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Editorial/introduction to special issue

Inflammatory bowel diseases (IBD), comprised of Crohn's disease (CD) and Ulcerative colitis (UC), are complex diseases with heterogeneous and multi-phenotypic presentation causing significant impact on the quality of life of patients (Torres et al., 2017; Ungaro et al., 2017). The introduction of tumor necrosis factor (TNF) antagonists into clinical practice, more than 20 years ago, constituted a major breakthrough, both for patients and clinicians. These novel therapies significantly improved care beyond the conventional therapeutic arsenal, offering advances in the ability to induce and maintain remission, heal the intestinal mucosa, restore quality of life, and reduce surgeries and hospitalizations. However, there remains a considerable proportion of patients that will be refractory to TNF antagonists or will lose response over time, resulting in the expansion of novel therapeutic targets. Despite these current advances, with novel drugs, novel therapeutic strategies and targets, and novel monitoring tools, there remain many unmet needs that clinicians face in their daily practice. Selecting the best drug for each patient remains a difficult decision, and there are many clinical situations where evidence is lacking to guide the best therapeutic approach.

In this special issue, dedicated to advances and challenges in the management of IBD, we start by a comprehensive review from Revés et al. highlighting some of the unmet needs in IBD. Among the most important challenges faced today are patient stratification and selection of the best therapy for each patient (personalized medicine). The authors discuss ongoing trials that will hopefully advance positioning of therapies, potentially based on the molecular profile of each patient. In the interim, clinical stratification and adequate monitoring of response to therapies remain the standard of care, highlighting the need for non-invasive monitoring strategies. Last, the authors discuss the topic of therapy de-escalation, as well as specific challenging clinical phenotypes and patient populations.

One of such phenotypes discussed by Michalopoulos et al. is refractory ulcerative proctitis (UP). While UP is usually considered a milder form of ulcerative colitis, there are many patients refractory to mesalazine therapy with disabling symptoms. In their state-of-the-art review, the authors provide useful recommendations on how to exclude alternative diagnoses and provide a management strategy based on the best available evidence.

Perianal fistulizing disease in CD represents one of the most debilitating phenotypes in daily clinical practice. Yzet et al. provide useful hints on how to optimize management and the use of TNF antagonists in this patient population. They also review evidence on the use of other biologics in perianal disease. The efficacy and safety of mesenchymal stem cell therapy is discussed as well out of the box approaches such as hyperbaric oxygen therapy or combination therapy of different biologics. Importantly, the authors emphasize the need for a combined medical-

surgical approach, discussing the place for different surgical approaches in the management of fistulae.

Currently, therapeutic choices in IBD patients are mostly driven by clinical factors, efficacy and safety considerations, and reimbursement policies. Despite the increasing number of novel drugs with different mechanisms of action, there remains a therapeutic ceiling in clinical practice with roughly 50% failing to reach remission. Therefore, there is a pressing need to identify biomarkers that predict response to a given drug or mechanism of action, that could allow personalized therapy. In their paper, Alsoud et al. discuss the current research on predictive biomarkers in IBD treatment selection. In particular, the authors review the challenges and best practices for current and future studies aiming to develop precision medicine approaches in IBD.

Despite advances in medical therapy for UC, many patients still require surgery with eventual construction of an ileal pouch anal anastomosis (IPAA or "pouch"). Management of patients with pouch disorders, in particular chronic antibiotic dependent pouchitis (CADP) or chronic antibiotic refractory pouchitis (CARP), can be challenging due to a limited evidence base. Kayal et al. review the current approach to patients with chronic pouch inflammation including the role of antibiotics and steroids as well as evidence on use of biologic agents to treat CADP and CARP. The authors also discuss emerging therapeutic areas including hyperbaric oxygen and fecal microbiota transplant.

One of the most recent classes of targeted therapies for IBD are the Janus Kinase (JAK) inhibitors. Speiwak et al. review the mechanism of these drugs as well as the current clinical trial efficacy data. Importantly, this paper discusses various safety concerns with the JAK inhibitors including infections, cardiovascular events, and thromboembolism. The authors conclude by reviewing special populations of patients and positioning of JAK inhibitors in the current therapeutic armamentarium.

The heterogeneity of CD has long been acknowledged. Indeed, one of the most important clinical risk factors for disease progression is disease location. Across population-based studies it has been demonstrated that ileal involvement is more frequently associated with stenosing and fistulizing complications and need for surgery compared with colonic CD. Currently, clinical trials do not take into account this phenotypic variability, but it has become evident from post-hoc analyses, that endoscopic and transmural healing is less often achieved in ileal versus colonic disease. In a comprehensive review on the topic, Atreya et al., present available efficacy data of various therapies in relation to ileal versus colonic disease, providing some immunological data that could serve as the basis for such differences.

The COVID-19 pandemic has impacted all fields of medicine and has been of particular concern in patients with IBD as they are frequently on immunosuppressive therapies that may increase risk of infectious disease

and complications. Kamath et al. review the current data on the impact of COVID-19 on treatment of patients with IBD. The authors review evidence on the association of IBD medications with COVID-19 outcomes and highlight that the vast majority of medications are low risk for COVID-19 adverse events.

This special issue finishes with a useful overview by Juillerat et al. on how to position biologics in clinical practice. In the past years there have been three novel classes of biologics arriving into the practice. In the absence of specific markers to guide selection of therapy, the authors detail on the available evidence of comparative efficacy and safety between, and on additional aspects to consider such as specific patient characteristics, extra-intestinal manifestations, patient comorbidities and specific indications.

The care of patients with IBD has been rapidly advancing and improving with expanding research and the introduction of new

therapies and strategies. This special issue aims to provide an overview of some the most challenging and interesting areas in IBD, providing practical information on current knowledge as well as emerging data and future directions.

References

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