

# Nurse Course: Update on Inflammatory Bowel Disease

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# Objectives

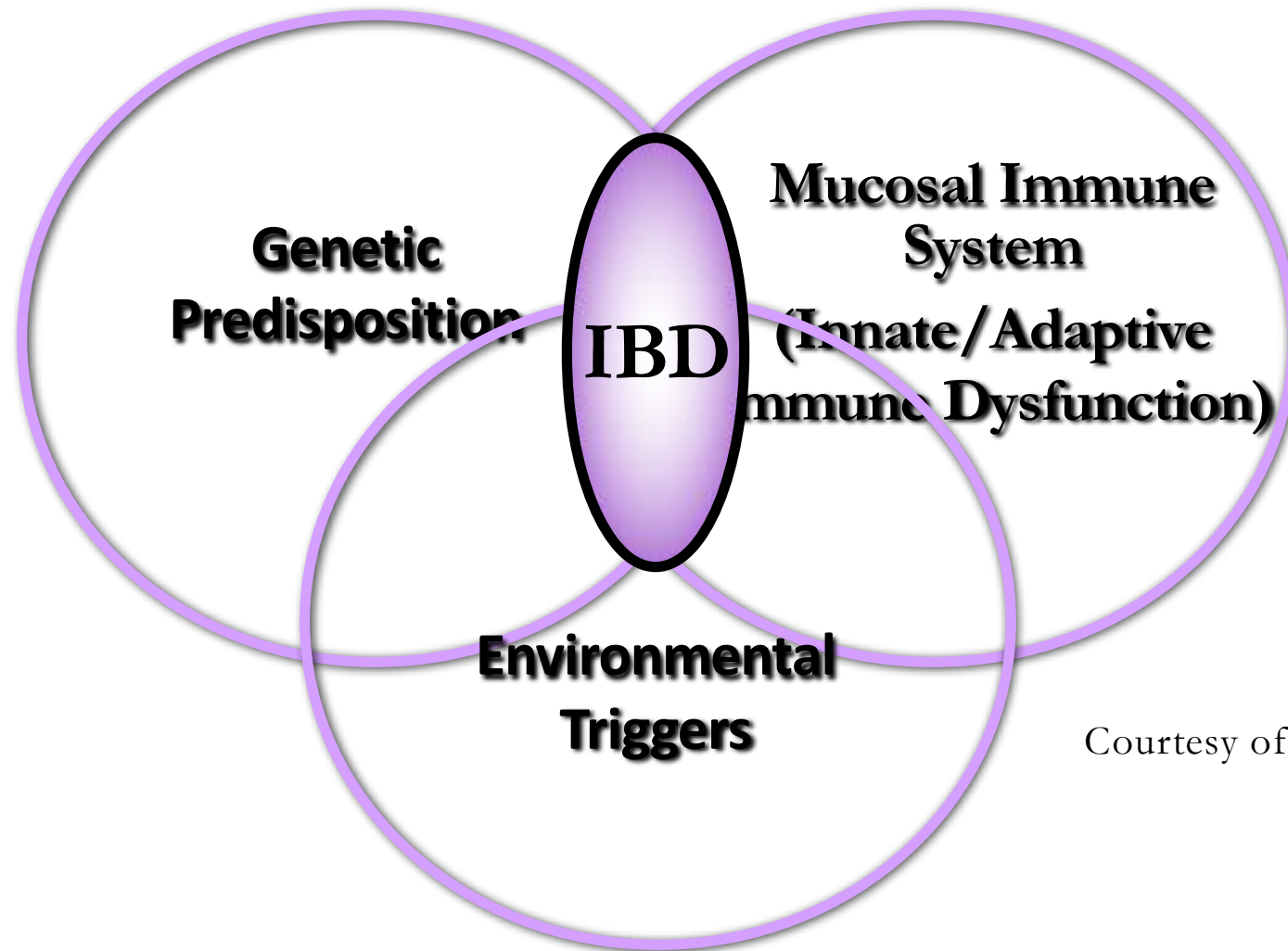
- Review of Ulcerative Colitis and Crohn's Disease
- How to choose therapy
- Therapeutic drug monitoring
- Hot Topics



# Differences Between Crohn's and UC



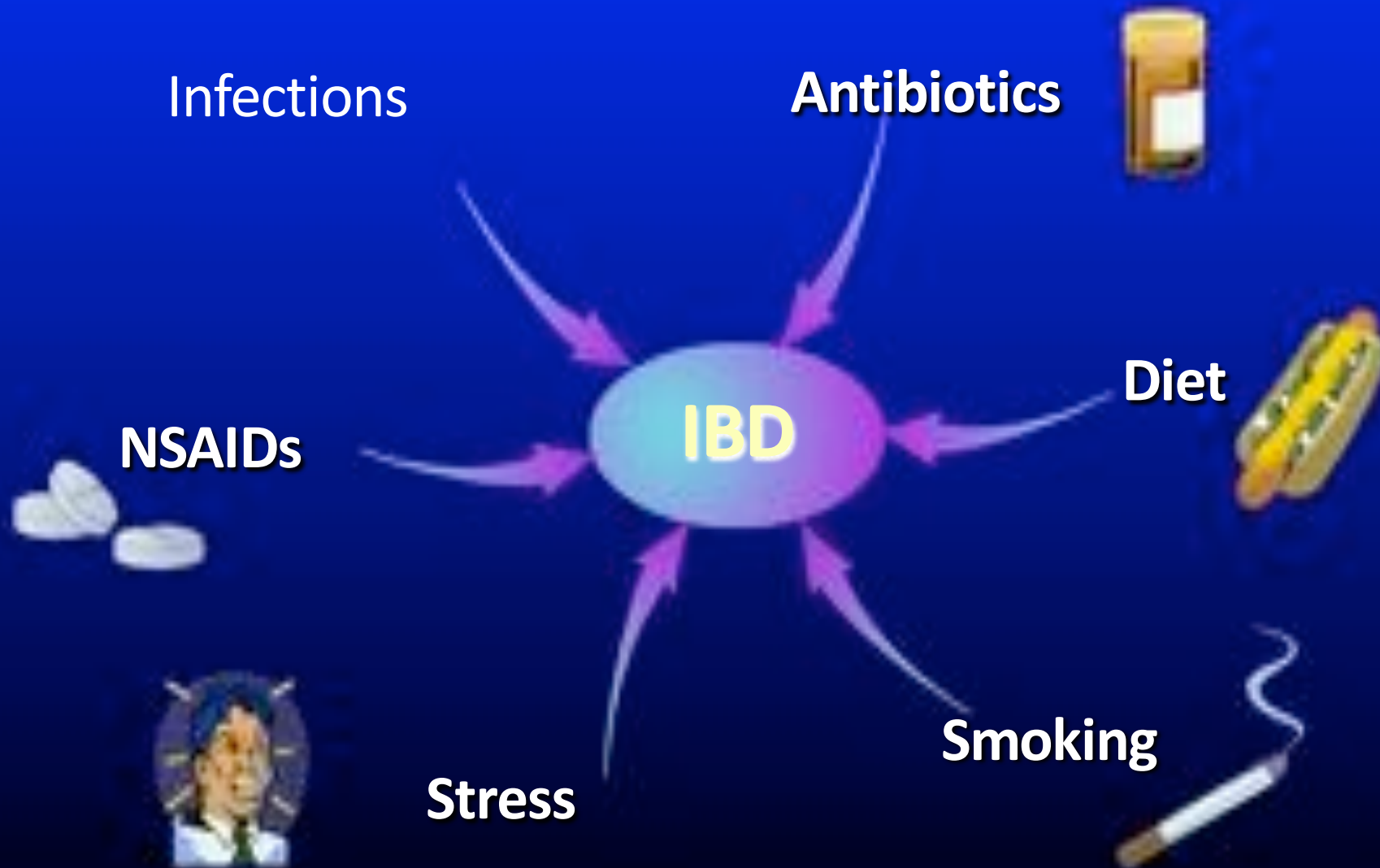
# What Causes Inflammatory Bowel Disease?



Courtesy of S. Targan

# Environmental Triggers

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# Symptoms in IBD

- ❖ Fever
- ❖ Loss of appetite
- ❖ Weight Loss
- ❖ Fatigue
- ❖ Night sweats
- ❖ Stunted growth in children
- ❖ Loss of normal menstrual cycle
- ❖ Extraintestinal manifestation



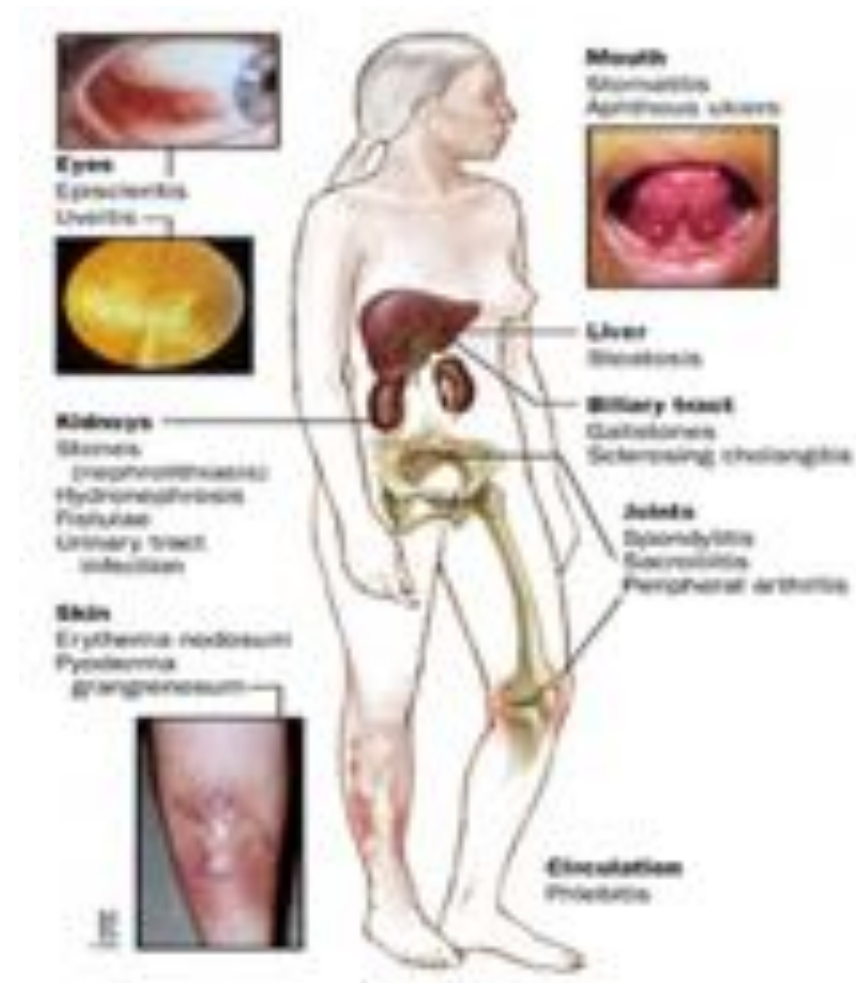
- ❖ Fever
- ❖ Loss of appetite
- ❖ Weight Loss
- ❖ Fatigue
- ❖ Night sweats
- ❖ Stunted growth in children
- ❖ Loss of normal menstrual cycle
- ❖ Extraintestinal manifestation

# Colitis/Diarrhea/Urgency



# Extraintestinal Manifestations of IBD

- ❖ Up to 36% of patients with IBD will develop an extra intestinal manifestation
- ❖ Occurs in up to 15% of patients with CD and about 10% of patients with UC
- ❖ PG is an ulcerative neutrophilic dermatosis seen in only 1–5% of IBD patients.
- ❖ Uveitis and episcleritis occurs in 4 – 12% of UC and Crohn's patients.





IBD Therapies in 2018:  
Help is on the way!!



# How do you decide?

1. Severity of Disease
2. Extent and Location of Disease
3. Prior medications
4. Co-Morbidities
5. Patient Preference
6. Insurance Considerations

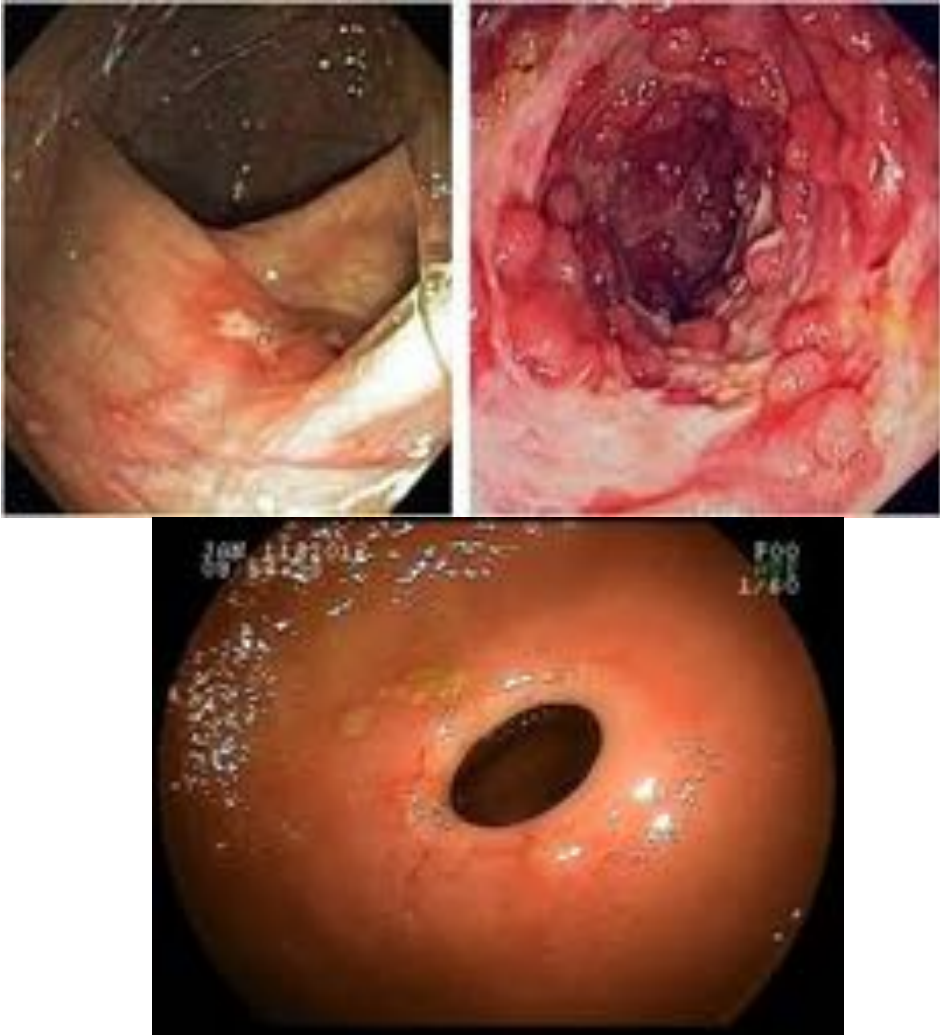
# Picking therapy based on patient

Symptoms	Severity of Inflammation	Location
Mild—bothered but functions at a normal capacity	Superficial ulcerations	Limited ileal disease
Moderate (affects daily life)	Deep ulcerations/inflammatory stricture	Extensive small bowel involvement
Severe (close to or needing hospitalization)	Fibrotic stricture	Extensive colonic involvement
	Internal perforating disease (+/- abscess)	
	Perianal perforating	Rectal disease

# Ulcerative colitis Severity



# Crohn's Disease Severity



# Current Medications for IBD

Crohn's Disease		Ulcerative Colitis
Sulfasalazine	<b>5-Aminosalicylates</b>	Sulfasalazine Mesalamine* , olsalazine* , balsalazide*
Prednisone Budesonide EC* Foams/ Enemas/ suppository	<b>Corticosteroids</b>	Prednisone Budesonide MMX* Foams/ Enemas/ suppository
Azathioprine/ 6MP Methotrexate Tacrolimus	<b>Immunomodulators</b>	Azathioprine/ 6MP Cyclosporine Tacrolimus
Infliximab Adalimumab Certolizumab Natalizumab Vedolizumab Ustekinumab	<b>Biologics/ Small Molecules*</b>	Infliximab Adalimumab Golimumab Vedolizumab Tofacitinib

\* FDA approved for IBD



# Case 1

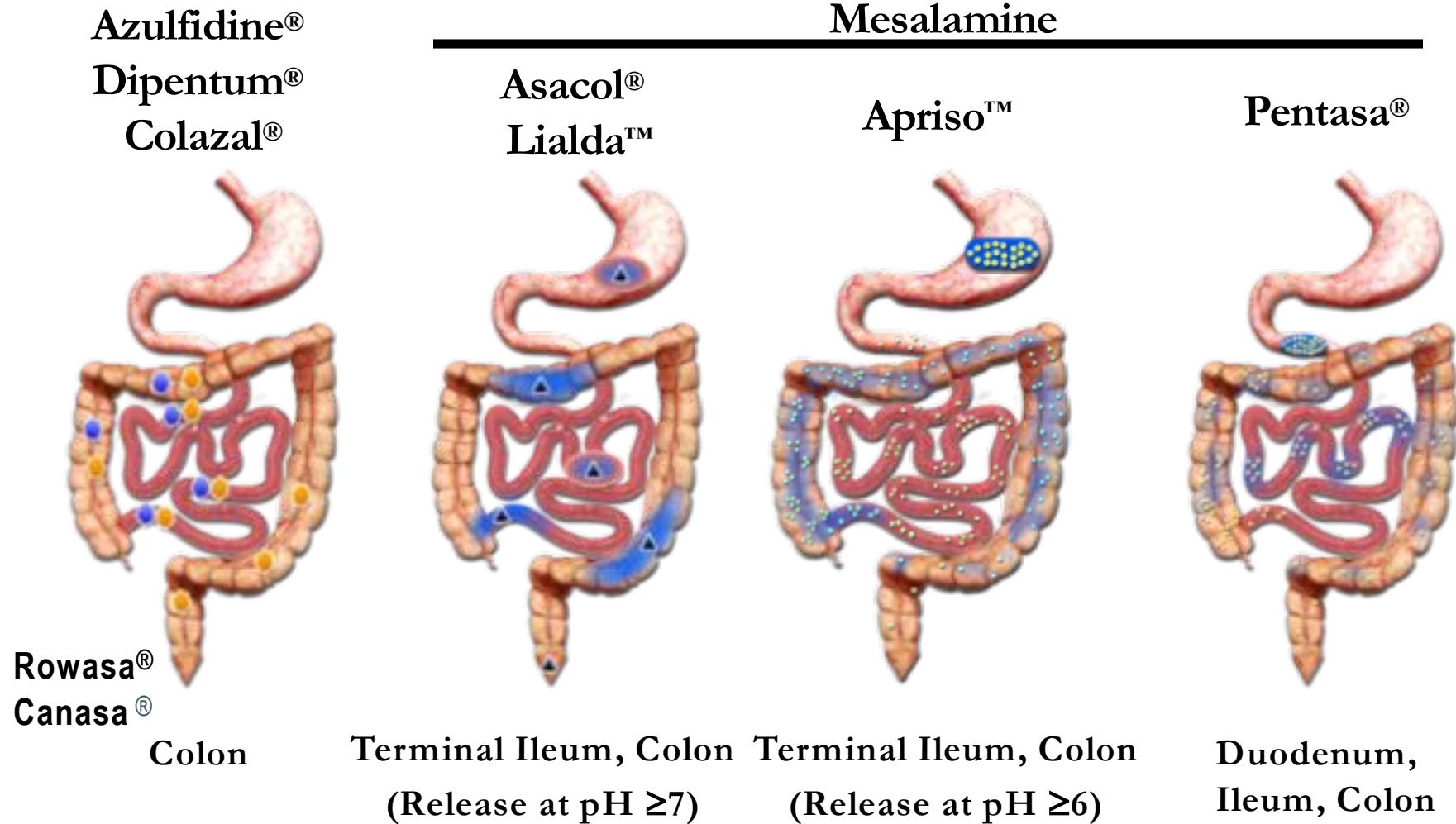


- 25 year old female with no past medical history or family history presents with rectal bleeding, urgency and diarrhea 5 times a day for the past 4 weeks onset. She denies NSAIDs. Infectious are ruled out. She undergoes colonoscopy and is diagnosed with left sided ulcerative colitis.
- What do you recommend for therapy?
  - Location of disease, severity of disease





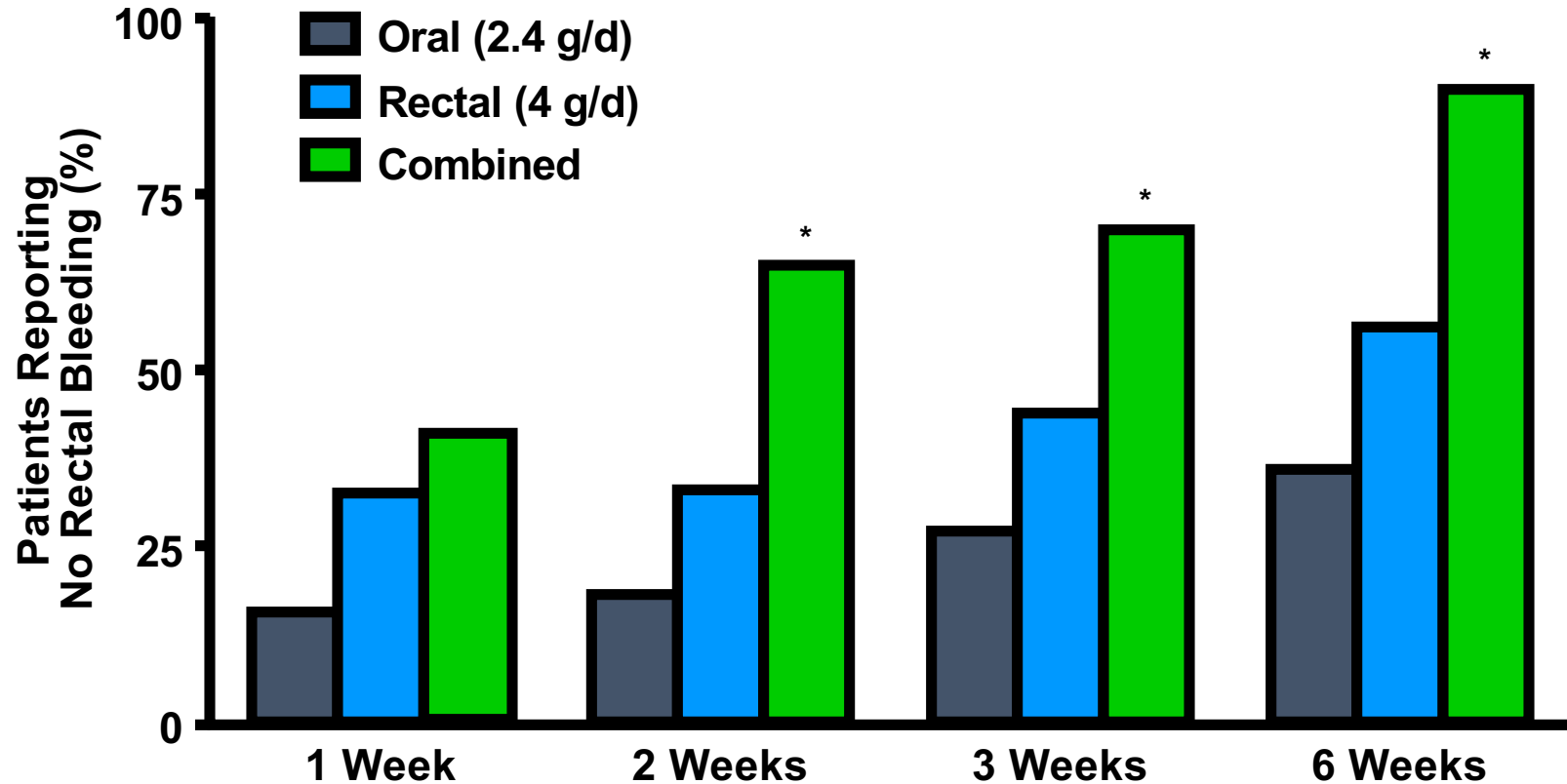
# 5-ASA Formulations: Sites of Delivery



Adapted from Baumgart DC, Sandborn WJ. *Lancet*. 2007;369:1641–1657.

Adapted from Sandborn WJ. *J Clin Gastroenterol*. 2008;42:338–344.

# Treatment of Distal UC: Combination Oral and Rectal Mesalamine Therapy



\* $P < 0.05$  vs oral alone



This rectum is so inflamed  
it's unfamed!

inflamed-and-unfamed.com



Hi, I'm a  
rectum!



Look at all  
this  
inflammation

Using mesalamine  
enemas allows you to  
put medication directly  
into the rectum where  
the inflammation is  
located.

Inflamed  
&  
Unfamed

## How to Insert a Suppository



1. Breaking the suppository

2. Inserting the suppository  
half into the rectum  
inserting only about 1/2 inch



Insert the suppository into the rectum as far as possible. The suppository will melt and the medication will be absorbed into the rectum.

© 2000 American Medical Association

# Case 1



- Patient is put on oral mesalamine 2.4g daily and mesalamine enemas nightly.

# Case 2



- 68 year old male with past medical history of CAD, DM has a diagnosis of colonic Crohn's disease 2 months ago. He currently is having 6 to 8 bloody bowel movements, nocturnal symptoms, urgency and abdominal pain. He remains anemic with a Hgb of 10.3. He has been on mesalamine 4.8g daily and unable to come off of prednisone. He has recurrent symptoms when prednisone at 30mg daily.
- What do you recommend for therapy?
  - Disease locatin, Severity of disease, Co-morbidities, prior medications

# Tipping point to choosing other medications

- Steroid dependent disease
  - Immunomodulators
  - Biologics
  - Small Molecule
- Steroid resistant disease
  - Immunomodulators
  - Biologics
  - Small Molecule



# Corticosteroids: Short- and long-term efficacy in Crohn's disease



30-day  
responses  
(n=74)

**Complete**  
58%  
(n=43)

**Partial**  
26%  
(n=19)

**None**  
16%  
(n=12)

1-year  
responses  
(n=74)\*

**Prolonged  
response**  
28%  
(n=21)

**Steroid  
dependent**  
32%  
(n=24)

**Surgery**  
38%  
(n=28)

\*One patient lost to follow-up

Faubion et al, *Gastroenterology* 2001; 121: 255



# Current Medications for IBD

Crohn's Disease		Ulcerative Colitis
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# Overview of Results of Long-Term Anti-TNF Crohn's Disease Trials

Week 26-30



Remission = Crohn's Disease Activity Index (CDAI) score <150

<sup>a</sup> Decrease in CDAI score of  $\geq 70$  points and  $\geq 25\%$

<sup>b</sup> Decrease in CDAI score of  $\geq 100$  points

<sup>\*</sup>P < 0.002; <sup>\*\*</sup>P < 0.003; <sup>\*\*\*</sup>P < 0.001

TNF<sup>®</sup> = tumor necrosis factor.

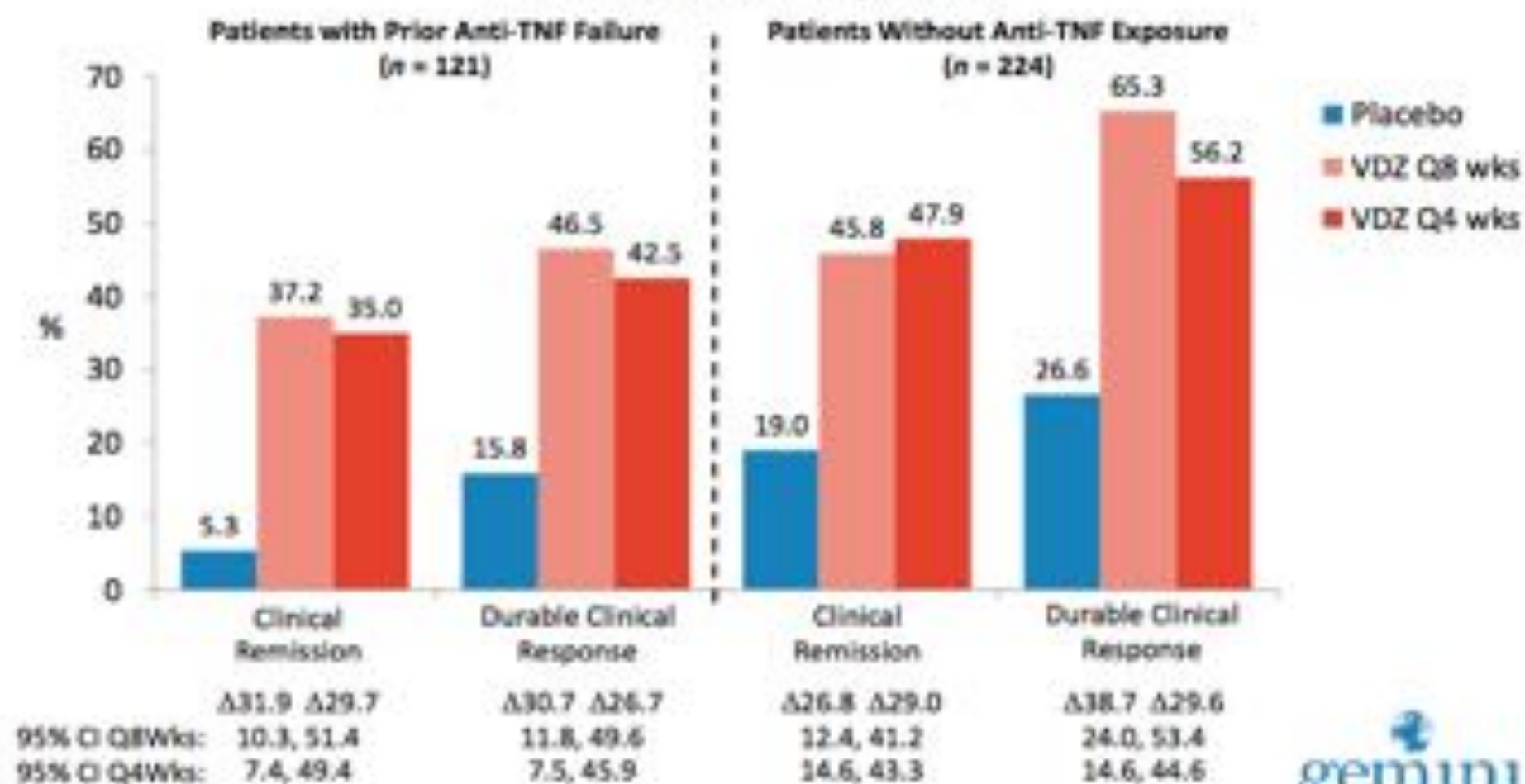
Hanauer SB, et al. *Lancet*. 2002;359:1541-1549.

Colombel JF, et al. *Gastroenterology*. 2007;132:52-65.

Schreiber S, et al. *N Engl J Med*. 2007;357:239-250.

## Clinical Remission, Durable Clinical Response at 52 Weeks: Prior Anti-TNF $\alpha$ Failure vs No Anti-TNF $\alpha$ Exposure

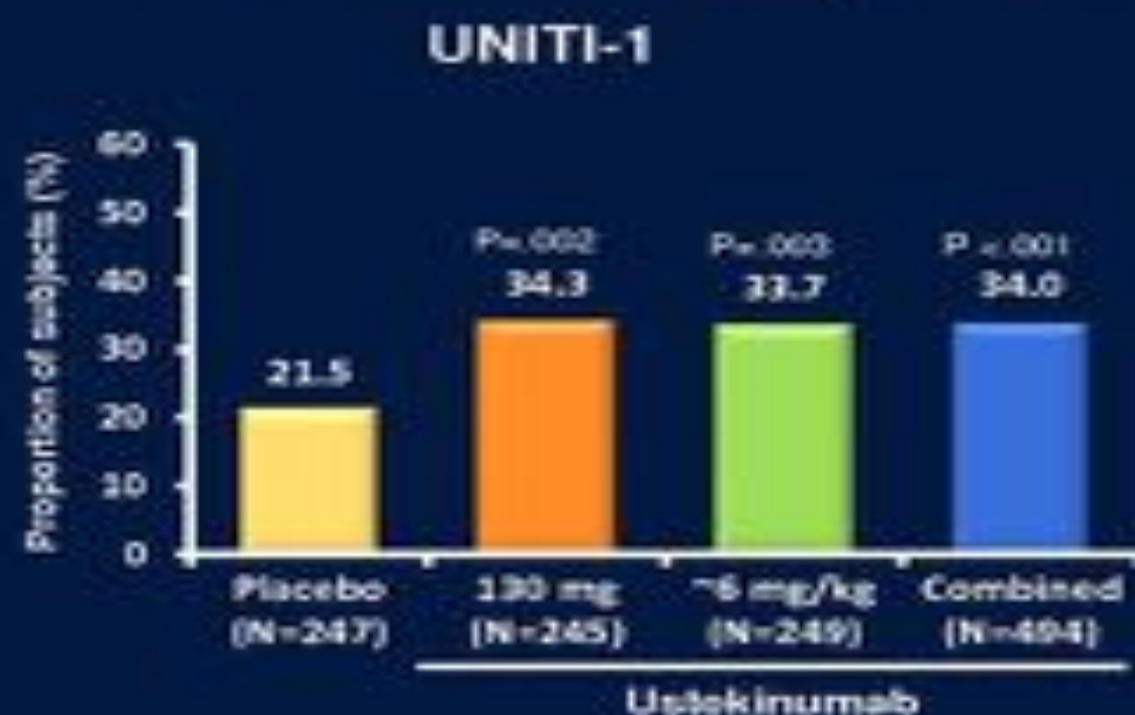
### Maintenance ITT Population





# Ustekinumab in CD: Clinical Response at Week 6

Randomized subjects in clinical response<sup>a,b</sup> at Week 6



<sup>a</sup>Subjects who had a prohibited CD-related surgery or had prohibited concomitant medication changes are considered not to be in clinical response, regardless of their CDAI score.

<sup>b</sup>Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical response.

Feagan BG, et al. N Engl J Med. 2016;375:1946-1960.

# Case 2



- Due to co-morbidities, patient was started on vedolizumab. He was able to come off of steroids within 7 weeks. He had a colonoscopy at 6 months later and had mucosal healing.

# GAME OF CROHNS



DAY 100 - FOUR YEARS

# Case 3



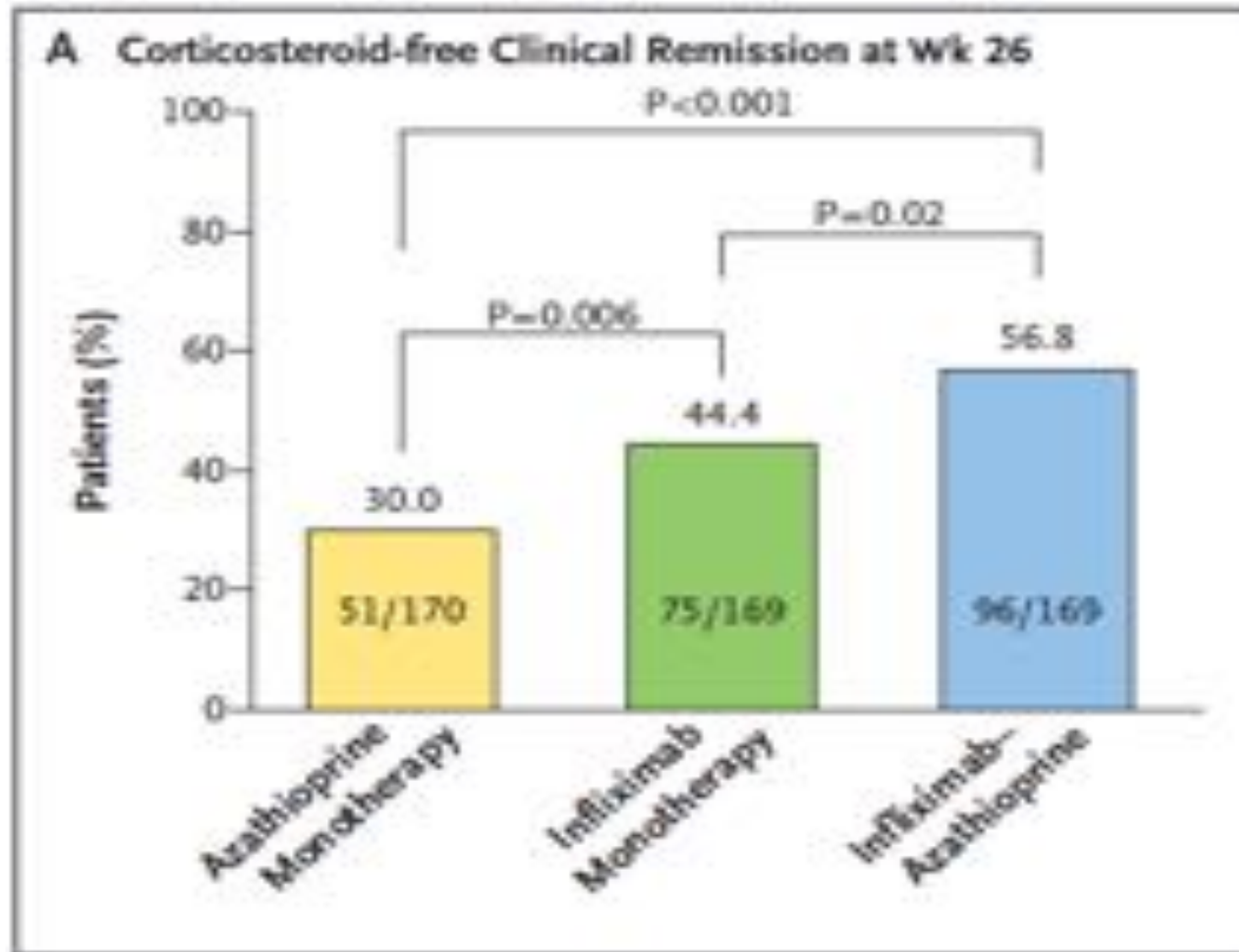
- 19 year old male college student presents to the Student Health Center (during finals week) with complaints of 4 weeks of diarrhea and now with some blood on toilet paper. He has intermittent bilateral lower quadrant pain. He reports unintentional weight loss of 10 pounds. He did travel to Mexico 1 month ago. He takes NSAIDs intermittently for headaches. He is stressed because of finals.
- He is diagnosed with moderately ileocolonic disease.
- Patient is started on combination therapy of infliximab 5mg/kg every 8 weeks and Methotrexate 12.5mg po weekly.
- He improves. He has colonoscopy 6 months later that shows histologic healing.
- 18 months later, he has a flare-up. What do you recommend?

# Optimization of Biologic Therapy

- Timing of starting therapy
- Dual therapy
- Target to assess response of therapy
- Therapeutic Drug Monitoring
  - Reactive versus proactive



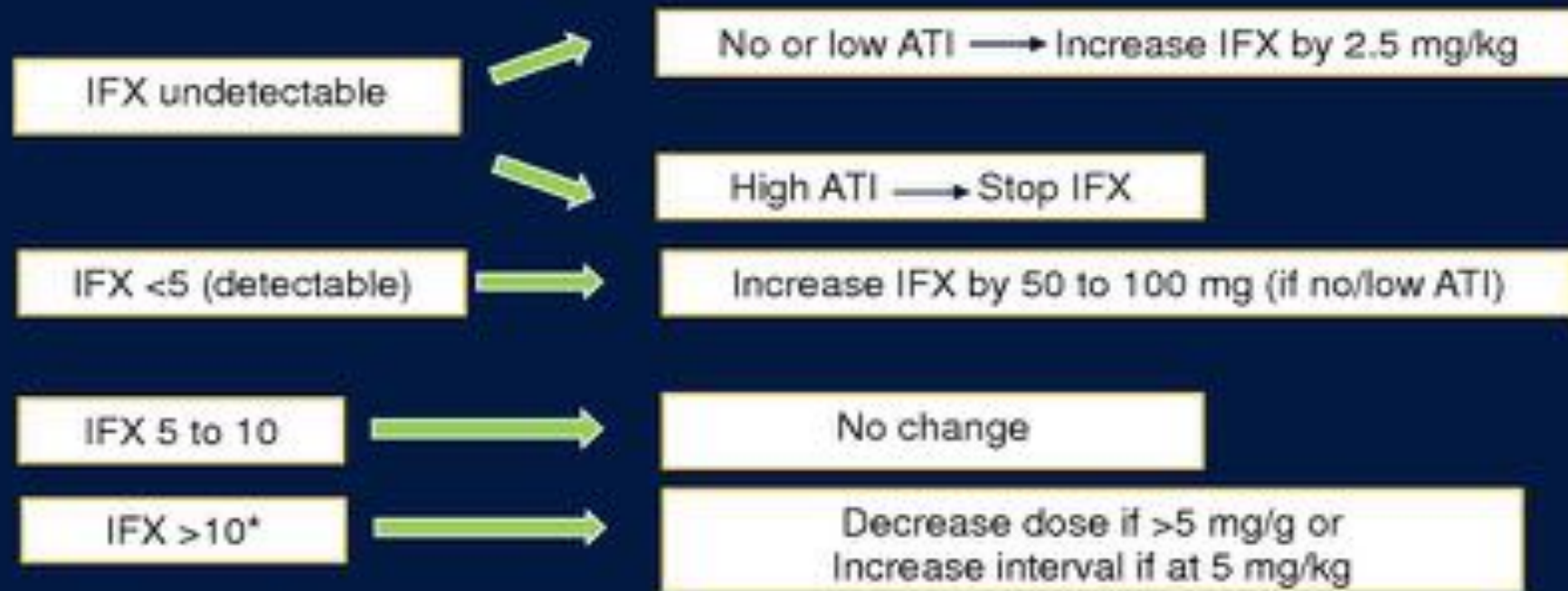
# Results of SONIC





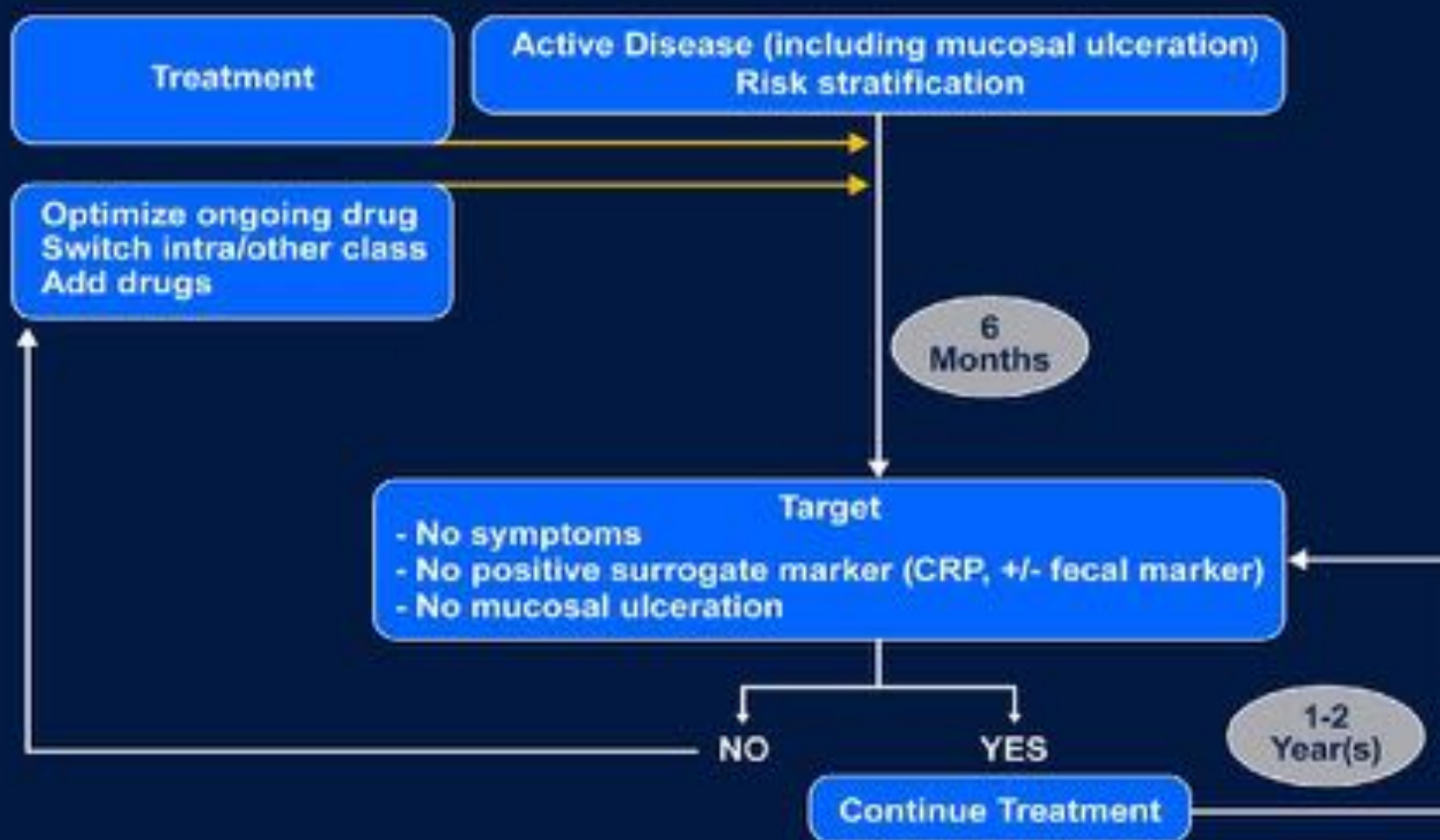
# Therapeutic Drug Monitoring

## Typical protocol for dose adjustment



\* On 2 occasions

# Treat-to-Target Algorithm



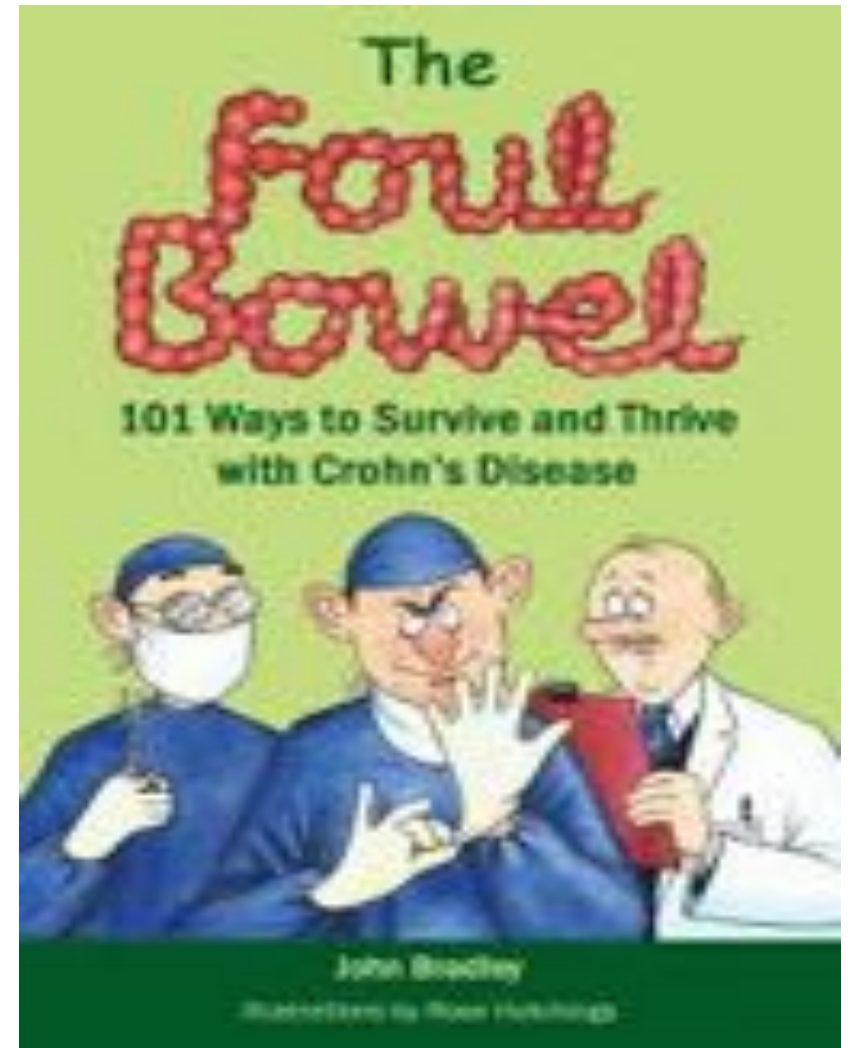


# Case 3

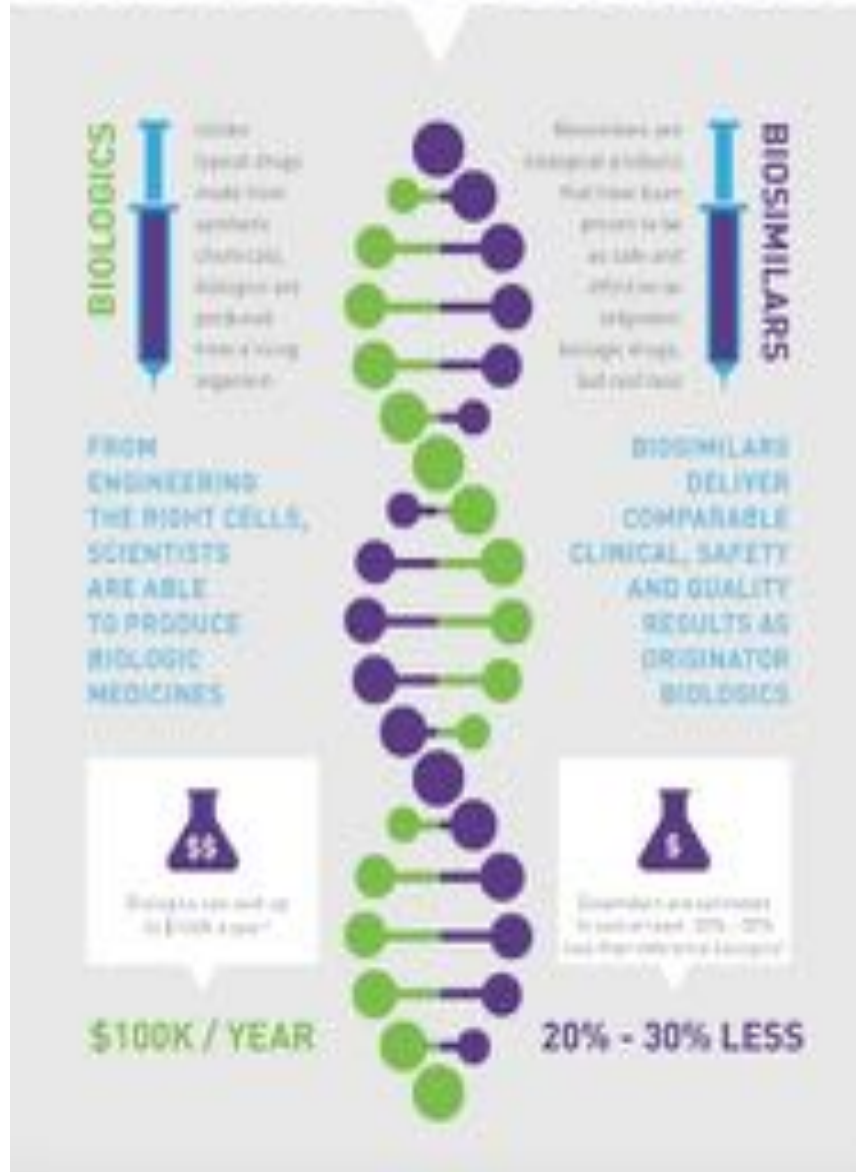


- Infliximab trough level is 2.5, no antibodies to infliximab
- Dose of infliximab was increased to 10mg/kg every 8 weeks and continued on methotrexate 12.5mg po weekly
- He is back in clinical remission.
- Repeat drug levels 4 months later done
  - Infliximab drug level is 9.3, no antibodies to infliximab.

# Hot Topics



# WHAT ARE BIOSIMILARS?



## What is a «biosimilar» ?

World Health Organization:

“A biopharmaceutical product which is **similar in terms of quality, safety and efficacy** to an already licensed reference biopharmaceutical 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:

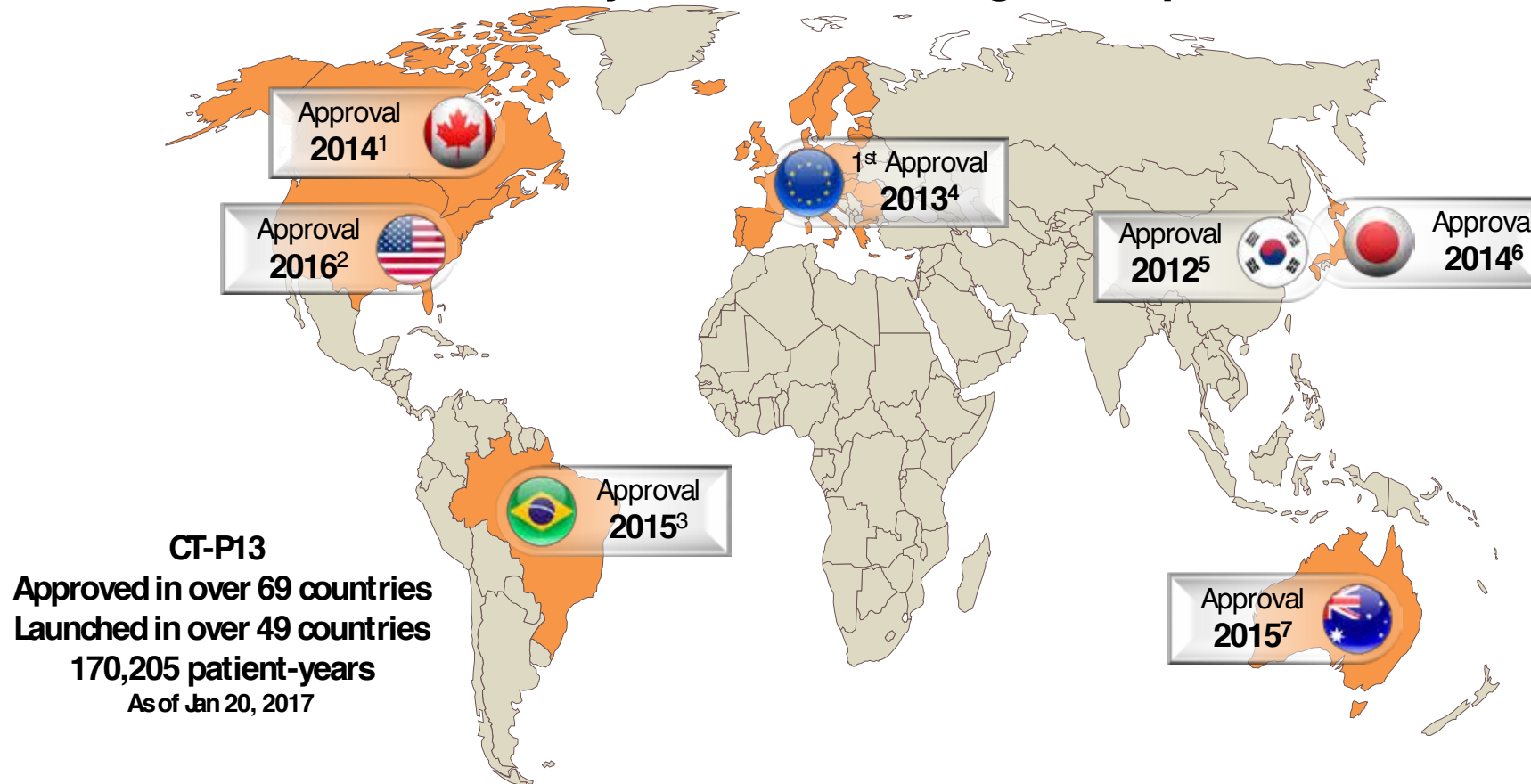
A biological product that “(a) ...is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and for which “(b) there are **no clinically meaningful differences** between the biological product and the reference product in terms of safety, purity,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

**Biosimilars for Infliximab**  
Inflectra  
Remsina  
Renflexis

**Biosimilars for Adalimumab**  
Amjevita  
Cyltezo

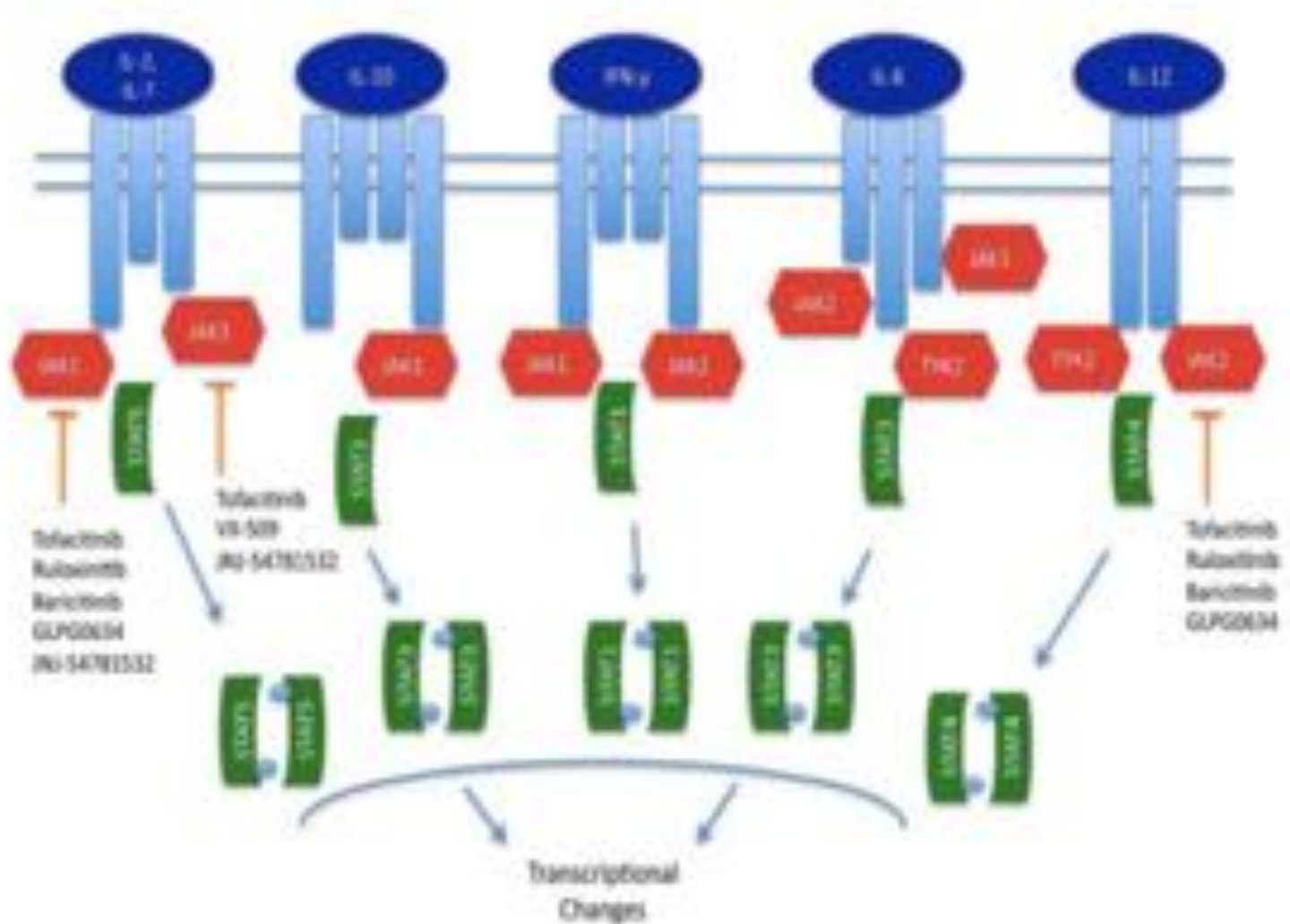
# The landscape of biosimilars: exposure and regulatory approvals

More than 4 years of real-world global experience



1. Health Canada. Femsima: Summary of Basis of Decision. [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd\\_smd\\_2014\\_remsima\\_160195-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_remsima_160195-eng.php) (Accessed May 2016).
2. FDA News release. FDA approves Inflectra, a biosimilar to Femicade. <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm494227.htm>. (Accessed May 2016).
3. ANVISA Press release <http://portal.anvisa.gov.br/wps/content/anvisa+portal/anvisa/sala+de+imprensa/menu+-+noticias+anos/2015/primeiro+medicamento+biologico+por+comparabilidade+e+registrado+pela+anvisa>. (Accessed May 2016).
4. European Medicines Agency. Public Assessment Report, Femsima. Published 10/09/2013.
5. Celltrion Healthcare Co. Ltd. History. [http://www.celltrionhealthcare.com/01\\_about/about02.asp](http://www.celltrionhealthcare.com/01_about/about02.asp) (Accessed May 2016).
6. Celltrion Healthcare Co. Ltd. Press release [http://www.celltrion.com/en/company/notice\\_view.asp?dx=451&code=ennews&intNowPage=1&menu\\_num=&align\\_year=all](http://www.celltrion.com/en/company/notice_view.asp?dx=451&code=ennews&intNowPage=1&menu_num=&align_year=all) (Accessed May 2016).
7. Therapeutic Goods Administration. Public ARTG summary. Inflectra. [https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=B88F4709D7B0055DCA257EF4003CAD8A&agid=\(PrintDetailsPublic\)&actionid=1](https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=B88F4709D7B0055DCA257EF4003CAD8A&agid=(PrintDetailsPublic)&actionid=1). (Accessed May 2016).
8. Hospira DOF

# Tofacitinib: Modulates Cytokine Signaling

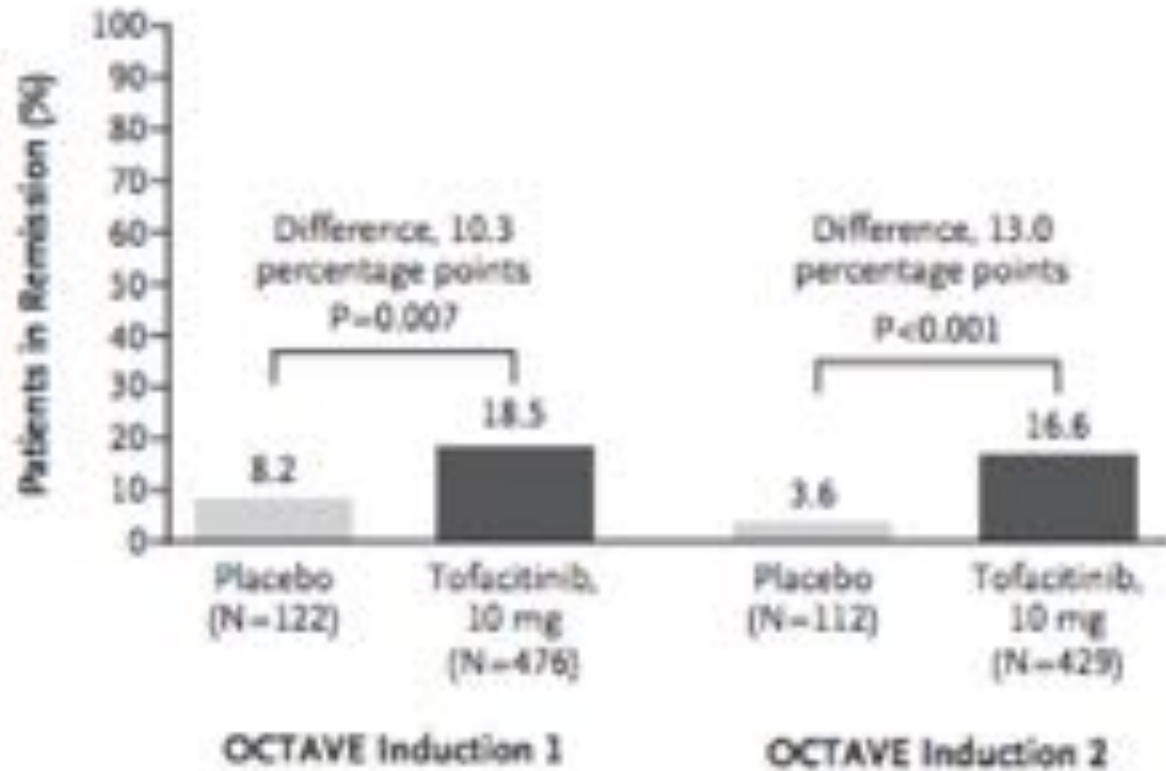


- Novel, small-molecule, oral JAK inhibitor
- Inhibits JAK1, JAK3 > JAK2
- Directly or indirectly modulates signaling for pro-inflammatory cytokines → IL-2, 4, 7, 9, 15, 21
- Xeljanz (Pfizer)
- **FDA Approved: May 31, 2018**

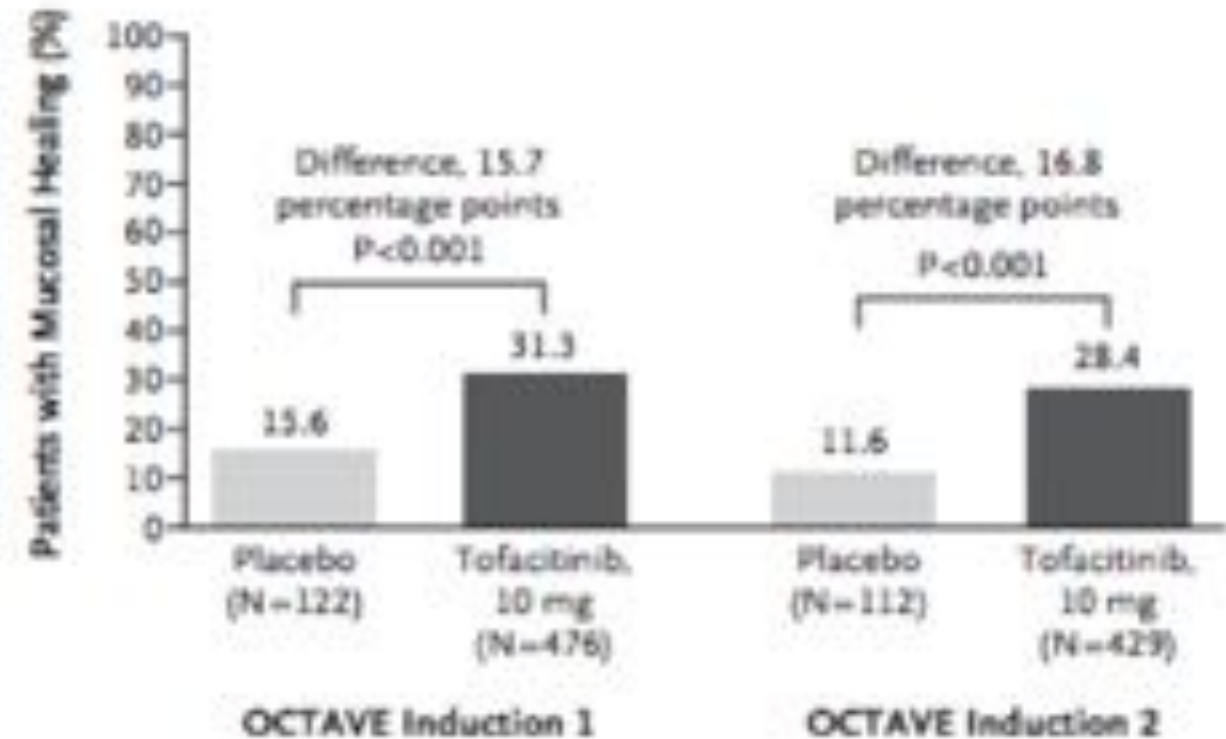


# OCTAVE 1 and 2: Tofacitinib as Induction and Maintenance for Ulcerative Colitis

Primary Endpoint  
Remission at Week 8

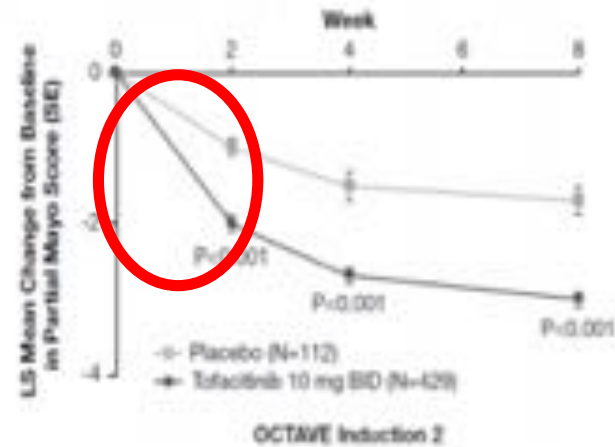
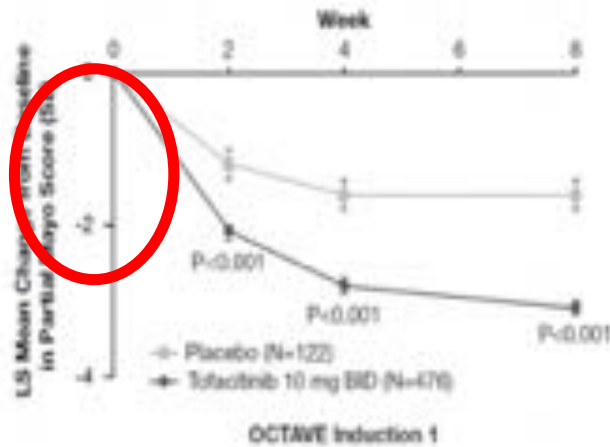


Key Secondary Endpoint:  
Mucosal healing at Week 8



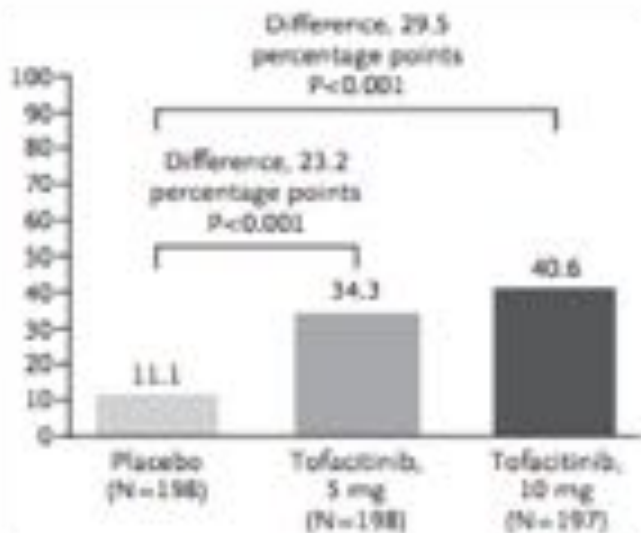
Remission: Total Mayo score  $\leq 2$ ; no subscore  $\geq 1$ , rectal bleeding subscore of 0, mucosal healing=ES of 0 or 1

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

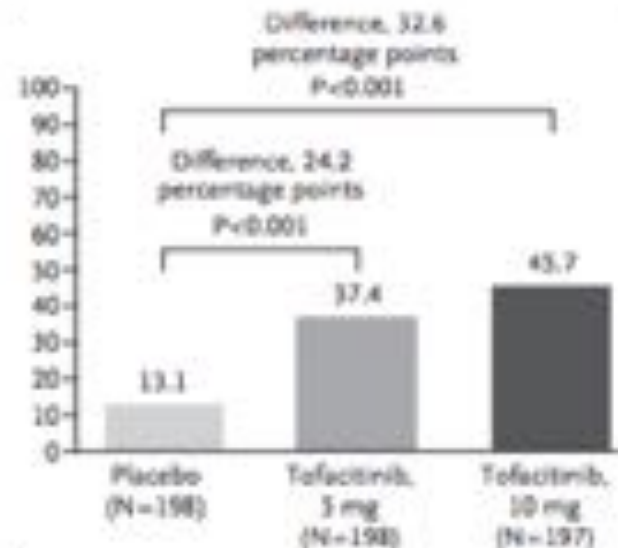


**Tofacitinib Works Quickly**

Maintenance: Remission at Week 52



Maintenance: Mucosal Healing at Week 52



# Safety Signals

- Infections
  - Herpes zoster, Get Shingrix vaccine
- Cancer
  - Non-melanoma skin cancer
- LDL and HDL cholesterol increases
  - Check cholesterol 4-8 weeks after starting therapy
- Gastrointestinal perforation



# Adherence is Complex and Multifactorial



## Treatment-Related Factors

- Dosage/dosing regimen
- Formulation
- Cost/reimbursement
- Adverse effects



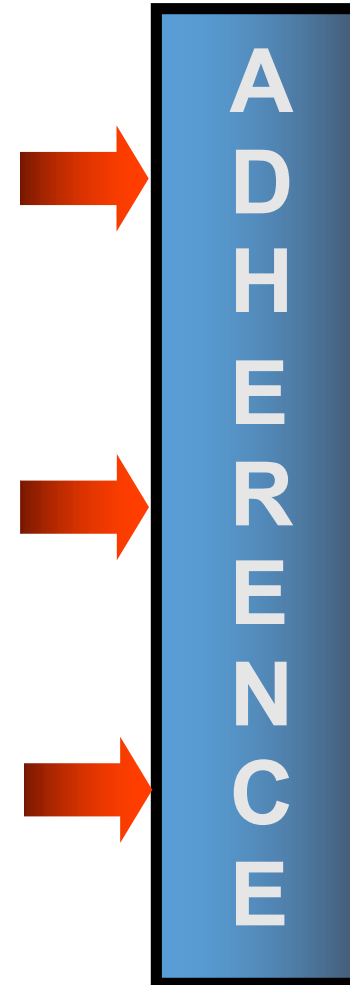
## Illness-Related Factors

- Severity, extent, duration of disease
- Frequency and intensity of flare-ups
- Complications



## Patient-Related Factors

- Skills/knowledge to follow regimen
- Belief systems
- Psychiatric disorders
- Male gender, nonmarried status



Our current goal for our patients:



