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The Potential for Therapeutic Misconception in Pulmonary Arterial Hypertension Clinical Trials: A Case-Based Discussion

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"//connect.facebook.net/en_US/all.js#xfbml=1"; fjs.parentNode.insertBefore(js, fjs);
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This case study illustrates several of the potential challenges frequently encountered by clinical investigators working in the area of pulmonary arterial hypertension (PAH). It raises the issues of therapeutic misconception and clinical equipoise, and illustrates the importance of informing potential research participants of all their options in explicit detail.²⁰ It also emphasizes the importance of explaining to patients that they are being asked to participate in a study to advance medical knowledge and develop therapies for the population of patients with PAH, and not for their own benefit. While they may benefit from the study drug, if they in

fact receive it, this should not be offered as a reason for their potential participation. In addition, investigators should disclose any potential conflicts of interest to potential participants. During the past 2 decades, such clinical trials have advanced the treatment of patients with PAH and continue to offer the possibility of further improvements in our treatment of this devastating disease.

Randomized, controlled clinical trials are often based on the fundamental ethical requirement of “clinical equipoise,” or a genuine uncertainty within the medical community as to whether any of the treatment arms are superior to the others.^{1–3} Conflict can arise when the physician is confronted with deciding whether to treat a patient with a proven therapy or to offer a clinical trial to that same patient resulting in “treatment” via randomization.⁴ Similarly, conflict might also arise if, based on the scientific rationale supporting the use of a therapeutic agent, the patient prefers to receive that therapy, even in the absence of sound clinical evidence of efficacy in the disease state in question. The case presented here illustrates both of these potential conflicts, as well as challenges faced when attempting to balance the duty to provide individualized care and the prospect of randomizing patients into clinical studies in order to answer important questions and develop new therapies.

As this case illustrates, the delineation between physician and investigator is sometimes murky in practice. While the physician is obligated to act in the best interests of individual patients, the role of the investigator is to advance knowledge for potential widespread benefit.⁵ The obligation of the investigator is to protect research participants through the minimization of potential risks, yet at the same time, inform participants that they should not expect individual benefit and, moreover, that their individual care could be compromised by a research protocol. The researchers' responsibility to minimize participants' tendency toward “therapeutic misconception” is a significant ethical concern.⁶

BACKGROUND FOR THE CASE PRESENTATION

The Disease State: Scleroderma-Associated Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) can occur in association with a variety of connective tissue diseases (CTD), most often in association with scleroderma. CTD-associated PAH often has a poor prognosis.^{7,8} In these patients, PAH is progressive and particularly difficult to manage, with 2-year survival rates (prior to availability of recently developed therapies) of 40%-60%.^{7,9} Potential therapeutic options for PAH include prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase inhibitors (PDE-I).^{10–13} Despite these therapies, scleroderma-associated PAH unfortunately remains a very challenging disease to treat.^{8,13–16}

The Clinical Trial: A Randomized, Double-blind, Placebo-controlled, Phase II Multicenter Trial of a Monoclonal Antibody to CD20 (Rituximab) for the Treatment of Systemic Sclerosis-Associated PAH (Sponsored by the NIAID)

Rituximab is a B-cell depleting monoclonal antibody that is approved by the Food and Drug Administration (FDA) for the treatment of non-Hodgkin's lymphoma, CD20-positive chronic lymphocytic leukemia, and moderate to severe rheumatoid arthritis. Since it has been suggested that the pathogenesis of scleroderma may be, at least partially, B-cell mediated, this study will investigate this immunomodulatory agent as a novel therapeutic approach to scleroderma-associated PAH. The study targets patients with scleroderma-associated PAH with relatively recent onset (within the last 3 years) that persists despite treatment with one or more of the currently available therapies. Main inclusion criteria include: age 18-70, clinical diagnosis of systemic sclerosis (either limited or diffuse), diagnosis of PAH within the past 3 years with mean pulmonary arterial pressure \geq 30 mm Hg, 6 minute-walk distance within a prespecified range, and functional class II, III, or IV.

THE CASE

A 53-year-old male was diagnosed with scleroderma-associated PAH approximately 2-3 years ago. Despite aggressive medical therapy with chronic intravenous treprostinil and oral sildenafil, his PAH has been rapidly progressive; he now has clinical evidence of right heart failure, including ascites and lower extremity edema. Because of this clinical deterioration, he was admitted to the hospital for diuresis, consideration of additional PAH-specific medical therapy, and evaluation for possible future lung transplantation.

The patient's treating physician and a second physician colleague who is a site investigator and protocol co-chair for the study described above, both discussed possible options with the patient. The options included addition of an FDA-approved ERA, participation in this clinical trial, or lung transplant evaluation. It was explained that triple therapy with a prostanoid, a PDE-I, and an ERA, while utilizing agents that are all FDA-approved, had not yet been shown to be of additional benefit, above what might be seen with a prostanoid and a PDE-1. The potential risks and benefits of the addition of an ERA were also explained to the patient and his wife. It was further explained to them that another option might be to participate in the randomized and placebo-controlled clinical trial of rituximab described above. The scientific rationale for the study was explained in lay terms, highlighting the fact that it is not known whether rituximab would be of benefit in his disease state, even though the drug was FDA-approved for treatment of a particular type of lymphoma and rheumatoid arthritis. The potential risks associated with rituximab were explained, including its immunosuppressive effects and the increased risk of infection. The fact that the study is randomized, placebo-controlled, and double-blinded was described to the patient. Following this discussion, the patient and his wife both asked whether he could receive commercially available rituximab (off-label).

In response, the investigator described to the patient his discomfort prescribing rituximab off-label for pulmonary hypertension, especially given the absence of sound evidence supporting clinical efficacy in this situation and the potential risks associated with the drug. The investigator further explained that the trial was being performed because we did not know whether the drug could be of benefit in this disease (he really did believe that the trial had "clinical equipoise"). The treating physician generally agreed, but indicated that he would

somewhat reluctantly prescribe rituximab off-label, if this is what the patient desired. After much discussion, the patient ultimately decided to add an ERA to his current therapeutic regimen; such a decision would delay, per protocol, his eligibility to participate in the rituximab study for at least 3 months due to this change in his background PAH therapy. He also chose to be evaluated for possible lung transplantation.

QUESTIONS RAISED BY THE CASE

Is there a potential conflict when a patient is offered the choice of additional therapy previously shown to be of benefit in a disease (although perhaps not on the background of other therapies) vs the possibility of participating in a randomized, placebo-controlled trial of an agent not known to be of benefit in the disease state?

Most clinical investigators would acknowledge the potential conflict that can arise in such a situation, although the absence of evidence supporting benefit from adding the approved therapy might make enrollment in a placebo-controlled trial of add-on therapy less of an ethical dilemma.

What motivating factors exist for the investigator to enroll a patient into a clinical trial? There are a number of factors that could motivate the investigator to encourage the patient to participate in a clinical trial: the advancement of knowledge, academic achievement and promotion for the investigator, and financial support for the investigator's program. Although not an issue in this particular case, personal financial incentive could be a motivating factor when the investigator has an equity interest in the study.

How can such a potential conflict be managed? The best approach is to ensure that the patient is fully informed of his or her potential options, and is allowed to make a carefully considered, informed decision. The risks of medical treatments should be communicated in a comprehensive and transparent way; thorough education is extremely important. It may also be prudent to ensure that the patient's treating physician is involved in this process. Patients need time to consider options and ask questions in a frank, open, and balanced dialogue. Additionally, any potential conflict of interest that exists should be disclosed to the patient.

What if the clinical investigator is the patient's treating physician? This is sometimes the case; in such circumstances, the investigator must be very careful to present a balanced perspective on the options available to the patient. Another option would be to include a second qualified professional in the consenting process to assist in presentation of the options available to the patient and to minimize any possibility of coercion, even if unintended.

Is there a potential conflict if, based on the scientific rationale supporting use of a therapeutic agent, the patient prefers to receive that therapy even in the absence of sound clinical evidence of efficacy in the disease state in question? In other words, the patient asks the investigator and/or treating physician to prescribe the agent under study off-label (the drug is not FDA-approved for use in this disease state). In the case presented above, the patient expressed an interest in the possibility of receiving the drug under study outside the context of a randomized, controlled trial. He preferred to avoid the possibility of being randomized to placebo. This certainly presents a potential conflict to both the clinical

investigator and the treating physician. Is it ethical to prescribe (off-label) a drug associated with potentially serious side effects, based on scientific rationale for potential efficacy, in the absence of sound evidence of clinical efficacy? Interestingly, in the example presented above, the clinical investigator and the treating physician seemingly differed in their opinions in response to this question. This illustrates the potential conflict that can arise between clinical investigators and treating physicians. There might also exist conflict between the interests of “the group” (the medical community and future patients who might benefit from the knowledge obtained from the trial), and the interests of the individual. This may be even more challenging when the patient is seriously ill despite aggressive therapy. A treating physician might suspect that there will be benefit to the patient from use of the agent under study, even when used for a nonapproved indication. Paradoxically, such an anecdotal experience, if associated with a favorable outcome, might lead to the future conduct of a formal clinical trial.⁷ The patient’s impression that the drug under study might be likely to help him or her is an example of “therapeutic misconception.”^{18,19} Unfortunately, many patients enter clinical trials with this misunderstanding. From a scientific perspective, this makes the use of a placebo control, and blinding of the treatment assignment, important. From an ethical perspective, it illustrates the importance of communicating “clinical equipoise” to the potential research participant. It is very important that the patient understands that the answer to the question being asked by the study is truly unknown.

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