EDITORIAL

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Treatment Evaluation in Inflammatory Bowel Diseases: a Move towards Validated Patient-Reported Outcome Measures (PROM)

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Common reasons for patients with inflammatory bowel diseases (IBD) to seek medical attention are a variety of physical and psychological symptoms, perceived illness, impaired physical and emotional health and wellbeing and impact of the disease on functioning in daily life [1]. Clinical evaluation of these patients commonly has focused on history, physical exam, laboratory values, imaging and endoscopic procedures to confirm diagnosis, document disease location and activity, and to exclude differential diagnoses. Establishing the diagnosis of IBD is the prerequisite for treatment, the success of which is evaluated by grouped outcome parameters, since no single biomarker that accurately reflects the full spectrum of IBD has been established [2, 3].

A large number and variety of outcome parameters and indices designed to quantify disease activity, measure response to treatment and identify remission have been used in the past [4], among them the Crohn's disease activity index (CDAI) for Crohn's disease [5, 6] or the Mayo Clinic Score for Ulcerative colitis [7]. Endpoints for these indices or scores have included signs and symptoms, laboratory findings and endoscopic and histologic assessments. However, these indices and scores have potential problems in that they may be influenced by frequent concomitant diseases such as irritable bowel syndrome [8, 9], or by including subjective elements which require physician assessment [10] and which may not correspond with the patients' perception of their disease [11]. These indices and scores, by including surrogate or composite parameters, subjective evaluations or complex scales, have been designed to reflect what physicians deem to be important for understanding the disease, its activity and its response to treatment. They may be difficult to apply, have methodological flaws and not necessarily reflect what is important to the patient [12]. It has been suggested that reliance on these health-care-professionals-determined outcomes (HCPDO) may be a reason why clinical trial outcomes may fail to translate into benefits for patients [13, 14]. It has been shown, that 30% of patients with IBD still suffer gastrointestinal symptoms in the absence of active inflammation [8]. There is a poor correlation between mucosal inflammation and symptom scoring [15]. Physicians frequently underestimate the impact of depression, anxiety, fatigue and sleep on the patient's health [16]. Scoring of symptoms may be confounded by stress or psychological comorbidities [17].

A review of outcome domains used in 83 randomised studies in ulcerative colitis published in three decades from 1987 until 2017 [4] has shown that the focus of outcome domains has shifted over time. Endoscopic outcomes have significantly increased in use, having been used in only 10% of studies (that is 1 of 10 studies) published in the first of the three decades and in 96% of studies (55 of 57 studies) in the last decade. The use of biomarker outcomes has increased from 0% in the first decade to 37%, and the use of safety outcomes from 70% to 96%. Clinical composite outcomes have been used in 100% of studies throughout all the three decades. The use of patient-reported outcomes only started at the beginning of the 21st century and has increased in the last decade to 39% of ulcerative colitis treatment studies.

Patient-reported outcomes (PROs) are any report of the status of a patients' health condition that comes directly from the patients, without interpretation of the patient's response by anyone else [12, 18]. They are used to measure various aspects of health including physical, emotional or social domains and how these aspects are influenced by a specific disease. The assessment of PRO shall improve the understanding of the patients' condition beyond disease activity or symptoms [18].

Recently the focus has been laid on patient-reported outcomes, because conventional endpoints in IBD clinical trials

and clinical care may fail to capture the full health status and disease experience from the patient perspective [13]. Many general and IBD-specific patient-reported outcome measures (PROMs) have been used in the past [19] but none of them have been designed and validated for their use in clinical trials and therefore may be prone to multiple types of biases [20]. They include severity scales of pain or faecal urgency, blood in bowel movements, counts of bowel movements, episodes of vomiting, health-related quality of life, and adherence to and satisfaction with treatment [16, 21]. The lack of validated PROMs has resulted in substantial variability in the definitions of clinical response or remission in clinical trials [4]. FDA strongly recommends the development of co-primary endpoints in research trials which combine an objective measure of inflammation with PROs to support labelling claims and improve safety and effectiveness in the drug approval process [10, 22]. The use of validated, reliable PROMs shall help to bring to the market treatments that are safe, effective and meaningful to the patient, by producing benefits to the patients and affecting how the patients feel or function.

A prerequisite for the development of validated PROMs is the identification of appropriate outcomes. They shall help in identifying effective new therapies and may be helpful in changing the clinical practice if the identified outcomes are relevant for both patients and doctors. IBD-specific core outcome sets are currently under development [23, 24].

Symptom assessments, which have been used in the past, were mostly not standardized, not validated, and may have been subject to doctor- and patient-related biases, which limit the confidence on the reported results. The need for the development of validated symptom measurement instruments has evolved from the clinical importance assigned to the validated assessment of patient-reported outcomes. A recent study has identified the most important issues for patients with Crohn's disease: patients are most bothered by the severity of pain, frequency of bowel movements and fatigue. Other important issues are nausea and vomiting, joint pain and blood in stool [12]. Table I lists bowel signs and symptoms, systemic symptoms, the impact of disease on daily life and emotional wellbeing and of coping activities which may be of importance to IBD patients and which may be included in future PROMs.

Recently the Crohn's Disease patient-reported outcomes signs and symptoms (CD-PRO/SS) measure was developed to standardize the quantification of gastrointestinal signs and symptoms due to Crohn's disease through direct reports from patient ratings [25]. Findings from qualitative interviews identified nine items covering bowel and abdominal symptoms. The final CD-PRO/SS daily diary includes two scales, each scored separately. Each scale showed evidence of adequate reliability, reproducibility and validity.

Development and validation of PROMs will have to focus on those aspects of IBD which are considered important by the patient and the doctor. Key attributes for PROMs [10] are first, high sensitivity with reasonable specificity in identifying patients with clinical worsening; second, availability for self-reporting that may prompt an early clinical visit; third, a short and simple structure preferably administered using mobile devices; and fourth, a low administrative burden for including in electronic patient record systems used in clinical practice [26].

Table I. Items of interest for patient-reported outcomes in IBD

Bowel signs and symptoms:
• number of bowel movements
• frequency of liquid bowel movements
• frequency of blood in bowel movements
• severity of faecal urgency
• severity of nausea
• severity of abdominal pain
• severity of bloating
• frequency of passing gas
Systemic symptoms: Severity of
• joint pain
• feeling tired
• feeling weak
• lack of appetite
• feeling thirsty
Impact on daily life: Interference with
• daily work or school
• tasks at home
• leisure activities
• sleep
• ability to concentrate
• leaving home
• ability to travel
• sexual desire or pleasure
• planning several days ahead
Emotional impact: Feeling
• alone
• embarrassed
• worried
• scared
• angry
• frustrated
• depressed
• to have no control over life
Coping activities
• schedule activities around bowel movements
• eat less to control bowel movements
• avoid foods to help control bowel movements
• only go to places where a toilet is close by
• carry always a change of clothes
• stay at home due to disease

Development of PROMs will have to follow established validation procedures, which will attest to the reliability of these symptom measurement instruments. Such validation procedures have been developed and used for a large variety of symptom measurement instruments, used in various medical fields, including gastroenterology [25, 27-29]. Criteria for the validity of symptom measurement instruments are [10]:

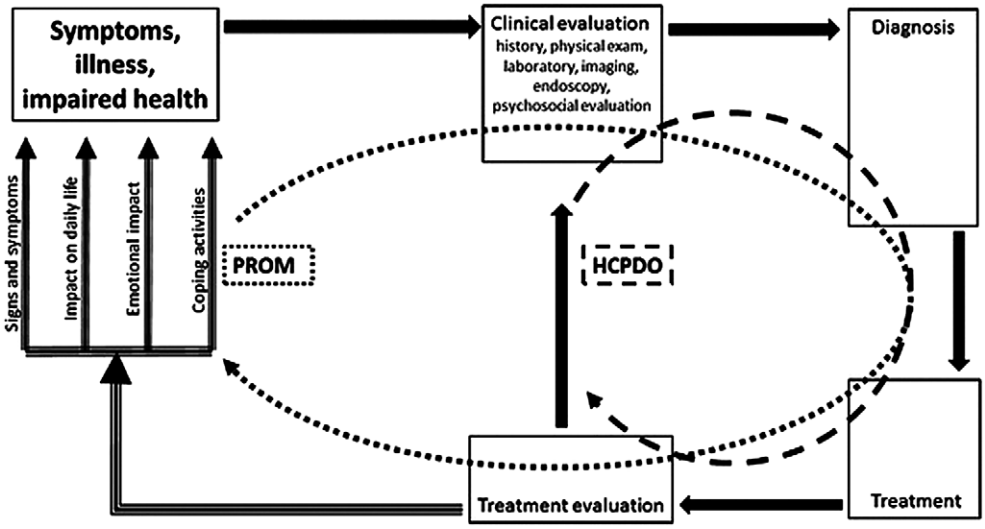

Fig. 1. Clinical approach and treatment evaluation in patients with IBD: adding patient-reported outcome measures (PROM) to health-care-professional determined outcome (HCPDO) for the scientific evaluation of treatment trials and clinical guidance of follow-up clinical evaluations and treatment adaptations.

1. Content validity – this is the extent to which the instrument measures the concept of interest, which is the patient's perspective. To assess content validity patients may be asked to rate statements such as the following ones by yes/indifferent/no: "The essential symptoms are considered in the questionnaire"; "I consider the questions useful to communicate my symptoms".

2. Construct validity – this is the evidence that a relationship exists with another accepted measure of disease activity. This includes investigation of the correlation between patient-reported and physician-determined outcomes or the correlation between online-administered and paper-versions of a questionnaire. Construct validity includes face validity, for which patients may be asked the following questions: "Is the questionnaire easy to understand?"; "Are the questions unambiguous and clear?"; "Is it easy to answer the questions regarding complaints?"; "Do you think that the questions cover all relevant complaints?"; "How difficult is it for you to grade the severity of symptoms?".

3. Concurrent validity – this is the extent to which a questionnaire is related to a generally accepted gold standard measure such as an interview by a blinded physician.

4. Test-retest reliability is assessed by repeating the questionnaire to the same patient after a predefined time interval and comparing results.

5. Responsiveness to change – this refers to the statistical exploration for the ability to detect changes in disease activity in subsequent tests performed by the same patient.

High value medical care of patients with IBD shall combine the management of biological and psychosocial factors to enable patients to regain their health through the control of symptoms and the reduction of the impact of disease on daily life, including emotions and activities. For future therapeutic studies and regulatory approval of new IBD drugs the FDA mandates to use co-primary endpoints for treatment studies which combine PROMs and HCPDOs. The use of PROMs and of modular endpoints focusing on items such as bowel signs and symptoms, systemic symptoms, impact on daily life, emotional impact or coping activities could allow trials and approval for treatments targeting other aspects of IBD beyond inflammation. As soon as they will be available, clinicians shall incorporate valid PROMs to their usual IBD care in order to better understand the impact of disease on patients and improve the quality of the care provider. A model of this approach is shown in Fig. 1. In the meantime, physicians are encouraged to use existing PROs to better allow them to address patients concerns and improve efficiency of the patients' visits to the doctor and the patient's satisfaction [16].

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