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Topical Therapies in Inflammatory Bowel Disease

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Ulcerative colitis · Topical therapy · Enema · Foam · Aminosalicylates

Abstract
Due to misunderstandings about their effectiveness and feasibility, topical (or rectal) therapies with aminosalicylates (5-aminosalicylic acid, 5-ASA) and steroids are often underused in patients with ulcerative colitis (UC). However, many of these patients could be treated solely with rectal/topical therapies, or could benefit from them in combination with oral therapies. We review the evidence for topical therapies containing 5-ASA and budesonide in UC and discuss how these therapies can be optimized in daily practice, thereby improving compliance. Finally, we provide a brief summary of studies on the use of other topical treatments in UC, the results of which were both promising and negative.

Introduction

Ulcerative colitis (UC) is characterized by a continuous inflammation of the colonic mucosa starting from the rectum. The extent of the disease can vary from proctitis to left-sided colitis and extensive colitis or pancolitis. In most patients, only the distal colon is affected [1–3]. Fifty to sixty percent of patients have a proctosigmoiditis, 20–30% have a left-sided colitis up to the splenic flexure and only 20% have extensive colitis or pancolitis. This distribution and the mucosal inflammation enable the use of topical therapies with a good clinical response or even remission in most UC patients. Topical therapies containing budesonide and 5-aminosalicylic acid (5-ASA) can be used both for the induction and the maintenance of remission.

Topical therapies can be applied by suppositories for the rectum in the case of proctitis, and by enemas (liquid) or foam preparations in the case of proctosigmoiditis and left-sided colitis. The distribution of topical therapies has been studied by γ-scintigraphy showing a distribution of enemas up to and sometimes even further than the splenic flexure [4, 5]. Foams seem to distribute more continuously in the rectum and sigma, but they likely do not reach as far as liquid enemas [6].

Induction of Remission by Topical Therapy

In mild to moderate UC, aminosalicylates are the first-line drugs used according to evidence based guidelines.

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Ulcerative proctitis is best treated in the first line with 5-ASA suppositories [7] which target the rectal mucosa better than foams or enemas [8]. However, all topical 5-ASA formulations are equally efficacious in the treatment of proctitis [9]. Suppositories with 1,000 mg 5-ASA are effective and appear to be the most feasible topical therapy [7, 10–12]. Suppositories can induce remission in about two thirds of patients with ulcerative proctitis [13]. A meta-analysis of 11 studies showed that topical 5-ASA induces remission in 67% of patients versus only 7–11% induced by placebo therapy. More than 1,000 mg topical 5-ASA did not show a greater benefit [11]. Topical 5-ASA is clearly more potent in inducing remission than topical steroids [14] which are the second-line therapy for patients who do not tolerate the topical 5-ASA therapy (this is rare). If symptoms persist despite adequate topical monotherapy with 5-ASA, topical agents should first be combined (topical steroids and 5-ASA) before switching to a combination with oral therapy [15].

Left-sided colitis should be treated with foam preparations or liquid enemas with an initial dose of at least 2 g of 5-ASA [16]. Topical formulations available in Europe are summarized in table 1. In Switzerland, topical 5-ASA is available as Asacol® liquid enemas (2 and 4 g 5-ASA in a volume of 50 and 100 ml, respectively), Salofalk® liquid enemas (2 and 4 g 5-ASA in a volume of 30 and 60 ml, respectively) or Salofalk® foam (1 g 5-ASA in a volume of 30 ml). If symptoms persist despite adequate topical monotherapy, topical therapy should first be combined (topical steroids and 5-ASA) [15]. In Switzerland, only budesonide is available as an active drug in steroid-containing enemas (Entocort® liquid enema with 2.3 mg budesonide in a volume of 115 ml or Budenofalk® rectal foam with 2 mg budesonide in a volume of 30 ml). If this does not induce remission, oral 5-ASA should be added to topical therapies [16]; this will further increase the chance of inducing remission. Under these conditions, topical therapies should not be stopped as is frequently seen in daily practice. For patients who complain about discomfort, topical therapy can be optimized. In moderate left-sided UC, it may be advisable to combine oral and topical aminosalicyates from the beginning. The combination of oral and topical 5-ASA is clearly more effective (in 88% of patients) than 4 g of rectal aminosalicyates (54%) and 2.4 g oral 5-ASA [16]. Indeed, current European Crohn's and Colitis Organization guidelines recommend initially treating mild to moderate left-sided UC with topical and oral 5-ASA [7].

In the case of extensive colitis, the treatment strategy is very similar to left-sided colitis. The combination of oral and topical 5-ASA therapy should be explored as the latter may specifically reduce the inflammation at the location, the rectum, which is mainly responsible for the patient's complaints of urgency. Indeed, the combination of topical 5-ASA with more than 2 g of oral 5-ASA has been shown to be substantially more potent in inducing remission in extensive colitis than oral 5-ASA therapy on its own [17] which induces remission in a significantly lower proportion of patients. Thus, topical 5-ASA also adds a clear benefit for the treatment of extensive colitis. The effectiveness of topical therapies should be evaluated after 2 weeks. However, if a combination of oral and topical 5-ASA is not sufficient for mild or moderately active UC, an oral/systemic steroid treatment is certainly justified. In extensive colitis, the threshold for using systemic steroids should be lower than in left-sided colitis [7].

Severe UC needs to be treated by intravenous steroids as the first-line therapy. The use of topical treatment has not been studied in severe UC, but topical application (budesonide or 5-ASA) may be considered appropriate in addition to intravenous therapy if the patient is able to retain the rectal therapy for at least 20 min [7]. Some experts, however, state that topical therapies should be avoided in the case of severe UC because they will not be tolerated by the patient. In our daily practice, this is the case in some but certainly not all the patients with severe colitis.

Maintenance of Remission by Topical Therapy

As for the induction of remission, aminosalicylates are the mainstay of therapy for the maintenance of remission in patients with UC. Topical 5-ASA is effective for proctitis and left-sided colitis [7, 13], and is possibly even more effective than oral 5-ASA [7]. Clinical trials with rectal 5-ASA preparations for the maintenance of remission have been performed with various 5-ASA formulations and dosages being administered per day, week or month, respectively [7]. Based on the data available, it can be concluded that in most patients, topical therapy is not necessary on a daily basis, but can be applied less frequently e.g. 7 days per month [18] or 2–3 times per week [19]. A clear dose-response relationship with topical 5-ASA for maintaining remission in distal UC has not been proven [7]. Probably 1 g or less of topically applied 5-ASA is sufficient to relieve inflammation in distal UC [9]. In clinical practice, finding the minimal dosage of 5-ASA for the maintenance of remission remains difficult; anyway, there should be no 'one-fits-all' approach with respect to

Table 1. Formulations for topical use in Europe and the USA

Active drug	Trade name	Formulation	Volume for foams and enemas	Countries
5-ASA	5-ASA 250 mg	supp		SRB
	Asacol 500 mg	supp		I, CZ, DK, FIN, GR, N, S, UK
	Asacol[1] 1 g	supp		I
	Asacolon 500 mg	supp		IRL
	Asamax 250 mg	supp		PL
	Asamax 500 mg	supp		I, PL
	Asazine 500 mg	supp		CH
	Canasa 1000 mg	supp		USA
	Claversal 250 mg	supp		A, B, G, P
	Claversal 500 mg	supp		A, B, E, G, P
	Colitan 250 mg	supp		PL
	Colitofalk 250 mg and 500 mg	supp		B
	Crohnax 250 mg	supp		PL
	Fivasa 500 mg	supp		F
	Laboxantryl 250 mg	supp		GR
	Mesalazin CC Pharma 500 mg	supp		G
	Mesalazine 250 mg and 500 mg	supp		N
	Mesasal 500 mg	supp		DK, N, S
	Pentasa[1] 1 g	supp		A, B, CZ, DK, E, F, FIN, G, I, IRL, N, NL, P, PL, S, SLO, UK
	Rowasa 500 mg	supp		F
	Salofalk 250 mg	supp		CH, CZ, G, GR, HR, P, PL, SLO, NL
	Salofalk 500 mg	supp		A, CH, CZ, G, HR, GR, NL, PL, SLO, SRB, UK
	Salofalk 1000 mg	supp		CH, CZ, E, G, IRL, NL, PL, SLO, UK
	Salazopyrin 500 mg	supp		N
	Asacol 1 g	foam		UK
	Asacol 2 g	foam	2 g/50 ml	CH, I, UK
	Asacol 4 g	foam	4 g/100 ml	CH, I
	Claversal 1 g	foam	1 g/60 ml	B, G, E
	Mesalazin CC Pharma 1 g	foam		G
	Mesalazin Eurim-Pharm 1 g	foam	1 g/30 ml	G
	Mesalazin-Kohlpharma 1 g	foam	1 g/60 ml	G
	Mesasal 1 g	foam	1 g/30 ml	S
	Pentacol 2 g and 4 g	foam		I
	Salofalk 1 g	foam	1 g/30 ml	A, CH, FIN, E, G, IRL, N, NL, PL, S, UK
	Asacol[1] 1 g	enema	1 g/100 ml	DK, FIN, N, S
	Asacol 2 g	enema	2 g/50 ml	B, I, N, NL, IRL, P
	Asacol 4 g	enema	4 g/100 ml	CZ, GR, I, P
	Asalex 2 g and 4 g	enema		I
	Asamax 2 g and 4 g	enema		I
	Asavixin 2 g and 4 g	enema		I
	Claversal 4 g	enema	4 g/60 ml	G
	Colitofalk 2 g and 4 g	enema	2 g/60 ml; 4 g/60 ml	B
	Enteraproct 500 mg	enema		I
	Enterasin 2 g and 4 g	enema		I
	Lextrasa 4 g	enema		I
	Mesaflor 2 g and 4 g	enema		I
	Mesaflor 500 mg	enema		I
	Pentacol 500 mg	enema		I
	Pentasa 1 g	enema	1 g/100 ml	A, B, DK, E, G, IRL, F, HR, N, NL, FIN, PL, S, SLO, UK
	Pentasa 4 g	enema		I
	Quadrasa 2 g	enema	2 g/100 ml	A, F
	Quota 2 and 4 g	enema		I
	Rowasa	enema	4 g/60 ml	USA
	Salofalk 2 g	enema	2 g/30 ml	CH, G, IRL, NL, SLO, UK
	Salofalk 4 g	enema	2 g/60 ml	NL
	Salofalk 4 g	enema	4 g/60 ml	A, CH, CZ, E, G, HR, NL, P, PL, SLO, SRB
Sulfasalazine	Salazopyrin 500 mg	supp		UK, IRL

Table 1 (continued)

Active drug	Trade name	Formulation	Volume for foams and enemas	Countries
Budesonide	Budenofalk rectal foam	foam	2 mg/20 ml	CH, DK, FIN, G, IRL, NL, S, UK
	Budo-San 2 mg	foam	2 mg/30 ml	A
	Entocort	enema	2 mg/100 ml	B, CH, G, FIN, N, NL, PL
	Entocord	enema	2 mg/100 ml	A, B, CZ, DK, E, FIN, G, GR, N, NL, P, S, UK
Hydrocortisone	Proctocort	supp	30 mg hydrocortisone acetate	USA
	Colifoam	foam	100 mg hydrocortisone/60 ml	A, B, DK, FIN, G, GR, I, IRL, S, UK
	Colofoam	foam	100 mg hydrocortisone/60 ml	F
	Cortifoam	foam	90 mg hydrocortisone acetate/? ml	USA
	Cortenema	enema	100 mg hydrocortisone/60 ml	USA
	Proctocort	creme	1%	USA
Prednisolone or similar drugs	Scheriproct	supp	1 mg prednisolone	B, CH, FIN, UK
	Neoproct suppository	supp	1 mg flucortolone-21-pivalate	CZ, DK, FIN, GR, I, S, UK
	Predsol	supp	5 mg prednisolone	UK
	Trianal	supp	0.5 mg triamcinolone	B
	Ultraproct	supp	2 mg fluocortolone	B
	Predfoam	foam	20 mg prednisolone	UK
	Prednisolone 20 rectal foam	foam	20 mg prednisolone/100 ml	UK
	Proctosteroid foam 1%	foam	10 mg triamcinolone	E
	Becloenema	enema	1 mg beclometasone	E
	Beclomethason Klysma FNA	enema	3 mg/100 ml	NL
	Beclomethason-mesalazin Klysma FNA	enema	3 mg beclometasone combined with mesalazine (1, 2, 3 or 4 g)/100 ml	NL
	Betnesol	enema	5 mg bethametasone/100 ml	F
	Pred-Klysma	enema	31.25 mg/100 ml	N
	Predenema	enema	20 mg/100 ml	UK
	Predsol	enema	20 mg prednisolone/100 ml	IRL, UK
	Rectovalone	enema	250 mg Betnesol/100 ml	F

This is a summary of topical therapies available in Europe, based on data from pharmavista.ch, information from pharmaceutical companies who were contacted by the authors and personal communications with gastroenterologists across Europe and the USA. Some names have been slightly modified (e.g. Budenofalk rectal foam is sold as 'Budenofalk Rektalschaum' in Switzerland or 'Budenofalk espuma rectal' in Spain and is listed as 'Budenofalk foam' in this table). Data should be complete for the following countries: Switzerland, Germany, France, UK, Spain, Belgium, Netherlands, Poland, Finland, Slovakia and the Czech Republic, but the authors cannot guarantee that the list of drugs is complete and correct for these and other countries. A = Austria; B = Belgium; CH = Switzerland; CZ = Czech Republic; DK = Denmark; E = Spain; F = France; FIN = Finland; G = Germany; GR = Greece; HR = Hungary; I = Italy; IRL = Ireland; N = Norway; NL = Netherlands; P = Portugal; PL = Poland; S = Sweden; SLO = Slovakia; SRB = Serbia; supp = suppository.

[1] Asacol suppositories and enemas as well as Pentasa suppositories are available in most European countries. Some countries were not specifically listed because of the lack of information on dosages of mesalazine in the specific formulations.

this maintenance. Predictive factors need to be taken into account, such as severity and the frequency of flares before the current remission. If topical therapy is not efficacious enough, combined oral and topical therapy should be considered.

Can Mucosal Healing Be Achieved by Topical Therapies only?

Many experts in the field advocate that mucosal healing should be achieved to gain an optimal prognostic benefit in IBD, irrespective of the treatment used [20]. According to a recent meta-analysis including data from 2513 patients treated with rectal 5-ASA, mucosal healing can be achieved in about 50% of UC patients treated with 5-ASA [21]. There was no evidence in this analysis that the rate of mucosal healing differs between 5-ASA foams and enemas [21]. There is further evidence for the effectiveness in inducing mucosal healing by topical 5-ASA, summarized by Sandborn et al. [22] in a recently published post hoc analysis. We conclude from their results that mucosal healing is possible when 'only' rectal 5-ASA therapies are used in distal colitis. There is no argument for a prescription of aggressive anti-TNF antibodies which give no guarantee for mucosal heal-

ing. In the ACT-2 (Active Ulcerative Colitis 2) trial, about 50% of the patients achieved mucosal healing under infliximab treatment [20]. Naturally, one has to be aware that anti-TNFs are usually given for moderate to severe UC and that these data are no head-to-head comparison.

Side Effects of Topical Therapy

Topical therapies may have disturbing side effects including leakage, problems with retention and bloating [11]. Serious complications such as rectal perforation are only described on the level of case reports [23] and can be assumed to be absolute rarities. Systemic drug-related side effects are rare. Topically applied (and orally administered) budesonide has a very low bioavailability of only 10–15% [24]; it therefore does have side effects such as cushingoid features or a measurable suppression of basal cortisol levels in the vast majority of patients [25, 26]. In contrast, with conventional systemic steroids such side effects occur often [27].

Topically applied 5-ASA does not have relevant systemic side effects. Idiosyncratic side effects such as interstitial nephritis, myocarditis or pancreatitis are very rare even when oral and systemic forms of 5-ASA are used, and there is no proven relationship between duration or cumulative dose and the risk of renal disease [28, 29]. We know of no published cases of interstitial nephritis induced by topical 5-ASA therapies. However, there is one case report on a 5-ASA-induced acute pancreatitis after the use of 5-ASA suppositories [30]. In addition, one case report has been published of a 5-ASA enema-induced relapse of acute pancreatitis in a patient who had already had a 5-ASA-induced acute pancreatitis after intake of oral 5-ASA [31]. This highlights that re-exposure to topical 5-ASA in the case of pancreatitis, myocarditis, epicarditis or interstitial nephritis and other forms of 5-ASA hypersensitivity reactions requires a very careful risk/benefit analysis.

Adherence to Topical Therapy

As is relevant for other therapies, adherence and compliance are crucial for the success of topical therapy in UC patients. Nonadherence in patients with IBD can be as high as 60% [32]. In a study on medication nonadherence in patients on 5-ASA for the maintenance of remission, the majority of patients with a relapse of UC were nonadherent [32]. Studies have shown that adherence is worse in maintenance therapies (50%) than in short-term IBD therapy [32, 33]. However, most patients with nonadherence simply forget to take their medication (because they feel better when in IBD remission) [34].

Despite problems with compliance and the fact that most patients (80%) prefer oral treatment alone [35], it is important to note that most UC patients are willing to use topical therapies [36, 37]. However, the efficacity of topical therapy is much less likely if it induces too much urgency [37–39]. A Spanish study showed that 5-ASA suppositories are well tolerated and are considered comfortable for a treatment lasting at least 1 year [5]. For enemas, it seems that urgency is associated with the higher the volume applied. Thus, most patients prefer foam preparations with less volume than liquid enema formulations [40, 41], although a Cochrane review in 2010 summarized conflicting experiences in clinical trials [12]. The urgency induced by topical therapies can be explained by the fact that the rectal compliance is clearly reduced in patients with active UC [42–44]. We advise taking 2 mg of loperamide 20–30 min before applying the enema in order to reduce urgency, although there is no evidence from clinical studies in UC for this approach. However, in a trial using loperamide in obese patients with loose stools as a side effect of orlistat treatment, loperamide had at least some effect on anorectal sphincter function [45], but no effect on rectal capacity or compliance. Furthermore, we advise lying down in a left-sided or prone position after applying topical therapy. There are no studies on how long topical therapy should be retained to be maximally effective, but even if part of the topical therapy gets evacuated, it can be assumed that enough of the drug will adhere to the mucosa [9]. So patients should be motivated to try topical therapies even if they cannot be retained for a long time.

The Doctor's Adherence to Guidelines and Evidence

A successful topical therapy not only necessitates adherence on the part of the patient, but also the doctor's adherence to evidence and guidelines. In an interesting survey among Spanish gastroenterologists, only 12–17% of gastroenterologists considered topical 5-ASA as a therapy of choice for distal colitis [46], and only 31% used the combination of oral and topical 5-ASA for extensive mild to moderate UC.

Furthermore, despite evidence that topical 5-ASA is more potent in reducing remission than topical steroids

[14], 31–47% of gastroenterologists considered rectal steroids to be as effective as topical 5-ASA [46]. In an analysis of 12 consecutive patients with UC, Reddy et al. [47] found that 75% of the patients with left-sided UC had not been on a topical therapy.

New or Rare Indications and Strategies for Topical Therapies

In patients with Crohn's proctitis or left-sided colitis, one could argue that topical steroids or 5-ASA might be useful. However, it is important to note that Crohn's disease is characterized by a transmural inflammation which may be more difficult to cure by topical application of steroids. Currently, there are no studies available on the effects of 5-ASA or steroid topical therapies in Crohn's disease, despite an extensive literature search. Furthermore, it must be kept in mind that there is also no evidence for oral 5-ASA in Crohn's colitis. Thus, topical therapies cannot be recommended for Crohn's proctitis or left-sided Crohn's colitis.

Besides topical therapies with 5-ASA and steroids, some small studies are available with conflicting results on new topical therapies in UC. The most promising alternative topical therapies include the use of probiotics and fecal transplantation, tacrolimus and alicaforsen. Several other therapeutic strategies have been reviewed by Lawrance [48] and are only mentioned briefly in this review.

- Probiotics: There is good evidence for *E*scherichia *coli* Nissle 1917 in the maintenance of remission in UC. *E. coli* Nissle was consecutively studied as a topical preparation in a double-blind study with 90 patients with moderate distal UC. Liquid enemas containing 10exp8 *E. coli* Nissle/ml were compared to placebo enemas over a treatment period of 2 weeks. A positive effect could only be demonstrated in the per protocol analysis ($p = 0.0446$), but not in the intention-to-treat analysis ($p = 0.4430$) [49].
- Fecal transplantation: Given the complexity of the fecal microbiota, it seems reasonable that the approach of fecal transplantation will be more effective than using only a single probiotic strain. Fecal transplantation has mainly been done for the treatment of recurrent *Clostridium difficile* infection, but also in patients with therapy refractory UC. More than 20 years ago, the first case of fecal transplantation in UC was published [50]. Since then, there have been various case reports showing that fecal transplantation (going by various other names such as 'stool transplant', 'fecal transfer' and 'fecal microbiota transplantation') can induce remission in UC patients [51]. In Crohn's disease, a pilot study showed no clinical or endoscopic efficacy of fecal transplantation in 4 patients [52]. Currently, at least 3 clinical trials are ongoing to study the efficacy of fecal transplantation in UC. NCT01560819 in the USA is a phase I pilot study in 10 pediatric UC and CD patients aged 7–12 years. Patients will receive 5 sessions of fecal transplantation by enema with feces from a donor chosen by the family. NCT01545908 in Canada is a phase II study for the induction of remission in active UC and aims at enrolling 130 patients. The active arm will be a fecal transplatation from a nonrelated donor and the placebo enema will be a saline enema. NTR2862 in the Netherlands ('turn trial') is a placebo-controlled trial in adults aged 18 years or older and aims at enrolling 40 patients. The active arm will be a fecal transplantation from nonspecified healthy donor by duodenal tube infusion and the placebo arm will receive their own feces.
- Tacrolimus: This is a strong immunosuppressant which is able to induce and maintain remission in severely active UC. However, high serum levels are necessary to induce remission, which predisposes to drug side effects such as tremor, headache or renal insufficiency. Interestingly, open-label studies with (not commercially available) topical tacrolimus preparations were able to induce remission in left-sided UC at a low dose of 1.8–4 mg (either as suppositories, enemas or ointments) and without leading to high serum levels of tacrolimus as is observed with oral intake [53, 54]. No relevant side effects were observed. Thirteen of 19 patients in 1 study showed a clinical improvement in disease activity after 4 weeks of local tacrolimus treatment. The other study reported clinical remission in 6 of 8 patients. These results are promising, but a commercially available topical tacrolimus preparation would be needed to allow a wide-spread use of this strategy in left-sided colitis.
- Alicaforsen: In an open-label study with nightly rectal enemas of alicaforsen, an antisense oligodeoxynucleotide against intercellular adhesion molecule 1 mRNA, 33% of patients reached remission at the end of the 6-week study period [55]. Similarly, 7 of 12 patients using alicaforsen with chronic unremitting pouchitis attained remission [56]. These results look very promising, but alicaforsen is still only a candidate as an orphan drug in Europe. Further randomized trials are clearly warranted.

Several small and early studies analyzed various other therapeutic approaches, some with promising but not convincing results to recommend their use in clinical practice. [48]

- Liquid enemas with cyclosporine initially looked promising in open-label studies [57], but were not shown to be active in placebo-controlled randomized trials [58].
- Butyrate enemas were likewise promising in open-label studies [59], but not in placebo-controlled randomized trials [60].
- Since impaired epithelial expression of peroxisome proliferator-activated receptor χ (PPARχ) ligand was described in UC, a topically administered rosiglitazone has been studied in a pilot study and was successful in IBD patients who had not been previously treated [61]. It was, however, withdrawn in 2010 due to cardiovascular side effects. We are not aware of ongoing or planned studies with other peroxisome proliferator-activated receptor γ ligands in IBD.
- Nicotine enemas containing 6 mg of nicotine have been studied in a large randomized double-blind study including 104 patients with active UC [62]. Topical nicotine 6 mg was not found to be efficacious for active UC.
- Arsenic suppositories (250 mg b.d. for 4 weeks) have been studied in only 1 small study with 10 patients [63]. In 9 of 10 patients, symptoms and endoscopic signs of proctitis resolved within 2 weeks, but 6 of 10 patients showed a relevant systemic arsenic absorption. Currently, arsenic suppositories are not often used.
- Further therapeutic strategies include the use of lidocaine, ecabet, epidermal growth factor, remapimide and thromboxane enemas [48].

Conclusions

Topical therapies are effective and feasible in proctitis and left-sided colitis for both the induction and maintenance of remission. If topical therapies are not sufficiently efficacous in left-sided UC, they should be combined with and not replaced by oral 5-ASA. Topical budesonide should be used if topical 5-ASA is not effective or in the case of intolerance to topical 5-ASA which is rare. In extensive colitis, oral and topical 5-ASA should be combined. Only in severe UC, may topical therapies be omitted due to insufficient efficacy and patient intolerance. There is insufficient evidence for the efficacy of topical therapies in Crohn's disease including Crohn's colitis. Some new topical therapeutics have recently been or are currently being studied for the treatment of UC.

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