Corticosteroids (CS) have been playing an important role in the treatment of inflammatory bowel disease (IBD) for over 50 years. The story of their use in IBD has passed through three crucial phases: the era of randomized controlled trials (RCTs) between the 1950s and 1980s, the era of observational studies between the late 1990s and the early 2000s and the era of long-term safety data in the last decade.

The first RCTs on CS were conducted in ulcerative colitis (UC) in the 1950s and in Crohn's disease (CD) between the end of the 1970s and the beginning of the 1980s [3, 4]. These pivotal trials clearly demonstrated the superiority of CS compared to placebo in inducing clinical remission both in UC and in CD, with a number needed to treat (NNT) comprising between 2 and 4 (Fig. 1). No more RCTs were conducted after these milestone studies while CS became the gold-standard in the treatment of active IBD worldwide. These studies, however, respond only to the question whether systemic CS are better than placebo in treating active IBD but they do not give any indications on how these drugs should be used in clinical practice; as a consequence, and not surprisingly, CS are still presently managed by physicians largely empirically, especially in terms of initial dosage, length of treatment and tapering modalities. It is curious that, despite their undisputed efficacy and widespread use in clinical practice, proper dose-response studies have never been performed. A small study, published by Baron and colleagues in 1962, compared three different doses of prednisone for the treatment of active UC.


In this study, 58 patients were randomized to receive 20, 40 or 60 mg/day of prednisone for three to five weeks [5] and the study showed that the doses of 40 and 60 mg/day were superior to the dose of 20 mg/day in inducing clinical remission. However, this was an open-label study which involved only 20 patients per treatment arm, hence it is not a suitable study for identifying a clear and reliable dose-response effect. Regarding CD, there is only indirect evidence of a dose-response effect derived from comparisons among different studies. In a well-known GETAID study published in 1990, oral prednisolone at the dose of 1 mg/kg/day, protracted for at least 3 and up to 7 weeks, induced clinical remission in more than 90% of patients with active CD [6], whereas the National Cooperative Crohn’s Disease Study [3] and the European Cooperative Crohn’s Disease Study [4] reported lower remission rates. In these two studies, however, lower doses of oral prednisone and 6-methyl prednisolone were respectively used. Besides the proper starting dose, also the length of the treatment and the tapering modalities are other important aspects of CS treatment that are still widely managed on empirical basis. There is only one small study that compared two different tapering modalities in CD and it concluded that the length of the tapering scheme (every week or every 3 weeks, after having achieved remission), did not affect the relapse rate [7]. One consequence of the lack of direct evidence in supporting any particular CS regimens is that therapy modalities vary largely between centres and countries. For example, for patients with moderately active UC or CD the British guidelines consider appropriate an oral prednisolone dose of 20-40 mg daily reduced gradually according to severity and patient response, but generally over 8 weeks [8]. Conversely, American guidelines recommend higher doses and longer courses, in the range of 40–60 mg/day or 1 mg/kg/day of prednisone or equivalent to taper by 5 mg/week to a dose of 20 mg/day and then 2.5–5 mg/week [9]. Peculiarly, the ECCO guidelines do not give clear recommendations on appropriate CS treatment schemes. Apart from these variations in clinical practice derived from lack of scientific evidence, what is universally recognized about CS in IBD is that they are ineffective in maintaining remission. Definite evidence about this came from the same historical RCTs that proved CS high efficacy in inducing clinical remission in active IBD: a meta-analysis of RCTs clearly showed that the use of chronic CS therapy in patients with clinically quiescent CD does not reduce the risk of relapse over a 2-year period of follow-up [10].

After the era of RCTs, a series of observational studies revisited the efficacy of CS in IBD: these observational studies, dated between the end of the 90s and the first years of the 2000s, were either population-based [11, 12] or conducted in referral centres [13, 14]. Generally speaking, observational studies reflect clinical practice at best and allow to expand awareness in respect to long-term outcomes. The results of these specific studies confirmed the short-term efficacy of CS and showed how, one month after a course of CS, up to 80% of patients may benefit from clinical remission. Interestingly however, one year after a steroid course, the probability that clinical remission is maintained without continuous or repeated use of CS or surgery plummeted to less than 50% [Fig. 2]. Considering that IBD are life lasting diseases, the results of these large observational studies must be taken into the greatest consideration because of their relevance in clinical terms: as a matter of fact, they reduce the overall benefit of systemic CS especially because steroid dependency and refractoriness seem to be more the rule than the exception in the long term. In light of these observations, the recent Italian guidelines on the use of biologics have redefined the concepts of steroid dependency and refractoriness in UC and CD including stricter criteria related to length of CS exposure [15].

The third pivotal era in the history of CS in IBD is the one of the safety registries. Corticosteroid side effects such as depression of the hypothalamus-pituitary-adrenal axis, hyperglycaemia, hypertension, emotional disturbances, osteoporosis, growth retardation in children, impaired wound repair, susceptibility to infections, cataract or glaucoma have always been fully acknowledged [16-18]. However, since the
beginning of the 21st century the new registries of adverse
events in IBD therapy, introduced as a consequence of the
increased use of immunomodulators and biologics, revealed
that CS might be associated with more serious problems such
as severe infections and even mortality [19]. This fact, in
addition to the above-mentioned limits of CS use in the long
term, renders the inappropriate use of CS dangerous as well
as not beneficial.

Finally, in addition to the efficacy limitations and the low
safety profile, CS use is being increasingly recognized as a
negative prognostic factor during the course of IBD [20, 21]
and major guidelines now issue warnings to abstain from using
CS for prolonged periods underlying that nowadays, under no
circumstances, a treatment that involves continuous use of CS
can be considered appropriate [22, 23].

Low bioavailability steroids
The pharmacologic effect of CS is mediated through
the glucocorticoid receptors that have a ubiquitous nature
which explains why these drugs act on a wide variety of cells
and, therefore, have systemic effects. The so-called “steroids
with low systemic bioavailability”, also defined “topically
acting steroids”, are characterized by a marked affinity for the
glucocorticoid receptors, high pharmacologic potency, but low
systemic activity due to a high hepatic first-pass metabolism
[24]. Initially developed and used for the treatment of asthma
and rhinitis, these newer steroids exert their activity topically:
administered as pro-drugs, orally in the case of IBD, they are
activated through hydrolysis via esterase enzymes of mucosal
cells where they exert their anti-inflammatory action with high
potency. After mucosal absorption, they get to the liver and
are metabolized into inactive products that reach the systemic
circulation. Thanks to this extensive first-pass metabolism, they
have a limited impact on the hypothalamus-pituitary-adrenal
axis and, consequently, fewer systemic effects compared to
traditional CS [25-28] [Fig. 3].

Since these drugs exert their anti-inflammatory activity
topically, it is essential for IBD treatment that appropriate
concentrations reach the targeted portions of the intestine.
Therefore, delivery systems are of pivotal importance for
these drugs. Following oral administration, their proximal
absorption should be minimal while they should reach high
concentrations in the distal ileum and colon. In practice,
oral formulations of these drugs contain granules, which are
coated to avoid dissolution at gastric pH, but dissolve into the
intestinal lumen of the ileum and caecum in a pH or time-
dependent manner [29]. A new technology for delivering
drugs to the colon, the so-called Multi Matrix System (MMX)
technology, has recently been developed: it has already been
applied to mesalazine and clinical studies are ongoing for its
allocation to low bioavailability steroids. This delivery system
allows delayed and prolonged release of the drug throughout
the colon via a pH-dependent gastro-resistant coating and a
double matrix formed by hydrophilic and lipophilic excipients
[30] that ensures consistent and homogeneous distribution
along the whole colon [31].

Budesonide (BUD) and beclomethasone dipropionate
(BDP) are the two compounds of the family of topically acting

Fig. 2. Schematic diagram showing the short and long term outcome
of IBD patients receiving systemic corticosteroids. Data are derived
from population-based [9, 10] and referral centre studies [11, 12].
Pooled short and long-term remission rates with 95% CI are shown:
ulcerative colitis and Crohn’s disease are pooled together.

Fig. 3. Schematic figure showing the main pharmacological characteristics of low bioavailability
steroids.
steroids that have entered the clinical scenario of IBD [32]. The two molecules share similar pharmacological properties [28]: BUD has been extensively studied in CD, mainly in ileo-caecal disease and more recently in UC in the MMX formulation. Beclomethasone dipropionate having been studied less extensively in the IBD setting, has been investigated mainly in UC.

**Budesonide**

The efficacy of BUD in the treatment of ileo-caecal CD has been largely demonstrated. Many RCTs compared BUD to placebo, 5-aminosalicylates (5-ASA) and conventional steroids. Three meta-analyses summarize the results of individual RCTs [33–35] and reach the same conclusions: the efficacy of BUD in active CD is slightly inferior to that of CS, the BUD remission rates being approximately 10% inferior to that of conventional CS. However, the safety profile of BUD is very favourable as the rate of steroid-related adverse events is approximately 20% lower than that of prednisone or prednisolone with a number needed to harm (NNH) between 4 and 5 [33–35]. For these reasons, BUD is currently recommended by major guidelines as a first-line treatment in mildly to moderately active ileo-caecal CD [22].

A critical analysis of the data of RCTs and meta-analyses addressing BUD vs conventional CS in active CD, leads to some important considerations. In most RCTs a somewhat sub-optimal dose of systemic CS has been used (40 mg/day) and, as a consequence, the remission rate in the conventional CS arm could be lower than expected thus reducing the rate difference in favour of BUD. In fact, the pooled remission rate in the conventional CS arm of the 4 main RCTs BUD vs systemic CS is 60% (95% CI 54%–66%) [Fig. 4] which is a rate lower than that expected with the dose of 1 mg/kg/day of prednisolone [6, 22]. The second observation arises from reviewing the data of the subgroups of patients with more severe disease, as done in the meta-analysis of the Cochrane Database [35]. In the subgroup of patients with a CDAI > 300 at study entry the difference in remission rates between CS and BUD reaches 29%, in favor of systemic CS. This is a very relevant figure in clinical terms, even though these data come from a subgroup analysis including a small number of patients from only two RCTs. As a consequence, in our opinion, the best scenario for BUD use is that of mild active disease, whereas its use in moderately active disease is less straightforward.

Another important issue about BUD is that, like conventional CS, it is not effective in maintaining clinical remission in the long term [33, 36]. However, a treatment with low doses BUD (3–6 mg/day) for up to one year is able to delay relapse in post-active CD (with clinical remission induced by BUD or systemic CS) [37]. Similarly, it has been shown that, in steroid dependent patients, switching from systemic CS to BUD 6 mg/day is better than placebo in delaying relapse and allows reduction of CS related adverse events [38]. However, delaying relapse is not a clinically relevant endpoint as the actual reduction of relapse rate. Protracting BUD treatment in post-active CD prolongs time to relapse probably by concealing steroid dependency in those patients who would presumably relapse earlier without continuative steroid treatment. Even though prolonged low dose BUD treatment leads to adverse events rates similar to that of placebo [33] this strategy, in our opinion, should not be preferred to proper CS sparing strategies.

As far as concerns the use of BUD in UC, few studies have been performed. In a first pilot study, oral BUD 10 mg/day was compared to oral prednisolone 40 mg/day in extensive or left-sided, mild to moderately active UC in a 9-week randomized double-blind controlled trial [39]. No statistically significant difference in endoscopic remission rates was observed between BUD and prednisolone (the primary study end point), but this study was small and not powered enough to evaluate the impact of BUD on clinical remission [40]. More recently, in a randomized, double blind, double-dummy, multicentre large study, 343 patients were randomized to receive oral BUD 9 mg/day or mesalazine 3 g/day for 8 weeks. Fewer patients in the BUD group achieved remission within 8 weeks (39.5% vs 54.8%; rate difference −15.3%, 95% CI −25.7% to −4.8%) [41]. In this study, pH-release BUD capsules were used: this formulation delivers BUD in the distal ileum and right colon and, therefore, is not optimal for the treatment of UC in which a release of the drug throughout the whole colon is required.

A novel oral formulation of BUD uses the MMX technology to improve the release of BUD throughout the colon [42]. In this regard, a small pilot study conducted on 36 patients with mild to moderately active left-sided UC [43] showed that BUD-MMX was better than placebo for reducing the Clinical Activity Index without suppression of adrenocortical functions. More recently, a RCT involving 509 patients with mild-moderate UC has been published [44]. Patients were randomized to receive BUD-MMX (9 or 6 mg/day), 5-ASA (2.4 g/day), or placebo for 8 weeks. The rates of symptomatic remission at week 8 were 28.5%, 28.9%, 25.0% and 16.5%, respectively (p < 0.05 BUD–MMX vs placebo). Considering a more restrictive end-point (clinical and endoscopic remission) the corresponding figures were 17.9%, 13.2%, 12.1% and 7.4%, respectively (p < 0.02 BUD–MMX 9 mg vs placebo).

In an extended-use study published only as an abstract [45] low dose BUD-MMX (6 mg/day) was compared to a placebo as maintenance treatment in UC. BUD was not significantly different from a placebo in influencing the probability of a clinical relapse in 12 months although the study was not powered to show statistical significance. However, BUD-MMX significantly prolonged...

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**Fig. 4.** Pooled remission rate (95% CI) of systemic steroids arm in major randomised controlled trials for oral budesonide vs prednisolone in active Crohn’s disease.
the time to relapse and this result is similar to that observed in maintenance studies with BUD in CD.

One last consideration has to be reserved to the use of oral BUD in pouchitis. Two small prospective open-label studies report an efficacy up to 80% of BUD 9mg/day for 8 weeks in inducing clinical and endoscopic remission in patients with chronic refractory pouchitis [46, 47].

**Beclomethasone dipropionate**

Beclomethasone dipropionate has been studied to a lesser extent compared to BUD. It has been used mainly in UC because its release system is characterized by a pH dependent coating that dissolves beyond the caecum [48]. The evidence around BDP in UC is limited and is based mainly on few RCTs [49-52] and observational studies [53, 54]. Finally, a RCT addressed the use of BDP in CD [55].

In the first two RCTs, conducted by the same group, oral BDP, at the dose of 5mg/day was compared to a standard dose of oral 5-ASA [49], or investigated as an add on therapy combined with oral 5-ASA vs 5-ASA alone [50] in adult patients with mild to moderately active left-sided or extensive colitis. The results of these two RCTs suggest that a dose of 5 mg of BDP is as effective as a standard dose of 5-ASA (2.4 g/day) and that combined therapy of BDP (5 mg/day) plus 5-ASA (3.2 g/day) is better than 5-ASA alone in inducing clinical remission at 4 weeks. The safety profile of oral BDP in the short term was favourable in both studies [49, 50]. In a small open-label study in paediatric patients with active UC, oral BDP at the dose 5 mg/day for 8 weeks was better than oral mesalazine in inducing clinical remission within 4 weeks (80% vs 33%, p < 0.025) [52].

The data of these trials, however, do not permit recommendations on the use of BDP in clinical practice also because, unfortunately, no studies have compared BDP to conventional steroids, with the exception of just one clinical trial that has only been presented in the form of abstract [51]. In this multicentre double blind randomized non-inferiority trial, 277 adult patients with mild to moderately active UC were randomised to receive oral BDP (5 mg/day for 4 weeks and 5 mg every other day for further 4 weeks) or prednisone 40 mg/day for 2 weeks with a tapering dosage of 10 mg every 2 weeks. The two treatments showed comparable efficacy regarding the primary end point (clinical response at 4 weeks): 64.6% in the BDP group and 66.2% in the prednisone group. The rate of steroid-related adverse effects was similar in the two groups: 10.2% in the BDP group and 14.5% in the prednisone group.

Finally, two observational studies suggest a possible role of BDP in the management of UC in clinical practice. In the first small study [53], 64 patients with mild to moderately active UC not responsive to optimized oral and topical 5-ASA therapy received a two-month course of oral BDP (10 mg/day for 4 weeks and 5 mg/day for further 4 weeks) as an add-on therapy. After 8 weeks, remission occurred in 75% of patients (95% CI 62.6–84.9%) and after one year 58% of patients (95% CI 44.8–70.0%) were still in remission without further steroid courses. Overall, 75% of patients (95% CI 62.6–84.9%) could avoid systemic CS over 1 year. The safety profile shown by oral BDP was good: only 4.7% of patients reported mild and reversible steroid-related adverse effects.

In a multicentre retrospective survey performed in Spain [54], 394 patients with mild to moderately active UC were treated with oral BDP according to clinical judgment. Most patients were on maintenance treatment with oral and/or rectal 5-ASA compounds. Oral BDP was used at a dose of 5 mg/day in most patients (88%) and treatment duration was 6.2 ± 3.8 weeks. Approximately two thirds of patients achieved remission or response (44.4% remission and 22.3% response) and approximately one third failed to respond. The overall safety profile was favourable: mild adverse effects were reported in 7.6% of patients.

Although these studies are limited by the open label and retrospective design, a possible role of oral BDP in clinical practice is suggested: a course of oral BDP could be a valid alternative to systemic steroids as a second-line treatment, for those patients who fail to respond to appropriate first-line treatment with 5-ASA, considering its efficacy as add-on therapy and its favourable safety profile.

Beclomethasone dipropionate has been studied only marginally in CD. In the only RCT published, patients with active ileal CD who achieved remission within 2 weeks after commencement of prednisone were randomized to oral BDP (15 mg for 2 weeks and 10 mg for 22 weeks) or to taper prednisone for 2 weeks followed by placebo for 22 weeks. The cumulative probability of relapse in the study period was significantly lower in patients receiving BDP compared to patients receiving placebo (38% vs 56%, p=0.025). These results can be explained by the fact that prolonging steroid treatment with oral BDP can delay the expected high rate of early relapse following systemic CS discontinuation as observed with prolonged low dose BUD treatment [37, 38]. Even if this study has some drawbacks such as the small number of recruited patients, the high number of dropouts and the rather unconventional treatment schedule with traditional CS, it suggests a potential use in clinical practice for BDP as “bridge strategy” towards immunomodulators, which require several weeks to reach efficacy.

**CONCLUSIONS**

Systemic CS are powerful drugs, very effective in inducing a rapid symptomatic relief and clinical remission in most patients in the short term. However, steroid dependency and refractoriness happen frequently in the long term. Furthermore, CS are unable to maintain clinical remission, have a low safety profile and, generally speaking, the need of CS is an established negative prognostic factor in the course of IBD. For all these reasons prolonged CS use is not useful, potentially dangerous, and always inappropriate.

Low bioavailability steroids represent an important weapon in the IBD armamentarium. Oral BUD, despite being slightly less effective than conventional CS, has a significantly better safety profile and finds its major indication in mild ileo-caecal CD. Likewise conventional CS, oral BUD is not effective for maintaining remission in CD although it may delay clinical relapse; however, in our opinion, long term BUD use is not appropriate. BUD-MMX in UC deserves further evaluation: although in one single RCT the superiority vs placebo has been documented, the results are not impressive.
Oral BDP, alone or as add on therapy with oral 5-ASA, is effective in mild to moderate active UC and may be an option as a second line treatment in patients unresponsive to aminosalicylates. The comparison of efficacy between oral BDP and systemic CS deserves further evaluation as well as the efficacy and safety of BDP in CD. Overall, the safety profile of oral BDP is favourable.

As a final consideration, systemic CS are still a gold-standard treatment for active IBD but only if they are used appropriately and always bearing in mind their limitations and potential risks. Low bioavailability steroids can be a useful tool to avoid over-exposure to systemic CS for those patients with mild IBD which could achieve remission with a less toxic drug. Low bioavailability steroids cannot replace conventional CS, but can be considered as an adjunctive option.

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