2018 SCSG POST-DDW SYMPOSIUM

Jointly provided by the Annenberg Center for Health Sciences at Eisenhower and Southern California Society of Gastroenterology.

Best of DDW: Inflammatory Bowel Disease

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Disclosures

Nimisha Parekh

Advisory Board: Salix, Pfizer

Clinical Research Trial: Genetech

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- Consultant: Corrona, LLC

Topics

- Safety
- Dysplasia Surveillance
- Pregnancy
- Therapeutic Drug Monitoring
- Comparative Effectiveness
- Clinical Trials: Novel Therapies
- Alternative Therapies
- Biosimilars
- Personalized Medicine

Safety

Case Scenario

- 55 year old female who is on monotherapy infliximab for small bowel Crohn's disease for 5 years. She is currently in clinical and endoscopic remission. She is planning to undergo hip replacement. What do you recommend to do with the infliximab?

- A. Hold one dose
- B. Have surgery at the trough of dose, and then give 2 weeks later
- C. No Change, have surgery whenever convenient

OUTCOMES AFTER JOINT REPLACEMENT SURGERY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Presentation Number: Sa1805

Martin H. Gregory[1], Andrew McKinnon[2], Dustin Stwalley[2], Edward V. Loftus[3], K. J. Hippensteel[4], Matthew A. Ciorba[5], Margaret A. Olsen[2,6], Parakkal Deepak[5]

Study Design

- Retrospective Case Series from 2006 to 2014
- 1 case to 10 controls were frequency matched
- Primary outcome was serious infection within first 90 days after surgery
  - Joint infection, surgical site infection, pneumonia, sepsis, c. difficile infection

Rates of complications 90 days after surgery

	IBD (N=1,455)	No IBD (N=14,550)	P value
Serious infection (n, %)*	62 (4.3)	347 (2.4)	< 0.01
Pneumonia	22 (1.5)	124 (0.9)	0.01
CDI	11 (0.8)	18 (0.1)	< 0.01
Joint infection**	22 (1.5)	178 (1.2)	0.35
Index length of stay (mean, days)	2.9	2.7	0.01
90-day readmission	152 (10.5)	1,052 (7.2)	< 0.01

Conclusions

- Patients with IBD had a higher incidence of serious infection following joint replacement surgery; however, this was not the case for IBD patients whose disease was well controlled for at least six months prior to surgery.
- Infections rates higher in IBD patients
  - C. Difficile Infection was significantly higher
  - UTI
- IBD did not have more joint complications to controls
- Opioids should be used cautiously in IBD patients, higher rates of infections
- 90 Day readmission rates for IBD patients higher than controls

Association of IBD Medications With Risk of Serious Infection within 90 days after Joint Replacement Surgery

Variable	HR	95% CI	P-value
IBD therapy			
5-ASA monotherapy	Ref	Ref	Ref
Immunomodulator monotherapy	0.7	0.3 - 1.8	0.5
Anti-TNF therapy*	1.2	0.5 - 2.8	0.7
Combination therapy	3.3	1.3 - 8.1	0.009
Diabetes mellitus	3.2	1.8 - 5.8	<0.001
Steroid failure	3.0	1.1 - 8.0	0.03

HR, hazard ratio; CI, confidence interval; 5-ASA, aminosalicylates; *Includes monotherapy or with immunomodulators and/or corticosteroids

VEDOLIZUMAB AND EARLY POSTOPERATIVE COMPLICATIONS IN NON-INTESTINAL SURGERY: A CASE-MATCHED ANALYSIS

Presentation SA 1692

Abdulelah A. Almutairdi[5,1], Paulo G. Kotze[5,2], Christopher Ma[5], Nicholas P. McKenna[3], Laura H. Raffals[4], Edward V. Loftus[4], Remo Panaccione[5], Amy L. Lightner[3]

Conclusions

- VDZ-treated IBD patients undergoing non-intestinal procedures did not have an increased risk of overall postoperative infections or other complications as compared to controls.
- Same rate of surgical site infections, reoperations, and readmissions

RISK OF POSTOPERATIVE SURGICAL SITE INFECTIONS AFTER VEDOLIZUMAB VS ANTI-TNF THERAPY: A PROPENSITY-MATCHED COHORT ANALYSIS

Presentation Sa1710

K. T. Park[1], Lindsay Sceats[2], Melody S. Dehghan[1], Amber W. Trickey[3], Anava Wren[1], Rachel Bensen[1], Berkeley Limketkai[4], Cindy Kin[2]

Study Design

- Optum Research Database from 2015 to 2016 (claims data)
- Primary outcome was post-operative occurrence of surgical site infection (SSI) within 30 days of surgery in patients who were on VDZ compared to Anti-TNF
- Propensity Matching was done based on
  - Age, gender, type of IBD, Charlson comorbidity score, Imm, steroids, opioids, malnutrition

Conclusion

- In the largest, risk-adjusted cohort analysis to date, perioperative exposure to VDZ therapy is not associated with a significantly higher risk of developing a SSI after IBD-related abdominal surgery compared to anti-TNF therapy.

- In multivariate analysis, malnutrition was only risk factor in developing surgical site infections

Dysplasia Surveillance

Next Colonoscopy?

Mr. T is 60 years old male and he comes to your office to discuss the frequency of colonoscopies. He has had ulcerative pancolitis for 25 years and has had a colonoscopy every 1-2 years for the last 17 years. He's tired of it. He feels fortunate that he has not had any dysplasia seen yet. His last colonoscopies have shown endoscopic and histologic remission. He asks if he still needs to have a colonoscopy so frequently? What do you say?

A) Yes, you still need to have colonoscopy every 1-2 years
B) You can have a colonoscopy in 5 years
C) You no longer need colonoscopies
D) You can have a colonoscopy in 3 years

CRC Risk Stratification in IBD and Surveillance Intervals According to Various Societies

	Low	Intermediate	High
AGA 2010	**Every 1-2 years** • After 2 negative examinations, can perform 1-3 years	**"More frequent" surveillance** • Ongoing endo/ histo inflammation • Anatomic abnml (stricture/ foreshortened colon/ pseudopolyp) • Family history CRC in FDR	**Every year** PSC
ASGE 2015	**Can be lengthened beyond 1-3 years** • Endo/histo normal on 2 or more exams	**Every 1-3 years** • No risk factors requiring annual surveillance	**Every year** • PSC • Active Inflammation • Hx of Dysplasia • Anatomic abnml (stricture/ pseudopolyps) • Family history CRC in FDR
BSG 2010	**Every 5 years** • Extensive colitis with no active endo/histo inflammation • Left-sided colitis • Crohn's colitis <50% involvement	**Every 3 years** • Ext. colitis w/ mild endo/histo inflamm • Post-inflamm polyp • Family history CRC in FDR >50	**Every year** • Moderate/severe active inflammation • Stricture/ dysplasia in last 5 years • PSC • Family histroy CRC in FDR <50
ECCO 2017	**Every 5 years** • Neither intermediate nor high risk features	**Every 2-3 years** • Extensive colitis mild/mod inflamm • Post-inflammatory polyps • Family history CRC in FDR >50	**Every year** • Stricture/ dysplasia in past 5 yrs • PSC • Extensive severe active inflamm • Family hsitroy CRC in FDR <50
NICE 2011	**Every 5 years** • Extensive but quiescent UC/ Crohn's colitis • Left-sided UC or Crohn's colitis	**Every 5 years** • Extensive UC or Crohn's w/ mild inflamm • Post inflamm pseudopolyps • Family history CRC in FDR >50	**Every year** • Moderate/severe active inflammation • PSC • Colon stricture in last 5 years • Family hx CRC in FDR <50

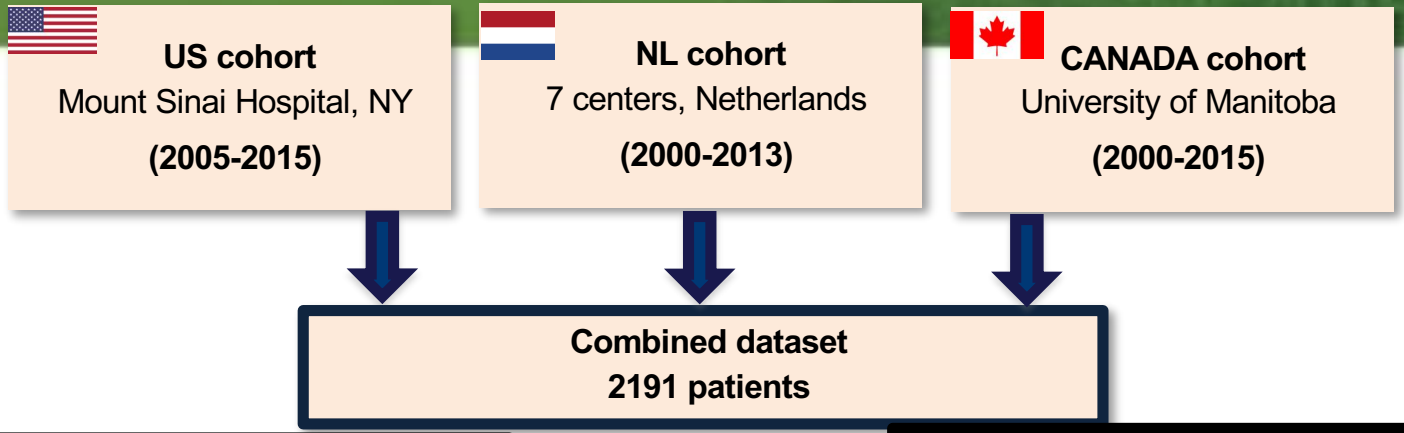
Repeated negative findings on colonoscopy during surveillance predicts a low risk of advanced neoplasia in patients with longstanding colitis: Results of a 15-year multicenter, multinational cohort study
Presentation number: 604

Shailja C. Shah, Joren R. ten Hove, Seth R. Shaffer, Charles N. Bernstein, Daniel Castaneda, Carolina Palmela, Erik Mooiweer, Jordan Elman, Akash Kumar, Jason Glass, Jordan Axelrad, Thomas A. Ullman, Jean-Frédéric Colombel, Joana Torres, Ad A. van Bodegraven, Frank Hoentjen, Jeroen M. Jansen, Michiel de Jong, Nofel Mahmmod, Andrea E. van der Meulen-de Jong, Cyriel Y. Ponsioen, Christine J. van der Woude, Steven H. Itzkowitz, Bas Oldenburg

STUDY AIM:

To assess whether two consecutive negative surveillance colonoscopies reliably predict a low risk of advanced colorectal neoplasia (ACRN) during follow-up

Methods – Patient Selection



Inclusion:

- Patients enrolled in a CRC surveillance protocol (during study period)
- Colonic disease duration of at least 8 years or concomitant PSC
- At least left-sided colitis (UC) or >30% involvement of the colonic surface (CD)

Exclusion:

- Crohn's disease without colonic involvement
- Ulcerative colitis with localized proctitis
- Prior history of ACRN (HGD, CRC) or colectomy
- ACRN at the time of the first recorded colonoscopy within the study period

At least two *surveillance* colonoscopies (with pathology) followed by at least one other mode of pathologic assessment on follow-up (e.g. colonoscopy, colectomy)

Courtesy of Dr. Itzkowitz

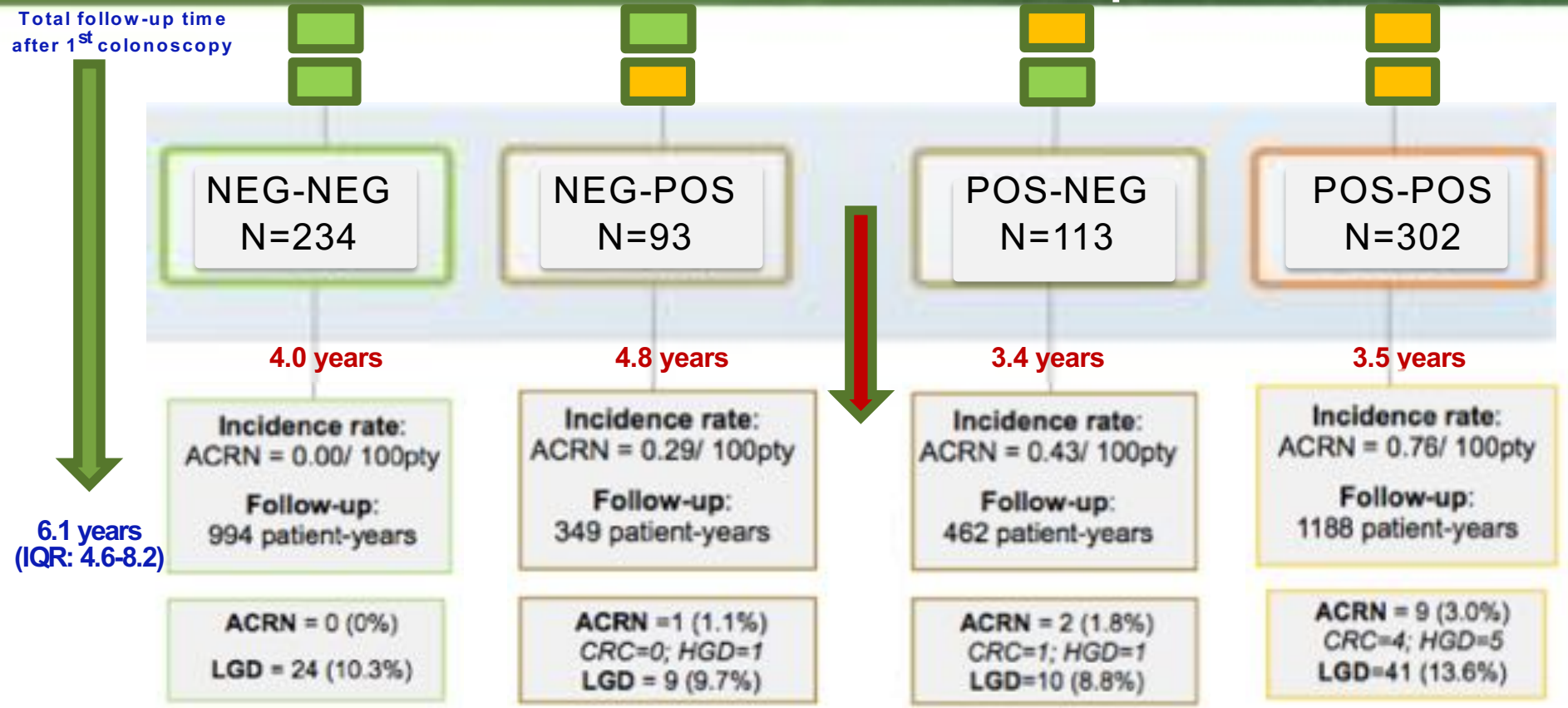
Methods – Definitions

- **"Surveillance colonoscopy"**:
  - Indication stated as "surveillance"
  - Technically adequate procedure
    - Cecal intubation, adequate bowel prep
  - Segmental random biopsies performed and/or chromoendoscopy
- **"Negative" colonoscopy**:
  - No dysplasia
  - No endoscopic disease activity
  - No stricture
  - No post-inflammatory polyps
- **"Positive" colonoscopy**:
  - At least one of the above
- **"High Risk" Patients: (excluded from primary analysis)**
  - Prior diagnosis of low-grade dysplasia (HGD excluded at outset)
  - Primary sclerosing cholangitis
  - First-degree relative with CRC

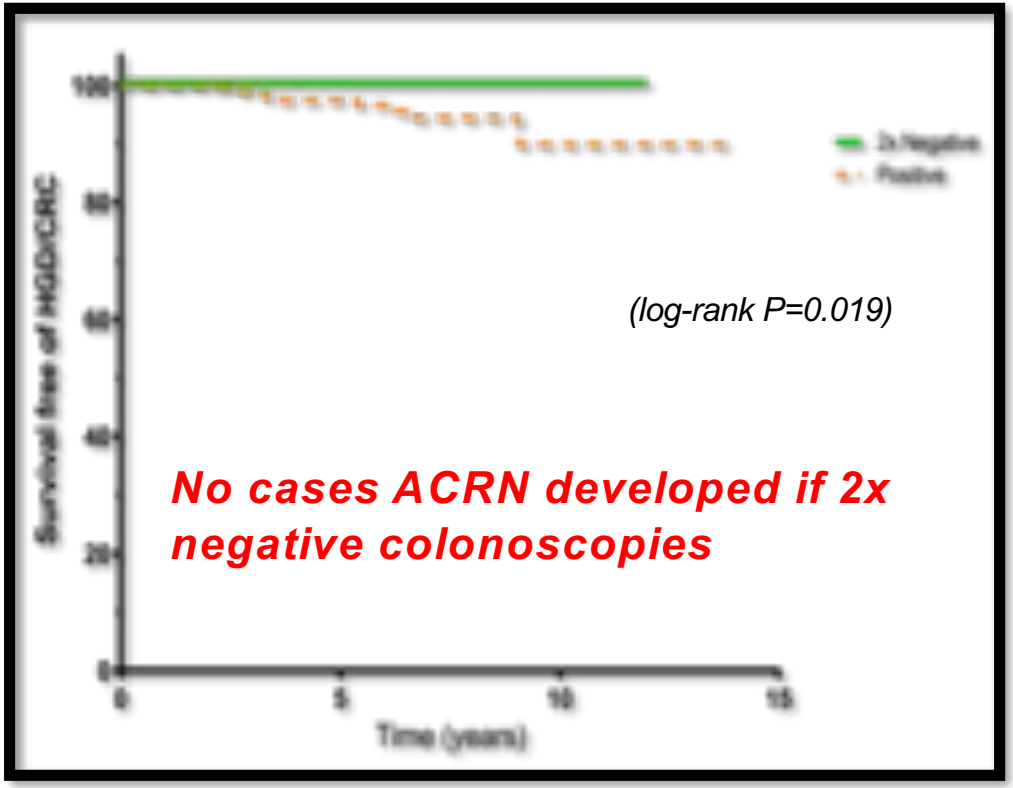
- **Primary Outcome:**
  - Incidence rate of ACRN following consecutive negative surveillance colonoscopies in low risk group
    - *Number of cases per 100 patient-years (pty) follow-up*
- **Secondary Outcome**:
  - Incidence rate of any neoplasia (i.e. LGD, HGD, CRC) following two consecutive negative colonoscopies, including high-risk patients

Courtesy of Dr. Itzkowitz

ACRN occurrence based on consecutive surveillance colonoscopies



ACRN-free survival: Double Negative vs. (Any) Positive



(log-rank P=0.019)

No cases ACRN developed if 2x negative colonoscopies

Secondary analysis: Outcomes of initially excluded patients

High-risk patients, N=619

High-risk features, N=587
LGD prior to 2nd colonoscopy, N=32

* *Prior history of LGD*
* *PSC*
* *First degree relative with CRC*

Incidence rate (overall):
ACRN = 0.49/ 100 pty

NEG-NEG: 0.15
NEG-POS: 0.44
POS-NEG: 0.65
POS-POS: 0.73

ACRN = 40 (1.6%)

Courtesy of Dr. Itzkowitz

Why Important?

- Significant proportion of patients with longstanding colitis undergoing surveillance colonoscopy have negative colonoscopies:
  - 30% with low risk features had two negative colonoscopies in study period
- Having two consecutive negative surveillance exams predicted a **low, potentially negligible, risk of advanced neoplasia on follow-up** up to 3-5 years after the 2nd negative surveillance
  - 0 per 100 patient-years
- Unclear risk of ACRN in the longer-term
  - Median duration of follow up *after 2nd surveillance* colonoscopy was 4 years [IQR: 2.3-5.6]
- Surveillance is still warranted since a substantial minority of patients developed low-grade dysplasia despite two consecutive negative examinations
  - 10.3% LGD upon follow up

Ten Hove, J *et al. Gut* 2018; 0:1-8

Case: Low Grade Dysplasia. Now what?

- Mr. T, our 60 year old male with long-standing ulcerative colitis for 25 years in remission on mesalamine 2.4 grams once a day has a recent colonoscopy with you. He had findings of low grade dyplasia (LGD) with flat visible, discrete lesion noted on chromoendoscopy that you removed.

- How do you counsel him on risk of progression of LGD to advanced lesion (high grade dysplasia/colorectal cancer)?

Low Grade Dysplasia: What We Know

- Endoscopic surveillance programs aim to reduce ACRN risk by detecting and removing precancerous lesions (SCENIC guidelines)

- Variable rates of progression from LGD to high grade dysplasia (HGD) or colorectal cancer (CRC) in small studies with variable follow up

  - 50% (9 of 18) to more advanced disease (HGD or CRC) at 32 months
  - 15% (7 of 46) progressed to CRC at 5 years
  - 10% (3 of 29) progressed to HGD or CRC at 10 years

STUDIES HAVE BEEN SMALL AND COVER SHORT FOLLOWUP

Laine L *et al. GIE* 2015; 81:489-501e26
Ullman T *et al. Gastroenterol* 2003; 125:1311

Lim CH, *et al. Gut* 2003; 52:1127
Ullman TA *et al. AM J Gastroenterol* 2002; 97:922

Long-Term Risk of Advanced Neoplasia After Colonic Low-Grade Dysplasia in Patients with Inflammatory Bowel Disease: A Nationwide Cohort Study

Presentation Number: 162

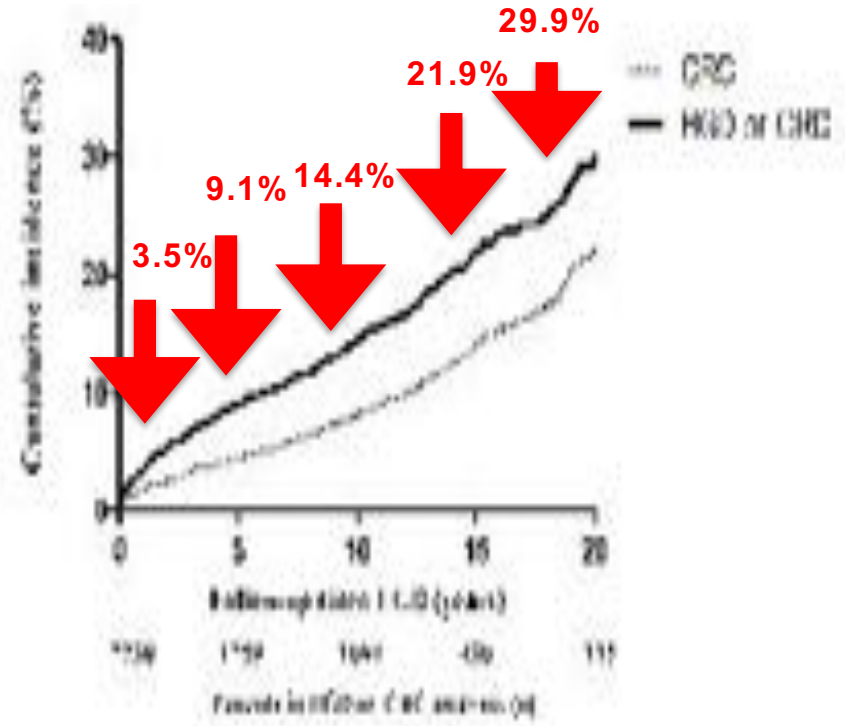
Michiel Erik de Jong, Sanne van Tilburg, Loes Nissen, Wietske Kievit, Iris D. Nagtegaal, Frank Hoentjen, Lauranne Derikx

STUDY AIMS:

- **To determine long-term cumulative advanced neoplasia (HGD and/or CRC) incidence**
- **To identify risk factors for advanced neoplasia development in a nationwide cohort of IBD patients with LGD**

Results

- Using Dutch National Pathology Registry (PALGA), all IBD patients with LGD between 1991 and 2005
- 2738 patients with colonic LGD
- Median follow up 9.5 years (IGR:4.2-13.7 yrs) after initial LGD diagnosis
- 15.5% underwent subtotal colectomy
- Advanced neoplasia in 397/2738 patients (240 with CRC)
- Median time to develop advanced neoplasia: 4.7 years (IQR: 1.3-10 yrs)
- Higher age(≥ 55yrs), IBD>5yrs before LGD, male gender: RF for ACRN development



Why Important?

- Largest cohort to date of LGD patients
- Median follow-up time of almost 10 years
- Clarifies cumulative incidence of progression of LGD to advanced neoplasia

9.1% at 5 years

14.4% at 10 years

21.9% at 15 years

Allows for better discussion of risks and benefits of further surveillance versus proctocolectomy

Pregnancy

Case Scenario

- 33 year old female with small bowel Crohn's disease for 10 years who is currently on Ustekinumab. She is now asking about getting pregnant. In addition to recommending consult with maternal fetal medicine specialist, What do you recommend?

- A. Stop Ustekinumab
- B. Change to Certolizumab
- C. Continue Ustekinumab
- D. Stop all medications
- E. Change to Vedolizumab

PREGNANCY OUTCOMES IN WOMEN EXPOSED TO USTEKINUMAB

Presentation Su 1799

Uma Mahadevan[1], Saule Naureckas[2], Bhawna Sharma[2], Ilia Tikhonov[2], Philippe Szapary[2], Christopher Busse[3], Alexa Kimball[4]

Study Design

- Cases retrieved from the Company safety database through 30 June 2017 include prospectively reported cases with maternal Ustekinumab use for Psoriasis, Psoriatric Arthritis, or Crohn's Disease during pregnancy or within 2 months prior to conception and with a known outcome

- Two hundred and six reports (164 PSO, 6 PsA, 36 CD; 130 prospective, 76 retrospective) were available for analysis.
  - Average maternal age was 30.3 years.
  - The reported cases were from clinical trials (23.3%), other solicited sources (43.2%), spontaneous reports (27.1%) and literature sources (6.3%)

Conclusion

- The rate of spontaneous abortions (SAs) (17%), was comparable to the rate reported for the general population (15% to 20%).
- The percentage of congenital anomalies (4.4%) was similar to the overall incidence of congenital anomalies (4%) in the United States general population.
- Based on the limited available data, no specific risks have been identified with Ustekinumab exposure during pregnancy.

OUTCOME OF PREGNANCIES IN VEDOLIZUMAB TREATED FEMALE IBD PATIENTS

Presentation SA 1697

Annick Moens[1,2], Karen van Hoeve[3,2], Evelien Humblet[4], Jean-Francois Rahier[5], Peter Bossuyt[6], Sophie Dewit[7], Denis Franchimont[8], Macken Elisabeth[9], Jochen Nijs[10], Annelies Posen[11], Anneleen Van Hootegem[12], Wouter Van Moerkercke[13], Severine Vermeire[1,2], Marc Ferrante[1,2]

Methods

- Human study shows expression of MAdCAM 1 in placenta during first trimester but not mature placenta.[1]
- Aim of Study to evaluate pregnancy outcomes in VDZ treated female IBD patients.
- Retrospective, national observational study to evaluate the outcome of pregnancies in IBD patients on VDZ

1. Zelinkova et al Gastro 2016

Results

- 23 pregnancies identified (18 in remission & 5 active at time of conception)
  - Maternal complications: 1 eclampsia, 2 premature rupture of membranes, 1 lost fetus due to chorioamnioitis at wk 22, 1 had active termination, 1miscarriage, 5 c- sections for Crohn's disease
  - Infant complications: 1 IUGR, 2 congenital anomalies, 1 small for gestational age, 4 preterm birth (<37weeks)

Conclusion

- Due to low number of pregnancies, no clear conclusions can be made but prenatal and congenital abnormalities were noted.
- Continue strict vigilance of use of Vedolizumab in pregnancy

- Su1899: VEDOLIZUMAB IS SAFE FOR USE IN PREGNANT PATIENTS WITH IBD; REPORT OF OUR PRELIMINARY DATA

Therapeutic Drug Monitoring

Therapeutic Drug Monitoring

- **Why helpful?**
  - Inter and intra-individual variability in drug pharmacokinetics
    - Personal factors (gender/ BMI)
    - Disease factors (disease severity)
    - Drug factors (dosing/ immunogenicity)
  - Association between drug exposure and response

- **When should this be done?**
  - Reactive: Patients with active disease to evaluate reasons for LOR
  - Proactive: Patients with quiescent disease to optimize therapy

Reactive Therapeutic Drug Monitoring (rTDM)

Guidelines/Consensus	Year	Recommendations
ACG Ulcerative Colitis	2018	If losing response to assess reason
AGA Therapeutic Drug Monitoring in IBD	2017	rTDM to guide treatment changes
ECCO Crohn's	2017	Loss of response rTDM
Australian TDM consensus	2017	rTDM for primary and secondary loss of response
BRIDGe group	2016	End of induction therapy in primary and secondary non-response
Toronto Consensus UC	2015	Loss of response before switch in and out of class

TDM at Secondary Loss of Response- rTDM

	Sub-Therapeutic Drug Concentration	Therapeutic Drug Concentration
Undetectable ADAb	Non-immune mediated drug failure: 51%	Mechanistic or Pharmacodynamic Failure: 25%
Detectable ADAb	Immune-mediated pharmacokinetic failure: 19%	Mechanistic or pharmacodynamics failure: 5%

Switch to drug in class and consider adding immunomodulator

Interest in the addition of azathioprine (AZA) to the switch of anti-TNF in IBD patients in clinical relapse with undetectable anti-TNF trough levels and anti-drug antibodies: A prospective randomized trial

Presentation Number: 345

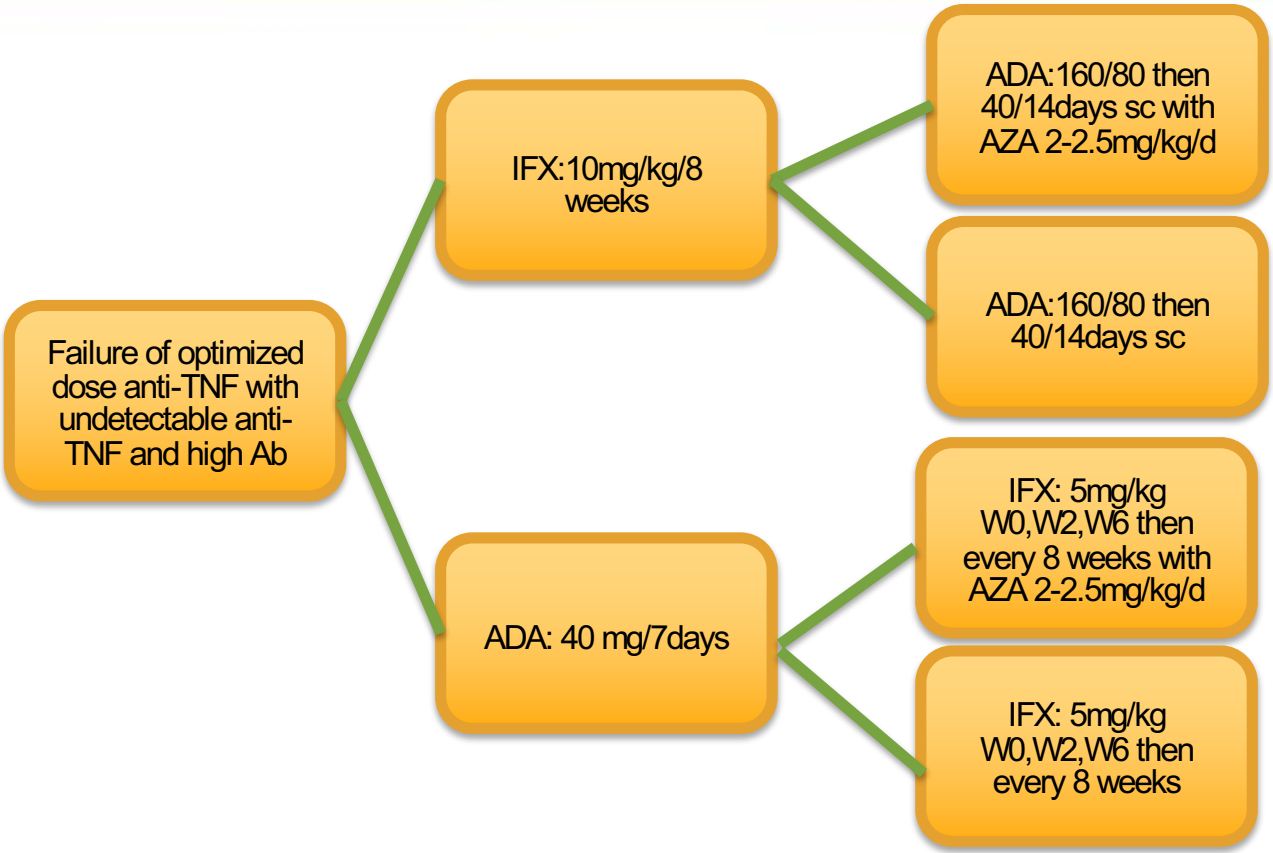
X. Roblin, S. Paul, G. Boschetti, JM Phelip, E Del Tedesco, A Berger, S. Nancey, N. Williet, B Flourie

Study Aim:

To compare two therapeutic strategies to the loss of response to first anti-TNF optimized with unfavourable pharmacokinetics

- **Monotherapy: Switch to second anti-TNF**
- **Combination Therapy: Switch to second anti-TNF with azathioprine**

Study Design



Patients:

- 45 combination therapy
- 45 monotherapy

Clinical failure:

- HBI >5 with fecal calprotectin >250 ug/g
- Mayo score >4 with endoscopic subscore >1
- Associated with change in treatment

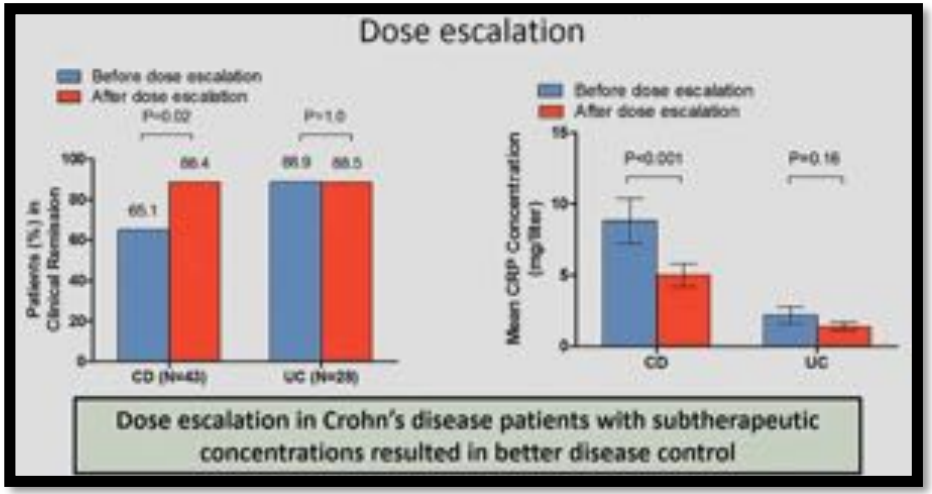
Unfavorable pharmacokinetics: Undetectable serum concentration of second anti-TNF with high ADAb (20 ng/mL for IFX or ADA)

Follow up: 24 months

AGA Therapeutic Drug Monitoring in IBD: Proactive TDM (pTDM)?

"In patients with quiescent IBD treated with anti-TNF agents, the benefit of routine pTDM over no therapeutic monitoring is uncertain."

TAXIT Trial Optimization Phase: Concentration-based (Target 3-7 ug/mL vs. Clinically-based dosing)



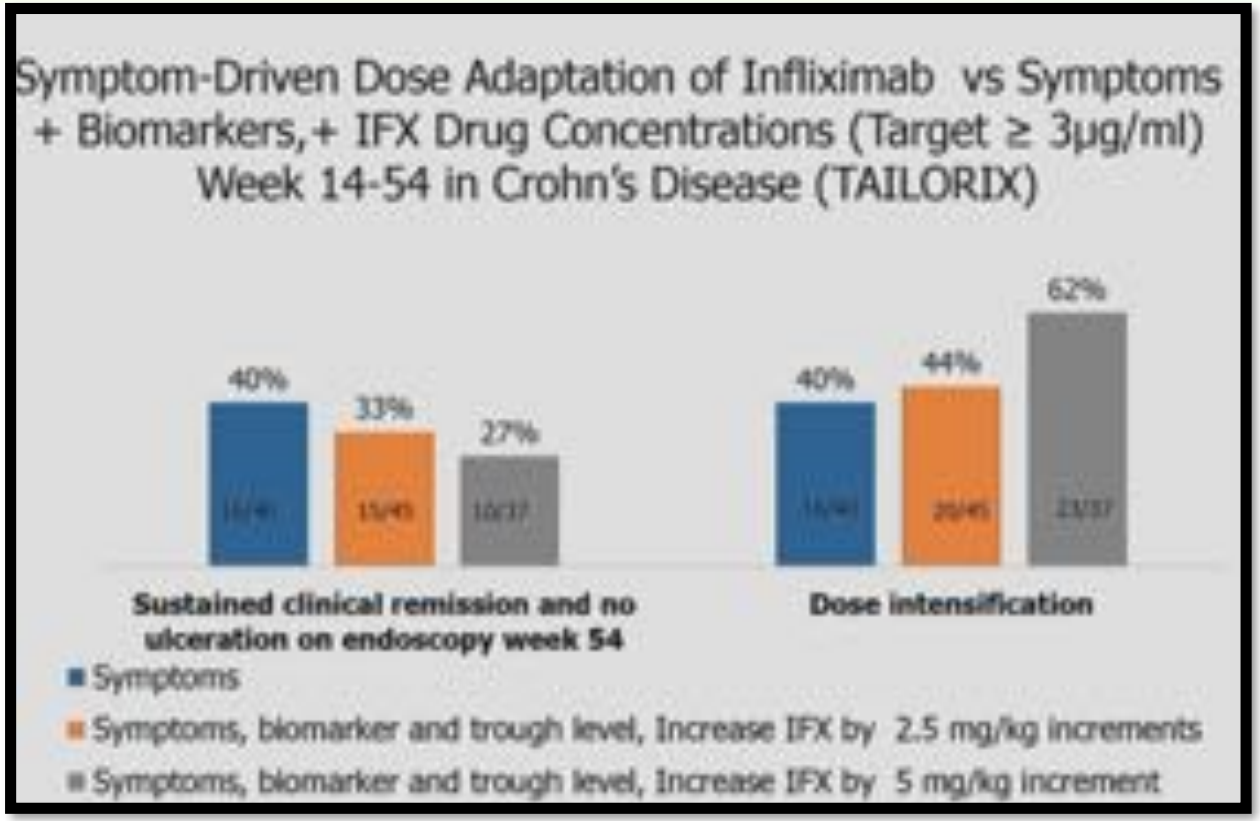
263 patients: Stable responders on maintenance infliximab
21% with TC <3; 9% undetectable TC; 44% with TC 3-7 ug/mL; 26% TC >7 ug/mL

TAXIT Trial Maintenance Phase: Concentration-based (Target 3-7 ug/mL vs. Clinically-based dosing)

	pTDM	Clinical	P value
Remission after 1 year (primary endpoint)	**69%**	**66%**	**0.69**
Rescue Therapy	7%	17%	0.02
Stayed in IFX target range	74%	57%	0.001
ATI (n)	0	3	0.12

Van de Casteele *et al. Gastroenterology* 2017; 153:827-834
Vande Casteele et al. Gastroenterol 2015; 148:1320-1329

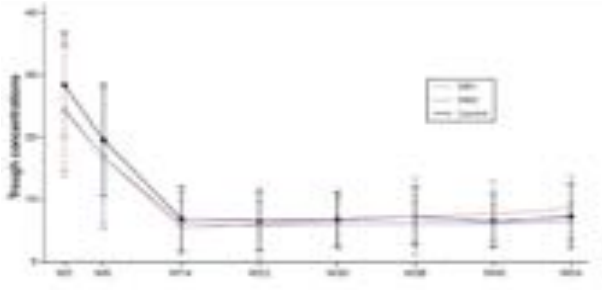
TAILORIX Trial



D'Haens G *et al. Gastroenterology* 2018; 154(5):1343-1351

Week 14 Randomization: 1:1:1

- **Control**: 60% dose escalation (based on symptoms only) had normal CRP and/or fecal calprotectin
- **DIS**: 53% of possible dose escalation based on symptoms avoided as biomarkers not elevated
- There was no TDM only arm
- Clinical symptoms may have diluted effect of TDM
- IFX trough concentrations similar in 3 groups
- Not powered to determine superiority of TDM



Controversy with pTDM

Two randomized controlled trials could not confirm superiority of proactive TDM management

QUESTIONS:

- When are the right time points for proactive TDM?
  - During induction or in maintenance
- What is the optimal trough concentration for desired outcomes?
- How often should proactive TDM be performed for optimal outcome?

Comparative Effectiveness

Case Scenario

25 year old male with moderately active Pan-UC for 1 year who currently has steroid dependent disease and unable to come off of prednisone. The patient has questions about safety with biologics.

At this point what do you recommend?

A. Start Anti-Tnf therapy
B. Start Vedolizumab
C. Start 6mp
D. Start Tofacitinib

VICTORY Study Methods

AIM: Compare the effectiveness of VDZ to anti-TNF therapy for UC and CD in clinical practice

COHORT: Multicenter, US-based consortium (VICTORY) of patients who completed induction with either VDZ or an anti-TNF between 2014-2017

DESIGN: Retrospective cohort, propensity score matching (1:1) accounting for:

- **Patient characteristics**: Age, sex
- **Disease characteristics:** Prior hospitalization, disease extent, disease severity
- **Treatment history**: steroid refractoriness/dependence, prior anti-TNF therapy failure

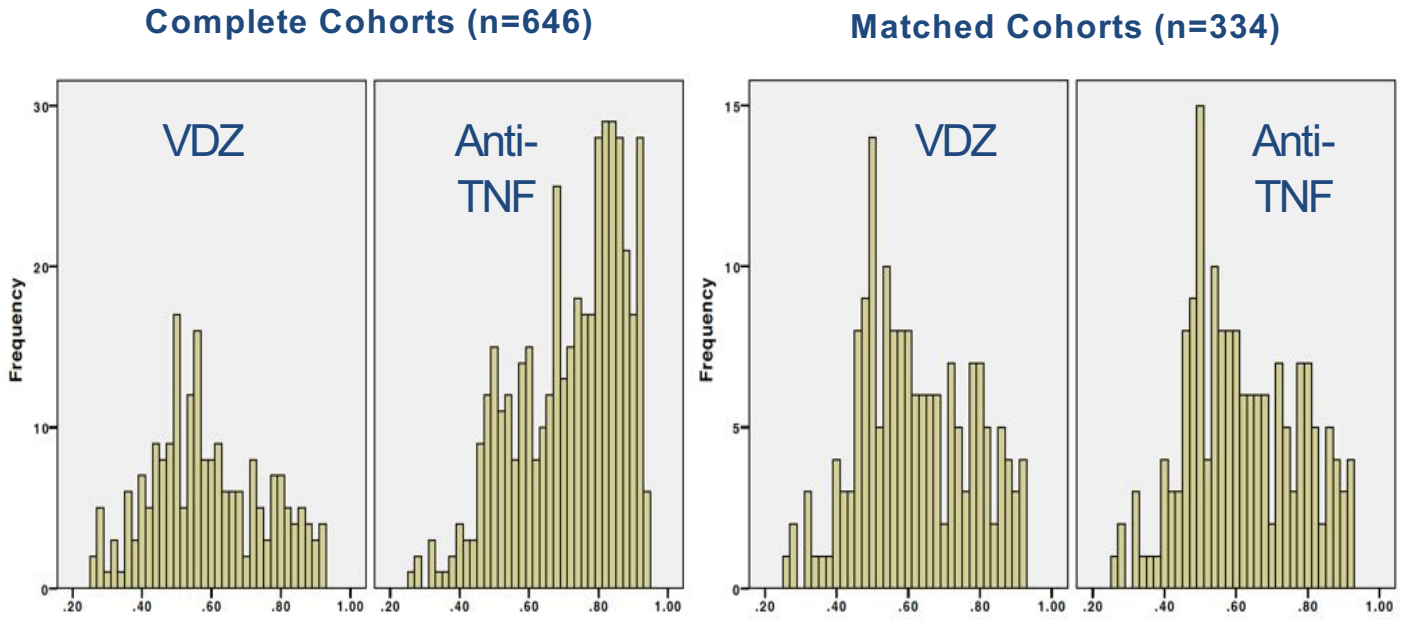
OUTCOMES:

- **Clinical remission:** Physician global assessment
- **Steroid-free remission:** Achieving remission, tapering off steroids, and requiring no repeat steroid prescription for 4 weeks
- **Endoscopic healing**

Results: Demographics of Matched Cohorts

	VDZ (n=167)	Anti-TNF (n=167)
Age, median (IQR)	35 (25 – 50)	37 (26 – 52)
Male, n (%)	79 (47%)	84 (50%)
Hospitalized previous 1 year, n (%)	48 (29%)	48 (29%)
Steroid refractory/dependent, n (%)	62 (37%)	60 (36%)
Extensive disease, n (%)	99 (59%)	106 (64%)
Anti-TNF failure, n (%)	52 (31%)	51 (31%)
# Prior anti-TNF agents		
0	87 (52%)	106 (64%)
1	48 (29%)	52 (31%)
≥ 2	32 (19%)	9 (5%)
Concomitant steroids, n (%)	84 (50%)	90 (54%)
Concomitant immunomodulator, n (%)	54 (32%)	61 (37%)

Results:
Propensity Matching



The propensity score accurately predicted VDZ vs. anti-TNF therapy with an area under the curve (AUC) of 0.73

Results:
Primary Outcomes

Outcomes at 12 Months	VDZ (n=167)	Anti-TNF (n=167)	aHR 95% CI
Clinical remission	54%	37%	**1.54** 1.08 – 2.18
Steroid-free remission	49%	38%	1.43 0.79 – 2.60
Endoscopic healing	50%	42%	**1.73** 1.10 – 2.73

*Adjusted for # of prior anti-TNF agents and concomitant steroid or immunomodulator use

Conclusion

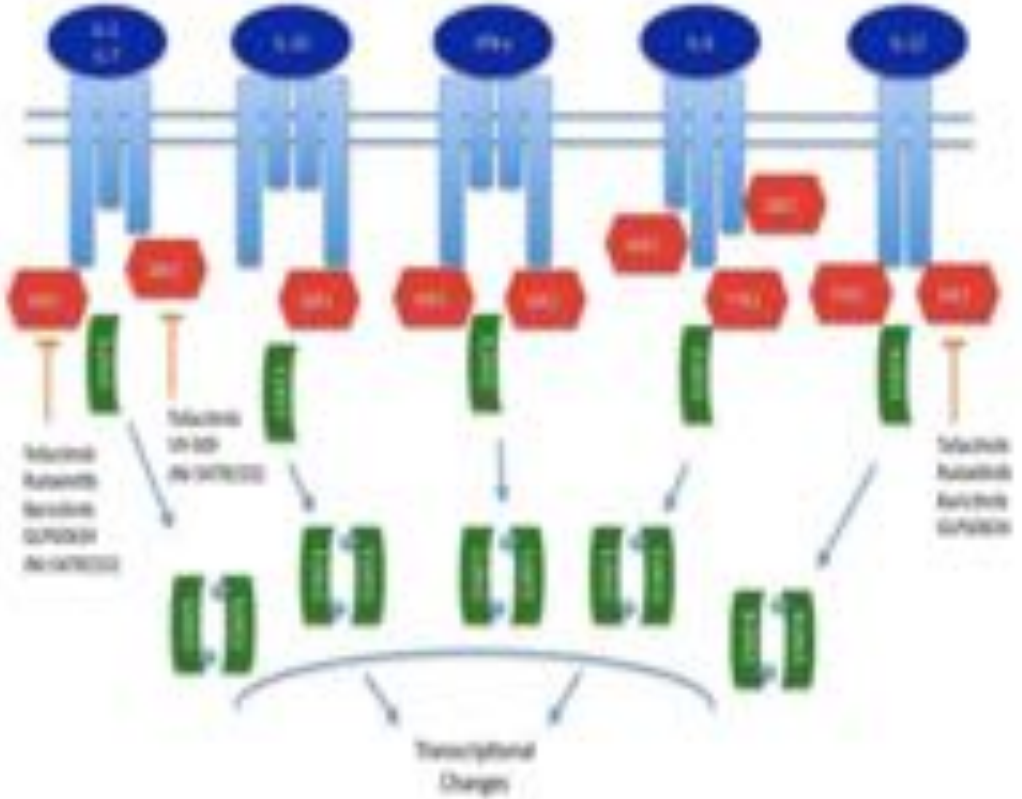
- Observation of VDZ treated UC patients had significantly higher 12 month cumulative rates of clinical remission and endoscopic healing, and steroid free remission rates when compared to anti-TNF treated patients

Other studies from the VICTORY Consortium

- 328 Faleck D, Shashi P, Meserve J, et al. **Comparative effectiveness** of vedolizumab and TNF-antagonist therapy in **ulcerative colitis**: a multicentre consortium propensity scorematched analysis. DDW 2018
- Sa1723 Bohm M, Sagi SV, Fischer M, et al. **Comparative effectiveness** of vedolizumab and tumour necrosis factor-antagonist therapy in **Crohn's disease**: a multicenter consortium propensity score-matched analysis. DDW 2018
- 277 Lukin D, Weiss A, Aniwan S, et al. **Comparative safety profile** of vedolizumab and tumour necrosis factor–antagonist therapy for inflammatory bowel disease: a multicentre consortium propensity score-matched analysis. DDW 2018.
- Sa1701 Meserve J, Aniwan S, Koliani-Pace JL, et al. A multicentre cohort study to **assess the safety of vedolizumab f**or inflammatory bowel disease. *DDW 2018*
- Sa1726 Hudesman D, Chang S, Shashi P, et al. Impact of **concomitant immunomodulator** use on **vedolizumab** effectiveness: a multicentre consortium propensity score-matched analysis. DDW 2018
- Mo1867 Faleck D, Winters A, Chablaney S, et al. Shorter **disease duration** is associated with higher response rates to **vedolizumab** in Crohn's disease but not ulcerative colitis: a multi-centre consortium analysis. *DDW 2018*

Clinical Trials: Novel Therapeutics

Tofacitinib: Modulates Cytokine Signaling

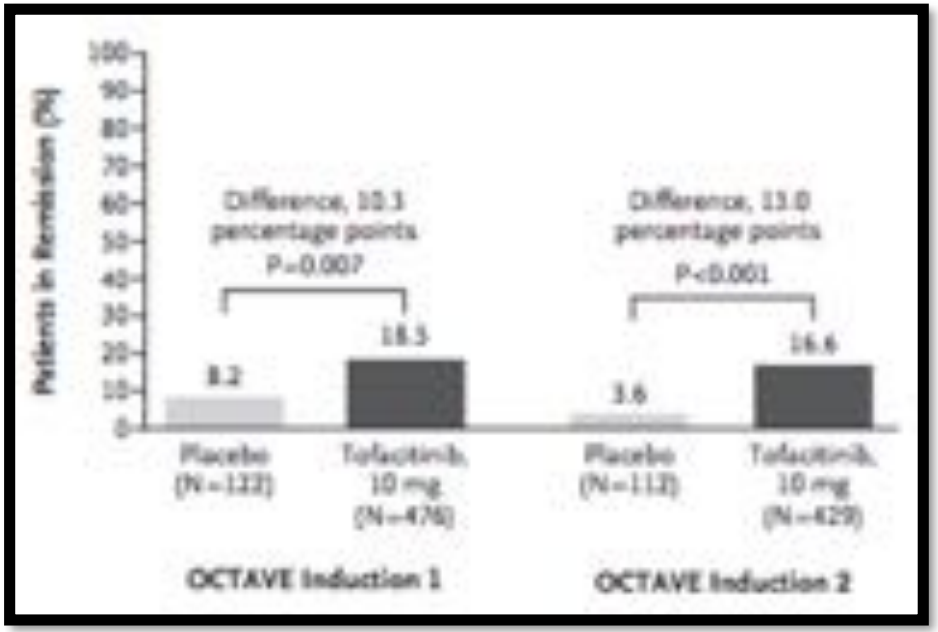


- Novel, small-molecule, oral JAK inhibitor
- Inhibits JAK1, JAK3 >JAK2
- Directly or indirectly modulates signaling for pro-inflammatory cytokines→ IL-2, 4, 7,9, 15, 21
- Xeljanz (Pfizer)
- **FDA Approved: May 31, 2018**

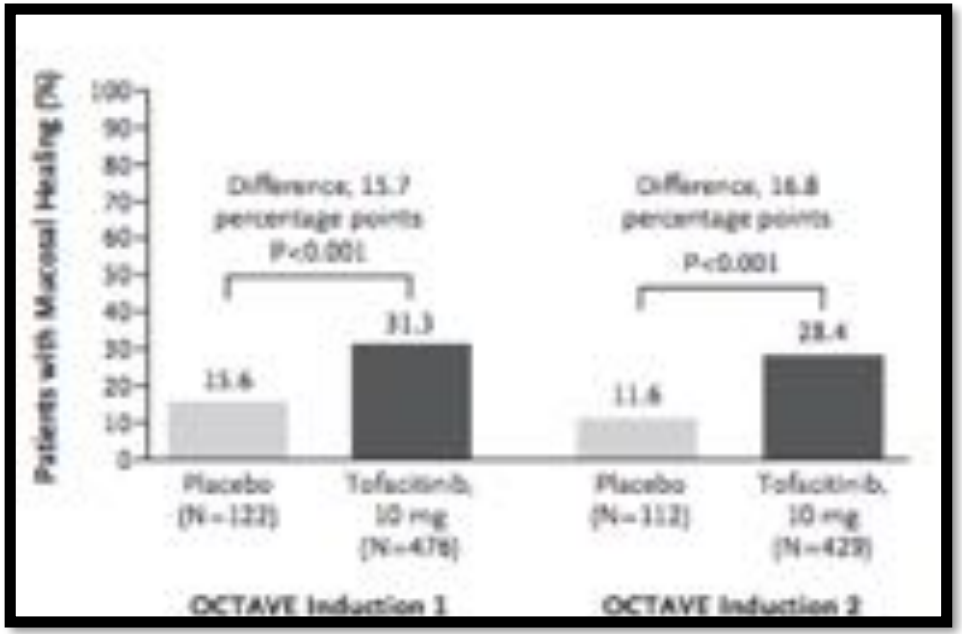
Boland B *et al. Gastroenterol Clin North Am.* 2014 Sep;43(3):603-17

OCTAVE 1 and 2: Tofacitinib as Induction and Maintenance for Ulcerative Colitis

Primary Endpoint
Remission at Week 8



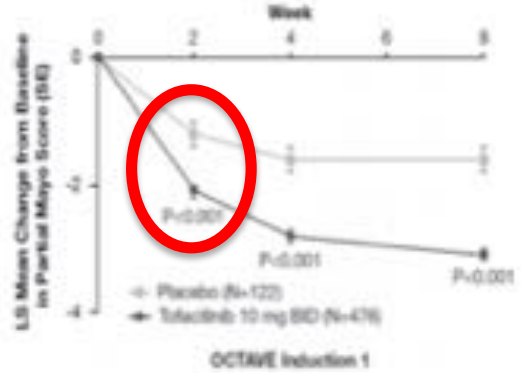
Key Secondary Endpoint:
Mucosal Healing at Week 8

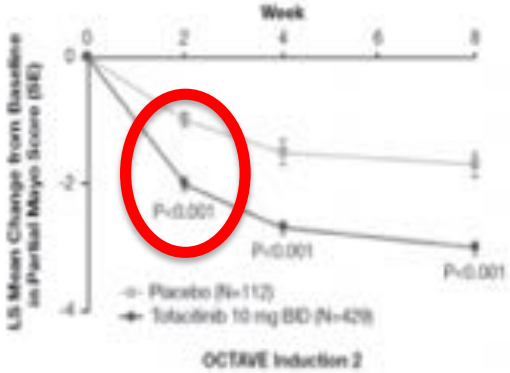


Remission: Total Mayo score ≤ 2; no subscore > 1, rectal bleeding subscore of 0, mucosal healing=ES of 0 or 1

Sandborn WJ *et al. NEJM* 2017; 376: 1723-36

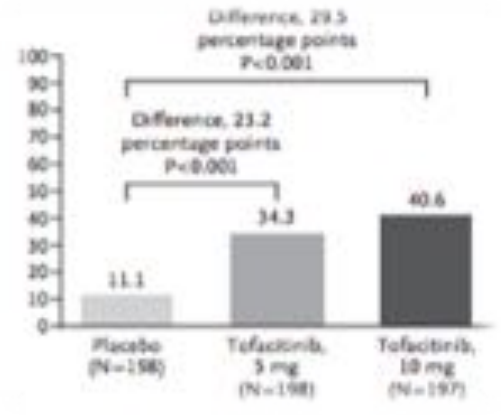
OCTAVE 1 and 2: Tofacitinib as Induction and Maintenance for Ulcerative Colitis



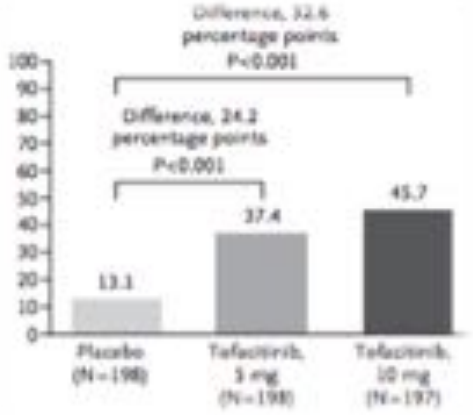


Tofacitinib Works Quickly

Maintenance: Remission at Week 52



Maintenance: Mucosal Healing at Week 52



Sandborn WJ *et al. NEJM* 2017; 376: 1723-36

Safety Signals

- Infections
  - Herpes zoster
- Cancer
  - Non-melanoma skin cancer
- LDL and HDL cholesterol increases
- Gastrointestinal perforation
- Lymphopenia

Sandborn WJ *et al. NEJM* 2017; 376: 1723-36

Tofacitinib for the Treatment of Ulcerative Colitis: Up to 4.4 Years of Safety Data from Global Clinical Trial

Presentation Number: 904

WJ Sandborn, J Panes, G D'Haens, B Sands, C Su, M Moscariello, TV Jones, RD Pedersen, GS Friedman, N Lawendy, G Chan

Study Aim:

Determine updated integrated analysis of long-term safety profile observed during UC global clinical development program, with tofacitinib exposure up to 4.4 years

Incidence Ratios Adverse Events

	Induction 10mg BID (N=938)	Maintenance 5mg BID (N=198)	Maintenance 10 mg BID (N=196)	Overall (N=1157)
Death	0	0	0	0.2
Serious Infxn	1.9	1.4	0.6	2.0
Herpes Zoster	**1.0**	**2.1**	**6.6**	**4.1**
OI	1.0	1.4	2.6	1.3
Non-herpes OI	0	0	0	0.2
Malignancy (excl. NMSC)	1.0	0	0	0.5
NMSC	1.0	0	1.9	0.7
MACE	0	0.7	0.6	0.2
Gastrointestinal perforations	1.0	0	0	0.2

1613 patients-years of exposure

Safety Considerations

- Shingrix Vaccine
  - Inactivated Recombinant Herpes Zoster Vaccine
  - Approved for immunocompetent adults ≥ 50 years old
  - 2 doses (0, months, then 2-6 months later)
    - 97% efficacy rate in person ≥ 50 years

- Check LDL/HDL before and 4-8 weeks after starting tofacitinib
- Check CBC/CMP at 1 month, then every 3-4 months

Efficacy and Safety of Tofacitinib Retreatment for Ulcerative Colitis After Treatment Interruption: Results from the OCTAVE Clinical Trials

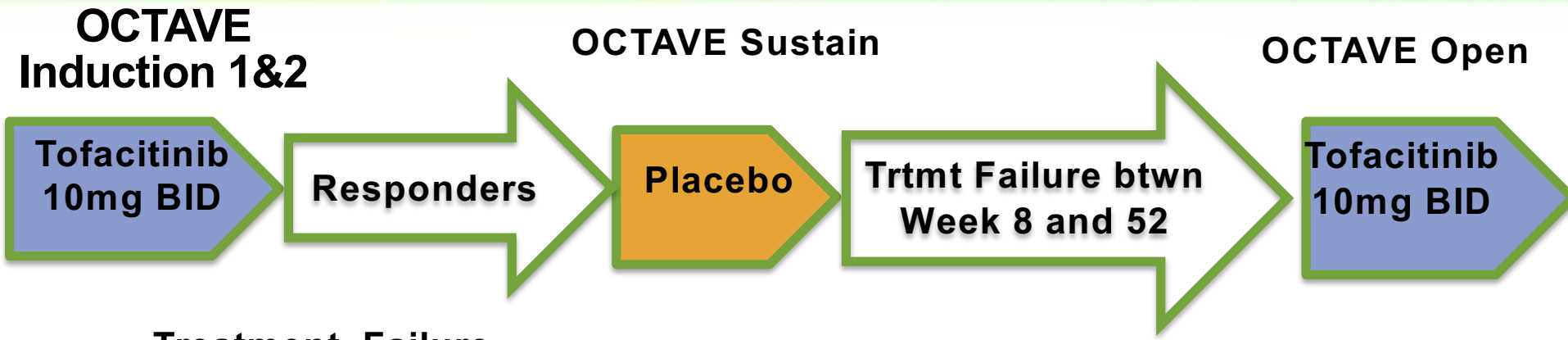
Presentation Number: 905

J Panes, B Bressler, JF Colombel, N Lawendy, ES Maller, H Zhang, DA Woodworth, G Chan, L Salese, C Su

STUDY AIM

To evaluate tofacitinib retreatment efficacy and safety after treatment interruption in UC patients in an ongoing, open-label, long-term extension study (OCTAVE Open)

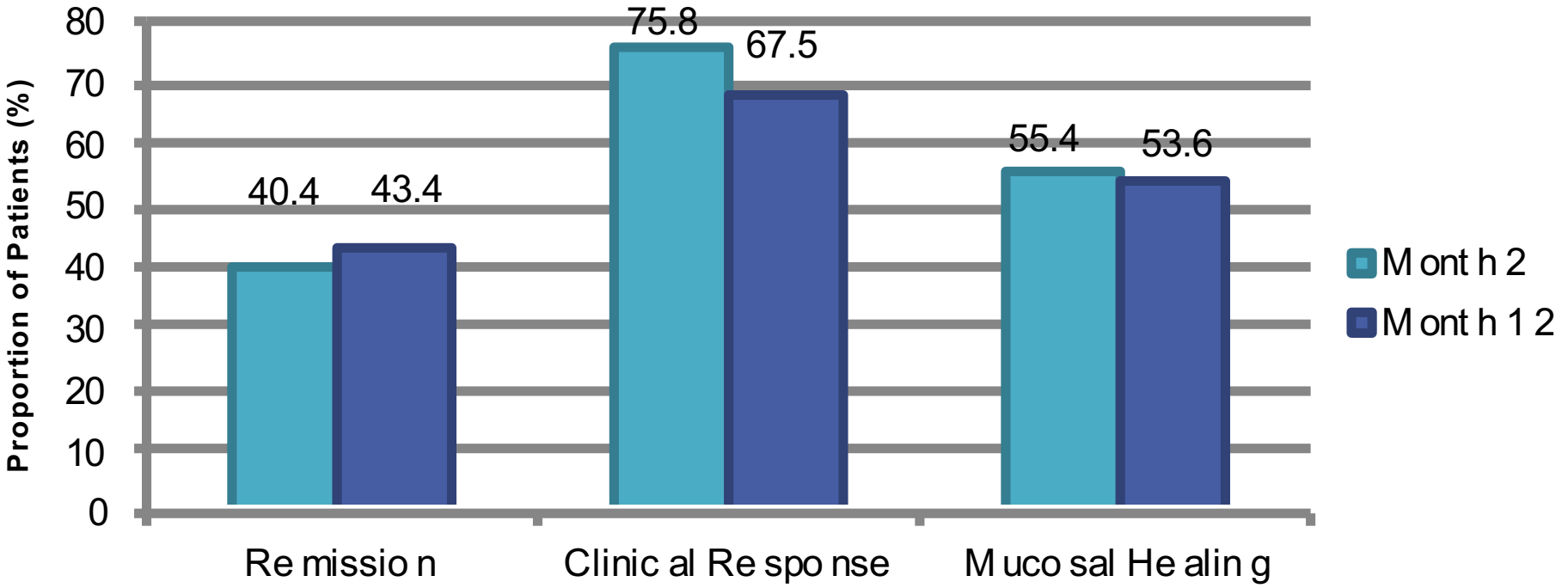
Methods



- **Treatment Failure**
  - Increase ≥ 3 points from maintenance study baseline total Mayo score + increase in rectal bleeding subscore +endoscopic subscore > 1 point
  - Absolute endoscopic subscore ≥ 2 after > 8 wks maintenance therapy

- **Evaluate:** Clinical response, mucosal healing and remission at month 2 and 12

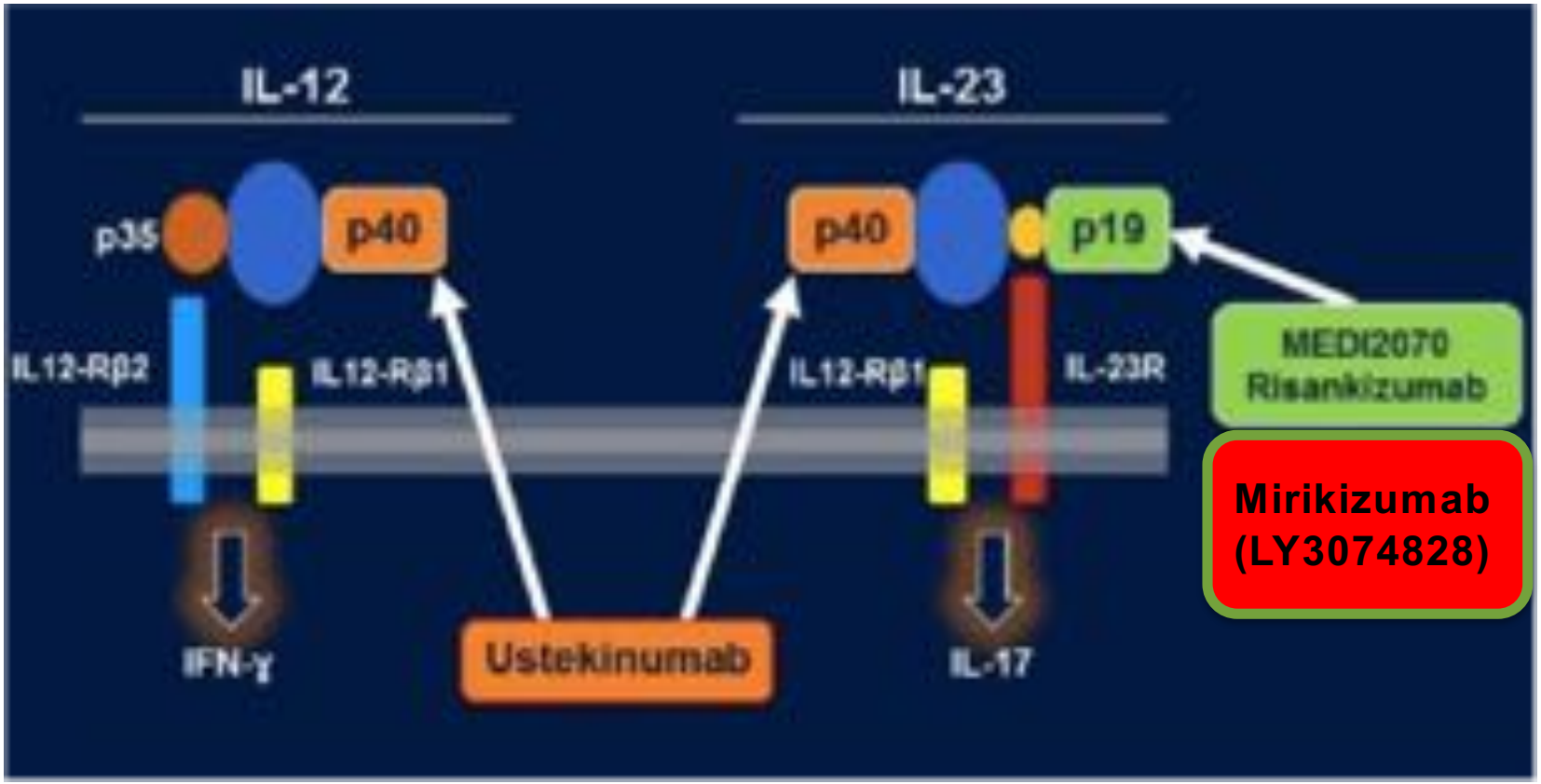
Results: Efficacy at Month 2 and 12 after treatment interruption



In patients with prior response to tofacitinib, retreatment with 10mg twice a day after treatment interruption efficacious and well-tolerated.

Roughly 75% of patients by Month 2 with clinical response recaptured/generally sustained

IL-12 and IL-23 Inhibitors



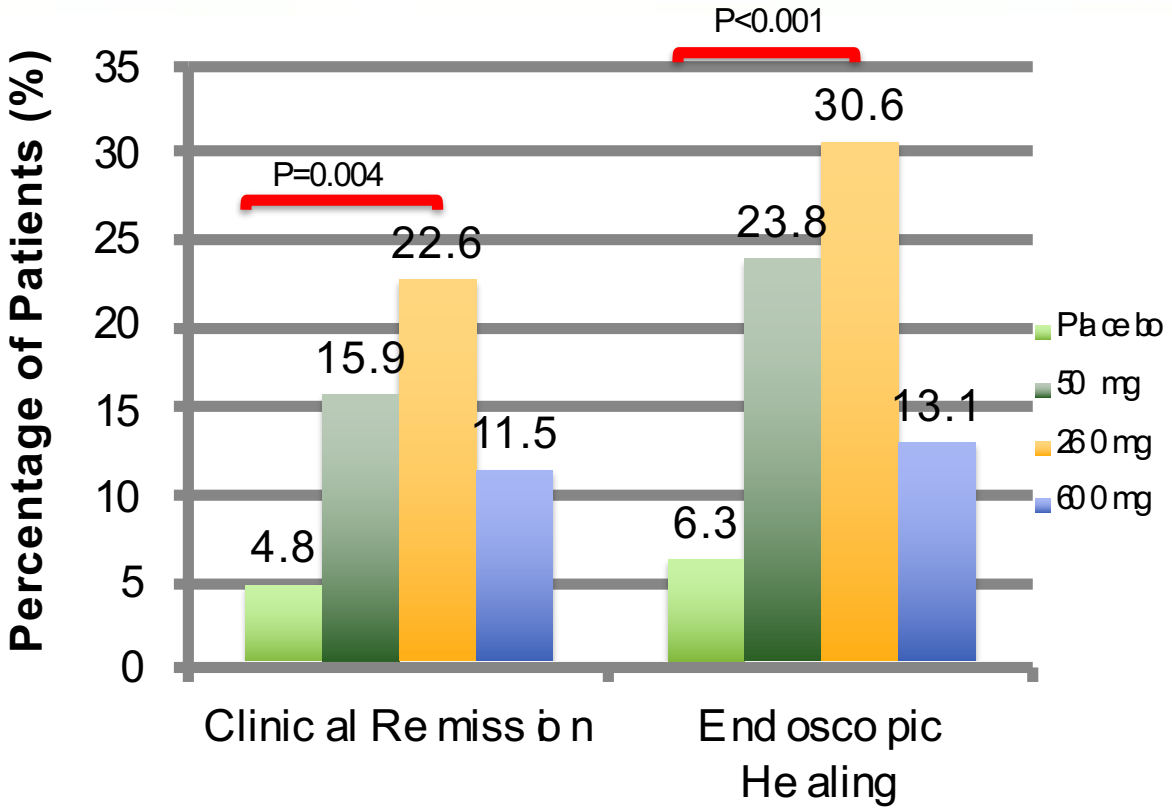
Efficacy and Safety of Anti-Interleukin 23 Therapy with Mirikizumab (LY3074828) in Patients with Moderate to Severe Ulcerative Colitis in a Phase 2 Study

Presentation Number: 882

W Sandborn, M Ferrante, BR Bhandari, G D'Haens, E Berliba, BG Feagan, J Laskowski, S Friedrich, M Durante, J Tuttle

Phase II: Mirikizumab for Moderate-Severe Ulcerative Colitis

- 249 patients
- Mayo score: 6-12, endoscopic score ≥ 2
- 63% previous biologic use
- **Clinical Remission Week12:**
  - 9 point Mayo score, excluding PGA
    - Rectal Bleeding =0
    - Stool frequency 0-1
    - Endoscopy =0 or 1
    - ≥ 1 point decrease from baseline
- **Endoscopic Healing**: 0 or 1
- No significant difference in adverse effects



Why Important?

- First data evaluating efficacy of IL-23 antibody in patients with ulcerative colitis
- Mirikizumab demonstrates efficacy in the induction treatment for patients with moderate-severe ulcerative colitis
- Trend towards efficacy in both biologic-naïve and biologic-experienced patients
- Adverse effect frequencies equal in mirikizumab and placebo treated patients

Apremilast for Active Ulcerative Colitis:

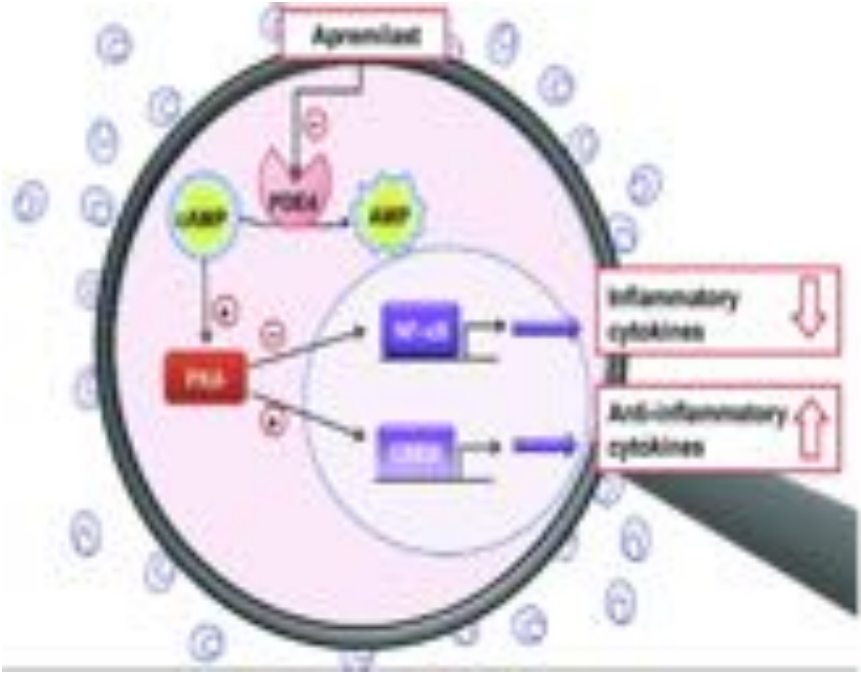
A Phase 2, randomized, double-blind placebo controlled study

Presentation Number: 813

S Danese, M Neurath, A Kopon, S Zakko, TC Simmons, RP Fogel, J Maccarone, X Zhan, K Usiskin, D Chitkara

Apremilast: Oral PDE4 Inhibitor

- **Phosphodiesterase 4 (PDE4) inhibitor (Otezla; Celgene)**
- **PDE4 inhibition:**
  - Increased intracellular cAMP levels
  - Decrease inflammatory cytokine production
- **Currently FDA approved (2014):**
  - psoriatic arthritis
  - moderate-severe plaque psoriasis
- **Reported side effects for psoriasis population:**
  - Depression
  - Weight loss
  - Drug interactions(RIF/ phenytoin)
  - Headache



Cauli A *et al. ImmunoTargets Therapy* 2014; 3:91-96

Phase 2: Apremilast in Ulcerative Colitis

- **Active Ulcerative Colitis**
  - Total Mayo Score (TMS) 6-11 with Mayo Endoscopic Subscore ≥ 2
  - Failed at least 1 conventional therapy for UC
  - *NAÏVE TO BIOLOGICS*
- **Phase 2: Randomized, double blind placebo-controlled**
  - Apremilast 30 mg BID (APR 30)
  - Apremilast 40 mg BID (APR 40)
  - Placebo
- All endoscopy centrally read
- **Primary Endpoint:**
  - TMS clinical remission Wk12 (TMS ≤ 2 with no individual subscore>1)

Results

Week 12 Study Endpoints	PBO n=58	APR30 n=57	APR40 n=55
TMS clinical remission[1]	13.8%	31.6%*	21.8%
MMS clinical remission[1]	19%	43.9%*	27.3%
TMS clinical response[1]	46.6%	61.4%	67.3%*
Decrease from baseline MES of at least 1 point	41.4%	73.7%*	47.3%
MES ≤1	24.1%	56.1%*	34.5%
Geboes score <2	29.3%	43.9%	41.8%
Mucosal healing[1]	15.5%	33.3%*	21.8%

*P<0.05 vs PBO.

Why Important?

- Possible therapeutic option in ulcerative colitis in biologic-naïve population
- Biomarker:
  - 50% with hsCRP <3 by week 12
  - Fecal calprotectin <250 ug/g in 56% by week 12
- Side effect profile will need to be clearly understood
  - Headache 20%
  - URI ~5%

Alternative Therapies

Case Scenario

35 year old female with newly diagnosed ulcerative colitis is asking about dietary recommendations and CAM as part of management strategy. What do you recommend?

- A. Refer to the internet
- B. Send her to a dietician
- C. Have her buy Cannabis

CANNABIS INDUCES CLINICAL AND ENDOSCOPIC IMPROVEMENT IN MODERATELY ACTIVE ULCERATIVE COLITIS

Presentation SA 1744

Timna Naftali[1,2], Lihi Bar Lev Schlieder[3], Fabiana Sklerovsky Benjaminov[1,2], Ido Lish[1,2], Fred M. Konikoff[1]

Aims and Study Design

- To assess effects of Cannabis in moderatively active UC,
- Randomized (14 patients enrolled in each group)
  - 2 Cigarettes of Cannabis (0.5g=11.5mg THC)
  - Or 2 Cigarettes of Placebo (had cannabis leaves)
- All other medications stayed the same
- Clinical, labs and endoscopic followup

Patient Characteristics

	Study	Placebo
Patients	14	14
Age	34+/-11	32+/-7
Gender(m/f)	6/7	11/4
Smoking	0	1
UC (left/extensive)	6/8	8/6
Disease Duration (yrs)	8.2+/-4	6.5+/-5
5 ASA	7	9
Steroids	2	3
Thiopurine	2	4
Biologics	2	2

	Week 0	Week 8	P value
Lichtiger score Cannabis	**10 +/- 3**	**4 +/- 3.2**	**<0.1**
Lichtiger score Placebo	10 +/- 2.7	8 +/- 2	<0.03
Mayo Score Cannabis	**2**	**1**	**0.01**
Mayo Score Placebo	2	2	0.59
CRP Cannabis	**0.8+/- 0.9**	**0.7 +/- 1.2**	**0.5**
CRP Placebo	1.8 +/- 1.9	1 +/- 1.6	0.5
Calprotectin Cannabis	**135+/-113**	**115+/- 103**	**0.7**
Calprotectin placebo	226+/-100	229 +/- 230	0.7

Conclusions

- Use of THC in UC patients led to the following
  - Clinical improvement
  - Endoscopic improvement of Mayo Score
  - Lab parameters with no improvement
- Side effects: memory decline and dizziness
- Further larger studies warranted

Biosimilars

Case Scenario

- 38 year old female is newly diagnosed with moderately active pan-UC. Hgb is 10, crp is 15. At this time, you recommend dual therapy with infliximab and 6MP. Patient is an agreement to take this therapy. Insurance states you must use the biosimilar.
- What do you?

- A. Proceed with biosimilar with 6mp
- B. Appeal to insurance company to get infliximab
- C. Unsure what to do

What is a «biosimilar» ?

World Health Organization:

"A biotherapeutic product which is **similar in terms of quality, safety and efficacy** to an already licensed reference biotherapeutic product"

European Medicines Agency:

"A biosimilar is a copy version of an already authorised biological medicinal product with **demonstrated similarity** in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise"

FDA:

A biological product that "(a) … is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and for which "(b) there are **no clinically meaningful differences** between the biological product and the reference product in terms of safety, purity, and potency of the product"

Personalized Medicine

Case: Thiopurine Induced Myelosuppression

- Ms. A is a 39 yo woman who has moderate to severe ulcerative colitis. You decide to start her on azathioprine and infliximab. Her TPMT is normal. Despite starting her on lower than weight-based dosing at 100 mg once a day, she develops neutropenia within 1 month of starting azathioprine. Why is this?

Thiopurine-Induced Myelosuppression (TIM)

- Pre-treatment pharmacogenetic testing for TPMT variants recommended to identify enzyme deficient population with distribution below (based on white population):
  - 89.5% normal to high methylations
  - 9.9% intermediate
  - **0.6% deficient methylation**
- TPMT only identifies 25% of European patients with TIM
- Asian population, TPMT variants more rare (3% vs. 10%) but leukopenia more frequent (30% vs. 5%)
- In Asian population, **NUDT15 gene variant** significantly associated with thiopurine-related leukopenia (OR: 35.6; $p=3.88 \times 10^{-94}$)

Cascorbi I. *Advances in Pharm* 2018: 276-296

NUDT15 Variants Contribute To Thiopurine-Induced Myelosuppression in European Populations

Presentation Number:472

G Walker, JW Harrison, MD, Voskiul, GA Heap, N Heerasing, PJ Hendy, J Koskela, MJ Daly, H Sokol, RK Weersma, D McGovern, CM Bewshea, M Weedon, J Goodhand, NA Kennedy, T Ahmad

Methods/Results

- Participants:
  - 491 cases with TIM (total white cells $\leq 2.5 \times 10^9$/L and/or neutrophils $\leq 1.0 \times 10^9$/L)
  - 734 thiopurine-tolerant IBD controls
- Main outcomes:
  - Association of genetic variants in cases and controls
- Exome sequencing

- TPMT in TIM confirmed
- Seven coding deleterious NUDT15 variants in TIM
- Verified in independent cohort

- **Carriage of any NUDT15 coding variant**
  - **22-fold increase in odds of TIM ($p=2.9 \times 10^{-8}$), independent of TPMT or thiopurine dose**

Why Important?

Clinical Validity Estimates

- For every 100 patients genotyped, 2 patients will carry NUDT15 mutation and need alternative treatment to prevent TIM in 1 patient
- Pre-treatment NUDT15 genotyping could reduce TIM cases by 13% and can be added to TPMT testing for safer thiopurine prescribing
- Greatest risk of TIM in patients with both TPMT and NUDT15 variants in European population

Case: Combination Therapy Mandatory?

Mr. G is a 30 year old male with h/o Crohn's ileocolitis. You would like him to start combination therapy with infliximab and azathioprine for his moderately -severe Crohn's disease. He is not keen on combination therapy. How could we better counsel him on risk of immunogenicity to biologic monotherapy?

HLA-DQA1 Contributes to the Development of Antibodies To Anti-TNF Therapy In Crohn's Disease

Presentation Number: 590

A Sazonov, NA Kennedy, CM Bewshea, L Loutsiana, GJ Walker, KD Lange, J Goodhand, C Anderson, J Barrett, T Ahmad- PANTS Investigator Consortium

PANTS (Personalized Anti-TNF Therapy in Crohn's Disease) Trial

- 3 year prospective observational UK-wide study investigating infliximab, adalimumab, CT-P13:
  - Primary Non-Response (PNR)
  - Loss of Response
  - Adverse Drug Reaction
- Inclusion:
  - CD patients ≥ 6 years
  - Active inflammatory disease
    - CRP >3mg/L
    - Calprotectin ≥ 50µg/g
  - No prior anti-TNF therapy

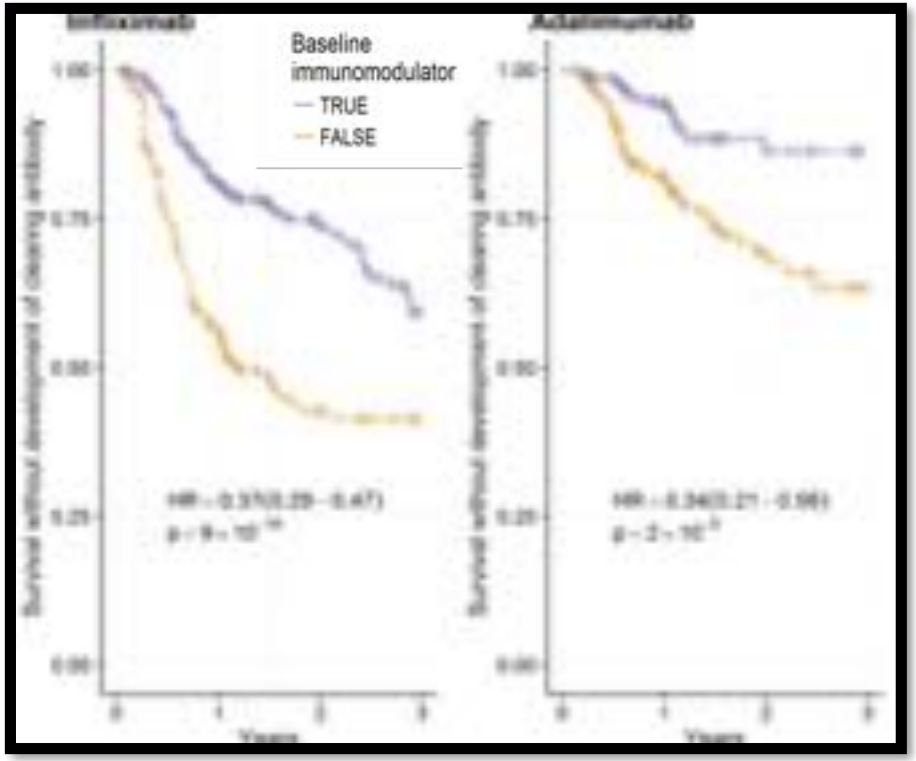
Definitions

- **Primary Non-Response (PNR)** defined at week 12-14
  - Requirement for ongoing steroids **OR BOTH**
  - HBI failed to fall by ≥ 3 points or to ≤ 4 **AND** CRP failed to fall by ≥ 50% or to ≤ 3mg/L
- **Remission** at week 14 and week 54
  - HBI ≤ 3 points and CRP ≤ 3 mg/L **AND**
  - No concomitant steroids
- **Treatment failure:** Stopped drug other than elective, pregnancy or loss-to follow up
- **Immunogenicity** : Drug tolerant ELISA assay
  - ADA titer ≥ 10 AU/mL + undetectable drug level

Results

	IFX	CT-P13	ADAL
PNR (wk 12-14)	21%	21%	26%
Remission (wk 54)	40%	50%	34%
Immunogenicity (wk 54)	26%	28%	11%
Immunogenicity (year 3)	42%	38%	23%

- 1601 patients; median age: 33 years
- Median duration disease: 3 years
- Steroid: 27%; AZA: 44%: MTX:5%:; 6MP:8%
- PNR associated with:
  - Older age
  - Higher BMI
  - Low Drug levels
- Immunonogenicity was associated with non-remission at week 54 (p<0.0001)



Concomitant immunomodulator use reduced the risk of immunogenicity for both infliximab and adalimumab

Why Important?

- Pre-treatment genetic testing might allow us to clarify individual risk profiles and targeted use of immunomodulatory therapies
- 40% of European ancestry carries HLA-DQA1*05 risk allele
- Presence of HLA risk allele on infliximab monotherapy increases risk of developing immunogenicity within 1 year
- Subset of patients may need to remain on combination therapy with infliximab

Thank You!