or paired with provider notification in cases of low adherence improve tacrolimus adherence compared to adherence monitoring alone. We considered the trial a pilot because of minimal preliminary data about pill bottle−measured adherence in the 6 months posttransplantation. The primary outcome was the percentage of correctly taken tacrolimus doses as estimated by pill-bottle openings. Given evidence of providers' limited ability to detect nonadherence, a secondary aim was to examine the accuracy of pharmacists' predictions of each participant's adherence during the trial.

METHODS

Overview

This study trial enrolled 120 kidney transplant recipients or kidney-pancreas recipients at the Hospital of the University of Pennsylvania. Each participant was provided with a wireless pill bottle (Vitality GlowCap; Vitality Inc) that recorded pill-cap openings; these data were transmitted in real time to the study database.[30] Participants were instructed to store only tacrolimus in the bottle and refill as necessary. Participation lasted 6 months and was approved by the University of Pennsylvania Institutional Review Board (protocol #814788).

Inclusion and Exclusion Criteria

The study was conducted in adults (aged ≥18 years) who were taking immediate-release tacrolimus. Exclusions included patient inability to manage medications, poor English comprehension (because of the requirement for direct communication with study staff), HIV-positive serostatus (because of drug interactions that often require unusual tacrolimus dosing regimens),[31] living more than 120 miles from the center (because these patients return to local care soon after transplantation), and/or discharge to an acute-care facility (where a patient would not personally manage medications). Participants could remain in the trial if prescribed immediate-release tacrolimus twice a day (usual practice) or a thrice-a-day regimen (1 participant).

Enrollment

Patients were approached for informed consent during the first 2 weeks after transplantation. During enrollment, the study coordinator provided a wireless pill bottle and demonstrated its use. Participation lasted for 180 days, including a 2-week initial wash-in period to become accustomed to the wireless device.

Participants indicated the times when they intended to take tacrolimus. The study coordinator created an account for each participant on the Vitality website and entered these times. Adherence data were transferred from the Vitality website to a web-based secure research platform called Way to Health.[32]