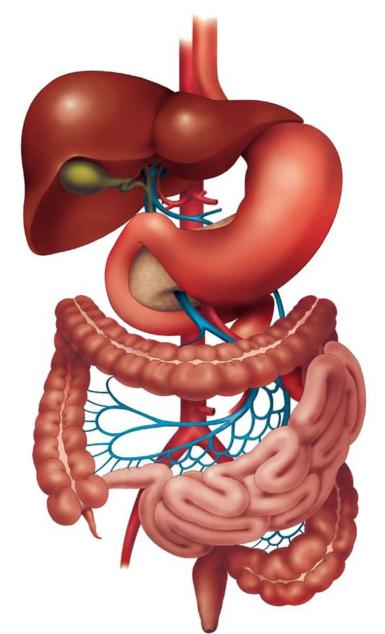
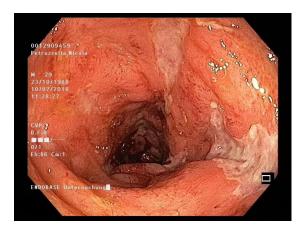
IBD highlights from DDW

July 11th, 2018 Alain Schoepfer + Pascal Juillerat



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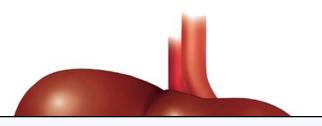






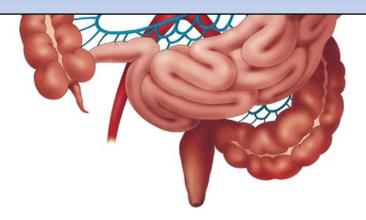








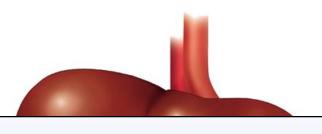
Epidemiology Basic and translational science Clinical science New drugs / combinations



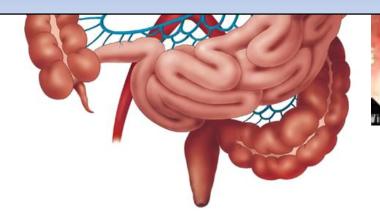








Epidemiology Basic and translational science Clinical science New drugs / combinations







Is aspirine a risk factor for IBD activity?



DAILY ASPIRIN USE DOES NOT IMPACT CLINICAL OUTCOMES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

P. Patel et al, University of Chicago

Background

Although several studies have associated the <u>use of other NSAIDS with disease flares</u> in IBD patients, little is known about the impact of daily aspirin use on clinical outcomes.

Methods

- retrospective analysis (5/2008 6/2015) of a prospective registry of IBD patients
- IBD Patients (>18 Mo Fup) with daily aspirin use were **matched 1:4 to controls** by age, sex, disease, disease location and presence of cardiac co-morbidity (atrial fibrillation, coronary artery disease, hypertension, cerebrovascular disease).

primary outcomes: IBD-related hospitalization, IBD-related surgery, and Steroids use

 To test for an association between each outcome and the use of aspirin while controlling for co-variables, we used a zero-inflated Poisson regression model evaluating for a binary association of each outcome with aspirin use.

DAILY ASPIRIN USE DOES NOT IMPACT CLINICAL OUTCOMES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

P. Patel et al, University of Chicago

Results

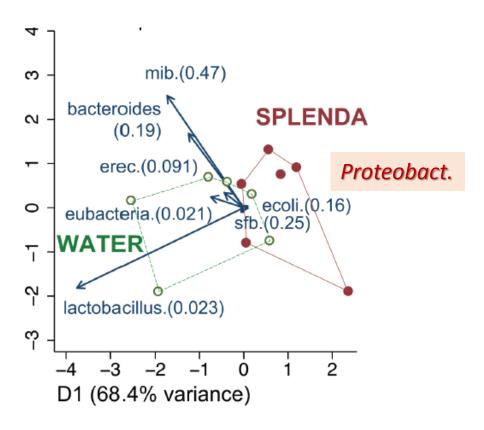
- **764 IBD patients** , **80% CD** / 174 patients with ASA.
- median follow up: 54 months (IQR 38-79).
- 74% (n=128) patients were on 81 mg of ASA and the median duration of ASA use was 45 mo

 CONCLUSIONS:

 Bas ulce me

 Aspirine use is safe in IBD
- After controlling for co-variables and length of follow up in the entire population, aspirin use was not associated with a risk of being hospitalized for an IBD-related complication (Poisson regression estimate (PRE) =-0.38, p=0.12), corticosteroid use (PRE=0.08, p=0.70), or having an IBD-related surgery (PRE=0.01, p=0.96).
- younger age, biologic use, cardiac comorbidities, and an elevated C-reactive protein at baseline were associated with all three outcomes.





Rodriguez-Palacios A¹, et al. The Artificial Sweetener Splenda Promotes Gut Proteobacteria, Dysbiosis, and Myeloperoxidase Reactivity in Crohn's Disease-Like Ileitis. Inflamm Bowel Dis. 2018 Apr 23;24(5):1005-1020.

Qin X. What made Canada become a country with the highest incidence of inflammatory bowel disease: could sucralose be the culprit? Can J Gastroenterol. 2011 Sep;25(9):511.

SWEETENED BEVERAGE CONSUMPTION AND RISK OF CROHN'S DISEASE AND ULCERATIVE COLITIS: RESULTS FROM TWO LARGE PROSPECTIVE COHORT STUDIES

H. Khalili¹; et al. ¹Gastroenterology, Massachusetts General Hospital, Boston, United States

Introduction:

- sweetened beverages consumption linked to <u>increased systemic inflammation</u> as measured by C-reaction protein and TNF-alpha.
- + associated with several immune-mediated disorders (e.g rheumatoid arthritis).
- → role in development of IBD ???

→ Methods:

- prospective cohort study of 83,042 participants enrolled in the Cohort of Swedish Men (CoSM) and Swedish Mammography Study (SMC).
- Dietary and lifestyle data were collected using a validated food frequency questionnaire at baseline in 1997 and updated in 2009.
- Diagnoses of CD and UC were ascertained from Swedish Patient Register.
- Cox proportional hazards modeling was performed to calculate hazard ratios (HR) and
 95% confidence intervals (CIs) while adjusting for potential confounders.

SWEETENED BEVERAGE CONSUMPTION AND RISK OF CROHN'S DISEASE AND ULCERATIVE COLITIS: RESULTS FROM TWO LARGE PROSPECTIVE COHORT STUDIES

H. Khalili¹; et al. ¹Gastroenterology, Massachusetts General Hospital, Boston, United States

Results:

- **320** incident **UC** cases (incidence rate = 24 cases/100,000 person-years) and
- 131 incident CD case (incidence rate = 10 cases/100.000 person-vears)

we/ Conclusions:

In two large prospective cohort studies, we did not observe an association between sweetened beverages and risk of CD or UC. Our finding that sweetened beverage is associated with increased risk of UC among younger participants warrants further investigation.

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.80-

ay.

- The association between consumption of sugar-sweetened beverage and risk of UC appeared to be modified by age ($P_{interaction} = 0.03$).

= > age < 60 and UC : **HR 1.26 (95% CI 1.03-1.54)**

Vaccination in children of mothers with exposure to biologics during pregnancy



Plan de vaccination suisse (BAG)

Alter ¹⁾	Diphtherie (D/d) ³⁾ Tetanus (T) ⁴⁾ Pertussis (P _a /p _a) ³⁾	influenzae Typ b (Hib)	Poliomyelitis (IPV)	Masern (M) Mumps (M) Röteln (R)	Hepatitis B (HBV) ¹⁶⁾	Varizellen (VZV)	Humane Papillo- maviren (HPV)	Influenza
Geburt					16)			
2 Monate 2)	DTP _a	Hib	IPV		(HBV) ¹⁷⁾			
4 Monate 2)	DTP _a	Hib	IPV		(HBV) ¹⁷⁾			
6 Monate	DTP _a	Hib	IPV		(HBV) 17)			
12 Monate		8)		MMR 12)				
15-24 Monate	DTP _a	Hib ^{8) 9)}	IPV	MMR 12)	(HBV) ¹⁷⁾			
4-7 Jahre	DTP _a /dTp _a ^{3) 5)}		IPV	13)				
11-14/15 Jahre	dTp _a ^{5) 6)}		10)	13)	HBV ¹⁷⁾	VZV 19)	HPV ²¹⁾	
25-29 Jahre	dTp _a ⁷⁾		11)	14)	18)	20)		
45 Jahre	dT 7)		11)	14)	18)	20)		
≥65 Jahre	dT ⁷⁾		11)		18)			22)

Vaccination: êtes-vous à jour?

2018
calendrier simplifié
des vaccinations

				V4.001W4.710.W0.001104.701070					ues vaccinations					
			VACCINATIONS OBLIGATOIRES pour les nourrissons nés à partir du 1º janvier 2018											
	Âge approprié	1 mois	2 mais	4 mois	5 mais	11 mais	12 mais	16:18 mais	63NS	11-13 ans	14 3NS	25 ans	45305	65 ans et *
VACCINATIONS OBLIGATOIRES	BCG													
	Diphtérie-Tétanos- Poliomyélite													Tous les 10 ans
	Coqueluche													
	Influenzae de type b													
	Hépatite B													
	Pneumocoque													
	Méningocoque C													
	Rougeole-Oreillons- Rubéole													
	Papillomavirus humain (HPV)													
	Grippe													Tous les ans
	Zona													



Chez les nourrissons nés à partir du 1^{er} janvier 2018, les vaccinations contre la diphtérie, la poliomyélite, le tétanos, l'Haemophilus b, l'hépatite B, la coqueluche, la rougeole, les oreillons, la rubéole, le pneumocoque et le méningocoque sont obligatoires.

Qu'est-ce que ça veut dire « être à jour »?

« Être à jour » c'est avoir reçu les vaccins nécessaires en fonction de son âge et avec le bon nombre d'injections pour être protégé.

Si mes vaccins ne sont pas « à jour »?

Il n'est pas nécessaire de tout recommencer, il suffit de reprendre la vaccination au stade où elle a été interrompue. On parle de « rattrapage ».

Pour en savoir plus



Le site de référence qui répond à vos questions

BCG (Tuberculose)

La vaccination contre la tuberculose est recommandée à partir de 1 mois et jusqu'à l'âge de 15 ans chez certains enfants exposés à un risque élevé de tuberculose.

Diphtérie-Tétanos-Poliomyélite

Les rappels de l'adulte sont recommandés à âges fixes soit 25, 45, 65 ans et ensuite tous les dix ans.

Coqueluche

Le rappel coqueluche se fait à 25 ans. Les futurs parents sont particulièrement concernés, car la vaccination protège les nourrissons de moins de 6 mois dont la vaccination n'est pas complète.

Hépatite B

Si la vaccination n'a pas été effectuée au cours de la première année de vie, elle peut être réalisée jusqu'à 15 ans inclus. À partir de 16 ans, elle est recommandée uniquement chez les personnes exposées au risque d'hépatite B.

Pneumocoque

Au-delà de 24 mois, cette vaccination est recommandée dans des situations particulières.

Méningocoque C

À partir de l'âge de 12 mois et jusqu'à l'âge de 24 ans inclus, une dose unique est recommandée pour ceux qui ne sont pas déjà vaccinés.

Rougeole-Oreillons-Rubéole

Pour les personnes nées à partir de 1980, être à jour signifie avoir eu deux doses de vaccin.

Papillomavirus humain (HPV)

La vaccination est recommandée chez les jeunes filles âgées de 11 à 14 ans avec un rattrapage jusqu'à 19 ans inclus. La vaccination est proposée aux hommes ayant des relations sexuelles avec des hommes (HSH) jusqu'à l'âge de 26 ans.

Grippe

La vaccination est recommandée chaque année pour les personnes à risque y compris les enfants à partir de 6 mois, les femmes enceintes et pour toutes les personnes âgées de 65 ans et plus.

Zona

La vaccination est recommandée chez les personnes âgées de 65 à 74 ans inclus.

Une question? Un conseil? Parlez-en à votre médecin, votre sage-femme ou votre pharmacien.





VACCINATION PRACTICES DURING THE FIRST YEAR IN CHILDREN BORN TO MOTHERS WITH INFLAMMATORY BOWEL DISEASE EXPOSED TO ANTI TNFα DURING PREGNANCY. DESCRIPTIVE ANALYSIS FROM THE FRENCH NATIONAL HEALTH INSURANCE DATABASE M. Luu¹; et al. ¹Clinical Investigation Center - Plurithematic, CHU DIJON, DIJON, France

Background:

- An increasing proportion of children born to mothers with IBD are being *exposed in utero to* anti - $TNF\alpha$.
- European and North American recommendations: postponing live vaccines after 6 months.

Aim: to assess appropriateness of physicians' vaccine practices during the first year of life in light of the current recommendations.

Methods:

- Data from children born to mothers with IBD between 2013 and 2014 were retrospectively collected from the French Health Insurance Database.
- We considered <u>all vaccines recommended</u> to be administered before or at 1 year old (Bacillus Calmette-Guerin for tuberculosis (BCG), diphteria-tetanos-poliomyelitis, pertussis, Haemophilus Influenzae B, Hepatitis B virus, pneumococcus, meningococcus C and measles-mumps-rubella).

VACCINATION PRACTICES DURING THE FIRST YEAR IN CHILDREN BORN TO MOTHERS WITH INFLAMMATORY BOWEL DISEASE EXPOSED TO ANTITNF α DURING PREGNANCY. DESCRIPTIVE ANALYSIS FROM THE FRENCH NATIONAL HEALTH INSURANCE DATABASE

M. Luu¹; et al. ¹Clinical Investigation Center - Plurithematic, CHU DIJON, DIJON, France

Results:

- **4741** children analyzed, 670 (<u>14.1%</u>) were exposed in utero to anti-TNFα, (IFX 53 % & ADA 47%, 16% thiopurins). NB: 61.5% Exposition during the last trimester.
- Children exposed to anti-TNF agents were **less likely** than non-exposed **to receive BCG** (88/670 (13.1%) vs. 780/4701 19.2%, p<0.05) and received it **later** (128 days vs. 71, p<0.001).
- In the exposed group, BCG vaccination was mostly done before 6 Mo of age (64/88, 73%).
- No case of disseminated BCG infection was observed during the 1st year in the 88 children. \rightarrow maintenance of anti-TNF α during the last pregnancy trimester had no impact on the time of BCG vaccination.

- Vaccine coverage was similar and >85% for both groups for the other recommended vaccines before 6 months.

largest cohort to date of children born to IBD mothers exposed to antiTNF α during pregnancy.

physicians consider postponing live vaccine injections in their practice, but regardless of the current recommendations, and duration of in utero exposure.

Our report, on the biggest number of children receiving BCG vaccination during their first 6 months of life after in-utero exposure, do not suggest any increased risk for disseminated BCG infection.

In children at risk for tuberculosis infection, the <u>decision to administer</u>

<u>BCG vaccine early in life</u> may be considered assuming further studies confirm our findings.

exposed g CONTIFM OUR TINGINGS.

children vaccine coverage (%) 13.1 96.9 96.9 96.2 90 96.7 62.7 77.9

Figure 1. Moment of first injection (mean±SD) of vaccines in children before 1 year old

BCG = Bacillus Calmette-Guerin (tuberculosis); DTP = dipheteria-tetanos-poliomyelitis; HiB = Haemophilus Influenzae B; HBV = Hepatitis Virus B; pneumo = pneumococcus; meningo C, = meningococcus C; MMR = measles-mumps-rubella; NS = non significant.

non-exp vaccina vaccine

VACCINE-PREVENTABLE DISEASES IN HOSPITALIZED PATIENTS WITH INFLAMMATORY BOWEL DISEASE: A NATIONWIDE COHORT ANALYSIS

• Author: Daniela Guerrero Vinsard¹, Dorothy B. Wakefield², Haleh Vaziri³, Raffi Karagozian^{4,5}

¹Internal Medicine, University of Connecticut, United States

Background: Inflammatory bowel disease (IBD) entails a **higher risk of life-threatening infections**, including those that could be prevented with immunizations.

Vaccination strategies exist for patients with IBD but there are **contradictions regarding risks and benefits** of vaccinations.

Aim: To determine the need for more rigorous vaccination strategies in IBD patients and investigate the most prevalent diseases nationwide for which IBD patients are hospitalized, that could be potentially prevented with immunizations.

Methods: <u>Population-based cohort study</u> using the **2012 USA National Inpatient Sample** (NIS) ICD-9 codes

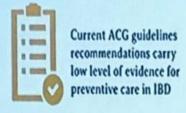
-1-frequency of IBD patients being admitted to the hospital with a vaccine-preventable disease such as: pneumococcal pneumonia, herpes zoster, varicella zoster, meningococcal meningitis, influenza, tetanus, diphtheria, pertussis, hepatitis A, hepatitis B, HPV.

Frequencies and demographics were determined and compared amongst IBD and non-IBD patients using chi-square analysis.

VACCINE-PREVENTABLE DISEASES IN HOSPITALIZED PATIENTS WITH IBD: A NATIONWIDE COHORT ANALYSIS

Population-based cohort study of patients with IBD who were hospitalized with vaccine preventable disease







Patients with IBD are at increased risk for vaccine-preventable illness



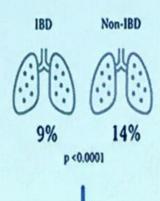
7180 patients with IBD were admitted with vaccine preventable diseases (VPD) from 2012-2015

PREVALANCE OF VPD IN IBD PATIENTS VERSUS NON IBD PATIENTS



Both CD and UC, are associated with higher odds of hospitalizations with HZV in patients 18-65 years old.

PNEUMOCOCCAL .P



IBD was associated with less hospitalizations due to pneumococcal pneumonia and influenza.

INFLUENZA



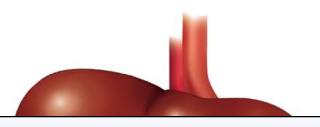
IBD patients are associated with lesser odds of hospitalizations with influenza infection

OTHERS



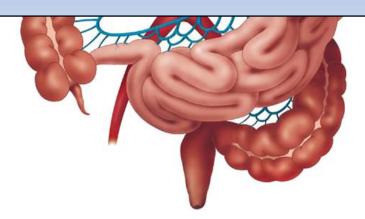
There was no difference on hospital admissions due to other VPD between IBD and non-IBD patients.

ACG 2017: Adults with IBD over the age of 50 should consider vaccination against HZV including certain subgroups of immunosuppressed patients. Strong recommendation, low level of evidence.



Epidemiology Basic and translational science Clinical science New drugs / combinations



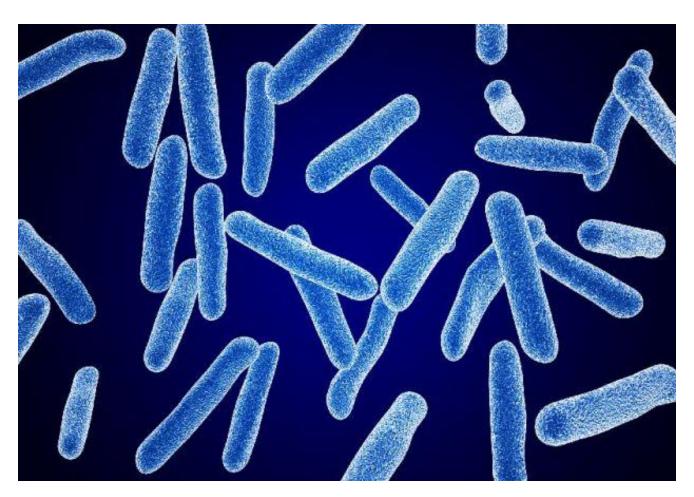








Faecalibacterim prausnitzii: the peace-keeping bacteria in the gut



FAECALIBACTERIUM PRAUSNITZII PRODUCES BUTYRATE TO MAINTAIN TH17/TREG BALANCE AND TO AMELIORATE COLORECTAL COLITIS BY INHIBITING HISTONE DEACETYLASE 1

M. Zhang¹; L. Zhou¹; C. Yu¹. ¹Department of Gastroenterology, Nanjing Drum Tower Hospital, Nanjing, China

Background:

- IBD-associated dysbiosis is characterized by a loss of *F. prausnitzii*, whose supernatant exerts an anti-inflammatory effect.
- However, the anti-inflammatory substances in *F. prausnitzii* supernatant and the mechanism in ameliorating colitis in IBD have not yet been fully investigated.

Methods:

- Experimental colitis models were induced and evaluated by clinical examination and histopathology.
- Levels of cytokines and ratio of T cells were detected by enzyme-linked immunosorbent assay and flow cytometry analysis, respectively.
- F. prausnitzii supernatant was separated by microporous resins.
- After extraction, the substances in supernatant were identified by gas chromatographymass spectrometer. T cell differentiation assay was conducted *in vitro*. Changes in signaling pathways were examined by western blot, immunohistochemistry and immunofluorescent staining.

FAECALIBACTERIUM PRAUSNITZII PRODUCES BUTYRATE TO MAINTAIN TH17/TREG BALANCE AND TO AMELIORATE COLORECTAL COLITIS BY INHIBITING HISTONE DEACETYLASE 1

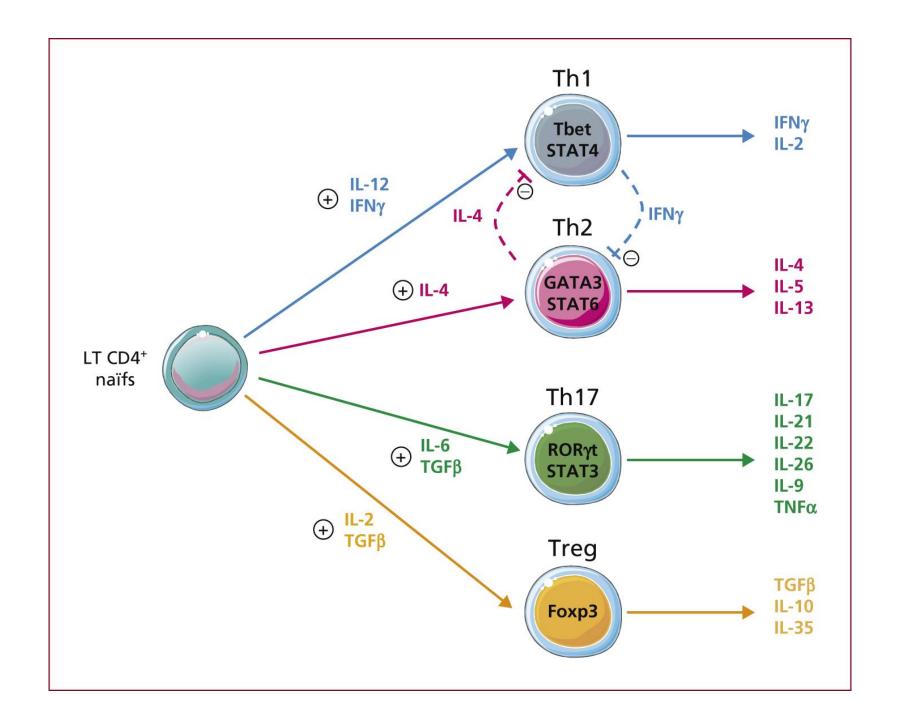
M. Zhang¹; L. Zhou¹; C. Yu¹. ¹Department of Gastroenterology, Nanjing Drum Tower Hospital, Nanjing, China

Results:

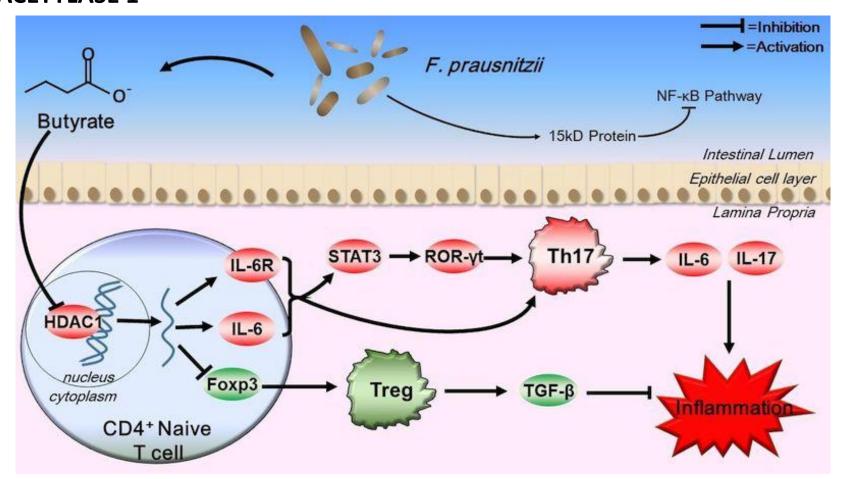
- We found that the supernatant of *F. prausnitzii* could regulate T helper 17 cells (Th17)/ regulatory T cells (Treg) differentiation.
- Then, we identified that butyrate produced by F. prausnitzii that played the anti-inflammatory effects by inhibiting interleukin (IL)-6/signal transducer and activator of transcription 3 (STAT3)/IL-17 pathway and promoting forkhead box protein P3 (Foxp3). Finally, we demonstrated the target of butyrate was histone deacetylase 1 (HDAC1).

Conclusions:

- F. prausnitzii could be an option for further investigation for IBD treatment.
- Targeting the butyrate-HDAC1-T cell axis offers an effective novel approach in the treatment of inflammatory disease.



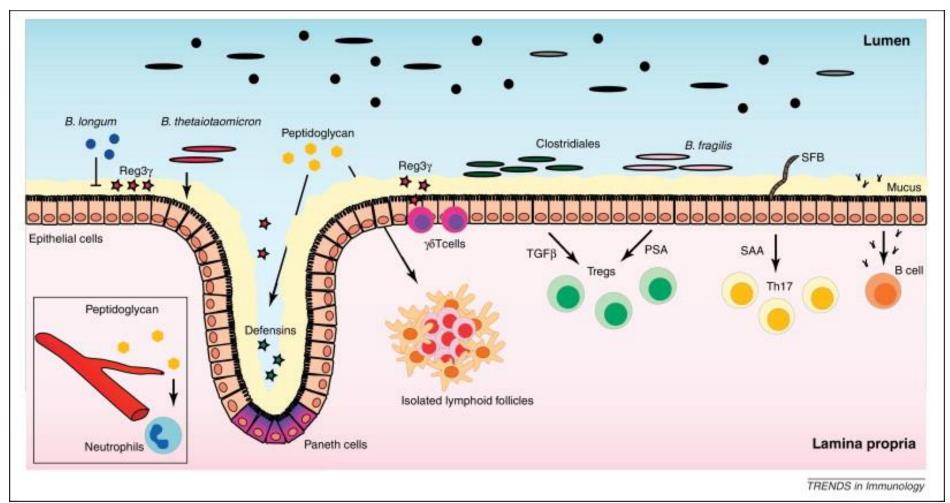
FAECALIBACTERIUM PRAUSNITZII PRODUCES BUTYRATE TO MAINTAIN TH17/TREG BALANCE AND TO AMELIORATE COLORECTAL COLITIS BY INHIBITING HISTONE DEACETYLASE 1



Schematic model of *F. prausnitzii*-derived butyrate's anti-inflammatory effects on colitis in IBD. *F. prausnitzii*-derived butyrate inhibits HDAC1 activity. The inhibition of HDAC1 leads to the down-regulation of IL-6/STAT3/IL-17 pathway and induction of Foxp3 expression, thus reducing inflammatory Th17 cell activation and promoting the differentiation of anti-inflammatory Treg cells. The change of Th17/Treg cell ratio affects cytokines, in turn ameliorated colitis lesions in IBD.

Defensins





ORAL DELIVERY OF HUMAN BETA-DEFENSIN 2 IS REVERSIBLY INCREASING MICROBIOME DIVERSITY AND IS EFFECTIVE IN THE TREATMENT OF EXPERIMENTAL COLITIS.

L. Koeninger¹; ... J. Wehkamp¹ University Hospital Tuebingen, Germany.

Background:

- A decreased complexity and diversity of the gut microbiota are common in IBD.
- **Defensins are anti-microbial peptides** (innate immunity, endogenous antibiotics)
- Aim: to test the human host defence endogenous antimicrobial defensin in terms of (A) microbiome modulation and (B) therapeutic efficacy in experimental colitis.

Methods:

- Mice were treated orally with a dose of 1.2 mg/kg hBD2 per day for one week.
- Alterations in bacterial composition were analysed by next-generation sequencing on day 0, day 7 and day 14.
- Based on these results we tested the bacteriocidal and static effect of hBD2 on different commensal species using MIC in vitro.
- In a second approach, we tested oral administration of hBD2 in an experimental induced DSS colitis mouse model, compared to the standard therapy with prednisolone.

ORAL DELIVERY OF HUMAN BETA-DEFENSIN 2 IS REVERSIBLY INCREASING MICROBIOME DIVERSITY AND IS EFFECTIVE IN THE TREATMENT OF EXPERIMENTAL COLITIS.

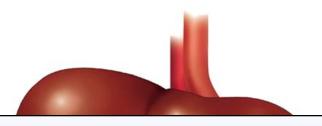
L. Koeninger¹; ... J. Wehkamp¹ University Hospital Tuebingen, Germany.

Results:

- Analysing the gut microbiome, a significant increase of diversity was observed during hBD2 treatment.
- Of note, these changes shift backwards after stopping the application.
- Testing the same dose in an experimental colitis model, the treatment resulted in a significantly lower weight loss (p<0.05) and a strongly improved disease activity index (p<0.001).
- Furthermore hBD2 reduced mucosal damage (p<0.001).
- In this setting, the oral administration of hBD2 significantly improved the health in DSS colitis model.

Conclusion and Outlook:

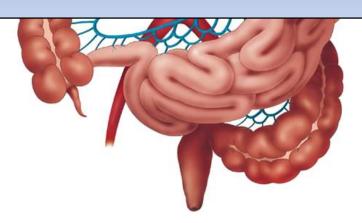
- It seems that this effect is dependent on the ability of hBD2 to modulate the microbiome towards homeostasis.
- HBD2 shows promising effect in experimental DSS colitis model.
- The results and the better effect than prednisolone support a therapeutic application as a drug for IBD.



Epidemiology Basic and translational science Clinical science New drugs / combinations













IMPACT OF DRUG LEVELS, ANTI-DRUG ANTIBODIES AND $\alpha 4\beta 7$ TARGET OCCUPNACY ON THE RESPONSE TO VEDOLIZUMAB THERAPY IN PATIENTS WITH INFLMMATORY BOWEL DISEASE

Bella UNGAR et al., Israel

Aim: To explore vedolizumab's clinical outcomes in relation to drug concentrations, antivedolizumab antibodies (AVA) and $\alpha 4\beta 7$ integrin receptor-occupancy.

Methods: Vedolizumab/AVA levels were measured in 106 prospectively-followed inflammatory bowel disease (IBD) patients receiving vedolizumab induction and maintenance therapy. Fluorescent conjugated-vedolizumab was used to investigate $\alpha 4\beta 7$ occupancy on effectormemory T-cells in peripheral blood (PB) and intestinal lamina propria (LP) by FACS analysis.

What we know from Post hoc analyses from Gemini trials & real life cohort?:

- lower W2 level associated with LOR
- maximal receptor saturation , already with low dose (2 mg/KG 300 mg = 4-5 mg/Kg)

Results – clinical outcome

106 IBD (67 CD, 39 UC)

Clinical remission by week 14:50/106 (48%)

Primary non response: 9 (8.4%)

Loss of Respojnse during maintenance: 17 (18%)

Interval shortening

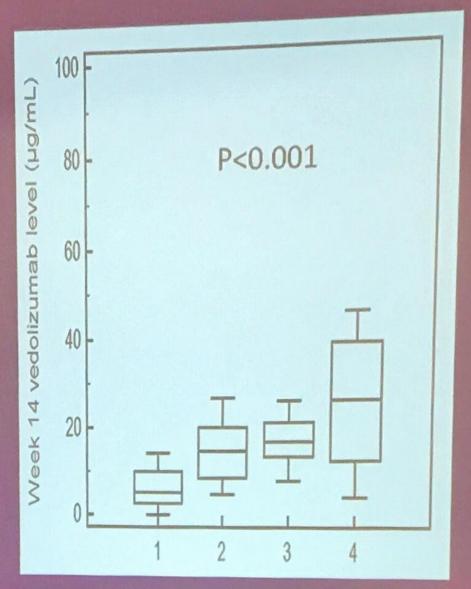
12 (11.3%) during induction et 11 patients (11.5%) during maintenance



Results: pharmacokinetics - induction

Baseline albumin: only factor correlated with vedolizumab levels

Week 2 (p=0.009, rho=0.3) Week 6 (p=0.002, rho=0.4) Week 14 (p<0.001, rho=0.6)

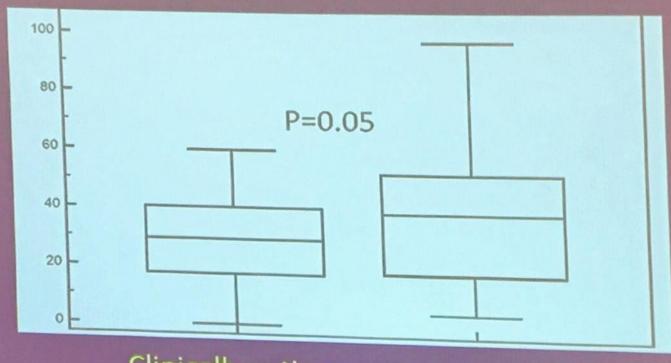


Quartiles of baseline albumin levels

Results: Induction period pharmacokinetics

Of all time-points examined, only week 6 levels associated with week 6 clinical remission (median 40.2μg/mL, 29.7μg/mL)

Vedolizumab Level (µ/ml)



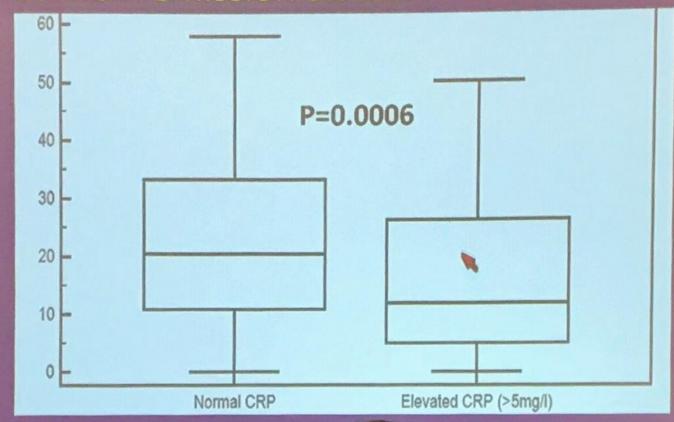
Clinically active at week 6

Clinical remission



Results: Maintenance period pharmacokinetics

✓ Drug levels associated with CRP normalization, but not with remission status.



Vedolizumab level (µ/ml)

Results maintenance period pharmacokinetics

Vedolizumab levels before interval – shortening (n=11)

→ similar to levels in patients not requiring this intervention (n= 47, median 27.8 mcg/ml in interval shortened and 15.4 mcg/ml in not shortened p=0.09

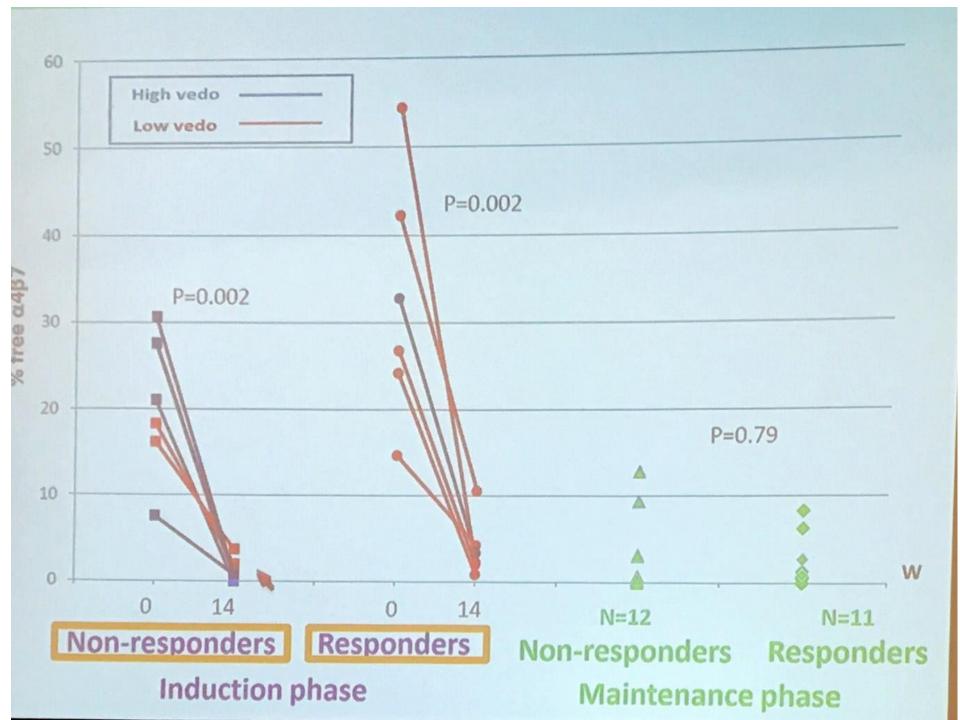
Week 6 level among responders not different than levels in patients with subsequent low (median 35.7, n=42 vs. 31.5, n=17, p0.98)

Results

Immunogenicity assessed in 40 patients during induction / maintenance

Indution: antibodies aagainst Vedolizumab (AVA) 17% And 2.5 % with negative drug level

Maintenance; AVA rate 3%



Conclusion /Bella et al.

Baseline *albumin* – only parameter associated with vedolizumab induction level.

Week 6 levels are higher in week 6 responders

There was no association between clinical outcomes and drug level

associated with CRP normalization, especially during maintenance

Low incidence of Anit vedolizumab antibodies & Imited clinical impact.

BIOMARKER CORRELATION WITH ENDOSCOPIC OUTCOMES IN PATIENTS WITH CROHN'S DISEASE: DATA FROM CALM

W. Reinisch¹; et al. ¹Medical University of Vienna, Vienna, Austria

Background:

- Management of Crohn's disease (CD) is moving towards the therapeutic goal of mucosal healing using biomarkers of inflammation, faecal calprotectin (FC) and C-reactive protein (CRP), to optimize therapy.
- CALM demonstrated superior endoscopic outcomes in patients whose treatment
 was escalated based on a tight control algorithm using symptoms and biomarkers
 than in patients managed conventionally,¹ but the optimal biomarker cut-offs to
 predict mucosal healing have not been established.
- In this analysis from CALM, association of endoscopic outcomes with FC and CRP cut-offs was investigated.

Methods:

- Adult patients with CD (N=244) were assessed for association of mucosal healing (CD Endoscopic Index of Severity [CDEIS] <4) and no deep ulcers (primary endpoint in CALM) and endoscopic response (CDEIS decrease >5 from baseline [BL]) with levels of FC and CRP at 48 weeks using Chi-square test.
- Analysed cut-offs for FC (<250 µg/g or ≥250 µg/g) and CRP (<5 mg/L or ≥5 mg/L)
 at 48 weeks were based on criteria for treatment escalation in the tight control
 group

Table. Proportion of patients meeting endoscopic endpoints by biomarker status at 48 weeks.

Biomarker Cut-off	1083877	ng and No Deep , n (%)	P value	Endoscopic Response, n (%)		P value	
	Yes	No	0.500.00105003501	Yes	No		
CRP	3 <mark>4.</mark> 26.111		₹# 1				
<5 mg/L, n=98	65 (66.3)	33 (33.7)	- <0.001 -	73 (74.5)	25 (25.5)	0.001	
≥5 mg/L, n=69	21 (30.4)	48 (69.6)		30 (43.5)	39 (56.5)	- <0.001	
FC							
<250 μg/g, n=97	72 (74.2)	25 (25.8)	um uso	75 (77.3)	22 (22.7)	- <0.001	
≥250 µg/g, n=59	8 (13.6)	51 (86.4)	<0.001	21 (35.6)	38 (64.4)		
CRP and FC							
<5 mg/L <250 μg/g, n=70	55 (78.6)	15 (21.4)		56 (80.0)	14 (20.0)		
<5 mg/L ≥250 μg/g, n=18	3 (16.7)	15 (83.3)	- <0.001	9 (50.0)	9 (50.0)	_	
≥5 mg/L <250 µg/g, n=25	16 (64.0)	9 (36.0)		17 (68.0)	8 (32.0)	- <0.001	
≥5 mg/L ≥250 µg/g, n=41	5 (12.2)	36 (87.8)		12 (29.3)	29 (70.7)		

Table. Proportion of patients meeting endoscopic endpoints by biomarker status at 48 weeks.

Biomarker	Mucosal Healing and No Deep		Endoscopic Response,	
Cut off	History n (9/1	Dunling	n (9/)	Dundye

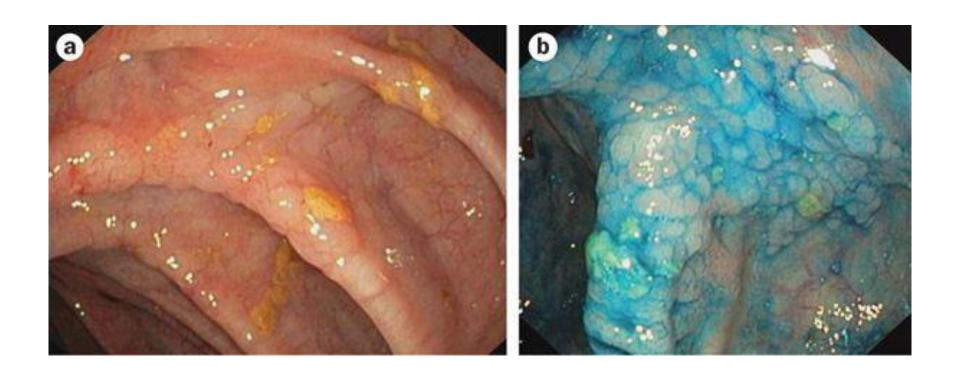
CONCLUSIONS

Correlation of biomarker cut-offs with endoscopic outcomes is an important finding for future management of CD.

Additional studies are needed to further define the biomarker cut-offs.

≥250 µg/g, n=18			- <0.001			- <0.00
≥5 mg/L <250 µg/g, n=25	16 (64.0)	9 (36.0)	V0.001	17 (68.0)	8 (32.0)	VO.00 .
≥5 mg/L ≥250 µg/g, n=41	5 (12.2)	36 (87.8)		12 (29.3)	29 (70.7)	

Dysplasia detection in UC



META-ANALYSIS OF RANDOMIZED AND NON-RANDOMIZED CONTROL TRIALS OF CHROMOENDOSCOPY FOR THE SURVEILLANCE OF COLORECTAL CANCER IN INFLAMMATORY BOWEL DISEASE

J. D. Feuerstein¹; et al. ¹Beth Israel Deaconess Medical Center, Brookline, Massachusetts, United States

Background and Aims:

- UC pts have an increased risk of developing colorectal cancer (CRC).
- Historically, screening for CRC involved use of white light endoscopy with at least 32 4-quadrant biopsies every 10cm throughout the colon.
- Recently, SCENIC guidelines recommended the use of chromoendoscopy to further enhance the detection of dysplasia.
- Aim: to compare efficacy of standard white light endoscopy (SDWLE) or high definition white light endoscopy (HDWLE) versus dye-based chromoendoscopy with methylene blue or indigo carmine

Methods:

- systematic review of the literature in PubMed, EMBASE, and Web of Sciences.
- Randomized control trials (RCT) and observational studies that evaluated SDWLE or HDWLE compared to chromoendoscopy were included.
- Studies without a comparator arm or in whom only one group served as internal crossover controls were excluded.
- Primary outcome was number of patients in whom dysplasia was identified using a perpatient analysis in RCT and also analyzed separately for non-RCT.

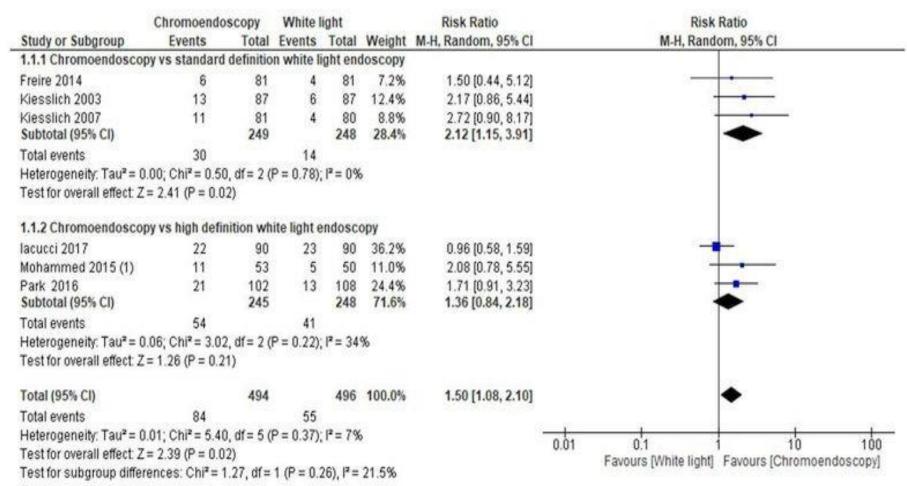
META-ANALYSIS OF RANDOMIZED AND NON-RANDOMIZED CONTROL TRIALS OF CHROMOENDOSCOPY FOR THE SURVEILLANCE OF COLORECTAL CANCER IN INFLAMMATORY BOWEL DISEASE

J. D. Feuerstein¹; et al. ¹Beth Israel Deaconess Medical Center, Brookline, Massachusetts, United States

Results:

- 14,679 studies were identified.
- 3 RCT of SDWLE and 3 RCT of HDWLE were included in the analysis.
- 17% (84/494) of patients were noted to have dysplasia using chromoendoscopy compared to 11% (55/496) of patients with white light endoscopy (RR 1.50, 95% CI 1.08-2.18).
- When analyzed separately, chromoendoscopy was more effective at identifying dysplasia compared to SDWLE (RR 2.12, 95% CI 1.15-3.91) but not when compared to HDWLE chromoendoscopy (RR 1.36, 95% CI 0.84-2.18) (Figure 1).
- The quality of evidence was moderate quality due to concerns for imprecision.
- There were 4 non-RCT of SDWLE and 5 non-RCT of HDWLE compared to chromoendoscopy.
- In the non-RCT dysplasia was identified in 16% (114/698) of patients with chromoendoscopy compared to 6% (62/1069) of patients with white light endoscopy (RR 3.41, 95% CI 2.13-5.47).
- Chromoendoscopy was more effective than SDWLE for identification of dysplasia (RR 3.52, 95% CI 1.38-8.99) and also more effective than HDWLE (RR 3.15, 95% CI 1.62-6.13) (Figure 2). The quality of the evidence was very low given very serious risk for bias and serious imprecision.

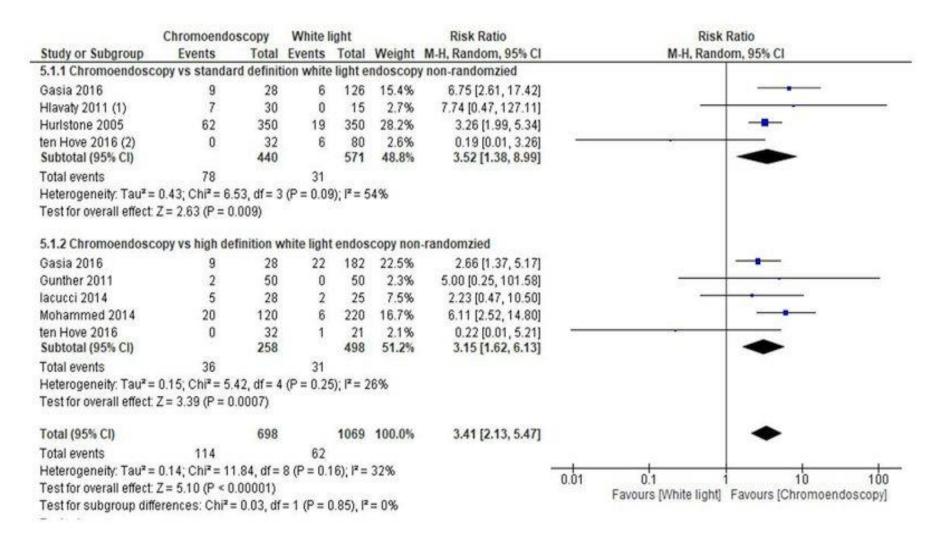
randomized control trials chromoendoscopy vs white light endoscopy



Footnotes

(1) abstract only

Non-randomized control trials chromoendoscopy vs white light endoscopy



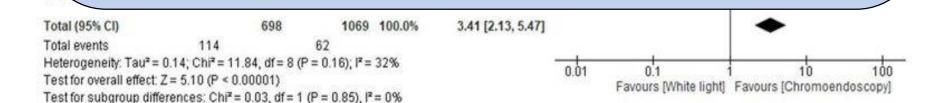
Non-randomized control trials chromoendoscopy vs white light endoscopy

CONCLUSIONS:

non-RCT demonstrate a benefit of chromoendoscopy over SDWLE and HDWLE

RCT only show a small benefit of chromoendoscopy over SDWLE, but not over HDWLE.

Further RCT are needed comparing HDWLE to chromoendoscopy to determine the best method to identify dysplasia in patients with UC.



Gastrointestinal infection in IBD: how often is it the case?



J. Limsrivilai¹; et al. University of Michigan, Ann Arbor, Michigan, United States

Background/Aims:

- GI infections (e.g. Clostridium difficile [CDI]) can worsen IBD
- By conventional methods, only 10% of symptomatic IBD patients have detectable GI infections.
- Using the BioFire FilmArray GI PCR panel, a stool test capable of detecting 22
 enteropathogenic organisms, we investigated the prevalence of GI infections in
 symptomatic flares of IBD vs. inactive IBD and healthy controls with the aim to
 determine the prevalence and impact of detected infectious agents in IBD patients.

Methods:

We collected stool samples from 5 patient cohorts:

- Active Crohn's disease (CD, n = 112),
- Inactive CD (n = 53),
- Active ulcerative colitis (UC, n = 128),
- Inactive UC (n =39), and
- Healthy student Controls (HC, n = 52).
- The prevalence of positive stool tests was compared in patients with active inflammation (as defined by biomarkers, endoscopy, and imaging) and those without inflammation. In active IBD patients, clinical characteristics, medication use, and disease course were compared between those with positive and negative tests.

J. Limsrivilai¹; et al. University of Michigan, Ann Arbor, Michigan, United States

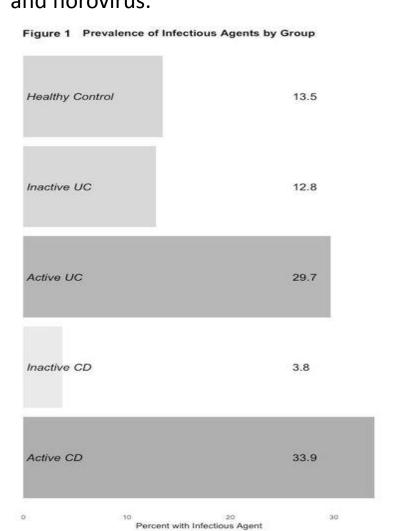
Results:

- Overall, 31.25% of active IBD subjects had an infectious agent detected
- The prevalence of detectable infectious organisms by group (Figure 1) was 33.9% in the CD-active group, 3.8% in CD-inactive, 28.9% in UC-active, 12.8% in UC-inactive (12.8%) and 13.4% in HC.
- Both CD-active and UC-active had significantly higher prevalence rates than inactive IBD or healthy controls.
- This increased to 50% in those active IBD patients with an acute onset (<7 days) of symptoms.
- The prevalence of infectious agents was 9-fold higher in active vs. inactive CD (p = 0.0001) and 2-fold higher in active vs inactive UC (p = 0.04).
- presence of infectious agents was significantly associated with current use of vedolizumab with an odds ratio of 3.9 (95% CI: 1.7-9.2), and tacrolimus (OR 31.6, 4.0-247.2), but not with the use of anti-TNFs, ustekinumab, or thiopurines (Table).
- CDI was the most common infection detected, but multiple coliform bacteria and seasonal norovirus outbreaks were also seen (Figure 2).

J. Limsrivilai¹; et al. University of Michigan, Ann Arbor, Michigan, United States

Medications Used in Subjects with Active IBD	Use in Biofire Positive (N=75)	Use in Biofire Negative (N=166)	p value	Odds Ratio
Corticosteroids	28/75 (37.3%)	61/166 (36.8%)	0.93	
Immunomodulato rs	26/75 (34.7%)	51/166 (30.7%)	0.54	
Tacrolimus	9/75 (12%)	1/166 (0.6%)	<0.001	31.6 (4.0-247.2)
Tofacitinib	0/75 (0%)	2/166 (1.2%)	0.99	
Anti-TNF	29/75 (38.7%)	49/166 (29.5%)	0.16	
Vedolizumab	15/74 (20.3%)	10/166 (6.0%)	0.001	3.9 (1.7-9.2)
Ustekinumab	0/75 (0%)	2/166 (1.2%)	0.99	

J. Limsrivilai¹; et al. University of Michigan, Ann Arbor, Michigan, United States **Figure 2.** Prevalence of Each Detected Infectious Agent in All Enrolled Subjects. Clostridium difficile was the most common infection, followed by several coliforms and norovirus.



Clostridium difficile toxin A/B	9.8
Enteropathogenic E. coli (EPEC)	4.7
Norovirus GI/GII	3.8
Enteroaggregative E. coli (EAEC)	2.7
Salmonella	1.1
Campylobacter	1.1
Yersinia enterocolitica	0.7
Sapovirus	0.7
Enterotoxigenic E. coli (ETEC) lt/st	0.4
Cryptosporidium	0.4
Astrovirus	0.4
Vibrio cholerae	0.2
Vibrio	0.2
Shiga-like toxin-producing E. coli (STEC) stx1/stx2	0.2
Rotavirus A	0.2
Adenovirus F 40/41	0.2
Shigella/Enteroinvasive E. coli (EIEC)	0
Plesiomonas shigelloides	0
Giardia lamblia	0
Entamoeba histolytica	0
E. coli O157	0
Cyclospora cayetanensis	0

Percent with Infectious Agent

7.5

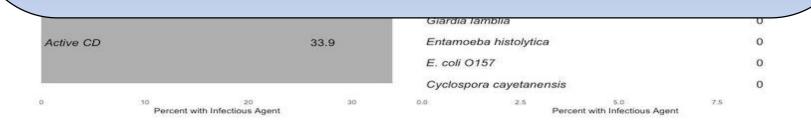
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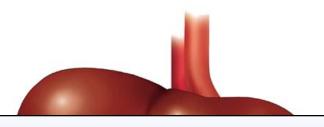
CONCLUSIONS:

Active CD and UC have a higher rate of detectable infectious agents than patients with quiescent disease vedolizumab and tacrolimus are associated with increased risk.

These infections (other than C. difficile infection [CDI]) appear to be mostly transient, and treatable with fluids and supportive care.

Reflexive use of steroids for symptomatic flares could be harmful in the many IBD flares associated with an intestinal infectious agent.

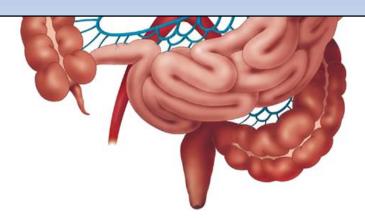




Epidemiology Basic and translational science Clinical science New drugs / combinations













COMBINATION THERAPY OF CYCLOSPORINE AND VEDOLIZUMAB IS EFFECTIVE AND SAFE FOR SEVERE, STEROID-RESISTANT ULCERATIVE COLITIS PATIENTS: A PROSPECTIVE STUDY

D. Tarabar¹; et al. ¹Military Medical Academy, Belgrade, Serbia

Background:

- Concurrent use of calcineurin inhibitors to VDZ was not studied in the original clinical trials,
- Aim: to describe the efficacy and safety of cyclosporine in conjunction with VDZ for severe, steroid-resistant UC.

Methods:

- prospective study of 17 UC patients treated with cyclosporine in conjunction with VDZ
- UC patients, not responding to IV steroids for 3 days were treated with IV cyclosporine at doses of 2 mg/kg titrated to goal trough level of 300-400.
- At day 8 after IV cyclosporine was started (defined as week 0),
- those who responded were given vedolizumab 300 mg IV.
- After vedolizumab was administered, cyclosporine was continued orally at double the IV dose and discontinued after 8 weeks of cyclosporine use.
- Vedolizumab was dosed 300 mg at weeks 2 and 6, followed by 300 mg IV every 8 weeks.
- Patients completed initial follow-up including colonoscopy at week 10.
- Lichtiger score (at admission and week 0), the Mayo endoscopic subscore, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and calprotectin levels were followed at baseline and at various pre-defined times of follow-up.

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D. Tarabar¹; et al. ¹Military Medical Academy, Belgrade, Serbia

Results:

- 17 pts (mean age 40 (20-67 yrs)); mean disease duration 4.9 ± 4 yrs with severe, steroid-resistant UC were treated with cyclosporine.
- Two patients did not respond to IV cyclosporine and were referred to surgery.
- Fifteen patients (9/15 male) responded to IV cyclosporine (median cyclosporine dose 200 mg (100-300) IV and 400 mg (200-600) oral.
- At admission, patients' median Lichtiger score was 12 and the Mayo score was
 3. Average level of CRP was 21.8 mg/L, ESR was 51.2 mm/hr and calprotectin was 1947 ug/g.
- Patients' mean Lichtiger score decreased to 5 at week 0 and 10/15 patients had a Mayo score of ≤1 at week 10.
- Average CRP levels decreased to 15.9, 5.8 and 3.8 mg/L at weeks 0, 2 and 6, respectively.
- Average FC levels were 1024 and 808 ug/g weeks 2 and 6, respectively.
- At week 20, 14/15 patients are stable and continue to be in remission, with no adverse effects reported from either cyclosporine or vedolizumab to date.
- One patient was referred to surgery due to recurrence of symptoms.

COMBINATION THERAPY OF CYCLOSPORINE AND VEDOLIZUMAB IS EFFECTIVE AND SAFE FOR SEVERE, STEROID-RESISTANT ULCERATIVE COLITIS PATIENTS: A PROSPECTIVE STUDY

D. Tarabar¹; et al. ¹Military Medical Academy, Belgrade, Serbia

Res

St

- This is the first prospective study of cyclosporine and vedolizumab in steroid-refractory severe UC patients.
- We demonstrate significant effectiveness and safety of this treatment on week 10 after vedolizumab was started.
- Further trials are warranted.
- Average FC levels were 1024 and 808 ug/g weeks 2 and 6, respectively.
- At week 20, 14/15 patients are stable and continue to be in remission, with no adverse effects reported from either cyclosporine or vedolizumab to date.
- One patient was referred to surgery due to recurrence of symptoms.

Anti-IL23 in UC

POTENTIAL KEY EVENTS IN 2018



PHASE 3 INITIATIONS

Baricitinib for psoriatic arthritis
Mirikizumab for psoriasis
Mirikizumab for ulcerative colitis
Dulaglutide alternate doses for type 2 diabetes
Empagliflozin for chronic kidney disease 1

PHASE 3 DATA INTERNAL READOUTS

Flortaucipir (18F AV-1451) tau imaging agent
Tanezumab for osteoarthritis pain (dosing study) ²
Tradjenta CAROLINA CV outcomes study ¹
Trulicity REWIND CV outcomes study
Ultra rapid insulin for type 1 and type 2 diabetes
Ramucirumab RANGE for 2L bladder cancer (final analysis)
Ramucirumab RELAY for 1L EGFR NSCLC cancer (PFS readout)

PHASE 3 DATA EXTERNAL DISCLOSURES

Galcanezumab for cluster headache
Ixekizumab for axial spondlyoarthritis
Empagliflozin for type 1 diabetes ¹
Tradjenta CARMELINA CV outcomes study ¹
Ramucirumab REACH 2 in 2L high AFP hepatocellular cancer

REGULATORY SUBMISSIONS

Lasmiditan for acute migraine
Empagliflozin + linagliptin + metformin XR (US)
Nasal glucagon for hypoglycemia

REGULATORY ACTIONS

Baricitinib for rheumatoid arthritis (US)
Galcanezumab for migraine prevention
Ixekizumab for psoriatic arthritis (EU)
Abemaciclib + fulvestrant for 2L breast cancer (MONARCH 2) (EU/J)
Abemaciclib + Als for 1L breast cancer (MONARCH 3) (US/EU/J)
Alimta sNDA to include KEYNOTE-021G data (US) ³
Fruquintinib for 3L metastatic colorectal cancer (China) ⁴

OTHER

Rulings in ongoing Alimta patent litigation:
US IPR Appeal to CAFC
US alternative salt forms
Japan (Nipro)
Germany

Not for promotional use

¹ in collaboration with Boehringer Ingelheim

² in collaboration with Pfizer

³ in collaboration with Merck

⁴ in collaboration with Hutchison China MediTech

EFFICACY AND SAFETY OF ANTI-INTERLEUKIN-23 THERAPY WITH MIRIKIZUMAB (LY3074828) IN PATIENTS WITH MODERATE-TO-SEVERE ULCERATIVE COLITIS IN A PHASE 2 STUDY

- W. J. Sandborn¹; M. Ferrante²; B. R. Bhandari³; G. R. D'Haens⁴; E. Berliba⁵; B. G. Feagan⁶; J. Laskowski⁷; S. Friedrich⁷; M. Durante⁷; J. Tuttle⁷
- 882 Tuesday, June 5, 2018 | 10:15 AM 10:30 AM | Location: 146A (Washington Convention Center) **Session** Clinical Science Late-Breaking Abstract Plenary

Late-Breaking Abstract Session

Background and Objectives:

- IL-23 pathway blockade has been demonstrated to have efficacy in Crohn's disease.
- A Phase 2, multi-center, randomized, double-blind, placebo (pbo)-controlled trial (AMAC, NCT02589665) of mirikizumab (miri), a p19-directed anti-IL-23 antibody, was conducted to evaluate miri's efficacy and safety in patients with moderate-to-severe ulcerative colitis (UC).
- The primary study objective was to evaluate superiority of miri to pbo in inducing clinical remission at wk 12,

Methods:

Patients with moderate-to-severe UC (Mayo score of 6 to 12 with endoscopic subscore ≥2) were randomized at a 1:1:1:1 ratio to receive pbo (N=63), miri 50 mg (N=63) or 200 mg (N=62) with possibility of exposure-based¹ increases (2-12 fold or 1.5-3 fold respectively, to a maximum 600 mg dose), or a fixed miri 600 mg (N=61) intravenously at wks 0, 4, and 8.

EFFICACY AND SAFETY OF ANTI-INTERLEUKIN-23 THERAPY WITH MIRIKIZUMAB (LY3074828) IN PATIENTS WITH MODERATE-TO-SEVERE ULCERATIVE COLITIS IN A PHASE 2 STUDY

Methods:

Eligible patients could receive oral 5-ASA or corticosteroids (≤20 mg/d prednisone equivalent), thiopurines, must have failed at least one conventional therapy for UC, and were either naïve to or had prior exposure to biologics. E

Results:

- Baseline characteristics were similar among treatment groups.
- Most patients (63%) had been either exposed to or failed therapy with a biologic.
- At wk 12, clinical remission rates were greater (p<0.01) in patients treated with miri 200 mg, but not miri 50 mg or miri 600 mg, compared to pbo-treated patients (Table).
- Clinical response rates at Wk 12 were greater (p<0.05) for all miri groups, compared to pbo group.
- Endoscopic healing rates were greater (p<0.05) for the miri 50 and 200 mg groups compared to pbo-treated patients.
- Endoscopic remission rates were similar between all groups. Symptomatic remission rates were greater (p<0.01) for miri 200 and 600 mg groups compared to pbo-treated patients.
- Although miri exposure increased with dose, efficacy did not follow a typical plateauing dose or exposure response.
- There were similar rates of serious adverse events and treatment-emergent adverse events (TEAEs) across the treatment groups.

		T	reatment Gro	ups	
Mean (SD), (unless otherwise indicated)	Placebo (N=63)	Miri 50 mg (N=63)	Miri 200 mg (N=62)	Miri 600 mg (N=61)	Miri All (N=186)
Baseline Chara	cteristics a	t Week 0			
Age, years	42.6 (13.5)	41.8 (14.1)	43.4 (14.7)	42.4 (13.4)	42.5 (14.0)
Male, n (%)	36 (57.1)	38 (60.3)	37 (59.7)	38 (62.3)	113 (60.8)
Weight, kg	74.1 (16.9)	77.0 (17.2)	75.6 (17.3)	73.0 (15.1)	75.2 (16.6)
Concomitant UC therapy, n (%) Corticosteroid 5-ASA Thiopurines	33 (52.4) 47 (74.6) 25 (39.7)	29 (46.0) 41 (65.1) 14 (22.2)	25 (40.3) 56 (90.3) 18 (29.0)	34 (55.7) 39 (63.9) 11 (18.0)	88 (47.3) 136 (73.1) 43 (23.1)
Number previous biologic therapies, n (%) 0 1 2 ≥3	25 (39.7) 17 (27.0) 15 (23.8) 6 (9.5)	27 (42.9) 14 (22.2) 16 (25.4) 6 (9.5)	22 (35.5) 27 (43.5) 7 (11.3) 6 (9.7)	23 (37.7) 15 (24.6) 14 (23.0) 9 (14.8)	72 (38.7) 56 (30.1) 37 (19.9) 21 (11.3)
Modified Mayo score	6.65 (1.18)	6.58 (1.34)	6.39 (1.38)	6.53 (1.26)	Not calculated
V	leek 12				
Overall Induction Dose, mg, mean (min, max)	Not applicable	100 (50, 600)	260 (200, 600)	600 (fixed)	Not applicable
Clinical remission ² , n (%)	3 (4.8)	10 (15.9)	14 (22.6)**	7 (11.5)	31 (16.7)*
Clinical response ³ , n (%)	13 (20.6)	26 (41.3)*	37 (59.7)***	30 (49.2)**	93 (50.0)***
Endoscopic healing4, n (%)	4 (6.3)	15 (23.8)*	19 (30.6)***	8 (13.1)	42 (22.6)**
Endoscopic remission ⁵ , n (%)	1 (1.6)	2 (3.2)	2 (3.2)	1 (1.6)	5 (2.7)
Symptomatic remission ⁶ , n (%)	13 (20.6)	23 (36.5)	36 (58.1)***	28 (45.9)**	87 (46.8)***
TEAEs, n (%)	32 (50.8)	36 (57.1)	32 (51.6)	32 (53.3)	100 (54.1)
Serious adverse event, n (%)	2 (3.2)	0 (0)	2 (3.2)	3 (5.0)	5 (2.7)
Discontinuations from study due to adverse event, n (%)	3 (4.8)	0 (0)	1 (1.6)	2 (3.3)	3 (1.6)

P-value vs. Placebo *p<0.05; **p<0.01; ***p<0.001

¹ Exposure-based dosing- dose increased at day 29 or 57 if [Miri]serum < 0.5 or 2.0 μg/mL for miri 50 mg and 200 mg, respectively.

² Clinical remission- 9-point Mayo subscore for rectal bleeding=0, stool frequency=0 or 1 with ≥1 point decrease from baseline, and endoscopy=0 or 1, excluding PGA

³ Clinical response- 9-point Mayo subscore decrease ≥2 points and ≥35% change from baseline, excluding PGA

⁴ Endoscopic healing-Mayo endoscopic subscore=0 or 1

⁵ Endoscopic remission- Mayo endoscopic subscore= 0

⁶ Symptomatic remission- Stool frequency score=0 or 1 and rectal bleeding score=0

	Treatment Groups				
Mean (SD), (unless otherwise indicated)	Placebo (N=63)	Miri 50 mg (N=63)	Miri 200 mg (N=62)	Miri 600 mg (N=61)	Miri All (N=186)
Baselin	ne Characteristics a	t Week 0			
Age, years	42.6 (13.5)	41.8 (14.1)	43.4 (14.7)	42.4 (13.4)	42.5 (14.0)
Male, n (%)	36 (57.1)	38 (60.3)	37 (59.7)	38 (62.3)	113 (60.8)

Conclusions:

Miri demonstrated efficacy in the induction treatment for patients with moderate-to-severe UC, as assessed by multiple measures.

Overall adverse event frequencies were similar for miri and pbo-treated patients.

These are the first data evaluating the efficacy of an IL-23 monoclonal Ab in patients with UC.

Serious adverse event, n (%)	2 (3.2)	0 (0)	2 (3.2)	3 (5.0)	5 (2.7)
Discontinuations from study due to adverse event, n (%)	3 (4.8)	0 (0)	1 (1.6)	2 (3.3)	3 (1.6)

P-value vs. Placebo *p<0.05; **p<0.01; ***p<0.001

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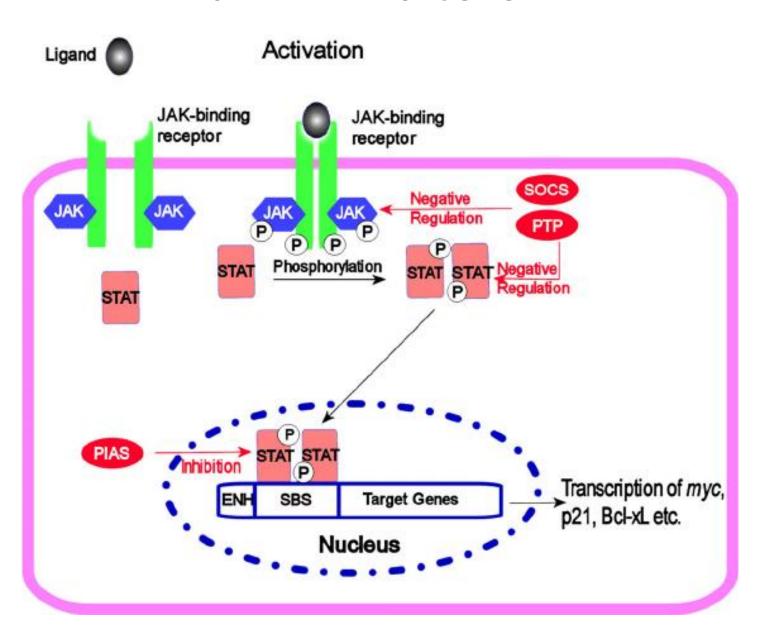
³ Clinical response- 9-point Mayo subscore decrease ≥2 points and ≥35% change from baseline, excluding PGA

⁴ Endoscopic healing-Mayo endoscopic subscore=0 or 1

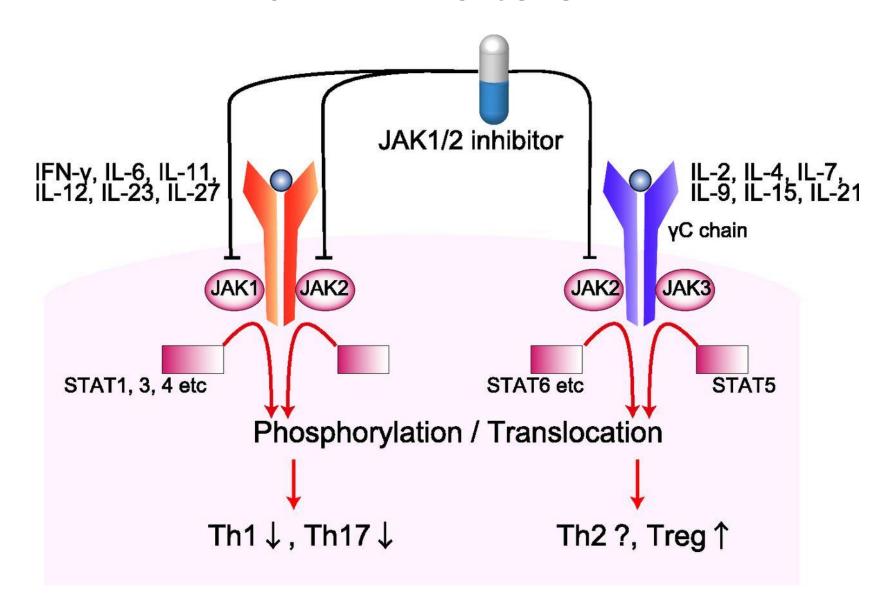
⁵ Endoscopic remission- Mayo endoscopic subscore= 0

⁶ Symptomatic remission- Stool frequency score=0 or 1 and rectal bleeding score=0

JAK inhibitors



JAK inhibitors



Approved JAK inhibitors

- <u>Ruxolitinib</u> (trade names **Jakafi/Jakavi**) against JAK1/JAK2 for psoriasis, <u>myelofibrosis</u>, [8][9][10] and rheumatoid arthritis.[11] Approved by the <u>U.S. FDA</u> in November 2011 for myelofibrosis (intermediate- or high-risk) and <u>polycythemia vera</u>, in patients with an inadequate response or intolerance to <u>hydroxyurea</u>.[12]
- <u>Tofacitinib</u> (trade names **Xeljanz/Jakvinus**, formerly known as tasocitinib and CP-690550) against JAK3 for <u>psoriasis</u> and <u>rheumatoid arthritis</u>. [13] U.S. FDA approved it in November 2012 for rheumatoid arthritis (moderately-to-severely active) in patients who had an inadequate response or intolerance to <u>methotrexate</u>. [14]
- Oclacitinib (trade name Apoquel) against JAK1^[15] for the control of <u>pruritus</u> associated with allergic <u>dermatitis</u> and the control of <u>atopic dermatitis</u> in dogs at least 12 months of age. [16][17]

JAK inhibitors in clinical trials

- <u>Baricitinib</u> (trade name **Olumiant**; LY-3009104, previously INCB-28050) against JAK1/JAK2 started phase IIb for rheumatoid arthritis. [18] It did not receive FDA approval in April 2017 but has received approvals from the <u>EMA</u> and <u>NICE</u>. [19]
- Filgotinib (G-146034, GLPG-0634) against JAK1 for rheumatoid arthritis and Crohn's disease. [20]
- Gandotinib (LY-2784544) against JAK2 for myeloproliferative neoplasms. [21]
- Lestaurtinib (CEP-701) against JAK2 for acute myeloid leukemia (AML).[22]
- <u>Momelotinib</u> (GS-0387, CYT-387) against JAK1 and JAK2 for myeloproliferative disorders^[23] and relapsed/refractory metastatic pancreatic cancer.^[24]
- <u>Pacritinib</u> (SB1518) against JAK2 for relapsed <u>lymphoma</u> and advanced <u>myeloid</u> malignancies, also myelofibrosis, myeloproliferative neoplasms and <u>myelodysplastic syndrome</u>.
- PF-04965842 against JAK1 for atopic dermatitis and moderate to severe psoriasis. Currently phase II. [28]
- <u>Upadacitinib</u> (ABT-494) against JAK1 starting phase III for rheumatoid arthritis. [29]
- <u>Peficitinib</u> (ASP015K, JNJ-54781532) mainly inhibits JAK3. Numerous clinical trials, many for rheumatoid arthritis. [30] e.g. phase II results [31]
- <u>Fedratinib</u> (SAR302503). Fedratinib is a JAK2 inhibitor that may potentially treat primary myelofibrosis (including in patients those previously treated with ruxolitinib), polycythemia vera and <u>essential</u> <u>thrombocythemia</u>.

TOFACITINIB ACHIEVES SYMPTOMATIC IMPROVEMENT WITHIN 3 DAYS IN MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS, REGARDLESS OF PRIOR TUMOUR NECROSIS FACTOR INHIBITOR TREATMENT STATUS: RESULTS FROM OCTAVE INDUCTION 1 & 2

S. B. Hanauer¹; et al. ¹Northwestern University, Evanston, Illinois, United States;

Background:

- Tofacitinib is an oral, small molecule JAK inhibitor that is being investigated for UC
- Aim: to evaluate the timing of onset of symptomatic improvement in a post-hoc analysis of patient-reported diary data and to evaluate treatment effect in patients with and without prior failure of TNF therapy

Methods:

- OCTAVE Induction 1 & 2 (NCT01465763; NCT01458951) were identical, randomized,
 placebo-controlled Phase 3 trials in adult patients with moderately to severely active UC
 who had failed or were intolerant to steroids, immunomodulators, or tumor necrosis factor
 inhibitors.
- Patients received placebo (N=234) or tofacitinib 10 mg twice daily (N=905) for 8 weeks.
- Pooled data for OCTAVE Induction 1 & 2 are presented.
- During the study, patients recorded their number of bowel movements per day, and the presence and a description of any blood in the stools.
- Binary endpoints were based on Mayo stool frequency and rectal bleeding subscores.
- Subgroup analyses were conducted by prior tumor necrosis factor inhibitor failure status,
 baseline C-reactive protein, and corticosteroid use at baseline.

TOFACITINIB ACHIEVES SYMPTOMATIC IMPROVEMENT WITHIN 3 DAYS IN MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS, REGARDLESS OF PRIOR TUMOUR NECROSIS FACTOR INHIBITOR TREATMENT STATUS: RESULTS FROM OCTAVE INDUCTION 1 & 2

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Results:

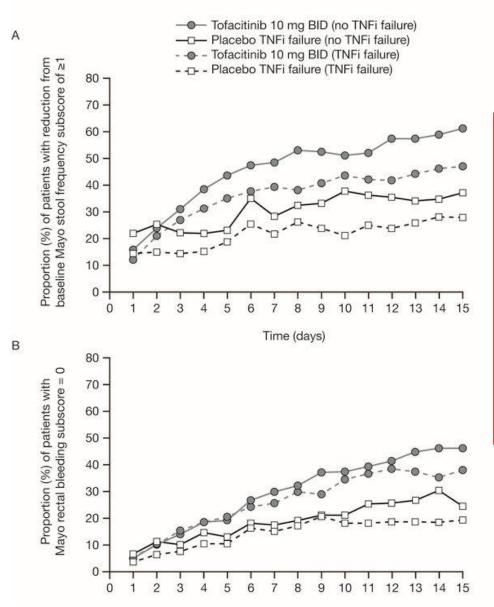
- At baseline, the mean Mayo subscores for the placebo and tofacitinib groups were 2.5 for stool frequency and 1.6 for rectal bleeding.
- By Day 3, significantly more patients achieved each of the binary efficacy endpoints (defined in Table) with tofacitinib vs placebo (all p<0.05).
- Among patients with prior tumor necrosis factor inhibitor failure, 117 (26.8%) tofacitinib-treated patients had reduction from baseline stool frequency ≥1 at Day 3, vs 16 (14.0%) with placebo, and 133 (30.6%) tofacitinib-treated patients had reduction from baseline rectal bleeding ≥1 at Day 3, vs 14 (12.5%) with placebo.
- Subgroup analyses demonstrated generally consistent effects of tofacitinib treatment vs placebo, regardless of prior tumor necrosis factor inhibitor treatment failure status (Figure), baseline C-reactive protein, and corticosteroid use at baseline.

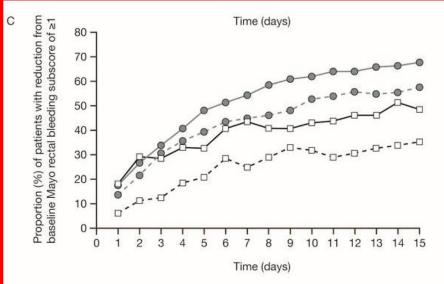
Table. Summary of binary efficacy endpoints based on Mayo stool frequency and rectal bleeding subscores in OCTAVE Induction 1 & 2 at Day 3

	Placebo	Tofacitinib 10 mg BID	Difference from placebo, % (95% CI)
Reduction from baseline in Mayo stool frequency subscore ≥1, n/N (%)	39/218 (17.9)	241/837 (28.8)	10.9 (5.0, 16.8)**
Mayo rectal bleeding subscore = 0, n/N (%)	18/219 (8.2)	122/849 (14.4)	6.2 (1.8, 10.5)*
Reduction from baseline in Mayo rectal bleeding subscore ≥1, n/N (%)	43/214 (20.1)	266/830 (32.0)	12.0 (5.7, 18.2)**
Reduction from baseline in either Mayo stool frequency or rectal bleeding subscore ≥1, n/N (%)	68/215 (31.6)	386/823 (46.9)	15.3 (8.2, 22.4)***
Reduction from baseline in both Mayo stool frequency and rectal bleeding subscore ≥1, n/N (%)	13/215 (6.0)	118/823 (14.3)	8.3 (4.3, 12.3)**

^{*}p<0.05; **p<0.01; ***p<0.0001 vs placebo based on Cochran-Mantel-Haenszel chi-square test; Data are full analysis set, observed case; Patients with baseline Mayo stool frequency subscore = 0 were excluded from analyses that included reduction from baseline in stool frequency subscore ≥1; Patients with baseline Mayo rectal bleeding subscore = 0 were excluded from analyses that included reduction from baseline in rectal bleeding subscore ≥1. BID, twice daily; CI, confidence interval; N, number of patients with non-missing data; n, number of patients meeting endpoint criteria.

Figure. Proportion of patients with (A) reduction from baseline Mayo stool frequency subscore ≥1 point over time, (B) Mayo rectal bleeding subscore = 0 over time, and (C) reduction from baseline Mayo rectal bleeding subscore ≥1 point over time, according to prior TNFI failure (yes/no)



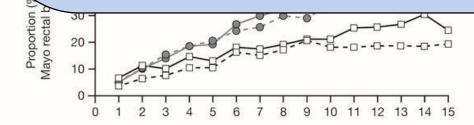


Data are full analysis set, observed case; Patients with baseline Mayo stool frequency subscore = 0 and those with Mayo rectal bleeding subscore = 0 were excluded from the analyses shown in panels A and C, respectively. BID, twice daily; TNFi, tumor necrosis factor inhibitor.

Figure. Proportion of patients with (A) reduction from baseline Mayo stool frequency subscore ≥1 point over time, (B) Mayo rectal bleeding subscore = 0 over time, and (C) reduction from baseline Mayo rectal bleeding subscore ≥1 point over time, according to prior TNFI failure (yes/no)

CONCLUSIONS

- Significant symptomatic improvements were observed with tofacitinib vs placebo as early as Day 3.
- A consistent treatment effect was observed regardless of whether patients had prior tumor necrosis factor inhibitor treatment failure.
- These results support the rapid onset of tofacitinib efficacy previously reported based on significant improvement vs placebo at 2 weeks in partial Mayo score, and extend this result to response at Day 3.1



UPADACITINIB IMPROVES STEROID-FREE CLINICAL AND ENDOSCOPIC ENDPOINTS IN PATIENTS WITH CROHN'S DISEASE: DATA FROM THE CELEST STUDY

R. Panaccione¹; et al. ¹University of Calgary, Calgary, Alberta, Canada

Introduction:

- upadacitinib (UPA) is an oral selective JAK1 inhibitor
- UPA's efficacy and safety were assessed in patients with moderate-to-severe Crohn's disease (CD) and with inadequate response/intolerance to an immunomodulator or tumour necrosis factor inhibitor (TNFi).¹
- We report the steroid-free endpoints in the 16-week induction phase of CELEST in patients receiving corticosteroid (CS) at baseline (BL).

Methods:

- Patients with CD Activity Index (CDAI) 220-450, average daily very soft/liquid stool frequency [SF] ≥2.5 or abdominal pain score [AP] ≥2.0 and Simplified Endoscopic Score for CD (SES-CD) ≥6 [or ≥4 for those with isolated ileal disease] were randomized equally to receive either placebo (PBO) or UPA 3, 6, 12, 24 mg twice daily (BID) or 24 mg once daily (QD) for 16 weeks.
- Patients were also randomised 1:1 at BL for follow-up ileocolonoscopy at either 12 or 16 weeks.
- Beginning at week 2, CS was tapered in patients on CS at BL.
- The proportion of patients who discontinued CS and achieved endoscopic remission, endoscopic response, clinical remission, modified clinical remission (all defined in Figure), and CDAI <150 were assessed at Week 16 in patients on CS at BL.

UPADACITINIB IMPROVES STEROID-FREE CLINICAL AND ENDOSCOPIC ENDPOINTS IN PATIENTS WITH CROHN'S DISEASE: DATA FROM THE CELEST STUDY

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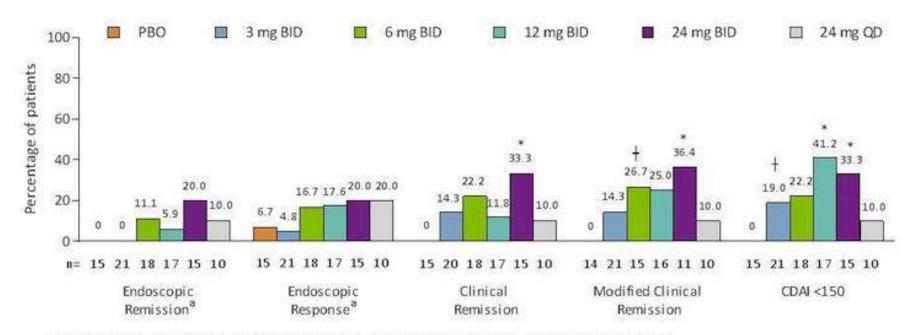
Methods continued:

- The proportion of patients who discontinued CS and achieved endoscopic remission, endoscopic response, clinical remission, modified clinical remission (all defined in Figure), and CDAI <150 were assessed at Week 16 in patients on CS at BL.
- Patients with missing data or who prematurely discontinued or received CS dose higher than BL were considered non-responders.
- Comparisons of each dose of UPA vs PBO were performed using Chi-square test.
- Treatment-emergent adverse events (AEs) collected throughout the study in patients with at least one UPA dose up to 30 days of the last dose were stratified by CS use at BL.

Results:

- Among 220 randomised patients, 96 (43.6%) received CS at BL:
- median (min-max) age 38.5 (19.0-69.0) years, CDAI 291.0 (162-599), CD duration 9.4 (0.1-44.7) years and 95 (99.0%) had failed one or more TNFi.
- More patients taking UPA were able to discontinue CS and achieve endoscopic endpoints at 12/16 weeks and clinical endpoints at 16 weeks than patients on PBO (Figure).
- Patients on 24 mg BID achieved a statistically significant difference from PBO in all clinical remission endpoints.
- The rates of any AEs were similar between patients with or without CS use in the UPA (85.2% and 80.4%, in all UPA arms, respectively) and PBO groups (73.3% and 72.7%).

Figure. Proportion of subjects who discontinued corticosteroid and achieved clinical and endoscopic endpoints at 16 Weeks



Endoscopic remission: SES-CD≤4 and ≥2-point reduction from BL, with no subscore >1.

Endoscopic response: SES-CD reduction >50% from BL or endoscopic remission.

Clinical remission: SF≤1.5 and AP≤1.0, and both not worse than BL.

Modified clinical remission: SF≤2.8 and AP≤1.0, both not worse than BL.

Modified clinical remission was analysed in patients with SF≥4.0, AP≥2.0 at BL; other endpoints were analysed in all randomised patients.

^{*, †} significant at ≤0.05 and ≤0.1 level. The follow-up ileocolonoscopy was performed at either week 12 or 16, per randomization schedule

CONCLUSIONS

- Patients with long-standing CD refractory to conventional/TNFi therapy who received CS at BL achieved statistically significant steroid-free endoscopic and clinical improvements at 16 weeks of treatment with UPA.
- The safety profile of UPA in patients taking CS at BL was consistent with the overall study population.

Endoscopic remission: SES-CD≤4 and ≥2-point reduction from BL, with no subscore >1.

Endoscopic response: SES-CD reduction >50% from BL or endoscopic remission.

Clinical remission: SF≤1.5 and AP≤1.0, and both not worse than BL.

Modified clinical remission: SF≤2.8 and AP≤1.0, both not worse than BL.

Modified clinical remission was analysed in patients with SF≥4.0, AP≥2.0 at BL; other endpoints were analysed in all randomised patients.

*, [†] significant at ≤0.05 and ≤0.1 level. ^aThe follow-up ileocolonoscopy was performed at either week 12 or 16, per randomization schedule

Thank you

