

Florida ACP Meeting Updates in Gastroenterology

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Agenda

■ Stomach

- Thromboembolism and GI bleeding after stopping anticoagulants

■ Colon

- C. Difficile
- Inflammatory bowel disease

■ Small bowel

- Sprue- a common problem
- Colon Cancer in IBD

The Risks of Thromboembolism Vs.
Recurrent Gastrointestinal Bleeding After
Interruption of Systemic Anticoagulation in
Hospitalized Inpatients With
Gastrointestinal Bleeding: A Prospective
Study

Sengupta N, et al, Am J Gastro 2015; 110:
328-335

Objectives

- Anticoagulants carry a significant risk of gastrointestinal bleeding (GIB)

Aims

- To determine the safety and risk of continuation of anticoagulation after GIB

Methods

- A prospective observational cohort study was conducted on patients admitted to the hospital who had GIB while on systemic anticoagulation.
- Patients were classified into two groups at hospital discharge after GIB: those who resumed anticoagulation and those who had anti coagulation discontinued.

Results

- Majority of patients were on warfarin.
- Warfarin (74%, n =145), enoxaparin (8%, n =15), dabigatran (6%, n =12), rivaroxaban (6%, n =11), unfractionated heparin (6%, n =12), and apixaban (1%, n =2).

Results

- 90 days after discharge the following outcomes were determined: – 197 patients who developed GIB while on systemic anticoagulation
- During the follow-up period, 7 (4%) patients suffered a thrombotic event and 27 (14%) patients were readmitted for GIB
- 1/121 (0.8%) who resumed anticoagulation develop thromboembolism in contrast to 6/76 (8%) in patients whose anticoagulation was interrupted. ($p=0.003$)

Results

Outcome	Unadjusted hazard ratio (95% CI)	<i>P</i> value	Adjusted hazard ratio (95% CI)	<i>P</i> value
Thromboembolism	0.073 (0.004–0.434)	0.003	0.121 (0.006–0.812)	0.03
Recurrent GIB	2.28 (0.929–6.83)	0.07	2.17 (0.861–6.67)	0.10
Death	0.471 (0.172–1.28)	0.138	0.632 (0.216–1.89)	0.40

Conclusions

- Restarting anticoagulation at discharge after GIB was associated with fewer thromboembolic events without a significantly increased risk of recurrent GIB at 90 days
- The benefits of continuing anticoagulation at discharge may outweigh the risk of recurrent GIB.

Clostridium difficile

**Frozen vs. Fresh Fecal Microbiota
Transplantation and Clinical Resolution
of Diarrhea in Patients With
Recurrent *Clostridium difficile* Infection:
A Randomized Clinical Trial.**

**Lee CH et al. JAMA 2016 Jan
12;315(2):142-9**

Introduction

- FMT is a promising treatment option for recurrent or refractory CDI.
- To determine whether frozen-and-thawed (frozen, experimental) FMT is noninferior to fresh (standard) FMT in terms of clinical efficacy among patients with recurrent or refractory CDI and to assess the safety of both types of FMT.

Methods

- Patients 18 years or older with a history of recurrent or refractory CDI were enrolled in the study.
- Patients randomized to receive fresh FMT received the suspension within 24 hours of collection; those randomized to receive the frozen FMT received the suspension within 24 hours of thawing.

Results

Table 2. Number of Fecal Microbiota Transplantations and the Proportion With Clinical Resolution at 13 Weeks After Last Transplantation

No. of FMTs	No. (%) With Clinical Resolution			
	mITT Population		Per-Protocol Population	
	Frozen (n = 108)	Fresh (n = 111)	Frozen (n = 91)	Fresh (n = 87)
1	57 (52.8)	56 (50.5)	57 (62.7)	54 (62.1)
2	24 (75.0)	22 (70.3)	19 (83.5)	20 (85.1)
3-5	13 (87.0)	12 (81.1)	9 (93.4)	9 (95.4)
>5	4 (90.7)	5 (85.6)	2 (95.6)	1 (96.6)
Total	98/108 (90.7)	95/111 (85.6)	87/91 (95.6)	84/87 (96.6)

Abbreviations: FMT, fecal microbiota transplantation; mITT, modified intention-to-treat.

Conclusion

- Among adults with recurrent or refractory CDI, the use of frozen compared with fresh FMT did not result in worse proportion of clinical resolution of diarrhea. Given the potential advantages of providing frozen FMT, its use is a reasonable option in this setting.

Bezlotoxumab for Prevention of
Recurrent *Clostridium difficile*
Infection

Wilcox M et al. N Engl J Med 2017;
376:305-317

Introduction

- *Clostridium difficile* is the most common cause of infectious diarrhea in hospitalized patients.
- 35% of patients have recurrent *C. difficile* infection.
- A new approach to the prevention of recurrent *C. difficile* infection is the administration of monoclonal antibodies against *C. difficile* toxins (in addition to antibiotic therapy) as a form of passive immunity.

Introduction

- Actoxumab (MK-3415/GS-CDA1/CDA1) and bezlotoxumab (MK-6072/MDX-1388/CDB1) are fully human monoclonal antibodies that bind and neutralize *C. difficile* toxins A and B, respectively.
- To study the safety and efficacy of bezlotoxumab, both alone and combined with actoxumab, for the prevention of recurrent *C. difficile* infection.

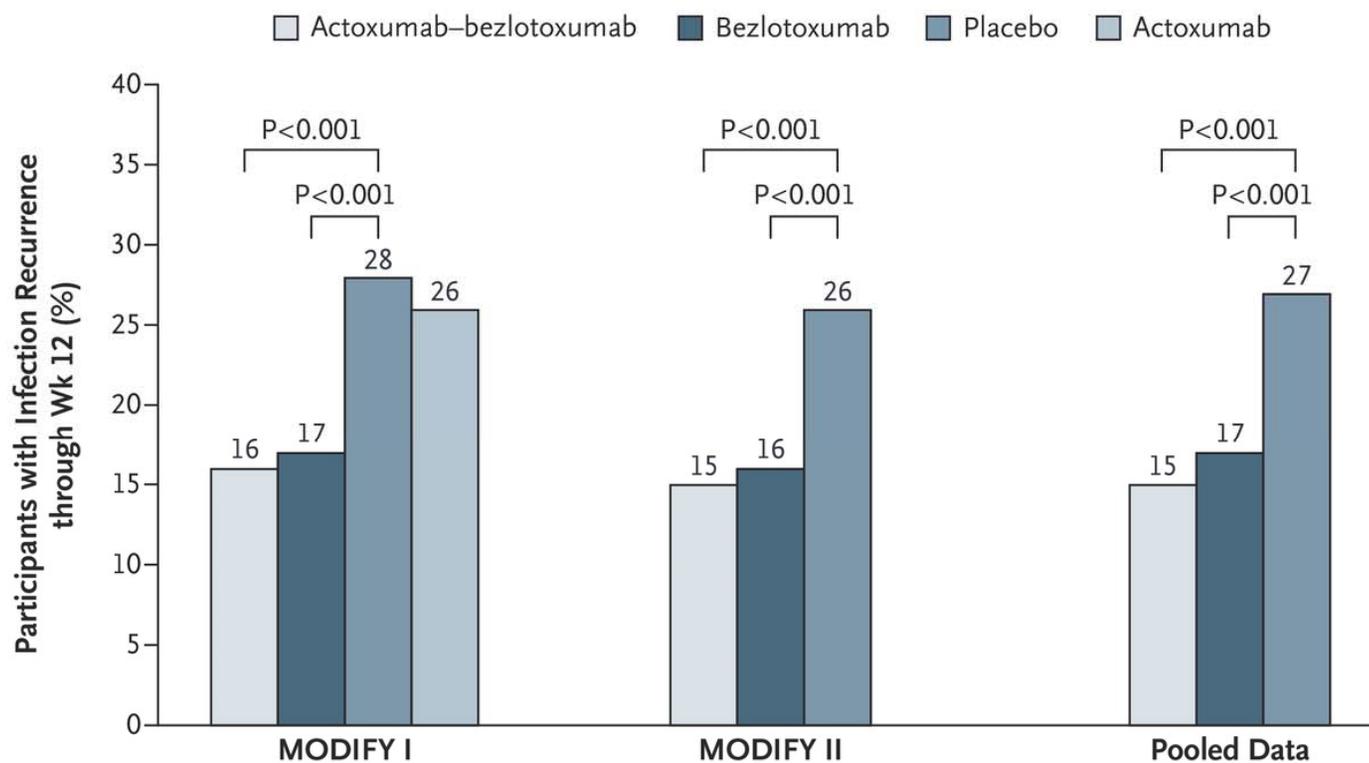
Methods

- Participants were randomly assigned in a 1:1:1:1 ratio to receive a single dose of bezlotoxumab (10 mg per kilogram of body weight), actoxumab plus bezlotoxumab (10 mg per kilogram each), placebo (0.9% saline), or, in MODIFY I only, actoxumab alone (10 mg per kilogram); actoxumab was not evaluated alone in MODIFY II because earlier results suggested a lack of efficacy for this antibody.

End Points

- The primary end point was the proportion of participants with recurrent *C. difficile* infection (defined as a new episode of *C. difficile* infection after initial clinical cure of the baseline episode) during 12 weeks of follow-up in the modified intention-to-treat population

Participants with Recurrent *Clostridium difficile* Infection during the 12-Week Follow-up

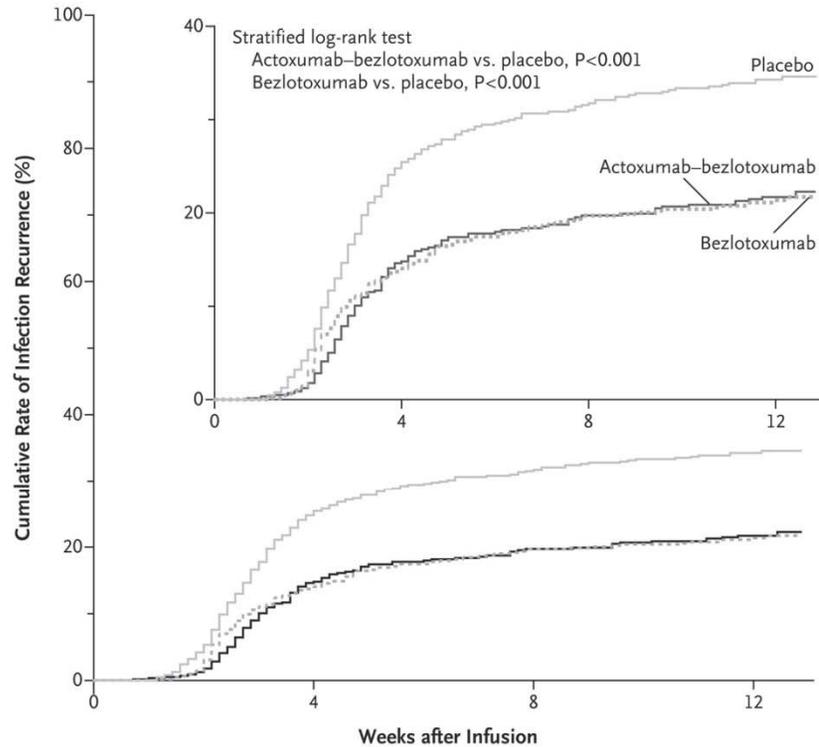


	61	67	109	60
No. of Events	383	386	395	232
No. of Participants at Risk				

	58	62	97
No. of Events	390	395	378
No. of Participants at Risk			

	119	129	206
No. of Events	773	781	773
No. of Participants at Risk			

KM Curve of Recurrence



No. at Risk

Actoxumab-bezlotoxumab	773	465	416	301
Bezlotoxumab	781	518	463	343
Placebo	773	443	386	272

Kaplan-Meier Rate Estimates (95% CI) — %

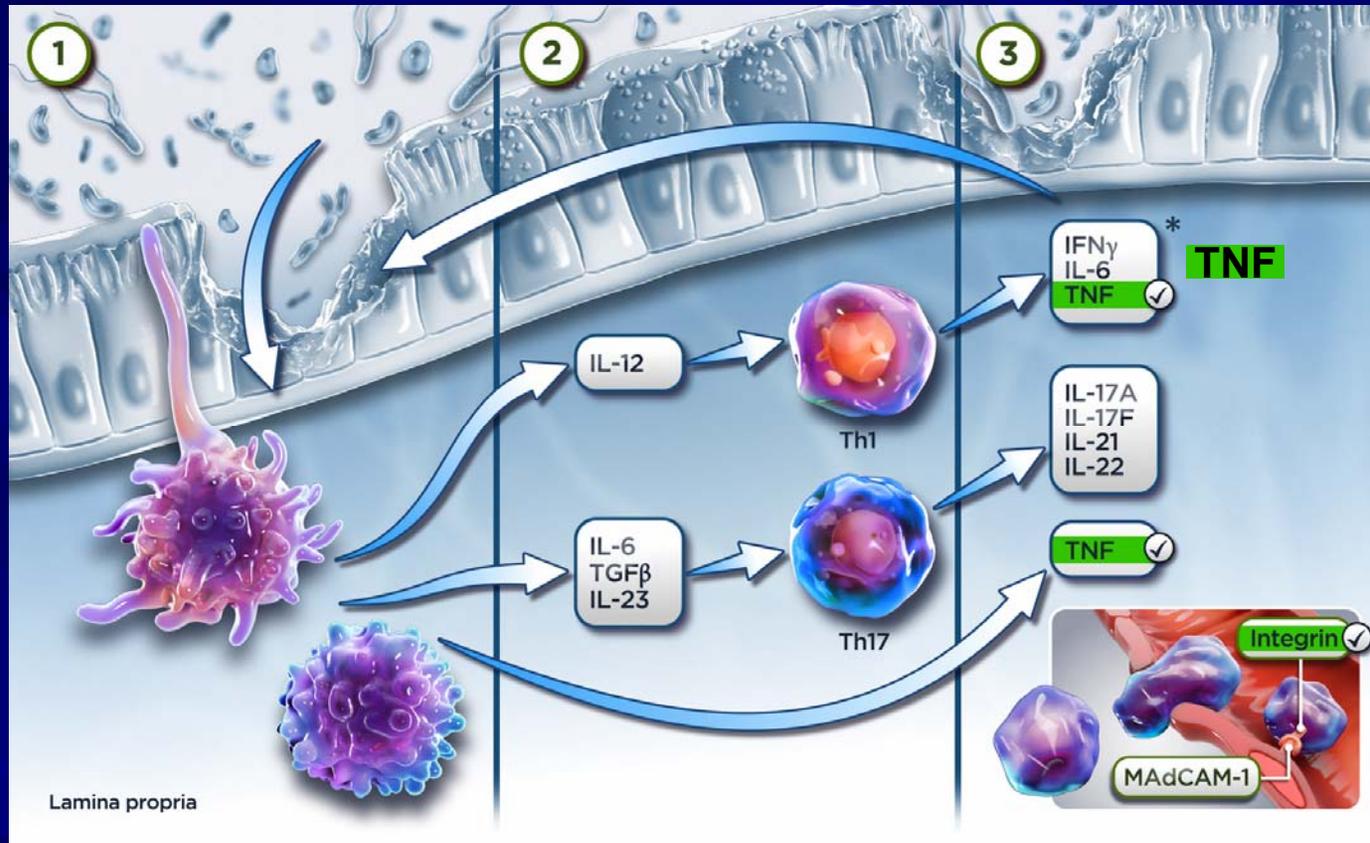
Actoxumab-bezlotoxumab	15 (12–18)	20 (16–23)	22 (18–25)
Bezlotoxumab	14 (11–17)	20 (16–23)	21 (18–25)
Placebo	26 (22–29)	32 (28–36)	34 (30–38)

Conclusion

- The results of MODIFY I and MODIFY II, separately and combined, show that among participants receiving standard-of-care antibiotic therapy for primary or recurrent *C. difficile* infection, bezlotoxumab was associated with a significantly lower rate of recurrent infection than was placebo.

Inflammatory Bowel Disease

Biologic therapy targeting in IBD



Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis

Sandborn WJ et al. N Engl J Med
2017; 376:1723-1736

Background and Aim

- Tofacitinib, an oral, small-molecule Janus kinase inhibitor, was shown to have potential efficacy as induction therapy for ulcerative colitis in a phase 2 trial.
- Tofacitinib inhibits JAK1 and JAK3 signaling resulting in reduced synthesis of pro-inflammatory cytokines.
- To evaluate the efficacy of tofacitinib as induction and maintenance therapy.

Methods

- Three phase 3, randomized, double-blind, placebo-controlled trials of tofacitinib therapy in adults with ulcerative colitis.
- In the OCTAVE Induction 1 and 2 trials, 598 and 541 patients, respectively, who had moderately to severely active ulcerative colitis despite previous conventional therapy or therapy with a tumor necrosis factor antagonist were randomly assigned to receive induction therapy with tofacitinib (10 mg twice daily) or placebo for 8 weeks. The primary end point was remission at 8 weeks.

Methods

- In the OCTAVE Sustain trial, 593 patients who had a clinical response to induction therapy were randomly assigned to receive maintenance therapy with tofacitinib (either 5 mg or 10 mg twice daily) or placebo for 52 weeks.
- The primary end point was remission at 52 weeks.

Results

- In the OCTAVE Induction 1 trial, remission at 8 weeks occurred in 18.5% of the patients in the tofacitinib group versus 8.2% in the placebo group ($P=0.007$); in the OCTAVE Induction 2 trial, remission occurred in 16.6% versus 3.6% ($P<0.001$).
- In the OCTAVE Sustain trial, remission at 52 weeks occurred in 34.3% of the patients in the 5-mg tofacitinib group and 40.6% in the 10-mg tofacitinib group versus 11.1% in the placebo group ($P<0.001$ for both comparisons with placebo). In the OCTAVE Induction 1 and 2 trials, the rates of overall infection and serious infection were higher with tofacitinib than with placebo.

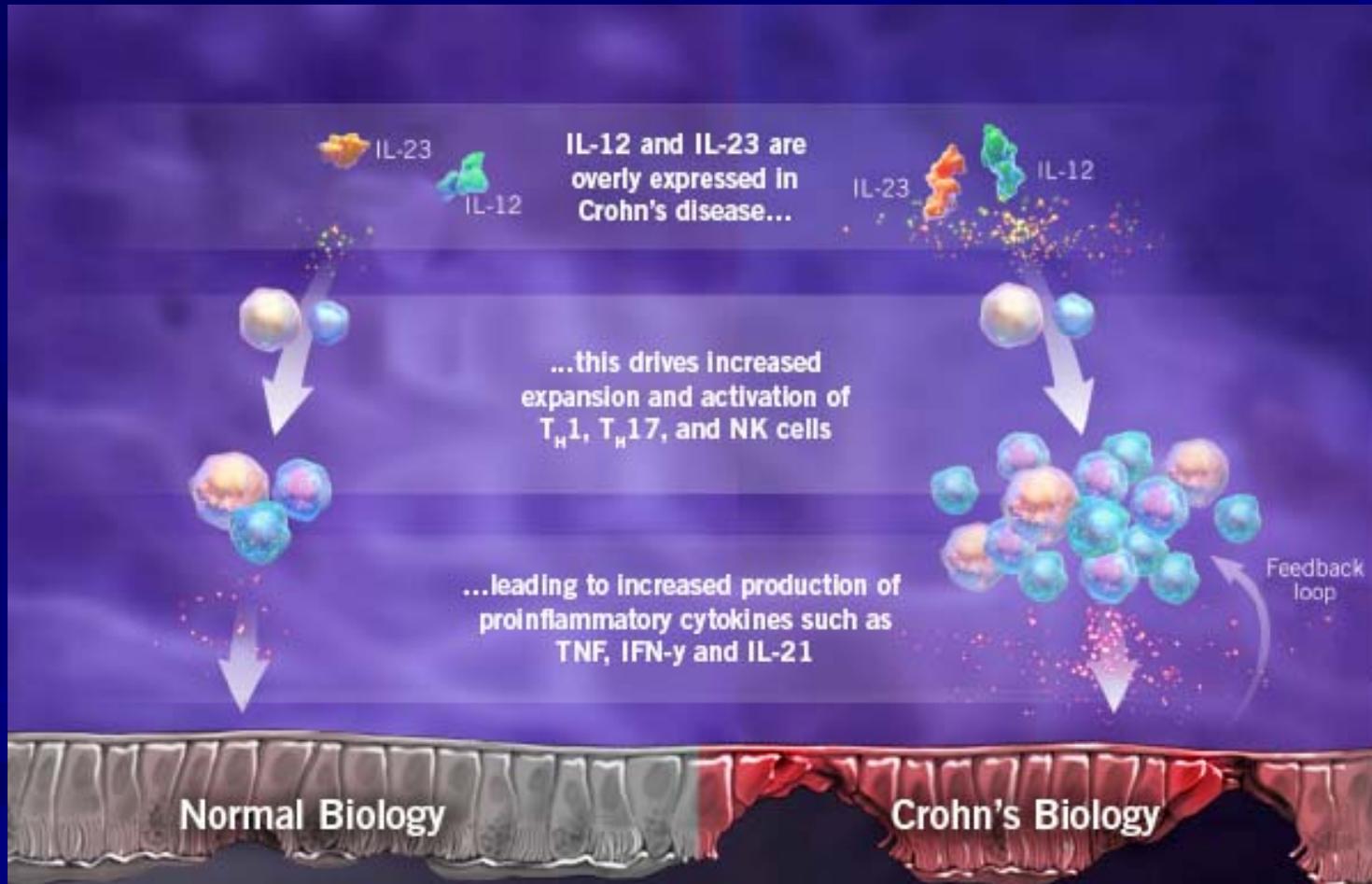
Conclusions

- In patients with moderately to severely active ulcerative colitis, tofacitinib was more effective as induction and maintenance therapy than placebo.

**Ustekinumab as Induction and
Maintenance Therapy for Crohn's
Disease.**

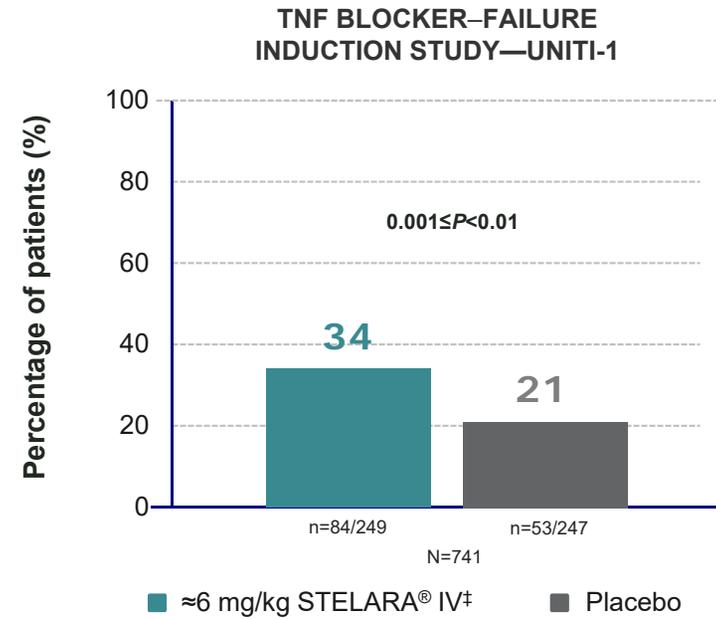
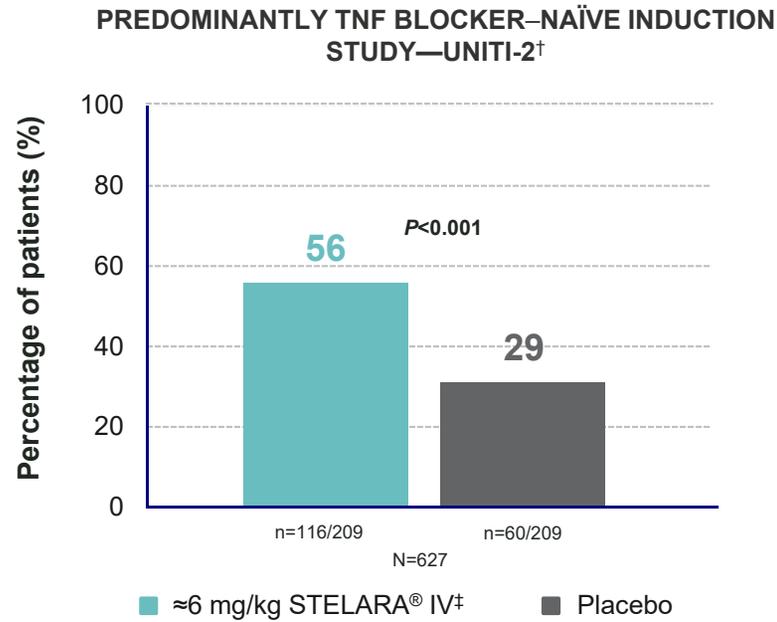
**Feagen BG et al. N Engl J Med. 2016
Nov 17;375(20):1946-1960**

Stelara (Ustekinumab)



Clinical Response Achieved Across Populations at Week 6

100-point Response at Week 6—Primary Endpoint*



More than half (56%) of patients taking STELARA® in the UNITI-2 study achieved clinical response at Week 6 vs 29% for placebo ($P<0.001$)

*Clinical response was defined as reduction in CDAI score of ≥ 100 points or CDAI score of < 150 .¹

[†]69% of patients were TNF blocker naïve. Remaining population was patients previously exposed to, but who did not fail, treatment with TNF blockers. All patients in the study failed or were intolerant to conventional treatment (eg, azathioprine, 6-mercaptopurine, methotrexate, or corticosteroids).¹

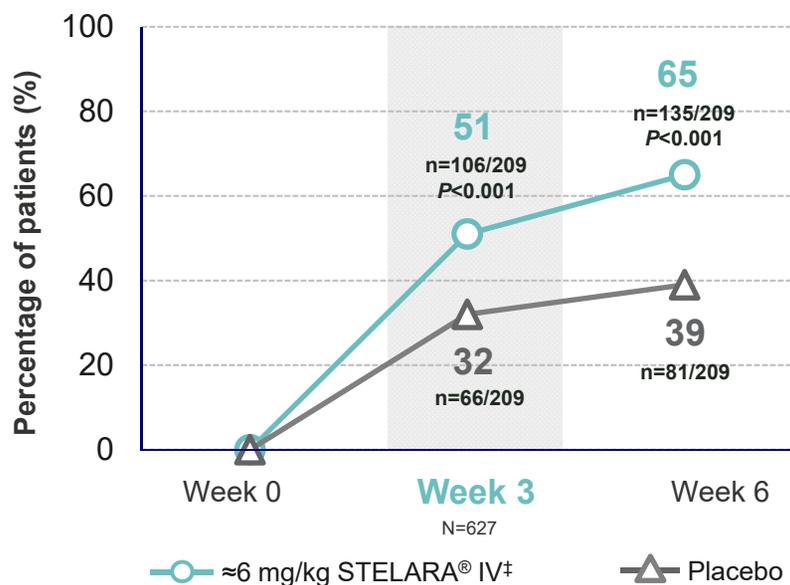
[‡]Weight-based induction dosage regimen: STELARA® 260 mg (weight ≤ 55 kg), STELARA® 390 mg (weight > 55 kg and ≤ 85 kg), STELARA® 520 mg (weight > 85 kg).¹

Reference: 1. STELARA® [prescribing information]. Horsham, PA: Janssen Biotech, Inc; 2016.

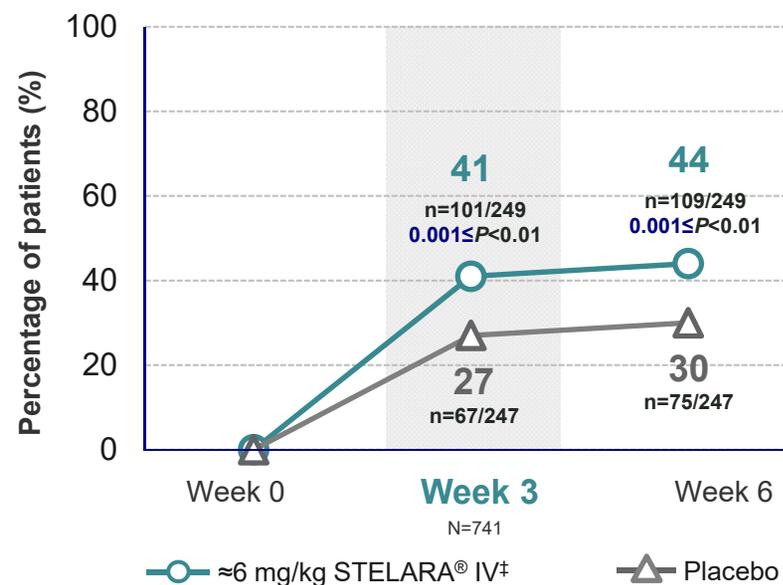
Rapid Response Achieved Across Populations at Week 3

70-point Response at Week 3 and Week 6—Major Secondary Endpoints*

PREDOMINANTLY TNF BLOCKER-NAÏVE INDUCTION STUDY—UNITI-2†



TNF BLOCKER-FAILURE INDUCTION STUDY—UNITI-1



*70-point response was defined as reduction in CDAI score of ≥ 70 points.¹

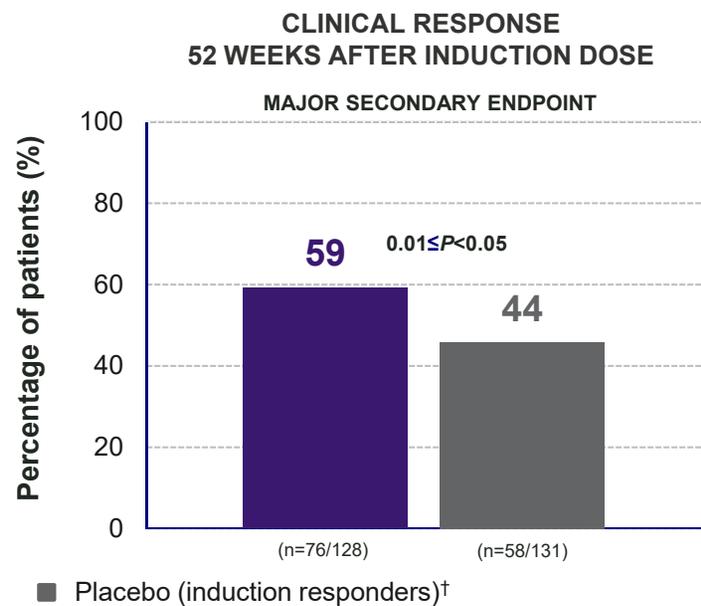
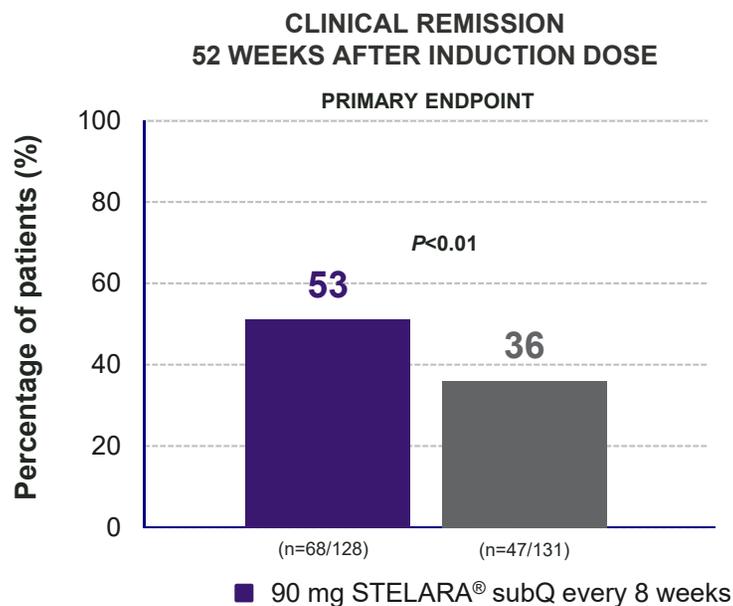
¹69% of patients were TNF blocker naïve. Remaining population was patients previously exposed to, but who did not fail, treatment with TNF blockers.

All patients in the study failed or were intolerant to conventional treatment (eg, azathioprine, 6-mercaptopurine, methotrexate, or corticosteroids).¹

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Reference: 1. STELARA® [prescribing information]. Horsham, PA: Janssen Biotech, Inc; 2016.

Clinical Remission and Response 52 Weeks After Induction Dose

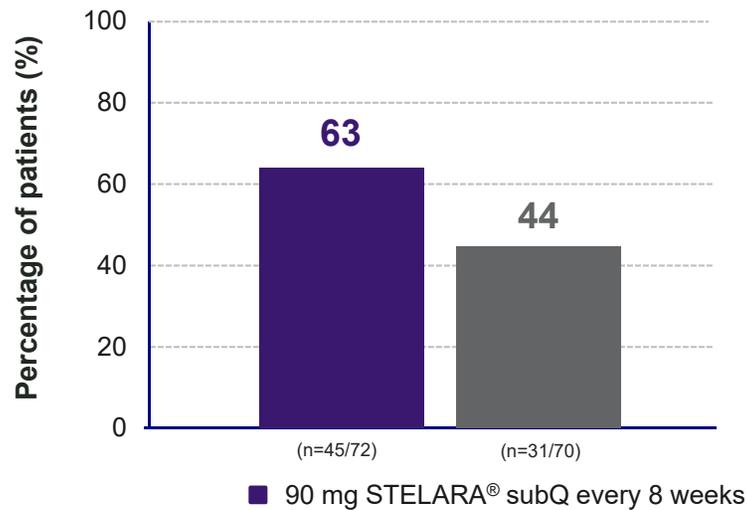


The majority of patients in the maintenance study
Achieved clinical remission 52 weeks after induction dose

Patients in Clinical Remission From UNITI-1 and UNITI-2 Populations

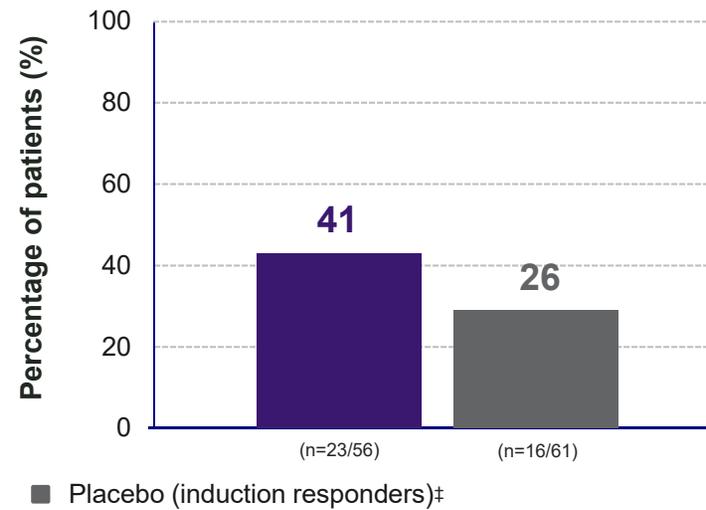
OTHER ENDPOINT: CLINICAL REMISSION 52 WEEKS AFTER INDUCTION DOSE

PREDOMINANTLY TNF BLOCKER-NAÏVE PATIENTS—
UNITI-2†



Nominal *P* value due to not being a major secondary endpoint

TNF BLOCKER-FAILURE PATIENTS—UNITI-1



63% of patients from UNITI-2 induction study
subgroup were in remission at 1 year

Conclusion

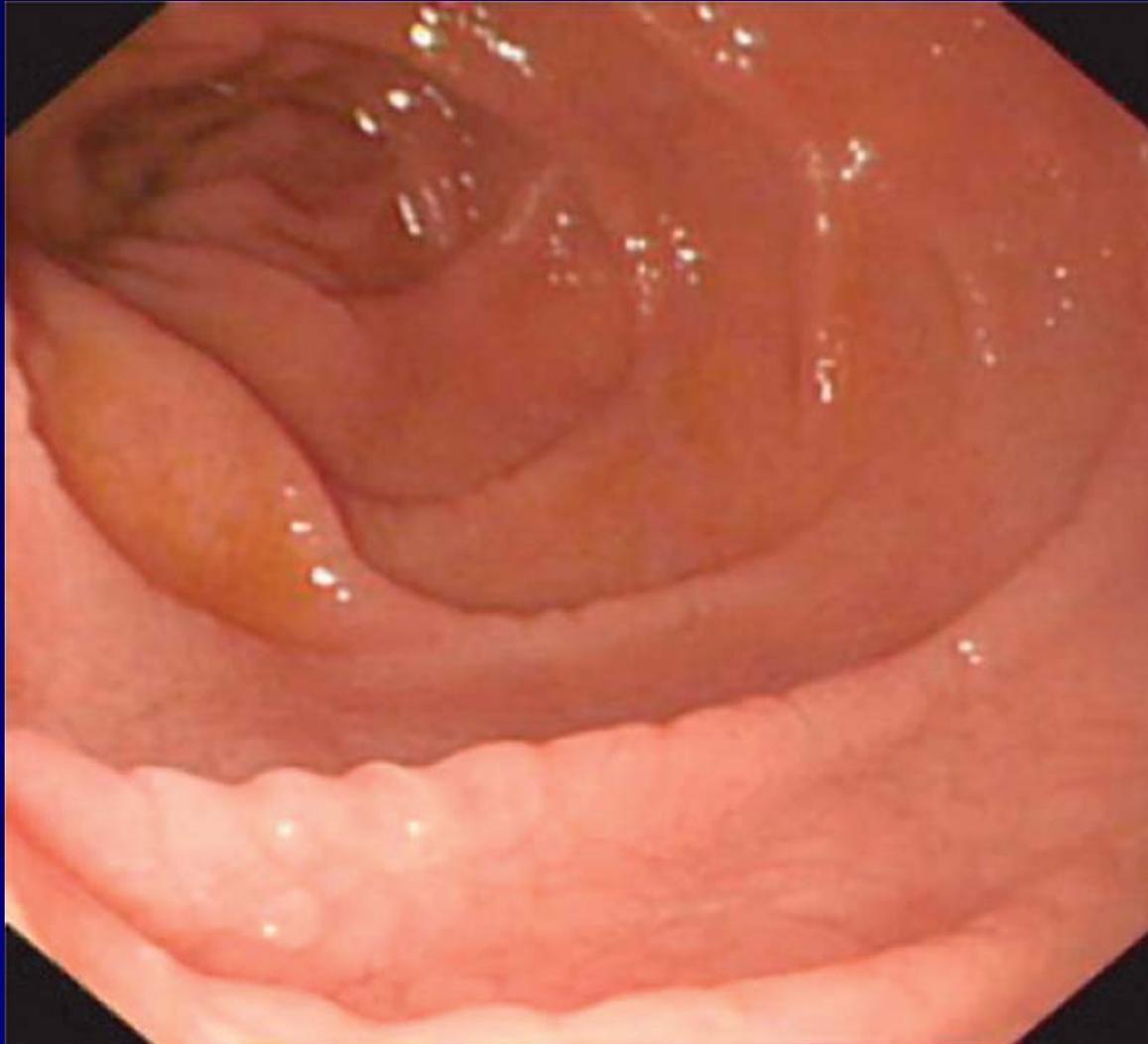
- Among patients with moderately to severely active Crohn's disease, those receiving intravenous ustekinumab had a significantly higher rate of response than did those receiving placebo.
- Subcutaneous ustekinumab maintained remission in patients who had a clinical response to induction therapy

Celiac Disease

Diagnosis of Celiac Disease

- Evidence of malabsorption (localized, generalized)
- Abnormal small bowel biopsy (spectrum of changes)
- Abnormal immunologic studies – 85-90% sensitivity 95% specificity
 - Anti-endomysial antibody
 - Anti-glutaminase antibody
- Improvement with gluten-free diet (clinical, lab studies, histology)

Celiac Disease



Celiac Disease Pearls

- Serologic titers of TTG IGA usually fall to normal by 2 years
- Histologic improvement is slow – 34% @ 2 years; 66% @ 5 years – 90% @ 9 years
- In patients with enteropathy on a gluten-free diet, CD can be excluded by absence of HLA DQ2 and DQ8

Celiac disease for Internist

- The immunoglobulin A tissue transglutaminase is the single best serologic test to use for the detection of CD.
- Consider serologic testing of first-degree relatives, patients with type 1 diabetes mellitus, Down's, Turner's, and Williams' syndromes, as well as those with premature osteoporosis, iron deficiency, abnormal liver biochemistries, and other manifestations of CD.

Celiac disease for Internist

- Patients already on a prolonged gluten-free diet (GFD) should be tested for the presence of HLA DQ2 or DQ8, thereby avoiding the need for further evaluation of CD in non-allelic carriers.
- The basic treatment of CD is a strict, lifelong GFD, enabled by an expert dietitian.

Celiac disease for Internist

- Newly diagnosed adults with CD should be assessed for micronutrient deficiencies (iron, B12, folate, zinc, copper), fat soluble vitamin deficiencies (vitamin D), and bone densitometry.
- In those with persistent or relapsing symptoms, the robustness of the original diagnosis should be reviewed, gluten exposure sought, and a systematic evaluation for alternative and associated diseases performed.

Colon cancer in IBD

Colorectal Cancer (CRC) and Ulcerative Colitis

- Cumulative Risk of CRC
 - 2% at 10 years of disease
 - 8% at 20 years of disease
 - 18% at 30 years of disease
- Overall prevalence of CRC in UC
 - All UC patients - 3.7%
 - Pancolitis patients – 5.4%

ACG/AGA/ASGE Surveillance Recommendations

■ Colonoscopy

- Extensive Disease - Start 8 - 10 years after disease onset
- Start immediately in PSC patients
- Left-sided disease - Start 15 years after disease onset
- Proctitis-no increased risk
- Repeat every 1-2 years

New SCENIC Guidelines

- Chromoendoscopy

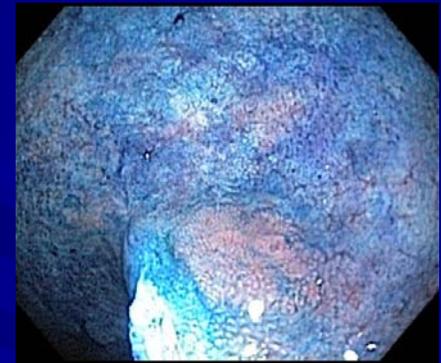


Laine L et al. SCENIC International Dysplasia Consensus Statement.
Gastroenterology. 2015

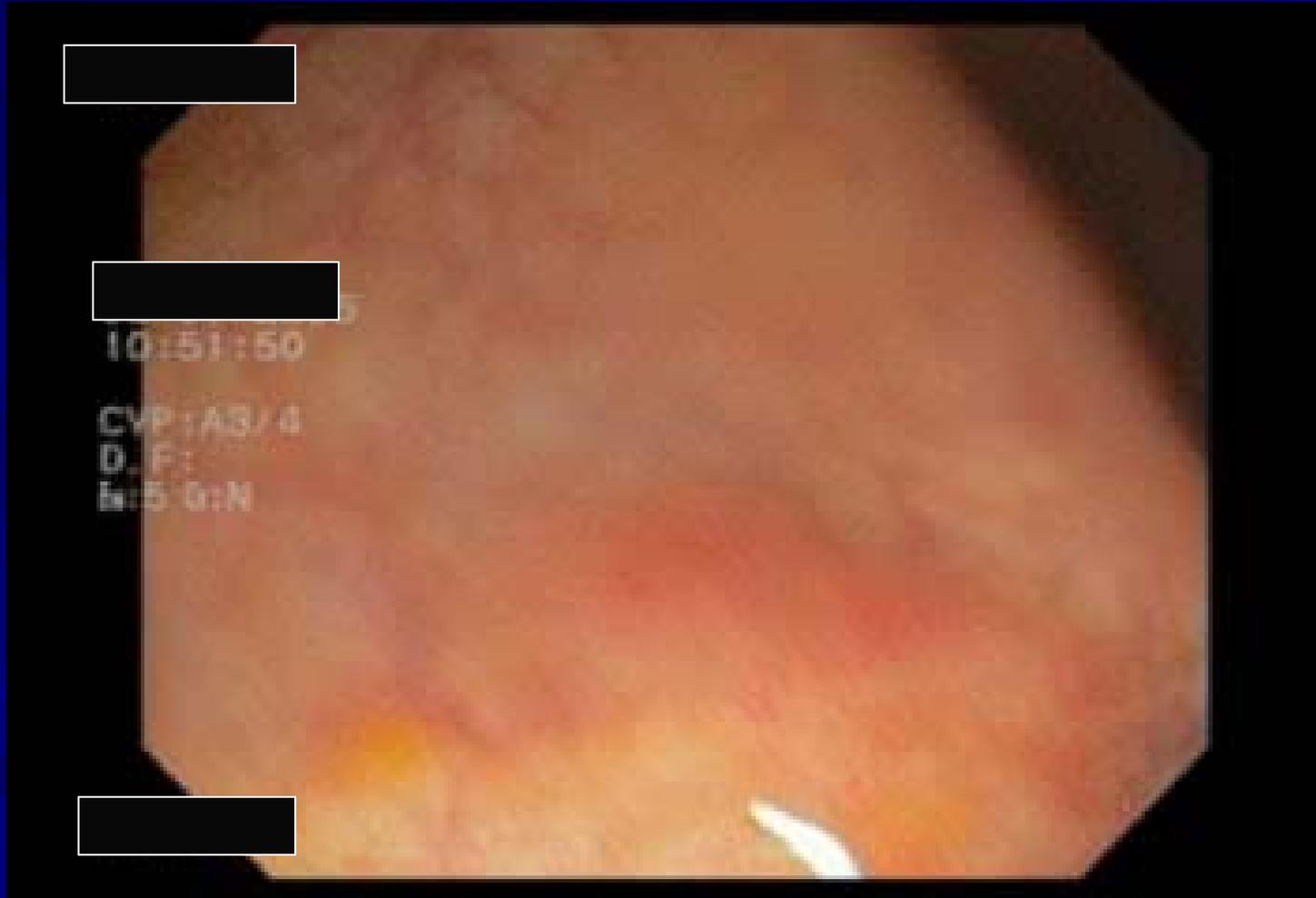
Surveillance for Colorectal Endoscopic Neoplasia detection and
management in Inflammatory bowel disease Consensus

SCENIC: Summary of Statements

- Narrow band imaging not better than white light, especially with HD scopes
- **Chromoendoscopy (dye spray) > white light HD endoscopy > Standard definition**
- Newer technologies enable ongoing surveillance instead of colectomy when certain types of dysplasia are found



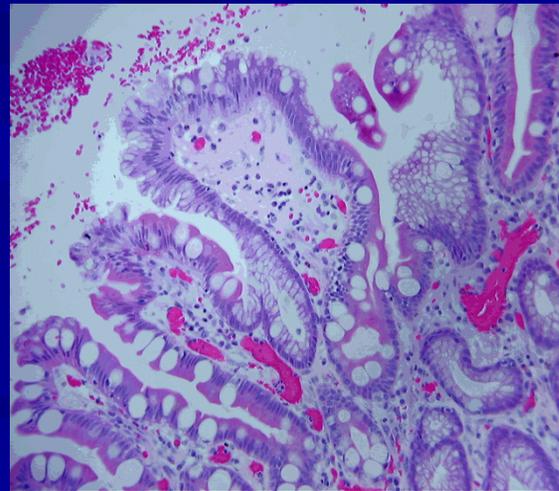
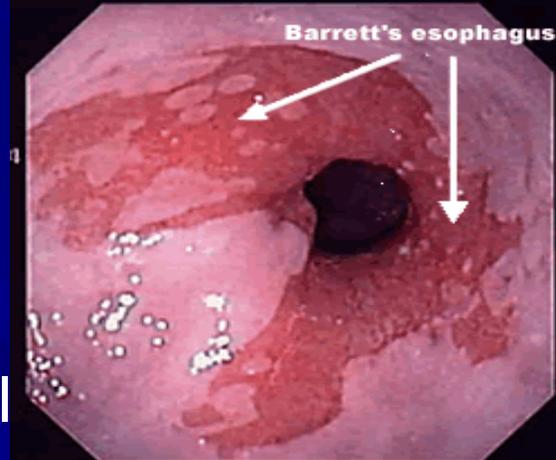
Low grade dysplasia



Barrett's Esophagus

Barrett's Esophagus

Condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces stratified squamous epithelium that normal lines distal esophagus



Screening for BE in Primary Care

- Screening for BE may be considered in men with chronic (>5 years) and/or frequent (weekly or more) symptoms of gastroesophageal reflux (heartburn or acid regurgitation) and two or more risk factors for BE or EAC.
- These risk factors include: age >50 years, Caucasian race, presence of central obesity (waist circumference >102 cm or waist–hip ratio (WHR) >0.9), current or past history of smoking, and a confirmed family history of BE or EAC

Screening for BE in Primary Care

- For BE patients without dysplasia, endoscopic surveillance should take place at intervals of 3 to 5 years

Candidates for Endoscopic therapy

- Patients with flat HGD
- Patients with nodular HGD
- Patients with IMC
- Patients with LGD
- No role of treatment of non-dysplastic BE

THANK YOU