Introduction to surrogates and evidence-based mini-reviews

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Building on the success of *Hematology 2008*, last year's American Society of Hematology Education Program Book, a series of focused mini-reviews is provided in this edition of the educational book. A faculty member working with a junior colleague (oftentimes someone who has completed the American Society of Hematology Clinical Research Training Institute Program) writes these reviews. The reviews are brief, focused on a particular area of the speaker's area of expertise, and amenable to a data review and presentation. The authors present the evidence available, make recommendations, and grade their recommendations based on the strength of the evidence supporting them. These reviews provide practical recommendations to clinicians who might encounter the specific clinical circumstance discussed in each article.

Systematic reviews of therapeutic areas have taken on an increasing role as medicine becomes more evidence-based.[1] Evidence-based reviews guide both guideline development and funding decisions—and thus will become even more important tools as time passes. Furthermore, well-done reviews inform the development of clinical guidelines that provide feedback when physicians' practices are being evaluated.

The methodology of systemic reviews is now highly refined. Well-performed systematic reviews are published in leading journals and funding agencies are recognizing the funding needs of groups that perform such analyses.

Although systematic reviews allow the gathering of data from multiple sources (and thus increase the power of the study to detect differences in outcomes that cannot be discerned from individual studies), the author of a systematic review is frequently faced with a choice of outcome measures to include in the analysis. In general, systematic reviews should confine their attention to patient-important outcomes such as survival or freedom from clinically relevant events. Systematic reviews should not, in general, present surrogate outcome data as their primary analysis since (a) most surrogates have not been well validated, and (b) the purpose of systematic reviews is to gather sufficient information to allow conclusions about less-common events, such as patient-important outcomes. A "patient-important outcome" is an event that is perceptible to the patient and is of sufficient value that changing its frequency would be of value to the patient. Surrogate outcomes are outcomes for which changes do not directly impact the patient's disease status or well-being, but which are theoretically tied to the patient's disease process. Examples of patient-important outcomes include fatigue, relapse and death. Surrogate markers may include changes in laboratory parameters (eg, hemoglobin, platelet count, monoclonal protein levels) or imaging (eg, venographic deep vein thrombosis).

Authors may be tempted to use surrogate endpoints in both original scientific research and in systematic reviews because surrogate endpoints usually occur more frequently than patient-important outcomes. The increased number of outcomes found when a surrogate marker is used allows more precise estimates of a treatment effect than are obtained using patient-important outcomes. Classic examples of surrogate outcomes include the frequency of cardiac arrhythmias as a surrogate for sudden cardiac death, cholesterol levels as a surrogate for myocardial infarction, and changes in CD4 counts as a surrogate for outcome in patients with HIV. Hematology research relies heavily on surrogate markers. Trials of therapies for hematological malignancies use a variety of such outcomes including the speed of resolution of serum or cellular markers of malignancy and patient-derived outcomes such as times to complete remission or the likelihood of an individual patient achieving a partial or complete remission. Use of these surrogate markers requires complete confidence that each outcome correlates reliably with a patient-important outcome (such as survival, freedom from need for treatment, or freedom from toxicity) since interventions that impact a surrogate, without an impact on patient important outcomes, are of little or no clinical use. Too often research is performed with the assumption that changes in the surrogate correlate directly with changes in the patient-important outcome. For example, it is well established that the international normalized ratio (INR) is an effective surro-

gate for bleeding risk in patients receiving warfarin; thus as the INR becomes elevated the risk of bleeding increases.[2] Based on this observation our research group has shown that low-dose oral vitamin K rapidly returns coagulation to the desired range in patients presenting with excessively prolonged INR values.[3-5] However, a large randomized trial, powered to detect differences in bleeding rates between patients allocated to vitamin K and those allocated to placebo showed a rapid reduction in the INR with vitamin K, but no reduction in bleeding.[6] Thus, the assumption that changes in the INR reflect changes in bleeding risk was proven incorrect, invalidating the INR as a surrogate marker for bleeding risk in this setting. Other examples wherein as surrogate was proven invalid include platelet counts in essential thrombocytosis[7] and the hemoglobin value in critically ill patients.[8]

There are circumstances within which surrogate endpoints may be of specific value. In early phase research a "proof of concept" study oftentimes uses a surrogate marker (for example, changes in monoclonal protein levels in myeloma research) since if the intervention does not reduce the surrogate it is biologically implausible that it will reduce patient-important events. Similarly, dose-finding studies may use response of surrogate markers to gauge the effect of differing intensities of therapy. However, and in both cases, the hypothesis that a novel agent or intervention is effective should be confirmed in studies powered to detect patient-important events.

To avoid the issues inherent with the use of surrogate markers we have asked the authors of our mini-reviews to confine their attention to outcomes of importance to patients. In so doing we hope to increase the clinical relevance of our findings. More generally, as readers of the medical literature and consumers of systematic reviews, it is critically important that we examine the endpoints presented in research. Any paper that uses surrogate endpoints (even well-established ones) should be regarded as hypothesis generating—studies (or reviews) that focus on patient important outcomes allow us to better judge the impact of our interventions on patient outcomes.

Disclosures

Conflict-of-interest disclosures: The author is a consultant for Sanofi-Aventis, Leo Pharma, Pfizer, Bayer, Boehringer-Ingelheim Pharmaceuticals, and Artisan Pharma; receives honoraria from Sanofi-Aventis, Leo Pharma, Pfizer, Bayer, and Boehringer-Ingelheim Pharmaceuticals; receives research funding from Sanofi-Aventis, Leo Pharma, and Pfizer; and sits on advisory committees for Sanofi-Aventis, Bayer, Boehringer-Ingelheim Pharmaceuticals, and Artisan Pharma.

Off-label drug use: None disclosed.

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