ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Defining Severity in Inflammatory Bowel Disease

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G&H Why is it important to define severity in inflammatory bowel disease?

LP-B The guidelines that have been developed for the treatment of inflammatory bowel disease (IBD), as well as the treatment that clinicians end up selecting, are based on the severity of the disease. Clinicians are often asked how to manage IBD—for example, how to manage mild-to-moderate Crohn's disease (CD) vs severe CD. These inquiries are based on the gradient of severity of the disease; that is how clinicians evaluate IBD. However, there are no validated specifications derived from a consensus of what defines mild, moderate, and severe IBD.

G&H What guidelines have clinicians been using to grade the severity of the disease?

LP-B The biologic agents being used to treat moderate-to-severe CD and ulcerative colitis (UC) are licensed according to the definitions used in clinical trials. Namely, the Crohn's Disease Activity Index (CDAI) assigns a score for CD, and the Mayo Score is used for UC.

G&H Why are these scores problematic?

LP-B These scores are rarely used in routine clinical practice, so applying them at the time of marketing approval is inappropriate. The definitions guiding licensing should reflect how IBD is treated in the real world, not how patients are evaluated within the context of a clinical trial. In addition, these scores do not measure disease severity, which encompasses more than disease activity. Disease activity provides a snapshot of what is occurring at a given moment; it does not provide a view of the overall picture. Ideally, all clinicians treating IBD worldwide should be using the same definitions of severity, and these definitions should be as accurate as possible so that treatment recommendations are appropriate for each individual patient.

G&H What other parameters are important to consider when evaluating disease severity?

LP-B To correctly determine the severity of IBD, clinicians need to consider the clinical symptoms, the impact of the disease on the patient, the patient's quality of life, the inflammatory burden, the extent of bowel involvement, and the location of the problem. Clinicians then need to consider the patient's history. The current symptoms need to be understood in the context of the course of the disease since diagnosis. Severity also depends on the extent of structural damage, if any.

G&H Have such definitions been proposed in the past?

LP-B A great deal of work has been performed to define severity in IBD. The American College of Gastroenterology has proposed definitions, as have the European Crohn's and Colitis Foundation, the Japanese Society of Gastroenterology, and other organizations. Adopting these definitions has been difficult because they are based on expert opinion and not on formal consultations among a large, international body of clinicians. However, these efforts have spurred a project endorsed by the International Organization for the

Study of Inflammatory Bowel Disease (IOIBD) to establish definitions for severity in IBD.

G&H Could you describe the process for this IOIBD project?

LP-B We are using a 3-step process to develop agreeable and broadly applicable definitions for severity in IBD. The first step, as is always the case with such projects, was a systematic international review. This review was performed and is currently awaiting publication.

In December 2014 in Frankfurt, Germany, a conference was held to select the parameters that will be taken into account to define severity in IBD, which was the second step of the process. The clinicians at this conference decided on 8 separate measures that contribute to severity.

The third step was a meeting, which took place in April 2015 in Montreal, Canada, to conduct a conjoint analysis of the working definitions. This conjoint analysis, a statistical approach used in market research, acted as a poll to gauge the response to the proposed definitions by clinicians in the field.

G&H What are the different measures being proposed for defining severity in CD?

LP-B As noted above, the first step is to look at clinical symptoms. We found that the available clinical indexes, including the CDAI, are all inadequate for different reasons.

The second measure when evaluating the impact of the disease on the patient is quality of life. It is important to understand how IBD is affecting a patient's physical, sexual, social, and emotional functions. Disability also needs to be considered. Recently, an IBD-specific disability index that was developed in close collaboration with the World Health Organization was validated and is now available for use in clinical practice and clinical trials. This tool will enable patients to describe their general health, body functions, environmental factors, and many other parameters.

To gauge the state of intestinal mucosa, biomarkers can be used that may indicate active inflammation, although the clinical usefulness of such biomarkers is still being evaluated. These biomarkers include C-reactive protein (CRP) and fecal calprotectin. Specific thresholds for different levels of severity still need to be determined for these biomarkers. Endoscopy should be used to classify patients according to whether ulcers are present or absent, and imaging such as magnetic resonance imaging can show wall thickness, edema, and the location of ulcers in the gastrointestinal tract.

Disease course has been difficult to define in the past. Disease may be classified as being complicated, disabling, aggressive, or several other adjectives. In addition, when it comes to disease history, some factors are easier to evaluate than others. For example, patients and clinicians can easily determine whether there have been repeated flare-ups or whether there is a need for surgery or repeated corticosteroid treatments. Several different systems for evaluating such factors are available in the literature. For structural damage in CD, the Lémann index, which is damage-driven and examines 4 separate organs, provides results in terms of disease severity. However, this index is not yet validated, and its construction is still a matter of debate.

G&H What 8 measures were chosen during the 2014 IOIBD conference to determine severity in IBD?

LP-B For CD, these measures are rectal symptoms (more than 10 loose stools per week or not, abdominal pain); anorectal symptoms (pain, urgency, incontinence, discharge, tenesmus, active fistula); impact on daily activities; serum biomarkers (anemia, elevated CRP level, albumin level); mucosal lesions (active or not); whether the patient has complicated disease (presence or absence of a fistula, abscess, stricture, stoma, and/or intestinal resection); whether the patient has responded to corticosteroids, biologic agents, and/or immunomodulators within the past 12 months; and whether the disease is extensive (the degree of ileal involvement and/or pancolitis).

For UC, these measures are the frequency of loose stools; anorectal symptoms; impact on daily activities; serum biomarkers; mucosal lesions; response to medication; whether the patient has extensive colitis; and whether the patient has been hospitalized within the past 12 months (with the same subcategories as above, when applicable).

G&H What challenges remain in order for these definitions to be broadly adopted?

LP-B First of all, these proposed measures need to be validated. Second, we need to understand how these measures interact in terms of building an overall picture. Which parameters are most important? Should these 8 measures be weighted in a particular way? Although these insights will help make a checklist of these 8 measures as useful as possible, the measures themselves are ready to be used at this stage in routine practice to evaluate disease severity in IBD patients.

Regardless of the challenges, however, the overall goals are to improve the lives of patients and the course of the disease. The upcoming IOIBD definition of disease severity for IBD will help achieve these goals.

Dr Peyrin-Biroulet has received consulting fees from Merck, AbbVie, Janssen, Genentech, Mitsubishi, Ferring, Norgine,

Tillotts, Vifor, Shire, Therakos, Pharmacosmos, Pilège, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Lilly, Pfizer, HAC-pharma, and Index Pharmaceuticals. He has also received lecture fees from Merck, AbbVie, Takeda, Janssen, Ferring, Norgine, Tillotts, Vifor, Therakos, and HAC-pharma.

Suggested Reading

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