Medical Management 1: General

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Abstract

In inflammatory bowel disease (IBD), no single cause initiates or triggers the disease. So far, medical treatment of ulcerative colitis (UC) and Crohn's disease (CD) has been aimed at decreasing the frequency and intensity of flares and limiting comorbidities and their consequences such as strictures, fistulae or cancer. Life-long therapy is usually required as there is to date no cure for IBD.

The goal in the treatment of IBD is to reach deep remission, meaning long-lasting clinical well-being combined with normal endoscopic (mucosal), biochemical (calprotectin and CRP) and histological findings. This status is currently considered to be necessary to alter disease course in IBD patients. Along with clinical reported outcomes (ClinRO), patient-reported outcome measures (PROMs) are gaining more and more weight in the judgement of remission. PROMs are validated and standardized questionnaires intended for completion by the patient to measure their perceptions of their own health condition or treatment. PROMs are aimed to allow decision-making at the level of individual patients.

As the causes of UC and CD are multifactorial, numerous and varying therapeutic strategies are needed to establish a sufficient treatment regime in IBD. However, as disease and patient expectations change over time, treatment often needs to be modified to meet the treatment goals required to optimize the disease outcome.

10.1 Introduction

Crohn's disease and ulcerative colitis are chronic, disabling diseases which not only have a significant impact on the daily life of our patients but could also lower life span due to several possible complications (Cosnes et al. 2011). This usually requires life-long therapy in both diseases, particularly because there is to date no cure for IBD. However, some patients can gain long-term drug-free remission after surgery.

Disease burden and the natural history of IBD are determined by the occurrence of inflammatory lesions, the manifestation and severity of symptoms, the development of complications and the need for surgery, disability and mortality (Latella and Papi 2012).

The therapeutic goal in the treatment of IBD is to reach long-lasting, sustained remission and prevent complications. Although remission is defined by many scores, the easiest definition consists of the absence of clinical IBD-related complaints.

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This symptom-free time, known as "sustained clinical remission", must last as long as possible. In most studies, clinical remission in Crohn's disease (CD) is defined as a Crohn's Disease Activity Index <150. In UC, the most often used score is the Mayo Score Clinical Score or Disease Activity Index (DAI). This score defines complete response (remission) as complete resolution of (1) stool frequency (normal stool frequency), (2) rectal bleeding (no rectal bleeding), (3) patient's functional assessment score (generally well), (4) endoscopy findings (normal) and (5) a PGA (Physician's Global Assessment) score of 0 (Bernstein 2015).

10.2 Background of Treatment

For decades, clinical remission was the ultimate goal both clinically and scientifically. It has more recently become clear that clinical remission needs to be accompanied by mucosal healing in order to prevent long-term complications such as the need for surgery (Fig. 10.1). Mucosal healing leads to an improved outcome of both UC and CD as evidenced by less need for surgery, use of immunosuppressants or hospital stay. However, there is no validated definition of what constitutes mucosal healing in IBD (Peyrin-Biroulet et al. 2011).

An International Organisation of IBD (IOIBD) task force proposed defining mucosal healing in UC as the absence of friability, blood, erosions, and ulcers in all visualized segments of gut mucosa (Vuitton et al. 2017). Similarly, for Crohn's disease, the IOIBD put forward a consensus definition of mucosal healing that includes the absence of ulcers. Simply stated, the absence of ulcerations and erosions should indicate mucosal healing (Bryant et al. 2014). Although it seems obvious that decreased visible mucosal inflammation would indicate better control of the disease, it has not yet been determined what minimum degree of endoscopic improvement is associated with improved clinical outcomes.

Clinical remission combined with endoscopic or mucosal remission and biomarker remission (calprotectin and CRP normal) is called deep remission, a status which is currently considered to be necessary to alter disease course in IBD patients. In the near future, the concept of deep remission might include transmural healing in CD and histologic healing in UC (Pineton de Chambrun et al. 2016).

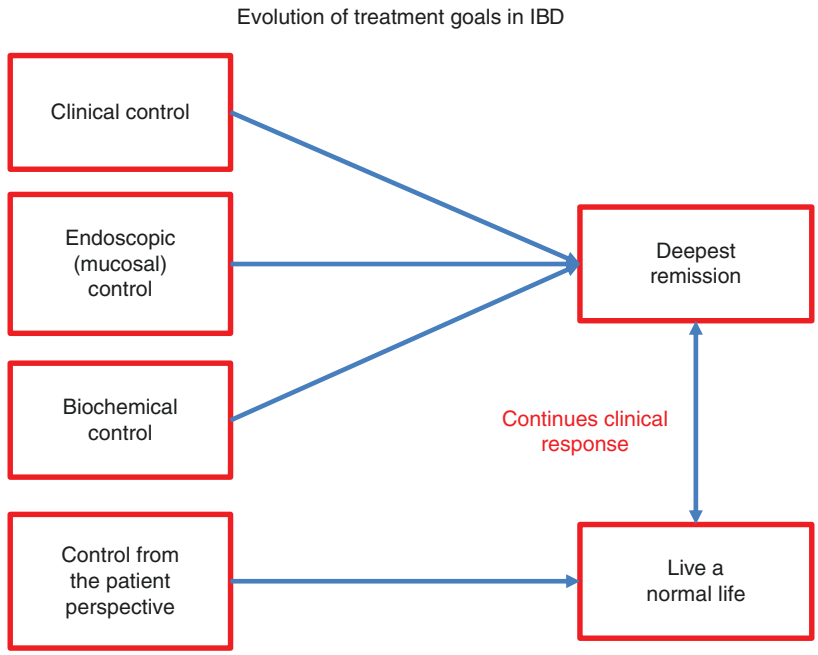

Fig. 10.1 Evolution of treatment goals in IBD

Healing of the bowel mucosa is not a predictor of remission after discontinuation of drug treatment. Being chronic diseases, both UC and CD will most likely reoccur if medical therapy is stopped even if deep sustained remission has been reached. This applies to both steroids and azathioprine (Doherty et al. 2018). Healing of the mucosa will, at best, be associated with a modest prolongation of the symptom-free interval in comparison with the non-healed bowel, but eventually the disease will resume its course. Strikingly, endoscopy upon relapse in patients who achieved mucosal healing with biological treatment shows exactly the same pattern and location of the disease as before mucosal healing. This strongly suggests that the "basic disease mechanism in the mucosa" does not disappear with healing of the ulcers and that the intraluminal trigger ends up damaging the mucosa again in a "predisposed manner" (Rutgeerts et al. 2007).

In addition to clinical remission defined by scores, endoscopic or biochemical remission, patient-reported outcomes are important psychometric instruments created and defined by patients to quantify symptoms (Kim et al. 2018). As patient satisfaction is one of the most important outcomes in IBD treatment, a combination of goals including not only the objective evaluation of inflammation by endoscopy and calprotectin but also patient-reported outcomes seems to be the most clinically and scientifically meaningful target of medical treatment. Unlike composite indices, response definitions based on endoscopic and biochemical markers as well as patient-reported outcomes can be readily applied in practice.

This convergence of outcome assessment in clinical trials and practice could expedite implementation of "treat-to-target" algorithms, in which therapy is progressively intensified until a specific treatment goal is reached. This approach could improve patient care by reducing rates of disease-related complications, surgery and hospitalization (Peyrin-Biroulet et al. 2015).

IBD are heterogeneous diseases, and there is not one single cause which initiates or exacerbates CD or UC. Often, multiple and varying therapeutic strategies are needed to identify a sufficient treatment regime in IBD. These treatments will often need to be adapted to reflect changes in the course of IBD due to complications such as intestinal resection changing the response to drugs. It is important to keep in mind that the patient's individual treatment and therapeutic needs often change over time.

Medical therapy often causes adverse side effects which lead to its own complications and negatively affect disease prognosis. Immunomodulators commonly used in IBD and which are associated with an increased risk of infections include corticosteroids, thiopurines, methotrexate, calcineurin inhibitors, anti-TNF agents, anti-integrins, anti-cytokines (Rahier et al. 2014) or JAK-kinase inhibitors. Despite different mechanisms of action, any of those drugs can lead to varying types of infection. No strict correlation between a specific immunomodulator drug and a certain type of infection has been observed. Moreover, as these drugs are commonly prescribed together, adverse events might amplify.

In clinical trials, a distinction is made between an adverse event and a serious adverse event. Generally, any event which causes death, permanent damage and birth defects or requires hospitalization is considered a serious adverse event.

The patient must be aware of risk-benefit ratios and willing to accept the possibility of any unavoidable side effects (Bewtra et al. 2015). As patient advocate, it is a crucial mission of the IBD nurse to know the pros and cons of medical therapy in order to communicate both effectively and compassionately with the patient.

There are probably four types of mistakes in defining the treatment strategy for a IBD patient:

- Under treatment of a patient who will develop disabling, complicated or severe disease
- Suboptimal use of steroids and immunosuppressants
- Continue ineffective medication
- Overtreatment of a patient with a benign disease course

However, the disease course changes over time and not only the will responsiveness towards medical treatment vary over time,

comorbidities and age increase the risk of adverse effects. However, IBD patients are willing to accept the known risks associated with IBD therapies while demanding substantial treatment benefit to make this trade-off (Bewtra et al. 2015; Siegel 2009).

10.3 Overview

- UC and CD are chronic, potentially disabling diseases. Both diseases cannot be cured, and thus, life-long therapy is needed in most patients.
- The therapeutic aim in UD and CD is to limit inflammation, achieve long-term clinical remission, prevent steroids, heal the mucosa, and guarantee a high quality of life.
- Continuous remission, both on the clinical and mucosal level, without the use of steroids, is needed to change the course of the disease and prevent complications.
- There are crucial mistakes in IBD medical therapy including the undertreatment of a patient who will develop disabling, complicated or severe disease or overtreatment of a patient with a benign disease course which might cause potential adverse events.

10.4 Summary

IBD affects a broad spectrum of physical, psychological, familial and social dimensions of life. The treatment aims consist of a long-term, deep, steroid-free remission including a symptom-free life, mucosal healing and normalization of inflammation and malabsorption markers, leading to the ultimate goal in IBD treatment: improving and normalizing the quality of life of our patients. This ambitious goal can be difficult in clinical practice, especially in patients with long-standing disease. The goal of the patient and healthcare professional needs to be re-evaluated over time in order to adapt the therapeutic approach to the course of a changing disease.

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