Inflammatory Bowel Disease

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NONBIOLOGIC THERAPY

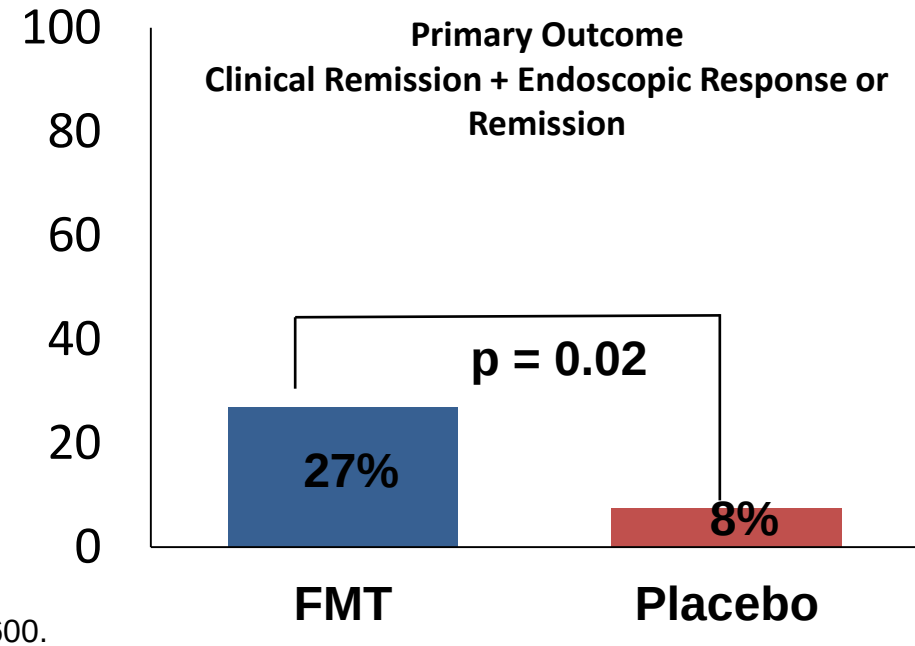
Multi Donor FMT is an Effective Treatment for Resistant UC: A Randomized Placebo-Controlled Trial

- Methods
  - Double-blind study of pooled donor FMT therapy for UC pts with active disease (n=81)
  - FMT or placebo on day 1, then FMT or placebo 5 times weekly x 8 wks
  - Primary endpoint: steroid-free clinical remission+endoscopic remission or response based on Mayo score at week 8
  - Secondary endpoint: including steroid free clinical remission (based on Mayo score); endoscopic remission (UCEIS≤1), endoscopic response, QoL

Even though UC patients with FMT had higher rates of clinical/endoscopic response, they may not have completely tapered off corticosteroids

Results

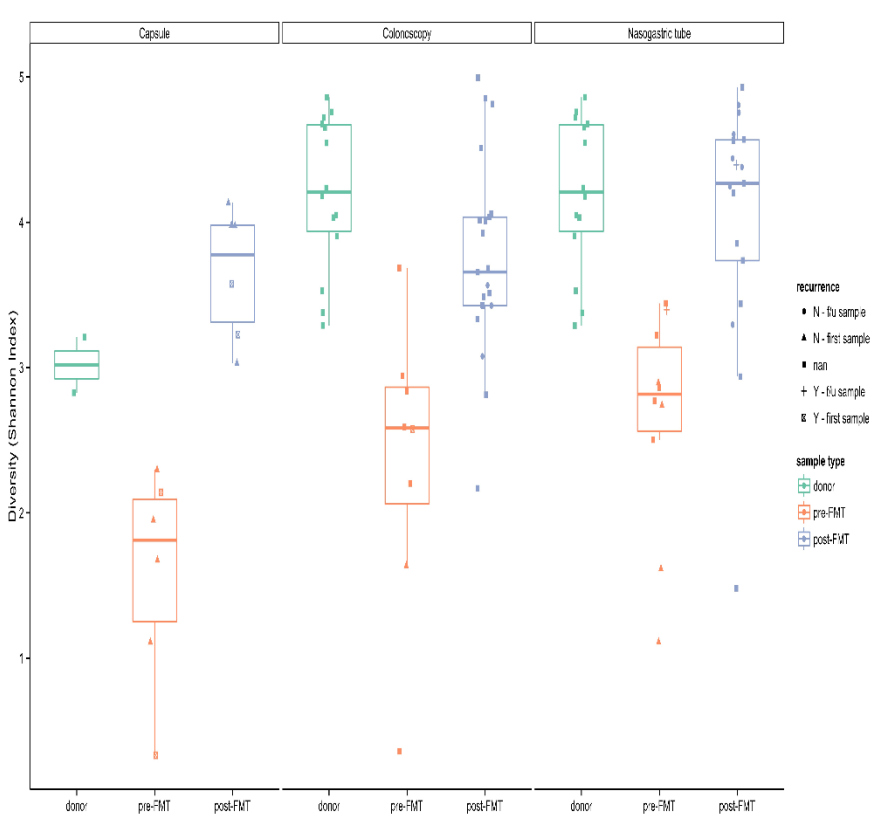
- **Compared to placebo, FMT led to higher rates of:**
  - **Clinical remission (44% v. 20%, p=0.02)**
  - **Clinical response (54% v. 23%, p<0.01)**
  - **Endoscopic remission (17% v. 8%, p=0.19)**
  - **Endoscopic response (37% v. 10%, p<0.01)**



Paramsothy S, et al. Presented at DDW; May 23, 2016. Abstract 600.

FMT via Capsule is Able to Achieve Microbial Engraftment Similar to NGT/Scope FMT

- Methods
  - Open label study of 19 pts with rCDI at 2 sites, one site randomized to low dose FMT (30 pills once) and other site to high dose FMT (30 pills on 2 days)
  - Primary endpoint: safety and clinical resolution of diarrhea at 8 wks
- Results
  - No difference in resolution of diarrhea between high dose and low dose groups at 8 weeks (p=0.15)
  - Microbiome of recipient after FMT different from their baseline
  - Microbiome of recipients after FMT similar to donors



FMT by capsules, colonoscopy and NGT able to recover the diversity found in donor community

Allegretti J, et al. Presented at DDW; May 22, 2016. Abstract 1738. and 1739.

Dairy fat and coconut oil are associated with UC flares among patients in remission

- Methods:
  - Prospective, multicenter enrollment
  - 412 patients with:
    - Mild-mod UC on stable 5-ASA monotherapy
    - Flared w/in 18 mos but not in last 3 mos
  - Validated food frequency questionnaire
  - F/U every 3 months for 1 year
- Results
  - 11% had flare within 1 year
  - Higher lactose, alpha linolenic acid, and myristic fatty acid (coconut oil) were associated with increased flare risk with possible dose response

Table: Association of medium/high (vs. low) dietary intake with odds of UC flare

	Medium Intake OR (95% CI)	High Intake OR (95% CI)
Dairy Protein	2.44 (1.02, 5.82)	2.57 (1.09, 6.10)
Alpha linolenic acid	2.94 (1.19, 7.25)	2.94 (1.19, 7.25)
Linolenic acid	2.44 (1.19, 7.25)	2.57 (1.09, 6.10)
Myristic acid	1.52 (0.63, 3.67)	2.87 (1.28, 6.45)
Lactose	3.52 (1.45, 8.55)	2.45 (0.98, 6.17)

UC patients on 5-ASA monotherapy have an increased risk of flare with high dietary intake lactose, myristic acid, and alpha linolenic acid.

Barnes E, et al. Presented at DDW; May 21, 2015. Oral 17.

Dose reduction of AZA is effective and safe in patients on dual IFX/AZA therapy

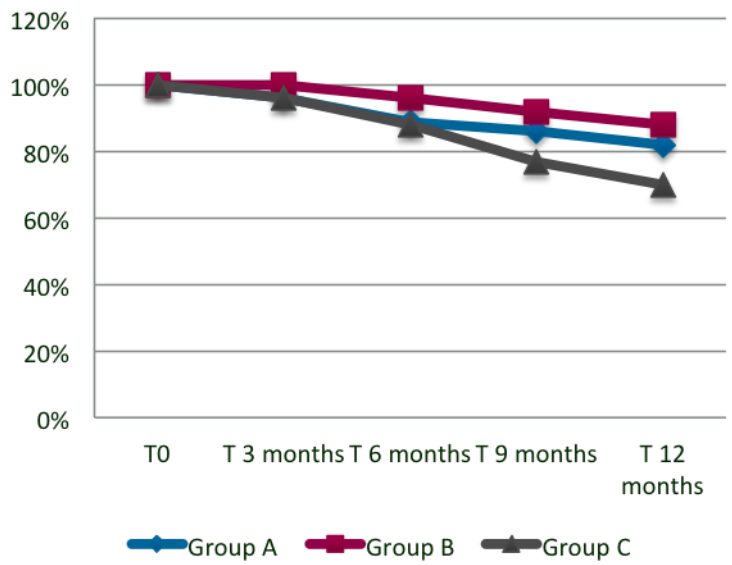
- Methods
  - Prospective, 3 cohorts of IBD pts treated w/ IFX-AZA ≥1 year and in deep clinical/endoscopic remission ≥ 6 months
    - Cohort A: AZA-IFX unchanged
    - Cohort B: AZA halved
    - Cohort C: AZA stopped
  - Primary endpoint: failure (CDAI>220 w/ FC >450 µg/g) or need to change regimen because of adverse events

AZA dose reduction should be considered in IBD patients in remission who are on combination therapy with IFX

Results

- **Failure seen in 17.8% cohort A, 11.5% cohort B, 30.7% cohort C, p=0.1 across groups**
- **3 pts in cohort A stopped or reduced AZA due to AEs**

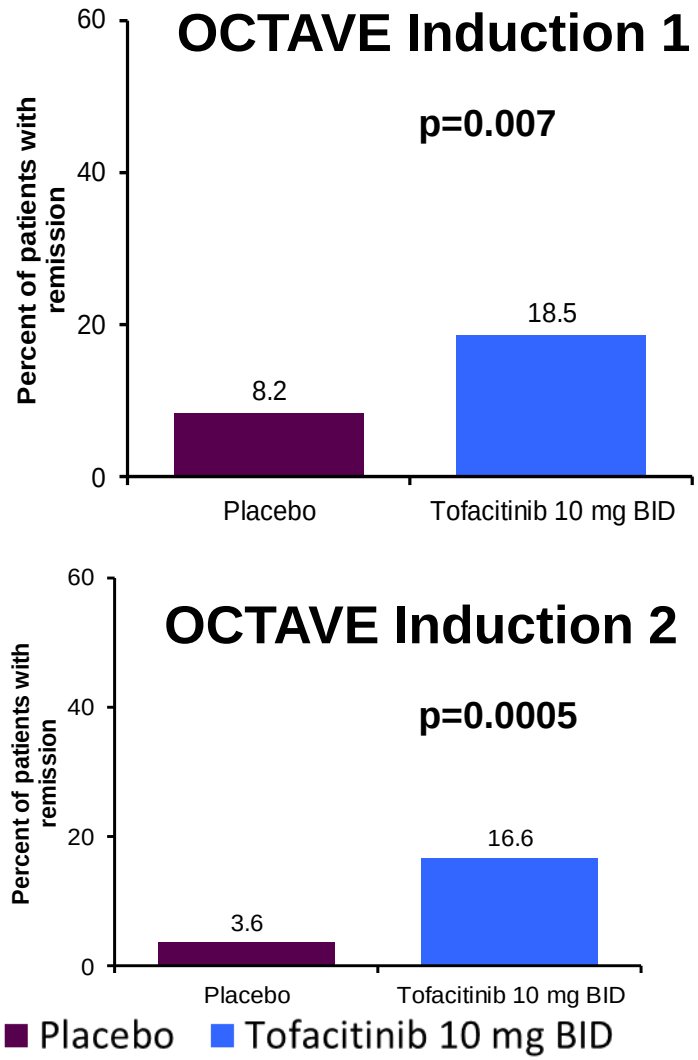
Figure 1: Failure at 1 year



Roblin Z. et al., Presented at DDW May 23, 2016

Tofacitinib is Safe and Effective as Induction Therapy for Moderate-Severe UC

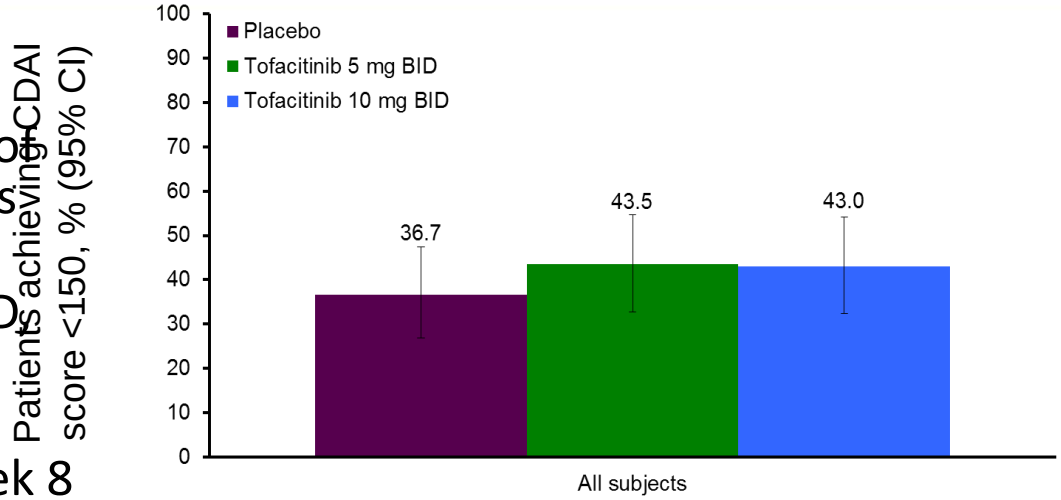
- Methods
  - Phase 3 studies (Octave 1 and Octave 2) randomized to receive tofacitinib 10 mg BID or placebo x 8 wks
  - Primary endpoint at week 8: clinical remission (Mayo score≤2, no subscore>1, rectal bleeding subscore of 0)
  - Key secondary endpoint at week 8: mucosal healing (Mayo endoscopic subscore≤1)
- Results
  - Compared to placebo, tofacitinib had greater efficacy for induction
  - Efficacy similar in anti-TNF naïve and exposed patients
  - Tofacitinib may not require therapeutic drug monitoring given similar remission rates at varying tofacitinib concentrations
  - Improved IBDQ remission at week 4 and 8



Sandborn W, et al. Presented at DDW; May 23, 2016. Abstract 767.;
Mukherjee A, et al. Presented at DDW; May 23, 2016. Abstract 1781; Panes J, et al. Presented at DDW; May 24, 2016. Abstract 2003.

Tofacitinib Provides Small, Modest Treatment Effects for Induction of CD Remission

- Methods
  - Multicenter phase 2b study of moderate-severe CD patients (CDAI=220-450), n=280
  - Placebo , tofacitinib 5 mg BID, tofacitinib 10 mg BID
  - Primary endpoint: clinical remission (CDAI<150) at week 8
  - Secondary endpoints: Clinical response; Changes in CDAI, CRP, fecal calprotectin over time
- Results
  - Compared to placebo, tofacitinib does not significantly increase clinical remission

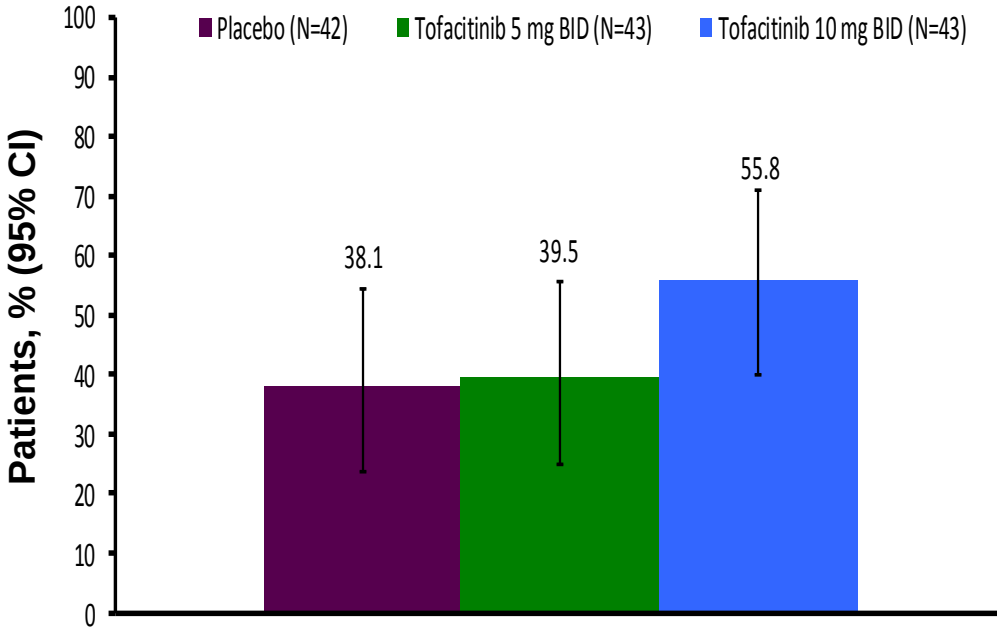


- **Tofacitinib does reduce CDAI scores and CRP concentration from baseline compared to placebo**

Panes J, et al. Presented at DDW; May 24, 2016. Abstract 855.

Tofacitinib Not Significantly More Effective than Placebo at Maintaining Response in CD

- Methods
  - Phase 2b study of 26 week maintenance therapy of moderate-severe CD (placebo-59, 5 mg BID-60, 10 mg BID-61)
  - Primary endpoint: Clinical response (CDAI 100) or clinical remission at wk 26
  - Secondary endpoints: Clinical remission/response, FCP, CRP, CDAI over time
- Results
  - Tofacitinib 10 mg BID with higher proportion of patients maintaining clinical response, but no significant difference to placebo
  - Significant decrease in CRP and fecal calprotectin with higher dose tofacitinib

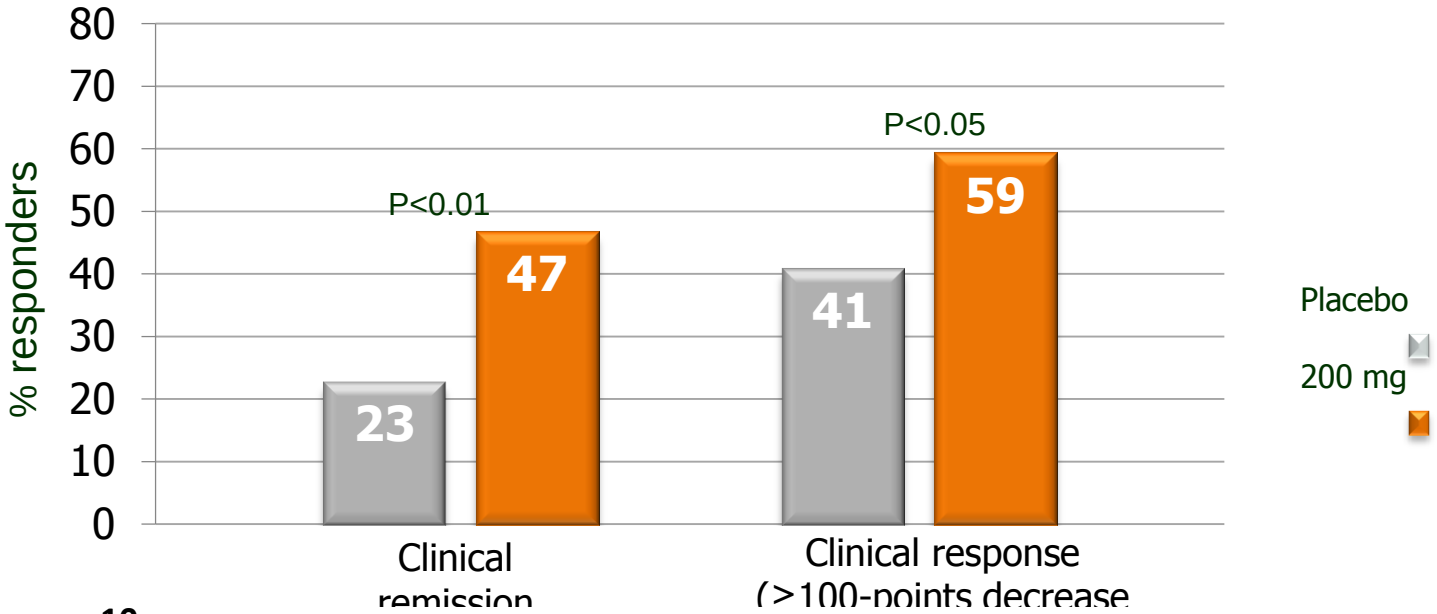


D'Haens G, et al. Presented at DDW; May 24, 2016. Abstract 856.

Filgotinib is safe and effective for treatment of moderate to severe Crohn's disease

- Filgotinib: a selective once daily dose JAK1 inhibitor
- Tested for efficacy in 10 week multicenter/multinational European study: FITZROY

- **No concomitant TNFi or IMM allowed**
- **Awaiting maintenance, endoscopic data**
- **First Jak1 inhibitor safe/effective in Crohn's**



Vermeire S, et al. Presented at DDW; May 24, 2016. Abstract 812c.

Ozanimod improves histology in mod-severe UC

- Background
  - Ozanimod previously shown to induce clinical response, remission, and mucosal healing in TOUCHSTONE
  - Does it improve histologic score?
- Methods
  - 197 patients randomized to placebo, ozan 0.5mg, ozan 1mg
  - Biopsies scored at week 0, 8, 32 using Geboes score

- **Results**
  - **Histologic improvement greater in 1mg than placebo at week 8 (-4.37 v. -2.2, p=0.0345) and 32 (-5.5 v. -2.24, p=0.0033)**
  - **Histologic remission at week 32 in 1mg group occurred in 21/67 (31.3%) (p=0.0006 c/w placebo) and in 0.5mg group 15/65 (23.1%) (p=0.0164 c/w placebo)**

High-dose ozanimod results In progressive histologic improvements and remission in mod-severe UC at 32 weeks

Sandborn W, et al. Presented at DDW; May 24, 2015.

Temporary diverting ileostomy is seldom a successful treatment in severe perianal Crohn's

- Methods
  - Retrospective review
  - 39 patients who underwent ostomy creation (total proctocolectomy w/ end ileostomy vs. diverstion) for perianal Crohn's
- Results
  - 16/39 (41%) had TC w/ EI
  - 23/39 (59%) with diversion
    - 7 then underwent takedown but 6 of these (86%) had perianal recurrence

INSERT FIGURE*

There is a high rate of recurrent perianal disease in patients who undergo early diverting ileostomy for perianal CD

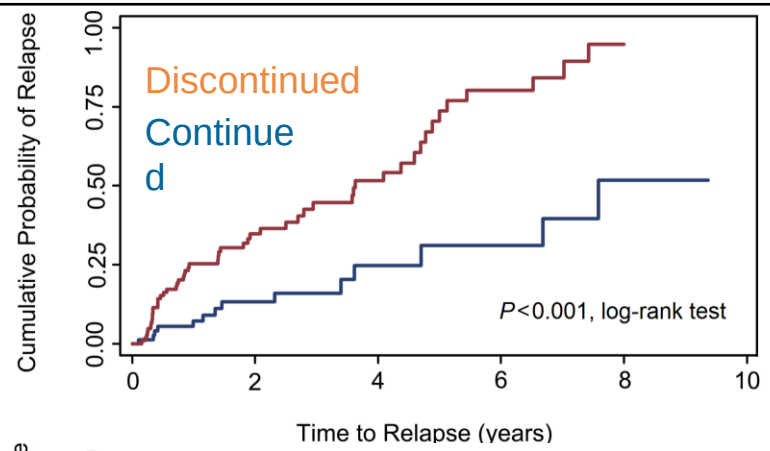
Lodhia N. et al., Poster Presented at DDW May 21, 2016

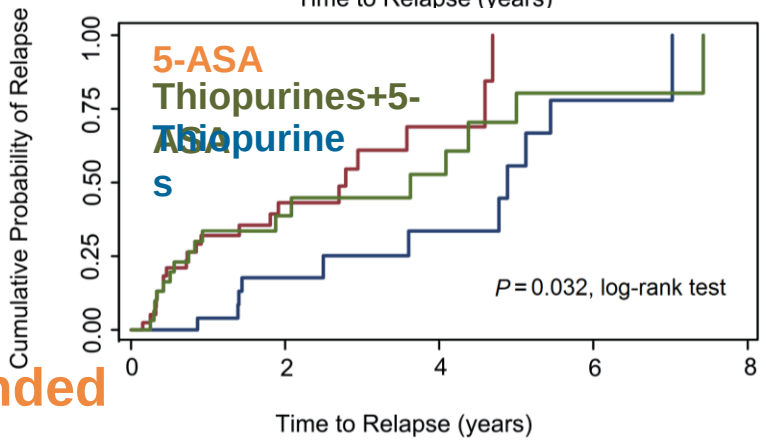
BIOLOGIC THERAPY

High Relapse Risk After Infliximab Discontinuation in Ulcerative Colitis

- Methods
  - Multinational retrospective study
  - 193 patients with sustained clinical and endoscopic remission for ≥1 year
- Results
  - No difference in rates of hospitalization or surgery
  - De-escalation to thiopurines was the most effective strategy to reduce relapse risk
  - Limited success when IFX resumed: only 51.4% regained remission, 17.1% had infusion reactions

	Relapse Rate	Time to Relapse (Median)
IFX Discontinued (n=111)	47.7%	3.6 years
IFX Continued (n=82)	17.1%	7.6 years





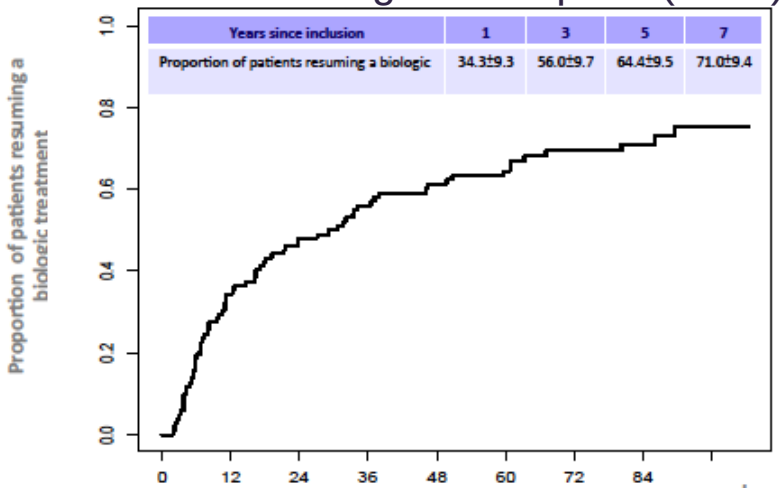
Infliximab discontinuation not recommended

Fiorino et al. Presented at DDW May 21, 2016. Oral Presentation 19.

Long Term Outcomes after IFX withdrawal after sustained remission in Crohn's disease

- Methods:
  - Median follow up 7 yrs of the STORI cohort (n=102).
  - Results:
  - No biologic restarted in 22/102 (21%)
  - Severe failure (surgery, new perianal disease) before biologic resumption in 8/102 (8%; mean time to event =45mths (22-64))
  - Biologic restarted in 72/102 (IFX 64, ADA 8), mean drug holiday = 13 mths (6-33)
  - Outcomes after IFX resumption
    - Successful remission in 42/64 (65%)
    - Unsuccessful 22/64 (35%)

Cumulative incidence of biologic resumption (n=72)



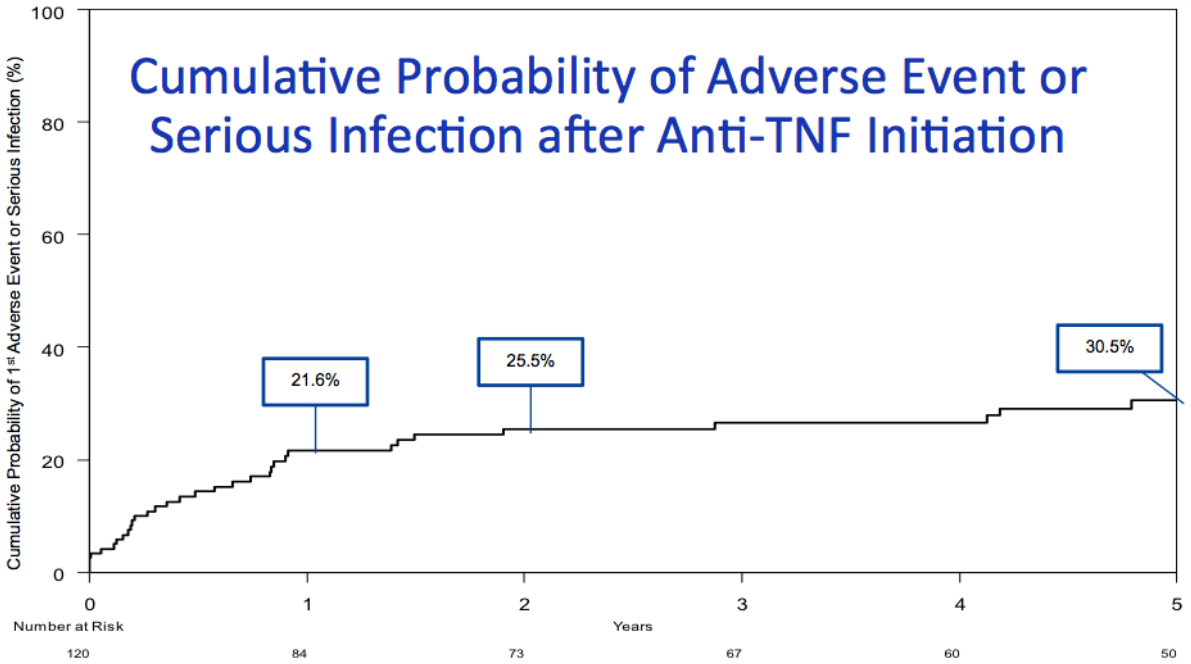
	P value	HR	95% CI
UGI (L4)	0.027	5.8	1.5 – 21.8
WCC ≥ 5.0 (10^9/L)	0.002	10.5	1.3 – 83.0
Hb ≤12.5g/dL	0.014	4.1	1.5 – 21.8

Factors associated with severe failure (i.e. requiring surgery or new complex perianal disease)

Reenaers et al. Presented at DDW May 22, 2016. Oral Presentation 313.

Rates of adverse events and serious infections are stable over time with anti-TNF therapy

- Methods
  - Olmsted County, US
  - Medical record review – Crohn's patients (1970 – 2010)
  - Anti-TNF therapy
- Results
  - 424 patients (50.7% women, 29.4y [IQR 20.9-46.6])
  - Cumulative probability of anti-TNF use at 10 years was 23.7%

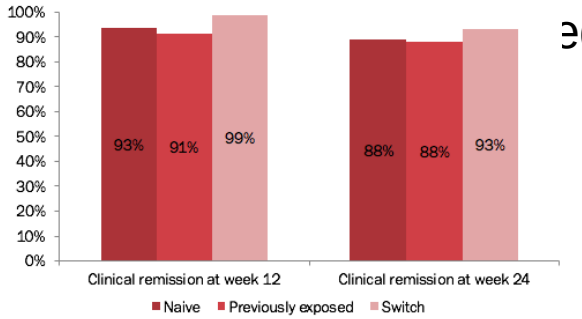


AE rate for anti-TNF therapy remains unchanged over long term follow up

Shivashankar et al, presented at DDW May 2016. Presentation 990

IFX biosimilar is as effective and safe when switching from original IFX

- Methods
  - Multicenter study of consecutive patients on CT-P13 (IFX biosimilar). Largest cohort, n=547. Included: IFX naïve, previous TNF exposure, and switched from remicade
- Results
  - 311 TNF-naïve. 139 previous TNF exposure (IFX 31, ADA ed from

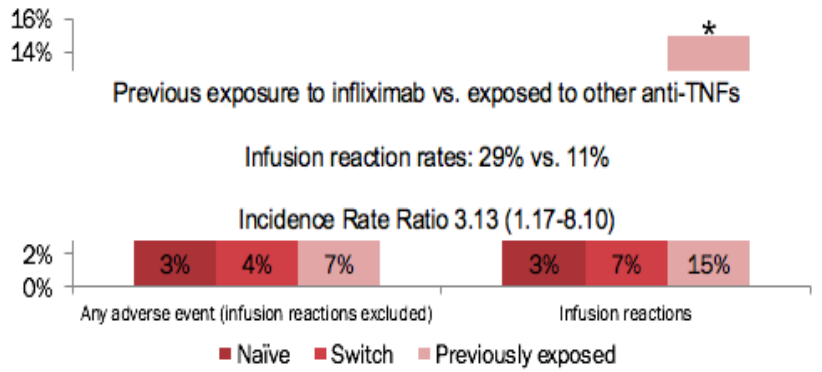


* estimates of efficacy come from a time-to-event analysis for censored observations

Preliminary efficacy estimates*

Adverse Events

	Other AEs	P value	Infusion reactions	P value
Naive vs. previously exposed	IRR: 0.54 (0.21–1.39)	NS	IRR: 0.21 (0.09–0.47)	< 0.001
Naive vs. switch	IRR: 1.46 (0.44–6.21)	NS	IRR: 0.70 (0.24–2.15)	NS
Previously exposed vs. switch	IRR: 2.71 (0.78–11.8)	NS	IRR: 3.25 (1.33–9.06)	< 0.001

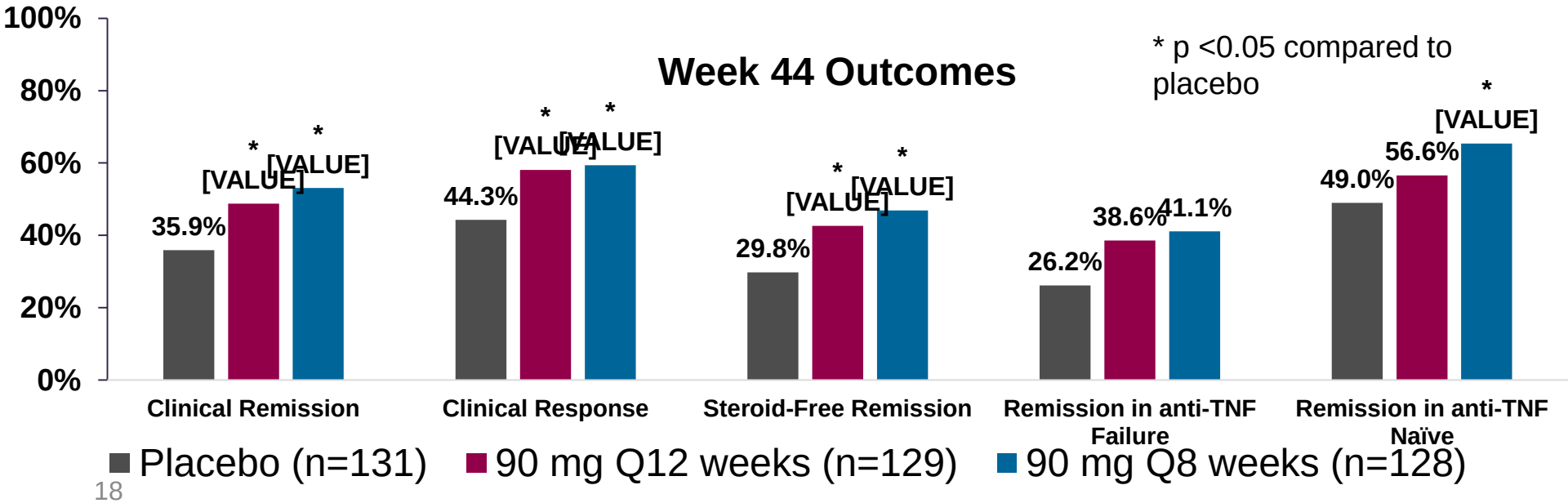


- Infusion reactions
  - Occurred predominantly in patients restarting after a drug holiday

Fiorino et al. Presented at DDW May 22, 2016. Oral Presentation 439.

Ustekinumab (anti-IL-12/23 monoclonal antibody) Maintenance Therapy is Efficacious in Crohn's

- Methods:
  - Phase 3, double-blind, placebo-controlled, 44-week maintenance trial (IM-UNITI)
  - Responders to IV ustekinumab induction were re-randomized to receive either placebo, 90 mg SQ Q8 weeks, or 90 mg SQ Q12 weeks
  - 60% of patients entered the maintenance study in remission
- Results:
  - Q8 week dosing more consistently demonstrated efficacy than Q12 week dosing across a range of endpoints



Sandborn et al. Presented at DDW May 23, 2016. Oral Presentation 768.

Ustekinumab (anti-IL-12/23 monoclonal antibody) Has a Favorable Safety Profile Through 44 Weeks

- Results:
  - No notable new safety issues identified
    - No deaths or serious opportunistic infections
  - 2.3% developed antibodies, but these did not preclude drug efficacy

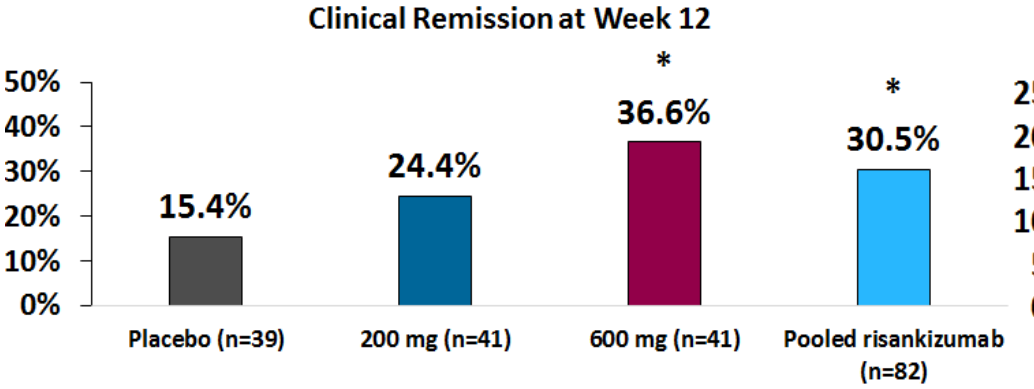
Subjects With (%)	Placebo	90 mg SC Q12w	90 mg SC Q8w
Death	0%	0%	0%
Adverse Events	83.5%	80.3%	81.7%
Serious Adverse Events	15.0%	12.1%	9.9%
Serious Infections	2.3%	5.3%	2.3%
Discontinuation due to AE	6.0%	7.6%	3.1%
Malignancies	0.8%	0%	0.8%

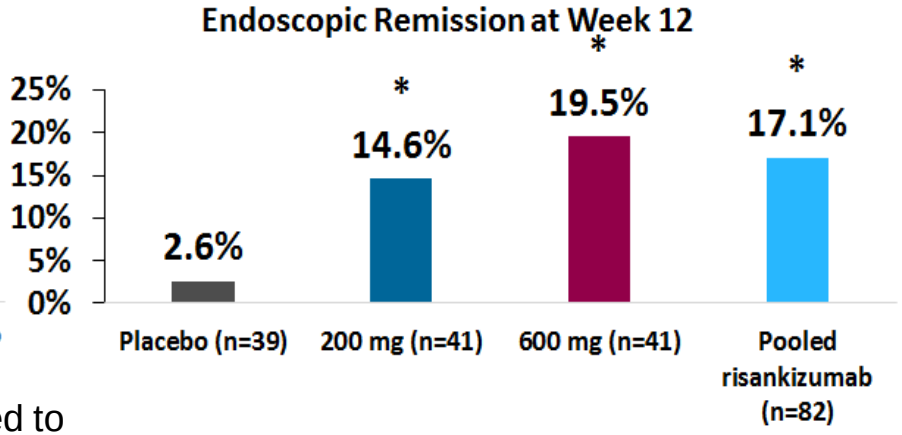
Sandborn et al. Presented at DDW May 23, 2016. Oral Presentation 768.

Selective IL-23 Blockade with Risankizumab Shows Promise in Moderate-to-Severe Crohn's Disease

- Background:
  - Risankizumab was superior to ustekinumab in a head-to-head psoriasis trial
- Methods:
  - Phase 2, placebo-controlled, double-blind, 12-week induction trial
  - Endoscopies at baseline and at Week 12 assessed by blinded central reader
  - 94.2% were anti-TNF experienced; 56-59% had ≥3 prior anti-TNFs

Primary Endpoint





* p <0.05 compared to placebo

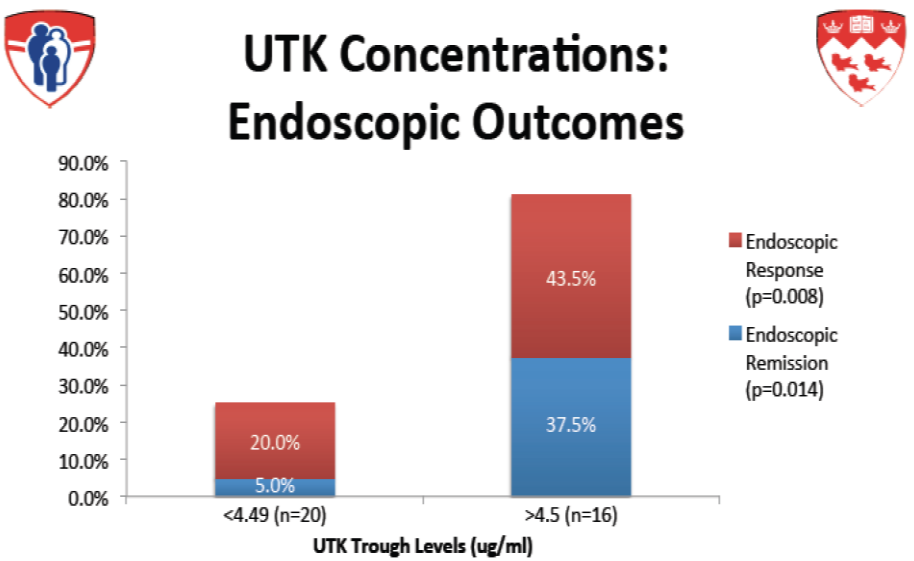
Feagan et al. Presented at DDW May 24, 2016. Oral Presentation 768.

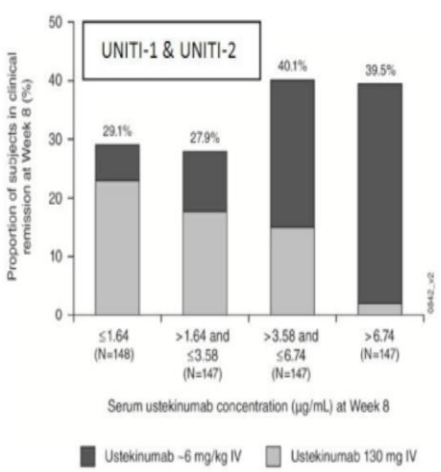
THERAPEUTIC DRUG MONITORING

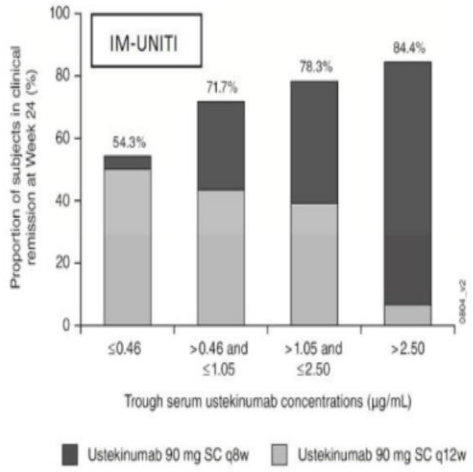
Evidence of an Exposure-Response (E-R) Relationship for Newer Biologic Agents: Ustekinumab

- Combined prospective & retrospective cohort of 59 CD patients[1]
- Week 8 UTK TL > 4.5 µg/mL (HMSA) are associated with endoscopic response (sens 72.2%, spec 83.3%, p=0.0006, AUC 0.782)

- Post-hoc analysis demonstrated UTK levels were dose-proportional and a positive E-R relationship was observed during induction (UNITI) and maintenance (IM-UNITI) phases[2]







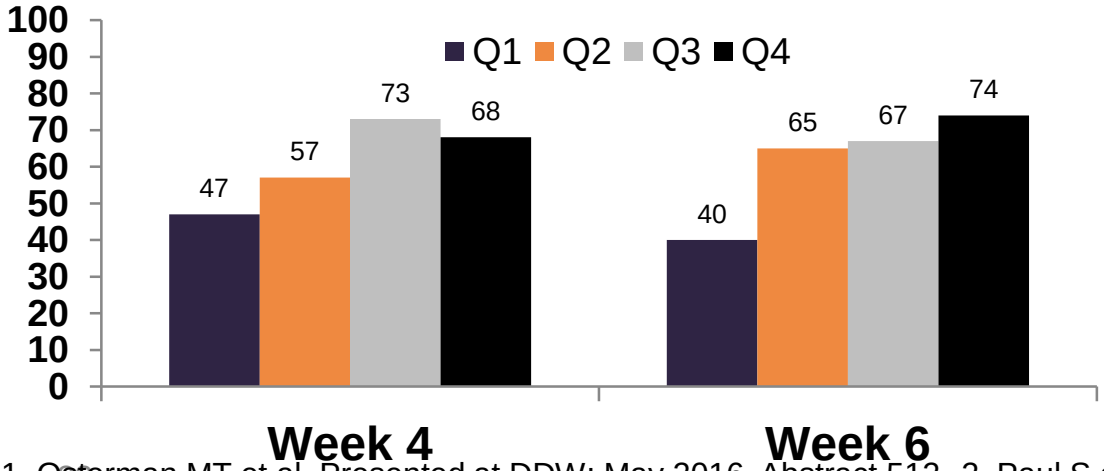
1.Battat R et al. Presented at DDW; May 2016. Abstract 696

2. Adedokun O et al. Presented at DDW; May 2016. Abstract Sa1934

Evidence of an Exposure-Response (E-R) Relationship for Newer Biologic Agents: Vedolizumab

- Post-hoc analysis of GEMINI 1 demonstrated that VDZ TL taken at week 6 (but not 2 or 4) correlated with clinical remission of UC at week 14 and 52[1]
- Prospective ROC analysis of 34 patients (22 CD, 12 UC) found a VDZ TL threshold of 40.1 ug/ml at week 6 predicted sustained remission at week 14 (AUC 0.84, sens 100%, spec 70%) and reduced need for week additional week 10 administration[2]

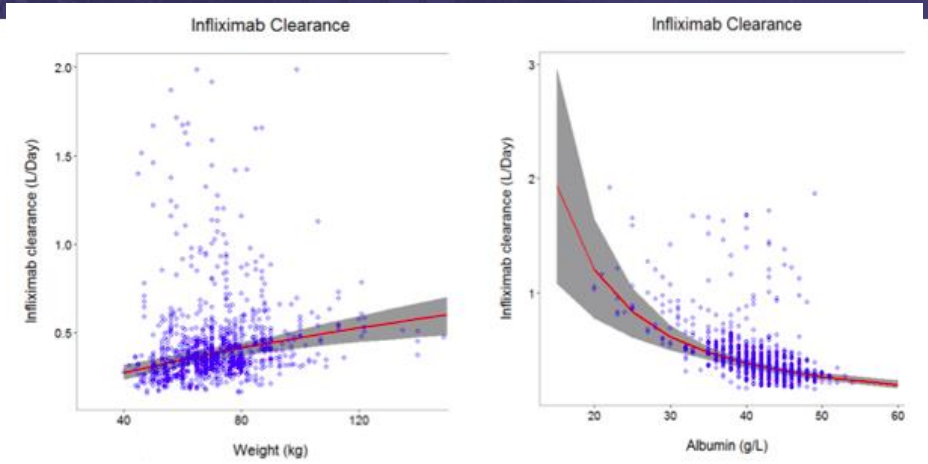
Week 14 remission rate by VDZ quartile at Weeks 4 and 6



Quartile	Week 4	Week 6
Q1	<34	<20
Q2	35-44	21-26
Q3	45-59	27-38
Q4	60-139	39-79

1. Osterman MT et al. Presented at DDW; May 2016. Abstract 512 2. Paul S et al. Presented at DDW; May 2016. Abstract Sa1939

Infliximab drug levels <30 AU/mL (3 mg/L) Predisposes to Immunogenicity



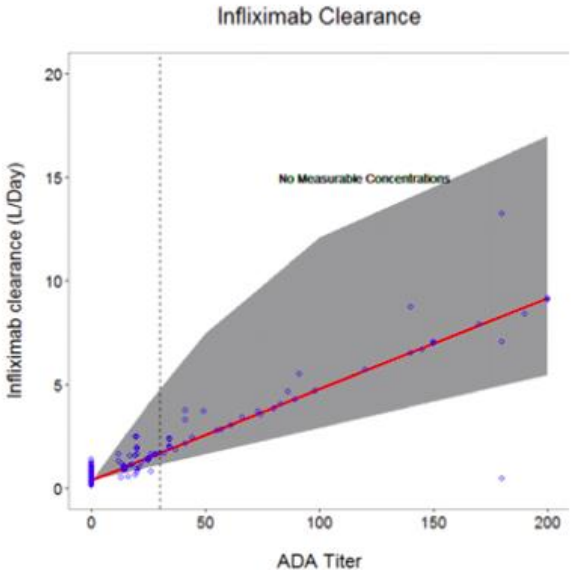
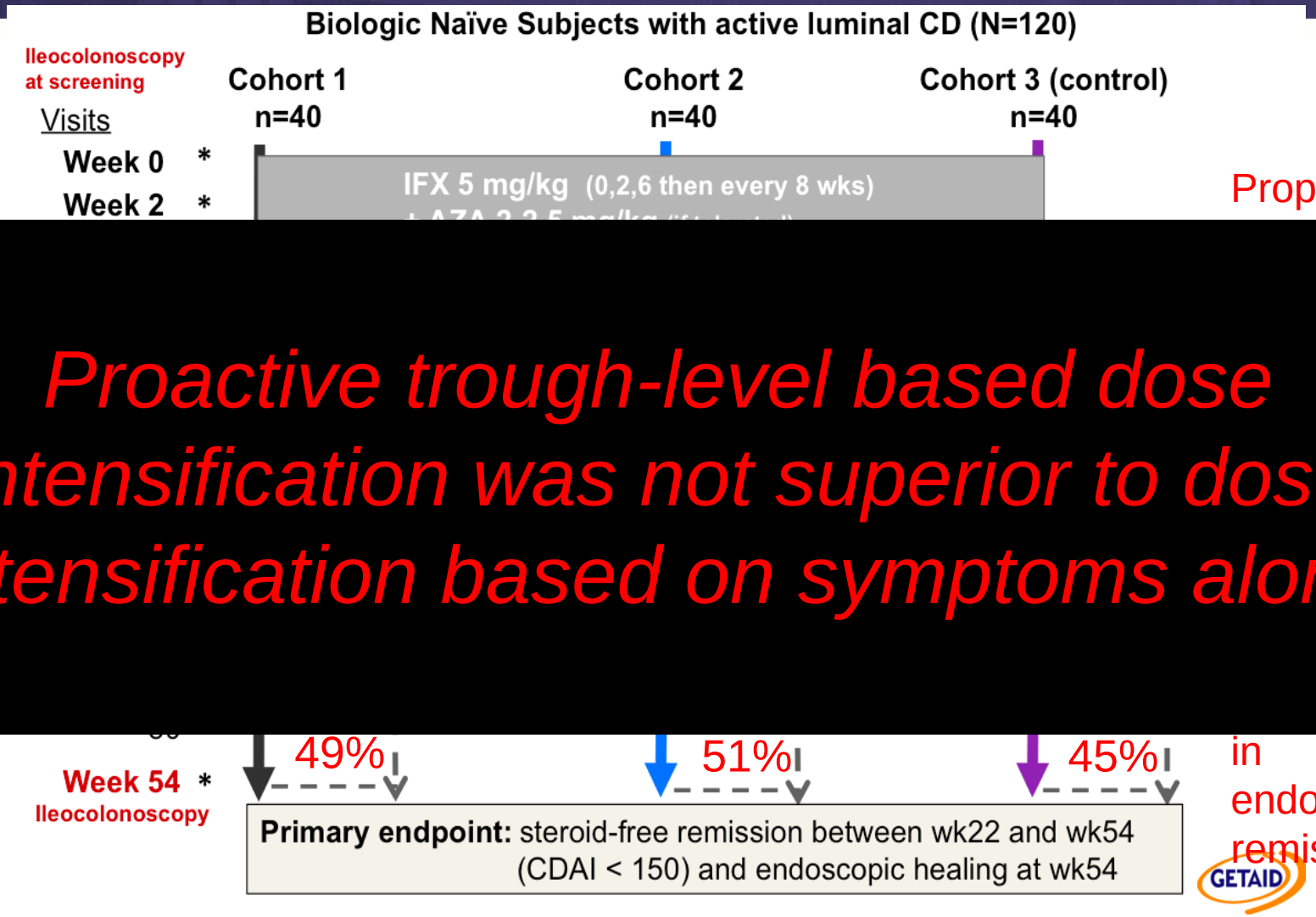


Table Proportional change in clearance for body weight, serum albumin, anti-drug antibodies and previous anti-TNF exposure

Body weight (kg)	Clearance (L/Day)	Percent reference
40	0.27	74.63
70	0.36	100.00
100	0.43	120.51
149	0.53	148.45
Albumin (g/dL)	**Clearance (L/Day)**	**Percent reference**
2	0.93	260.27
3	0.53	148.74
4	0.36	100.00
5.4	0.24	66.09
ADA titer (AU/ml)	**Clearance (L/Day)**	**Percent reference**
0	0.36	100.00
1	0.38	105.99
10	0.45	124.71
30	0.53	148.09
100	0.72	199.44
300	1.05	292.72
1000	1.79	497.64
3000	3.13	869.81
53000	15.93	4425.67
Previous anti-TNF exposure	**Clearance (L/Day)**	**Percent reference**
IFX 1st anti-TNF	0.34	94.92
IFX 2nd anti-TNF	0.36	100.00
IFX 3rd anti-TNF	0.38	105.35

Brandse J, et al. Presented at DDW May 23, 2016. Abstract 695.

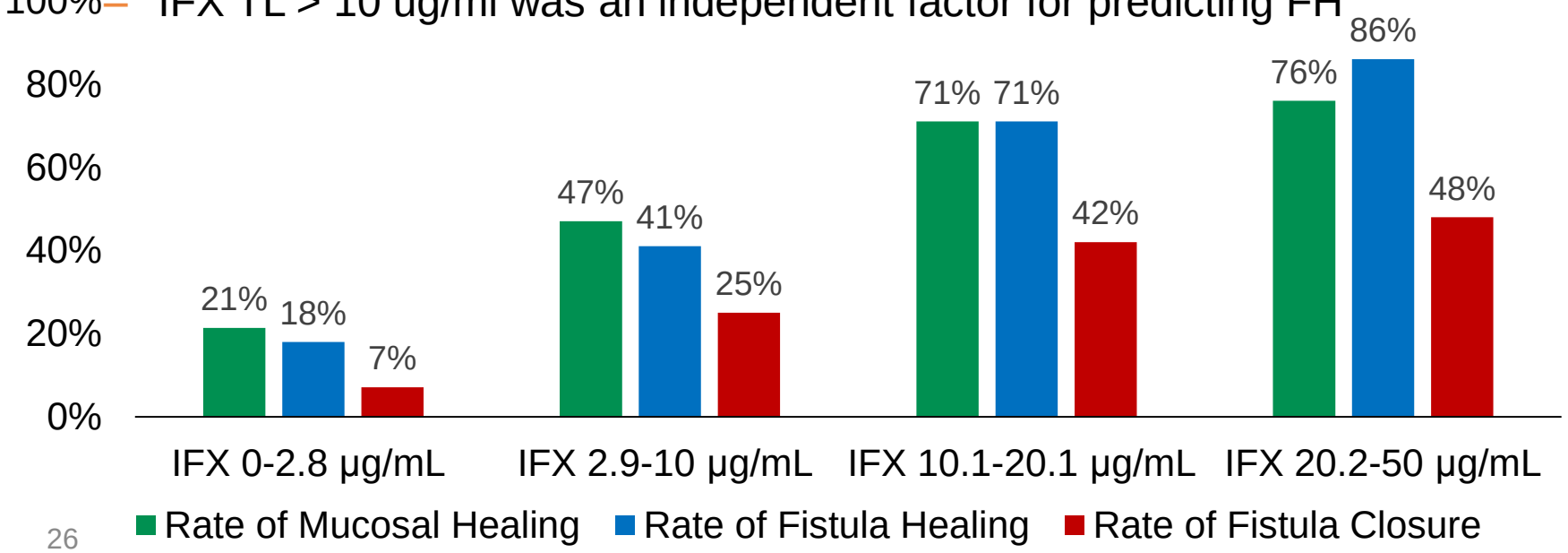
TAILORIX: Dose Intensification Based on Trough-levels Not Superior to That Based on Symptoms Alone



D'Haens G, et al. Presented at DDW May 23, 2016. Abstract 672.

Evidence of an Exposure-Response Relationship for Established Biologic Agents: Infliximab

- Higher Infliximab (IFX) Trough Levels Are Associated With a Higher Rate of Perianal Fistula Healing and Closure
  - Cross sectional study of 117 CD patients with active fistulas on IFX for > 24 wk
  - Patients with fistula healing (FH) had a significantly higher IFX TL (using HMSA) than those with active fistulas (18.5 vs. 6.5 ug/ml, p<0.0001)
  - Patients with antibodies to infliximab (ATI) had a lower chance of FH
  - IFX TL > 10 ug/ml was an independent factor for predicting FH



Yarur A. et al. Presented at DDW; May 2016. Abstract 514

SAFETY

Clostridium difficile Infection in IBD

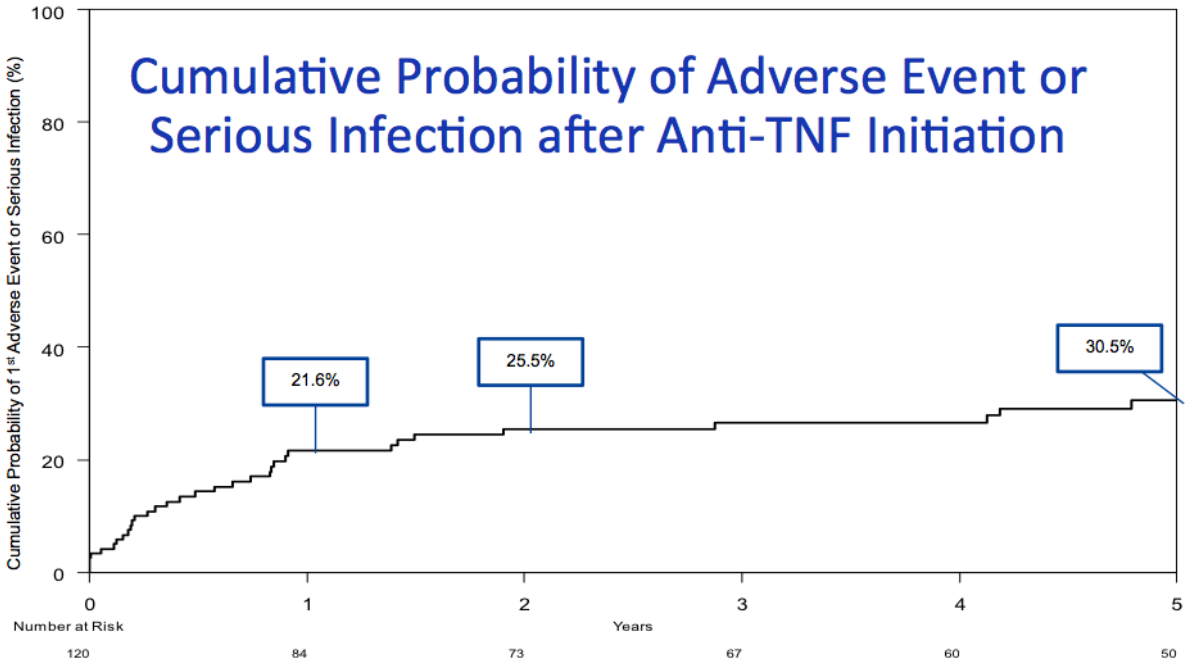
	IBD (n=161)	Non-IBD (n=11,919)	*P*-value
Age	53.7	74.4	<0.001
Healthcare associated infection	47.4%	91.6%	<0.001
Antibiotic use	57.8%	92.9%	<0.001
PPI use	25.0%	52.5%	<0.001
Immunosuppressant use	56.9%	26.4%	<0.001
Surgery	**1.72%**	**0.20%**	**0.026**
Recurrence	**7.76%**	**7.64%**	**0.86**

- **Traditional risk factors needs not be present in IBD**

Wong et al, Mo1803; presented at DDW May 2016.

Rates of adverse events and serious infections are stable over time with anti-TNF therapy

- Methods
  - Olmsted County, US
  - Medical record review – Crohn's patients (1970 – 2010)
  - Anti-TNF therapy
- Results
  - 424 patients (50.7% women, 29.4y [IQR 20.9-46.6])
  - Cumulative probability of anti-TNF use at 10 years was 23.7%



AE rate for anti-TNF therapy remains unchanged over long term follow up

Shivashankar et al, presented at DDW May 2016. Presentation 990

PREGNANCY

Women with IBD less likely to achieve successful assisted reproduction

Danish health registry 1994-2013 data

CROHNS - 567 ART in 186 CD women and 149,887 ART in non-IBD controls.

COLITIS - 1,360 ART in 432 UC women and 149,094 transfers in 52,661 non-IBD controls

Conclusion – IBD has negative impact on the success of ART and this should help guide treatment decisions regarding timing of attempts at conception (and timing of surgery in women with CD)

	CD (N=554)	Non IBD (N=148,540)	aOR (95% CI)
Live births	94 (16.97)	35,321 (23.78)	**0.77** (0.52-1.14)
Preterm birth	18 (16.98)	9,708 (23.00)	0.44 (0.09-2.21)

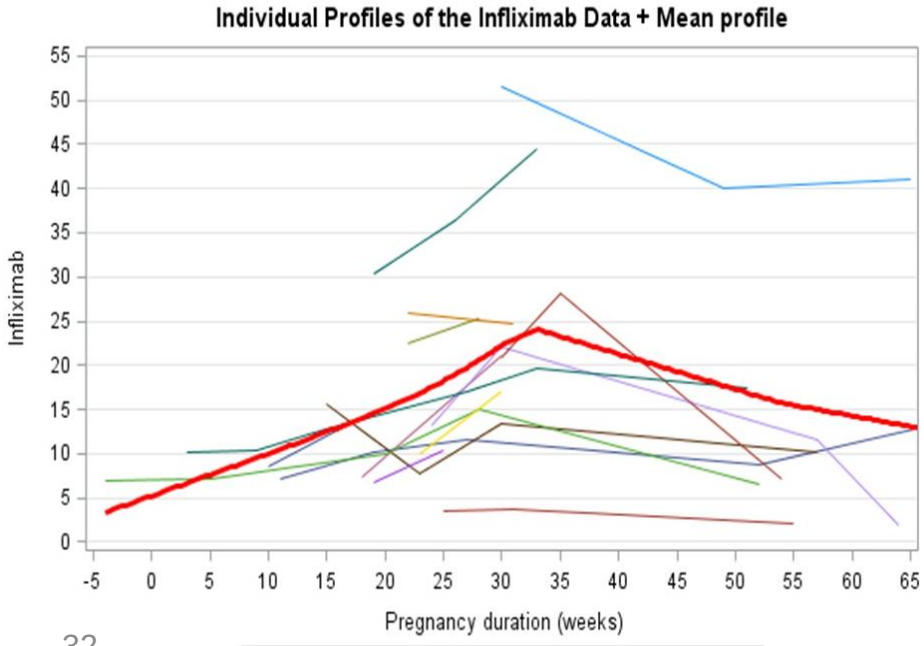
	UC (N=1360)	Non IBD (N=148,540)	
Live birth	272 (20.00)	35,321 (23.78)	**0.73** (0.58-0.92)
Preterm birth	100 (30.77)	9,708 (23.00)	**5.29** (2.41-11.63)
PTB singletons	33 (15.10)	2,593 (9.20)	**1.80** (0.49-6.62)

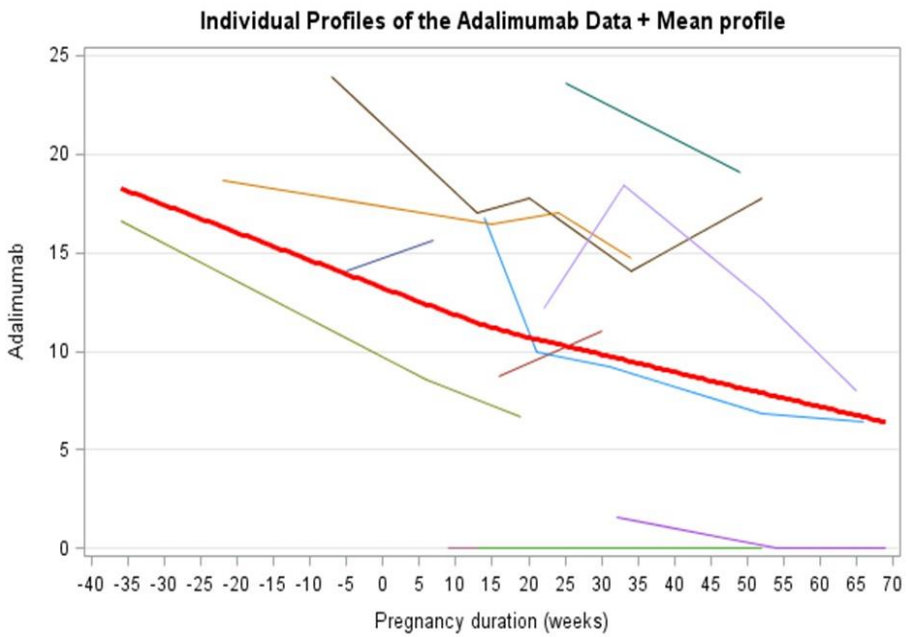
	Live birth prior surgery	No prior surgery	
CD (N=355 v 199)	50 (14.08)	44 (22.11)	**0.51** (0.29-0.91)
UC (N=468 v 891)	89 (18.98)	183 (20.54)	0.91 (0.61-1.36)

1. Friedman, S. et al. Presented at DDW, May 21 2016. Abstract 75 2. Friedman, S. et al. Presented at DDW, May 22 2016. Abstract 441

Infliximab Levels Increase While Adalimumab Levels Decrease in Pregnancy Despite Fixed Dosing

- Aims: To understand if pregnancy alters pharmacokinetics of anti-TNF agents
- Methods: Patients recruited prospectively; serial serum biobanking performed each trimester. Stable doses of anti-TNF therapy throughout pregnancy.
- Results:
  - Infliximab: 15 women (8 CD, 7 UC) with 15 pregnancies. Significant change in levels, with peak in mid 3rd trimester (p = 0.04)
  - Adalimumab: 10 women (9 CD, 1 UC) with 11 pregnancies;. Levels decrease steadily during pregnancy and post partum (p <0.001)





Seow C, et al. Presented at DDW May 23, 2016. Abstract 513.

Placental Transfer of Biologics to Infants not Associated with Infections or Adverse Outcomes

- 143 patients from PIANO
- 57% IFX Mothers with levels >10 mcg/ml at birth
  - Mean days since last infusion 41 [10-63]
- Risk of Infections:
  - not increased out to one year
  - Analyzed Infant, maternal, cord levels at birth
- Developmental Milestones
  - Improved at 12 months based on HIGHER drug levels in infant and cord at birth

	N	Infant:Maternal ratio (day birth)
IFX	68	2.4
ADA	44	1.4
UST	3	1.4
VDZ	7	0.7
NAT	4	0.5
CZP	17	0

Mahadevan U, et al. Presented at DDW Presented May 20, 2016. Abstract 437.

POTPOURRI

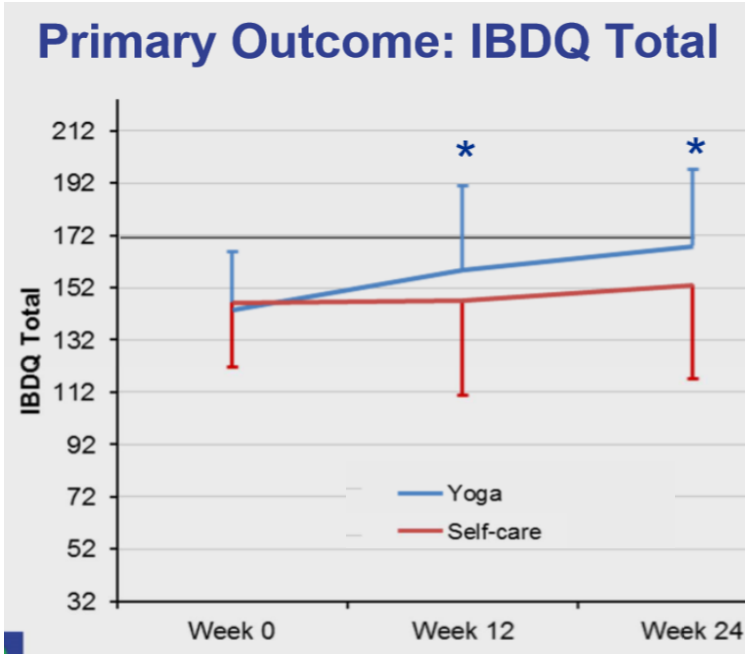
Update on Environmental Risk Factors for IBD

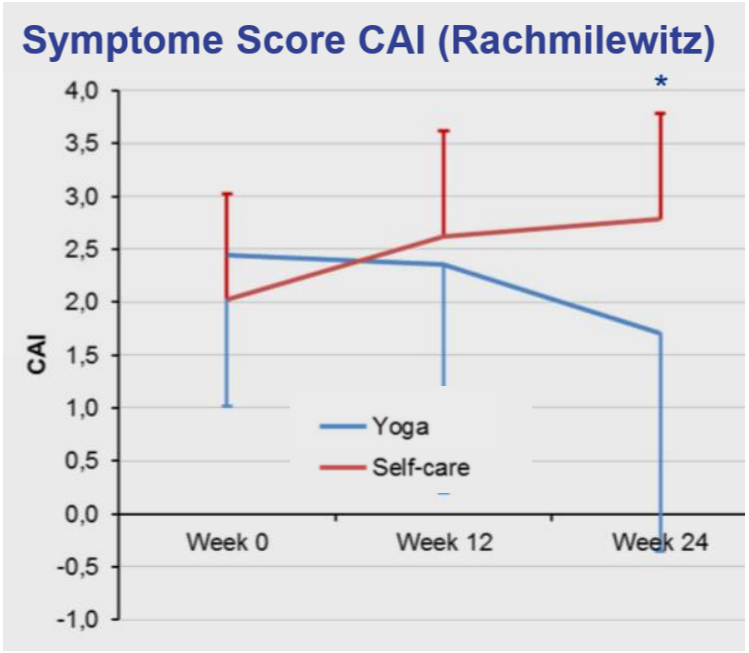
- Milk consumption significantly decreases risk of new onset Crohn's disease (aOR 0.30, 95% CI 0.13-0.65) in an analysis of 401,326 participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort[1]
- In a meta-analysis of 29 studies, exposure to farm animals (OR 0.45, 95% CI 0.29-0.62) or pets (OR 0.76, 95% CI 0.63-0.88) were associated with decreased risk of IBD[2]
- A meta-analysis of 29 case-control studies found that H. pylori infection inversely associated with risk of Crohn's disease (OR 0.62, 95% CI 0.57-0.67)[3]

1. Op[illegible]ract Mo1796
2. Cholapranee A et al. Presented at DDW May 23, 2016. Abstract Mo1804
3. Shah A et al. Presented at DDW May 23, 2016. Abstract Mo1828

A 12-week yoga intervention improves quality of life and mental health in UC in remission

- Patients with UC in remission (no steroids, CAI <5) and impaired quality of life (IBDQ<170)
- Effect of 12 weeks weekly 90 minute Hatha yoga session versus written self-care advice





Langhorst, J. , W. et al. Presented at DDW, May 22 2016. Abstract 387