Inflammatory Bowel Disease

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Disclosures

• Speakers Bureau
  – Salix, Actavis, Romark
Forces Leading to IBD

- Risk Genes
- Bacterial Antigens
- Environmental Triggers
- Immune Response
<table>
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<tr>
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**Diagram:**
- Bacteria
- Goblet
- Mucus layer
- Zonulin
- Occludin
- Enterochromaffin
- Paneth cells
- Submucosal plexus
- Mesenteric plexus
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<th>Dysbiosis</th>
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Increased vascular permeability
Phase 1: Pre-disease Stage – Triggers Impair Barrier Function and allow Bacterial Translocation

- Genetic factors
  - Antimicrobial factors
  - Autophagy
  - Handling of bacteria
  - Chemokines
  - Cytokines

- Environmental factors
  - Microorganisms
  - Diet
  - Infections
  - Stress
  - NAIDs
  - Appendectomy
  - Smoking
  - Antibiotics
Phase 2: Acute Intestinal Inflammation

Translocation of bacteria *

Immune activation *

* Important for LDN
Phase 3: Chronic Inflammation

• Failure of regulatory mechanisms
  – Loss of Treg cell *

• Activation of Effector Cells
  – Macrophages
  – Effector T cells *

* Important for LDN
Phase 4: Tissue Destruction and Complications

• Deep ulceration
  – Fibrosis leading to Stenosis
  – Fistula
  – Abscess

• Chronic inflammation
  – Leading to Cancer

• Extra-intestinal manifestations
  – Autoimmune
Overview of IBD Therapy

• “Suppress inflammation”
• Alter functions & abilities of WBCs
• Reduce prostaglandins & free radicals
• Alter microbiome & mucosal immunity
  — Antibiotics, Probiotics, Dietary, IgG, FMT
• Role LDN: improve innate regulation of immunity, reduce inflammation, and improve vascular integrity
Drug-induced Infection & Mortality in IBD

6273 CD pts followed 5 yrs
3420 had infliximab
2853 had other-Rx-only

Mortality increased with:
Prednisone, narcotic use, and age

Infections increased with:
Moderate-to-severe disease activity, narcotic use, prednisone, infliximab
Prednisone

MOA

- Suppress neutrophils activity
- Alter vascular permeability
- Decrease macrocyte Fx
- Altered Arachidonic acids
- Suppress circadian IL-6

Protection

- Vitamin D and Ca^{++}
- Alternative steroids
  - Budesonide
  - Topical Rx

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)

**Protection**

- Check creatinine
- pH & distribution
- Alternative forms
  - Local

**Adverse Events**

- Diarrhea
- Hair loss
- Headache
- Hypersensitivity
  - Fever
  - Bone marrow
  - Pancreatitis
  - Rash
  - Renal failure
# Thiopurines

## MOA
- Block lymphocyte proliferation, activation, & effector mechanisms

## Protection
- Check TPMT
- Correct dosing
- Vaccines
- Avoid infections
- Check CBC/LFT
- Check drug levels

## Adverse Events
- Pancreatitis
- Leukopenia
- Anemia
- Hepatotoxicity
- Infections
- Lymphoma
- Skin cancer
Anti-TNF-α therapy

• **MOA**
  - Neutralizes TNF-α released by T-cells
  - Splits lymphocytes via complement fixation or cytotoxicity

• **Protection**
  - Vaccination:
    • dead viruses
    • Wait 2 mo after live viruses
  - Exclude Tb & his top.

• **Adverse Events**
  - Infusion reactions
  - Injection pain
  - Increased risk of infections
  - Antibodies
    • Lupus
    • Arthritis
    • Antibodies vs. drug
  - Lymphoma
# Anti-TNF-α – CD Rx: Infliximab

**Infliximab - 70 pt drop in CDIA at wk 30**

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**Graph showing the percentage of patients (pt) with a 70 pt drop in CDIA at wk 30 for placebo, 5 mg/kg, and 10 mg/kg Infliximab.**

- **46%** for 10 mg/kg
- **39%** for 5 mg/kg
- **25%** for placebo
Anti-Integrin therapy

**MOA**

- Inhibits T-cell movement into inflamed GI tissue
- Binds to integrin blocking MadCam-1 cell adhesion on gut endothelial cells

**Adverse Events**

- Potential increased risk of infection
- Rare malignancy – similar to plc

**Protection**

- Observe
# Anti-Integrin Rx - CD: Vedolizumab

<table>
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Anti-Interleukin Therapy: Ustikamab

MOA

- Binds to IL-12 and -23 preventing immune cell differentiation, proliferations, and activation

Protection

- Dermatology surveillance

Adverse Events

- Increased risk of infection
- Skin malignancy
## Anti-Interleukin Therapy:
Ustikamab (N=741 and 627, 100 pt drop)

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Herbal Rx in UC

14 randomized controlled trials

- Aloe vera gel, wheat grass juice, Andrographis paniculata extract (HMPL-004) and topical Xilei-san superior to plc in inducing remission or response
- Curcumin superior to plc in maintaining remission
- Boswellia serrata and Plantago ovata effective as mesalazine
- Evening primrose oil - similar relapse rates as omega-3 fatty acids
Probiotics

MOA

- Improve immunity

Examples

- VSL#3 and S. boulardii for UC
- E. coli Nissele for CD

Adverse Events

- Bloating
- Constipation
- Diarrhea
- Cost
- Infection of central lines
- Sepsis in immuno-compromised pts
Anti-Inflammatory Diets

Specific examples

- Specific carbohydrate diet (SCD)
- Gluten free diet (GFD)
- GAPS (Gut and Psychology Syndrome) diet
- Dr. Weil’s diet
Vitamin D

• Always use in setting of steroid use
• Vit D as an anti-inflammatory agent
Immunoglobulins

- Serum bovine immunoglobulins
- Purified from bovine blood
- 25 yr use in early weaned piglets have reduced infections and poor growth
- Introduced in 2013 for Rx enteropathy in man
Immunoglobulins: SBI
Potential LDN MOA in IBD

- Regulate cell growth
- Decrease inflammation
- Decrease permeability
- Stabilize Toll-like receptors
  - Decrease microglia activation
  - Decrease cytokine release
- Shift from TH2 to TH1
- Improve GI motility
LDN effect

Endorphins & receptors lead to decreased T- and B-cell activity & less permeability
LDN MOA – Toll receptors

- Endothelial receptors – possible MOA for IBD
  - Toll receptor allows bacterial translocation – exacerbated by exogenous opioids
  - LDN may stabilize receptor and decrease bacterial translocation

Methionine enkephalin: role in immunoregulation

- MENK binds to opioid receptors on immune and cancer cells.
- Binding site: CD4+Foxp3+ regulatory T cells (Tregs) which suppressing immune system to keep balanced immunity
- Tregs reveal a relationship between the endocrine and immune systems

Zhao. Int Immunopharmacol 2016;37:59-64.
Crohn’s disease and LDN

Open label studies
• Weinstock. J Clin Gastroenterol 2014;48:742

Double blind studies
• Smith. Dig Dis Sci 2011; 56:2088-97
Crohn’s disease – RCT #1

• LDN as adjunctive therapy in adults
• Biologic therapy was an exclusion
• 88% of LDN (N=18) had 70-point decrease in CDAI scores vs. 40% of control (N=16)
• After 12 wks, 78% of LDN had response in CD endoscopy index severity score vs. 28% controls
• 33% of LDN had endoscopic remission vs. 8% controls

Crohn’s disease – RCT #2

• LDN as sole therapy in 14 children
• LDN (0.1 mg/kg) vs. placebo for 8 wks
• CDAI: 34±3 decreased to 22±4 (P=0.005)
• 25% went into remission
• No serious AE
Crohn’s disease and LDN

- 33 adults - mod-severe CD
- Failing 5-ASA followed by 6-MP and/or IFX
- LDN 4.5 mg: 40 ± 43 wks (max 200 wks)
- 5 withdrew - AE (mild-moderate)
- Positive clinical response in 15/33 pts
- 11 of the 15 responders: C-scope before and after Rx: 8 complete, 1 partial & 2 no healing

Crohn’s Disease: LDN Rx

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

- CRC screening of severe MS pt – ileitis w/o sx
- 2 weeks: MS clinical benefit
- 1 year: MS clinical benefit; ileal ulcers healed
Ulcerative Colitis: LDN Rx

- Pt failing Remicade – high risk of colectomy
- LDN added to biologic Rx - remission 7 yrs
Ulcerative colitis – St. Louis

• Open label study: 4.5 mg LDN in moderate to severe UC (N=12)
• Failing 5-ASA followed by 6-MP and/or IFX
• LDN Rx: 46 ± 75 wks (max 270 wks)
• 1 withdrew d/t insomnia
• Positive clinical response in 6/12 pts
• 2 of 6 responders: C-scope before and after Rx
  • 2 complete healing
### UC LDN Rx: Additional Cases

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LDN Rx for IBD

• 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