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First-Line Therapies in Inflammatory Bowel Disease

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Inflammatory bowel disease · First-line treatment · Steroids · Crohn's disease · Ulcerative colitis

Abstract
Background and Aims: Medical therapy of inflammatory bowel disease (IBD) is becoming more complex, given the increasing choice of drugs to treat Crohn's disease (CD) and ulcerative colitis (UC). We aimed to summarize the current guidelines for first-line treatments in IBD. ***Methods:*** An extensive literature search with focus on the guidelines of the European Crohn's and Colitis Organisation for the diagnosis and treatment of CD and UC was performed. First-line treatments were defined as the following drug categories: 5-aminosalicylates, budesonide, systemic steroids, azathioprine, 6-mercaptopurine, methotrexate, infliximab, adalimumab and certolizumab pegol. The following drug categories were not included: cyclosporine and tacrolimus (not yet approved by Swissmedic for IBD treatment). ***Results:*** Treatment recommendations for the following clinically frequent situations are presented according to disease severity: ileocecal CD, colonic CD, proximal small bowel CD and perianal CD. For UC the following situations are presented: ulcerative proctitis, left-sided colitis and pancolitis. ***Conclusions:*** We provide a summary on the use of first-line therapies for clinically frequent situations in patients with CD and UC.

Introduction

Inflammatory bowel diseases (IBD) are characterized by the presence of chronic, noninfectious inflammatory processes of the bowel of unknown origin. Current evidence suggests that, based on several genetic abnormalities, a dysbalanced mucosal immune system reacts in an uncontrolled way to luminal antigens [1]. The diagnosis of IBD is made based on a mixed picture consisting of symptoms, endoscopic findings, histology, radiologic exams and laboratory markers, once other causes for IBD such as infections have been ruled out. The two main diseases are Crohn's disease (CD) and ulcerative colitis (UC). CD is characterized by a transmural inflammation classically involving the terminal ileum and the proximal colon. One third of the patients present only a colonic in-

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volvement and another third have a more diffuse disease involving the small bowel as well as the stomach or the esophagus. Characteristic for CD is the transmural inflammation that may lead to structural complications such as internal or external stenoses and perianal fistulas. Inflammation in UC is typically limited to the colon and histologically to the mucosa (and submucosa). Depending on the extent, an ulcerative proctitis is discriminated from a left-sided colitis and a pancolitis. Both CD and UC can be complicated by the appearance of extra-intestinal manifestations (due to antigen cross-reactivity) such as inflammation of the eyes (uveitis and conjunctivitis), joints (arthritis), skin (pyoderma gangrenosum and erythema nodosum) or liver (primary sclerosing cholangitis) [2].

The choice of medical management for IBD patients depends on disease activity, location, extension and the potential involvement of other organs. The assessment of these items allows a tailored therapeutic approach. Treatment is divided into an induction phase with the aim of a response or remission and then the maintenance treatment which should enable the response or remission to continue. The following paragraphs will review the first-line treatment choices for CD and UC, including such induction and maintenance therapies. The following drug categories are summarized under first-line therapies: 5-aminosalicylates, budesonide, systemic steroids (prednisone and derivates), azathioprine, 6-mercaptopurine, methotrexate, infliximab, adalimumab and certolizumab pegol. The following second-line treatments will not be discussed: cyclosporine and tacrolimus.

Crohn's Disease

Ileocecal CD

The ileocecal location represents the typical CD presentation. In mild to moderately active ileocecal CD [Crohn's Disease Activity Index (CDAI) up to 300 points], budesonide 9 mg per day is the best choice to induce clinical remission. Budesonide has shown its superiority to placebo and to mesalazine and has fewer side effects than systemic corticosteroids [3]. However, in one recent study, the authors found that mesalazine 4.5 g per day was comparably efficient to budesonide to induce remission (69.5% for budesonide compared to 62.1% for mesalazine) [4]. A CDAI drop of 100 points was observed in 89% of budesonide-treated patients compared to 79% of mesalazine-treated patients [4].

In the case of severe clinical activity (defined as CDAI >300 points) systemic corticosteroids (either prednisolone per os or intravenous hydrocortisone) should be administered [3]. In CD patients with steroid-refractory or steroid-dependent disease, an early introduction of anti-TNF therapies can be beneficial. The step-up versus top-down study showed that even treatment-naïve patients could benefit from this strategy [5].

Surgery is not the primary focus of this review; it should be considered in cases of ileocecal CD that are resistant to medical therapy.

Maintenance therapy is usually indicated after the induction of response and/or remission by corticosteroids as these drugs are not effective in maintaining the response or remission, respectively, and they are furthermore associated with adverse treatment effects such as osteoporosis or an increased risk of infection [6].

Azathioprine (2–2.5 mg/kg/day) is the most commonly used drug for this situation and has proven efficacy for maintaining CD in remission and also for having steroid-sparing effects [7]. Methotrexate at weekly doses of 15 mg i.m. has also demonstrated efficacy in maintaining CD in remission [8, 9].

Colonic CD

Active colonic CD should be treated with systemic steroids for induction of response and remission. Budesonide is not effective for colonic CD due to its limited action on the proximal colon. Azathioprine, 6-mercaptopurine or methotrexate can be used as steroid-sparing agents for maintaining the medically induced remission [7–9]. In relapsing disease, anti-TNF drugs (infliximab, adalimumab or certolizumab pegol) can be administered for induction and maintenance of remission with or without an immunomodulator [10]. The SONIC trial evaluated the efficacy of infliximab monotherapy, azathioprine monotherapy and the 2 drugs combined in 508 adults with moderate to severe CD who were naïve to previous treatments with either an immunomodulator (azathioprine, 6-mercaptopurine or methotrexate) or biologic therapy [11]. Of the patients receiving combination therapy, 56.6% were in corticosteroid-free clinical remission at week 26 compared to 44.4% who received infliximab monotherapy ($p = 0.02$) and 30.0% who received azathioprine monotherapy ($p < 0.001$ for the comparison with combination therapy and $p = 0.006$ for the comparison with infliximab). Similar numerical trends were found at week 50. Whether or not combination therapy is associated with similar benefits in CD populations no longer naïve to immunomodulators and/or anti-TNF drugs remains to be investigated.

Extensive Small Bowel CD

Extensive small bowel CD is defined as disease affecting >100 cm of the small bowel and therefore carrying the risk of nutritional deficiencies [12]. Treatment of extensive intestinal CD is equivalent to other localization of CD. Systemic steroids should be used to induce clinical remission. The early introduction of immunomodulators (azathioprine, 6-mercaptopurine or methotrexate) is recommended, given their steroid-sparing effects in the long-term [12].The early introduction of anti-TNF therapy should also be considered, particularly for the population with clinical indicators of poor prognosis such as a young age at diagnosis, an initial need for steroid therapy and the presence of perianal disease [13].

Perianal CD

Perianal fistulae in CD are classified into simple and complex fistulae [14]. Before deciding on specific treatment for perianal CD, a pelvic MRI should be performed for the assessment of disease location and severity [15]. The imaging will also detect the presence of perianal abscesses which should be drained as soon as possible. In addition, a proctosigmoidoscopy should be performed as the presence of ongoing rectosigmoid inflammation influences the treatment success [15]. In fact, evidence suggests that fistula treatment is not successful without treatment of the underlying active disease [16]. Only symptomatic perianal fistulae should be treated [15].

The treatment of the fistulizing CD itself is based on antibiotics, immunomodulators (azathioprine, 6-mercaptopourine or methotrexate) or anti-TNF drugs.

Metronidazole and/or ciprofloxacin have been studied only in small patient series. They are effective in reducing symptoms but less so in inducing fistula healing [17]. There are no randomized controlled trials which have evaluated the efficacy of azathioprine and mercaptopurine on the closure of perianal fistulae as the primary end point in CD patients. A meta-analysis of 5 randomized controlled trials where closure of perianal fistulae was assessed as the secondary end point favor the use of azathioprine and 6-mercaptopurine for the induction and maintenance of perianal fistula closure [18].

Infliximab was the first anti-TNF agent to demonstrate in a randomized controlled trial effectiveness in inducing closure of perianal fistulae and maintaining this response over 1 year. An induction treatment with 5 mg infliximab/kg at weeks 0, 2 and 6 led to a complete closure (defined as cessation of all drainage on 2 visits 1 month apart) in 17/31 (55%) of patients [19]. In the ACCENT II trial, 33/91 (36%) of patients on infliximab had complete fistula closure at week 54 compared to 19/98 (19%) on placebo ($p = 0.009$) [20].

In the CHARM trial (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance), CD patients treated with adalimumab showed a fistula remission of 30% compared to 13% on placebo ($p = 0.04$) at week 26 and a fistula remission of 33% compared to 13% in the placebo group ($p = 0.02$) at week 56 [21].

The Swiss FACTS survey (First Approved Certolizumab Therapeutic Experience in Switzerland) demonstrated that certolizumab pegol was associated with a perianal fistula closure rate of 36% at week 6 and of 55% closure rate at week 26 [22].

Ulcerative Colitis

Ulcerative Proctitis

Active proctitis should first be treated topically. Topical mesalazine (5-aminosalicylates) was able to induce remission in active proctitis and distal colitis in 31–80% (median 67%) of patients compared to 7–11% in patients treated with placebo in a meta-analysis evaluating 11 trials with a total of 778 patients [23]. It proved to be at least twice as effective as topical corticosteroids with regard to symptom improvement (OR 2.42 and 95% CI 1.72–3.41), endoscopic improvement (OR 1.89 and 95% CI 1.29–2.76) or histologic improvement (OR 2.03 and 95% CI 1.28–3.20) [24]. It should be applied with a dosage of 1 gram per day. Combining topical and oral mesalazine is more effective than either one only for colitis <50cm from the anal verge [25], and in the case of an insufficient response to topical mesalazine, the combination of these with topical steroids (beclomethasone dipropionate) can be beneficial [26]. Patients failing to improve on such a combination should be treated with oral prednisolone [25].

Left-Sided Colitis

As for distal proctitis, treatment of left-sided colitis is based on mesalazine. The combination of oral and topical mesalazine therapy is recommended [25]. A meta-analysis of mesalazine showed a dose response for clinical improvement from <2.0 g, 2.0–2.9 g and > 3.0 g being administered daily ($p = 0.002$), but not for remission [27]. Thus, induction of remission of left-sided UC should be performed by prescribing mesalazine at a daily dosage of at least 3 grams. In severe left-sided UC as well as in mesalazine-refractory moderate left-sided UC, oral steroids (prednisolone) are the treatment of choice for induction therapy. Maintenance of remission can be achieved using

Table 1. Induction therapies for IBD depending on disease location and severity

	Mild activity	Moderate activity	Severe activity
Crohn's disease			
Ileocaecal	budesonide	budesonide	corticosteroids
Colonic	corticosteroids	corticosteroids	corticosteroids anti-TNF
Extensive small bowel	corticosteroids anti-TNF	corticosteroids anti-TNF	corticosteroids anti-TNF
Perianal	antibiotics surgical drainage	antibiotics surgical drainage anti-TNF	antibiotics surgical drainage anti-TNF
Ulcerative colitis			
Proctitis	topical aminosalicylates	topical aminosalicylates	topical aminosalicylates topical steroids
Left-sided colitis	topical and oral aminosalicylates	topical and oral aminosalicylates corticosteroids	topical and oral aminosalicylates corticosteroids
Pancolitis	topical and oral aminosalicylates corticosteroids	topical and oral aminosalicylates corticosteroids	topical and oral aminosalicylates corticosteroids anti-TNF cyclosporine

mesalazine in lower dosages than is used for induction treatment [28].

Pancolitis

As for left-sided UC, pancolitis should be treated following the same rules, but systemic steroids should be used sooner than in left-sided colitis, depending on the severity. Again, the combination of both oral and topical mesalazine is more effective for the induction of remission [29]. Steroids should be weaned progressively by 10 mg per week until 20 mg and then by 5 mg per week for the timely recognition of steroid-dependence. In the case of steroid dependency, immunomodulators should be started.

In mild to moderate pancolitis, mesalazine can also be used as maintenance therapy [28]. In moderate to severe pancolitis azathioprine proved to be more effective than placebo for maintaining remission [30]. Azathioprine should be started when frequent relapses are observed while the patient is on maintenance therapy with mesalazine or in the case of steroid dependence.

Acute severe colitis is a particular condition carrying a substantial risk for colectomy. Intravenous steroids should be started early and their effect should be monitored closely and response assessed at 3–5 days [25]. If an adequate response is not achieved under intravenous administration of steroids, second-line treatment with infliximab or cyclosporine should be initiated. Maintenance therapy can be achieved either by continuing infliximab or with azathioprine that replaces cyclosporine after the acute phase [25].

Conclusions

Therapy of CD and UC is based on disease location and disease severity, also taking into account the presence of prognostic factors for a disabling disease course in the case of CD. The recommendations for induction therapies are summarized in table 1.

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Disclosure Statement

The authors declare no conflict of interest.

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