STUDY DESIGN:
PILOT STUDIES

Charles Flexner, MD
Johns Hopkins University

Pilot Studies:
Some published examples

An Open-Label Dose-Escalation Trial of Oral Dehydroepiandrosterone Tolerance and Pharmacokinetics in Patients with HIV Disease


California Pacific Medical Center, California Center, *Neudirfel, Inc., Miami, Florida; Department of Laboratory Medicine, University of California, San Francisco; Hemophagocytic Lymphoma, San Francisco, California; *Pediatric Section, San Juan Cappistrano, California; *NK Pharmaceuticals, Aherlow, Ireland; Department of Medicine, University of California, San Francisco, and the Medical Service, San Francisco General Hospital, San Francisco, California, U.S.A.
Summary: Dehydroepiandrosterone (DHEA) is a steroid reported to have immunomodulatory and anti-inflammatory effects in vitro and animal models, as well as modest in vivo at high doses. A phase I dose-escalation study was performed to evaluate the safety and pharmacokinetics of DHEA in subjects with symptomatic HIV disease and an absolute CD4 lymphocyte count of 200 to 500 cells/μl. Thirty-one subjects were evaluated and monitored for safety and tolerance. The oral drug was administered three times daily in doses ranging from 750 mg/day to 2,250 mg/day for 16 weeks. Some immunological and virological parameters were monitored as well. The drug was well tolerated and no dose-limiting side effects were noted. The drug was well tolerated and no dose-limiting side effects were noted. The drug was well tolerated and no dose-limiting side effects were noted. Dose proportionality was evidenced neither by the serum DHEA nor by DHEA-S time-concentration curves for the three dosing groups. However, the study cohort appeared to consist of two subpopulations with markedly different bioavailability for a given DHEA dose. No sustained improvements in CD4 counts nor decreases in serum p24 antigen or β2-microglobulin levels were observed. However, serum neopterin levels decreased transiently by 23-40% at week 8 compared with baseline in all dosing groups. DHEA was well tolerated by patients with mild symptomatic HIV disease; evaluation of this agent for efficacy in HIV disease would require randomized, controlled trials. Key Words: DHEA—HIV—Open label trial—Dose escalation trial.
What is a Pilot Study???
What is a Pilot Study?

- A small preliminary clinical study whose primary objective is to prove that more studies need to be done.
  
  ~ C. Flexner

Semantics

- Pilot Study
- Developmental Study
- Feasibility Study
- Phase I Study
- Small Exploratory Clinical Trial
- Hypothesis Generating Study
  
  As opposed to hypothesis-testing
- Etc.
What is a Pilot Study?

- The initial study examining a new method or treatment.

- A small scale preliminary study conducted before the main research in order to check the feasibility or to improve the design of the research.

--- NCI Dictionary of Cancer Terms

--- Wikipedia!

“...In a comprehensive literature search using Medline and the Web of Science we could find no formal methodological guidance as to what constitutes a pilot study.”


The Bottom Line
What question is usually being asked in a pilot study?

- “How do I get started?”
- “Is this technique / intervention / data mining exercise feasible?”
- “Do I need preliminary data to prove that my sample size is correct?”
- “How much data do I need to justify doing further studies related to this hypothesis?”

Good reasons to do a “Pilot Study”
- Educated uncertainty
- Feasibility concerns
- Sample size concerns
- Critical developmental needs
  - Assay development and/or standardization
  - New study instrument
  - New device or technique for endpoint measurement
Bad reasons to do a “Pilot Study”

- Inadequate literature review
- Need to generate hypotheses
- Running out of:
  - Time
  - Money
  - Patients
  - Patience
- Laziness

PILOT STUDIES: “Pretesting”

- Test integrity & feasibility
  - Recruitment & consent
  - Intervention (e.g. tolerance, compliance, retention)
  - Data collection (e.g. forms, interface, time)
  - Equipment
  - Other procedures (e.g. randomization)
- Refine methods and procedures
- Confirm or revise sample size estimates

PILOT STUDIES: “Pretesting”

- Recruitment & consent:
  - Will we get the types of participants that we think we will get?
  - Are any important segments of the target population being left out?
  - Will people turn down the opportunity to participate in our study? (what proportion? able to meet the sample size requirement in time? recruitment pool large enough? expand the inclusion criteria or go multi-center?)
  - Is it obvious who meets and who does not meet the eligibility requirements?
  - Can this be learned without a formal feasibility study?
PILOT STUDIES: “Pretesting”

Compliance and Retention:
- Acceptability / tolerability of intervention
- Will participants fail to comply with protocol requirements? (what proportion? need to modify protocol? revise analytic plan?)
- Will participants fail to finish our study? (what proportion? reduce participant burden? add run-in? increase sample size?)

PILOT STUDIES: “Pretesting”

Data Collection:
- Are all the important/required data items collected? (run through the analytic plan)
- Is there enough room on the data collection form for all of the data you receive?
- Who will be recording the data? (standardized training? standardized equipment & calibration? standardized procedures? blinding/masking procedures?)
- Any problems entering collected data?
- Are the data collection instruments validated and reliable in the target population?

“Murphy’s Law: anything that can go wrong will go wrong. “The reason to run a pilot study is to ensure that the things that do go wrong, go wrong during the pilot study so we can fix them before we start the full study!” – Nae-Yuh Wang
PILOT STUDIES: Endpoints

- Hard Endpoints
- Soft Endpoints
- Clinical Endpoints
- Surrogate Endpoints
- Biomarkers
- Genes (SNP's, Haplotypes, GWAS)

Don’t forget!
The value of n-of-1 studies and self-experimentation

ORIGINAL ARTICLES
Attempt to fulfill Koch’s postulates for pyloric campylobacter

Barry J. Marshall, John A. Armstrong, David B. McGeehan and Ross J. Glenny

The association between the newly identified bacterial, pyloric campylobacter (C. pylori), and gastritis has been studied extensively. The hypothesis that this bacterium plays a role in the etiology of chronic gastritis has been supported by a large number of epidemiological studies and clinical trials. In the present study, we describe a prospective, double-blind, placebo-controlled, randomized, multicenter trial designed to evaluate the efficacy of a new antibiotic regimen for the treatment of C. pylori infection. The regimen consisted of a combination of amoxicillin and clarithromycin, administered for 14 days. The primary endpoints were the proportion of patients who achieved cure at 14 days, defined as the absence of C. pylori colonization in the stomach at the end of treatment. The secondary endpoints included the proportion of patients who remained free of symptoms of gastritis at the end of the follow-up period. The results of the study demonstrated a high rate of cure and a low rate of recurrence, indicating that the regimen is an effective treatment for C. pylori infection. The study also provided further evidence for the role of C. pylori in the pathogenesis of gastritis and for the need for new, effective antimicrobial strategies.
Importance of adhering to the classical experimental method

- Hypothesis testing
- Sample size calculation
- Proper endpoint selection
- Proper study population

Give preference to publishable endeavors!

The Bottom Line

Do it right the first time!!!

- Scott Zeger, PhD