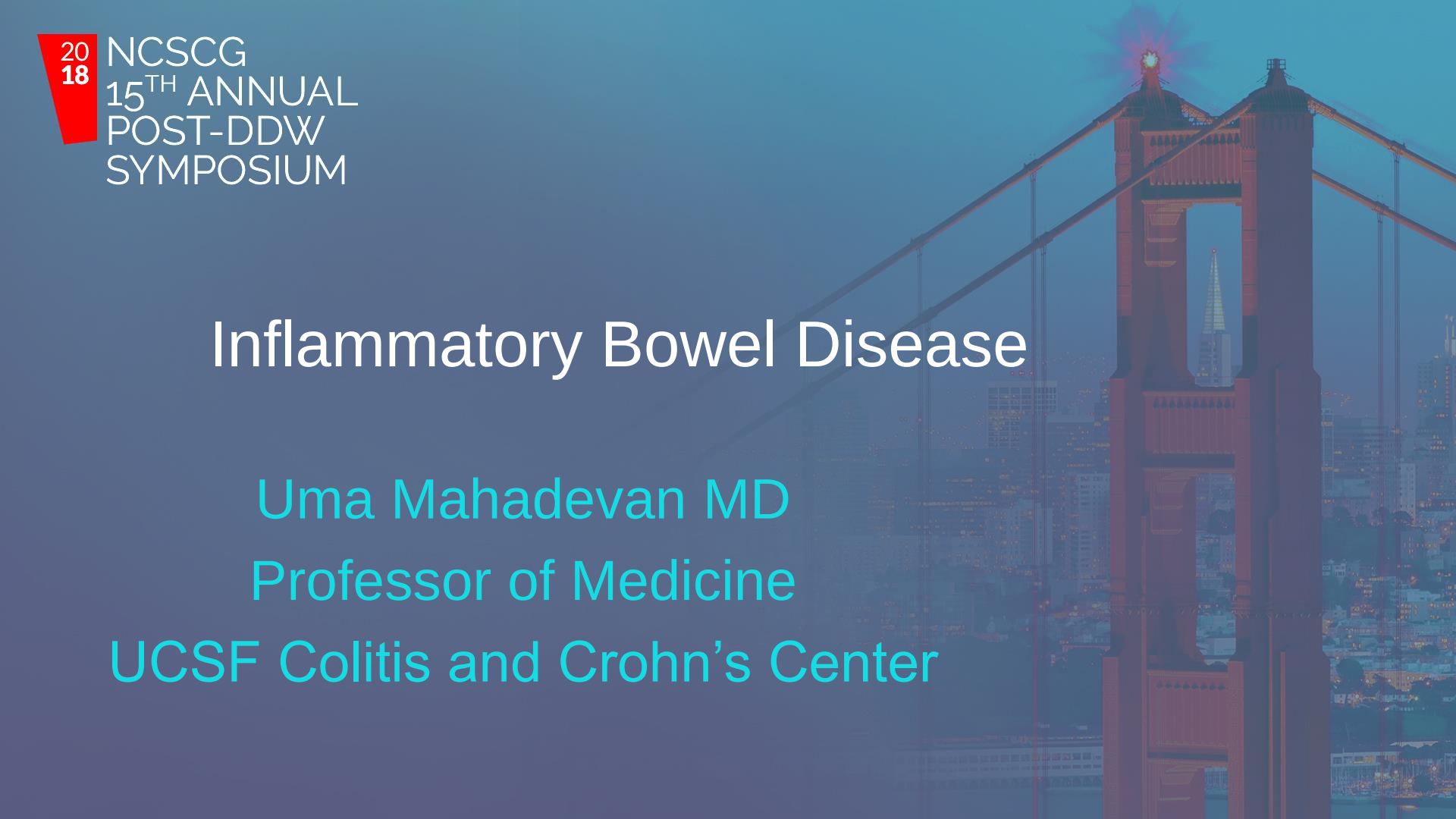
2018

NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM

Rehoboth McKinley Christian Health Care Services

Northern California Society for Clinical Gastroenterology

Jointly provided by the New Mexico Medical Society (NMMS) through the joint providership of Rehoboth McKinley Christian Health Care Services (RMCHCS) and the Northern California Society for Clinical Gastroenterology.



Inflammatory Bowel Disease

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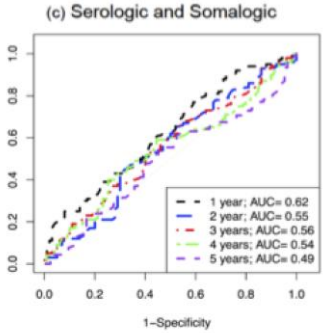
Early detection of asymptomatic Crohn's disease using specific antibodies and proteomic markers

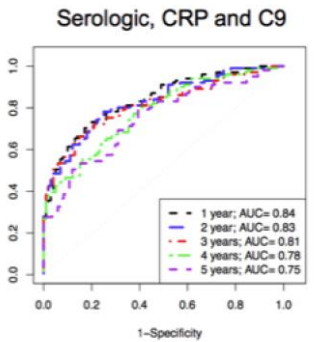
- Methods
  - 1872 serums samples from military cohort included inflammatory bowel disease (IBD) (CD n =200, UC n= 200) and controls (n= 200)
  - Prometheus and Somologics panel
  - Random forest model selected markers
- Results
  - ASCA IgA, ASCA IgG, anti-FlaX are elevated 5 years prior to diagnosis in IBD patients ($P < 0.01$, $P < 0.0005$, $P < 0.05$)
  - CRP, C9 are elevated at least 5 years prior to the onset of diagnosis of CD
  - Serologic markers had 60-70% overlap at all time points
  - No single marker was accurate for predicting UC

- Conclusion
  - Altered immune related markers predate clinical disease
  - Combination of serological plus protein markers predicts CD up to 5 years prior to diagnosis
  - Clinical utility in time to develop predictive algorithms and disease prevention

UC



CD

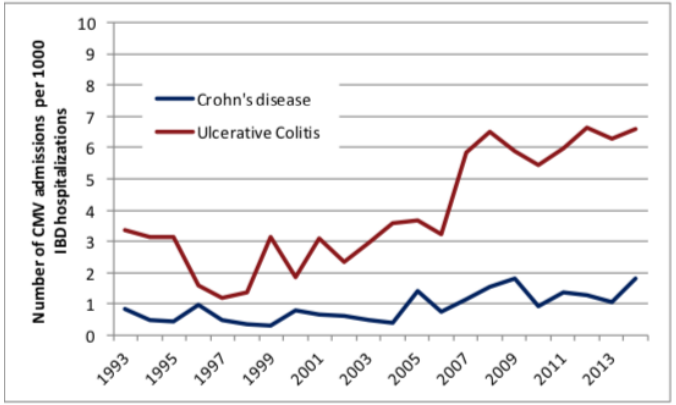


UC, ulcerative colitis; CD, Crohn's disease

Colombel JF, et al. Presented at DDW. June 2018. Abstract 735.

Longitudinal incidence and impact of CMV infection on IBD hospitalizations

- Methods
  - National inpatient sample analyzed from 1993-2014 using ICD-9 CM codes for Crohn's disease (CD), ulcerative colitis (UC), and cytomegalovirus (CMV) colitis
- Results/Conclusions
  - IBD hospitalizations with CMV rising, especially in UC
  - Independent associations (table)



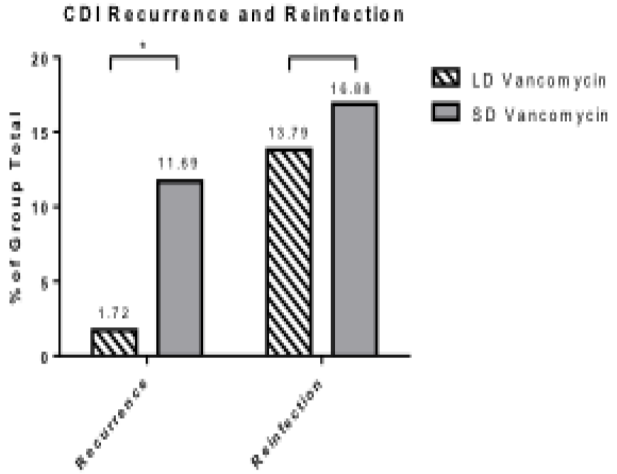
	Ulcerative Colitis			Crohn's Disease		
	CMV+	95% CI	p-value	CMV+	95% CI	p-value
Death (aOR)	2.81	1.56 – 5.06	<0.001	4.47	1.77 – 11.33	0.002
Colectomy (aOR)	1.03	0.79 – 1.35	0.816	-	-	-
Bowel Surgery (aOR)	-	-	-	0.68	0.45 – 1.02	0.065
Malnutrition (aOR)	3.02	2.41 – 3.78	<0.001	2.80	2.01 – 3.91	<0.001
Anemia (aOR)	1.67	1.38 – 2.01	<0.001	2.10	1.56 – 2.84	<0.001
Renal Failure (aOR)	1.79	1.23 – 2.61	0.002	2.17	1.26 – 3.74	0.005
Length of stay (additional days)	6.93	5.73 – 8.13	<0.001	8.44	6.36 – 10.53	<0.001
Total charges (additional dollars)	$51,704	$39,790 - $63,618	<0.001	$51,916	$34,869 – $68,963	<0.001

LOS, length of stay; IBD, Inflammatory Bowel Disease

Hendler S, et al. Presented at DDW. June 2018. Abstract Sa1807.

Longer duration of vancomycin prevents recurrence of CDI in patients with IBD

- Methods
  - Retrospective, single-center study of 135 patients with IBD with positive *C. difficile* PCR between 2010-2016
  - Longer duration (LD) = 21-42 days vs short duration (SD) = 10-14 days of oral vancomycin
  - Median follow up time was 685 days
- Results
  - CDI Recurrence (positive *C. difficile* result **within** 8 weeks of ending vancomycin therapy)
    - 12% SD vs 2% LD (*P = 0.043)
  - CDI Reinfection (positive *C. difficile* result **after** 8 weeks of ending vancomycin therapy)
    - 17% SD vs 14% LD (P = NS)



- Conclusion:
  - LD vancomycin associated with significantly less CDI recurrence in IBD patients.

CDI, *Clostridium difficile* infection; IBD, Inflammatory Bowel Disease

Lei D, et al. Presented at DDW. June 2018. Abstract Sa1731.

Daily Aspirin Use Does Not Impact Clinical Outcomes in Patients with IBD

- Methods
  - Investigate if daily aspirin use is associated with increased disease activity
  - Analysis of a prospectively collected registry of IBD patients
  - 174 pts were matched with 590 patients not on aspirin
  - Patients were matched for age, sex, disease, location, and cardiac comorbidities
- Results
  - Sub-group analysis of Crohn's and UC patients did not show an association with these outcomes and aspirin
  - Dose higher than 81 mg/d was also not associated with higher risk for poor outcome

	Estimate	Confidence Interval		p-value
Hospitalizations	0.38	-0.09	0.86	0.10
Surgeries	-0.01	-0.53	0.50	0.96
Steroid use	-0.08	-0.45	0.30	0.70

Patel P, et al. Presented at DDW. June 2018. Oral presentation 94

Risk of factors for Infection After Joint Replacement Surgery in IBD patients

- Method
  - Retrospective case-control study using Truven claims database
  - Inclusion:
    - Joint replacement surgery (Hip, knee, shoulder)
    - 1:10 non-IBD controls matched to IBD patients for joint surgery, duration of follow-up
- Results

Complications within 90 days

	IBD (n = 1,455)	Controls (n = 14,550)	P value
Serious infections	3.9%	2.4%	<0.01
Joint infection	1.5%	1.2%	0.35
C.Diff infection	0.8%	0.1%	<0.01

Risk factors for serious infections

	HR	P value
IBD	1.53 (1.15-2.03)	<0.01
Opiates	1.46 (1.19 – 1.78)	<0.01
Obesity	1.35 (1.07-1.71)	0.01
anti-TNF	1.14 (0.52-2.52)	0.75
Steroid use	2.81 (1.54-5.13)	<0.01

- **Conclusion**
  - IBD patients are at increase risk of serious infection after joint surgery
  - Steroid and opiate use were associated with increased risk of infection while IM and anti-TNF we not

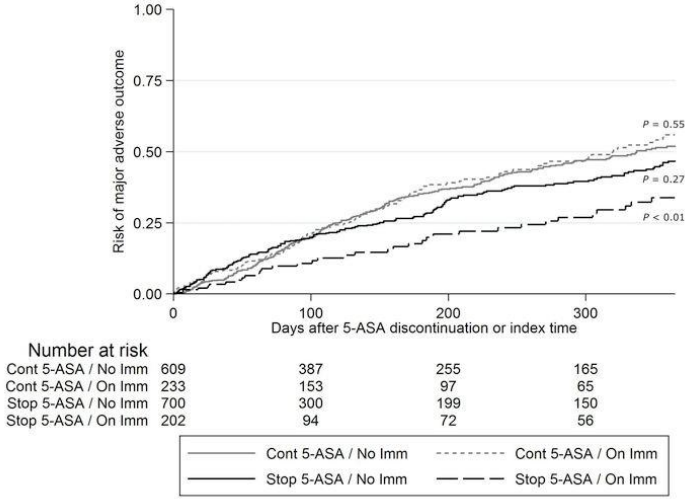
Gregory M, et al. Presented at DDW. June 2018. Abstract 160.

The concomitant/discontinuation of 5ASA in UC patients escalated to biologics, does not modify outcomes

- Methods
  - Analysis of patient level data for participants in clinical trials of infliximab and golimumab in moderate-severe UC[1]
  - Data regarding UC patients on a 5-ASA regimen and started on a biologic therapy per health claims database[2]
- Results 5-ASA vs. no concomitant 5-ASA in TNFi-treated patients

Outcome	Adjusted OR (95% CI)	p-value	Outcome
Clinical Remission	0.67 (0.45-1.01)	0.06	Clinical Remission
Clinical Response	0.89 (0.60-1.33)	0.58	Clinical Response
Endoscopic Remission	1.12 (0.82-1.51)	0.48	Endoscopic Remission
Biochemical Remission	0.94 (0.61-1.46)	0.79	Biochemical Remission

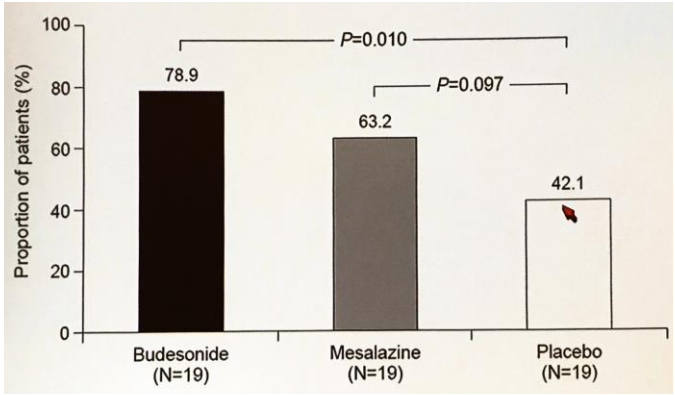
Risk of major adverse outcomes according to 5-ASA use



Oral Budesonide in Lymphocytic Colitis

- Background
  - Budesonide and Mesalazine in lymphocytic colitis only validated in small studies
- Method
  - Double-blind RCT in 57 patients
  - Randomised to Budesonide 9mg/day Mesalazine 3g/day, Placebo for 8 weeks
  - Primary endpoint: clinical remission defined by Hjortswang Criteria
- Results
  - significantly higher proportion of patients in clinical remission at week 8 treated with budesonide than placebo (see figure) associated with improved quality of life
  - significantly higher proportion of patients inhistological remission at week 8 with budesonide (68%) than with mesalazine (26%; p=0.02) and placebo (21%; p=0.008)
  - Mean time to response is 3 days

Figure 1: Clinical Remission (Hjortswang Criteria)



- Conclusion
  - Budenisode 9mg/day is safe and efficacious for induction of clinical and histologic remission in lymphocytic colitis, associated with improved quality of life

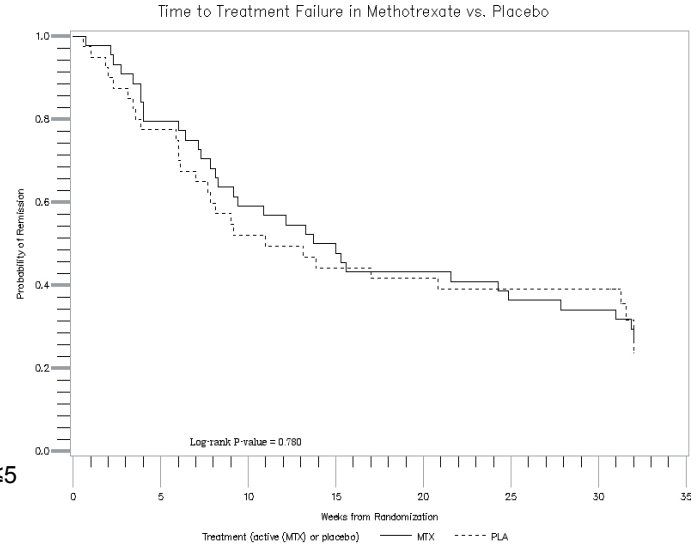
Miehlke S, et al. Presented at DDW, June 2018. Oral presentation 816.

Methotrexate is Not Superior to Placebo in Maintaining Remission in UC (MERIT-UC STUDY)

- Background
  - Parenteral methotrexate (MTX) is effective in inducing and maintaining remission in patients with CD. In the METEOR trial, MTX induced steroid free clinical remission but not endoscopic healing
- Aim
  - to determine the efficacy and safety of MTX in maintaining steroid free remission in moderately-severely active UC (defined by Mayo 6-12, endoscopic subscore ≥2)
- Method
  - 16-week open label induction period followed by a 32-week double-blind placebo-controlled maintenance period for responders*
  - MTX 25mg weekly subcutaneously
  - Primary end point: relapse free at 32wk (Mayo ≤2, without interval increase ≥3 or steroid use

*Response at wk 16 defined as clinical Mayo ≤5

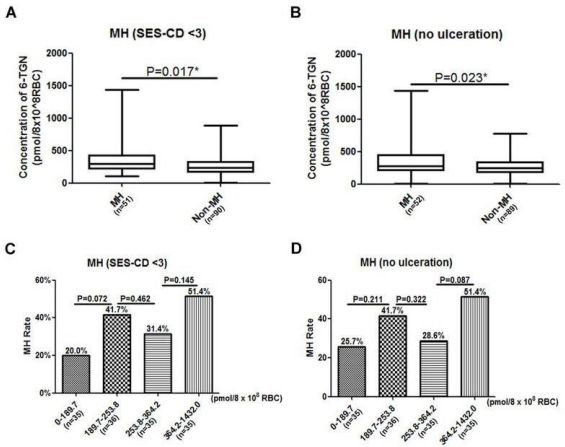
- Results
  - At 16wk 51% responded
  - At 32wk, relapse rates were similar
- Conclusion
  - MTX not effective for maintaining remission in UC



Herfarth H et, et al. Presented at DDW, June 2018. Sa1773.

Higher 6-TGN levels are associated with higher rate of mucosal healing in CD patients

- Methods
  - Retrospective cross-sectional observational study, aimed to assess the correlation between 6-TGN levels and MH in patients with CD
- Results

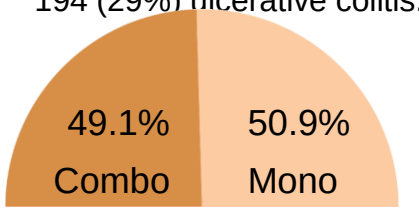


- 119 patients with CD treated with thiopurines in 3 IBD referral centers
- The cut-off 6-TGN concentration of 397.3 pmol/8x10^8RBC was 86.7% specific for MH, with a sensitivity of 35.3% and area under curve (AUC) of 0.631 (P=0.010)
- Late initiation of AZA (longer duration from disease onset) was inversely associated with MH (OR 0.972, 95%CI 0.954-0.991; P=0.004)

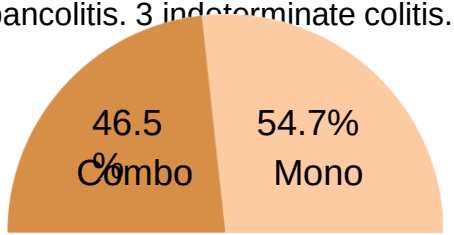
Mao R, et al. Presented at DDW. June 2018. Abstract Mo1907

No increase in combination therapy in the post SONIC era

- Methods
  - Retrospective chart review
  - Including all prescribers of TNFi for IBD in Manitoba
  - The pre-SONIC - first TNFi 2005-2009; post-SONIC 2011-2015
- Result
  - 476 (71%) Crohn's disease. 238 (50%) penetrating disease
  - 194 (29%) ulcerative colitis. 105 (54%) pancolitis. 3 indeterminate colitis.



226 anti-TNF users



447 anti-TNF users

  - **No difference in combination therapy rates between eras (p=0.53)**
  - **No difference when looking only at CD or IFX**

Elias E, et al. Presented at DDW. June 2018. Abstract oral 471

Low Reactivation Risk in Hepatitis B Core (+), Surface Antigen (–) on anti-TNFs

- Background
  - Guidelines offer conflicting recommendations on the need for antiviral prophylaxis in anti-HBc+, HBsAg- pts receiving anti-TNF (2015 AGA, 2014 ECCO, 2018 AASLD)
- Methods
  - 3 retrospective studies (2 single-center[1,2], 1 multinational[3]) from U.S. and Asia 2002-2017
  - Anti-HBc+, HBsAg- undergoing immunosuppression for IBD and other autoimmune diseases
  - Outcome - Hepatitis B reactivation (1 log increase in HB DNA level) or HBsAg+
- Results
  - 318 anti-HBc+, HBsAg- pts (70% IBD), 11% receiving antivirals
  - HBV reactivation in 1 pt (0.3%) on anti-TNF without concurrent antiviral[1]
  - 3 pts (0.9%) with previously undetectable viral load developed detectable viral load[1]
  - 1 steroid-dependent 85 yo male developed HBsAg+, died from hospital acquired infection[2]
  - No pts developed fulminant hepatic failure[1,2,3]
- Conclusion
  - Low rate of Hepatitis B reactivation in anti-HBc+, HBsAg- pts on anti-TNF
  - Close monitoring without antiviral prophylaxis may be reasonable strategy

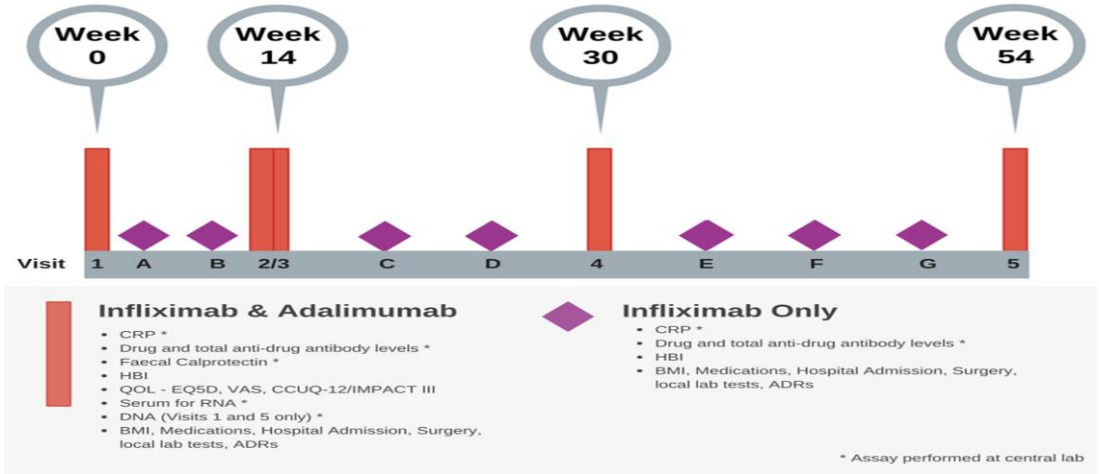
HBV – Hepatitis B Virus

1. Clarke WT, et al. Presented at DDW. June 2018. Abstract Sa1707
2. Ko KLM, et al. Presented at DDW. June 2018. Abstract 327
3. Lee KM, et al. Presented at DDW. June 2018. Abstract Sa1712

Clinical Effectiveness, Safety and Immunogenicity of Anti-TNF Therapy in Crohn's Disease

12 Month data from the Personalised Anti-TNF Therapy study (PANTS)

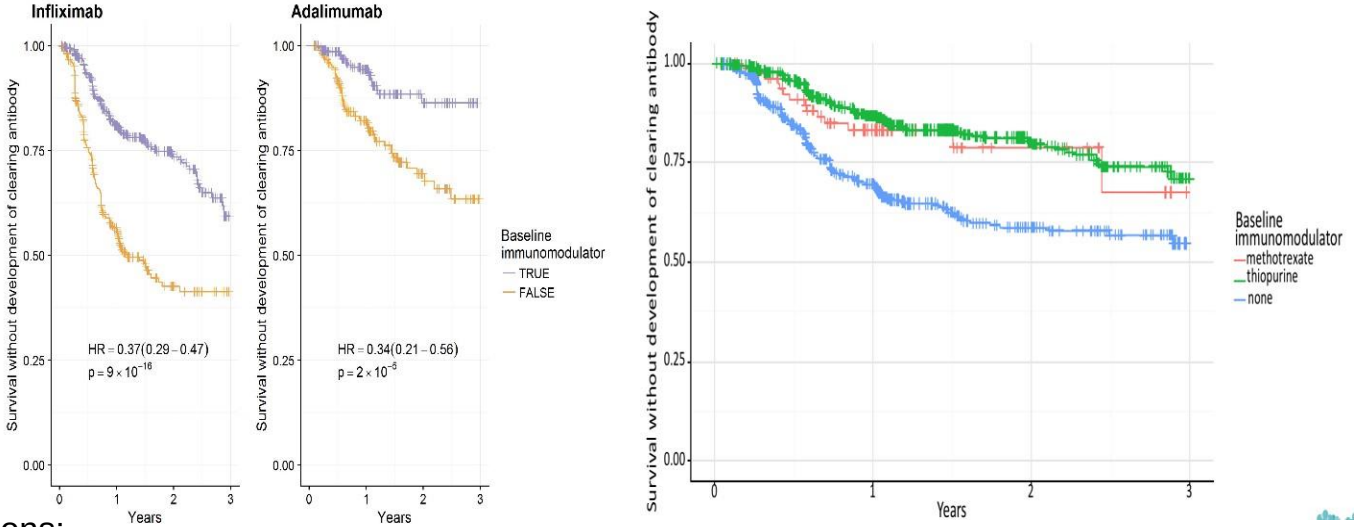
- 3-year prospective observational UK-wide study investigating primary non-response, loss of response and adverse reactions to IFX and ADA
- Cohort: 1601 CD patients recruited from 118 sites
  - Aged ≥6 years, active inflammation supported by raised CRP (>3mg/L) or calprotectin (≥50µg/g) and no prior anti-TNF therapy



Kennedy NA et al. presented at DDW June 2018. Abstract 159

Clinical Effectiveness, Safety and Immunogenicity of Anti-TNF Therapy in Crohn's Disease: PANTS

- **Rates of immunogenicity and benefit of immunomodulation with thiopurine or methotrexate**



- Conclusions:
  - **Drug level is the major determinant of PNR at week 12-14 and non-remission at week 54**
  - **ADAb formation is common (IFX>ADL), and associated with non-remission at week 54**
  - **Modifiable factor that increase efficacy: Immunomodulator use (thiopurine or MTX)**
  - **Modifiable factors that reduces efficacy: BMI, smoking**

Kennedy NA et al. presented at DDW June 2018. Abstract 159

Sustained efficacy and immunogenicity rates are similar after switching to biosimilar infliximab (CT-P13)

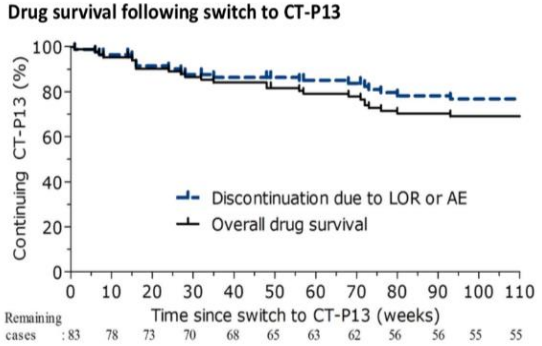
Two year follow-up of a prospective observational cohort

Prospective observational cohort study

All Remicade® treated IBD patients switched to CT-P13 and continued at the same dosing/interval

Endpoints:

Drug survival
Reasons for discontinuation
Antidrug antibodies, trough levels
Harvey-Bradshaw Index (HBI)
Simple Clinical Colitis Activity Index (SCCAI)
CRP



- Antidrug antibodies:
  - 5/83 (6%) at baseline
  - 2/83 (2%) in year 1
  - None in year 2

- **68% of IBD patients continued CT-P13 beyond 2 years after switching**
- **Main reasons for discontinuation were loss of response, adverse events and stable disease remission**

Smits L. et al. presented at DDW June 2018. Abstract Mo1844

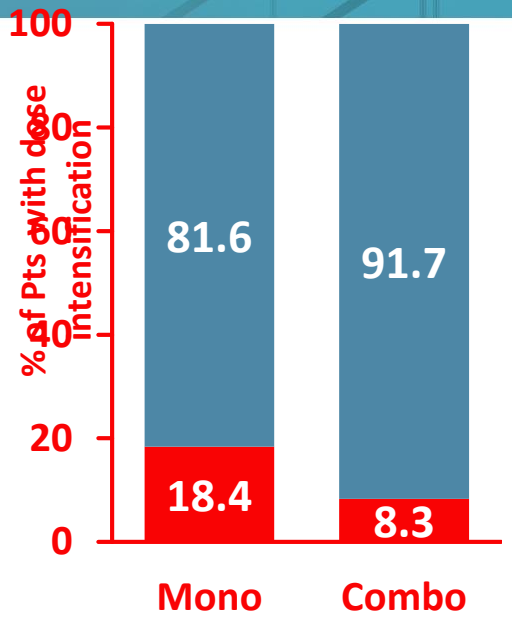
Lower Need for Adalimumab (ADA) Dose Intensification in combination vs. monotherapy

Methods

- 3 large centers in Slovakia
- ADA trough measured routinely for all patients
- Outcome: Patients on higher ADA dose based on chart review

Results

- 241 patients. 171 in remission
- More patients on ADA monotherapy required dose intensification



Conclusion

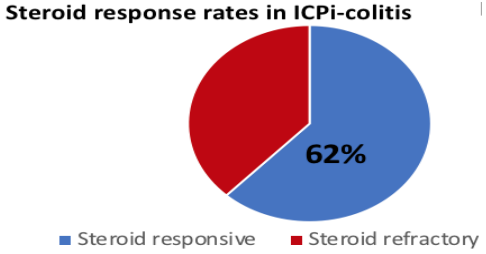
- Patients on ADA monotherapy need dose intensification more frequently than patients using ADA + thiopurines

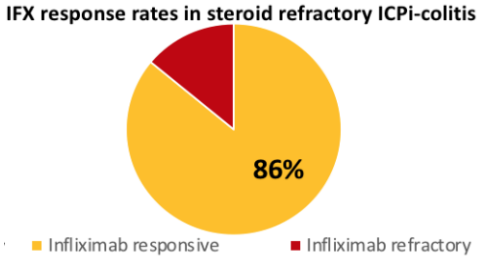
UC, ulcerative colitis; ADA, adalimumab.

Kovacs J, et al. Presented at DDW June 2018. Abstract Mo1850.

The effectiveness of anti-inflammatory therapies in immune checkpoint inhibitor induced colitis

- Background:
  - Immune checkpoint inhibitors (ICPi) including anti-CLTA-4 (e.g. ipilimumab) and anti- PD-1 (e.g. nivolumab) have transformed cancer outcomes
  - However, treatment success is limited by high rates of immune-mediated toxicity
  - ICPi-induced diarrhoea/colitis occurs in up to 44% of patients
- Methods: Systematic review
  - 1838 studies reviewed, 26 met the inclusion criteria, of which 17 (65%) were retrospective studies
  - A total of 983 patients were reported to have diarrhoea and/or colitis
    - 558 (57%) patients were treated with corticosteroids
    - 297 (30%) patients with steroid refractory disease received infliximab





- **Results:**
  - About two-thirds of patients respond to high-dose steroids
  - Rescue therapy with IFX captures response in the majority of steroid refractory cases

Ibraheim H et al. presented at DDW June 2018. Abstract Tu1244

Combination cyclosporine and vedolizumab is effective for severe, steroid-resistant UC

Methods

- 17 UC patients treated with cyclosporine plus vedolizumab after failing steroid therapy.
- Cyclosporine IV 2 mg/kg followed by VDZ at 300 mg q8 weeks and cyclosporine PO 4 mg/kg for 8 weeks

Results

- 15/17 patients responded to IV cyclosporin

	Baseline	End of Induction
Lichtiger Score	12 (on admission)	5 (Week 6)
CRP	15.9	3.8 (Week 6)
FCal	1024 (week 2)	808 (Week 6)
Mayo endoscopic score	3	≤1 (Week 10)
ESR	39.9	26.1)

Conclusion

- In steroid-refractory severe UC patients responding to cyclosporine, combination with vedolizumab is effective and safe at week 6

UC, ulcerative colitis; FCal, fecal calprotectin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
Tarabar D, et al. Presented at DDW June 2018. Presentation number 330.

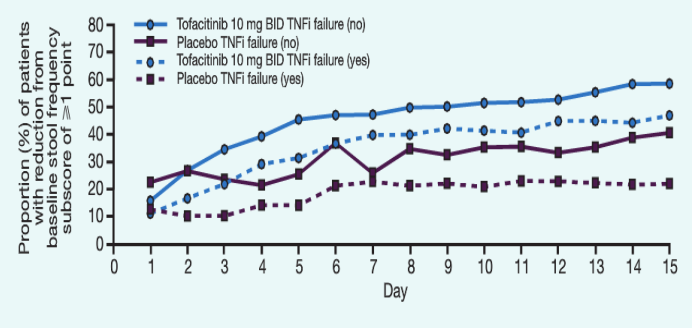
Tofacitinib Users Guide

- **Indication**: Moderate to Severe UC
- **Pre-check**: quantiferon, HBV, cbc, lft
  - Vaccinate (shingrix)
- **Dose**: 10 mg BID for 8-16 weeks
  - Responders 10 mg or 5 mg BID
- **Post-check**:
  - Lipids week 8
  - Cbc, lfts week 4 and then every 3 months if normal

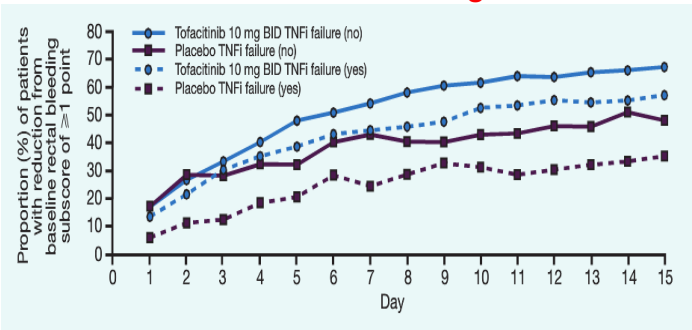
Significant symptomatic improvements were observed with tofacitinib as early as Day 3

- Post-hoc analysis of OCTAVE 1&2 induction studies to evaluate the timing of onset of symptomatic improvement

Diarrhea



Rectal bleeding



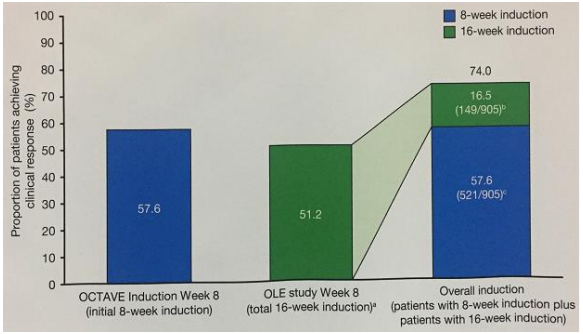
- Day 3:
  - 117 (26.8%) had reduction from baseline stool frequency ≥1 (14.0% with placebo)
  - 133 (30.6%) had reduction from baseline rectal bleeding ≥1 (12.5% with placebo)
- Subgroup analyses demonstrated consistent effects regardless of prior TNFi treatment failure status, baseline CRP, or corticosteroid use at baseline

Hanauer S, et al. Presented at DDW. June 2018. Abstract Sa1753

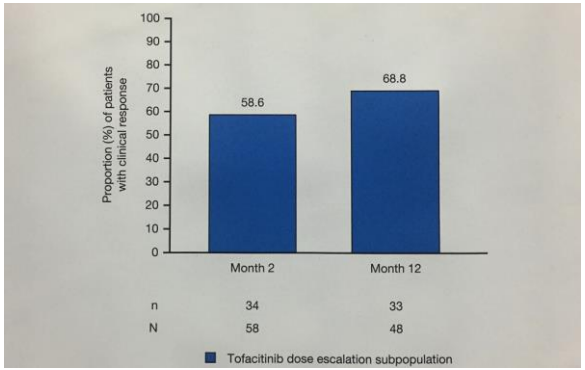
Trends in treatment with Tofacitinib Results from OCTAVE-Open

- 429 induction non-responder patients enrolled in OCTAVE Open (295 previously received tofacitinib 10 mg BID)
- The majority of patients who failed to achieve clinical response to tofacitinib induction studies, responded to an additional 8 weeks of open-label tofacitinib 10 mg BID[1]
- Patients who lost initial clinical response while on tofacitinib 5 mg BID maintenance therapy, responded to escalation back to 10 mg BID[2]

Clinical response after induction with 10 mg BID



Clinical response after dose escalation

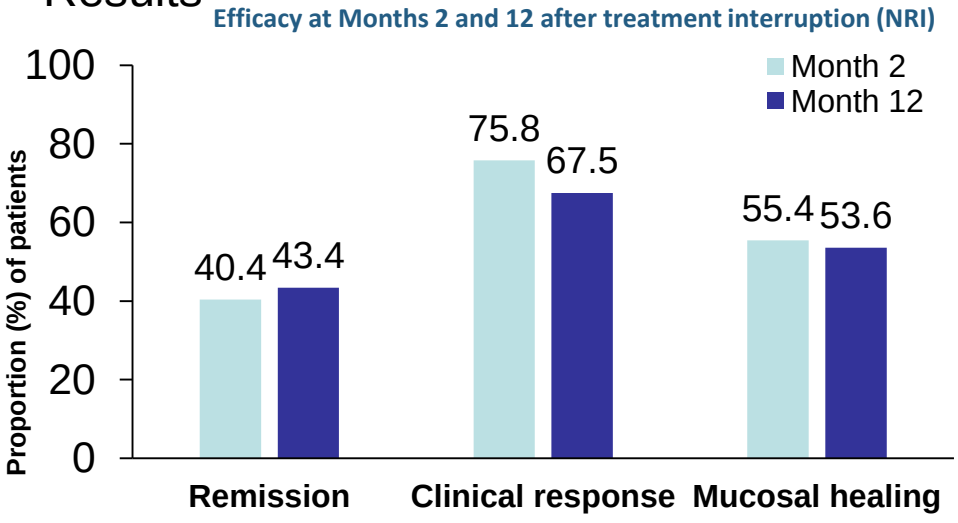


Feagan B, et al. Presented at DDW. June 2018. Abstract Sa1742
Sands E, et al. Presented at DDW. June 2018. Abstract Sa1761

Retreatment with tofacitinib following a period of treatment interruption is efficacious, well-tolerated, and sustained

- Methods
  - Data from Octave induction and sustain studies

- Results

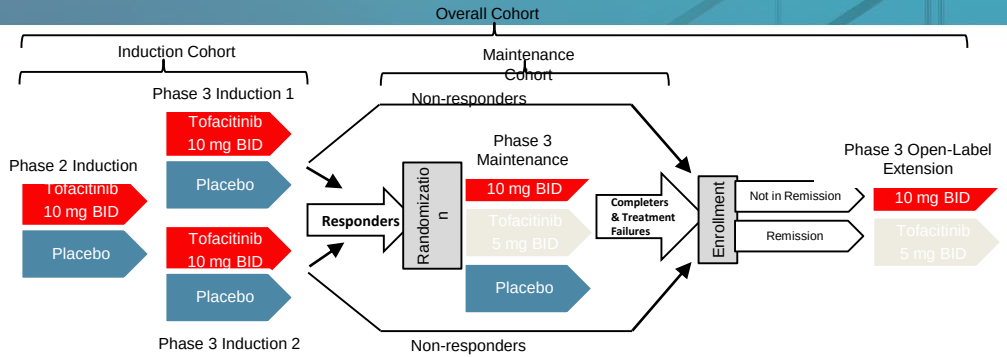


Panes J, et al. Presented at DDW. June 2018. Abstract 905

	Retreatment (N=101)		All tofacitinib-(N=1157)
	n (%)	IR (95% CI)[b] in OCTAVE Open	IR (95% CI)[b]
SAE	17 (16.8)	12.4 (7.2, 19.9)	10.7 (9.1, 12.4)
Serious infection events	3 (3.0)	2.1 (0.4, 6.2)	2.0 (1.4, 2.8)
HZ	5 (5.0)	3.6 (1.2, 8.3)	4.1 (3.1, 5.2)
HZ SAE	0 (0.0)	0.0 (0.0, 2.6)	0.2 (0.1, 0.6)
OI[a]	1 (1.0)	0.7 (0.0, 3.9)	1.3 (0.8, 2.0)[d]
Malignancies excluding NMSC	2 (2.0)[e]	1.4 (0.2, 5.1)	0.7 (0.3, 1.2)[d]
NMSC[a]	0 (0.0)	0.0 (0.0, 2.6)	0.7 (0.3, 1.2)[d]
MACE[a]	0 (0.0)	0.0 (0.0, 2.6)	0.2 (0.1, 0.6)[d]
GI perforation events[a]	0 (0.0)	0.0 (0.0, 2.6)	0.2 (0.1, 0.6)[d]
Deaths	2 (2.0)[e]	1.4 (0.2, 5.1)	0.2 (0.1, 0.6)

Tofacitinib Safety in Ulcerative Colitis Clinical Trials

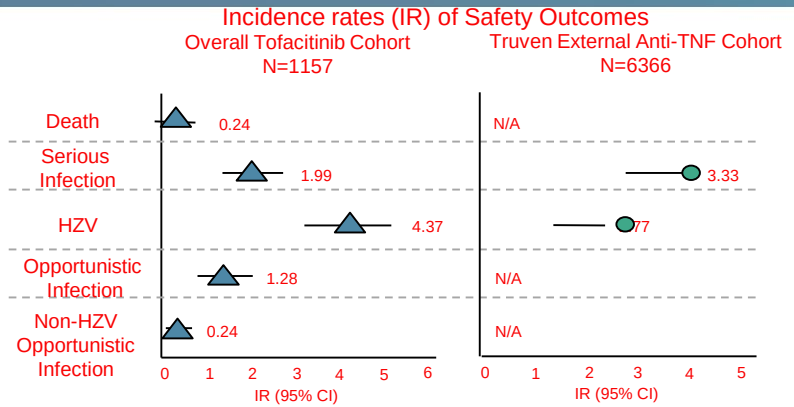
- Background
  - Tofacitinib is oral, small molecule JAK inhibitor recently approved for UC
  - Updated safety data up to 4.4 yrs follow-up

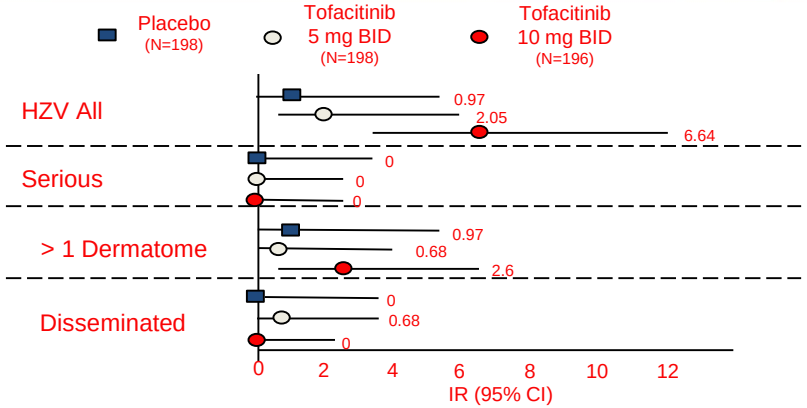


- **Methods**
  - General safety profile: adverse events, serious adverse events, events resulting in discontinuation and deaths
  - Safety events of interest: serious and opportunistic infections, herpes zoster (HZV), cardiovascular events, GI perforations
  - Truven Marketscan database comparison cohort
- **Results**
  - 1157 patients, 1613 yrs tofacitinib exposure

Sandborn WJ, et al. Presented at DDW. June 2018. Abstract 904.

Infections: Dose-Dependent and Sustained Risk of Herpes Zoster (HZV) Reactivation





Risk Factors for Infectious Safety Outcomes

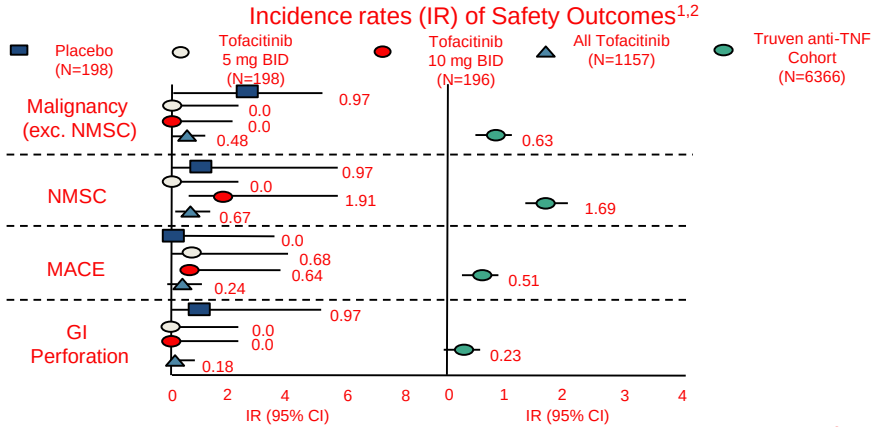
	HR	95% CI
Serious Infection		
Weight >90 kg	2.26	1.1-4.8
Low ANC	8.94	1.2-68.8
Opportunistic Infection		
Age (per 10 yrs)	1.54	1.2-2.1

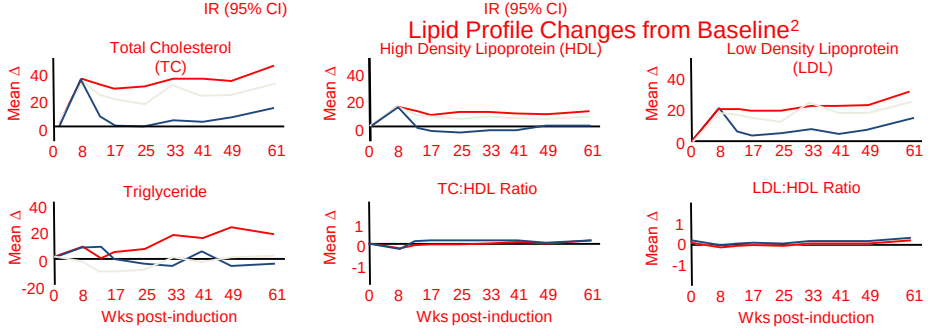
- Results
  - HZV risk stable over time on tofacitinib
- Conclusion
  - Increased risk of HZV with tofacitinib
  - Other infections not significantly increased

HZV: herpes zoster virus; ANC: absolute neutrophil count

1. Sandborn WJ, et al. Presented at DDW 2018. Abstract 904
2. Withrop KL, et al. Presented at DDW 2018. Abstract Sa1748
3. Withrop KL, et al. Presented at DDW 2018. Abstract Sa1770

Malignancy Rates and Lipid Alterations in Tofacitinib





- Results
  - No clustering of type of cancer
  - 10/11 pts with NMSC previously exposed to thiopurines and prior anti-TNF
  - Dose-dependent risk of non-melanoma skin cancer not seen
  - Increase in lipid profile significantly correlated with reduction in CRP[3]
- Conclusions
  - Low malignancy risk with tofacitinib
  - Increase is lipid profile, but unchanged ratios, possibly related to improvement in inflammation

NMSC: non-melanoma skin cancer; MACE: major adverse cardiovascular events; LDL: low density lipoprotein; HDL: high density lipoprotein; TC: total cholesterol

1. Lichtenstein GR, et al. Presented at DDW 2018. Abstract Sa1763.
2. Sands BE, et al. Presented at DDW 2018. Abstract Sa1750.
3. Feagan BG, et al. Presented at DDW 2018. Abstract Sa1765.

NOVEL THERAPIES

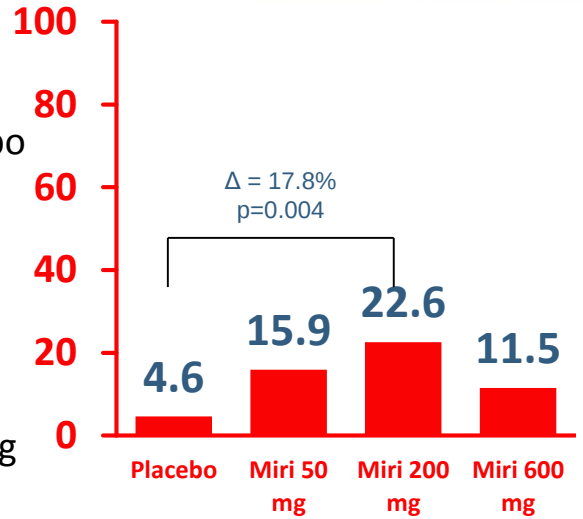
Mirikizumab is effective in the induction treatment for patients with moderate-to-severe UC

Methods

- Mirikizumab (miri) is a p19-directed anti-IL-23 antibody
- A Phase 2, multi-center, randomized, double-blind, placebo trial
- Miri 50 mg, 200 mg or miri 600 mg

Results

- 60% exposed or failed prior biologics
- Clinical remission rates were greater in patients treated with miri 200 mg (22.6%), but not miri 50 mg or miri 600 mg



Conclusion

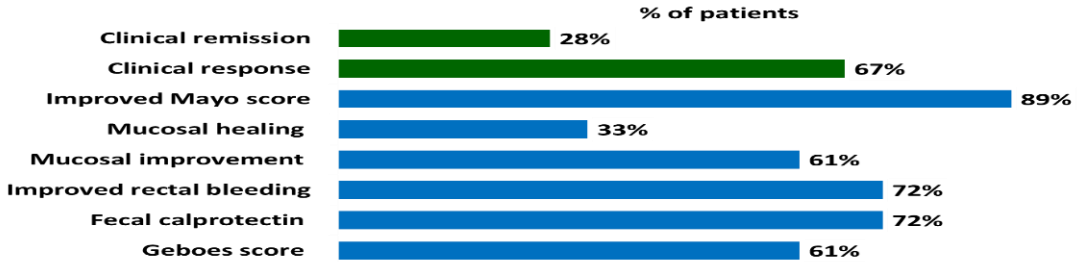
- Mirikizumab demonstrates efficacy in the induction treatment for patients with moderate-to-severe UC. Overall adverse event frequencies were similar for miri and placebo-treated patients.

UC, ulcerative colitis.

Sandborn W, et al. Presented at DDW June 2018. Presentation number 882.

Oral anti-TNF agent for mild-to-moderate UC: Results of an open-label phase 2A clinical trial

- OPRX-106: tobacco plant cells expressing the recombinant TNFR2-Fc fusion protein (rTNFR2-Fc)
  - Plant cell wall, cellulose, serves as protective agent against the gastric environment
- Methods:
  - 24 mild to moderate ulcerative colitis patients
    - Age: ≥18 years
    - Active mild to moderate UC, as defined by a Mayo score of 4 to 9 (inclusive) at screening
    - High level of calprotectin (>100 mg/kg)
  - Oral OD administration one of two doses (2mg or 8mg) for 8 weeks
- Results:

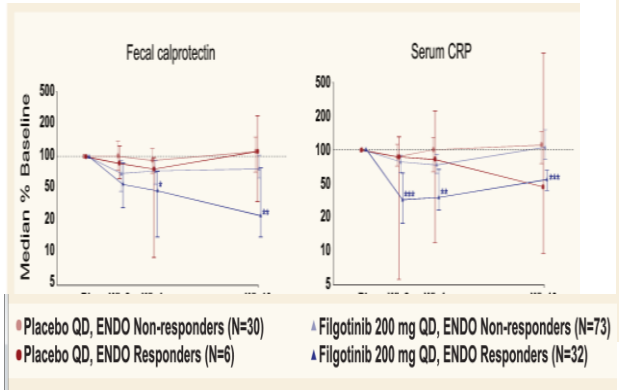


- **Conclusions:**
  - **Oral administration using OPRX-106 was effective, safe and well tolerated**
  - **OPRX-106 was not absorbed systemically**
  - **OPRX-106 was effective as demonstrated by clinical response and improvement in various disease parameters and not associated with immune suppression**

Almon E et al. presented at DDW June 2018. Abstract 739

Filgotinib decreases systemic and mucosal markers of inflammation if Crohn's patients

- Post-hoc analysis of results from FITZROY study for biomarkers response
  - 128 filgotinib treated patients compared to 44 patients with placebo
    - adjusting for baseline biomarker levels, steroid use, prior anti-TNF exposure
- Results



Week 2		Week 4		Week 10		
–8	–35*	–11	–35^	2	–30*	CALPR
–10	–34*	–1	–29^	–2	–16	CRP
8	–11^	3	–13*	–3	–20^	IL-6
–5	–8*	2	–12***	3	–8*	VEGF-A
–4	–1	4	–3	2	–15*	IL-17A
6	1	–4	–3	1	–9	IFN-γ
–7	0	–8	–1	6	–4	IL-10
8	–1	4	–1	1	–7	IL-8
PBO (n=44)	FIL (n=128)	PBO (n=44)	FIL (n=128)	PBO (n=44)	FIL (n=128)	

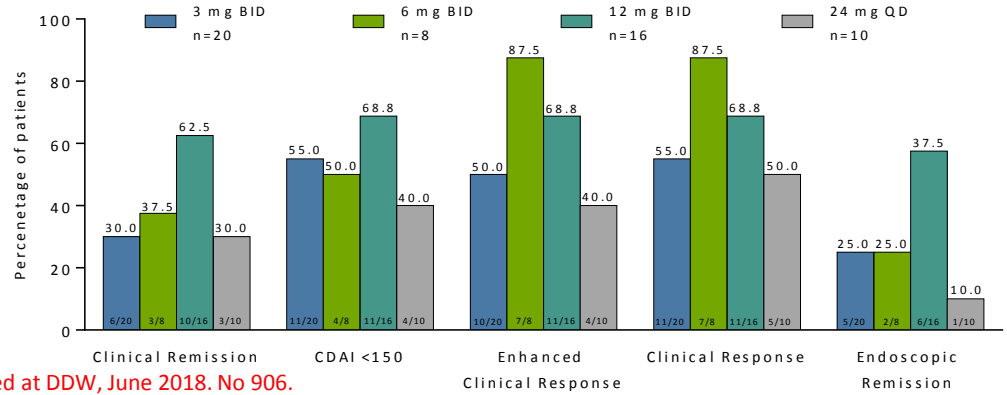
Sandborn W, et al. Presented at DDW. June 2018. Abstract Sa1757.

Upadacitinib - Extension Phase of CELEST

- Background
  - Upadacitinib (UPA) is a JAK1 inhibitor
  - CELEST demonstrated efficacy and safety for induction of moderate to severe CD (CDAI 220-450) refractory/intolerant of immunomodulator or TNFa
- Method
  - Phase 2 study
  - 180 patients who completed the 16wk induction phase were re-randomized to different doses of UPA for 36wk maintenance

- Results
  - Maintenance with UPA associated with continued improvements in clinical, endoscopic and laboratory* parameters to 36 weeks
  - Greatest improvements seen with 12mg BD
  - Safety comparable with studies in rheumatoid arthritis. No dose-dependent effect observed

Figure: Clinical and Endoscopic Endpoints at Week 52



Legend

- Clinical remission = Stool frequency ≤1.5/day and abdominal pain score ≤1
- Modified clinical remission = Stool frequency ≤2,8/day and abdominal pain score ≤1
- Endoscopic response = SES-CD ≤4
- Endoscopic remission = >50% reduction in SES-CD

Nb: 24mg daily dose rater stopped as not demonstrated to be effective in induction phase

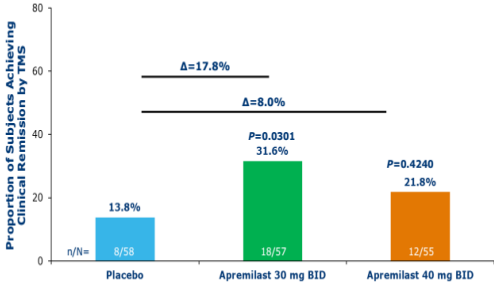
* CRP and calprotectin

Pane J, et al. Presented at DDW, June 2018. No 906.

According to a phase 2 study, Apremilast is effective for treatment of moderate to severe UC

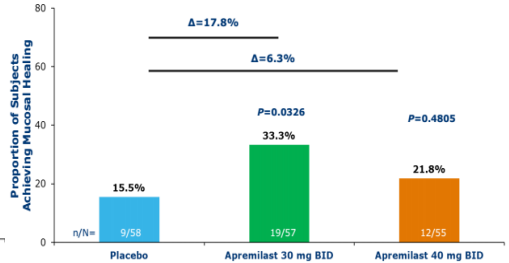
- Methods
  - Double-blind, placebo-controlled to evaluate apremilast (oral inhibitor of PDE4) for UC patients
  - Active UC (Mayo ≥6 to ≤11, and MES ≥2)
  - Patients have failed ≥1 conventional therapy and were **biologic naïve**
  - Primary end-point was Mayo score ≤ 2 with no sub-score > 1
- Results

PRIMARY END POINT: PROPORTION OF SUBJECTS ACHIEVING CLINICAL REMISSION BY TMS* AT WEEK 12 (ITT, NRI)



*TMS ≤2, with no individual subscore >1.

EXPLORATORY END POINT: PROPORTION OF SUBJECTS ACHIEVING MUCOSAL HEALING (MES ≤1 AND GEBOES <2) AT WEEK 12 (ITT, NRI)



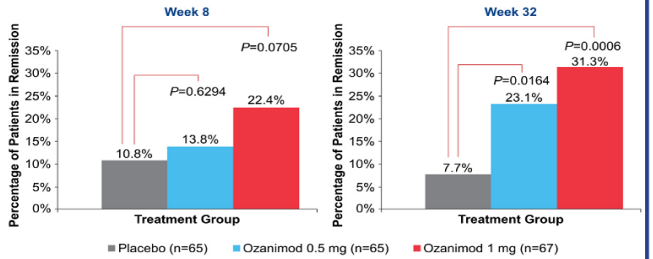
	Placebo n=58	Apremilast 30 mg BID n=57	Apremilast 40 mg BID n=55
Subjects, n (%)			
Any TEAE	30 (51.7)	28 (49.1)	36 (65.5)
Any serious TEAE	2 (3.4)	0 (0.0)	1 (1.8)*
Any TEAE leading to drug withdrawal	4 (6.9)	0 (0.0)	2 (3.6)
Any TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs in ≥5% of subjects, n (%)			
Viral URI	1 (1.7)	5 (8.8)	2 (3.6)
Headache	4 (6.9)	13 (22.8)	14 (25.5)
Nausea	5 (8.6)	3 (5.3)	6 (10.9)
Abdominal pain	1 (1.7)	3 (5.3)	1 (1.8)
Ulcerative colitis	3 (5.2)	0 (0.0)	0 (0.0)
Back pain	1 (1.7)	0 (0.0)	3 (5.5)
Asthenia	2 (3.4)	3 (5.3)	1 (1.8)

Danese S, et al. Presented at DDW. June 2018. Abstract 813

Ozanimod induced and maintained histological remission in patients with UC

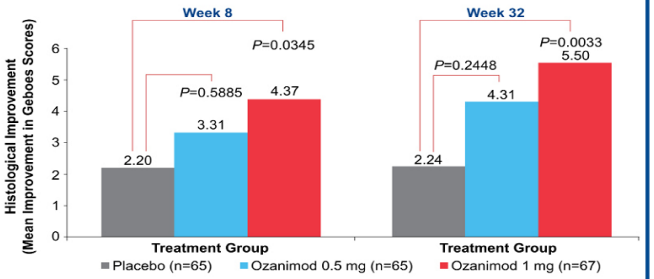
- Methods
  - Exploratory analysis from the TOUCHSTONE study to assess the concordance between histological remission and components of the Mayo score
  - 197 patients randomized to ozanimod 1 mg (n=67), 0.5 mg (n=65), or placebo (n=65)
- Results
  - High concordance in patients treated with ozanimod 1 mg and 0.5 mg between mucosal healing and:
    - Histological remission (87.1% and respectively)
    - Clinical remission (77.6% and 87.7% respectively)
    - Rectal bleeding (59.7% and 70.8% respectively)
    - Absence of diarrhea (70.1% and 76.9% respectively)

Figure 3. Histological Remission



- Histological remission was significantly greater in the 1 mg and 0.5 mg groups than in the placebo group at Week 32
- Both the 0.5 mg and the 1 mg groups showed numerical improvements over the placebo group at Week 8, but the differences were not significant

Figure 2. Histological Improvement

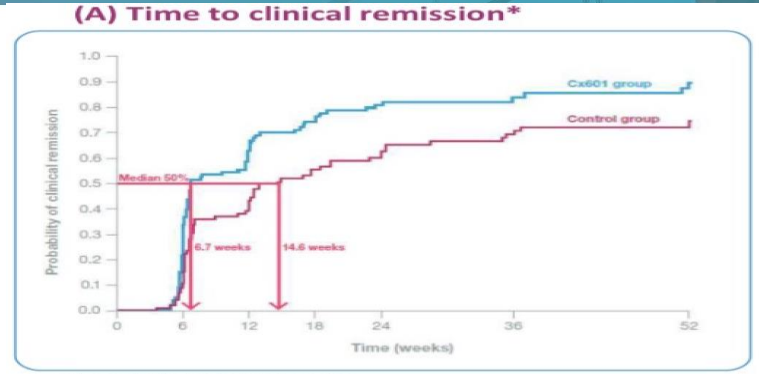


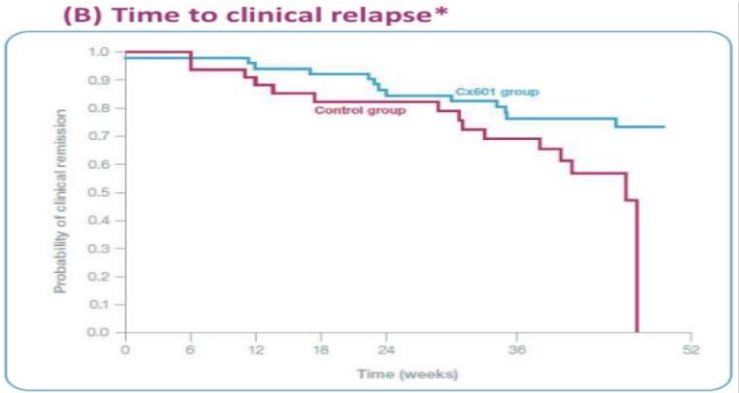
- Histological improvement was greater in the 1 mg group than in the placebo group at both Week 8 and Week 32
- The 0.5 mg group showed numerical improvement over the placebo group, but the difference was not significant at Week 8 or Week 32

Sandborn W, et al. Presented at DDW. June 2018. Abstract Sa1752.

Cx601 Mesenchymal Stem Cells for Complex Perianal Crohn's has Rapid Clinical Remission and Low Relapse

- Background
  - Cx601 local therapy has been shown to be superior to placebo in achieving clinical remission in the ADMIRE-CD study.
  - However, time to clinical remission and duration of response for Cx601 is unknown
  - Phase 3 double-blind RCT in patients with surgically treated fistulae
- Results
  - Median time to clinical remission is 6.7 weeks in Cx601-treated patients compared to 14.6 weeks in standard care arm
  - At week 52, relapse rate is 25% in Cx601-treated patients compared to 44% in standard care
- Conclusion:
  - Patients receiving Cx601 experienced a shorter time to clinical remission and a longer duration of remission





Clinical remission = closure of external openings
Relapse = reopening with active drainage and/or >2cm perianal collection on MRI

Garcia-Olmo D et al. Presented at DDW. June 2018. Abstract Sa1724.

Sugar consumption and IBD activity

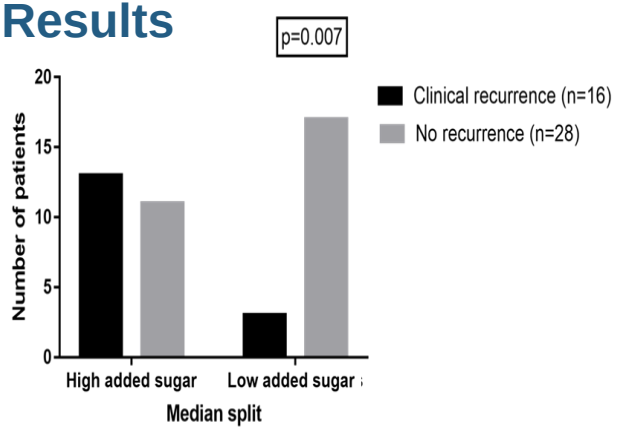
- Methods
  - Prospective diet data questionnaire including sugar intake
  - Tertiary referral center 2 year f/u
  - Patients were classified into 5 categories
  - Low sugar consumption group (Categories 1 and 2) were compared with the high sugar consumption group (Categories 4 and 5)
- Results
  - 859 patients (69.2% CD, 41.7% male)
  - The low sugar group (37.7% male, 66.3% CD) had a lower occurrence of abnormal CRP when compared to the high sugar group (37.7% vs. 60.6%; p=0.042)
  - The high sugar group utilized more IMM than the low sugar group (p=0.005)
  - Disease activity scores were significantly lower for the low sugar group when compared to the high sugar group (p=0.002)
  - Quality of life scores were significantly better for the low compared to the high sugar group (p=0.01)

Ahsan M, et al. Presented at DDW. June 2018. Abstract Su1890
Boland K, et al. Presented at DDW. June 2018. Abstract Sa1733.

Methods

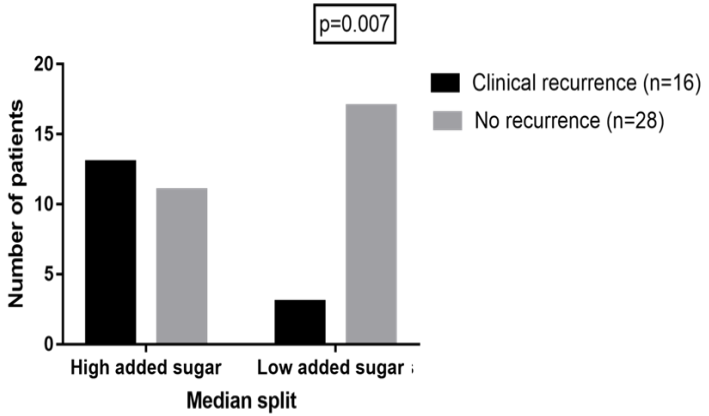
- Clinical and endoscopic data recorded at baseline and follow up colonoscopy
  - Clinical recurrence = HBI ≥ 4
  - Endoscopy recurrence = Rutgeert's score i2-i4
- Patients recorded 2 day food diaries, with calculated daily intake of 169 nutrients
- n=42 patients with 354 two-day food diaries

Results

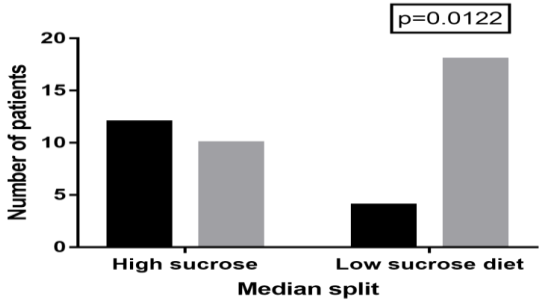


Dietary fat and sugar intake is associated with post-operative CD recurrence after ileal resection

- Methods
  - Clinical and endoscopic data recorded at baseline and follow up colonoscopy
    - Clinical recurrence = HBI ≥ 4
    - Endoscopy recurrence = Rutgeerts score i2-i4
  - Patients recorded 2 day food diaries, with calculated daily intake of 169 nutrients
  - n=42 patients with 354 two-day food diaries



- Results
  - Hierarchical clustering in patients with Rutgeerts i0
  - Hierarchical clustering in patients that are TNF-naïve (n = 24)
- Conclusion:
  - Higher added dietary sugar and lower mono-unsaturated fatty acid intake is associated with recurrence of Crohn's disease (CD) after ileal resection

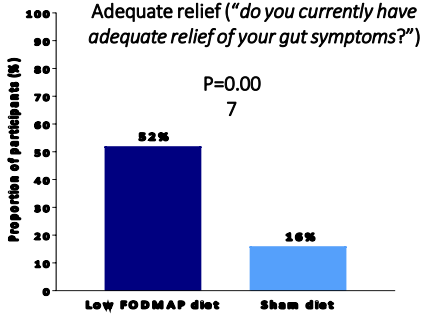


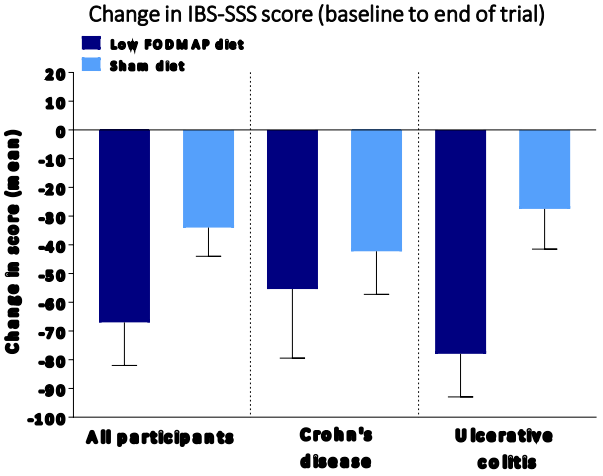
HBI, Harvey Bradshaw Index; TNF, tumor necrosis factor

Boland K, et al. Presented at DDW. June 2018. Abstract Sa1733.

Low FODMAP Diet Improves Functional Symptoms in Quiescent IBD

- Background
  - 35% of patients with quiescent IBD suffer from IBS-like symptoms
  - Only uncontrolled trials to date
- Method
  - First placebo-controlled trial of low FODMAP diet for management of IBS in IBD
  - UC and CD patients with CRP <10 and Calprotectin <250 meeting ROME III criteria for IBS
  - Randomized to low FODMAP or placebo (sham) dietary advice for 4 weeks
- Results
  - 27 low FODMAPP, 25 Sham
  - 75% self-reported compliance, supported by food diary
  - 'Adequate gut symptom relief' reported by 52% patient in FODMAP group (vs 16%, p 0.007)
  - Significant improvement in IBD-SSS and QoL scores seen for UC patients only
  - Bifidobacterim longum and adolescentis, F prausnitzii lower in FODMAP group. Lower SCFA concentration seen in UC patients only





Cox, R et al. Presented at DDW, June 2018. Oral Presentation 902.

Vitamin D Supplementation Reduces Inflammation in UC

- Background
  - VitD possesses anti-inflammatory properties
  - VitD deficiency prevalence in IBD due to poor absorption and decreased dietary intake
  - Nano VitD has better bioavailability
- Method
  - Double blind RCT in 60 patients with UC (UCDAI ≥3) and Vit D < 40mg/mL
  - Randomized 1:1 to receive oral VitD 60000IU daily for 8 days or placebo.
- Results
  - At 4 weeks, increase in VitD level to >40 correlated with reduction in UCDAI score (53% vs 13%, p 0.002), CRP and fecal calprotectin
- Conclusion
  - Oral nano Vitamin-D supplementation to achieve a target level >40ng/ml reduces disease activity and inflammatory markers in active UC
  - Longer periods of follow up and endoscopic evaluation required

Ahamed R, et al. Presented at DDW, June 2018. Oral presentation 9(

Fig 1: Clinical response to Nano VitD

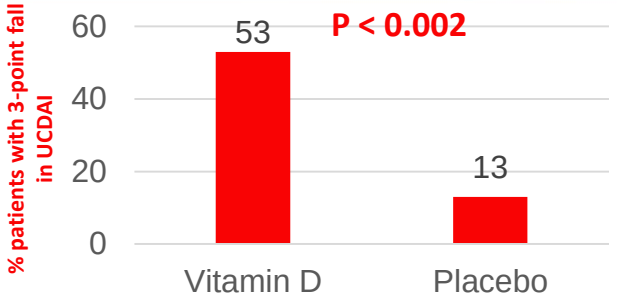
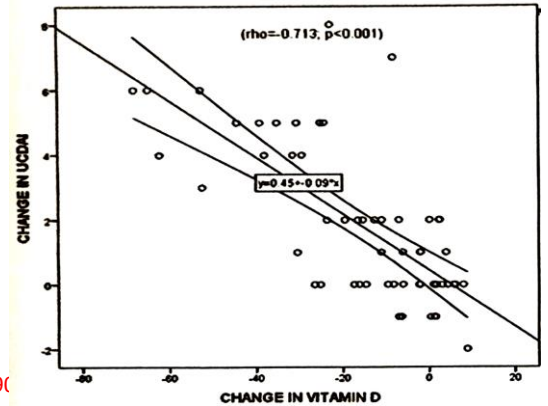


Fig 2: Change in disease activity vs change in Vit D



Cannabis in UC: Clinical and Minor Endoscopic Improvement Demonstrated in a Small RCT

- Method
  - Randomized placebo-controlled study
  - Active arm: cigarettes containing total 23mg THC daily.
  - Placebo: cannabis leaves with THC extracted
  - Left-sided and extensive UC failed to response to conventional therapy
- Results
  - 14 patient in each arm, 8 weeks of treatment
  - In the THC-treated arm, there were reductions in Disease Activity Index (10 → 4, and Mayo endoscopic score (2 → 1)
  - THC-treated arm had higher rates of memory decline.

	Study	Placebo
Patients number	14	14
Age (Y ±SD)	34±11	32±7
Gender (m/f)	6/7	11/4
Smoking	0	1
Colitis (extended/left sided)	8/6	6/8
Disease duration (Y ±SD)	8.2±4	6.5±5
Medication:		
5 ASA	7	9
Steroids	2	3
Thiopurine	2	4
Biologics	2	2

	Week 0	Week 8	p
Lichtiger score Cannabis group	10±3	4±3.2	<0.01
Lichtiger score Placebo group	10±2.7	8±2	<0.03
Mayo endoscopic score Cannabis group (median)	2 (IQR2-2.5)	1 (IQR 0-2)	0.01
Mayo endoscopic score placebo group (median)	2 (IQR2-2)	2 (IQR 1.2-2)	0.059
CRP Cannabis group	0.8±0.9	0.7±1.2	0.5
CRP placebo group	1.8±1.9	1±1.6	0.5
Calprotectine Cannabis group	135±113	115±103	0.7
Calprotectine placebo group	226±100	229±230	0.7

Naftali T et, et al. Presented at DDW, June 2018. Sa1744.

Novel Therapies in IBD

Therapy	Phase / n	Diagnosis	Highlights
GATA3 DNAzyme Enema (SB012)	2a / 20	UC	Improvement in Mayo score and endoscopic Mayo score
Indigo Naturalis	2a / 86	UC	Rates of clinical response, clinical remission and mucosal healing rates were higher in treatment group in dose-dependent fashion
Vagus nerve stimulation	1/16	CD	Induced clinical, biologic, and endoscopic improvement in refractory CD
Acupuncture and moxibustion	1/47	CD	Improved clinical response and remission compared to placebo in mild CD

Naganuma et, et al. Presented at DDW, June 2018. Sa1749.
D'Haens G, et al. Presented at DDW. June 2018. Abstract Mo1906
Atreya R, et al. Presented at DDW, June 2018. Oral Presentation 817.
Bao C, et al. Presented at DDW. June 2018. Abstract oral 476

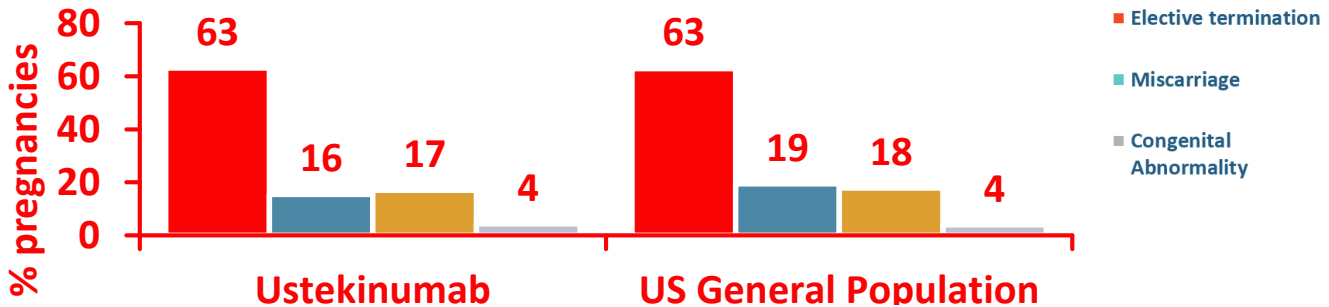
Risk Factors for Perineal Tear and Poor Wound Healing After Vaginal Delivery in IBD are similar to the general population

- Aims
  - Report the incidence of perineal injury in IBD
  - Identify risk factors for poor wound healing post-partum
- Method
  - PIANO cohort (prospective population-based cohort), 33 US centres
  - Patient completed questionnaires during pregnancy and post-partum
- Results
  - 536 births
    - 55% (297/536) vaginal delivery (Maternal perianal disease 19.6%)
      - 69% (206/297) episiotomy &/or tear
        - Associated with nulliparity
      - 11% (23/206) delayed wound healing
        - **Rates comparable to general population**
        - Associated with BMI >30
        - Not associated with disease activity or IBD medication exposure
- Conclusion
  - Risk factors for episiotomy, tear and poor wound healing are the similar to the general population
  - Limitations – self-reported outcomes, degree of tear unknown

Lewin S, et al. Presented at DDW. June 2018. Abstract 161.

Ustekinumab is not associated with increased rates of congenital abnormalities or miscarriage

- Methods:
  - Cases identified using company global safety database
  - Exposure to UST during or >2 months prior to conception
- Results:
  - n = 206 pregnancies; 9 congenital abnormalities
  - 83% psoriasis, 17% Crohn's
  - 5/9 congenital abnormalities were heart defects



- **Conclusion**
  - Comparable rates of miscarriage & congenital abnormalities in ustekinumab exposed to the general population and anti-TNF exposed

Mahadeven U, et al. Presented at DDW. June 2018. Abstract Su1799.

Opioid Use: Increases in year following IBD diagnosis with new persistent use increasing after flare

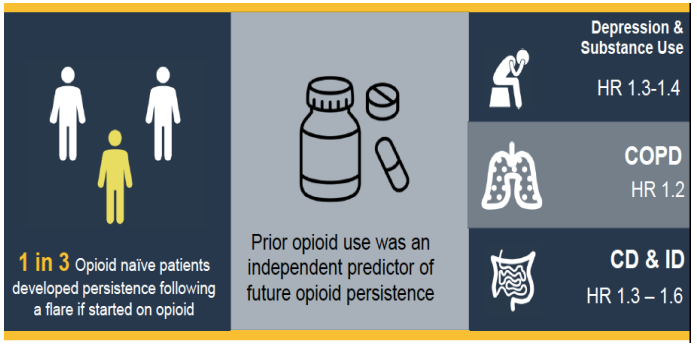
Increased Use in Year 1

- Aim
  - Estimate rates of opioid use prior to and after IBD diagnosis
- Methods
  - Retrospective cohort analysis
  - Continuous enrollment, 3 years (year prior and after diagnosis)
- Results
  - Increased use in year 1
  - Opioids + IBD = ↑ ED and inpatient stays

Cohort	% patients with ≥ 1 opioid claim (95% CI)		
	Year 0	Year 1	Year 2
CD	32 (31.3, 32.6)	43.7 (43, 44.4)	36.1 (35.5, 36.3)
UC	27.7 (27.2, 28.3)	37.4 (36.8, 38)	32.5 (31.9, 33.1)
Non-IBD	18.1 (17.7, 18.5)	20 (19.7, 20.4)	21.4 (21, 21.8)

New Persistent Opioid Use After Flare

- Aims
  - Assess incidence of new persistent (90-365 days) opioid use after flare
  - Assess associated factors
- Methods
  - Retrospective cohort analysis
  - Privately insured IBD patients with flare (steroid use for ≥ 14 days)
- ResultS: N = 15,119 (36% naïve, 49% chronic use)



IBD, Inflammatory Bowel Disease. ED, emergency department.
Noureldin N, et al. Presented at DDW June 2018 Abstract 90. Lin X, et al. Presented at DDW. June 2018. Abstract Sa1811

Patients with unresectable colonic dysplasia in UC are frequently unwilling to proceed with colectomy

- Methods:
  - Retrospective single center study in South Korea
  - 82 patients with UC-associated colorectal dysplasia or cancer
  - Based on the initial histologic diagnosis, patients divided into dysplasia group (n=61) and cancer group (n=21)

- Results:
  - Only 43% of endoscopically unresectable dysplasia patients willingly accepted colectomy
  - Considerable proportion of colectomy candidate dysplasia already had invasive cancer beneath the surface (> 50%), even if the forceps biopsy histology did not suggest invasive cancer

UC, ulcerative colitis

Yang DH et al. Presented at DDW June 2018. Abstract Sa1817

Consecutive negative findings on colonoscopy predicts low risk of advanced neoplasia

- Background
  - Limited data re: surveillance colonoscopy in patients with longstanding IBD
- Results*

N = 775

Neg-Neg 31.5% (234)
- No ACRN, 10.3% LGD

Neg-Pos 12.5% (93)
- ACRN 0.29/100 pty; 1 HGD

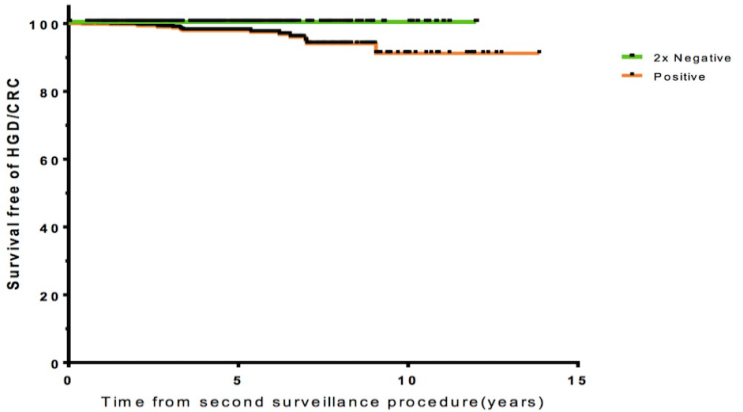
Pos-Neg 15.3% (113)
- ACRN 0.43/100 pty; 1 CRC, 1 HGD

Pos-Pos 39% (302)
- ACRN 0.76/100 pty; 4 CRC + 5 HGD

*Negative: no post inflammatory polyps, no stricture, no endoscopic disease, no neoplasia WITH adequate bowel prep + cecal intubation
Positive: one of the above

- Methods
  - Multicenter, multinational database of IBD colitis patients without high risk features, undergoing regular surveillance
  - Median duration of follow up after 2nd surveillance colonoscopy was 4 years

Figure 1: Rate of aCRN according to consecutive surveillance procedure findings (double negative versus at least one positive). Log-rank test, p=0.02

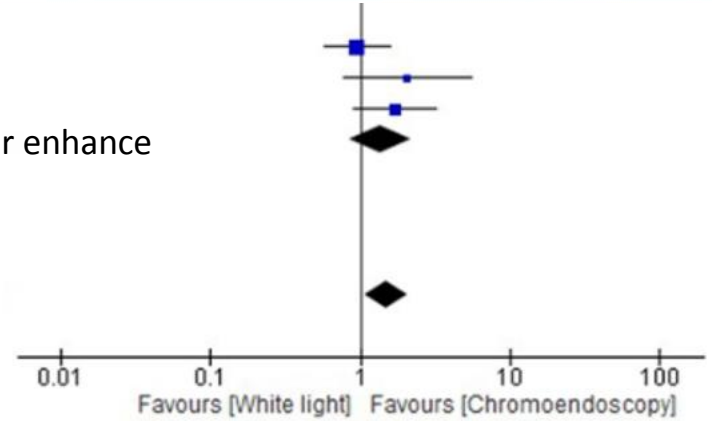


IBD, Inflammatory Bowel Disease. ACRN, advanced colorectal neoplasia. LGD, low grade dysplasia. PTY, patient years. HGD, High grade dysplasia. CRC, colorectal cancer.

Shah S, et al. Presented at DDW, June 2018, Abstract 604.

HDWLE was equivalent to chromoendoscopy for the detection of dysplasia

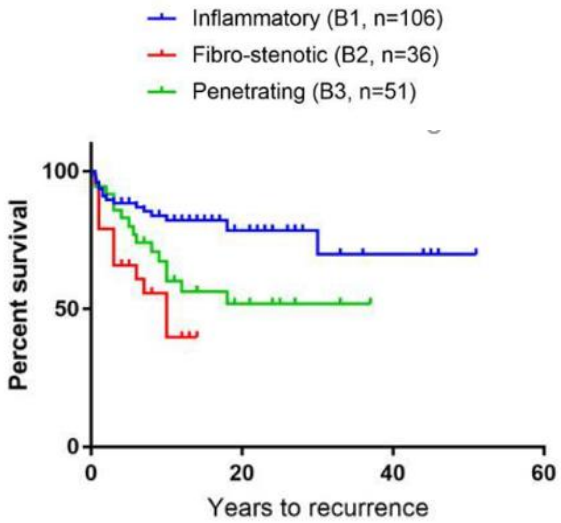
- Background
  - SCENIC consensus statement has recommended use of chromoendoscopy to further enhance the detection of dysplasia in ulcerative colitis
  - Recommendations were mainly based on trials comparing chromoendoscopy to SDWLE
- Methods
  - Systematic review and meta-analysis
- Results
  - 3 RCT of SDWLE and 3 RCT of HDWLE were included in the analysis
  - 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)



RCT, Randomized controlled trial. HDWLE, high definition white light endoscopy. SDWLE, standard definition white light endoscopy
Feuerstein JD et al. Presented at DDW June 2018. Presentation 163

Recurrence after ileostomy for Crohn's disease more common than previously reported

- Methods
  - Retrospective review from a prospectively maintained database of patients
  - All ileostomies with colectomy for confirmed Crohn's disease between 1975 and 2016 were reviewed
- Results
  - 239 patients were included with recurrence (>i2) recorded in 30.1% of patients
  - Patients with ileocolonic disease and/or inflammatory behavior were more likely to have recurrent disease (Figure 1)
  - Since the introduction of anti-TNF therapy, recurrence rates remain similar



Boland K et al. Presented at DDW June 2018. Presentation 475