The Design of Clinical Trials That Evaluate Antifungal Prophylaxis and Combination Therapy: Introduction and Overview

John H. Rex,1,2 John R. Wingard,3 Richard Wenzel,4 Raoul Herbrecht,5 Jack Sobel,6 and John E. Edwards, Jr.7

1AstraZeneca Pharmaceuticals, Macclesfield, United Kingdom; 2Department of Medicine, University of Texas Medical School–Houston, Houston; 3Department of Medicine, Blood and Marrow Transplant Program, Clinical and Translational Research, University of Florida Shands Cancer Center, Gainesville, Florida; 4Department of Medicine, Virginia Commonwealth University, Richmond Virginia; 5Department of Hematology and Oncology, Hôpital de Hautepierre, Strasbourg, France; 6Wayne State University School of Medicine, Detroit, Michigan; and 7Division of Infectious Diseases, Harbor-UCLA Medical Center, St. John’s Cardiovascular Research Center, Torrance, California

On 8 February 2003, the second in a series of meetings in honor of John E. Bennett, M.D., was convened in New York City. A report from the previous meeting was published in 2003. The goal of this second meeting was to discuss the design of clinical trials in prophylaxis and combination therapy. This supplement presents 12 articles by leading clinicians who are currently active in trials in this area and presents a current view of the unmet needs and challenges.

The options for treatment of serious fungal infections have broadened notably over the past 15 years with the introduction of fluconazole, itraconazole, voriconazole, caspofungin, and the lipid formulations of amphotericin B. The next few years promise further additions to this list, with the introduction of additional agents of the echinocandin and azole classes. These agents have provided new options, in particular for the treatment of candidiasis and aspergillosis. For example, these agents have shown that infections can be prevented in high-risk settings [1], that some infections can be treated with oral agents that have minimal toxicity [2], and that mortality rates of defined infections can be reduced [3]. However, there are still opportunities for improvements in therapy. For example, mortality rates remain at ~30% for invasive aspergillosis [3], and candidemia fails to clear promptly in >10% of cases [4]. In this context, the availability of multiple agents with non-overlapping modes of action presents an opportunity for combination antifungal therapy. Although this approach offers the tantalizing idea that it might dramatically improve outcomes [5], a large trial found that combination therapy might produce a trend toward a better microbiological outcome but that host factors still dominated response [4].

In light of these issues, a second meeting of the John E. Bennett Forum on the design of antifungal trials was convened on 8 February 2003. The meeting focused on issues in the design of clinical trials in prophylaxis and combination therapy. This is an area with far more questions than answers, and the articles in this supplement reflect this by providing insights into many debates on the best approaches to this area.

ANTIFUNGAL PROPHYLAXIS IN THE ALLOGENEIC STEM CELL TRANSPLANT RECIPIENT

Invasive fungal infections after allogeneic hematopoietic stem cell transplantation (HSCT) are major causes of morbidity and mortality. Candida and Aspergillus are the most common fungal pathogens. A number of observational studies have shown a bimodal distribution of infection [6, 7]. The first peak occurs early, before engraftment. The major risk factors for this early peak are neutropenia, damage to the gastrointestinal mucosa, use of antibacterial antibiotics, and indwelling central venous catheters. Several studies have shown the risk to be ~15%–20% during this period [8, 9]. Most of the fungal infections have been caused by Candida. Occasionally, aspergillosis also occurs during this interval. Many cases of aspergillosis before engraftment are due to a flare of infections that occurred during earlier chemotherapy courses; because of this, for
years many transplant centers excluded patients with prior aspergillosis from consideration for transplantation. Another risk factor for early aspergillosis is prolonged neutropenia.

The second peak occurs later, after engraftment, during the second and third months after HSCT. Several studies have shown the risk to range from 5% to 35%. Centers that have reported their rates at different intervals have noted an increase in rates of infection over time, and the time at onset has shifted to later times [6, 10, 11]. The major risk factors are the occurrence of acute or chronic graft-versus-host disease and the use of corticosteroids to either prevent or treat graft-versus-host disease. Other risks include T cell depletion of the donor stem cell graft and mismatches between the donor and recipient. Aspergillosis accounts for the majority of fungal infections during this second peak. Other mold pathogens, including the agents of zygomycosis and scedosporiosis, occasionally cause late fungal infections.

During the forum, 3 areas of current interest were debated at length. As discussed by Marr [12], several prospective randomized trials have demonstrated the effectiveness of fluconazole prophylaxis to prevent invasive Candida infections. Fluconazole during the pre-engraftment period has been endorsed as an appropriate infection-control measure in the consensus guidelines for infection control produced by the American Society of Bone Marrow Transplantation, the Infectious Diseases Society of America, and the Centers for Disease Control and Prevention [13]. Accordingly, the early peak of invasive fungal infections before engraftment has decreased enormously [14–16]. Also contributing to the decrease in early infection are advances in care of the transplant recipient, including the use of hematopoietic growth factors, the increased use of nonmyeloablative conditioning regimens, and the optimization of stem cell content in the hematopoietic graft to speed engraftment and shorten the neutropenic risk period.

Unfortunately, there is, to date, no proven strategy to prevent mold infections. Moreover, changes in transplantation practices have contributed to an increase in infections, including the more frequent use of alternate donors (e.g., unrelated donors and mismatched family members), alternate donor sources (e.g., cord blood), graft-manipulation techniques (e.g., use of T cell depletion or CD34+ cell selection), and the use of anti-T cell antibodies, all of which are associated with a slower pace of immune recovery. Not surprisingly, these forces have been associated with a relentless climb in late-onset fungal infections, primarily aspergillosis.

Mortality due to aspergillosis following allogeneic HSCT is exceedingly high, and the case-fatality rate in HSCT recipients is the greatest of all patient risk groups. In a recent randomized trial of first-line treatment that compared initial therapy with voriconazole (2 iv doses of 6 mg/kg of body weight on day 1, then 4 mg/kg b.i.d. for at least 7 days, followed by 200 mg orally b.i.d.) versus amphotericin B (1–1.5 mg/kg/d) [3], the response rate in the subset of allogeneic HSCT recipients treated with amphotericin B was only 13%. The response rate among HSCT recipients treated with voriconazole was significantly higher, but still was only 32%.

Clearly, new approaches are needed. Thus, participants in the forum also debated additional studies and ideas. Wingard [17] captures these concepts in an analysis of the design issues in a prospective randomized double-blind trial of prophylaxis with fluconazole versus voriconazole after allogeneic hematopoietic cell transplantation.

ANTIFUNGAL PROPHYLAXIS IN THE LEUKEMIC PATIENT

Although effective prevention of candidal infection is accepted in patients undergoing HSCT, the question is still controversial in patients with leukemia who are undergoing induction or consolidation chemotherapy. Numerous studies have addressed this issue and provide different conclusions based mainly on differences in the incidence of fungal infection in the placebo control group [18, 19]. In particular, a meta-analysis found that effective prophylaxis is achieved with fluconazole when the incidence of candidal infection in the placebo arm is >15% [18]. Another meta-analysis of 7 studies with 2181 episodes supports prophylactic efficacy of itraconazole oral solution (but not the capsules) in reducing the rate of fungal infections in patients with neutropenia [20].

Voriconazole, posaconazole, and the echinocandins have the spectrum, pharmacokinetic profile, and efficacy in documented infections that make them suitable for prophylactic studies. In a summary of this session, Menichetti [21] addresses several issues concerning the design of prophylactic studies with these new drugs in patients with leukemia, including what comparator to use for the assessment of new drugs, how to select the patient population to ensure that these patients are at risk and would benefit from prophylaxis, and what the appropriate end points are for a prophylactic study.

ANTIFUNGAL PROPHYLAXIS IN PATIENTS IN THE SURGICAL AND INTENSIVE CARE UNIT

Candida is the fourth leading cause of nosocomial bloodstream infections in US hospitals [22, 23]. These infections are associated with a crude mortality rate of 40% on average and an estimated attributable mortality of 25%, which suggests that five-eighths of the deaths are directly related to the infection and three-eighths to the underlying disease conditions. Antifungal therapy can be effective only for that fraction of deaths directly related to the infection.

At least half of nosocomial bloodstream infections, including those caused by Candida species, are found in patients in critical care units, with patients in surgical intensive care units disproportionately af-
fected. Thus, it should not be a surprise that much work has been directed at seriously ill surgery patients. Key risk factors were discovered 15 years ago and have been confirmed repeatedly: the presence of an indwelling central vascular catheter, exposure to a large number of antibiotic classes, renal insufficiency, and an increase in body sites colonized with Candida [24]. Thus, it is now possible to identify high-risk surgery patients at risk of subsequent infections. This is important because effective prophylaxis would have an important role in reducing morbidity and mortality associated with these infections.

From this section of the forum, Calandra and Marchetti [25] and Lipsett [26] review the clinical trials of antibiotic prophylaxis directed at fungal infections in patients in surgical and surgical intensive care units, respectively. Success has been achieved in both arenas (especially with respect to identification of such high-risk factors as recurrent gastrointestinal leakage and surgery for necrotizing pancreatitis), and the principles of improved clinical trials have been elucidated. These authors set the stage for future clinical trials of prophylaxis in high-risk patients.

ANTIFUNGAL PROPHYLAXIS CLINICAL TRIALS: OTHER CONCERNS

This session focused on other concerns for designers of antifungal prophylaxis trials. Singh [27] tackles the challenging area of antifungal prophylaxis and solid-organ transplantation. Prophylaxis trials in solid-organ transplant recipients have often been frustrated by small sample sizes and year-to-year variations in predicted event rates (e.g., better technical approaches appear to be reducing the rate of candidal infection after liver transplantation). However, some groups of transplant recipients (e.g., lung transplant recipients [28]) show significant and sustained event rates, and prophylaxis is often thought to be desirable.

Perfect, Ashley, and Drew [29] examine a specific twist with respect to prophylaxis following lung transplantation. The transplanted lung is exposed to a wide variety of potential environmental sources of fungi, and the idea of local prophylaxis with a drug delivered by the aerosol route has long intrigued. The authors review their work in this area and, in particular, focus on the potential advantages of amphotericin B lipid complex as a nebulized prophylactic agent.

Finally, Powers [30] surveys the regulatory issues surrounding prophylaxis trials. By reviewing definitions and the selection of appropriate patient populations and end points, he provides detailed insight into the effect of different design choices on the strength of a clinical study and on the likelihood of yielding a convincing result.

COMBINATION ANTIFUNGAL THERAPY

The forum closed with a discussion of the knotty issues surrounding combination antifungal trials. To date, only a small number of large randomized combination therapy studies have been done [4, 31, 32], and these have answered only a limited number of questions. In the coming years, there are critical questions to be asked about a wide variety of possible combination approaches to antifungal therapy—the possibilities include antifungal agents with other antifungal agents, antifungal agents with cytokines, and antifungal agents with antibodies. Given the difficulty with enrollment of large numbers of patients with proven mycoses [33], fully powered multiarm studies that compare all possible combinations of strategies will be few and far between. Thus, careful thought needs to be given to innovative approaches.

In the first article in this segment, Kullberg, Lashof, and Netea [34] discuss the potential for combinations of antifungal agents with cytokines or other immune system modulators. They review the theory behind this approach and discuss some of the issues that would have to be resolved if such studies are to be successfully implemented.

Sobel [35] reviews the available clinical information on the use of combinations of antifungal agents in large trials. Only a limited number of such studies have been done, and their strengths and weaknesses are educational. Afterwards, Powers [36] discusses the regulatory issues surrounding combination therapy trials. Consideration of the issues he raises is critical to serious progress in this arena.

SUMMARY

Antifungal therapy has made great strides over the past 15 years. Paradoxically, and in part as a consequence of this success, the field is now entering a phase during which additional improvements in therapeutic response are going to be more difficult to achieve and to convincingly prove. Thoughtful evaluation of the possible novel approaches (and combinations of novel approaches) is going to require significant cooperation among the partnership of industrial, academic, and regulatory workers in this challenging field.

On the basis of the material presented and discussed during the forum, key future studies and projects for the field as a whole include the following:

1. Randomized multicenter studies of candidal prophylaxis in the intensive care unit setting. Such studies could test various approaches to prediction of candidal infection.
2. Randomized multicenter studies of combination antifungal therapies. The most interesting at present would arguably be that of an echinocandin with an azole as therapy for aspergillosis (e.g., voriconazole with and without caspofungin). Even if exploratory and limited in size, randomized studies that followed the ideas proposed by Powers [36], focused on patients with proven disease, and attempted to use
novel response markers might yield valuable information for future work.

3. Systematic validation of surrogate markers for candidiasis and aspergillosis. The currently available diagnostic tests have not been formally linked to outcome, yet doing so is a key requirement for their use as clinical response measures. Such tools would permit investigators to address some of the more difficult trial-design issues raised in this forum. In particular, validated surrogate markers would be of tremendous help in simplifying the current challenges of end-point rules. Such markers could be used to improve the scoring of patients whose treatment was changed to empirical antifungal therapy, to permit better approaches to interpretation of fever (including the possibility that fever might be discounted entirely as an outcome measure), and to provide better interpretation of outcomes among subjects who die during a clinical trial.

Some of these steps are either currently under way or are being discussed as possible studies. Implementing these trials and developing these tools will require sustained effort but could provide opportunities to generate significant new and valuable information.

References

17. Wingard JR. Design issues in a prospective randomized double-blinded trial of prophy-