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2017 中国 IBD 高端专家峰会
暨第一届 IBD 青年医生论坛

溃疡性结肠炎 临床诊断和治疗进展



主要内容

诊断篇

- 指南推荐UC诊断标准
- 2017 ECCO最新诊断指南更新内容简述
- 2017 ECCO会议 UC诊断新进展

治疗篇

- 指南推荐UC治疗推荐
- 2017 ECCO会议 UC治疗新进展

中国UC共识诊断标准

UC 缺乏诊断的金标准



主要结合临床、内镜
和组织病理学表现进行综合分析



在排除感染性和其他非感染性结肠炎的
基础上作出诊断

UC的临床表现

- 持续或反复发作的腹泻、黏液脓血便伴腹痛、里急后重和不同程度的全身症状
- 病程：多在4-6周以上
- 可有皮肤、黏膜、关节、眼和肝胆等的肠外表现
- 黏液血便是UC的最常见症状，超过6周的腹泻病程可与多数感染性肠炎鉴别

UC的临床类型及病变范围

临床类型

初发型

慢性复发型

病变范围

采用蒙特利尔分类

- E1：局限于直肠
未达乙状结肠
- E2：累及左半结肠
(脾曲以远)
- E3：广泛病变累及脾曲
以近乃至全结肠

结肠镜检查并活检是UC 诊断的主要依据

结肠镜下UC 病变
多从直肠开始，
呈连续性、弥漫
性分布，表现为：

01

黏膜血管纹理模糊、紊乱或消失、充血、水肿、质脆、自发性或接触性出血和脓性分泌物附着，亦常见黏膜粗糙、呈细颗粒状

02

病变明显处可见弥漫性、多发性糜烂或溃疡

03

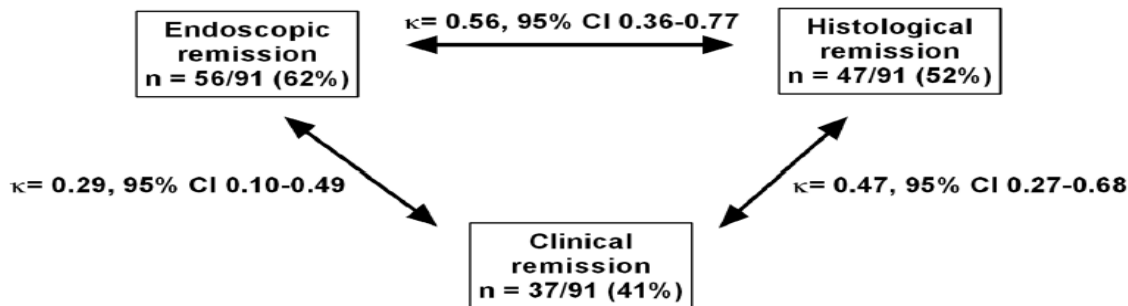
缓解期可见结肠袋变浅、变钝或消失以及假息肉、黏膜桥等

活动期和缓解期UC 有不同的组织学表现

活动期	缓解期
固有膜内弥漫性急性、慢性炎性细胞浸润，包括中性粒细胞、淋巴细胞、浆细胞、嗜酸性粒细胞等	固有膜内中性粒细胞消失，慢性炎性细胞减少
隐窝急性炎性细胞浸润，尤其是上皮细胞间有中性粒细胞浸润和隐窝炎，甚至形成隐窝脓肿，可有脓肿溃入固有膜	隐窝大小、形态不规则和排列紊乱加重
隐窝上皮增生，杯状细胞减少	腺上皮与黏膜肌层间隙增宽
可见黏膜表面糜烂、浅溃疡形成和肉芽组织增生	Paneth细胞化生(结肠脾曲以远)

有研究显示， 组织学可能会更好的预测UC患者的临床结局

- 内镜检查是UC患者最稳固的检测方法，然而，组织学价值尚不清楚
- 研究人员在对UC患者长达6年的随访过程中发现组织学可能会更好的预测皮质类固醇使用和住院治疗
- 研究共纳入91名UC患者，平均随访72个月，评估测定住院率和结肠切除术,包括 κ 统计和Cox回归多元分析



Measure of remission	Concordance with other measures of remission		
Clinical (n=37)	Clinical	Endoscopic	Histological
Endoscopic (n=56)	100% (n=37)	81% (n=30)	81% (n=30)
Histological (n=47)	54% (n=30)	100% (n=56)	75% (n=42)
	64% (n=30)	89% (n=42)	100% (n=47)

- 研究结果显示，内镜下和组织学缓解适中的整体一致($\kappa=0.56$ ；95%[CI]，0.36 ~ 0.77)。尽管在内镜检查线有所缓解，但24%的患者持续炎症。组织学缓解可预测糖皮质激素的使用和住院治疗降低([HR]，0.42[95%CI]，0.2 ~ 0.9；P=0.02]；HR，0.21[95%CI]，0.1 ~ 0.7；P=0.02])。然而，内镜下缓解则没有(使用糖皮质激素：HR，0.86[95%CI]，0.5 ~ 1.7；P=0.65]；住院治疗：HR，0.83[95%CI]，0.3 ~ 2.4；P=0.74])

- 定义内镜下缓解为Baron评分(定义评分 ≤ 1)和组织学缓解使用Truelove和Richards指数

ECCO会议上TOUCHSTONE开放标签性延伸试验也证实了这一观点

Oral presentations (2017)

OP014 Histological remission is predictive of improved clinical outcomes in patients with ulcerative colitis: results from the TOUCHSTONE open-label extension

Sandborn W.¹, Feagan B.^{*2}, D'Haens G.³, Levesque B.², Pai R.⁴, Hanauer S.⁵, Wolf D.⁶, Vermeire S.⁷, Ghosh S.⁸, Li C.⁹, Penenberg D.⁹, Aranda R.⁹, Olson A.⁹

¹University of California San Diego, San Diego, United States ²Robarts Research, London, Canada ³Academic Medical Center, Amsterdam, Netherlands ⁴Mayo Clinic, Department of Laboratory Medicine and Pathology, Scottsdale, United States ⁵Feinberg School of Medicine, Chicago, United States ⁶Atlanta Gastroenterology Associates, Atlanta, United States ⁷University of Leuven, Leuven, Belgium ⁸University of Calgary, Calgary, Canada ⁹Receptos, a wholly owned subsidiary of Celgene, San Diego, United States

Conclusion

Histological remission is predictive of CR in patients with UC receiving ozanimod 1 mg in OLE. All patients, whether naïve to or having received ozanimod in TOUCHSTONE, showed additional improvements in CR upon continued treatment with ozanimod 1 mg in OLE. Patients naïve to ozanimod had a rapid improvement in CR over the first 8 weeks of treatment with ozanimod 1 mg in OLE.

- 临床研究表明，组织学改善与溃疡性结肠炎的临床结果改善有关，虽然有时更难以衡量，一些端点，如组织学改善或缓解正在成为患者和医生的重要治疗目标

UC指南：2017 ECCO第三个欧洲询证共识发布



1. European Crohn's and Colitis Organisation (ECCO). J Crohns Colitis. 2008 Mar;2(1):1-23
2. European Crohn's and Colitis Organisation (ECCO). J Crohns Colitis. 2012 Dec;6(10):965-90
3. European Crohn's and Colitis Organisation (ECCO). J Crohns Colitis. 2017 Feb 2

UC的临床表现更加明确具体

2017年

ECCO statement 3A

Symptoms of ulcerative colitis are dependent upon extent and severity of disease and include bloody diarrhoea, rectal bleeding, **tenesmus, urgency and faecal incontinence**. Nocturnal defecation and fatigue are often reported. **Increasing bowel frequency, abdominal pain, anorexia, and fever suggest severe colitis [EL5]**

2012年

ECCO statement 3A

Symptoms of ulcerative colitis are dependent upon extent and severity of disease, and most commonly include bloody diarrhoea, rectal bleeding, **and/or rectal urgency**. Nocturnal defaecation is also often reported. Systemic symptoms of **malaise**, anorexia, or fever are features of a severe attack [EL5, RG D]

EL：证据等级

- UC的症状取决于病程和疾病的严重程度，包括血性腹泻、**直肠出血、里急后重、尿急和大便失禁**。夜间排便和疲劳也常见报道。**增加肠蠕动、腹痛、厌食和发烧提示严重结肠炎[EL5]**

1. European Crohn's and Colitis Organisation (ECCO). J Crohns Colitis. 2012 Dec;6(10):965-90

2. European Crohn's and Colitis Organisation (ECCO). J Crohns Colitis. 2017 Feb 2

将影像学检查列入ECCO声明中

2017年

ECCO statement 3E

A “gold standard” for diagnosis of ulcerative colitis does not exist. It is established by clinical, laboratory, **imaging** and endoscopic parameters, including histopathology. An infective cause should be excluded. Repeat endoscopy with histopathological review after an interval may be necessary if diagnostic doubt remains [EL5]

2012年

ECCO statement 3E

A gold standard for the diagnosis of ulcerative colitis is not available. The diagnosis should be established by a combination of medical history, clinical evaluation, and typical endoscopic and histological findings. An infective cause should be excluded. Where there is doubt about the diagnosis, endoscopic and histological confirmation is necessary after an interval [EL5, RG D]

- UC诊断的“金标准”仍缺乏。主要结合临床、实验室、**影像学**和内镜参数，包括组织病理学确诊。排除感染性。如诊断仍存疑，间隔一段时间后需要内镜检查组织病理学[EL5]

2017年

初诊时增加检查肾功能和维生素D水平

ECCO statement 3F

Initial investigations should include full blood count, electrolytes, liver and renal function, iron studies, vitamin D level, C-reactive protein and faecal calprotectin [EL5]. The immunisation status should be assessed [EL5]. Infectious diarrhoea including *C. difficile* should be excluded [EL2]. Endoscopy and histology should be performed

2012年

ECCO statement 3F

Initial laboratory investigations should include a full blood count, serum urea, creatinine, electrolytes, liver enzymes, iron studies, and C-reactive protein (CRP) [EL5, RG D]. Faecal calprotectin is an accurate marker of colonic inflammation. CRP and erythrocyte sedimentation rate (ESR) are useful markers to monitor the response to treatment in severe colitis [EL2b, RGB]. Microbiological testing for infectious diarrhoea including *Clostridium difficile* toxin is recommended [EL2b, RG B]. Additional stool tests may be necessary for patients who report a recent travel abroad [EL5, RG D]. Patient's immunization status to various viral diseases and tuberculosis status should be assessed [EL5, RG D]

初诊检查包括全血计数、电解质、肝脏和肾脏功能、铁指标、维生素D水平、C反应蛋白和粪钙卫蛋白[EL5]。评估机体免疫状态[EL5]。排除*C. difficile* 在内的感染性腹泻[EL2]。应进行内窥镜检查和组织学检查

1. European Crohn's and Colitis Organisation (ECCO). J Crohns Colitis. 2012 Dec;6(10):965-90
2. European Crohn's and Colitis Organisation (ECCO). J Crohns Colitis. 2017 Feb 2

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活动期的治疗——轻度UC

- 氨基水杨酸制剂：仍为治疗轻度UC的主要药物
- 柳氮磺吡啶(SASP)和其他不同类型5-ASA制剂相似，但不良反应更多见。
- 对氨基水杨酸制剂治疗无效者，特别是病变较广泛者，可改用口服全身作用糖皮质激素

表9 氨基水杨酸制剂用药方案

药品名称	结构特点	释放特点	制剂	推荐剂量*
SASP	5-ASA 与磺胺吡啶的偶氮化合物	结肠释放	口服：片剂	3 ~ 4 g/d, 分次口服
5-ASA 前体药				
巴柳氮	5-ASA 与 P-氨基苯甲酰 β 丙氨酸偶氮化合物	结肠释放	口服：片剂、胶囊剂、颗粒剂	4 ~ 6 g/d, 分次口服
奥沙拉秦	两分子 5-ASA 的偶氮化合物	结肠释放	口服：片剂、胶囊剂	2 ~ 4 g/d, 分次口服
5-ASA				
美沙拉秦	a: 甲基丙烯酸酯控释 pH 值依赖 b: 乙基纤维素半透膜控释时间依赖	a: pH 值依赖药物释放部位：回肠末端和结肠 b: 纤维素膜控释时间依赖药物释放部位：远段空肠、回肠、结肠	口服：颗粒剂、片剂 局部：栓剂、灌肠剂、泡沫剂、凝胶剂	口服：2 ~ 4 g/d, 分次口服或顿服 局部：详见正文中“二、(二)”中“远段结肠炎的治疗”部分

注：SASP；柳氮磺吡啶；5-ASA；5-氨基水杨酸；* 以 5-ASA 含量计，SASP、巴柳氮、奥沙拉秦 1 g 分别相当于美沙拉秦 0.4、0.36 和 1 g

活动期的治疗——中度UC

- **氨基水杨酸制剂：仍是主要药物**
- **糖皮质激素：**
 - 足量氨基水杨酸类制剂治疗(一般2~4周)，症状控制不佳者，尤其是病变较广泛者，应及时改用糖皮质激素。
 - 泼尼松剂量：0.75 - 1 mg/Kg/d
达到症状缓解开始逐渐缓慢减量至停药
- **硫嘌呤类药物：**
 - 包括硫唑嘌呤(AZA)和6-巯基嘌呤(6-MP)
 - 适用于激素无效或依赖患者
 - AZA欧美推荐的目标剂量为1.5~2.5/kg/d
 - 有学者认为亚裔人种剂量宜偏低如1mg/kg/d，对此尚未达成共识
- **英夫利西(IFX)：当激素及上述免疫抑制剂治疗无效或激素依赖、或不能耐受上述药物治疗时**

Efficacy and safety of two pH-dependent-release mesalamine doses in moderately active ulcerative colitis: a multicenter, randomized, double-blind, parallel-group study

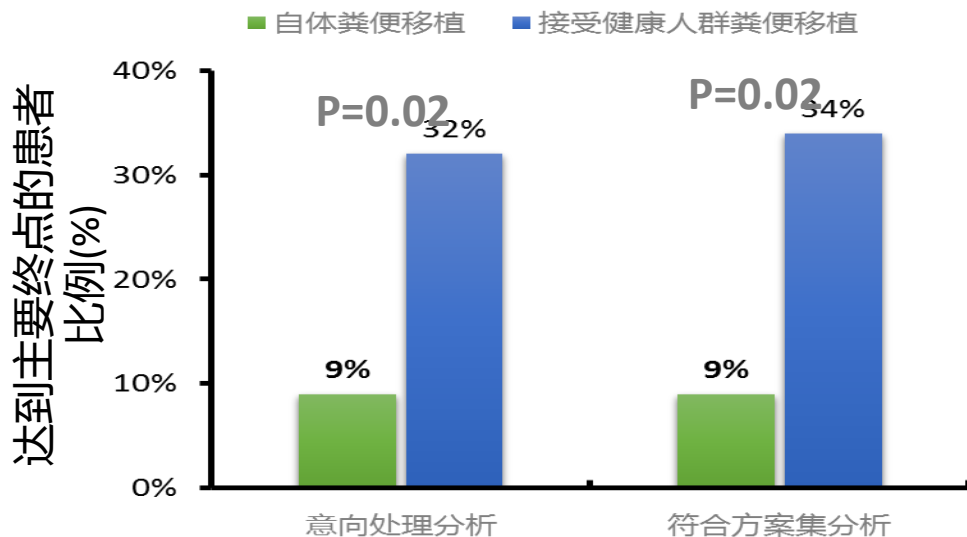
Table 5. Subgroup Analysis According to the Prior Dose of pH-Dependent-release Mesalamine

Characteristic	3.6 g/day group (n=33)	4.8 g/day group (n=35)
Prior dose of oral mesalamine		
2.4 g/day	3	6
Decrease in UCDAI ^a , mean (95% CI)	2.3 (-4.8- 9.5)	4.5 (1.1-7.9)
Difference in decrease in UCDAI ^a , difference (95% CI)		2.2 (-3.1-7.4)
3.6 g/day	30	29
Decrease in UCDAI, mean (95% CI)	2.1 (1.1-3.1)	2.1 (1.1-3.2)
Difference in decrease in UCDAI, difference (95% CI)		0.0 (-1.4-1.5)

对于既往使用5-ASA 2.4g/d疗效欠佳的患者，调整pH依赖5-ASA剂量至4.8g/d较3.6g/d改善症状作用更佳

粪便微生物群移植 可诱导缓解轻中度活动期UC患者

- 对于轻中度活动期UC患者，接受健康人群FMT较自体FMT治疗更有效诱导改善临床和内窥镜结局



- 一项多中心、随机、双盲、安慰剂对照研究，共纳入73例轻中度活动期UC患者
- 随机分为两组，38例患者接受接受健康人群粪便移植(FMT)，35例接受自体粪便移植FMT

活动期的治疗——重度UC

一般治疗

- 防治水电解质、酸碱平衡紊乱，必要时输血、胃肠外营养
- 检查是否合并艰难梭菌及巨细胞病毒感染，如有则作相应处理
- 忌用止泻剂、抗胆碱能药物、阿片制剂、NSAIDs
- 对中毒症状明显者可考虑静脉用广谱抗生素

静脉用糖皮质激素

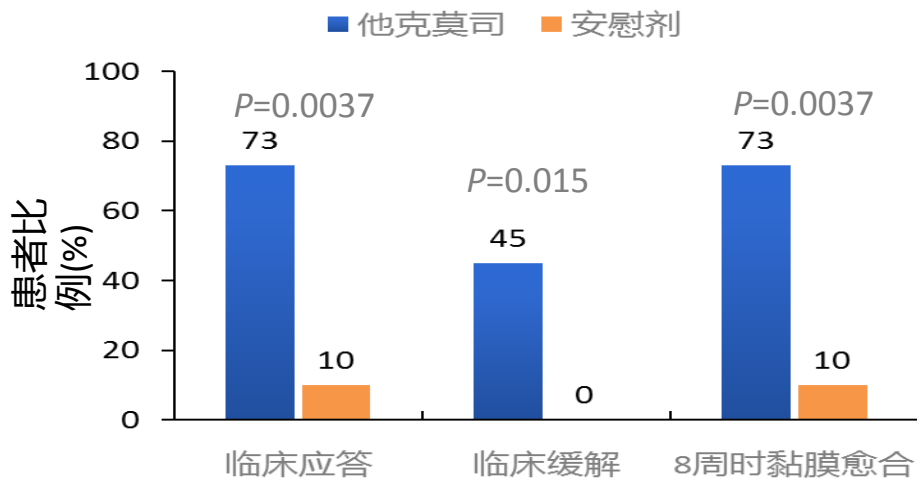
- 为首选治疗
- 甲基泼尼松龙40~60mg/d，或氢化可的松300~400mg/d
- 剂量再大不会增加疗效，但剂量不足亦会降低疗效



图1 重症溃疡性结肠炎的内科治疗程序

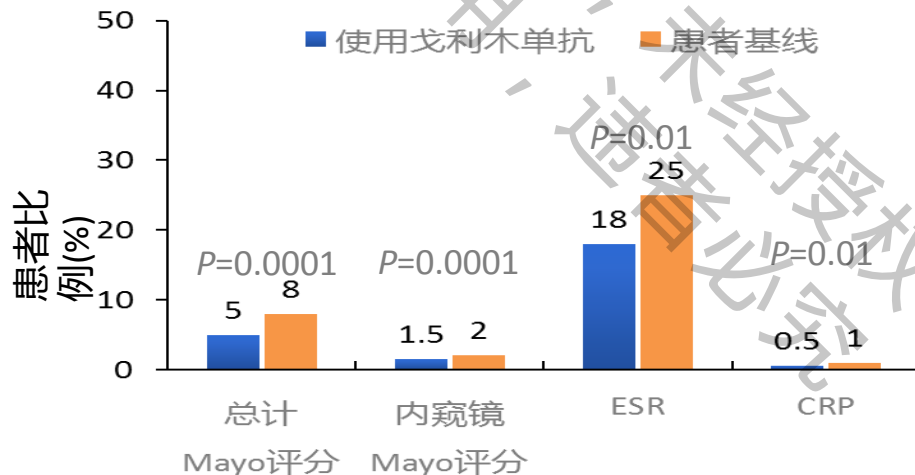
免疫抑制剂或生物制剂治疗活动期UC患者 有较好的临床结果

- 与安慰剂相比，他克莫司治疗活动期UC患者显著**提高临床应答率、临床缓解率及黏膜愈合率**¹



- 一项澳大利亚随机、双盲、安慰剂对照研究，纳入活动期UC患者21例，11例患者使用他克莫司治疗，10例患者使用安慰剂治疗

- 与基线相比，使用戈利木单抗治疗3个月后，UC患者**临床情况得到显著改善**²



- 一项意大利的多中心研究，纳入度UC患者114例

1. ECCO 2017. OP007.
2. ECCO 2017. Abstract P621.

缓解期的维持治疗

- **需要维持治疗的对象：**

- 除轻度初发病例、很少复发且复发时为轻度而易于控制者外，均应接受维持治疗

- **维持治疗的疗程：**

- 氨基水杨酸制维持治疗的疗程为3~5年或更长
- 对硫嘌呤类药物及英夫利西维持治疗的疗程未有共识，视病人具体情况而定

- **氨基水杨酸制：**

- 由氨基水杨酸制剂或糖皮质激素诱导缓解后以氨基水杨酸制维持，用原诱导缓解剂量的全量或半量
- 如用SASP维持，剂量一般为2~3g/d，并补充叶酸
- 远段结肠炎以美沙拉秦局部用药为主，加上口服氨基水杨酸制更好

- **硫嘌呤类药物：**

- 激素依赖者、氨基水杨酸制剂不耐受者
- 剂量与诱导缓解时相同

A randomized trial comparing 4.8 vs. 2.4 g/day of oral mesalazine for maintenance of remission in ulcerative colitis

Abstract

BACKGROUND: Mesalazine is used as maintenance therapy in ulcerative colitis but the optimal dosage is still controversial.

AIM: To compare the remission-maintenance efficacy and tolerability of two daily doses of oral mesalazine (4.8 g and 2.4 g) in patients with ulcerative colitis with frequent relapses in a randomized controlled trial.

METHODS: 112 ulcerative colitis patients in remission were enrolled and randomly allocated to treatment for 1 year with oral mesalazine at a daily dose of 4.8 g (n=56, Group A) or 2.4 g (n=56, Group B).

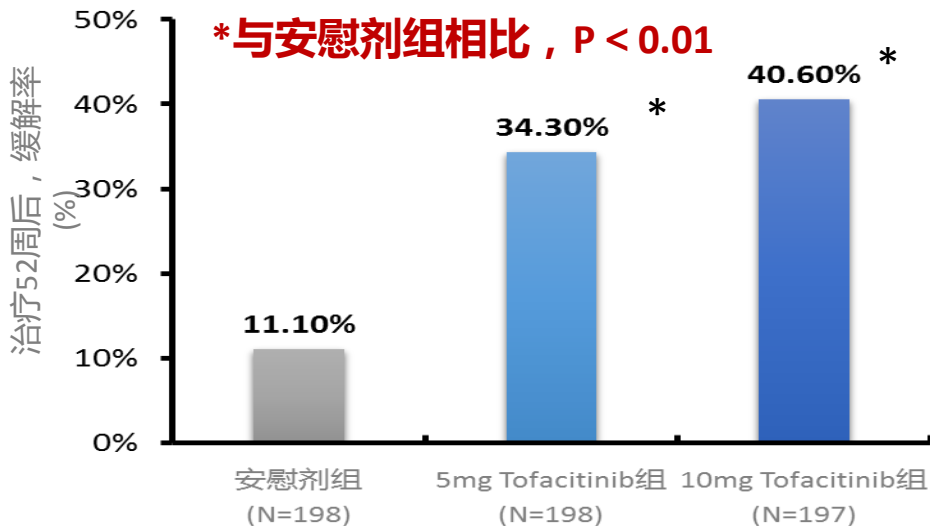
RESULTS: At the end of the 12 months, intention to treat analysis revealed persistent remission in 42 (75%) in Group A and 36 (64.2%) in Group B ($p=0.3$). The higher daily dose (4.8 g) proved to be significantly more effective for maintaining remission in patients under 40 years of age (90.5% Group A vs. 50% Group B; Fisher's exact test, $p=0.0095$) and in those with extensive disease (90.9% Group A vs. 46.7% Group B; Fisher's exact test, $p=0.0064$).

CONCLUSIONS: In ulcerative colitis patients younger than 40 years and/or with extensive disease, a daily dose of 4.8 g oral mesalazine results in increased rates and duration of remission compared to 2.4 g.

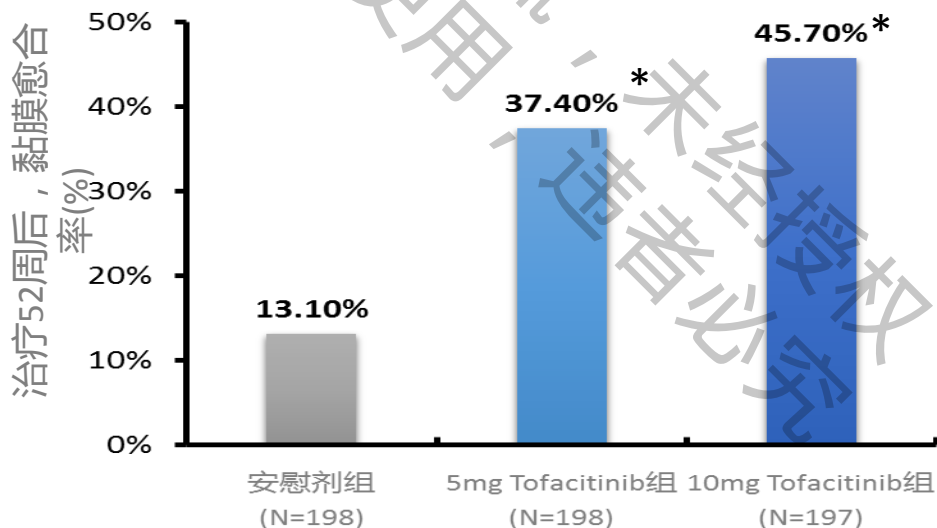
对于年龄小于40岁的广泛结肠型UC患者使用美沙拉秦4.8g/d较2.4g/d具有更高的缓解率和更长的缓解时间

JAK抑制剂治疗治疗中重度UC疗效显著

与安慰剂组相比，5mg、10mg Tofacitinib组患者主要疗效终点显著提高



与安慰剂组相比，5mg、10mg Tofacitinib组患者黏膜愈合比例更高



- OCTAVE Sustain是一项III期、随机、双盲、安慰剂对照研究，共纳入593例患者
- 随机服用5毫克、10毫克Tofacitinib或安慰剂，用药52周
- 评估口服tofacitinib 10mg BID和5mg BID作为维持疗法，治疗中重度UC成人患者的疗效和安全性

JAK抑制剂治疗治疗中重度UC安全性良好

Tofacitinib组患者出现的不良反应与安慰剂组相似，且未出现新的不良反应事件

	安慰剂组 (N=198)	5mg Tofacitinib组 (N198)	10mg Tofacitinib组 (N197)
治疗中出现 不良反应，n(%)	149(75.3)	143(72.2)	156(79.6)
治疗中出现 严重不良反应，n(%)	13(6.6)	10(5.1)	11(5.6)
感染，n(%)	48(24.2)	71(35.9)	78(39.8)
带状疱疹，n(%)	1(0.5)	3(1.5)	10(5.1)
严重感染，n(%)	2(1.0)	2(1.0)	1(0.5)
恶性肿瘤(NMSC除外)，n(%)	1(0.5)	0(0.0)	0(0.0)
NMSC，n(%)	1(0.5)	0(0.0)	3(1.5)
因不良反应中止，n(%)	37(18.7)	18(9.1)	19(9.7)

- OCTAVE Sustain是一项III期、随机、双盲、安慰剂对照研究，共纳入593例患者
- 随机服用5毫克、10毫克Tofacitinib或安慰剂，用药52周
- 评估口服tofacitinib 10mg BID和5mg BID作为维持疗法，治疗中重度UC成人患者的疗效和安全性

巯嘌呤类药物维持治疗UC患者降低复发风险

- 一项法国回顾性研究，共纳入UC患者130例，患者经巯嘌呤类药物或氨基水杨酸治疗6个月以上
- 患者分为接受接受巯嘌呤类药物维持治疗组（87例，67%）与治疗失败组（43例，33%）
- 治疗失败定义为：需要抗TNF α 或手术治疗，或因副反应等撤销维持治疗

Results

We included 130 patients (52% males), with a median follow-up of 86 months (IQR 55–130). UC was predominantly left-sided (53%) and pancolitis (35%). Major indication for thiopurine was steroid-dependence (45%), and 19 patients (15%) had severe acute colitis prior to thiopurine. Median duration of treatment was 42 months (IQR 23–80), with 119 (92%) patients having azathioprine.

Eighty-seven patients (67%) maintained clinical remission on thiopurine, and 43 (33%) underwent treatment failure. Mean duration of treatment was 25 months in failure group vs 52 months in remission group. Five years after initiation, 36% (n=47) of patients were still on thiopurine. Reasons of treatment withdrawal were: secondary failure (n=31), major side effect (n=9), persistent remission (n=40) and other reason (n=3). In univariate analysis, older age at diagnosis (RR 1.02; CI95% 1.0–1.04; p=0.04) and clinical response at T0 (RR 1.98; CI95% 1.03–3.82; p=0.04) were associated to treatment failure. In multivariate analysis, only clinical response at T0 vs remission was associated with failure (RR 2.07; CI95% 1.07–3.4; p=0.03).

Relapse rate after withdrawal for persistent remission was 43%, with a median time of 29 months.

Forty patients (31%) had a significant side effect, and 9 of them (7%) stopped treatment due to it. Side effects were mainly hematologic and hepatologic. Nine neoplastic and pre-neoplastic lesions were observed during follow-up: 2 colorectal high risk adenomas, 3 basal cell carcinomas, 1 in situ cervix carcinoma and 3 other cancers (prostate, breast, lung).

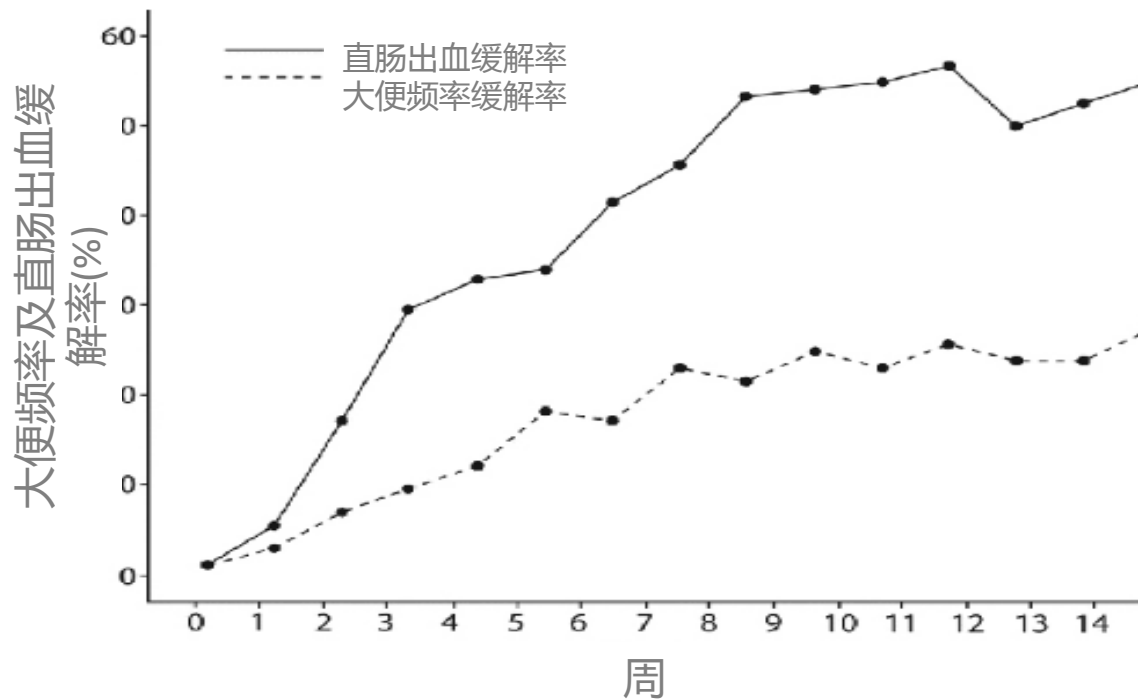
Conclusion

This study shows a long term efficacy of thiopurine as a maintenance treatment in UC. Risk of relapse after thiopurine withdrawal is significant. Neoplasia rate due to thiopurine seems to be acceptable in this cohort.

- 维持治疗组与治疗失败组**维持期分别为52个月、25个月**

- **撤销维持治疗后复发率为43%，复发时间为29个月**

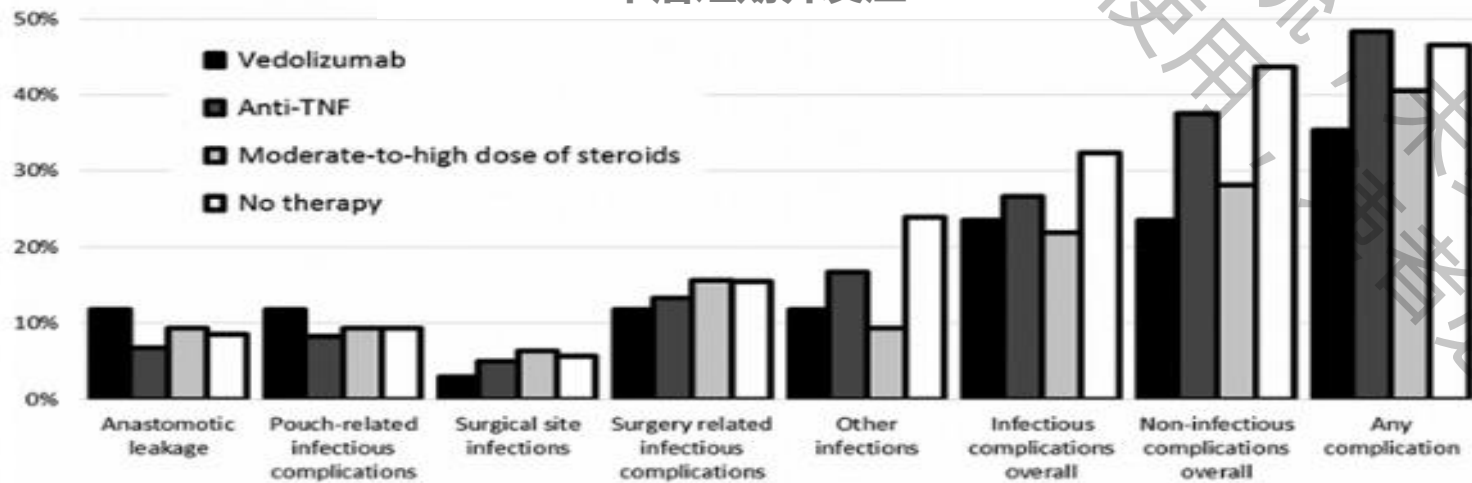
整合素 $\beta 7$ 拮抗剂可有效治疗 anti-TNF生物制剂抵抗或不耐受的中重度UC



- HICKORY研究是一项多中心、随机、双盲、安慰剂对照III期研究，共纳入130例患者
- 观察终点为4周和12周时临床症状缓解率
- 比较Etrolizumab(整合素 $\beta 7$ 拮抗剂)和安慰剂治疗anti-TNF生物制剂抵抗或不耐受的中重度UC疗效
- 结果显示，4周和12周时，治疗组的症状缓解率明显高于安慰剂组，而12周时的生物学缓解(CRP和粪便钙卫蛋白)治疗组亦明显高于对照组

行回肠袋-直肠吻合术UC患者 围术期使用维多珠单抗不增加术后短期并发症

术后短期并发症



- 既往有研究显示，维多珠单抗增加术后短期感染并发生风险
- 本研究是一项单中心队列研究，共纳入170例行回肠袋-直肠吻合术UC患者
- 其中，围术期34例患者(20%)使用VDZ 14 周, 60例患者(35%)使用anti-TNF 8周, 32例患者(19%)使用中高剂量(≥ 20 mg/day)泼尼松，71例患者(42%)未使用药物

总结

- UC是一种以结肠黏膜连续性、弥漫性炎症改变为特点的慢性非特异性肠道炎症性疾病
- 近年来国内就诊人数呈逐步增加趋势
- 目前UC 缺乏诊断的金标准，主要结合临床、内镜和组织病理学表现进行综合分析
- ECCO会议中发布了多项研究证实了氨基水杨酸制剂、糖皮质激素、免疫抑制剂、生物制剂在UC 治疗的疗效及安全性