Ulcerative Colitis: LDN Rx

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Disclosures

- Speakers Bureau
  - Salix, Entera Health, Actavis, Romark
- Consultant
  - Actavis
- Off label use of medicine – educational information, not promotional

Pathogenesis of UC

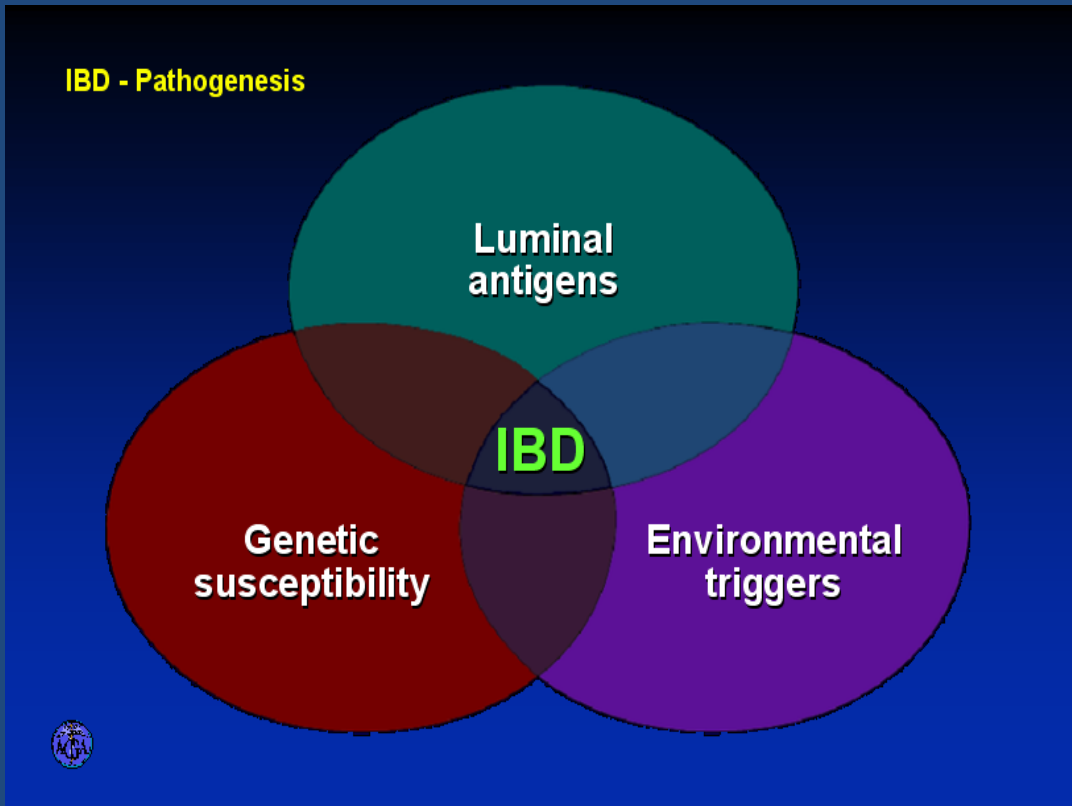
Role for LDN

Problems w current Rx

LDN and UC results

Pathogenesis of UC

- Bacterial trigger
  - Dysbiosis – alters protective mucus layer
- Autoimmune change
- Inflammation



Autoimmune Changes in UC

Autoantibodies

- Perinuclear antineutrophil cytoplasmic antibodies (pANCA) – anaerobic antigen leads molecular mimicry
- Antibodies against epithelial tropomyosin fraction 5

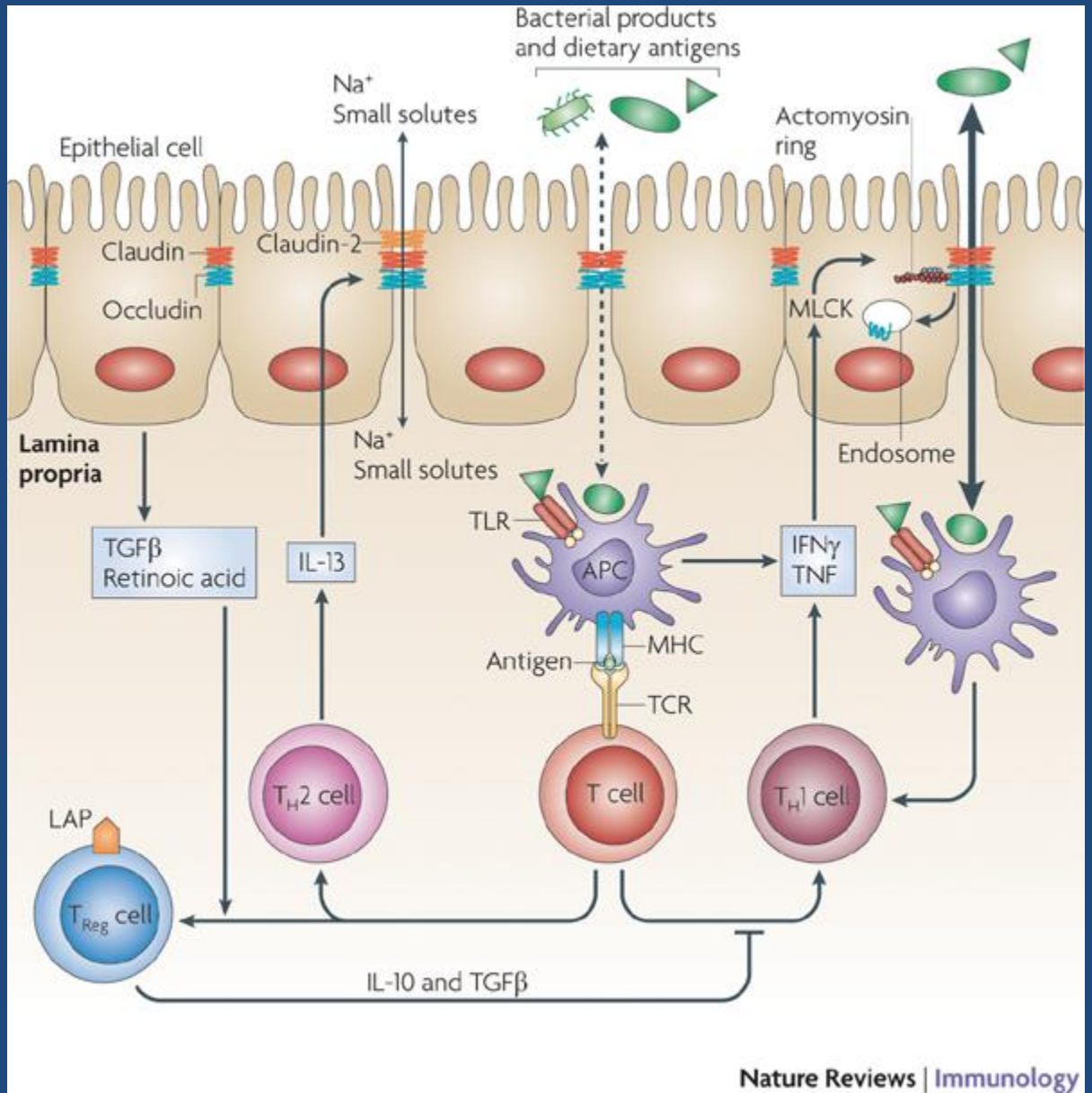
Immune Dysfunction and Inflammation in UC

Inc. reactivity against bacterial antigens

Loss of tolerance against normal bacteria:

- Excessive stimulation of mucosal dendritic cells involved in bacterial antigen recognition
- Defects in regulatory T-cell Fx
- Increased # T-cells
- Increased cytokines – IL-13 attacks epithelium

IBD: Inflammation



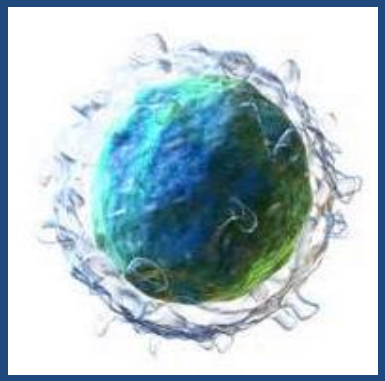
IBD: Inflammation

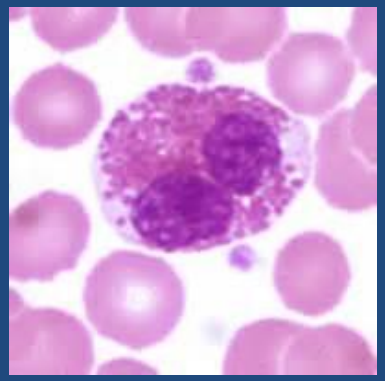
Leukotrienes TNF-α Interleukins TH1

Prostaglandins O_2 radicals Arachidonic acids

Antigens Antibodies Integrins

Neutrophils Lymphocytes Eosinophils





Potential LDN MOA in IBD

- Regulate cell growth
- Stabilize Toll-like receptors
  - Decrease cytokine release
  - Alter bacterial translocation
- Decrease vascular permeability
- Shift from TH2 to TH1
- Decrease Killer T cells (?)

LDN MOA – Toll receptors

- Endothelial receptors
  - GI receptor allows for increase in bacterial translocation
  - LDN may stabilize receptor and decrease bacterial translocation

Li. Med Hypotheses 2012;79:754-6.

LDN and Killer Cells

- Killer cells in mucosa of UC – interacts with lyso-sulfatide a self-antigen suggesting an autoimmune response
- Animal data – continuous naltrexone increased killer cells and cytokines

  --- inverse true for LDN???

Fuss. Gut. 2014;63:1728.
Boyadjieva. J Interferon Cytokine Res. 2010;30:15-22.

Traditional UC Therapy

- Suppress inflammation
  - Alter functions & abilities of WBCs
  - Reduce prostaglandins & free radicals

- Expensive, toxic and variable efficacy (30-70%)

Drug-induced Infection & Mortality in IBD

6273 CD pts followed 5 yrs

Mortality increased with:

Prednisone, narcotic use (1.5), & age

Infections increased with:

Increased disease activity, prednisone, narcotic use (3.0), & infliximab

Lichtenstein. Am J Gastroenterol. 2014.

Prednisone

- **MOA**
  - Suppress neutrophils activity
  - Alter vascular permeability
  - Decrease macrocyte Fx
  - Alter arachidonic acids
  - Suppress circadian IL-6
- **Remission**
  - **Suppression only**
- **Adverse Events**
  - Mood swings
  - Insomnia
  - Edema
  - Hypertension
  - Hyperglycemia
  - Weight gain
  - Thin skin, bruising
  - Increased risk of infections
  - Adrenal insufficiency
  - Glaucoma, Cataracts
  - Osteoporosis

5-ASA

- **MOA**
  - Inhibit 5-lipoxygenase (and leukotrienes)
  - Free-radicle scavenger (blocks bad effects of neutrophils)
- **Remission**
  - 65%
- **Adverse Events**
  - Diarrhea
  - Hair loss
  - Headache
  - Hypersensitivity
    - Fever
    - Bone marrow
    - Pancreatitis
    - Rash
    - Renal failure

Thiopurines: 6MP & Purinethol

- **MOA**
  - Block lymphocyte proliferation, activation, & effector mechanisms
- **Remission**
  - Maintains remission only

- **Adverse Events**
  - Pancreatitis
  - Leukopenia
  - Anemia
  - Hepatotoxicity
  - Infections
  - Lymphoma
  - Skin cancer

Anti-TNF-α: IFX, ADA, Golimumab

- **MOA**
  - Neutralizes TNF-α released by T-cells
  - Splits lymphocytes via complement fixation or cytoxicity
- **Remission**
  - 18-50%
- **Adverse Events**
  - Infusion reactions
  - Injection pain
  - Increased risk of infections
  - Antibodies
    - Lupus
    - Arthritis
    - Antibodies vs. drug
  - Lymphoma

Following Dr. Smith's Lead in Crohn's disease

Open label studies

- Smith et al. Am J Gastroenterol. 2007.
- Shannon et al. Inflamm Bowel Dis. 2010.

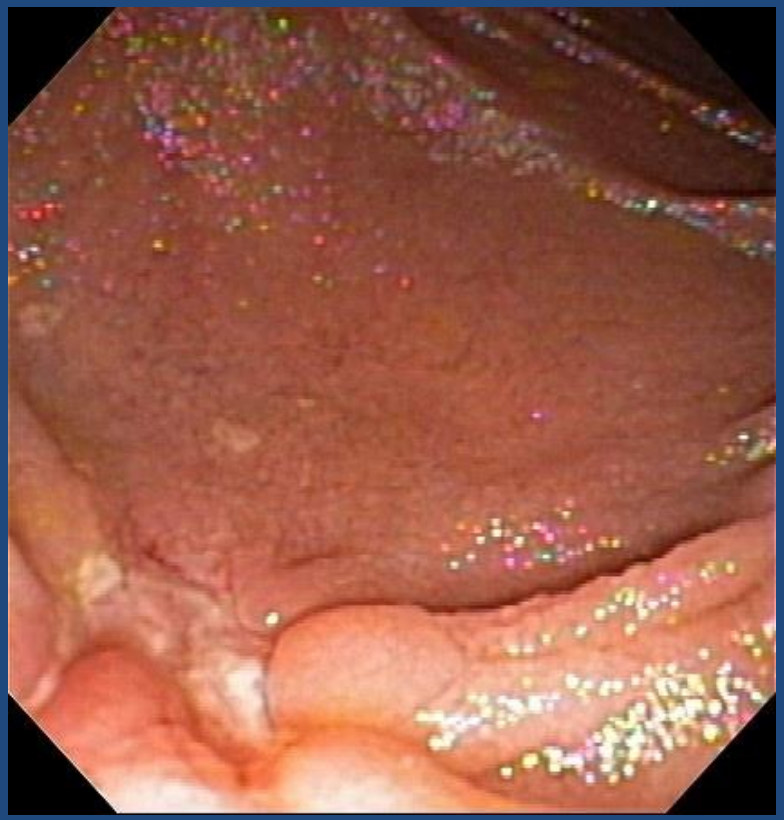
Double blind studies

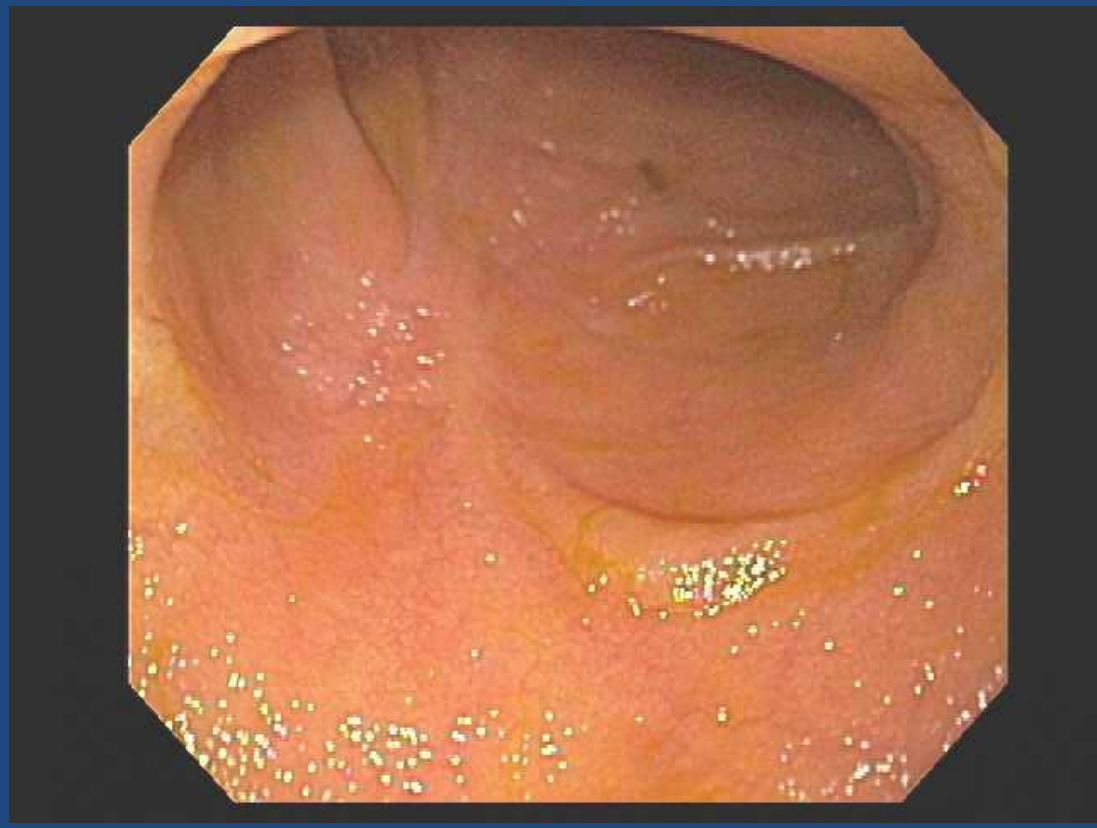
- Smith et al. Dig Dis Sci. 2011.
- Smith et al. J Clin Gastroenterol. 2013.

(Note: 60% on 6MP, none on biologic Rx)

Crohn's Disease: LDN Rx

- 40 y.o. WF s/p total colectomy; intestinal recurrence 4 yrs later; failing IFX: diarrhea & fatigue
- LDN 4.5 mg added; endo & clin remission in 2 mo
- Remission 6 yrs





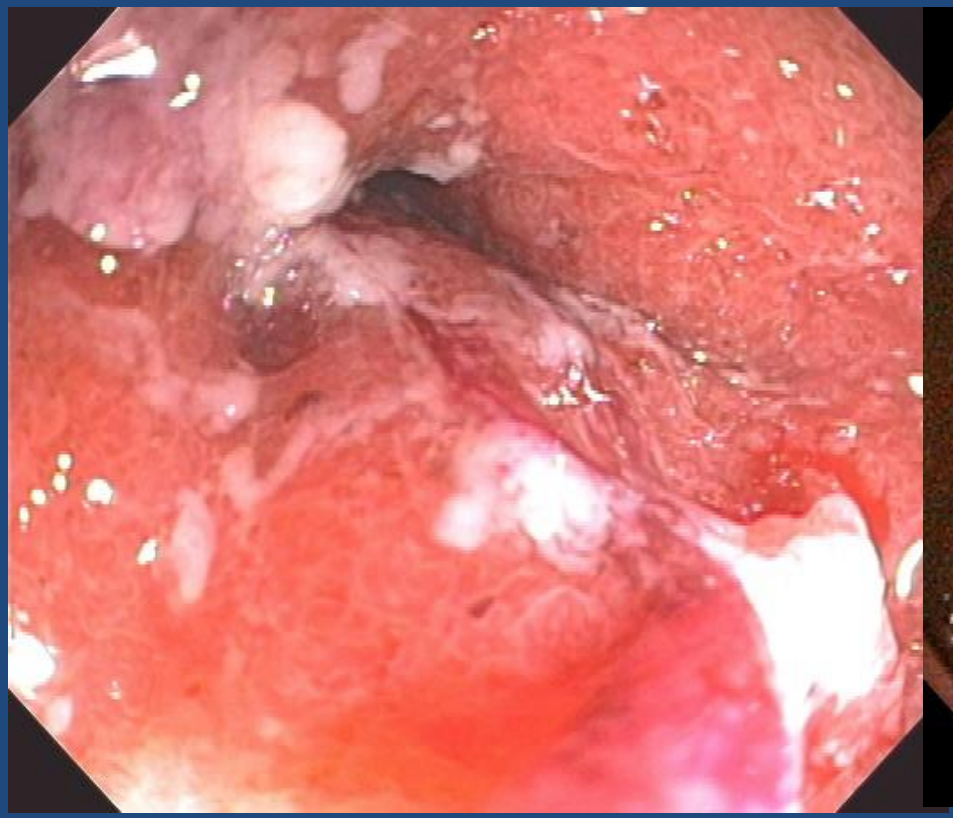
Crohn's disease and LDN

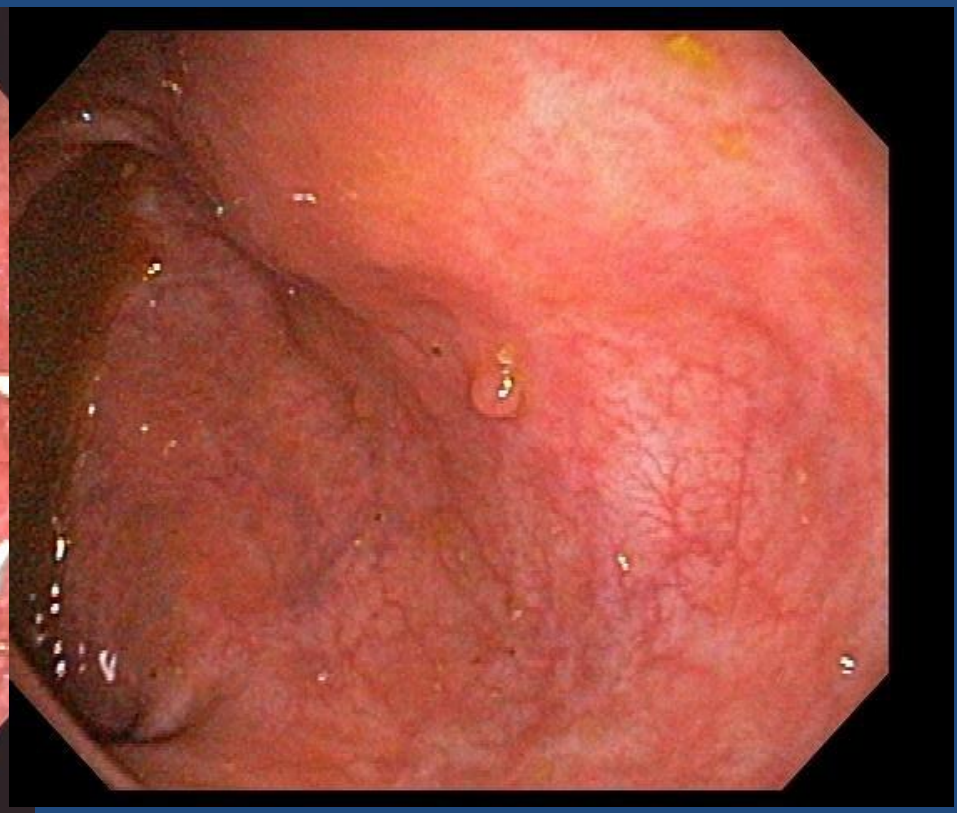
- 33 adults - mod-severe CD
- Failing 6-MP and/or IFX
- LDN 4.5 mg: 40 ±43 wks (max 200 wks)
- 5 withdrew - AE
- Marked or moderate improvement: 15/33
- 11/15 responders had re-scope:
  - 8/11 complete healing
  - 2/11 partial healing
  - 1 no healing

Weinstock. J Clin Gastroenterol 2014;48:742

Ulcerative Colitis: LDN Rx

- 45 y.o. man failing IFX
- LDN added to biologic Rx - remission 7 yrs





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Adjunctive Rx in Tough Cases

12 Pts	IFX	6MP	Pred	5ASA
43 ±16 y 6M/6F	7	6	2	9
Notes	6MP in 3/7		1 on all 4	all on other Rx

10 on biologic and/or 6MP; 6 failed 6MP in past; all had or were failing 5-ASA

Weinstock. J Clin Gastroenterol 2014;48:742.

Adjunctive LDN Rx: Outcome

Marked improvement	Moderate improvement	LDN failure
3	3	6

- **Duration - LDN for 69 ±88 wks (up to 270)**
- **6MP: 3/6 responded (2 failed, 1 stopped d/t AE)**
- 2 of 6 responders re-scoped - complete response

- Other failures: two IFX, one 3-drug combo pt, one 4-drug combo pt, and one 5-ASA pt who failed 6MP in past

Weinstock. J Clin Gastroenterol 2014;48:742.

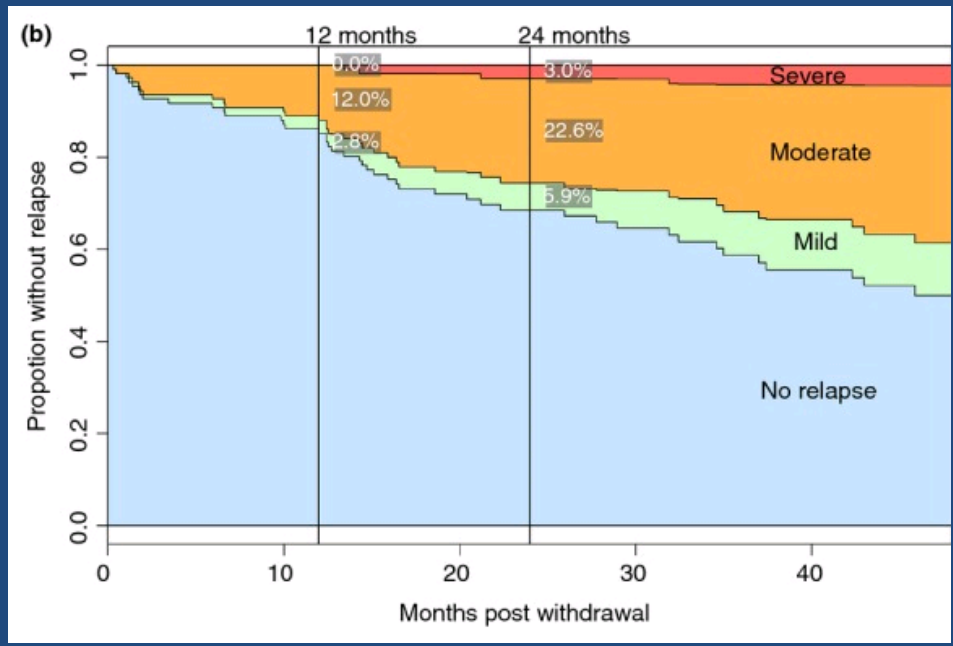
UC LDN Rx: Recent Cases

Pt #	Dur. (1/16)	Response	Type Rx	Comments
1	4.5 mo	Marked	Mono	
2	10 mo	Marked	Mono	
3	11 mo	Moderate	Combo	5-ASA
4	19 mo	Moderate	Combo	EntyVio, MTX, d/c pred
5	1.5 mo	Mild-Mod	Mono	
6	2 mo	Mild	Mono	Added other Rx
7	1 mo	Failed	Mono	
8	2 mo	Failed	Combo	IFX, MTX
9	6 mo	Failed	Combo	5-ASA

LDN use to stop 6MP

Pt #	Dur. (1/16)	Response	Type	Comments
10	10 mo	Stable	Combo	5-ASA
11	3 mo	Stable	Combo	5-ASA

Relapse:
12% in 12 mo
26% in 24 mo
(76% on 5-ASA)



LDN Rx for UC

- Low toxicity, low cost
- Additive owing to different MOA
- Safe/effective with biologics for long time
- Can work with 6MP
- Role as monotherapy to be determined
- RCT important
  - High-placebo Sx response
  - Need endoscopic outcomes