Finding the right index for inflammatory bowel disease

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EJ IRVINE. Finding the right index for inflammatory bowel disease. Can J Gastroenterol 1995;9(7):397-400. Several activity indices have been developed to assess the efficacy of new therapies for inflammatory bowel disease. The ideal index should be simple to administer and quantitative. It should be a composite of subjective symptoms, objective findings and laboratory markers of inflammation. Any newly developed indices should be assessed for validity, reliability and responsiveness before application in clinical trials. Obstacles to standardizing disease activity relate to the heterogeneity of disease manifestations, the characteristics of the study population, the therapy being tested, the investigators' preference for which index to apply and the attributes of the index. Examples of available indices are identified, some of their limitations are discussed, and guidelines for how to select an index for a clinical trial are outlined.

Key Words: *Activity index, Crohn's disease, Health status instrument, Inflammatory bowel disease, Ulcerative colitis*

À la recherche du bon indice d'activité pour classer la maladie inflammatoire de l'intestin

RÉSUMÉ : Plusieurs indices d'activité ont été développés afin d'évaluer l'efficacité des nouveaux traitements contre la maladie inflammatoire de l'intestin. L'indice idéal devrait être simple à administrer et quantitatif. Ce devrait être un indice composite des symptômes subjectifs, des observations objectives et des marqueurs de l'inflammation. Tout nouvel indice devrait être évalué sur le plan de sa validité, de sa fiabilité et de sa souplesse avant qu'il ne soit appliqué à des essais cliniques. Il est difficile de standardiser les mesures d'activité de la maladie à cause de l'hétérogénéité des manifestations pathologiques, des caractéristiques de la population étudiée, du traitement à l'étude, des préférences des investigateurs quant à l'indice à appliquer et des attributs de cet indice. Le présent article décrit certains des indices disponibles et leurs limites, ainsi que les directives quant au choix d'un indice à utiliser lors d'un essai clinique.

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A BROAD LIBRARY OF HEALTH status instruments has been developed and applied to assess the impact of inflammatory bowel disease (IBD) or its treatment upon patients' lives. These instruments include conventional disease activity indices and health-related quality of life instruments that are complementary in the appraisal of IBD (1). The focus of this report is a review of the clinical disease activity indices and their limitations, and a proposal of guidelines that may assist in selecting an index for a particular situation.

APPLICATIONS OF CLINICAL DISEASE ACTIVITY INDICES

Many disease activity instruments have been generated to permit assessment of therapy efficacy or to predict the clinical course of disease in individuals or groups of patients. The model index for determining therapeutic efficacy differs considerably from an index to predict long term outcome.

Consider an activity index to assess drug treatment in active disease. Possible primary outcomes of such a study (2) would include the proportion of patients 'in remission' ('improved' 'unchanged' or 'worsened') at the end of the trial. Other less important outcomes might be the 'mean' or 'median' change in index score or median 'time to improvement'. Similarly, if assessing a drug for prevention of relapse, the analagous outcomes would be the proportion of patients who remain 'in re-

TABLE 1
Properties of a predictive index for inflammatory bowel disease

1. Has an easily recognizable clinical or laboratory parameter
2. Uses categorical data (discrete categories, usually not numerical)
3. Has an objective feature (not subjective)
4. Has a feature that is relatively constant with time
5. Discriminates between groups of patients

TABLE 2
The ideal activity index

1. Simple to administer (acceptable to physicians and patients)
2. Quantitative (numerical value)
3. Composite –subjective symptoms –objective features –signs, endoscopy, histology –blood, urine, tissue parameters of inflammation
4. Valid (able to measure clinical disease activity)
5. Reliable (limited measurement error or observer bias)
6. Responsive (able to reflect important clinical change)
7. Relative to the study question, population and intervention being evaluated

mission', the mean change in disease activity score' in the population study groups and the median time to worsening' in each treatment group (2).

In contrast, the outcomes of interest in natural history studies are features such as mortality rate, rate of disease complications or disease-related surgeries, hospitalizations, extension of disease or rate of drug resistance. Conventional activity indices are generally poor predictors of clinical course. Useful predictive features must be present early in the natural history, are usually discrete categorical parameters and should remain stable with time (Table 1). A few examples are site or extent of disease, number of prior surgeries and prior resistance to corticosteroids. Predictive traits can be used in clinical trials to define homogeneous study populations (eligibility criteria) or prerandomization stratification variables, or in post hoc analyses to generate new hypotheses. The remainder of this report focuses on activity rather than predictive indices.

IDEAL CLINICAL ACTIVITY INDEX

To be able to define study outcomes in clinical trials clearly, a newly developed activity index should be adequately assessed for the psychometric properties of validity (ability to reflect clinical activity and intestinal inflammation), reliability (high precision and limited measurement error) and ability to detect a clinically important change in health state (3). Only then is there a good chance that it will reflect the clinical state at each assessment, give consistent results when no change in clinical status has occurred and be sensitive to important changes during the study.

The ideal index should be simple to administer and quantitative, and should evaluate sub ective symptoms, physical findings (radiologic or endoscopic attributes) and laboratory (blood, urine, stool or tissue) markers of inflammation. When possible it should be applied in a fashion that relates to the specific research question, the qualities of the study population (eg, patients with perianal Crohn's disease, fibrostenotic symptoms), and the expected actions or mechanisms of the drug or intervention under evaluation. Many activity indices' have been developed and applied in Crohn's disease and ulcerative colitis but few fulfil all these requirements (Table 2).

AVAILABLE INDICES AND THEIR LIMITATIONS

Indices of disease activity available for ulcerative colitis and Crohn's disease (1, ,5) are rarely used in daily practice because clinicians perform a quick assessment of global' activity based on a few criteria. During clinical trials, however, ob ective reproducible criteria are necessary to ensure that there is standardization among many clinicians or centres involving large groups of patients.

One of the first activity indices devised was the Truelove and Witts (6) classification of mild, severe and fulminant ulcerative colitis which was used to assess the efficacy of cortisone in patients with active ulcerative colitis. This semiquantitative index has no clear definition of what constitutes moderate exacerbation, which complicates the classification of patients with some but not all features in a single category and leads to difficulty in defining improvement or worsening except when patients are in complete remission with absence of all features of active disease. An improvement on some of these shortcomings was observed when the St Marks' index for extensive ulcerative colitis furnished 11 different features, including symptoms of bowel function, physical findings of temperature, abdominal tenderness and sigmoidoscopic appearance, grading each item from 0 to 3 with a quantitative score range of 0 to 22 (7). However, many of the features of this index are not pertinent to patients with distal proctocolitis because few of these patients experience constitutional symptoms, abdominal tenderness or impaired daily activities. This resulted in the development of a relevant index (8) that assessed rectal bleeding, stool frequency, sigmoidoscopic appearance and global physician assessment, giving a range of 0 to 12.

These and other indices were developed using the technique of face validation' in which clinicians identified the items and response scales based on intuition and experience. Although improvement could be defined by changes in category or score, clear definitions of remission, improvement and

worsening were not given before application.

Review of a series of recent trials in patients with proctosigmoiditis revealed substantial variability in the subjective symptoms chosen for assessment. Many but not all authors evaluated stool frequency, consistency and rectal bleeding but none evaluated fecal incontinence or straining. A larger proportion of recent studies have evaluated sigmoidoscopic appearance as described in the method by Baron et al (9) which grades activity on a four-point scale from 0 (inactive) to 3 (severely active). This scale was evaluated for interobserver variation when it was first defined. As well, morphological grading of inflammation has been standardized, and minor adaptations of the grades used by Riley and co-workers (10) appear in much of the recent ulcerative colitis literature. Because of the heterogeneity of Crohn's disease features, neither endoscopic nor histological assessments have been as consistently useful in determining activity.

The Crohn's disease activity index (CDAI) (11,12), probably the most familiar index used in North America, was developed by using 'construct validation' techniques in which 18 candidate items were evaluated in 112 patients at 187 visits. Multiple regression analysis was used to identify the eight features that best predicted the physician's global assessment of very well, fair, poor or very poor. The scores of the final eight items of disease activity are variably weighted to yield a score range from 0 to approximately 700. Active disease is considered at a score greater than 150 and severe disease greater than 450. The full validation of this score was performed during the National Cooperative Crohn's Disease Study (13).

Major criticisms of the CDAI (1,3,5) are the need to keep a seven-day diary of subjective symptoms, interobserver variation in index calculation and substantial weighting given the subjective symptoms. As well, the only laboratory indicator, the hematocrit, may be influenced by nondisease problems, and active perianal disease or obesity will give a falsely low activity score while prior surgery and frequent stools will yield an overly high one. These problems resulted in the development of the Simple Index (14) which reduced the number of features from eight to five and eliminated the weighting coefficients and the need for patients to keep a diary (score range 0 to 29). The Dutch Activity Index (15), which also attempted to address the criticisms of the CDAI, consists of nine items identified by stepwise regression and construct validation techniques. However, this index is heavily influenced by the serum albumin and confounded by nutritional state, disease extent and duration of exacerbation. Despite the drawbacks of these indices, each has been applied successfully in clinical trials and shown therapeutic benefits, such as obtaining a good rate of remission with prednisone or sulfasalazine (13) and a more rapid response when these two drugs were combined (16). It has also been shown that 5-aminosalicylic acid 4 g/ day provides greater therapeutic gain than 1 g/day (17).

In the past decade, a large number of indices have been developed for Crohn's disease, with the differences occurring in the subjective symptoms, objective findings and laboratory markers assessed (3,5). Several studies have shown variable correlation of these activity scores with one another in the same or similar groups of patients (18). Not surprisingly, no single index of disease activity or severity in either Crohn's disease or ulcerative colitis has achieved universal acceptance.

Obstacles to standardizing disease activity or comparing results among trials of IBD relate to differences between Crohn's disease and ulcerative colitis, the heterogeneity of each disease, the characteristics of the particular study population, the therapy being tested, the investigators' preferences for which index to apply and the attributes of the index. We are now beginning to see new indices for specific populations; for example, new indices for the pediatric population are required because of the problems of growth and maturation, which are poorly assessed by adult indices (19). Similarly, the author has developed and validated an index specifically for assessment of activity of perianal Crohn's disease (20).

TABLE 3
Selecting an index for a particular study

Take into account the following parameters:
1. Disease characteristics
2. Study population characteristics
3. Intervention being tested
4. Investigators' preference or comfort
5. Index attributes

Laboratory blood, urine and tissue markers are increasingly being assessed in clinical trials (3,5) and are not necessarily incorporated into the composite indices. The potential advantages of these biochemical markers, acute phase reactants, cytokines, adhesion molecules, etc, are that they may more precisely reflect the tissue inflammation, and are often automated and thus more easily assessed in a blinded fashion. Nevertheless, like clinical indices, they must be tested for validity, measurement error and responsiveness to change in clinical state. As with endoscopy and histology in Crohn's disease, it is possible to observe improvements in IBD symptoms with residual perturbation of inflammatory parameters.

SELECTING THE INDEX

No single index can satisfy the needs of all trials. Nevertheless, the clinical symptoms, objective findings and laboratory measurements may be selected independently based on the study objectives and target population (Table 3). Thus, a trial testing a new drug for perianal disease requires application of an index reflecting severity of subjective perianal problems (20), objective assessment of the anatomical disease using endoscopy or ultrasound (21) and a laboratory evaluation such as the serum haptoglobin (5) which may reflect the degree of inflammation.

Definitions of remission, improvement, absence of change or worsening – the important outcome events in any clinical trial – must be defined by the investigators based on the study objectives and expected mechanism of treatment. Although available disease

activity indices have been adequate for previous trials, as patient populations are stratified more homogeneously and different therapeutic interventions are tested, more refined 'indices' and health status instruments will be needed to assess subpopulations of patients. Endoscopic indices for Crohn's disease need to be simplified and made more user-friendly. As newer imaging techniques are refined, so too will new endoscopic or imaging indices be developed. Laboratory indices should be determined by both the disease parameters and the presumed mechanism of drug action. Finally, it should be emphasized that to assess the full spectrum of outcomes in clinical trials, health-related quality of life and adverse effects of treatment should be included.

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