Clinical Trials for the Treatment of Secondary Wasting and Cachexia

Introduction

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This workshop was the second in which the Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences (ASNS) together with a consortium of supporters from Federal Agencies and the corporate community attempted to assess the state of the art, identify gaps in knowledge, and make recommendations about strategies for addressing critical needs in the area of nutrition and disease. The first workshop, “Nutrition in Pediatric HIV Infection: Setting the Research Agenda,” culminated in the publication of the proceedings (Raiten 1996) and led to continued discussions about key questions in research related to nutrition and clinical care.

One of the needs identified in that earlier effort was the lack of clearly defined endpoints for the assessment of the impact of interventions on secondary wasting associated with not only HIV infection/AIDS but several other chronic diseases and conditions, including chronic renal and gastrointestinal diseases, cancer, and diseases in the elderly. A Planning Committee consisting of Drs. Steven Hirshfeld, Marianne Mann, and Elizabeth Koller of the FDA and Dr. Elizabeth Higgs of the National Institute of Allergy, Immunology and Infectious Diseases of the NIH was responsible for delineating the scope and approach to be used to address this important question.

The goal of this workshop was to create a forum for an exchange of ideas and experiences regarding wasting trials and to use this forum as an opportunity to discuss the appropriateness and meaning of endpoints used in these trials. Specifically, the workshop was designed to:

- Review the pathophysiology of wasting and cachexia across various clinical conditions including HIV infection/AIDS, cancer, gastrointestinal disorders and chronic renal disease, and in geriatrics and pediatrics. A particular emphasis was placed on differences and commonalities between and among these conditions with a specific focus on changes in body composition and the clinical relevance of such changes to morbidity and quality of life.
- Identify available methodologies for the determination of body composition. A logical concomitant of this discussion was the impact of nutritional status, physiological state (e.g., exercise and activity level), and metabolic status on body composition using data from healthy subjects as the reference point. A particular focus was placed on the determination of the utility of methodologies within the context of monitoring changes over time in clinical trials.
- Present and discuss the appropriateness of measuring changes in body composition for each given clinical entity. Other relevant issues discussed in this context were special consideration for developmental and gender differences both within and between conditions.
- Include discussions of the relationship between changes in body composition and quality of life, e.g., physical function and endurance.
- Discuss appropriate endpoints to be used in clinical trials of interventions for the treatment of clinically relevant weight loss. Breakout groups were designed to allow input from various stakeholders in the design of clinical trials and the development of new therapies. Representatives from the corporate, regulatory, academic/clinical research, and patient communities were involved in these discussions and selection of endpoints for each clinical group.
- The rationale for the workshop was based in part on an increasing body of evidence that weight loss, and particularly loss of body protein, contributes to shortened survival in people with a variety of conditions including HIV infection/AIDS, cancer, chronic gastrointestinal and renal diseases, and the elderly. In light of the prevalence of these conditions, the potential burden of wasting both from a clinical and public health perspective is large.
- A general perception is that wasting and cachexia in illness are secondary to the more fundamental underlying pathologic process, and that improvement is possible only when the disease process is attenuated or eliminated. However, recent clinical findings suggest that successful treatment of the primary disease does not always ameliorate the problems associated with wasting and/or cachexia. Consequently, a need exists for interventions, e.g., drugs, nutrition, or life-style changes, designed to stabilize or reverse the wasting process and its concomitants. Currently, there is no consensus for the analysis, evaluation, or treatment of patients presenting with weight loss, wasting, or cachexia. Understanding of the patho-


genesis of wasting as it relates to specific diseases is fundamental to the provision of appropriate care.

Wasting, often accompanied by cachexia, is a multifactorial process involving complex interactions of the gastrointestinal, endocrine, and immune systems. Recent advances in endocrinology, physiology, and pharmacology have led to the development of new treatments for enhancing weight gains in chronically ill patients. Technological advances in the measurement of body composition now allow for the assessment of changes in specific body compartments that might be impacted by these new therapies. However, despite these therapeutic and methodological advancements, confusion remains in the scientific community about the interpretation of a given change in body composition.

With the advent of new treatments comes an increased burden on both the developers and the regulatory communities to generate data that are sensitive, specific, reliable, and comparable across protocols. To date, studies focusing on the treatment of wasting have been limited both in terms of number and appropriateness of design. Few have addressed the long-term ramifications or the functional implications of the investigated treatment. Changes in body composition remain the sine qua non of endpoints in clinical trials involving new interventions for the treatment of wasting. It was clear to the members of the Planning Committee involved in the evaluation of these protocols that a more sophisticated level of understanding of the significance of a change in body composition is required as more new therapies emerge. The workshop was designed to address this and related issues.

The workshop began with a presentation by Dr. Janet Woodcock, Director of the FDA’s Center for Drug Evaluation, of the key issues faced by those responsible for making decisions about new treatments based on the weight and quality of available data. This was followed by an overview of the pathophysiology of wasting presented by Dr. Alfred Goldberg. Reviews of secondary wasting in HIV Infection/AIDS, cancer, chronic renal and gastrointestinal diseases, and aging were presented by Drs. Macallan, Tisdale, Kopple, Fisher, and Roubenoff, respectively. Throughout these presentations two common themes emerged of metabolic dysregulation and the concomitant loss of lean body mass. Based on these presentations there does appear to be disease-specific differences in the mediators of these changes that, if appropriately considered, could lead to insights into the role of disease-specific clinical changes in the pathophysiology of wasting and the identification of endpoints for evaluating new interventions.

In addition to the individual disease states and conditions, there were presentations on special considerations associated with developmental stage of the patients to be evaluated in clinical trials of new interventions. Dr. Poehlman presented a perspective on those issues to be considered in studies involving a geriatric patient population. Dr. Louis Underwood discussed considerations relative to the involvement of children in such studies.

The presentations on specific endpoints included body composition by Dr. Gilbert Forbes, nutritional and metabolic endpoints by Dr. Morey Haymond, physical function and endurance by Dr. Jay Shah, and performance and quality of life parameters presented by Dr. Marcia Testa. The final session of the didactic phase of the workshop included presentations on currently available interventions including a brief exposition of the evaluative process by Dr. Marianne Mann. Overviews of two prime interventions were also provided by Dr. Bruce Bistrian, who discussed dietary intake and Dr. Elsworth Buskirk who reviewed the field of exercise physiology in terms of the potential impact on outcomes in clinical trials.

Following the plenary talks, workshop attendees participated in breakout groups designed to address issues and make recommendations about the selection of appropriate endpoints for clinical trials in specific clinical populations. Through LSRO’s experience in previous workshops of this type, it was found that an effective way of utilizing the collective expertise and energy of workshop attendees is through a discussion group format. The Planning Committee agreed that this would be an essential component of this effort and decided the focus of the discussion groups should be on the clinical disorders and conditions covered in the presentations. Consequently, the breakout groups were HIV/AIDS, cancer, chronic renal and gastrointestinal diseases, geriatrics, and special considerations for trials involving children. The activities of each group were coordinated, recorded, and summarized by discussion group leaders chosen for their expertise in the particular focus area. The groups themselves were constituted so as to contain a cross representation of members with specific clinical experience in the subject area, as well as members of the regulatory and corporate communities.

These proceedings represent the presentations of the workshop speakers and the collective efforts of the workshop attendees in their respective breakout groups. LSRO staff wishes to express its gratitude to all of the sponsors for their generosity and cooperation in this effort. Special acknowledgment goes to the efforts and contributions of the members of the Planning Committee, particularly Drs. Hirshfeld, Koller, and Mann, and the workshop attendees for their enthusiasm and contributions.

It is gratifying to note that in the intervening months since the workshop, a Wasting Working Group (Appendix A) has continued to focus on defining the critical components for trials of new drugs and treatments for wasting and cachexia. A product of this ongoing effort has been the development of a proposed listing of inclusion and exclusion criteria for such trials. This draft list is presented in Appendix B. Hopefully, the conclusions and recommendations provided herein along with the continued efforts of the Wasting Working group will form the foundation for a more effective, focused, and cooperative effort aimed at the further elucidation of the pathophysiology and role of secondary wasting in chronic diseases and the identification of the most meaningful endpoints for the evaluation of new interventions to address this important public health problem.