

REVIEW

Oral budesonide in gastrointestinal and liver disease: A practical guide for the clinician

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Abstract

Oral budesonide is a second-generation steroid that allows local, selective treatment of the gastrointestinal tract and the liver, minimizing systemic exposure. The results of randomized trials comparing budesonide *versus* placebo or active comparators have led to expert recommendations that budesonide be used to treat mild or moderate active ileocecal Crohn's disease, microscopic colitis (including both collagenous and lymphocytic colitis), ulcerative colitis, and non-cirrhotic autoimmune hepatitis. The mechanism of budesonide action obviates the need for dose tapering due to safety reasons after induction therapy. Where low-dose budesonide is used to maintain remission, usually in microscopic colitis, it does not appear to have adverse safety implications other than slight reductions in cortisol levels on rare occasions. As a gut-selective and liver-selective corticosteroid, budesonide offers an appealing alternative to conventional systemic glucocorticoids in diseases of these organs.

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Budesonide: A second generation steroid

Conventional systemic glucocorticoids remain the cornerstone of management for inflammatory bowel conditions and certain autoimmune liver diseases, but up to 90% of patients can experience adverse events¹ including weight gain, gastrointestinal ulceration, suppression of the pituitary–adrenal axis, cataracts, and infections.¹ In response, an intensive research effort has led to the development of new corticosteroid compounds with less systemic toxicity than classic therapy with prednisolone, prednisone, or cortisone.

Budesonide is a second generation corticosteroid that allows local, selective treatment of the gastrointestinal tract and the liver, exerting potent anti-inflammatory effects at the site of

inflammation by high-affinity binding to the intracellular glucocorticoid receptor.² Extensive (90%) pre-systemic metabolism within the mucosa of the small intestine and the liver³ results in low systemic availability.³ By acting locally and minimizing systemic exposure, oral budesonide preparations offer a broadly similar efficacy to systemic glucocorticoids^{4–6} but with an improved safety profile.^{4,5,7}

Dose tapering: Budesonide *versus* systemic glucocorticoids

The low systemic exposure of oral budesonide obviates the need for dose tapering after induction therapy. Sudden withdrawal of

conventional systemic glucocorticoids after achieving induction can lead to adrenal insufficiency, and stepwise dose tapering is required before discontinuation to allow gradual restoration of cortisol production by the adrenal cortex. Compared with systemic glucocorticoids, oral budesonide has a markedly reduced effect on endogenous cortisol production,^{8–10} and expert recommendations do not consider dose tapering before discontinuation to be necessary.^{11–14} The safety of this approach has been confirmed by randomized trials in which patients who achieved remission with budesonide in Crohn's disease^{9,15} or collagenous colitis^{10,16,17} were then randomized to either abruptly discontinue budesonide and switch to placebo therapy or to continue low-dose budesonide, with 6–12 months follow-up. Results showed no evidence for “rebound” adverse events related to suppression of adrenal function or other complications in the placebo arms after abrupt budesonide discontinuation, confirming that budesonide does not need to be tapered. Although dose tapering is not required on the grounds of safety, stepwise dose reductions may be advantageous on pharmacodynamic grounds when withdrawal of maintenance therapy is planned, that is, for steroid-dependent patients who have been receiving budesonide for prevention of relapse in microscopic colitis.

Oral budesonide preparations

Because oral budesonide is absorbed rapidly from the gastrointestinal tract and partially metabolized in the gut wall,³ controlled-release oral formulations have been developed that target the release of active drug to the required gastrointestinal segments. Three different oral preparations of budesonide are available: (i) a gastro-resistant, pH-modified formulation (brand names Budenofalk, Budo-San, Intestifalk, Mikicort, Budeson, Intesticort); (ii) a gastro-resistant controlled-ileal release formulation (brand names Entocort, Entocord); and (iii) a relatively new multi-matrix (MMX) formulation (brand names Cortiment MMX, Uceris). As a result of these different drug delivery systems, the pharmacokinetics of the three preparations vary (Table 1). The time to first detection of budesonide in plasma (t_{lag}) is delayed by approximately 2 h with pH-modified budesonide and

approximately 10 h with MMX budesonide (Fig. 1). There is no delay in drug release using controlled ileal-release budesonide, but the peak plasma concentration is lower (Fig. 1).

pH-modified and controlled ileal-release budesonide are licensed for mild to moderate active Crohn's disease affecting the ileum and proximal colon, but not for the treatment of isolated, more distal colonic inflammation. pH-modified budesonide is also licensed for the induction of remission in active collagenous colitis and for the induction and maintenance of remission in autoimmune hepatitis (AIH). Controlled ileal-release budesonide has a license for the treatment of active collagenous colitis in some European markets. MMX budesonide is licensed for the induction of remission in mild to moderate active ulcerative colitis (UC) for patients in whom mesalazine (5-ASA) treatment is not sufficient, reflecting its colonic release of budesonide.

The characteristics and indications for each oral preparation are summarized in Table 2.

Oral budesonide in Crohn's disease

Induction of remission. Numerous randomized trials have compared budesonide *versus* placebo^{21,22} or comparator therapies,^{4,22–28} and assessed different dosing regimens,^{27,29,30} for the induction of remission in Crohn's disease. Meta-analyses based on these trials have shown that oral budesonide is more efficacious than mesalazine or placebo when used for the induction of remission in mild to moderate active Crohn's disease, with no difference in side effects.^{31–33} Randomized trials have shown statistically similar rates of remission with budesonide or prednisolone, albeit with varying trends in favor of one treatment or another,^{4,22,24,25,28} and comparable success in achieving remission has been confirmed in a meta-analysis by Coward *et al.*³³ Expert guidelines recommend budesonide as the preferred treatment for mild or moderate active ileocecal Crohn's disease¹¹ (Table 3). In prospective trials of patients with steroid-dependent Crohn's disease, switching from systemic glucocorticoid therapy to oral budesonide was associated with a reduction in glucocorticoid side effects, while remission was maintained in the majority of recipients.^{36,37}

Table 1 Pharmacokinetic characteristics of budesonide following a single oral dose of Budenofalk (1 × 3 mg capsules or 3 × 3 mg capsules),¹⁸ Entocort (1 × 3 mg capsules or 3 × 3 mg capsules),¹⁹ or Cortiment (1 × 9 mg tablet)²⁰ in fed healthy volunteers

	3 mg budesonide		9 mg budesonide		
	Budenofalk 1 × 3 mg <i>n</i> = 12	Entocort 1 × 3 mg <i>n</i> = 12	Budenofalk 3 × 3 mg <i>n</i> = 11	Entocort 3 × 3 mg <i>n</i> = 12	Cortiment 1 × 9 mg <i>n</i> = 12
T_{lag} (h)	2.0 (1.0)	0	2.1 (1.0)	0	9.8 (3.6)
T_{max} (h)	4.8 (1.3)	2.3 (1.1)	5.4 (1.4)	2.7 (1.7)	20.7 (8.7)
C_{max} (ng/mL)	1.8 (1.2)	0.8	3.6 (1.3)	2.3	1.0 (0.6)
C_{max}/mg dose (ng/mL × mg)	0.6 (0.4)	0.3 (0.1)	0.4 (0.1)	0.3 (0.1)	0.1 (0.1)
AUC (ng × h/mL)	9.4 (3.9) [†]	5.0 [†]	17.9 (5.8) [†]	15.9 [†]	13.5 (9.4) [‡]
AUC/mg dose (ng × h/L × ng)	3.1 (1.3) [†]	1.6 (0.5) [†]	2.0 (0.6) [†]	1.8 (0.7) [†]	1.5 (1.0) [‡]

[†]AUC_{0–24 h}.

[‡]AUC_{0–48 h}.

Values are shown as mean (SD).

AUC, area under the concentration-time curve; C_{max} , peak plasma concentration; t_{max} , time to peak plasma concentration; t_{lag} , time to first detection of budesonide in plasma.

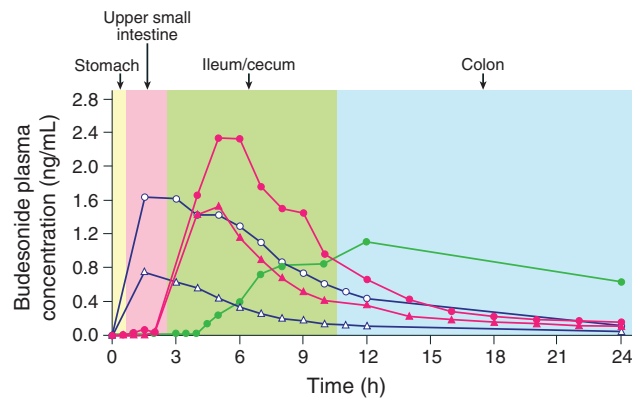


Figure 1 Plasma concentration profiles of budesonide following a single dose of Budenofalk (1× 3 mg capsules or 3× 3 mg capsules),¹⁹ Entocort (1× 3 mg capsules or 3× 3 mg capsules),¹⁹ or Cortiment (1× 9 mg tablet)²⁰ in healthy volunteers. —▲—, Budenofalk 3 mg; —●—, Budenofalk 9 mg; —△—, Entocort 3 mg; —○—, Entocort 9 mg; —●—, Cortiment MMX.

Both pH-modified and controlled ileal-release budesonide are licensed for the induction of remission in Crohn's disease. The choice of preparation could be based on the location of disease and approved indication: Controlled ileal-release budesonide may be effective in proximal ileal disease, with either preparation being effective for ileocecal disease, while pH-modified budesonide may be appropriate in cases with proximal colonic involvement.^{22,30}

For induction of remission, an oral dose of 9 mg/day is recommended, given as 9 mg once-daily or 3 mg t.i.d., to be continued for up to 8 weeks. Once-daily dosing appears to be as effective as 3 mg t.i.d.²⁹ and may support improved adherence.

Maintenance therapy. Randomized trials of oral budesonide maintenance therapy after remission has been achieved by induction therapy have shown only a modest benefit in terms of Crohn's Disease Activity Index scores and time to relapse,^{8,9,15,38–40} as confirmed in a recent Cochrane analysis.⁴¹ Budesonide is not recommended in European Crohn's and Colitis Organization guidelines for maintenance therapy in Crohn's disease.¹¹ Although budesonide-related adverse events are rare using a low-dose and its safety profile is similar to that of placebo,^{41,42} non-steroid options such as thiopurines are preferred.¹¹ Use of low-dose budesonide to maintain remission is generally restricted to patients in whom Crohn's disease is steroid-dependent and in whom immunomodulation should be avoided, or where the patient refuses alternative treatments.³⁷ In such cases, randomized trials of 6–12 months duration have shown low clinical relapse rates at a dose of 6 mg/day, at least in the short-term,^{15,38,40} whereas 3 mg/day appears inadequate.^{15,39}

Oral budesonide in microscopic colitis

Induction of remission. Randomized trials have also assessed the effectiveness of oral budesonide for inducing remission in collagenous colitis^{43–46} and lymphocytic colitis.^{47,48}

Meta-analyses have confirmed the effectiveness of budesonide in active microscopic colitis generally,⁴⁰ and in collagenous colitis specifically.⁴⁹ A rapid (<2 weeks) improvement in watery diarrhea is observed in response to oral budesonide.^{43–47} Other drugs, such as prednisolone, mesalazine, and bismuth subsalicylate, are considered second-line agents¹²; prednisolone⁵⁰ and mesalazine⁴⁶ have proven ineffective, and bismuth is unavailable in many countries. Accordingly, budesonide therapy is recommended in expert guidelines for the treatment of microscopic colitis (including both collagenous and lymphocytic colitis; Table 3).^{12,13,34}

pH-modified budesonide is licensed for the induction of remission in active collagenous colitis, and recently, controlled ileal-release budesonide has also received a license in certain countries. The license recommends that the full dose of 9 mg/day should be used for a maximum of 8 weeks for treatment of active collagenous colitis. In practice, most patients achieve remission by week 2.¹⁰

Budesonide is effective in lymphocytic colitis: Two large, randomized, double-blind, placebo-controlled trials in this indication have demonstrated good efficacy and safety.^{47,48}

Maintenance therapy. Recurrence of collagenous colitis is common after withdrawal of budesonide.^{12,13,34} Three randomized trials of 6–12 months duration have investigated budesonide for maintenance therapy after remission has been achieved.^{10,16,17} Each of these found budesonide to be effective in sustaining remission and to be well-tolerated without safety concerns.^{10,16,17} For maintenance therapy in collagenous colitis, a dose of 3–6 mg daily should be used.^{12,13} In a recently published placebo-controlled trial of gastro-resistant pH-modified budesonide in 100 patients, the dosing schedule was 9 mg/day for 4 weeks during active collagenous colitis, reducing to 6 mg/day for 2 weeks and then 4.5 mg/day (i.e., 6 mg/day and 3 mg/day on alternate days).¹⁰ The 4.5 mg/day regimen was then continued during a 12-month treatment period for maintenance of remission.¹⁰ At the end of 12 months, the dose was reduced over a period of 2 weeks to 3 mg/day for 1 week and finally 3 mg/day every other day for the last week before discontinuation. The majority of patients (82%) still relapsed after budesonide withdrawal,¹⁰ highlighting the chronic nature of the disease and the need of continuous treatment in many patients.

Oral budesonide in ulcerative colitis

Induction therapy. Randomized controlled studies^{51–53} and a recent meta-analysis⁵⁴ have demonstrated a treatment effect for MMX budesonide in achieving remission in mild to moderate active UC. However, the benefit is modest: The remission rate was 17.9% with MMX budesonide 9 mg, 13.2% with MMX budesonide 6 mg, 12.1% with mesalazine, and 7.4% with placebo in one study,⁵² and 17.4% with MMX budesonide 9 mg, 8.3% with MMX budesonide 6 mg, and 4.5% with placebo in a second study.⁵¹ Therefore, mesalazine remains the gold standard and budesonide MMX is licensed only in patients for whom combined oral or combined oral and rectal 5-ASA is insufficient.¹⁴ Mesalazine has the advantage of being suitable for maintenance of remission. In mesalazine-refractory mild to moderate UC, MMX budesonide has a limited effect on combined clinical and

Table 2 Indications, characteristics, and dosing of oral budesonide preparations

Preparation	Indications	Design of preparation	Time/site of release [†]	Recommended dose ^{†,‡}	Recommended duration [†]	Recommended discontinuation [†]
Budenofalk						
3 mg capsule	Crohn's disease	Induction of remission in mild to moderate active disease affecting the ileum and/or the ascending colon	2–3 h (4–6 h with food) Maximum release in the ileocecal region	3 capsules/day (1 capsule t.i.d. or 3 capsules in the morning)	≤8 weeks	Tapered (2 capsules/day for 1 week, 1 capsule/day for 1 week then stopped)
	Collagenous colitis	Not specified		3 capsules/day (morning)	≤8 weeks	
	Autoimmune hepatitis	Induction or maintenance of remission		Induction: 1 capsule t.i.d. Maintenance: 1 capsule b.i.d. (max 1 capsule t.i.d.) 1 sachet/day	Induction: until remission is achieved Maintenance: ≥24 months	
9 mg sachet	Crohn's disease	Induction of remission in mild to moderate active disease affecting the ileum and/or the ascending colon			≤8 weeks	Tapered (every other day for ≤2 weeks then stopped)
	Collagenous colitis	Not specified				
Entocort						
3 mg capsule	Crohn's disease	Induction of remission in mild to moderate active disease affecting the ileum and/or the ascending colon and replacement of prednisolone in steroid-dependent patients	4.5 h (6.8 h with food) ⁴ Ileum	3 capsules/day (morning)	"Full effect is usually achieved in 2–4 weeks"	Dose should normally be reduced for the last 2–4 weeks of therapy
Cortiment						
9 mg tablet	Ulcerative colitis	Induction of remission in mild to moderate active disease where 5-ASA (mesalazine) treatment is not sufficient	6.8 h (~11 h with food) ⁵ Throughout colon	1 tablet/day (morning)	≤8 weeks	It may be useful to gradually reduce the dose

[†]As per product prescribing information.[‡]For adults <18 years.

5-ASA, 5-aminosalicylic acid.

Table 3 Expert society recommendations for oral budesonide therapy in current guidelines

	Usage	Dosing regimen	Duration
Crohn's disease			
ECCO 2017 ¹¹	– Oral budesonide is the preferred treatment for mildly active localized ileocecal disease. – Moderately active localized ileocecal disease should be treated with budesonide or systemic corticosteroids.	9 mg/day	No recommendation
Microscopic colitis			
AGA 2016 ^{12,13}	– In patients with symptomatic microscopic colitis, the AGA recommends treatment with budesonide over no treatment for the induction of clinical remission. – In the event of clinical recurrence after stopping budesonide, initiate low-dose budesonide.	9 mg/day	8 weeks
		≤6 mg [†]	6–12 months
EMCG 2012 ³⁴	– Budesonide is the only drug that has been proven effective in microscopic colitis by randomized, placebo-controlled trials. There are currently no evidence-based alternatives to budesonide.	9 mg/day for remission	6–8 weeks for induction of remission
		9 mg/day followed by low-dose (≤6 mg/day) in the event of relapse	No recommendation
Ulcerative colitis			
ECCO 2017 ¹⁴	– Budesonide in its current formulation is not recommended in routine clinical practice.	No recommendation	No recommendation
Autoimmune hepatitis			
EASL 2015 ³⁵	– In patients without cirrhosis, budesonide plus AZA may be used as induction therapy and can be considered for patients with co-morbidities that might be exacerbated by prednisolone treatment. Long-term data on budesonide safety and efficacy in AIH are lacking. – If adequately dosed therapy with AZA is insufficient to maintain remission in prednisolone responders with severe steroid side effects, a switch from prednisolone to budesonide may be considered.	9 mg/day	Treatment for AIH should be continued for at least 3 years and for at least 24 months after complete normalization of serum transaminases and IgG levels [‡]
		Not stated	

[†]Tapered to lowest effective dose, which may range from 3 mg every other day to 6 mg/day.

[‡]Comment is not specific to budesonide.

AGA, American Gastroenterological Association; AIH, autoimmune hepatitis; AZA, azathioprine; EASL, European Association for the Study of the Liver; ECCO, European Crohn's and Colitis Organization; EMCG, European Microscopic Colitis Group; IgG, immunoglobulin.

endoscopic remission *versus* placebo, but no effect on clinical remission alone.⁵⁵

Maintenance therapy. Budesonide is not recommended or licensed for use as maintenance therapy to prevent relapse in UC. The available data relating to use of MMX budesonide for the maintenance of remission have indicated that it is not efficacious.⁵⁶

Oral budesonide in autoimmune hepatitis

Data are less extensive concerning the use of budesonide to treat AIH,^{57–59} but meta-analyses have supported its use in AIH⁴⁴ as well as primary biliary cirrhosis-AIH overlap syndrome.⁶⁰ The only randomized study to be undertaken in AIH demonstrated improved induction and maintenance of remission for budesonide with azathioprine *versus* prednisone with azathioprine over a

6-month study period with a further 6 months of follow-up.⁵⁷ pH-modified budesonide is licensed for both the induction and maintenance of remission in non-cirrhotic AIH, and European Association Study of the Liver guidelines advise that it can be used as combination therapy with azathioprine in non-cirrhotic AIH or in non-cirrhotic patients with severe steroid-related side effects who are inadequately managed with azathioprine.³⁵

When used to manage AIH, the recommended dose of gastro-resistant budesonide is 3 mg given three times daily for induction (until biochemical remission is achieved), then 3 mg twice daily for at least 24 months to maintain remission. European Association Study of the Liver guidelines advise that budesonide treatment should continue for at least 3 years and, more specifically, recommend that treatment should continue for at least 24 months after normalization of disease markers.³⁵

Safety of oral budesonide

Adverse events and tolerability. Pooled analyses of trials in Crohn's disease⁴² and microscopic colitis⁴⁹ have found a comparable rate of clinically important side effects to placebo. Recent Cochrane⁴¹ and network³² analyses have confirmed that there is no difference in the rate of adverse events⁴¹ or withdrawal due to adverse events³² between patients given low-dose (up to 6 mg/day) budesonide or placebo as maintenance therapy for Crohn's disease. Trials in collagenous colitis have shown low-dose budesonide to be well-tolerated when given for up to 12 months.^{10,16,17} One trial of 34 patients with collagenous colitis observed a similar rate of adverse events with budesonide 6 mg/day or placebo over 6 months and no relevant differences in laboratory values,¹⁶ while another study with a similar design documented higher patient-reported tolerability with budesonide *versus* placebo.¹⁷

Risk of infection. Studies in which budesonide has been used to maintain remission in collagenous colitis at a dose of up to 6 mg/day for up to 12 months^{10,17} have reported similar infection rates to placebo. Active monitoring for opportunistic infection is not required in patients given oral budesonide therapy.

Bone density. Randomized, double-blind trials have found addition of budesonide to UDCA therapy for up to 3 years to have no effect on bone resorption or bone mineral density in patients with primary biliary cirrhosis.^{40,61} In a recent retrospective analysis of patients with AIH who switched from systemic steroids to pH-modified budesonide, 14 out of 15 patients with osteopenia at the time of switch showed either an improvement or stabilization of bone mineral density after a median of 24 months follow-up.⁵⁹ At the clinical level, a large case-control study ($n = 124\,655$) found no increase in the overall risk of fractures with long-term low-dose maintenance oral budesonide therapy *versus* untreated controls.⁶² Nevertheless, in patients with microscopic colitis, a population dominated by older female patients at high risk for osteoporosis, it is advisable to use the lowest effective dose. Prophylactic use of calcium and vitamin D supplements during maintenance budesonide therapy for microscopic colitis appears advisable¹² and is recommended in European guidelines.³⁴

especially if other risk factors for osteoporosis such as smoking or proton pump inhibitor therapy are present. Calcium and vitamin D intake is not required during short-term induction therapy with budesonide.

Adrenal suppression. Short-term administration of budesonide can induce a transient, mild reduction in plasma cortisol,^{4,21,22,27} a dose-dependent effect^{21,63} which at doses of 9 mg/day is not considered to be of clinical concern. Placebo-controlled randomized trials of long-term low-dose budesonide therapy for maintenance of remission in Crohn's disease,^{8,9} or collagenous colitis,¹⁰ given at a dose of 3–6 mg/day for 6–12 months, have shown either no effect^{9,10} or limited effect^{8,9} on adrenal function, with normal cortisol levels. Oral budesonide can be used for an extended treatment period without the historical fear of steroid-related adrenal effects.

Safety versus classic steroid therapy. Randomized trials of budesonide 9 mg/day *versus* prednisolone for the induction of remission in active Crohn's disease^{4,22,28} or UC⁵ reported a lower^{4,28} or similar^{5,22} rate of short-term mild adverse events with either therapy. Moon face was less frequent under budesonide.^{4,22} There was significantly less suppression of pituitary–adrenal function under budesonide than prednisolone,^{4,5,22} with significantly fewer⁴—or no⁵—budesonide-treated patients having a plasma cortisol value below 150 nmol/L (the lower reference limit for normal). Long-term evidence has confirmed that there is less suppression of pituitary–adrenal function under budesonide.⁷ Additionally, one randomized trial observed a significant increase in mean fasting plasma glucose in patients given 10 weeks treatment with prednisolone for active Crohn's disease while no change was seen in the budesonide-treated cohort.⁴

Long-term randomized trials of budesonide *versus* prednisolone are scarce, but one 2-year trial of 272 patients with Crohn's disease reported significantly fewer steroid-related adverse events under budesonide (51% *vs* 71%, $P = 0.001$), with the difference largely arising from lower rates of insomnia, acne, bruising easily and, strikingly, moon face (9% *vs* 33% with prednisolone, $P < 0.001$).⁷ This trial was performed primarily to compare the incidence and extent of osteoporosis under budesonide or prednisolone and concluded that budesonide is associated with improved preservation of bone mass in steroid-naïve patients with active ileocecal Crohn's disease.⁷ A large case-control study has reported a dose-dependent increase in fracture risk with long-term oral prednisolone across various indications that was not seen with low-dose oral budesonide maintenance therapy.⁶²

Conclusions

There is now a substantial body of high-quality evidence demonstrating the efficacy and safety of oral preparations of budesonide in gastrointestinal and hepatic diseases. Numerous randomized trials have compared budesonide therapy *versus* placebo or active comparators, complemented by dose-finding trials, which validate decision-making regarding the use and optimal regimen of budesonide. The maximum duration of full-dose (9 mg/day) budesonide to induce remission in active gastrointestinal disease

has been established as 8 weeks. When used in AIH, gastro-resistant budesonide should be given for at least 24 months. The practice of dose tapering—long-familiar to many physicians when giving systemic glucocorticoids and often undertaken through habit—is not required with budesonide on the grounds of safety. In microscopic colitis, the dose should be reduced after achieving remission to determine the lowest effective dose for maintenance therapy, and reducing the dose before withdrawal after maintenance therapy in microscopic colitis and AIH is advisable to help minimize the risk of relapse. Unlike systemic glucocorticoids, budesonide can be used in certain conditions for long-term maintenance therapy without significant safety concerns.

As a topical glucocorticoid that can be used in a gut-selective manner, budesonide offers an appealing alternative to conventional systemic glucocorticoids. While its efficacy can vary between conditions, likely due to differences in the underlying inflammatory processes, it is a useful component of the treatment paradigm in gastrointestinal and liver disease. Future trials are awaited that will extend the evidence base, for example, comparing budesonide preparations or assessing different treatment durations for inactive disease.

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