EDITORIAL

On the second European Panel on the Appropriateness of Crohn's disease Therapy (EPACT-II)

In an era of evidence based medicine, what constitutes "evidence"? For aficionados, a large, statistically powered clinical trial that enrolls a specific type of patient, randomized to receive one of several alternative therapies, being evaluated in a blinded fashion would achieve that status. Even better, if multiple trials examined the same therapy in the same way, then a meta-analysis synthesizing those data provides even better "evidence" for patients and providers. In contrast, the second European Panel on the Appropriateness of Crohn's disease Therapy (EPACT-II) – reported in this issue of the Journal of Crohn's and Colitis (JCC) – uses a very different approach, developing clinical practice guidelines based upon the consensus judgment of a multi-national expert panel. This series of articles delineates the appropriateness of specific therapeutic interventions in patients with a diversity of Crohn's disease presentations. Comparing these two approaches, is the former "evidence" and the latter something else? For the practicing clinician and the patients whom they treat, do both approaches have utility?

Clinical trials represent the gold standard evidence required by regulatory groups such as the Food and Drug Administration in the United States and the European Union's European Medicines Agency. Prior to drug approval, these entities evaluate the efficacy and safety results from carefully designed and executed randomized trials. Trial protocols specify inclusion criteria, characteristics of the interventions, frequency of evaluation, and the metrics upon which the study will be statistically judged. Trials require years to complete, often at a cost exceeding 10–20 million euros for each one. The results from these trials provide the best answer to the proposed research question: in patients with specific demographic and clinical characteristics (with other patient groups consciously excluded from the study), who receive a specific drug, given in a specific way, under closely monitored care, when the patient does not have financial responsibility for the medication, what is the efficacy and safety of that medication? A randomized trial has substantial internal validity (likelihood that the answer is correct), but that result may not be generalizable or applicable outside of that patient population who received care in a very controlled environment. Would similar results occur in older patients?, in those with more extensive disease?, when the patient is not fully compliant with the regimen (due to inconvenience, forgetfulness, or cost?), or when dose adjustment occurs based upon differing criteria?

As an example, clinical trials have shown efficacy of infliximab in patients with moderate–severe Crohn's disease refractory to steroids. However, the patient sitting before you typically differs, in some fashion, from the published trial: perhaps a 37 year old woman with ileal Crohn's disease who obtained remission on steroids (with difficulty), experiences 2–4 relapses per year, previously failed both azathioprine and 6MP but has not yet received methotrexate. In this patient, would methotrexate provide the best outcome or should the patient receive infliximab (or adalimumab)? Would the outcomes on these potential drugs differ if she were pregnant? No randomized trial comparing relevant therapies in this patient population exists today; nor will they in the future. Too many constellations of clinical factors exist for enough trials to answer them all. For that reason, clinicians will always need to apply judgment as they examine an individual patient, review the relevant clinical studies, and then determine what might be the most appropriate intervention for him/her.

Rather than relying upon a single clinician and his judgment, a consensus process harnesses the views of a broader collection of individuals. Sometimes, consensus documents are prepared informally and the results may be suboptimal. In contrast, the RAND/UCLA Appropriateness Method, employed by the authors of these articles, uses a defined process and blends available evidence with a quantitative synthesis of expert opinion. They developed a series of 296 scenarios (or indications) with permutations of factors such as: disease severity, location, response to prior medications, the occurrence of adverse events to those medications, and the current therapy being considered. A broadly representative multidisciplinary group of clinicians reviewed an evidence summary and rated the appropriateness of each intervention in a quantitative fashion (each panelist rated each scenario on a 9-point scale). In an effort to balance each expert's viewpoint and avoid the bias of the loudest or most frequently spoken advocate, each of the panelists has equal weight in the statistical summaries performed. This method also does not force agreement.
When multiple experts widely differ in their viewpoint, that intervention for that scenario is labeled as “uncertain.” Areas of uncertainty often arise where clinical data are inadequate.

The RAND/UCLA Appropriateness Method has been used frequently and studied methodologically. Over 100 publications have used this approach, and it has undergone methodological validation, comparing the stability of individual experts' ratings over time, consistency of ratings with the underlying evidence, and the relationship between ratings of “appropriate” vs. “inappropriate” and the outcomes achieved by those patients. Although widely used, any consensus method has limitations. When multiple expert panels used the RAND approach and simultaneously developed guidelines on the same topic, agreement was rather close among 3 separate coronary revascularization panels, but less concordant for decisions regarding hysterectomy. Thus, any results based upon this technique must be viewed in this context.

The EPACT-II created a categorization of clinical scenarios for patients with Crohn's disease and the ratings provide an assessment of therapeutic appropriateness. These categorized scenarios have three potential uses. First, the scenarios can target future clinical research. One quarter of the scenarios was rated “uncertain”. This often occurs where evidence is relatively unavailable. Having identified these “uncertain” scenarios, future clinical studies could focus on the corresponding patient groups and examine differential outcomes based upon the therapies provided to them.

Second, an audit of Crohn's disease cases could ascertain how often care meets criteria of appropriateness. Although substantial resources are expended to care for this patient population, are these patients receiving appropriate care? Sometimes, guidelines are written as very broad statements into which a diversity of patients may fit. The current effort would place patients into discrete and mutually exclusive categories where distinctions of appropriateness could be made. A quantifiable chart audit could ascertain whether current care meets an adequate threshold (e.g., <5% of patients receive care rated as “inappropriate”).

Finally, these appropriateness ratings can be used prospectively. Before taking a therapeutic decision, clinicians could enter a patient’s specific clinical information into the EPACT website (www.epact.ch) and determine whether the proposed intervention was viewed as appropriate by the EPACT panel.

In an ideal world, every patient’s care would be based upon highly specific randomized trial information that accurately reflects their clinical characteristics and practice environment. Since this vision is unobtainable, efforts like those of the EPACT-II are an important adjunct, combining what is known from high quality evidence with the consensus assessment of experts. Understanding the limitations of their work will enable it to be used in the most productive fashion. These appropriateness criteria could guide decision making, but should not be the final determinant of care.

References


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