Current Concepts of Pharmacotherapy in Crohn's Disease

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Keywords

Crohn's disease · Targeted therapy · Anti-TNF · Anti-integrin · Anti-cytokine

Abstract

Background: The incidence of Crohn's disease (CD) is rising, and still many patients have to undergo repeated surgery due to failure of pharmacologic therapy. **Results:** While the introduction of anti-TNF agents started biologic therapy for CD and revolutionized the management of patients, the number of patients who do not respond to this treatment or lose their initial response to this treatment is still substantial. Therefore, the recent introduction of new therapeutic options with anti-integrins and new anti-cytokines was an important step to provide more effective treatment for our patients. Yet, next to new drugs also new treatment strategies have been proposed. **Conclusion:** In this article, we will review these new aspects of pharmacologic therapy for CD patients.

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Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease that as of now cannot be cured. Historically, about 80% of the patients required surgery during the first 20 years after diagnosis [1], and 35% of all patients requiring systemic steroids will undergo surgery within 1 year [2,

3]. However, surgical rates are decreasing [4], and this has been attributed to earlier and better diagnosis, closer follow-up, and more therapeutic options [5]. Current guidelines state that indications for surgery are complications of CD [6] and failure of conservative therapy [7].

However, this widespread notion has recently been challenged. In the LIR!C study [8], patients with active CD of the terminal ileum and failed conventional therapy were randomized to therapy with infliximab or ileocecal resection. Endoscopic follow-up after 7–18 months showed similar rates of endoscopic remission in both groups. Quality of life scores at 12 months of follow-up were higher for surgically treated patients, although the difference was statistically significant only for a subcomponent of one quality of life score. Another study with 123 CD patients referred for intestinal surgery revealed that a longer time between diagnosis and surgery was significantly associated with an increase in medical and surgical complications [9].

In light of these results, the current medical therapy and evolving strategies of medical management in adult CD patients are outlined herein.

Treatment Concepts

There are general recommendations valid for most CD patients: NSAIDs should be avoided [10], patients should refrain from cigarette smoking and should not reduce dietary fiber [11].

A simplified outline of therapy according to ECCO guidelines [12] distinguishes between induction therapy and therapy for maintenance of remission. For induction of remission, corticosteroids (topical or systemic) and TNF inhibitors are recommended options. Vedolizumab is an alternative option to induce remission. 5-ASA preparations are not effective for inducing remission in CD patients. Thiopurines are not recommended for induction therapy, as they do not act fast and have a considerable rate of side effects.

In every patient treated with remission-inducing medication, maintenance therapy should be considered. Recommendations are given for thiopurines or methotrexate. In patients with more severe disease, TNF inhibitors can be used as well.

Early versus Late Therapy

Already early during the introduction of biologics to CD therapy, there was evidence that therapy initiation in patients with long-standing CD was associated with a higher rate of relapse than in patients diagnosed only recently [13]. After biologics became available, many studies focused on the question whether the conventional “step-up” therapy of CD or a “top-down” approach was more effective. Several of these studies [14–17] have shown a significant reduction in complications. However, there is a risk of overtreatment and decreased cost-efficiency with these strategies, one reason being that CD patients have a high rate of spontaneous remission, best shown by the high placebo rate even in endoscopically controlled trials [18]. In addition, a definite long-term benefit has so far not been demonstrated [19].

Treat-to-Target

Now, in the light of improved diagnostic tools, new strategies are being tested. After positive experiences with “treat-to-target” strategies in rheumatoid arthritis, the STRIDE recommendations in 2015 suggested treatment goals both for ulcerative colitis and for CD [20]. In the landmark CALM study [21], CD patients with endoscopically active disease were randomized to two strategies: clinical management or tight control using patient-reported outcomes, clinical, and biomarker values as triggers for therapy adjustments. Although the study was criticized for the use of different cutoffs of clinical activity in both arms, a recent analysis [22] after 2 years could demonstrate an improved cost-effectiveness of the tight-CONTROL group in addition to the significantly higher remission rate. With the increased use of biosimilars, flexible treatment strategies could prove to be even more cost-effective.

New Treatment Options

In recent years, two new treatment principles have found their way into standard care of CD patients: integrin antagonists and IL-12/IL-23 inhibition.

Vedolizumab is an antibody against $\alpha 4\beta 7$ -integrin and prevents interaction of lymphocytes with endothelial adhesion molecules and their transmigration to the gastrointestinal tract, thereby reducing local inflammation. Advantages are a low rate of adverse effects [23] and a high rate of long-term remissions [24]. However, due to its way of action, vedolizumab takes longer for clinical response [25] than TNF inhibitors. In addition, in patients who did not achieve remission with TNF inhibitors, vedolizumab was not more successful than placebo in inducing remission [26]. However, there are data suggesting that in pretreated patients, identification of those with high $\alpha 4\beta 7$ expression on lymphocytes could increase the rate of response to vedolizumab [27]. Other studies have been able to identify patients who were more likely to respond to therapy with vedolizumab. In one study, absence of previous therapy with TNF inhibitors, absence of surgery, absence of fistulating disease, higher levels of albumin, and lower levels of C-reactive protein were associated with a higher rate of response to vedolizumab [28]. Another study was able to show that remission after 1 year was predicted by response and lower C-reactive protein at week 14 [29].

The search for alternative, proinflammatory cytokine-blocking drugs, lead to an intense investigation of the IL-12/IL-23 pathway. IL-12 and IL-23 are key players in linking the antigen-presenting cells to the subsequent differentiation of naïve CD4⁺ T cells into T_H1 or T_H17 cells by IL-12 or IL-23, respectively [30]. Especially IL-23 and consequently IL-17 seem to play an important role in the intestinal inflammation in inflammatory bowel disease [31] and ustekinumab, by binding the p40 subunit that is common to IL-12 and IL-23 thus blocks both molecules from interacting with their receptor. Ustekinumab has been successfully used in the treatment of psoriasis and psoriasis arthritis. Its efficacy for the treatment of CD has been proven in a series of multi-center, placebo-controlled trials [32]. In the group receiving 6 mg/kg of body weight, ustekinumab was most effective: 39.7% of the patients reached the primary endpoint of remission at week 6, compared to only 23.5% in the placebo group. In the patients who continued ustekinumab until week 22, the rate of clinical remission was 41.7% versus 27.4% with placebo. During the study period, there was no significant difference in the number of serious infections between the ustekinumab-treated group and the placebo group. Further trials across different indications confirmed this safety pattern [33].

In patients treated with ustekinumab, a history of intestinal resections is associated with a lower probability of long-term clinical benefit, and an initial response to the medication predicts long-term clinical benefit [34]. In another cohort, ileocolonic disease was positively and higher disease activity as evidenced by a higher HBI score and stricturing disease were negatively associated with clinical response [35]. Ustekinumab has demonstrated a favorable response against psoriatic skin lesions and peripheral arthritis, yet it failed to improve symptoms in axial spondyloarthritis. Ustekinumab seems to have some efficacy for fistulizing disease, yet all currently available data are derived from observational cohorts [36].

Considering the higher relevance of IL-23 pathways for the mucosal immune response a more selective approach seems to be promising. First encouraging results did demonstrate good efficacy for risankizumab, an antibody targeting the p19 subunit of IL-23, in CD patients [37].

Conclusion

While therapy with azathioprine is still considered an effective and especially cost-effective therapy, the introduction of biosimilars will make anti-TNF therapy an affordable and effective alternative for induction and maintenance therapy. A treat-to-target approach will help reduce the burden of disease for CD patients and very likely reduce the need for surgery in selected patient

groups. Yet, a number of patients fail to respond to anti-TNF therapy, and another substantial proportion of our patients loses response over time. Therefore, the urgent need for new drugs that use a different mode of action resulted in a huge effort to provide new drugs for a very promising market. Vedolizumab and ustekinumab are already available and have provided new opportunities for our patients. Many more compounds are in the pipeline. With more and more drugs available, a more informed way to choose the appropriate therapy for a given patient is one of the most important tasks for future research. Currently, the first head-to-head trial comparing efficacy between vedolizumab and adalimumab in ulcerative colitis has been published [38], and more head-to-head trials are recruiting patients. Yet, up to now the number of pre-treatment indicators is still small, and results of trials are partially conflicting. Taken together, early therapy of CD patients, improved selection of the appropriate therapeutic principle, a therapy that is continuously adjusted according to clinical and biochemical parameters as well as patient-reported outcomes are likely to improve outcomes in the future.

Disclosure Statement

The author of this publication received a honorarium and was a speaker for Takeda. The terms of this arrangement have been reviewed and approved by Klinikum rechts der Isar, Technische Universität München.

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