Digestive Diseases and Sciences (2020) 65:3411–3417
https://doi.org/10.1007/s10620-020-06635-2

PERSPECTIVE

Clearing of the Clouds in Inflammatory Bowel Disease Management

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Received: 4 June 2020 / Accepted: 22 September 2020 / Published online: 3 October 2020

Abstract
The skies over inflammatory bowel disease care are beginning to clear. Success is being achieved in the management of inflammatory bowel disease due to ongoing research, new medications, and most significantly to the recognition of the importance of patient selection and the definition of remission. Five answered questions provide the basis for recent successes and forecast for clearing of the clouds. How do we classify the inflammatory bowel disease (IBD) patient? How do we select our medications to best match the patients' classifications? How do we monitor and manage medications during the course of care? How can we predict the likelihood of response to a selected medication? Besides medications and surgery, what else is needed for best care in 2020 and beyond? These questions are addressed in this communication.

Keywords Inflammatory bowel disease · IBD classification · IBD diagnosis · IBD management · Crohn's disease · Ulcerative colitis

Introduction

For the past 20 years, the skies over inflammatory bowel disease (IBD) care have been partly cloudy. In the prior century, chronic ulcerative colitis (UC) and Crohn's disease (CD) were managed with a few marginally successful medications. The new century greeted us with significant advances in our still incomplete understanding of the complex pathogenesis of IBD [1, 2] and with the introduction of infliximab [3]. Although we have certainly not yet defined "the cause" of IBD, four factors are currently considered to be most prominent in the initiation and chronicity of IBD. These are: genetics [4], the environment [5], the gut microbiome [6], and pro-inflammatory immunologic dysregulation [2]. Our current understanding and the ongoing research in these arenas are richly reported in the above-listed references. These areas of research are of keen interest not only for their intellectual challenges but also for the direction they may supply for the pragmatic need to develop efficacious therapies. Such has been the case with the development of the infliximab, the monoclonal antibody antagonist to the pro-inflammatory cytokine tumor necrosis factor (TNF-α) and for the host of additional therapeutics now available and soon coming online for the management of IBD.

One would have thought that the arrival of this first inflammatory bowel disease (IBD) biologic therapy would have been the best news ever. Well, that happy gospel didn't sustain us for very long. With the entry of other anti-TNF-α agents, the first two decades have proved less productive than anticipated. Perhaps one in four patients with IBD experienced long-term benefit from our host of anti-inflammatory ammunition. We missed the correct recognition of what constitutes remission. When we eventually recognized that remission required endoscopically definable mucosal healing, we were again sent out into the rain as we learned that our best, newest, and safest drugs conferred long-term remission in only 20–30% of IBD patients [7–11]. No one was surprised when reading the Canadian report that infliximab, while emptying the government coffers, failed to provide improvement in the natural history of the treated Crohn's disease population [12]. When IBD is managed as was recommended in the first decade and a half of this century, any treatment offering a long-term benefit to a less than a third of the patients is not likely to reveal a readily definable class benefit. With these early management recommendations, the rather disappointing impact resided in both the limited, albeit definite, efficacy of the biologics and also how they were employed. With the realization that "top down" is favorable to the "bottom up" management paradigm,

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progress seemed possible [8, 13, 14]. Over the past several years, additional progress has been made because several questions have been addressed. The benefit of the answers is that perhaps now greater than 50% of carefully selected patients may achieve remission and a consequent improvement in the short- and long-term natural history of their disease [15]. The questions include: (1) How do we classify the patient with IBD? (2) How do we select our medications to best match the patients' classifications? (3) How do we monitor progress and manage the medications during the course of care? (4) How can we predict the likelihood of response to a given therapy? (5) Besides drugs and surgery, what else is needed for best care in 2020 and beyond? The answers provide some well-earned sunlight for the physician charged with providing the best care for his/her patients. They are discussed in this communication.

How Do We Classify the Patient with IBD?

For UC, the general clinical appraisal of diarrhea and bleeding is usually sufficient to tell the difference between mild, moderately severe, and severe colitis. To provide more specific data for categorizing the different clinical presentations of this colonic mucosal and submucosal disease, the Mayo Scoring System [14] is helpful for not only clinical trials but also for the practicing clinician as he/she defines just how sick their patient is and therefore how best to approach therapy. The system simply assigns points (0–3) for extent of stool frequency, rectal bleeding, endoscopic findings, and a physician global assessment. Mild, moderate, and severe UC incur scores of 3–6, 6–9, and 9–12, respectively. Hence, severe UC is defined by frequent (> 10/day) passage of stool, mostly bloody, pan-colonic, deep mucosal ulceration at endoscopy, in a demonstrably, clinically ill patient. Such a patient would collect a score of 3 in each of the four categories for a total of 12 and thus is defined as "severe" UC.

Of course, the handful of clinical disorders that can masquerade as UC (i.e., Clostridioides *difficile,* CD, ischemic disease, cytomegalovirus infection, bacterial enterocolitis) need to be eliminated from the differential cluster. Even the most accomplished IBD clinicians may occasionally make that error. With advancing duration of UC, the disease burden will include colorectal neoplasia, failed medications in a serial fashion, consequences of reduced quality of life, and debilitation—all of which may require consideration of disease-curing colectomy. However, the term "disease-curing colectomy" is employed thoughtfully as post-colectomy pouchitis, diarrhea, etc., may continue to interfere with quality of life of the patient with UC.

Whereas in UC, the general clinical appraisal aided by the more specific Mayo Scoring System is quite sufficient for distinguishing the categories of UC disease severity, such is most certainly not the case for CD. CD is an incurable, slowly progressive, transmural inflammatory disease which leads to fibrosis and stricture formation anywhere along the gastrointestinal tract. The natural history may be also punctuated by internal or penetrating fistulae, likely surgical interventions, risks for nutritional depletion, chronic pain syndrome, and psychiatric disorders all leading to an assault on quality of life. The slowly progressive, accumulating, and current burden of disease define its "severity"; the current gastroenterological signs and symptoms define its "activity." This severity–activity duality in assessing CD is currently viewed as necessary in order to confront its natural history as well as symptomatology. The goal is to so reduce the disease activity (i.e., mucosal healing plus clinical remission) such that the burden/severity and natural history (i.e., surgeries, hospitalizations, fistulae, nutritional depletion, reduced quality of life) are dramatically improved. We are only beginning to attain such success. As part of the sunlight shining through the clouds, we now assess not only the presenting stigmata of severe disease but also the factors which pose *high risk for advancing disease severity* and thus must be treated most aggressively [16, 17]. Patients with CD presenting with strictures, abscesses, fistulae, deep ulcers on endoscopy, failed prior treatments with any biologic or immunosuppressant, fecal incontinence, and chronic pain are high-risk patients. On the other hand, low-risk patients are those with only mild symptoms, limited endoscopic disease activity, and no prior surgery, strictures, fistulae, or exposure to steroids or biologics. These patients are categorized as *low-risk* for development of the listed burden of disease and may be managed more conservatively. The distinction between the low-risk and high-risk patients relates specifically to the probabilities of complications associated with the untrammeled natural history of CD. To thwart and modify the natural history of CD, the intermediate goal is therapy-promoted mucosal healing (i.e., endoscopic remission) wherever it may be found in association with clinical wellness. Indeed, the single greatest cloud clearing event in the IBD skies is the realization of that endoscopic remission is essential for success in altering the natural history of the disease [11].

Isolated ileal disease occurs in approximately one-third of patients with CD and is a hallmark for potential complications. Such patients are more likely, compared to those with isolated colonic involvement, to develop strictures, to progress to surgery, to do so more rapidly, and to require more than one surgery in the course of the disease [17]. Indeed, the case has recently been offered that ileal and ileocolonic CD may, on the basis of phenotype, molecular footprint, and pathology, be a separate disease from that of isolated colonic CD [18]. The severity of ileal disease is defined by clinical symptoms, radiologically confirmed fibrosis/stricture, and endoscopically observed ulceration. Grading the severity of

ileal ulceration is the province of the postoperative state. The physician may elect 6–12 months after surgery to endoscopically survey the neoterminal ileum and apply the Rutgeerts score in which the severity of ulceration may relate to the risk of clinical relapse [19]. This approach does not apply to all post-ileal resection patients with CD [20]. The Montreal Classification [21] of UC and CD includes patient age (i.e., < 16 years, 17–40 years, and > 40 years), location (i.e., ileal, colonic, both, upper GI), and behavior (structuring, penetrating, etc.). It has value in that it highlights high-risk patients, such as the youngster presenting with an ileal stricture and an internal fistula.

In summary, UC is defined clinically and endoscopically as mild, moderate, or severe disease. Progressively worsening diarrhea, rectal bleeding, and colonic mucosal ulceration are the factors that characterize severity of UC disease. CD is defined by risk for progressive, longitudinal disease burden, i.e., "severity" plus current extent of symptomatic "activity." The high-risk patient requires aggressive care; the low-risk patient may reach partial or complete remission with more conservative management. Ileal disease portends higher risks.

How Do We Select Our Medications to Best Match the Patients' Classifications?

The last two decades have produced an array of medications. Their benefits are more related to the characteristics of the disease and the patient than to the so far elucidated mechanisms of action of particular potions. Consider the following examples: Corticosteroids provide short-term but not long-term benefit in UC and CD; mesalamine is very helpful for mild and moderate UC but nearly useless in CD; the anti-TNF-α agents, their biosimilars, the anti-integrin lymphocyte migration inhibitors, the anti-IL 12/23 inhibitors, and the Janus kinase pathway (JAK) inhibitors are equally, but modestly effective; long-term remissions are more likely with the initial agent selected; and finally, the benefits of any treatment are best demonstrated in disease of short duration, i.e., less than 1–2 years.

For UC, moderate-to-severe disease may call for a limited course of steroids followed by biologics perhaps with an immunomodulator. Vedolizumab and ustekinumab may also be attractive initial choices. Tofacitinib is currently a second-line alternative. In patients with UC and a history of prior anti-TNF-α failures, then vedolizumab [22], ustekinumab [23], or perhaps tofacitinib may be in order. The relative benefits of these newer agents appear similar. High-risk CD requires an aggressive treatment program. Clinical trials helped solve the decades-old question of "bottom up" versus "top down" treatment paradigm in favor of the latter as the "top down" program is more often associated with remission [8, 13]. As relapses occur, second- and third-line programs are required.

As the options for drugs increase at a heated pace, clinicians ask whether any one therapeutic agent is more effective in promoting remission than any other agent. Additionally, a combination drug program is better than a singular agent program. The data from few controlled trials provide illumination. In the management of moderate-to-severe UC, the VARSITY trial is uniquely placed on the nearly endless list of this century's clinical trials in that two mainstream biologics were directly compared, adalimumab versus vedolizumab [22]. In patients with a prior history of anti-TNF-α failure, vedolizumab offered a higher proportion of remissions than did adalimumab. The proportions of patients obtaining steroid-free remissions were, however, no different. The study was more important for its design in that it directly compared two available agents. It was helpful in demonstrating a very circumscribed benefit of vedolizumab over adalimumab. Additionally, the VARSITY trial established vedolizumab as an excellent first- or second-line option for the management of moderate-to-severe UC. For CD, the SONIC trial [8] reported clinical remission and mucosal healing rates in patients with moderate-to-severe CD treated with infliximab, azathioprine, or the biologic plus the immunosuppressant. The combined treatment at 26 weeks provided the leading clinical remission and mucosal healing rates of 56% and 44%, respectively. With few comparative trials, we currently contend with the data demonstrating that nearly all advanced treatments for UC and CD offer only limited (25–40%) prospects for long-term remission. We anticipate additional sunlight when therapeutic breakthroughs provide 75–80% remission rates.

Current therapeutics offer similar and less than ideal response rates. However, there are still reasons for choosing one program over another. For patients with either high-risk CD or moderate-to-severe UC, the following limitations and cautions represent significant aspects of the clinical decision-making process: (1) Immunomodulators are best employed with an anti-TNF-α agent to limit immunogenicity [23]. (2) In cases where prior infection or malignancy is of concern, an anti-TNF-α agent may be avoided in favor of vedolizumab or ustekinumab which report more favorable side effect profiles. (3) In patients with a history of melanoma or non-melanoma skin cancer or lymphoma and in males under the age of 35 years, one may consider avoiding thiopurine immunosuppressants. (4) For tofacitinib [23], consider lower (5 mg twice daily) maintenance dosages, offering immunization against herpes zoster, perhaps avoiding use in elderly patients with a history of pulmonary embolic disease, and for now avoiding use in females considering pregnancy. 5. In patients with extra-intestinal manifestations of inflammatory bowel disease, systemic anti-inflammatory agents (i.e., anti-TNF-α agents, ustekinumab, tofacitinib) may be a

better choice than a gut-specific agent (i.e., vedolizumab). 6. Finally, subcutaneous and oral medications are more convenient and less expensive for the patient. In this regard, insurance companies seem too often to have the final say regarding the choice of therapy.

The benefits of current treatments are comparable. The upside of the similarities is that the patient and the physician may have significant preferences respected, i.e., infusion vs subcutaneous vs oral treatment, selection of medications with attention to comorbidities, risks of infection, prior history of cancer, disease burden, and current disease activity. Given all these variables, selection of the medication more likely to promote remission has been potentially improved by the application of a prediction model devised in the clinical decision support tool (CDST) recently published [16]. In managing CD, the CDST allows the clinician to make decisions with data that balances the risk of disease progression with the risk of medication-related complications. With this tool, one may choose most aggressive therapy (i.e., anti-TNF + immunomodulator) for the high-risk patient; a safer medication for the low-risk patient (i.e., vedolizumab); and perhaps ustekinumab for the intermediate-risk patient previously treated with anti-TNF agent. However, without providing a cloud of gloom, it must be stated that at the present time, there is no specific patient profile that requires a specific treatment program.

How Do We Monitor Progress and Manage Medications During the Course of Care?

For both moderate-to-severe UC and high-risk CD, the principles of management have changed dramatically and represent some of the brightest sunlight on IBD management. The singular most significant aspect of management is that symptomatology has been supplemented by objective endoscopic measurements for both UC and more so for CD. While the Crohn's Disease Activity Index [24] has value in defining the patients' clinical status, it has been fortified with the Crohn's Disease Endoscopic Index of Severity (CDEIS) [25] and the Simple Endoscopic Score for Crohn's Disease (SES-CD) [26]. For UC, the Global Mayo Score System [14] provides a similar utility. Other non-invasive, objective measurements of disease activity include: CBC, sedimentation rate, C-reactive protein, serum albumin, and stool fecal calprotectin (FCP). Because it is accepted that the majority of patients, particularly the patients with high-risk CD, will come out of remission at some point, these serologic markers and the FCP can be easily measured to determine whether relapse is present or imminent [15]. In such cases, treatment can be modified in a way to return the patient to a remission state. Hence, the clouds are beginning to part as we proactively, objectively define the presence or absence of remission during the course of care. These clinical monitoring advances constitute the "treat to target" era in IBD care designed to rapidly identify a relapse and take steps to re-establish mucosal healing, i.e., endoscopic remission. *The critical aspect of treat-to-target is that the target is continuous control of inflammation.* Relief of symptoms is important but any hope to improve the natural history of IBD rests in the necessity of mucosal healing as a by-product of suppression of inflammation.

Additional sunlight in IBD management is provided as we address patient symptoms following initiation of the chosen program. When a patient reports acceleration of symptoms, three critical questions must be addressed: (1) Is there evidence of inflammation? (2) Is there evidence of infection? (3) What is the status of therapeutic drug and anti-drug antibody levels? If the fecal calprotectin and endoscopy are normal, the patient may be experiencing a functional symptomatic event while in remission. If the stool studies report an intercurrent opportunistic infection such as Clostridioides *difficile* or cytomegalovirus, treatment can be specific. If the drug level is subtherapeutic without antibodies, compliance may be an issue. Remission may be recaptured by resuming or increasing the dose or shortening the interval. If anti-drug antibodies are present, a change in therapy may be successful. Without answering these questions, mistakes are likely.

Why did the patient not respond to the biologic, as is the case in one-third of patients? Why did the patient subsequently lose response? Enter the era of Therapeutic Drug Monitoring (TDM, [27–29]). The biologics are antibody proteins against inflammatory tissue pathways and, as such, may promote an immediate or delayed hypersensitivity response. Most of our current knowledge is derived from the study of infliximab. The anti-drug antibodies may reduce the effective level of the circulating biologic anti-inflammatory agent. Beyond immunogenicity, additional factors may reduce the circulating blood level of the intravenously or subcutaneously administered therapy [30, 31]. Prior agents, removal of protective drugs such as the immunomodulators (i.e., azathioprine, 6-mercaptopurine, methotrexate), protein-losing enteropathies, stress, obesity, sleep disorders, diabetes mellitus may all impact the therapeutic drug level. In addition to the merits of reactive TDM when patients relapse, proactive TDM (i.e., routine measurement during course of care even if apparently stable) is showing signs of influencing the natural history of IBD [29]. Currently, only reactive TDM is recommended by the leading gastroenterological societies [27]. With a bit more sunlight, that should change. In time, all the biologics may have reactive and proactive TDM programs.

How Can We Predict the Likelihood of Response to a Selected Medication?

The current therapies, particularly for severe UC and high-risk CD, are more likely to fail than to succeed in achieving

a durable remission. Until we find better drugs with universal profiles of success (i.e., not a cloud in the sky), we are challenged to establish prediction models which will tell us who is likely and who is not likely to respond to a given agent. Such models will promote efficiency, save money, grief for the patient, and perhaps allow a more personalized treatment program with better odds of success. The CDST [16] discussed above provides some direction for choosing medications on the basis of clinical presentation, prior history, laboratory data, and endoscopic findings. It represents a new tool the IBD physician may apply in order to select—rather than guess—which first- or second-line agent is best suited for the patient and more likely to lead to remission. The CDST [16] provides some structure to the concept that is too well cataloged in the experiences of physicians managing IBD, namely that patients with the greater disease severity and activity offer the greatest challenge in achieving sustained remission. To advance this concept, it would be most helpful if we could predict who is likely to respond to a given medication, who is likely to fail a medication, and who is likely to have an adverse effect of a medication independent of the severity and activity of disease. We are making progress in these areas.

Regarding the immunomodulators, it is standard practice to assess the capacity for thiopurine enzymatic degradation prior to initiating azathioprine or 6-mercaptopurine therapy. The risk of myelosuppression is progressively increased as the enzymatic activity of thiopurine *S*-methyltransferase decreases as dictated by genetic variants [32].

For the much-needed means of predicting benefits and risks of the biologics, substantial research is being devoted to the search for predictive biomarkers informing the response to anti-TNF-α agents. A superlative 2018 systematic review of 92 articles offered the conclusion in the title, "personalized medicine in its infancy [33]." In October 2019, Wilson et al. [34] reported that while 40% of IBD patients were positive for the HLA-DQA1*05 variant, that HLA variant occurred twice as often in patients who had developed immunogenicity to infliximab during the course of care. In May 2020, Bangma et al. [35] offered a "pharmacogenetic passport" to predict the efficiency of medications in treatment of IBD. Patients with and without immunogenicity to an anti-TNF-α were retrospectively genotyped using both whole-exome sequencing and Illumina Global Screening Array. HLA-DQA1*05 haplotype carried an increased risk of immunogenicity. This genetic relationship just barely escaped statistical significance. They reported that 32 patients would need to be genotyped prior to starting an anti-TNF-α agent to prevent one patient from developing immunogenicity and perhaps failing treatment. While not ready for routine clinical use and not necessarily a passport to where we need to go, these reports offer very encouraging evidence that with augmented specificity, genome-wide assay programs may lead to effective, personalized medicine in IBD care.

Besides Medications and Surgery, What Else Is Needed for Best Care in 2020 and Beyond?

The new century has ushered in myriad advances but also changes, forces, demands, and stresses on the patients with IBD patient and their physicians. Certain topics fall into one or more of these categories. Important current issues and the future of IBD care are very much inter-related. For example, the FDA mandate for patient-reported outcomes (PROs) connects seamlessly with the telemedicine era precipitated by the COVID-19 pandemic. Patient self-administered assessment of the clinical status will likely become part of an efficient telemedicine visit. A PRO report acceptable to the FDA and equally acceptable to the IBD clinician in practice will necessarily be part of a near future sunrise [36, 37]. The PROs movement is an extension of the decades-long awareness of the psychiatric, domestic, intimacy, financial, and quality of life disturbance facing many patients with IBD. PROs will hopefully advance these issues from general awareness to beneficial, actionable care. As part of the COVID-19 impact on the world of gastroenterology, all physicians must become fully familiar with the pandemic-demanded practices to protect the patient [38] and themselves [39]. The pandemic has brought into somewhat painful relief that the IBD world, like the world in general, has dramatically changed from the way it was just 1 year ago. That notwithstanding, the clouds over IBD are beginning to clear with advances in our understanding of pathogenesis, diagnosis, and management. The current harsh weather of the pandemic will pass but certainly leave its mark on the terrain. This and the forecast for the future of IBD are for favorable weather. However, we all recognize that weather prediction, like IBD care, is an inexact science.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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