The Evolution of Treatment Paradigms in Crohn's Disease: Beyond Better Drugs

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KEYWORDS

• Crohn's disease • Therapy • Treatment paradigms • Treatment algorithms • Treat to target

KEY POINTS

- Several new and effective therapies are available for the treatment of Crohn's disease.
- Recent clinical guidelines have advocated for the use of objective markers of inflammation in addition to clinical symptoms to assess response to therapy.
- Early use of effective therapies, prognostication to identify high-risk patients, objective end points, precision medicine, pharmacokinetic/pharmacodynamics factors, and frequent assessment of disease activity are key features of a new treat-to-target algorithm.

INTRODUCTION

Since the pathophysiologic mechanisms responsible for Crohn's disease (CD) have not been fully defined, conventional therapies have been intrinsically based on the use of broad-spectrum immunosuppression. Agents, such as corticosteroids, azathioprine, and methotrexate, suppress the pathologic immune response and control symptoms; but they frequently cause off-target side effects. As our knowledge of immune mechanisms has evolved, drug therapy has moved away from nonspecific immunosuppressives to agents with highly selective activity, such as tumor necrosis factor (TNF) antagonists, vedolizumab, and ustekinumab. Concordant with the availability of these improved therapies, treatment algorithms have also evolved to incorporate a focus on long-term management in distinction to episodic treatment,

Disclosure: See last page of article.
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Gastroenterol Clin N Am 46 (2017) 661–677
http://dx.doi.org/10.1016/j.gtc.2017.05.010
gastro.theclinics.com

increased use of combination therapy, therapeutic drug monitoring, and the earlier introduction of highly effective therapy in patients with a poor prognosis.[1]

To illustrate the potential of an ideal management algorithm that incorporates these principles, consider the results of 2 landmark randomized controlled trial (RCT) algorithms. In the ACCENT I study, which assessed infliximab (IFX) maintenance therapy in patients with an average disease duration of 8 years, a corticosteroid-free remission rate of 29% was observed at week 54.[2] In comparison, the remission rate in the SONIC trial[3] in patients with an average disease duration of 2 years who were assigned combination therapy with IFX and azathioprine (AZA) was 55.6%. Although these studies were performed 8 years apart and were conducted in different patient populations, the magnitude of the observed difference in efficacy supports the use of algorithms that feature early introduction of highly effective therapy. It is notable that SONIC did not exclusively enter high-risk patients, use therapeutic drug monitoring (TDM) to optimize IFX therapy, or use endoscopic healing as a treatment target. These potential strategies to improve management algorithms are discussed later.

HIGHLY EFFECTIVE THERAPIES

The conventional management algorithm for CD is based on step-care, in which treatments are introduced sequentially, starting with the least effective agents and proceeding, based on the symptomatic response to treatment, to more effective drugs (**Fig. 1**). Corticosteroids, which have been the backbone of this approach for more than half a century, are highly effective for controlling symptoms because they downregulate multiple inflammatory pathways[4,5]; however, this benefit comes at the cost of numerous off-target side effects.[6,7] Furthermore, corticosteroids are ineffective as maintenance therapy. Consequently, the use of corticosteroid-sparing immunosuppressives, such as AZA and methotrexate became established as the next step in the therapeutic pyramid, with AZA being the most widely used agent. However, recent studies have indicated that AZA has little, if any, efficacy as monotherapy.[8,9] Moreover, thiopurine use is associated with an increased risk of lymphoma and nonmelanoma skin cancer.[10] In contrast, TNF antagonists (infliximab, adalimumab, certolizumab) are highly effective for both induction and maintenance of remission in CD[2,11–14] and corticosteroid-sparing and are better tolerated than thiopurines.

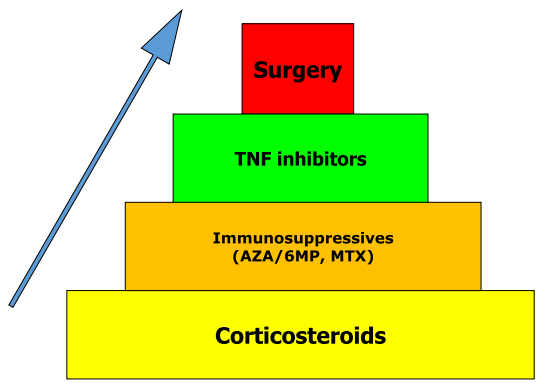

Fig. 1. Conventional therapeutic step-up algorithm. Traditional algorithms have featured the sequential use of therapies based on symptoms, whereby highly effective therapies are reserved for patients who have failed other options. MTX, methotrexate.