ABSTRACT

The wealth of research that is currently being conducted in cystic fibrosis (CF) may bring to fruition new treatments that may ultimately have a significant impact on progression of this disease. However, the research requirements involved in bringing these agents to the market are numerous and complex, patient expectations are high, and the general sense of optimism must be balanced against the knowledge that positive research study results may not necessarily materialize into clinically meaningful advances. This discussion explores the current research challenges that investigators face in meeting patient enrollment requirements, evaluating impact of therapy on critical patient outcomes (eg, survival), and extrapolating the available evidence. Also included are 2 brief case studies with audience discussion that illustrate the various issues that arise among patients participating in clinical research. (Adv Stud Med. 2010;10(1):24-28)

With the therapeutic pipeline filled with promising agents in phase II/III studies, patient and physician expectations appear quite high, and may even be analogous to those seen in the early 1990s, following discovery of the cystic fibrosis (CF) gene.1-3 Just this past year, Dr Richard Boucher was quoted by the New York Times as stating: “I do think we will see a cure . . . these therapies that hydrate the cystic fibrosis airway surface may be able to stop the progression of the disease in adults. And, very excitingly, in babies you may even be able to prevent it.”4

But just as in the past, when the prospect of gene therapy5 providing an imminent cure for CF was not realized, the positive research today may not materialize into clinically meaningful advances, and thus, the CF community must remain cautious. And although investigators are in the process of enrolling for and conducting numerous phase II/III studies, many challenges in CF research exist. Because the patient population is limited, researchers cannot address more than a few important study questions. Also, because multiple sites are necessary to reach adequate patient enrollment, clinical trial costs are high. Important outcomes related to the chronic changes in CF lung health (eg, lung function decline and exacerbation rate) require large sample sizes, and therapies that correct the basic defect will require long follow-up times to assess impact. Finally, the effects of therapy on survival cannot be directly studied.

In further examining the challenges that investigators face, it is important to consider where the majority of CF research is currently conducted and the expected enrollment requirements. The CF clinical trials network, or more formally known as the Cystic Fibrosis Therapeutics Development Network...
(CFTDN), was initiated with 8 centers in 1998, with support from the Cystic Fibrosis Foundation and the National Institutes of Health. Since then, CFTDN has conducted more than 50 therapeutic clinical trials, and in the past 5 years, CFTDN has enrolled more than 3150 patients into pediatric and adult CF trials. In 2009, CFTDN underwent a major expansion to include 77 therapeutic centers, which care for approximately 19 000 of the 30 000 US patients with CF. From these centers, an estimated 1160 patients (or 6% of the CF population) were enrolled into clinical trials. As a result of variability among the 77 sites in regard to research participation, study enrollment ranged from 1% to 16% of the patient population within each individual site. The estimated sample size necessary for trials in 2009/2010 is approximately 2300 patients, which is nearly twice that of the enrollment rate seen in the past year. The high enrollment requirements, as well as the increasing novel therapeutics under development, may lead to additional challenges at study centers. These centers must balance studies that compete for the same patient populations and increased patient expectations of new compounds being curative. To improve the prospects of meeting these increased study demands and improve clinical trial efficiency, study metrics (time to Institutional Review Board approval and time to first patient enrolled) are now being closely tracked.

Once clinical trials are complete, clinicians must weigh the evidence obtained from clinical research and decide whether a new therapy is appropriate for a specific patient. In assessing the available evidence, multiple sources (eg, Cochrane Collaboration and CF Foundation-sponsored systematic reviews) are ideal. Balanced treatment recommendations based on graded evidence and therapeutic benefits, such as those provided by Flume et al (Table), are considered very useful. In CF, strong evidence (grade A) is challenging to obtain, given the limited number of phase III clinical trials that have been conducted to date. In a systematic review of acute pulmonary exacerbations, published just this past year, no therapy received a grade of A. Only 2 therapeutic questions received a grade of B (continued use of chronic therapies during exacerbation and use of airway clearance during exacerbation), and the remainder received grades of C, D, or I. In settings where there is a lack of evidence, such as in pediatrics, off-label use of drugs is generally increased. In one study of inpatient pediatric wards in the United Kingdom, Sweden, Germany, Italy, and the Netherlands, more than 50% of children (421; 67%) received unlicensed or off-label medication during their hospital stay. Off-label use of medication may be more common in the United States, but there are no specific data on how often it occurs among patients with CF.

In examining just how much evidence is necessary to apply to new therapies for CF, a gap has been identified between empirical evidence and patient care. In overcoming this challenge when using off-label ther-

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<th>Therapy</th>
<th>Population</th>
<th>Evidence</th>
<th>Benefit</th>
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<tr>
<td>Inhaled tobramycin</td>
<td>Moderate to severe lung disease</td>
<td>Good</td>
<td>Substantial</td>
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<td></td>
<td>Normal to mild lung disease</td>
<td>Fair</td>
<td>Moderate</td>
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<td>Recombinant human DNase</td>
<td>Moderate to severe lung disease</td>
<td>Good</td>
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<td>Normal to mild lung disease</td>
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<td>Hypertonic saline</td>
<td>Fair</td>
<td>Fair</td>
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<td>Inhaled corticosteroids</td>
<td>Ages 6–18 yrs</td>
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<td>Inhaled β2 agonists</td>
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CF = cystic fibrosis; DNase = deoxyribonuclease.
Data from Flume et al.
therapy, patients’ expectations must be integrated into the decision-making process and patients must have a clear understanding of the risks and benefits of therapy. Clinicians must also be cautious in extrapolating study results to individual patients because the exclusion/inclusion criteria applied to the study population tend to be more stringent and involved than those used in practice. An important research question that is somewhat imbedded in this issue is whether the use of novel agents can be extended to patients outside of the study population. For example:

- Can an agent that was formally studied in small children be used in infants?
- Can a drug be used in patients with a different genotype?
- Can an agent be used for a duration that is far beyond that of the study window?
- If a drug is employed in non-label populations, how is it monitored?
- Can drugs be applied to different severity categories?

At this time, answers to these questions are not available, and thus, in the absence of important evidence-based information, choosing the best course of therapy remains a balancing act.

In conclusion, the advances made in CF have been dramatic. Clinical trials remain the key to advancing our knowledge, but enrollment needs in the future are expected to be high and expectations will need to be managed. Integrating results of trials into clinical care will also be challenging, but a challenge that we are fortunate to have. In the next section, 2 patient case scenarios are presented, along with audience discussion, to illustrate the strategies used in navigating through the various issues that arise among patients participating in clinical research.

**CASE #1**

A 23-year-old female patient with CF has a forced expiratory volume in 1 second of 55% of predicted. Her sputum culture is positive for *Pseudomonas aeruginosa*. The patient qualifies for 3 different ongoing clinical trials that are open for enrollment. The patient is reluctant to enroll in a research study because she does not want to receive placebo. She thinks she will “lose ground” and have disease progression during the study.

**Dr Goss**: If the study agent (a CF transmembrane conductance regulator [CFTR] modulator) is investigational and not US Food and Drug Administration (FDA) approved, what should the principal investigator (PI) do?

**Response**: I think this is an issue involving expectations, where patients may feel that if they do not receive the new medication, they might lose ground. In this situation, the patient should be educated that she will continue her current therapy even if she is randomized to a placebo group, and therefore, she will not lose ground. The other aspect to consider is that when patients are enrolled in a study, they are followed much more closely and there is a placebo effect just from participating in the study.

**Dr Goss**: I agree entirely. This is a situation where the patient must be educated about clinical research and should understand that she will have no access to the drug outside of the study anyway. I always emphasize to patients that, although the drug may appear exciting, clinical research is needed to show whether it is actually effective. There are many examples of early studies offering exciting results that were tempered by later, more definitive studies finding the therapy not to be effective. But had the study not been conducted and had patients started taking the drug without enrolling into a study, drug efficacy would never have been determined. In the CF community, the percentage of patients who participate in clinical research is higher than the percentage of patients with cancer participating in clinical research. So we have a very educated population with experience in research; however, continued patient education regarding the goals of clinical studies may benefit the overall care of patients and advance the science in CF. Overall, I have been amazed at the proportion of patients with CF who will participate in research. At some CF centers, up to 25% of patients are receiving investigational drugs.

**Dr Goss**: The patient wants to participate in a study and is eligible for 3 studies, one of which is underenrolled. How should the PI present the clinical research at the site?

**Response**: Ethically, all 3 studies should be explained to the patient, not just the study with under-enrollment.

**Dr Goss**: I agree. At our site, we have research nurses who present all the studies that the patients are eligible for; the patients then self-select for the studies that are feasible to them. We have, for example,
patients who cannot participate in tests that measure nasal potential difference. We clearly have to leave the decision to the individual patient.

Dr Goss: If the study agent is FDA approved for another indication, what should the PI do?

Response: I would try to convince the patient that even though the drug is FDA approved for another indication, we do not know if it will be efficacious in CF, thus we really do not know if the patient is going to gain any ground using it for the studied indication. The drug might actually be potentially harmful in the subset of patients being studied. That is why the first attempt with this therapy should involve a clinical trial.

Response: Another point I would like to add is that all patients tend to do better in studies by having more regular and careful follow-ups and frequent visits. Therefore, I would reassure the patient that, even if she were in the placebo group, she may do better than if she were not in the study at all.

Dr Goss: The patient really wants to participate in the study but is on an excluded agent. What should the PI do?

Response: First, I would ask the family what their motivation is for wanting their child to receive this treatment, and then I would ask about expectations in terms of risks and benefits. Rather than providing what the family is requesting, I think my obligation is to provide a risk/benefit assessment, which would require consideration of many factors such as the drug profile, the disease severity level that it was indicated for, and whether it is being used to treat or prevent complications.

Dr Goss: Most likely, the family’s expectations of risk are underestimated and their expectations of benefit are overestimated. I can guarantee that if some of the new agents are shown to be successful in adolescents and adults, families will request such agents for treatment in infants.

Dr Goss: A new study has started to enroll children who are 2 to 14 years of age in a randomized controlled clinical trial examining an FDA-approved agent. The family requests that the CF team treat the patient outside of the clinical trial. What should the physician do?

Response: Again, I think the benefits and risks have to be balanced in making this decision. As an example, statin drugs have recently been proposed to have theoretical evidence of anti-inflammatory effects in CF. The risks associated with statins are relatively low, but on the other hand, the benefits are low as well because efficacy studies are lacking. So in this case, I would most likely not comply with the patient’s request because I would not have enough confidence in the treatment.

Dr Goss: If physicians start offering a lot of treatments outside of the FDA-approved labeling, these studies will never be enrolled. We are seeing this with the MILES (Multicenter International LAM Efficacy of Sirolimus) trial for lymphangioleiomyomatosis.

CASE #2
A family meets with the CF team regarding their 2½-year-old child with CF. He was diagnosed on newborn screening and has no symptoms and a normal chest radiograph. The FDA has just approved a novel agent for CF, which improved CFTR function in adolescents and adults.

Dr Goss: The family requests that their child receive this novel treatment. No further clinical trials for this therapy are planned. What should the physician do?

Response: First, I would ask the family what their motivation is for wanting their child to receive this treatment, and then I would ask about expectations in terms of risks and benefits. Rather than providing what the family is requesting, I think my obligation is to provide a risk/benefit assessment, which would require consideration of many factors such as the drug profile, the disease severity level that it was indicated for, and whether it is being used to treat or prevent complications.

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Patient advocacy groups have realized that sirolimus, a potent anti-inflammatory immunosuppressant drug, appears to shrink kidney lesions in this disease. Because patients are being treated with this drug off-label, investigators are having difficulty enrolling patients into the study. So I think this is a really challenging question because, as a physician, your goal is to treat the patient, to be the patient’s advocate, and to provide the best possible care. I also think it is important to emphasize to patients the lack of knowledge about risks and benefits with off-label drugs. Hopefully, some of these agents will be tested in young children because most of us feel that intervention early in life may actually create a normal lung phenotype later in life.

REFERENCES


