



5-ASA Therapy for Ulcerative Colitis: Positioning and Efficacy

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DISCLOSURES

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Receipt of honoraria or consultation fees	Janssen, Abbvie, Pfizer, Celgene, Takeda, Ferring, MSD, Alfa-Sigma, Amgen, Gilead, Arena, Galapagos, Celltrion, Biogen, Eli-Lilly
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Mesalazine in Ulcerative colitis

Standard of care for the treatment and maintenance of mild to moderate ulcerative colitis

Mesalazine formulations

Topical Formulations Oral Branded Formulations Enemas Foams - pH-dependent Gels Eudragit S Eudragit L Eudragit FS30D - pH & T-dependent - Azoderivatives **Suppositories** - MMX Technology

Management of mild-moderate attacks

Distal Colitis

Extensive Colitis

Management of mild-moderate attacks

Distal Colitis

Extensive Colitis

Montreal Classification of Ulcerative Colitis by Endoscopic Extent of Disease



Appears to be useful in distinguishing patients by medical therapy, surveillance management and prognosis



Topical treatment in UC



Possibility to administer high doses of active ingredient directly to the superficially inflamed mucosa

Volume is the Key Factor



Gionchetti P, Aliment Pharmacol Ther 1997

Treatment of Active Distal UC

- Topical therapy preferred treatment
- Corticosteroids and 5-ASAs available in many forms
 - suppositories reach the upper rectum
 - enemas reach splenic
 flexure and the distal
 transverse colon



Efficacy of Oral, Topical, or Combined Oral and Topical 5-Aminosalicylates, in Ulcerative Colitis: Systematic Review and Network Meta-analysis



Limited exposure of distal colon to orally-dosed formulation in active distal UC

Stasis in the right colon together with the faster transit in active distal ulcerative colitis determine a reduced exposure of the distal colon to orally-dosed topical agents.

Rectal and colonic mesalazine concentration in UC: oral vs oral plus topical treatment



Oral vs combined (oral+rectal) mesalazine in the induction of remission in left-sided and extensive ulcerative colitis.

	Oral and top	ical 5-ASA	Oral 5-	ASA		Risk ratio				Risk	ratio	
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% Cl	Year			M-H, rando	m, 95%	CI
Fruhmorgen and Demling (1980)	2	12	7	11	5.7%	0.26 (0.07, 1.00)	1980	-	-			
Safdi et al. (1997)	4	20	12	22	10.5%	0.37 (0.14, 0.95)	1997	-				
Vecchi et al. (2001)	22	63	31	67	35.4%	0.75 (0.49, 1.15)	2001				_	
Marteau et al. (2005)	34	71	36	56	48.4%	0.74 (0.55, 1.02)	2005					
Total (95% Cl)		166		156	100.0%	0.65 (0.47, 0.91)				•		
Total events	62		86									NNT = 5
Heterogeneity: $\tau^2 = 0.0$	3; χ ² = 4.24, df:	= 3 (P=0.24	4); / ² =29%					<u> </u>	-		+	
Test for overall effect: 2	7 = 2.51 (P = 0.0)	01)						0.1	0.2	0.5 1	2	5
Toot for overeal encours		,						Favor	s oral	and topical	Favor	s oral 5-ASA

Management of mild-moderate attacks

Distal Colitis

Extensive Colitis

Non usiamo i generici della mesalazina orale!!! (non ne conosciamo il rilascio)

Oral mesalazine vs placebo in the induction of remission and improvement - Clinical -

Daily dosage	M/P	Failure to induce remission	M/P	Failure to Induce remission/improvement
<2.0 g	156/75	0.92 (0.84-1.02)	156/75	0.79 (0.64-0.97)
2.0-2.9 g	619/337	0.88 (0.82-0.94)	565/312	0.77 (0.67-0.88)
<u>></u> 3.0 g	775/425	0.83 (0.77-0.88)	738/410	0.57 (0.51-0.65)
Total	1550/837	0.86 (0.82-0.89)	1454/797	0.68 (0.61-0.75)

Oral Mesalazine vs placebo in the induction of remission and improvement - Endoscopy -

Daily dosage	M/P	Failure to induce remission	M/P	Failure to induce remission/improvement
<2.0 g	92/30	0.85 (0.64-1.14)	NA	NA
2.0-2.9 g	275/118	0.86 (0.70-1.05)	157/108	0.73 (0.58-0.92)
<u>></u> 3.0 g	438/201	0.70 (0.56-0.87)	98/53	0.69 (0.49-0.96)
Total	805/349	0.77 (0.67-0.89)	255/161	0.71 (0.59-0.86)

Mesalazine once-daily vs conventional dosage in ulcerative colitis

Induction of remission

	OD do	osing	Convention	al dosing		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
3.1.1 MMX once daily	(OD) versu	s twice dai	ly (BID)				
Lichtenstein 2007	65	94	60	93	11.2%	1.07 [0.88 , 1.31]	_
Subtotal (95% CI)		94		93	11.2%	1.07 [0.88 , 1.31]	
Total events:	65		60				
Heterogeneity: Not appl	licable						
Test for overall effect: Z	Z = 0.67 (P =	0.50)					
3.1.2 Salofalk granules	once daily	(OD) versi	us three times	daily (TID)			
Kruis 2009	40	191	46	189	8.6%	0.86 [0.59 , 1.25]	_
Subtotal (95% CI)		191		189	8.6%	0.86 [0.59 , 1.25]	
Total events:	40		46				
Heterogeneity: Not appl	licable						
Test for overall effect: Z	L = 0.79 (P =	0.43)					
3.1.3 MMX once daily	(OD) versu	s Asacol th	ree times dail	v (TID)			
Kamm 2007	50	85	57	86	10.5%	0.89[0.70, 1.12]	
Subtotal (95% CI)		85		86	10.5%	0.89 [0.70 , 1.12]	
Total events:	50		57				
Heterogeneity: Not appl	licable						
Test for overall effect: Z		0.32)					
3.1.4 Pentasa once dail	v (OD) vers	us twice d	ailv (BID)				
Flourié 2013	56	102	62	104	11.4%	0.92 [0.73, 1.17]	
Subtotal (95% CI)		102		104	11.4%	0.92 [0.73 , 1.17]	
Total events:	56		62				
Heterogeneity: Not appl	licable						
Test for overall effect: Z		0.49)					
3.1.5 Mesalazine once	daily (OD) y	versus twic	e daily (BID)				
D'Haens 2017	322	409	313	408	58.2%	1.03 [0.95, 1.10]	_
Subtotal (95% CI)		409		408	58.2%	1.03 [0.95 , 1.10]	—
Total events:	322		313			_ / _	T
Heterogeneity: Not appl							
Test for overall effect: Z		0.49)					
Total (95% CI)		881		880	100.0%	0.99 [0.93 , 1.06]	
Total events:	533		538				T
Heterogeneity: $Chi^2 = 3$		P = 0.52): I					
Test for overall effect: Z							Favours OD Favours convention
Test for subgroup differ		-	4 (P = 0.56). 1	$2^{2} = 0\%$			

ECCO Guidelines: medical treatment of mild-moderate active ulcerative colitis



- R1: We recommend 5-aminosalicylates at a dose of ≥2 g/ day [d] to induce remission in patients with mildly-to-moderately active UC [strong recommendation; quality of evidence low].
- R2: We recommend topical [rectal] 5-ASA at a dose of ≥1 g/d for the induction of remission in active distal colitis [strong recommendation, low-quality evidence].
- R3: We suggest the use of oral 5-ASA [≥2 g/d] combined with topical [rectal] 5-ASA over oral 5-ASA monotherapy for induction of remission in adult patients with active UC of at least rectosigmoid extent [weak recommendation; very low-quality evidence]

Mesalazine in mild-moderate active ulcerative colitis - Take-home messages: optimize!! -

- First choice!!
- Oral: dose-dependent effect (>3 g/d); once daily favours adherence while not affecting efficacy
- Rectal: early effect, likely not dose-dependent, volume more important, maybe the only treatment in distal forms
- Combined Therapy: more effective and more rapid, particularly needed in extensive forms
- Duration: 6 to 8 weeks but evaluation at 10-14 days
- Effectiveness in 70-80 %

Do not forget mesalazine, particularly the topical formulations, as adjuvants also in more complex/active patients!

Mesalazine in ulcerative colitis

Maintenance of remission

Extent of disease is a prediction of disease severity

At diagnosis:
-30–50% rectum or sigmoid
-20–30% left-sided
-20% pancolitis

Approximately 30-50% progress to more extensive disease

 More extensive disease is associated with: —More severe symptoms —Higher risk of colectomy (about 4x)

Mesalazine vs placebo in the maintenance treatment of ulcerative colitis

Daily dosage	M/P	Maintenance of clinical or endoscopic remission at 6-12 months
<1.0 g	90/43	0.77 (0.59-1.00)
1.0-1.9 g	665/451	0.65 (0.56-0.76)
<u>></u> 2.0 g	152/154	0.73 (0.60-0.89)
Total	907/648	0.68 (0.61-0.77)

Oral vs Rectal Mesalazine in the prevention of ulcerative proctitis recurrence

	Topical 5-ASA		Oral 5-ASA		Risk ratio			Risk ratio		
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% Cl	Year	M-H, rando	m, 95% Cl	
D'Albasio et al. (1990)	15	29	21	31	64.1%	0.76 (0.50, 1.17)	1990	+	_	
Mantzaris et al. (1994)	5	19	13	19	22.2%	0.38 (0.17, 0.87)	1994			
Andreoli et al. (1994)	4	16	6	15	13.8%	0.63 (0.22, 1.79)	1994			
Total (95% Cl)		64		65	100.0%	0.64 (0.43, 0.95)		-	NNT = 4	
Total events	24		40							
Heterogeneity: τ ² =0.02;	$\chi^2 = 2.26$, df =	=2 (P=0	.32); / ² =11	%			\vdash			
Test for overall effect: Z=	2.19 (P=0.0)3)					0.1	0.2 0.5 1	2 5	
	-	-					Fa	vors topical 5-ASA	Favors oral 5-AS	

Oral vs combined oral+rectal mesalazine in relapse prevention of left colitis



Pooled RR of relapse 0.48 (95% CI = 0.17– 1.38)





R8: We recommend the use of oral 5-ASA at a dose $\geq 2 \text{ g/day}$ for maintenance of remission in UC patients [strong recommendation; very low quality of evidence].

R9: We suggest the use of topical [rectal] 5-ASA for the maintenance of remission in patients with distal UC [weak recommendation, very low quality evidence]

No Disease Should Be Labeled as "Refractory" If It Has Not Received Optimal Therapy

Suboptimal care in inflammatory bowel disease

Parameters	Ν	Proportion
Suboptimal dose of 5-ASA	21/33	64%
No topical 5-ASA therapy in distal UC	9/12	75%
Steroids > 3 months	27/35	77%
Failure to use steroid sparing agent	16/27	59%
Inadequate prevention of osteoporosis	21/27	78%
Suboptimal dose of immunomodulatory agents	9/11	82%

67 consecutive patients, American tertiary center (Brigham & Women's)

Non-Compliance with 5-ASA Therapy is Associated with Clinical Recurrence



Time (months)

Kane et al, Am J Med, 2003

Mesalazine in ulcerative colitis in remission - Take-home messages -

- Oral route
- Dose: ≥ 2 g/day
- Single daily assumption
- Topical therapy alone in distal disease? (risk of extension of proctitis 45 %)
- Evaluate combined maintenance treatment in frequently recurrent disease before stepping up
- Check compliance

An open issue: mesalazine for maintenance treatment: how long?

- Go ahead for a long time. But how long?
 - Always for the entire life? Yes
 - Even in association with biologics or immunosuppressors? Yes

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"Science is important. But education is the vector that transmits to every new generation curiosity, passion, and commitment to reimagine the future, extend the limits of human possibility, and achieve a more just social world."

See Comment page 1666

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Grazie per la Vostra Attenzione