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Corticosteroids in inflammatory bowel diseases

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Abstract

Corticosteroids (CSs) were first introduced as therapy for inflammatory bowel disease (IBD) in the 1950s, since that time, CSs are mainstay in the treatment of IBD. CSs are an effective treatment for induction of remission and ineffective in the maintenance of remission. The negative aspects of these drugs are the possibility of occurrence of steroid dependency or steroid refractory and the development of multiple side effects during long-term treatment. This article reviews the role of conventional and novel CSs in the management of IBD. (IBD Rev. 2018;4:53-60)

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the main diseases that comprise the term inflammatory bowel disease (IBD). It is a set of chronic diseases, usually initiated at the stage of young adult, remaining along the life with courses of relapse and remission or, less commonly, as a chronic, progressive, and continuous course. The etiology is still unknown that has no permanent drug cure despite therapeutic advances based on immunosuppressants and biologicals, and can result in significant long-term morbidity. The global incidence is increasing worldwide[1], mainly in western countries (Fig. 1).

The treatment of IBD has as main goals the rapid control of the inflammatory process (induction of remission) and the conservation of this in the long term (maintenance of remission). However, the choice of the optimal therapeutic regimen can be complex because it is based on the location and extent of the disease, degree of activity, phenotype, and the presence of factors of worse prognosis. In addition to these variables, you must seek a balance between efficacy and adverse effects of each drug class.

Corticosteroids (CSs) have been playing an important role in the therapeutic strategy in IBD

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Figure 1. Overall annual incidence map of inflammatory bowel disease: "High" refers to incidence > $10/10^5$, "Medium" $5\text{-}10/10^5$, and "Low" < $4/10^5$, and "Low with increase" to low incidence that is continously increasing. Blank regions are indicative of lack of data *(adapted from Cosnes J, et al.[1]).*

during more than 50 years. CSs became the gold-standard in the treatment of active IBD worldwide during decades, and recently, the guidelines of the European Crohn's and Colitis Organization have ratified that despite the emergence of immunobiologic in the treatment of IBD, the glucocorticoids are still used as therapy for induction of remission of active disease[2,3]. These drugs work by modulating the immune response through the interaction with their receptors in cell nuclei, interfering in the expression of adhesion molecules, and minimizing the production of proinflammatory cytokines such as interleukins and tumor necrosis factor (TNF). These drugs inhibit the action of the nuclear factor kappa B, preventing the migration of inflammatory cells to the gastrointestinal tract (Table 1).

CSs considered as a conventional therapy can be separated into two types: the first and second generation.

The steroids of the first generation (prednisone, hydrocortisone, and prednisolone) considered traditional have a systemic action but with innumerous side effects, mainly when in a long-term use.

The steroids of the second generation (budesonide and beclomethasone dipropionate) are characterized by a systemic action with an anti-inflammatory action imminently topical, low systemic bioavailability by extensive first-pass effect, and lower toxicity. The budesonide, CS indicated for the induction of remission of CD, mainly if located in the ileocecal segment/ascendant colon, but not in maintenance of remission. More recently, the use of budesonide and beclomethasone dipropionate was established in UC treatment. These medications are administered as prodrugs, activated by esterases from the intestinal mucosa cells, where they exert anti-inflammatory action. After absorption, these drugs suffer extensive liver metabolism generating inactive products, therefore, causing low systemic bioavailability. The budesonide administered orally has a high affinity to the steroid hormone receptor (15 times higher than the prednisolone and 195 times that the hydrocortisone). It is metabolized in the liver by the cytochrome P-450 system generating inactive metabolites with low systemic bioavailability (10-15%) and

Table 1. Steroids formulations according to the administration form, compound, presentation, release mechanisms and standard dose used in inflammatory bowel disease patients

Route	Substance	Presentation/Release	Dose
Topical	Budesonide	Foam	2 mg
	Beclometasone dipropionate	Enema	3 mg/60 ml
	Prednisolone	Enema	100 mg
Oral	Prednisone	Tablet	0.5-1.0 mg/kg (or 40-60 mg/day in a single dose)
	Prednisolone	Tablet	40 mg/day
	Budesonide	Controlled ileal release pH-dependent release MMX	6-9 mg/day
Intravenous	Hydrocortisone	Ampoule	300-400 mg/day
	Methylprednisolone	Ampoule	30 mg IV every 12 h

MMX: multi matrix.

lesser toxicity as compared to conventional corticoids[4,5].

Once the second-generation steroids have essentially local and selective action, it is of utmost importance that they reach therapeutic concentrations on the target location of the gastrointestinal tract. In practice, the oral preparations are absorbed rapidly from gastrointestinal tract and have different mechanisms of release the active drug. The oral budesonide formulations contain granules which are coated to protect acid dissolution in gastric juice (gastroresistant) but which dissolve into the intestinal lumen of ileum, cecum, and ascending colon in a pH (at a pH ≥ 5.5) or time-dependent manner.

More recently, emerged a new technology that allows the delivery of these drugs in the colon more homogeneous, allowing greater concentration on more distal intestinal segments, entitled multi matrix (Fig. 2)[5].

Formulations related to different routes and release mechanisms were developed to increase efficacy and local action, and also reduce systemic effects and toxicity (Table 1).

In UC and CD inpatient with severe activity, hydrocortisone should be prescribed at a dose of 300-400 mg/day, while prednisone is generally used at a dose of 0.5-1.0 mg/kg (or 40-60 mg/day as a single dose in the morning). Prednisone with superior dose than 60 mg/day is not recommended, being related to higher toxicity without a significant increase in efficiency. The evaluation of the clinical response is up to 4-7 days for intravenous formulation and 2-4 weeks by oral therapy. There is a clear clinical improvement of CD evaluated by Crohn's Disease Activity Index (CDAI) score (drop ≥ 100 points), and the withdrawal should be gradual.

The lack of a meaningful clinical response to high dose of steroids after 4 weeks (prednisolone in doses up to 1 mg/kg/day or equivalent) is considered as steroid refractory disease. Steroid-dependent disease was defined if high dose of glucocorticoids cannot be tapered to < 10 mg/day of prednisolone or budesonide (< 3 mg/day) within 3 months of starting steroids, without recurrent disease, or if relapse occurs within 3 months of stopping glucocorticoids[2-4]. A Danish cohort study involving CD patients submitted at least one cycle of conventional CSs showed 20% of refractoriness and 36% of dependency[6].

The benefits of CSs in the treatment of IBD are counterbalanced by their adverse effects,

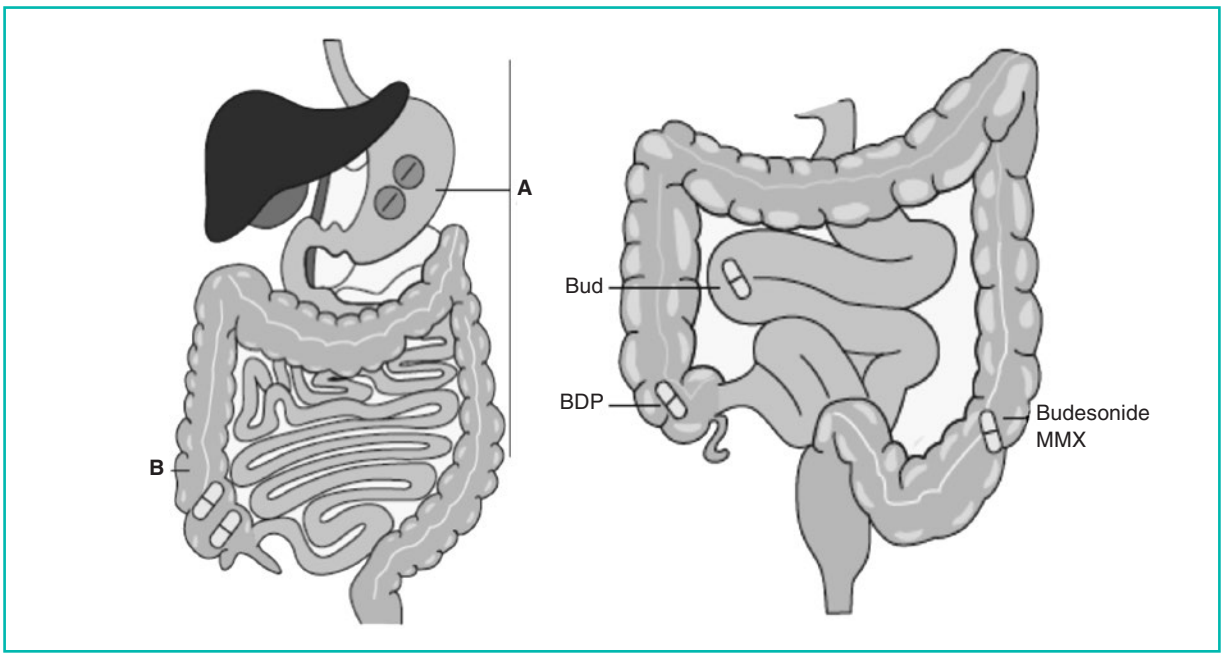

Figure 2. A: Conventional corticosteroids: proximal absorption, systemic anti-inflammatory effect, and unfavorable adverse effects profile. **B:** Second-generation corticosteroids: distal absorption, local anti-inflammatory effect, and low toxicity. Bud: ileal and pH-dependent budesonide; Bud MMX: budesonide colonic release; BDP: beclomethasone dipropionate *(adapted from Saibeni, et al. Expert Rev. Gastroenterol. Hepatol. 2014).*

being these directly related to the daily and accumulated doses. Approximately 50% of IBD patients using CSs will have side effects. In the short term, cosmetic effects (acne, full moon facies, and edema), mood and sleep disorders, and glucose intolerance and dyspepsia prevail. With prolonged use, usually more than 12 weeks, but it may occur earlier, there is an increased risk of cataracts, myopathies, osteoporosis, osteonecrosis, and susceptibility to infections[4]. In a prospective cohort of more than 6000 patients with CD, the use of CSs was determined to be an independent factor for the occurrence of severe infections (odds ratio [OR] = 2.21, 95% confidence interval [CI] = 1.46-3.34, $p < 0.001$) and increased risk of mortality (OR = 2.10, 95% CI = 1.15-3.83, p = 0.016)[7].

The withdrawal of CSs also involves adverse effects including weakness, muscular and articular pain (myalgia and arthralgia), increased intracranial pressure, and acute adrenal insufficiency (postural hypotension, nausea and vomiting, hyperkalemia, and hyponatremia). Any patient who is on long-term use of CSs, in particular, dosages > 7.5 mg of prednisolone or equivalent for more than 3 weeks, should receive additional CS doses during periods of stress, such as surgery, and the withdrawal of CS therapy should be gradual and slow[4]. Because there is no ideal weaning protocol, it is dose recommended dosage reductions each every 7-10 days, equivalent to 5-10 mg of prednisone up to the dose of 20 mg/day, followed by withdrawal of 2.5-5 mg, until the total interruption.

Recommendations on induction of remission in CD[2,4,8]

- Oral budesonide at a dose of 9 mg/day is the preferred therapy in inducing remission of ileocecal DC with mild activity. In moderate activity, the primary therapy is based on budesonide or systemic CS therapy.
- In acute ileocecal DC, budesonide has no indication and systemic CS is the initial therapy.
- DC with colonic involvement should be initially treated with systemic CSs.

- The extensive small bowel CD should be systemic CS therapy, but the early onset of biological therapy should be addressed.
- The mild esophageal or gastroduodenal DC can be treated with proton-pump inhibitors only. In the case of severe or refractory disease, there is indication of systemic CSs or an anti-TNF-based strategy.
- CSs are not effective in treating patients with perianal CD.

A randomized controlled trial (RCT), carried out in 1994, covering DC patients with mild-to-moderate activity limited to ileocecal region or with involvement to the ascending colon, demonstrated that 9 mg/day of budesonide controlled ileal release form was more effective than placebo in induction of remission (CDAI ≤ 150) after 8 weeks[9]. Another RCT (1998) with the same patient profile demonstrated that a single dose of 9 mg/day of budesonide controlled ileal release form was also more effective than the 4 g/day extended-release mesalazine, divided into two daily doses, in inducing remission of CD (at 8 weeks 69% vs. 45%, p = 0.001 and at the 16th week 62% vs. 36%, p < 0.001)[10]. In 2011, another ECR showed that budesonide in the presentation of a pH-dependent release (9 mg/day divided into three doses) is numerically superior than mesalazine (4.5 g/day in three doses) in the induction of remission (at 8th week 69.5% vs. 62.1%), but without achieving statistical significance, suggesting that the latter may have some space as therapy in this patient profile[11].

A RCT involving CD patients with active ileal or ileocecal compared budesonide to conventional CSs in inducing remission of disease. The authors demonstrated that after 10 weeks, 53% of budesonide group at initial dose of 9 mg/day and 66% of prednisolone group at dose of 40 mg/day obtained clinical remission, demonstrating the effectiveness of both drugs. However, there is a greater reduction of CDAI score in the group with systemic CSs (p = 0.001)[12]. Other RCTs with active CD patients demonstrated that budesonide either in the ileal release preparation or pH-dependent has similar efficacy to systemic CSs (prednisone 40 mg/day) in inducing remission in mild-to-moderate disease activity (51% vs. 52, 5% at 8th week). However, there is a variability of clinical response depending on disease location. The authors observed after stratifying patients according to location that cases of ileocecal involvement associated with distal colon were analyzed, the percentages of responses varied to 47% versus 62%, and in cases, disease location was only in the left colon, there is a greater disparity of results favoring systemic CS therapy (20% vs. 58.8%)[13].

In 2015, a meta-analysis comparing budesonide to conventional CSs demonstrated an inferiority of budesonide (relative risk [RR] = 0.85, 95% CI = 0.75-0.97, eight RCTs with 750 patients), mainly in the most severe disease (CDAI > 300) (RR = 0.52, 95% CI = 0.28-0.95) or in the patients with greater colonic involvement. However, budesonide at a dose of 9 mg/day is the treatment of choice for induction of remission in active, mild CD, limited to ileocecal region, and being superior to placebo (RR = 1.93, 95% CI = 1.37-2.73, analysis of three RCTs totaling 379 patients) with fewer side effects in comparison to conventional CSs (RR = 0.64, 95% CI = 0.54-0.76, six RCTs with 703 patients)[14].

Concerning the role of systemic CSs in CD patients, these are significantly more effective than placebo (RR = 1.99, 95% CI = 1.51-2.64, p < 0.00001) and that mesalazine (RR = 1.65, 95% CI = 1.33-2.03, p < 0.00001) in inducing remission. In contrast, these benefits are accompanied by a high proportion of side effects in comparison to placebo (RR = 4.89, 95% CI = 1.98-12.07, p = 0.0006)[15]. Thus, budesonide at a dose of 9 mg/day is recommended for use as primary therapy in CD patients with mild-to-moderate activity located in ileum and/or the right colon. Considering CD with the same location but with moderate activity, both budesonide and conventional CSs are appropriate therapies to induce remission; however, the latter has a higher risk of side effects.

Regarding CD with colonic involvement, systemic CSs, such as prednisolone or equivalent, are effective in inducing remission of active disease. Budesonide ileal release or pH-dependent forms have no indication when there is colonic involvement beyond the right colon. However, budesonide MMX has not yet been studied for these objectives[2].

The initial treatment of extensive ileal CD (> 100 cm) is based on systemic CSs, but an early introduction of immunosuppressive therapy must be done, due to their CS-sparing effect, mainly in cases of marked activity and/or the presence of worse prognostic factors[2].

Mild esophageal or gastroduodenal CD can be treated only with proton-pump inhibitors; however, severe or refractory diseases require systemic CSs or introduction of immunosuppressants[2,16].

No double-blind, randomized trials have investigated the induction of remission with BDP in CD.

Recommendations on induction of remission in UC[3]

- Systemic CSs, as well as thiopurines or biological agents, are therapeutic options for mesalazine-refractory proctitis.
- Systemic CS therapy was also indicated in moderate-to-severe active distal colitis or not responsive to aminosalicylates. However, those with mild-to-moderate activity refractory to aminosalicylates, budesonide at the dose of 9 mg/day may be considered.
- Extensive colitis with moderate-to-severe activity should be treated with systemic CSs as well as UC with mild activity non-responsive to aminosalicylates.
- Severe colitis is recommended to be treated with venous systemic CS in hospitalized patients. Then, reevaluated on the 3rd day and, in case of no response, rescues therapeutic options must be included as cyclosporine, infliximab, tacrolimus, or even surgical approach.

Considering the high effectiveness of 5-ASA compounds in UC treatment, the CSs have only a peripheral role, being used in refractory aminosalicylates cases or those UC patients with marked activity where there is a primary indication of systemic CS therapy.

Considering proctitis, topical mesalazine is the first line of treatment. The association with topical steroid (beclomethasone dipropionate enema at 3 mg/day) was shown to be beneficial, improving the clinical, endoscopic, and histological response after 4 weeks of use[17,18]. The degree of efficacy of BDP compared with other glucocorticosteroids is not well defined because of conflicting evidence.

One RCT has shown that budesonide foam is more effective than placebo (41.2% vs. 24%, $p < 0.0001$) in inducing remission after 6 weeks in mild-to-moderate proctosigmoiditis. However, when considering cases of mild-to-moderate left colitis, the association of topical and oral presentations of mesalazine is the first therapeutic choice. Systemic CSs are reserved for cases without clinical improvement after 7-10 days of adequate use of mesalazine, or clinical remission after 6 weeks or the presence of intolerance to this drug. Aiming to avoid the low tolerability profile of conventional CSs, one RCT demonstrated that budesonide MMX at a dose of 9 mg/day was more effective than placebo in inducing clinical, endoscopic, and histopathological remission after 8 weeks. This fact suggests that this medication can be an alternative before introduction of conventional CSs in cases of distal colitis[3,19-22].

The clinical approach of the extensive UC resembles to the initial therapy of the left colitis with mild-to-moderate activity that is based on the use of aminosalicylates. A more recent RCT evaluating the role of beclomethasone dipropionate in controlled release form (5 mg/day) demonstrated a reduction disease activity similar to oral mesalazine (2.4 g/day in three daily doses) when used in UC patients with the left colitis/extensive location, and mild-to-moderate disease activity[23].

In mild-to-moderate activity, refractory to aminosalicylates, the introduction of systemic CS therapy is recommended. However, an RCT demonstrated that UC patients using beclomethasone dipropionate enema (5 mg/day); the induction of remission is not inferior to the use of prednisone (40 mg/day for 2 weeks, with a reduction of 10 mg every 2 weeks) after 8 weeks[24].

The acute exacerbation approach is recommended in the hospital environment, with venous CS, being the initial therapy (methylprednisolone 60 mg/day or hydrocortisone 100 mg, 4 times a day) for 7-10 days, with no benefit beyond this period[3,25-27].

Recommendations on maintenance of remission in IBD

CSs are not recommended for the maintenance of IBD remission[2,3,28].

Meta-analysis evaluating budesonide at doses of 3 and 6 mg/day demonstrated the inefficacy of this drug as maintenance therapy in CD, not being more effective than placebo, with modest benefits in reduction of CDAI score and expansion of interval time to relapse, but compensated by higher rates of adverse events and adrenal suppression[29].

Another meta-analysis evaluating systemic CSs in the maintenance of clinical remission included only three studies but showed no significant difference when compared to placebo, with a recurrence OR of 0.71 (95% CI = 0.39-1.31), 0.82 (95% CI = 0.47-1.43), and 0.72 (95% CI = 0.38-1.35) after 6, 12, or 24 months, respectively. In conclusion, the conventional steroids do not appear to reduce the risk of relapses for 24 months in CD patient in remission[30].

Considering UC, the RCTs showed that systemic CSs were no more effective than placebo in relapse reduction[31].

Although the most important advantage of the new glucocorticosteroids are their improved safety profile, we must mention that there are no studies with a long-term use, over 1 year, to evaluate the importance of their side effects and the impact on mucosa healing, nowadays considered an important objective to be achieved.

Therefore, despite an important role in achieving clinical remission in active IBD, an early withdrawal strategy, mainly of systemic CS, should be planned to minimize their adverse effects, once its ineffectiveness in maintaining remission has been proven.

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