PERSPECTIVE

Endpoints for Clinical Trials Testing Treatment of Acute Graft-versus-Host Disease: A Joint Statement

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Currently, no agents are approved by the United States Food and Drug Administration (FDA) for either prevention or treatment of acute graft-versus-host disease (aGVHD). Formal precedents establishing a comparative basis for assessing the efficacy and safety of new investigational agents are still lacking. As a step toward addressing this problem, a panel of experts met on 2 occasions to reach consensus on recommendations for terminology describing a clinically meaningful primary endpoint in studies assessing treatment for aGVHD. The panel recommended terminology for "very good partial response" (VGPR) that includes both diagnostic and functional criteria. The central hypothesis leading to this proposal is that the potential harm of giving more treatment than needed to produce or maintain complete response exceeds the harm of slight undertreatment that may be associated with less than complete response. VGPR clearly cannot be used as the sole outcome measure in GVHD treatment trials, and must be considered in the context of survival and safety. The proposed use of VGPR as the primary endpoint in GVHD treatment trials will remain provisional until its use has been validated through experience.

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INTRODUCTION

Progress in the treatment of acute graft-versus-host disease (aGVHD) requires appropriate planning, conduct, and interpretation of results of clinical trials. Most of the historical studies that have assessed the efficacy of treatment for aGVHD were sponsored by academic investigators. As a result, clinical practice in the management of GVHD has been based largely on institutional and physician experience, with some consideration of evidence from the literature [1]. Currently, no agents are approved by the United States Food and Drug Administration (FDA) for either prevention or treatment of aGVHD. Numerous clinical trials with GVHD-related endpoints are in progress, although very few phase III studies have a primary endpoint directly related to treatment of GVHD. Because the field lacks formal precedents that could provide a consistent comparative basis for assessing the efficacy and safety of new investigational agents, the design of trials to demonstrate overall clinical benefit with statistical certainty remains extremely difficult both for academic and industry sponsors.

The challenges inherent in assessing response to treatment of aGVHD in the context of the complex and variable manifestations of the disease suggest the need for a more standardized and clinically meaningful approach to clinical trial design [2]. Such guidance would benefit regulatory agencies, the transplant community, sponsors, and ultimately the patients for whom these new treatments are intended. A similar effort for chronic GVHD (cGVHD) has resulted in the publication of a series of consensus documents describing unified recommendations for the diagnosis, staging, and response criteria for cGVHD. This effort was

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sponsored by the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease [3-8].

As an initial step in addressing clinical trial design for aGVHD, a panel of experts met on 2 occasions to reach consensus on recommendations for terminology describing a clinically meaningful primary endpoint in studies assessing treatment for aGVHD. The goal was to develop criteria for treatment success that are sufficiently flexible to allow interpretation according to institutional protocol and physician experience, whereas minimizing subjectivity and bias to achieve sufficient consistency of response for regulatory approval.

Overview of Regulatory Climate in Oncology and Autoimmune Disease

A regulatory approval pathway is clearly needed for products intended for treatment of aGVHD. Such pathways have already been established for products in other therapeutic areas such as oncology and autoimmune diseases. The overall goal of clinical trials is to provide direct evidence of clinical benefit for a treatment. Although improved survival would provide persuasive evidence of benefit in a GVHD treatment trial, experience has shown that successful control of GVHD does not necessarily lead to improved survival. For example, a recent study by Levine et al. [9] showed that despite impressive differences in day 28 response rates after treatment of aGVHD with etanercept plus steroids compared to steroids alone, survival differences were observed among patients who had related donors, but not among those with unrelated donors. Among patients with related donors, the difference in survival between the 2 treatment groups was much smaller than the difference in response rates. In GVHD treatment trials, differences in the magnitude of response and survival effects are likely related to complications such as infection, regimen-related toxicity, recurrent malignancy, and preexisting conditions unrelated to GVHD [10]. Even though most GVHD treatments are not likely to produce a survival benefit, survival remains as an appropriate secondary endpoint to consider in aGVHD treatment trials.

Although prolonged survival is considered the most reliable endpoint with clinical benefit in oncology trials, the FDA has accepted nonsurvival endpoints such as tumor response rates as the basis for both regular and accelerated approval. In studies of patients with serious or life-threatening diseases, accelerated approval status permits the use of nonsurvival endpoints if they are reasonably likely to provide clinical benefit. Postmarketing studies are usually required to confirm clinical benefit [11]. From January1990 to November 2002, 68% (39 of 57) of regular approvals and all 14 accelerated approvals for oncology drugs were based on nonsurvival endpoints [11].

Regulatory approval pathways based on nonsurvival endpoints have been established for products in autoimmune diseases that have some similarity to GVHD, including Crohn's disease, rheumatoid arthritis, and systemic lupus erythematosis (SLE). For these chronic inflammatory diseases characterized by episodes of flares and remissions, the goals of treatment are to control inflammation and suppress disease activity. The first biologic (infliximab) for Crohn's disease was approved in 1998 for reduction of signs and symptoms in patients with moderate to severe active disease. In 2002, a supplemental filing was approved for inducing and maintaining clinical remission of Crohn's disease [12]. Thus, infliximab was first approved based on induction of clinical response, whereas repeated therapy and maintenance of remission was assessed in a subsequent trial [13,14].

Treatment success in clinical studies of autoimmune diseases is not predicated on producing complete response (CR) or remission, but on demonstrating improvement in a validated score or index based on a set of established measures of activity in diseases such as rheumatoid arthritis [15], SLE [16,17], and Crohn's disease [18]. These indices have been periodically reviewed and updated as better understanding of disease pathophysiology and new treatments evolve. A disease index or score, however, might not be appropriate for treatment trials in aGVHD, because expectations for aGVHD differ from those for chronic autoimmune diseases. In autoimmune disease, mortality is not a key issue, whereas death is an appreciable risk with GVHD. Furthermore, a disease activity score is applicable for extended periods of time in patients with autoimmune diseases, but for only a short period time in patients with aGVHD. Typically, GVHD has 1 of 3 outcomes: death, progression to cGVHD, or complete resolution within a period of 4 to 10 weeks. In most cases, manifestations do not persist for longer periods of time without progression to cGVHD. Therefore, control of GVHD manifestations measured primarily as the response and secondarily as the durability of the response might have the greatest impact in determining these 3 possible outcomes.

Challenges Facing aGVHD Treatment Protocols

The close relationship between aGVHD and cGVHD and the lack of an accepted severity index complicate the measurement of outcomes in GVHD treatment trials. The introduction of nonmyeloablative conditioning regimens has highlighted some of the difficulties in distinguishing aGVHD and cGVHD [19]. Although aGVHD is often associated with the development of cGVHD, experts agree that aGVHD and cGVHD should be viewed as separate diseases, despite the extensive overlap in signs, symptoms, and management strategies [20-22]. Currently, no single