The JAK/STAT Signaling Pathway and Its Role in Immune-mediated Inflammatory Disease: Impact on the Treatment of IBD

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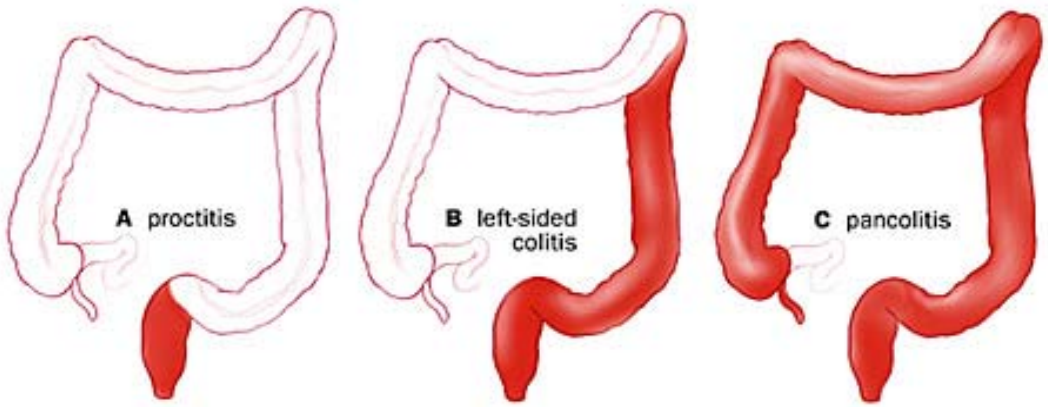
Learning Objectives

Upon completion of the formative assessment activity, participants will be able to:

- Outline the role of the JAK/STAT signaling pathway in the inflammation and disease progression of immune-mediated inflammatory diseases such as IBD
- Discuss unmet clinical needs and the need for novel targets in IBD
- Interpret clinical trial efficacy and safety data of JAK inhibitors under investigation for ulcerative colitis and Crohn's disease

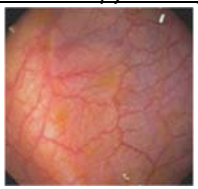
Ulcerative Colitis



Defining Disease Activity in Ulcerative Colitis

Mayo Endoscopy Scoring

0



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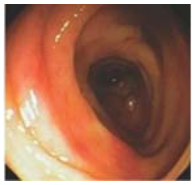

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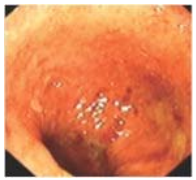

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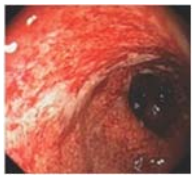
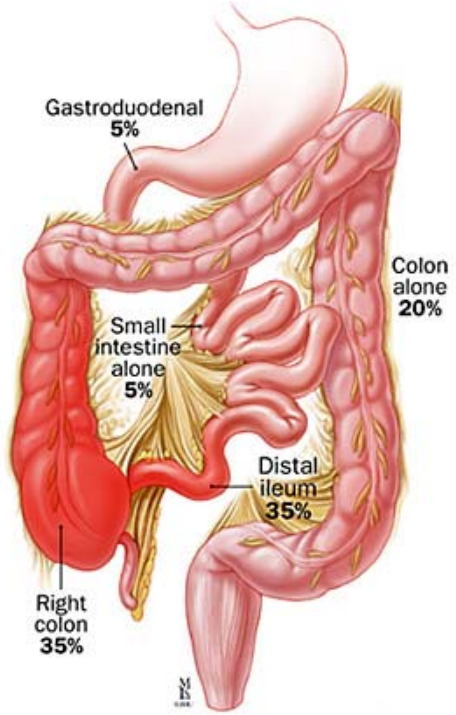


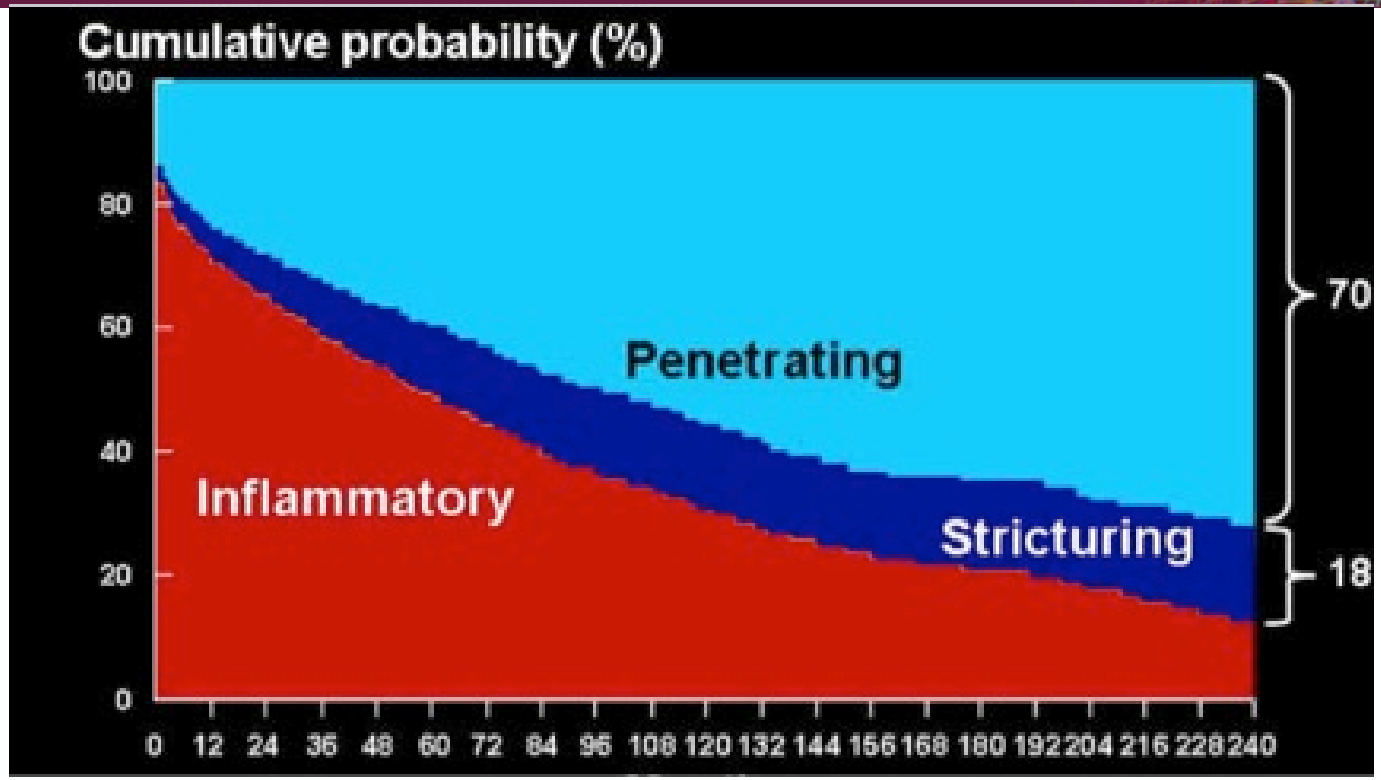
Score	Rectal Bleeding	Stool Frequency	Endoscopy	Physician Global Assessment
0	None	normal	inactive	normal
1	Streaks <50% of time	1-2>normal	mild	mild
2	Obvious Blood with stool	3-4>normal	moderate	moderate
3	Blood alone	>5 above normal	severe	severe

Images From Pineton de Chambrun et al. Nat Rev Gast Hepatol 2010;7:15-29

Crohn's Disease



Natural History of Crohn's Disease



Cosnes et al. Inflamm Bowel Dis 2002; 8: 244

Clinical Activity in Crohn's Disease

Variable	Weight
# liquid or soft stools each day for 7 days	x2
Abdominal pain (0-3) each day for 7 days	x3
General well being (0-4) each day for 7 days	x4
Presence of complications	x20
Taking lomotil or opiates for diarrhea	x3
Abdominal mass (0 no, 2 questionable, 5 definite)	x10
Hematocrit <0.47 or <0.42 for women	x6
Percent change from standard weight	x1

Typically used cut-offs

- Remission <150
- Mild-moderate 150-220
- Moderate-severe 220-450
- Severe-fulminant >450

Endoscopic scoring in CD – SES-CD

Variable	Score			
	0	1	2	3
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1–0.5)	Large ulcers (diameter 0.5–2)	Very large ulcers (diameter >2)
Ulcerated surface (%)	None	<10	10–30	>30
Affected surface (%)	Unaffected segment	<50	50–75	>75
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

*Total SES-CD: sum of the values of the 4 variables for the 5 bowel segments. Values are given to each variable and for every examined bowel segment (for example, rectum, left colon, transverse colon, right colon and ileum).

Medscape

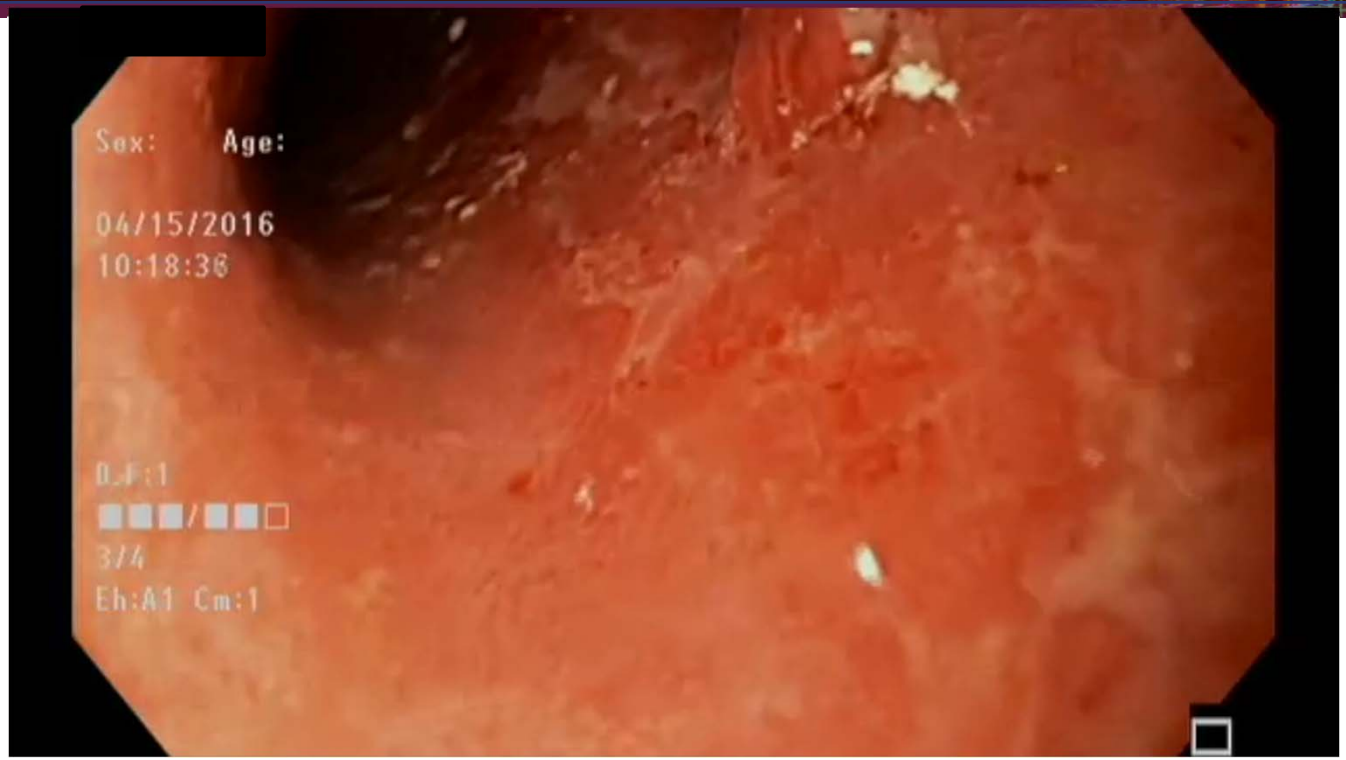

Case Presentation

Case

Date	Treatment
Previous medical history	A 36-year old woman with diagnosis of Crohn's colitis based on colonoscopy CDAI 300
April 2017	Infliximab initiated (5 mg/kg weeks 0, 2, 6, and then q8w)
October 2017	No apparent clinical response; active inflammation on colonoscopy Negative *C. diff* and CMV; infliximab trough 12 (no antibodies) Switched to vedolizumab (300 mg at weeks 0, 2, 6 then q8w)
March 2018	Never responds clinically; continued active inflammation on scope Negative infectious workup Switched to ustekinumab initiated (6 mg/kg IV, then 90 mg sc q8w)
August 2018	Poor clinical response; still inflamed on scope; "-" infectious workup

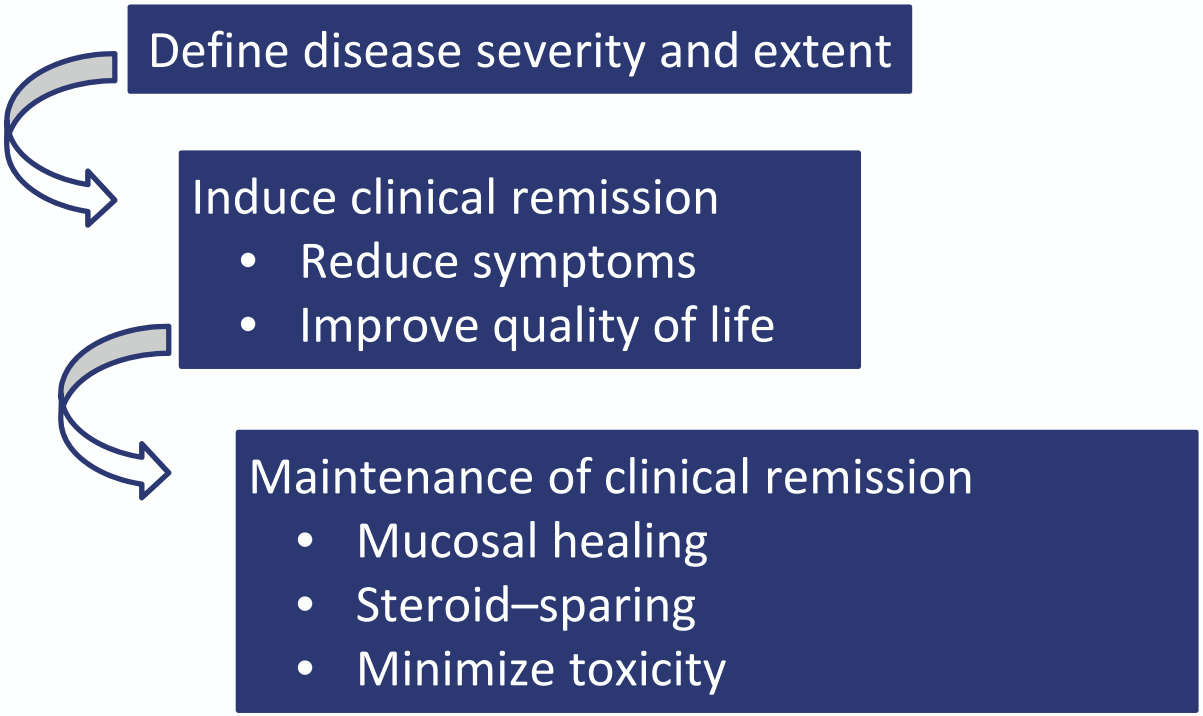
Patient did not respond to several different therapies.
What would you do now?

Endoscopy



Why do we need novel therapies in IBD?

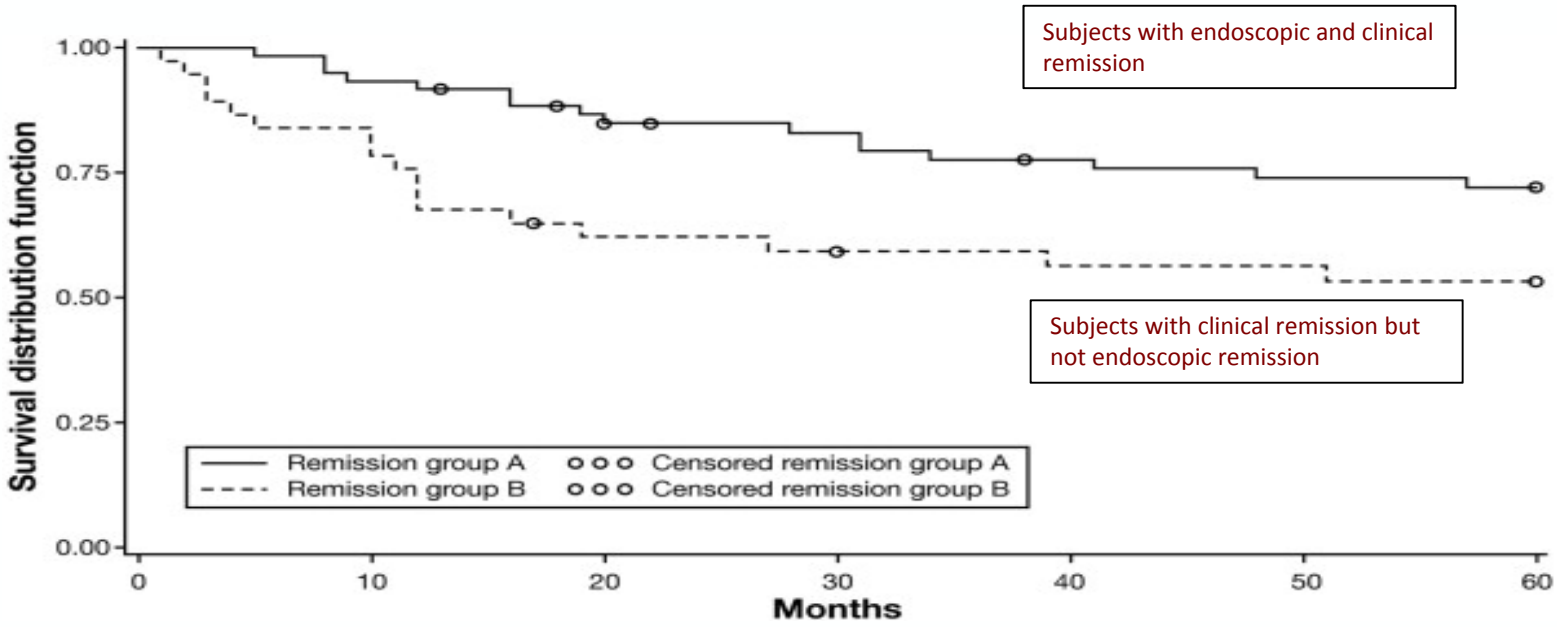
Goals of IBD Therapy



Why Treat?

- Symptom improvement
- Improve nutritional status
- Minimize risks of short-term complications
  - Corticosteroid use
  - Extraintestinal manifestations
  - Venous Thromboembolism
  - Flares of disease
- Minimize risks of long-term complications
  - Surgery
  - Colon cancer
  - Bowel obstruction
  - Short bowel syndrome (from extensive bowel resections)

25% of patients achieve clinical remission without endoscopic remission



Ardizzone et al. Clin Gastro Hepatol 2011;9:483-89.

Poor correlation between symptoms and mucosal inflammation in CD

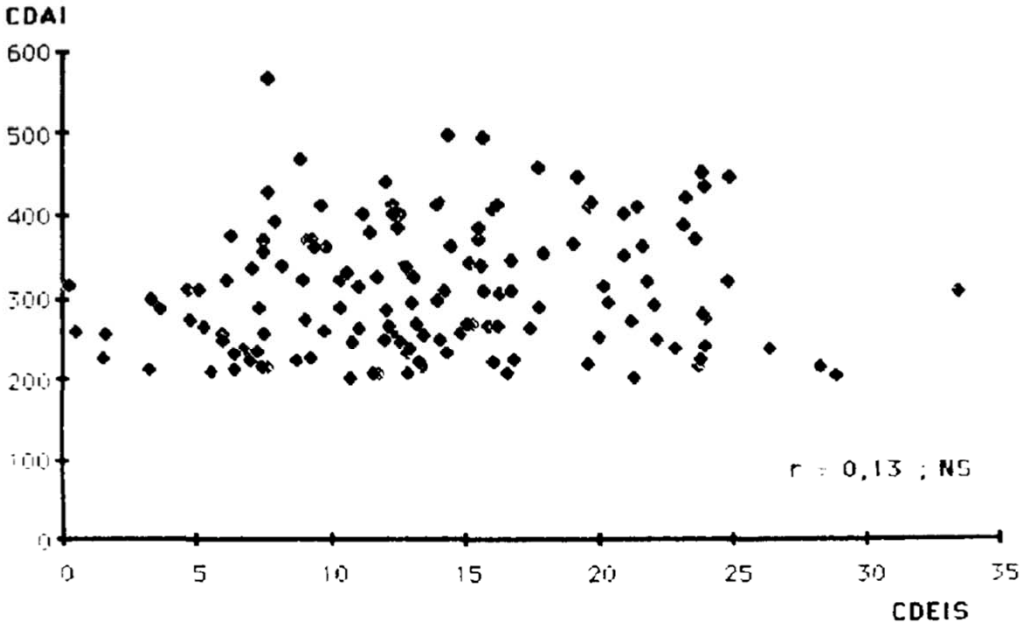
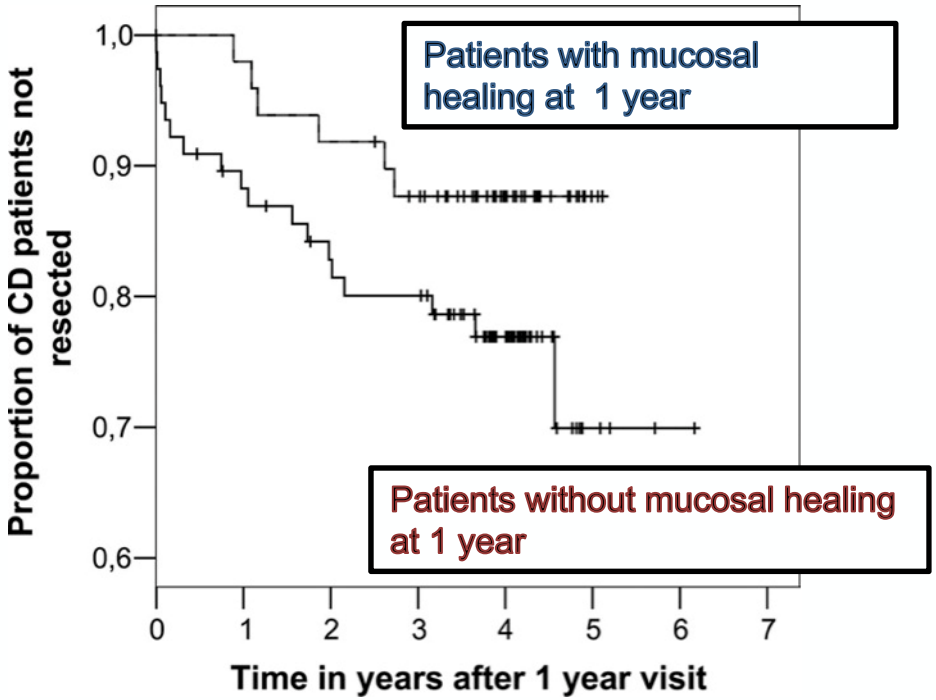


Figure 1. Correlation of CDAI vs. CDEIS at D_0 (n = 142).

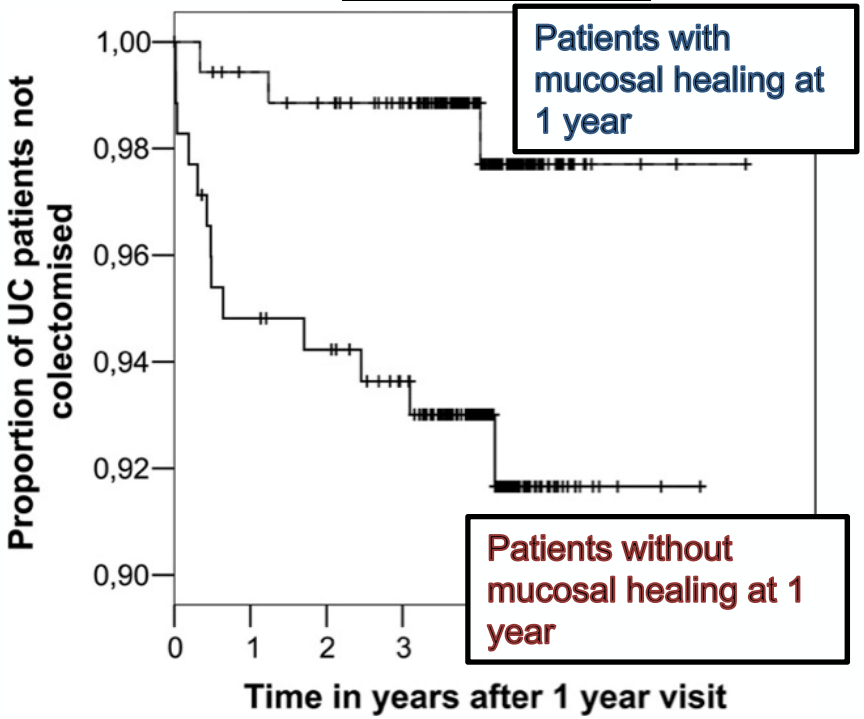
Modigliani et al. Gastroenterology 1990; 98:811-818

Mucosal healing on treatment improves long-term outcomes

Crohn's Disease



Ulcerative Colitis



Froslie et al. Gastroenterology 2007; 133:412-422

Current IBD Treatments

Conventional Approaches

- Aminosalicylates
- Immunosuppressants
- Corticosteroids

TNF alpha inhibitors

- Adalimumab
- Infliximab
- Certolizumab pegol
- Golimumab

Anti IL-12/IL-23

- Ustekinumab

Anti α4β7 integrin

- Vedolizumab

Targeted synthetic DMARD (JAK inhibitor)

- Tofacitinib

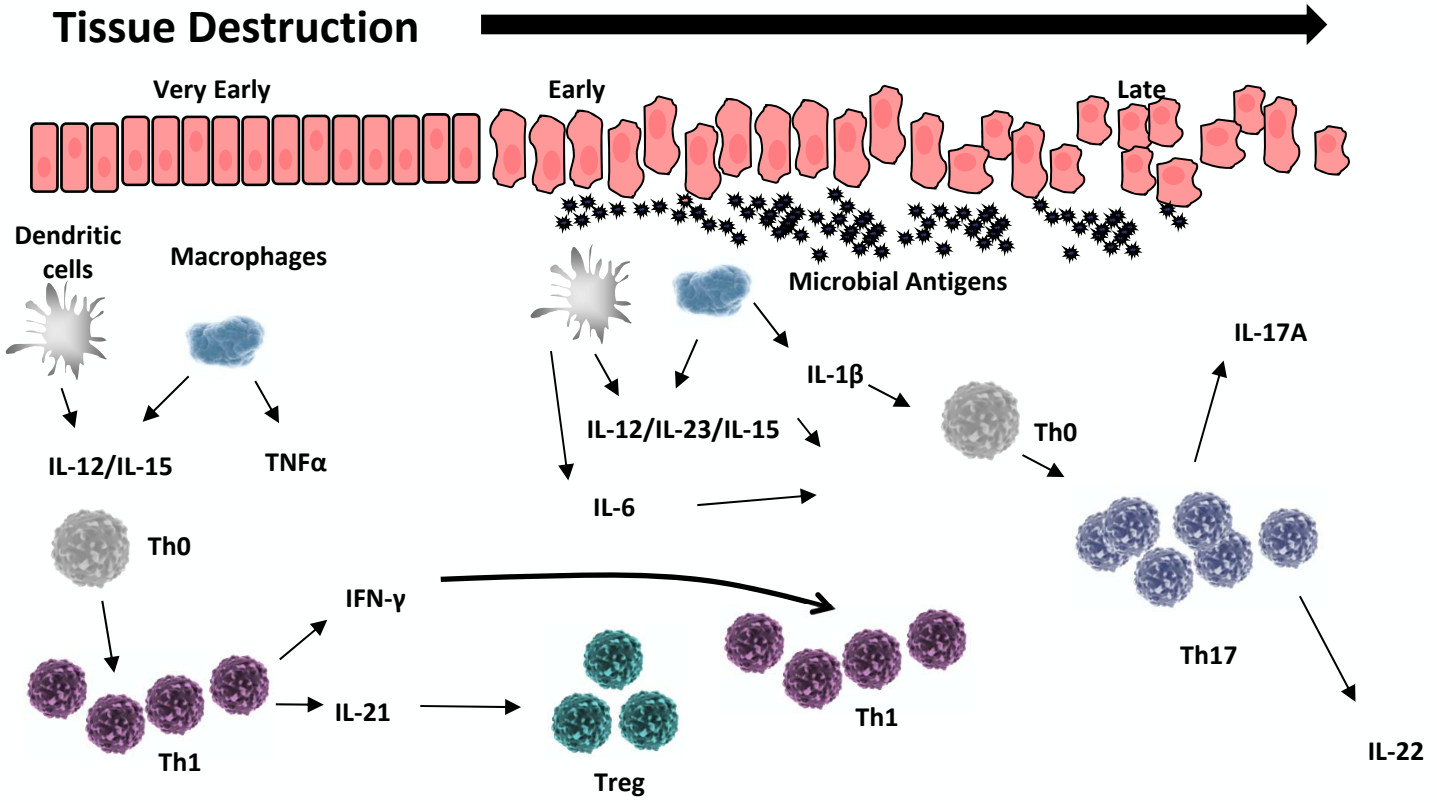
Induction and Maintenance of Remission in IBD Challenging

- ~30% patients do not achieve adequate response to initial therapy
  - Patients experience significant morbidity and decreased quality of life
  - Hospitalizations and surgery rates remain high
- 30-40% of patients experience failure during first year of maintenance therapy

D'Haens GR et al. *Am J Gastroenterol*. 2011;106(2):199-212; Sandborn WJ et al. *N Engl J Med.* 2017;376(18):1723-1736; Cohen RD. *Aliment Pharmacol Ther.* 2002;16:1603-9; Bewtra M et al. *Clin Gastroenterol Hepatol.* 2007;5:597-601.

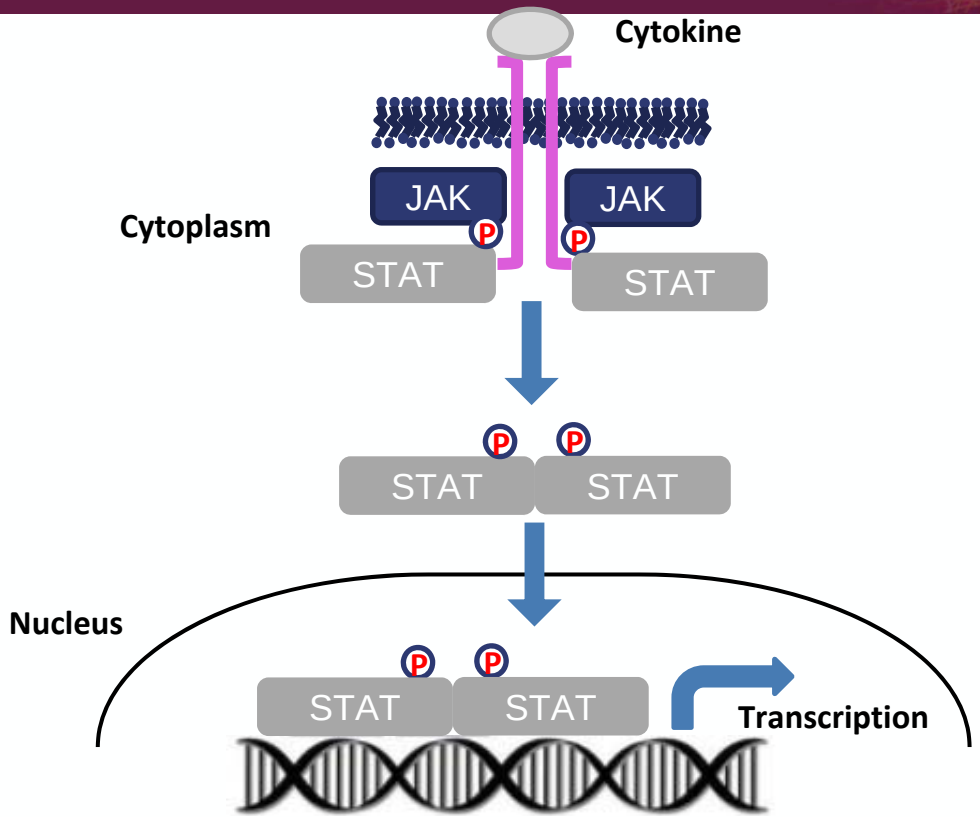
Why target the JAK/STAT signaling pathway in IBD?

IBD Immunopathogenesis

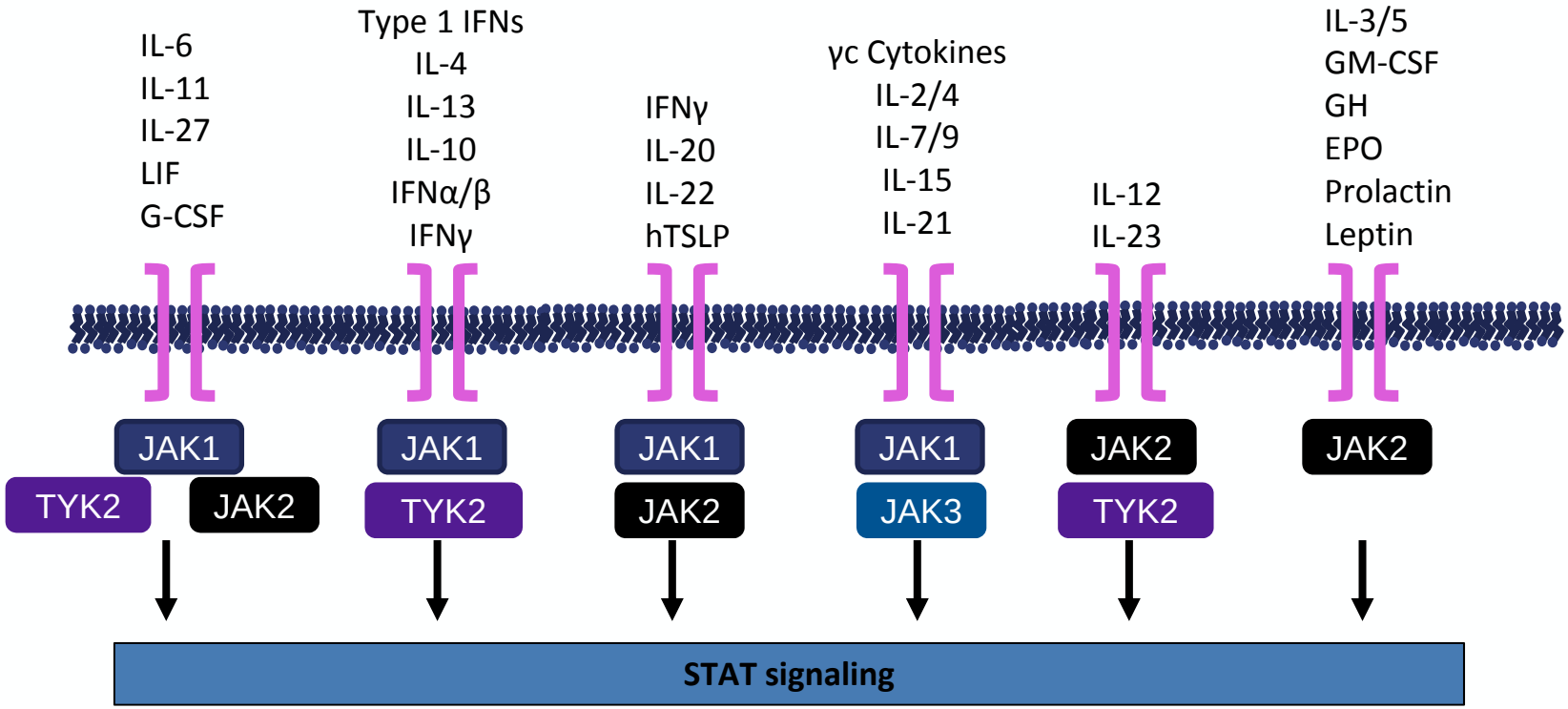


Adapted from Danese S et al. *Am J Physiol Gastrointest Liver Physiol*. 2016;310(3):G155-62.

JAK/STAT Signaling Pathway

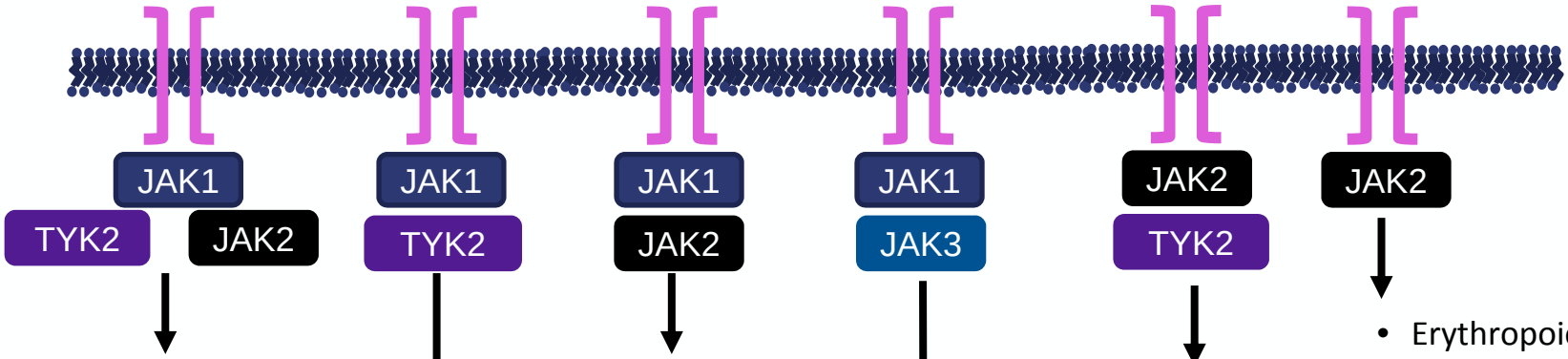


Members of the JAK/STAT Family



Clark JD et al. *J Med Chem*. 2014;57(12):5023-38; Danese S et al. *Am J Physiol Gastrointest Liver Physiol*. 2016;310(3):G155-62.

Activation of the JAK/STAT Family



- Naïve T cell differentiation
- T cell homeostasis
- Granulopoiesis
- Inflammation

- Antiviral
- Antitumor
- Inflammation

- Antiviral
- Antimycobacterial
- Inflammation

- Maturation lymphoid cells
- Differentiation/ homeostasis T cells, NK cells
- B cell switching
- Inflammation

- Innate immunity
- Differentiation / proliferation of Th17 cells
- Inflammation

- Erythropoiesis
- Myelopoiesis
- Megakaryocyte/ platelet production
- Growth
- Mammary development

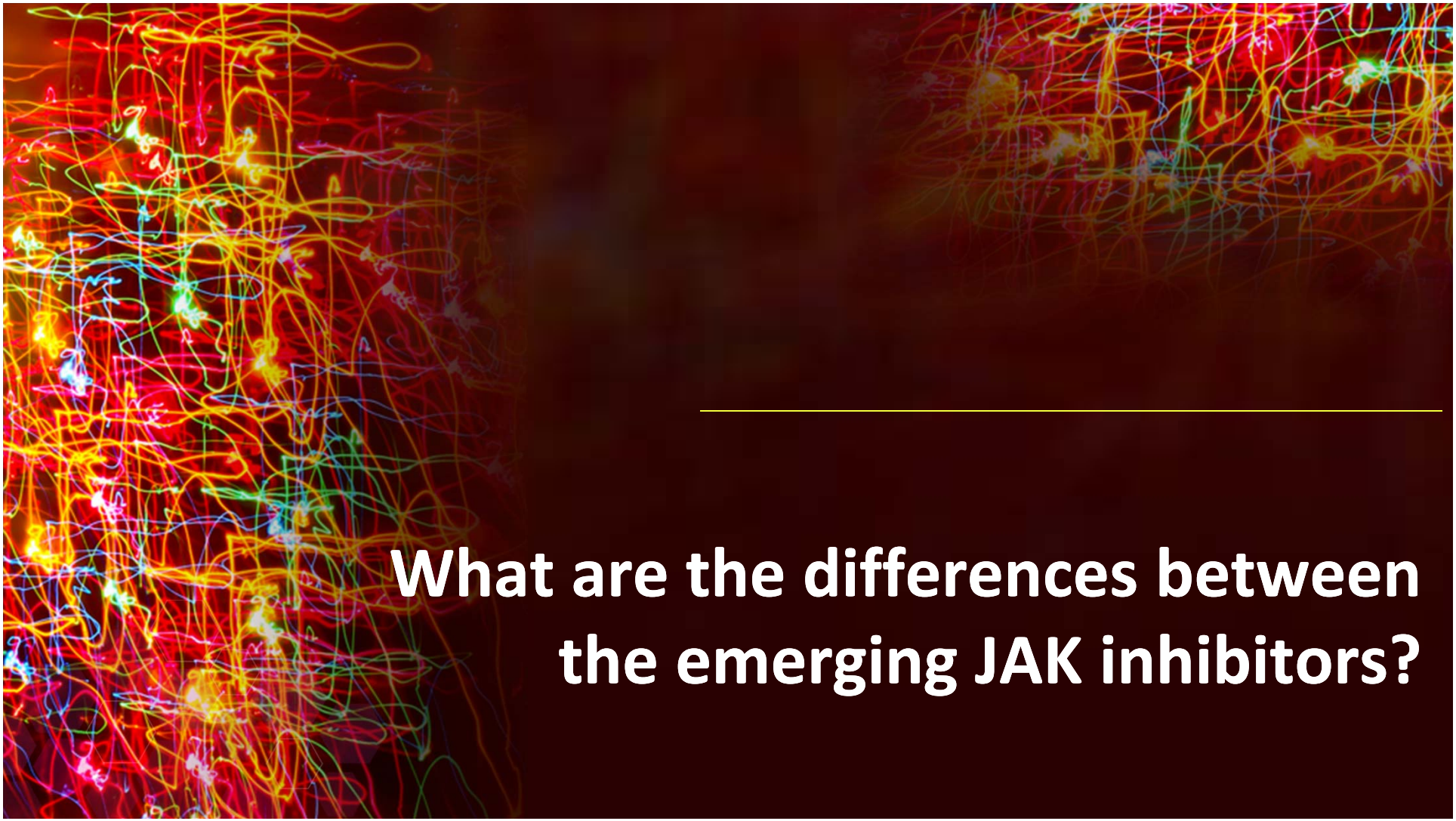
Clark JD et al. *J Med Chem*. 2014;57(12):5023-38; Danese S et al. *Am J Physiol Gastrointest Liver Physiol*. 2016;310(3):G155-62.

Rationale for Inhibiting the JAK/STAT Pathway

- A large subset of cytokines shares this mechanism of signal transduction
- JAK inhibitors directly inhibit activation of JAK/STAT signaling → downregulation of the IBD immune inflammatory reaction

How do the JAK inhibitors differ from the biologics?

- Work intracellularly
- Synthetic drugs, not proteins
- Small molecules = Oral administration


What are the differences between the emerging JAK inhibitors?

Available and Emerging JAK Inhibitors

Agent	Formulation	Mechanism of Action	Status
Tofacitinib	Oral	JAK1/3 inhibitor	Approved for RA, PsA, and UC
Baricitinib	Oral	JAK1/2 inhibitor	Approved for RA
Filgotinib	Oral	JAK1 inhibitor	Phase 3 for RA, CD, and UC
Upadacitinib	Oral	JAK1 inhibitor	Phase 3 for RA and PsA Phase 2 for CD and UC
Peficitinib	Oral	JAK1/2/3 and tyrosine kinase 2 inhibitor	Phase 2 for RA Phase 2 for UC

Theoretically different in mechanism of action

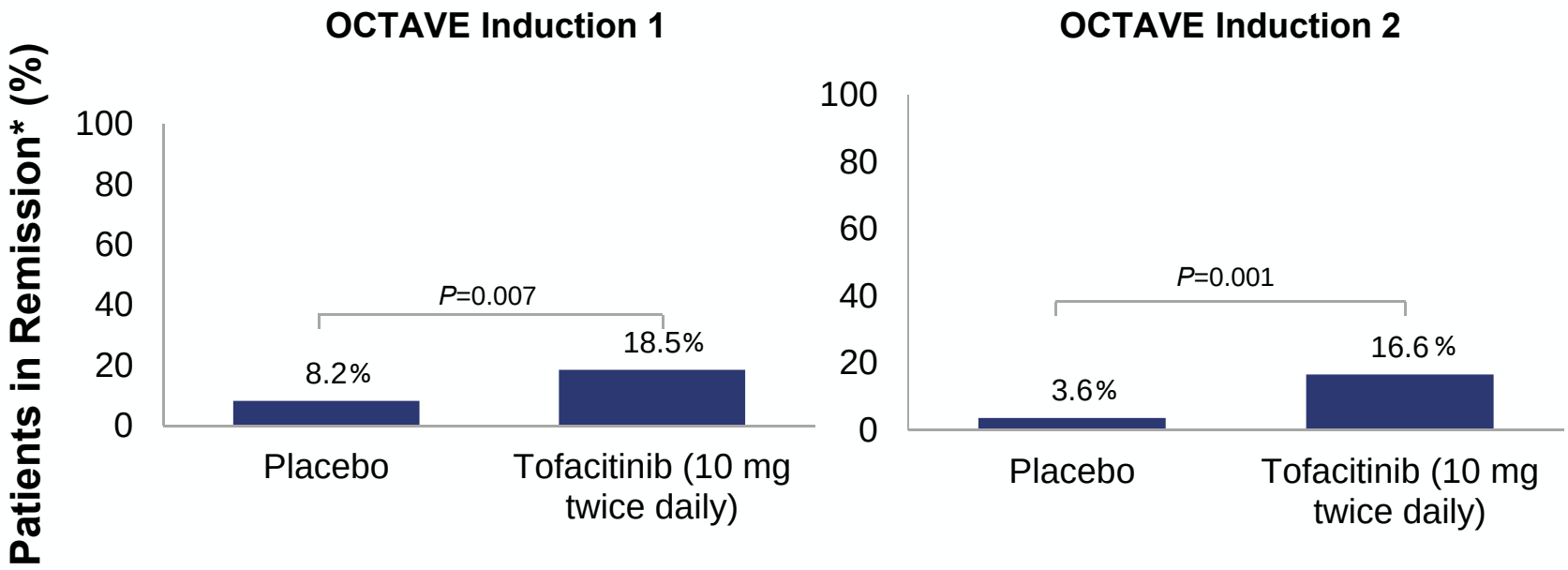
Potential Differences Between JAK Inhibitors

Cytokine	JAKs
IL-7	JAK1 JAK3
IL-15	JAK1 JAK3
IL-21	JAK1 JAK3
IL-6	JAK1 JAK2 TYK2
Type 1 IFNs (IFNα/β)	JAK1 TYK2
IL-10	JAK1 TYK2
IL-12	JAK2 TYK2
IL-23	JAK2 TYK2
IL-1	—
IL-17	—
IL-18	—
TGFβ	—
TNF	—

Tofacitinib: JAK1/JAK3
Baricitinib: JAK1/JAK2
Filgotinib: JAK1
Upadacitinib: JAK1
Peficitinib: JAK3*

*Peficitinib has 10-fold less activity against other JAK members.

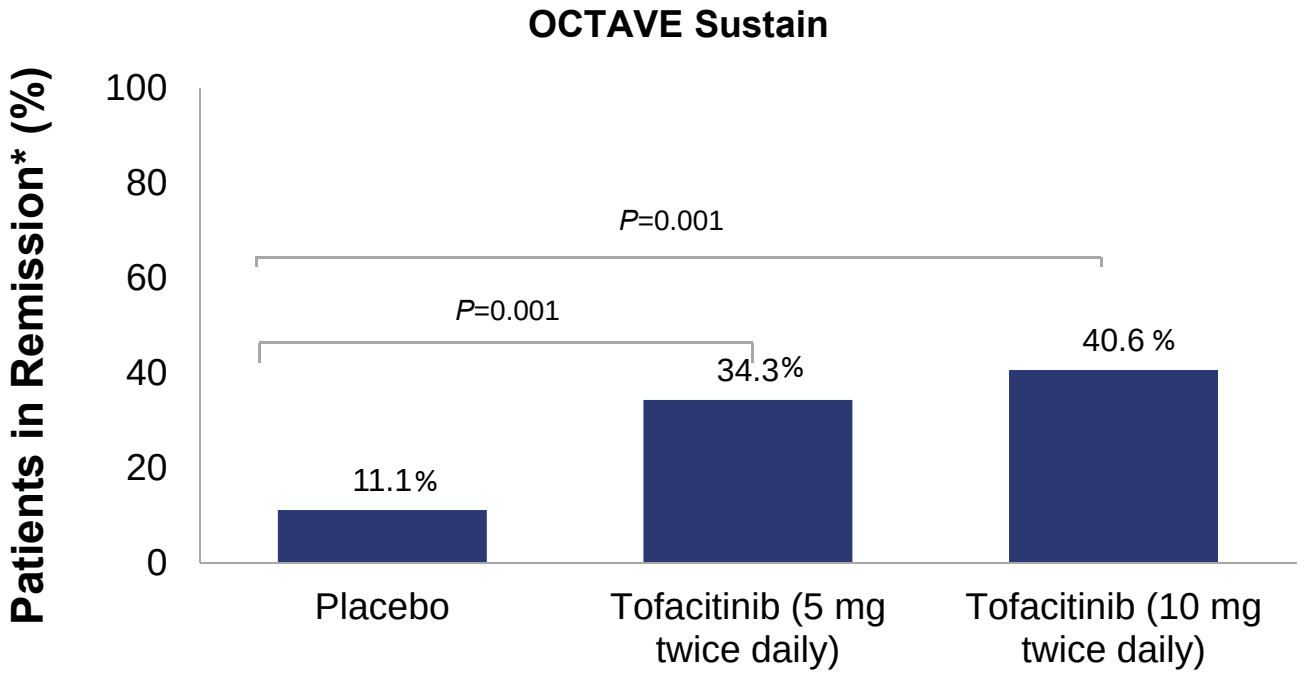
OCTAVE: Tofacitinib as Induction Therapy in UC



*Total Mayo score ≤2, with no subscore >1 and a rectal bleeding subscore of 0 at 8 weeks.

Sandborn WJ et al. *N Engl J Med*. 2017;376(18):1723-1736.

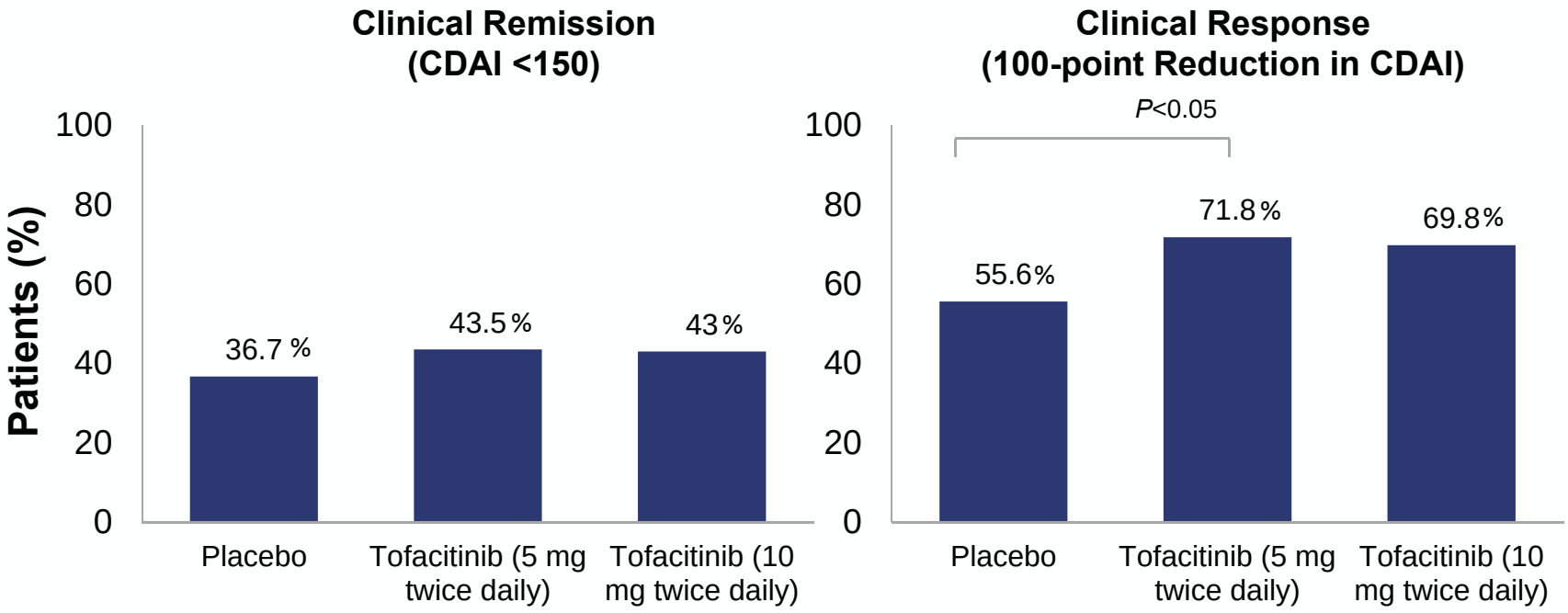
OCTAVE Sustain: Tofacitinib as Maintenance Therapy in UC



*Total Mayo score ≤2, with no subscore >1 and a rectal bleeding subscore of 0 at 52 weeks.

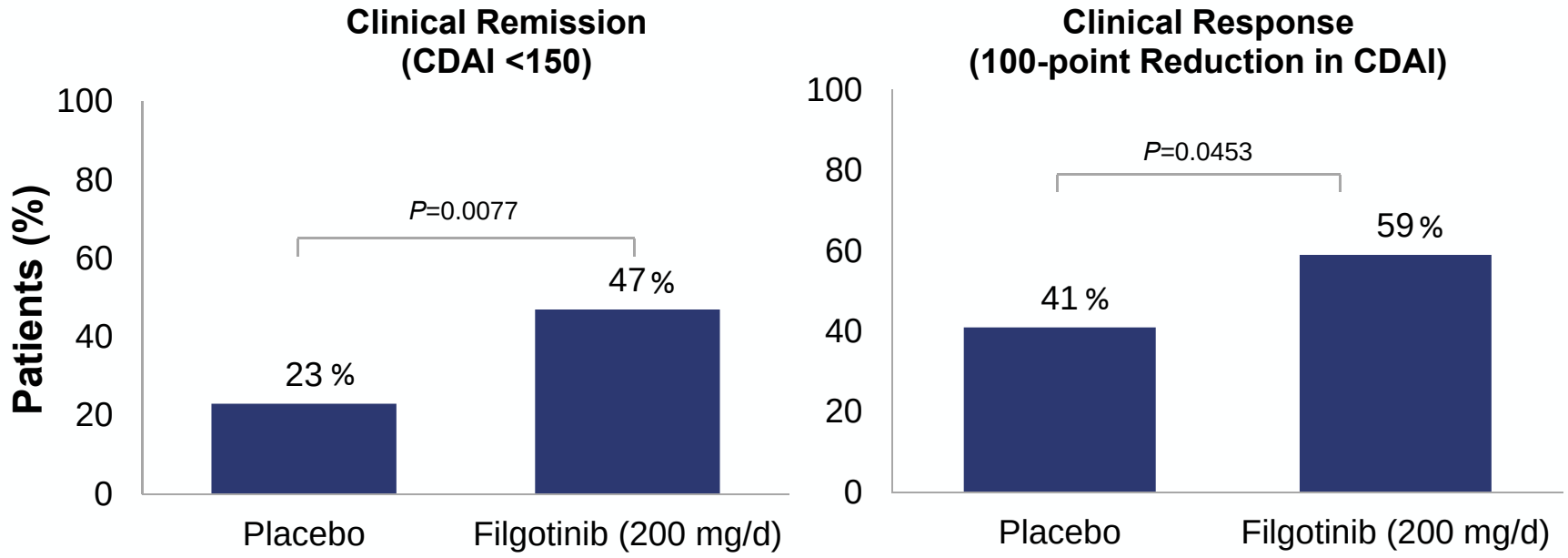
Sandborn WJ et al. *N Engl J Med*. 2017;376(18):1723-1736.

Tofacitinib: Phase 2b Trials in Crohn's Disease



Panés J et al. *Gut*. 2017;66(6):1049-1059.

Filgotinib vs. Placebo: Phase 2 Trial in Patients with Moderate-to-severe CD



Vermeire S et al. *Lancet*. 2017;389(10066):266-275.

Filgotinib vs. Placebo in CD: Response by Previous Anti-TNF Exposure

Endpoint	Overall Population		Anti-TNF Naïve		Anti-TNF Experienced	
	Placebo (n=44)	Filgotinib (n=128)	Placebo (n=16)	Filgotinib (n=57)	Placebo (n=28)	Filgotinib (n=71)
Clinical Remission (CDAI <150)	10 (25%)	60 (47%)	2 (13%)	34 (60%)	8 (29%)	26 (37%)
Clinical Response (100-point Reduction in CDAI)	18 (41%)	76 (59%)	7 (44%)	38 (67%)	11 (39%)	38 (54%)

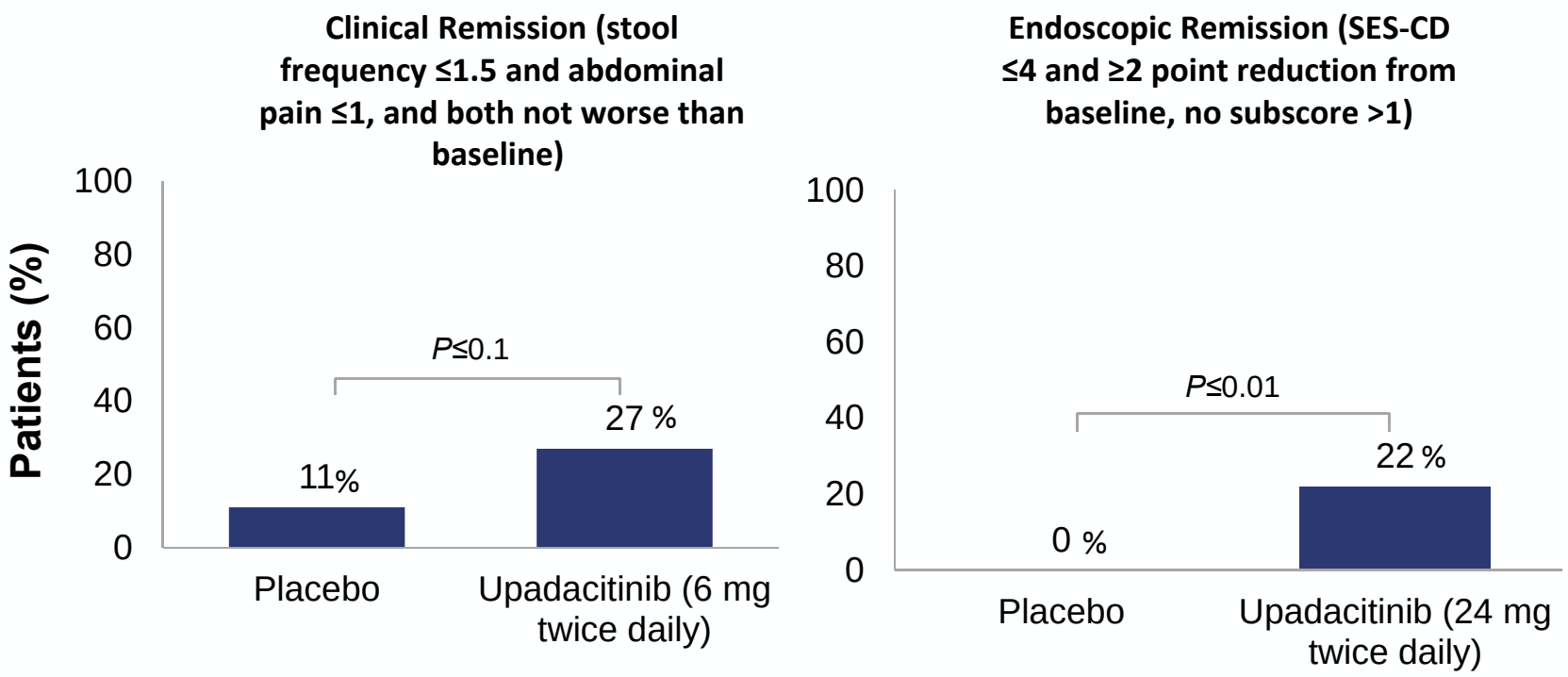
Vermeire S et al. *Lancet*. 2017;389(10066):266-275.

Filgotinib: Ongoing Clinical Trials

Trial	Patient Population	Treatment Arms
SELECTION1	Moderate to severe UC; biologic-naive and biologic-experienced	Filgotinib vs. placebo
SELECTIONLTE	Long-term safety in UC patients who completed or discontinued a prior filgotinib trial	Filgotinib vs. placebo
DIVERSITY1	Moderate to severe CD; biologic-naive and biologic-experienced	Filgotinib vs. placebo
DIVERSITYLTE	Long-term safety in CD patients who completed or discontinued a prior filgotinib trial	Filgotinib vs. placebo
Phase 2	Small bowel CD	Filgotinib vs. placebo
Phase 2	Perianal fistulizing CD	Filgotinib vs. placebo

Clinicaltrials.gov; accessed April 12, 2018.

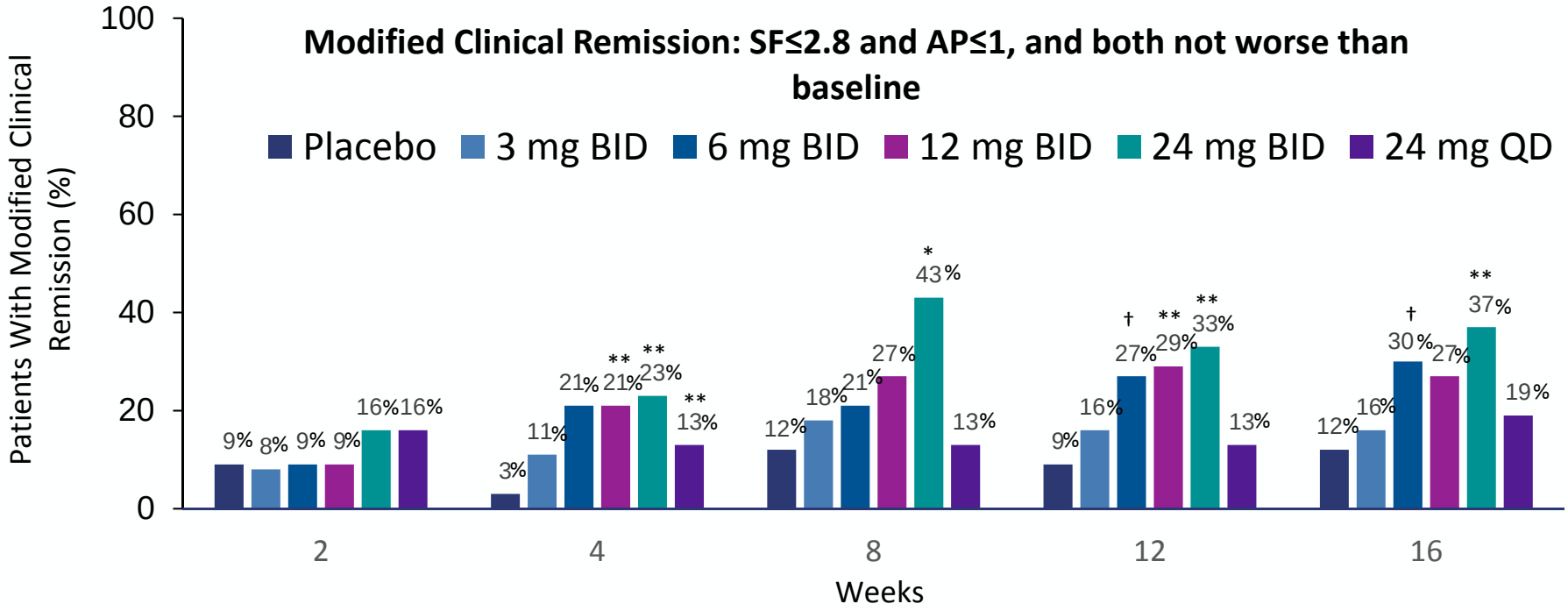
Upadacitinib vs. Placebo: Phase 2 Trial in Patients with Moderate-to-severe CD Who Failed ≥2 Biologics



SES-CD=Simplified Endoscopic Score for Crohn's Disease.

Sandborn W et al. *Gastroenterology*. 2017;152(5) Suppl 1: S1308-S1309.

Upadacitinib vs. Placebo: Maintenance Therapy for Moderate-to-severe CD



*P≤0.01; **P≤0.05; †P≤0.1

Upadacitinib: Ongoing Clinical Trials

Trial	Patient Population	Treatment Arms
M14-234	Moderate to severe UC	Upadacitinib vs placebo
M14-431	Moderate to severe CD; inadequate response or intolerance to biologics	Upadacitinib vs placebo
M14-433	Moderate to severe CD; inadequate response or intolerance to conventional therapies (not biologics)	Upadacitinib vs placebo
Maintenance and LTE	Long-term efficacy and safety in CD patients who completed M14-431 or M14-433 studies	Upadacitinib vs placebo

Clinicaltrials.gov; accessed April 12, 2018.


How safe are the JAK inhibitors?

Tofacitinib: Safety in 52-week OCTAVE Sustain

End point, no. (%)	OCTAVE Sustain		
	Placebo (N=198)	Tofacitinib (5 mg) (N=198)	Tofacitinib (10 mg) (N=196)
Adverse events	149 (75.3)	143 (72.2)	156 (79.6)
Serious adverse events	13 (6.6)	10 (5.1)	11 (5.6)
Adverse events leading to discontinuation	37 (18.7)	18 (9.1)	19 (9.7)
Worsening ulcerative colitis	71 (35.9)	36 (18.2)	29 (14.8)
Nasopharyngitis	11 (5.6)	19 (9.6)	27 (13.8)
Arthralgia	19 (9.6)	17 (8.6)	17 (8.7)
Headache	12 (6.1)	17 (8.6)	6 (3.1)
Any infection	48 (24.2)	71 (35.9)	78 (39.8)
Serious infection	2 (1.0)	2 (1.0)	1 (0.5)
Herpes zoster	1 (0.5)	3 (1.5)	10 (5.1)

Sandborn WJ et al. *N Engl J Med*. 2017;376(18):1723-1736.

Integrated Long-term Safety of Tofacitinib in RA

	All doses (n=6194)	5 mg bid (n=2239)	10 mg bid (n=3955)
Total patient years of exposure (PYE)	19406	6870	12536
Serious TEAEs for infs/100 PYE	2.7	3.1	2.6
Active TB/100 PYE	0.2	0.1	0.2
Herpes zoster/100 PYE	3.9	3.8	4.0
Herpes zoster (serious)/100 PYE	0.3	0.3	0.2
Malignancy (exc. NMSC)/100 PYE	0.9	1.0	0.8
NMSC/100 PYE	0.6	0.5	0.7
Lung/100 PYE	0.2	0.2	0.1
Breast/100 PYE	0.2	0.2	0.1
GI perf/100 PYE	0.11	0.14	0.14

TEAE=treatment-emergent adverse event; NMSC=non-malignant skin melanoma.

Cohen SB et al. *Ann Rheum Dis.* 2017;76(7):1253-1262.

Filgotinib: Safety in 20-week Phase 2b Trial in CD

End point, no. (%)	Placebo (N=22)	Filgotinib (200 mg to 100 mg) (N=30)	Filgotinib (200 mg) (N=77)
Adverse events	18 (82%)	24 (80%)	62 (81%)
Serious adverse events	3 (14%)	1 (3%)	12 (16%)
Adverse events leading to discontinuation	6 (27%)	4 (13%)	22 (29%)
Any infection	6 (27%)	9 (30%)	26 (34%)
Serious infection	0	0	4 (5%)
Urinary tract infection	2 (9%)	1(3%)	3 (4%)
Nasopharyngitis	2 (9%)	2 (7%)	1 (1%)
Herpes zoster	0	1 (3%)	0

Vermeire S et al. *Lancet*. 2017;389(10066):266-275.

Herpes Zoster Risk with JAK Inhibitors

- Approximately 1.5- to 2-fold greater risk of herpes zoster infection observed with tofacitinib in RA patients
  - Regional differences; highest in Asia
- 2017 ACG guidelines recommend that adults with IBD over the age of 50 should consider vaccination against herpes zoster, including certain subgroups of immunosuppressed patients
  - New, non-live, subunit vaccine now available
  - The CDC recommends this recombinant zoster vaccine for persons taking low-dose immunosuppressive therapy

Winthrop KL. *Nat Rev Rheumatol*. 2017;13(4):234-243; Farraye FA et al. *Am J Gastroenterol*. 2017;112(2):241-258; Dooling KL et al. *MMWR*. 67(3);103-108.

Patient Perspectives

- Concerns about safety
- Preference for oral therapy
- Obtaining access to newer drugs given formulary-related challenges

Conclusions

- The JAK/STAT pathway is a rational target to decrease inflammation in IBD
- JAK inhibitors effective at inducing clinical remission in UC and CD
  - JAK inhibitors are safe and well tolerated
- Role in current treatment paradigms?
  - First-line use?
  - Combination regimens?
  - Shared decision-making will be important