When Is Standard Treatment Sufficiently Active to Make Use of a Placebo-Controlled Trial Unethical?

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Investigator Blinding and the Use of Placebos in Randomized Controlled Trials

Case Vignette

Mrs K, a 58-year-old white woman living in Manhattan (who spends winters in Florida) was seen by her internist for her yearly check-up. The physician noted eight round, rough, sharply circumscribed skin lesions on the forehead and upper areas of both cheeks, with diameters ranging from 3 to 8 mm. The remainder of Mrs K's examination was normal, and the above-described lesions were limited to her face. The physician referred Mrs K to a dermatologist, who concurred in the diagnosis of actinic keratosis. The dermatologist took scrapings, and the cytology also suggested actinic keratosis.

The dermatologist explained to Mrs K that actinic keratosis may progress to skin cancer, and thus should be treated. She described the multiple treatment options available, including dermabrasion, cryosurgery, and topical ointments. Because of the number of lesions, she favored the application of topical ointments. She then went on to describe a recently approved clinical trial comparing a US Food and Drug Administration–approved proprietary ointment with a new generic formulation of the same agent and with an inert ointment containing the vehicle only. The assignment would be random and blinded so neither the patient nor the physician would know which was being applied. The trial randomization would be 40% proprietary ointment, 40% generic ointment, and 20% vehicle ointment (placebo). The consent form also indicated that the active agent is known to cause inflammatory reactions of the skin.

Mrs K agreed to participate in the trial, and was instructed to apply the ointment to the lesions twice weekly, and to return monthly to the dermatologist for follow-up examination. At the first month's visit, the dermatologist found the eight lesions unchanged, but no sign of cutaneous inflammation, thus making it likely that Mrs K was applying the placebo (inert) cream. On the second monthly visit, the dermatologist noted one of the lesions to have grown by 2 mm in diameter (although without major changes in appearance), and decided to take a biopsy (the involved lesion was not the one he had initially scraped). The biopsy revealed a squamous cell carcinoma, and it was thereafter resected with clean margins. A full work-up, clinically, radiologically, and by positron emission tomography, failed to demonstrate any metastatic lesion. Thereafter, Mrs K received treatment with the active

(proprietary) ointment, which induced not only the usual inflammatory reaction but also the slow regression of the actinic keratosis lesions.

Discussion

Research has demonstrated that double blinding can minimize the potential for bias in study outcomes. Retrospective studies provide evidence that both physicians and patients may expect new, experimental agents to perform better than current standards of care, and that this expectation could influence the conclusions drawn from clinical trials.¹ It has also been noted that drugs may be perceived as more effective when they are in the experimental arm of a study, rather than the reference arm.² This bias has been cited as one reason that measures of the effectiveness of some agents decrease over time. Effective double-blinding techniques minimize the influence of investigator and patient expectations.

In the double-blind trial discussed in this vignette, neither the physician nor the study participant is supposed to be aware of which agent the participant received. However, the vignette describes one of multiple examples where blinding of either the investigator or the patient is illusory. The dermatologist could easily conclude that Mrs K did not receive one of the active agents because she did not experience known effects already identified for that agent.

Whenever an active treatment is associated with a common and easily recognized toxicity (eg, alopecia as a result of chemotherapy, changes in laboratory results such as leukocyte counts) and is compared with a placebo or another agent that does not cause that toxicity, the investigator and/or patient may deduce which treatment is being applied. Another example comes from the ongoing international trial of adjuvant therapy for renal cancer after nephrectomy, which compares sunitinib (4 weeks on followed by 2 weeks of placebo), continuous sorafenib, and continuous placebo. A patient recently announced with confidence that he is on sunitinib because he felt lousy for 4 weeks and well for 2.

Because of ineffective double blinding, physicians may become aware that a given patient was randomly assigned to the placebo arm of a trial. Physicians may then feel obliged to ensure that the patient receives what the physician perceives to be the best treatment and recommend that the patient withdraw from the study. Because investigator expectations could affect study results, it is helpful when authors of articles that report on blinded studies discuss the specific blinding methods used. Disclosing this information allows readers to

evaluate the effectiveness of those methods for themselves, and draw independent conclusions about the potential for bias in the study data.

The vignette raises both the problem of false blinding and also whether random assignment to placebo is justifiable in a particular clinical scenario. In the vignette, Mrs K's dermatologist should have recommended that the patient enroll in the study only if he considered all of the arms to which she might be randomly assigned to be acceptable. When Mrs K enrolled in the study, she had not tried any of the standard effective treatments available for actinic keratosis, including the proprietary cream, which she could have accessed by prescription. The delay in treatment that resulted from her random assignment to the placebo arm of the study might have caused preventable harm. If so, the best course of action would have been to treat Mrs K's lesions immediately, without adding the specter of a delay raised by accrual to the placebo arm of a randomized trial.

When considering recommending a clinical trial for a patient, physicians should evaluate any use of placebo in accordance with methodological and ethical criteria. Daugherty et al³ note that use of placebo controls may be justified to blind physicians and patients regarding treatment assignment so as to minimize bias in assessment of study end points, provided patients are fully informed about blinding methods and the use of placebos. However, when an active therapy is available, comparison to placebo becomes problematic. If the nature of

an agent becomes apparent during the course of the trial, ethical concerns can be minimized by offering participants the opportunity to cross over to the active agent once primary end points are met. However, a trial that could require a participant to forego what is already known to be an effective standard treatment—and risk significant, adverse consequences—raises concerns. Physicians should investigate the scientific and ethical foundations of any trial before suggesting it for their patients.

If you have comments concerning this ethics vignette or topic suggestions for future ethics discussions, please contact us at jopeditorsdesk@asco.org.

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