


Ulcerative Colitis Therapy

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GI for GP's Jasper AB

Faculty Disclosure

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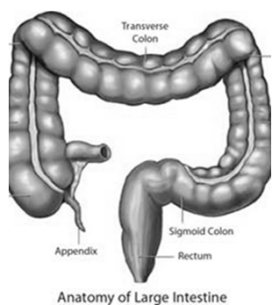
- Karen Kroeker has kindly let me sample from her slide bank for this presentation

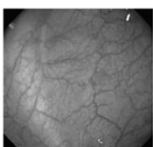
Objectives

- Goals of therapy in UC
- Review common therapies
- Review side effects
- Review biologic therapy
 - What options
 - When its used
 - Contraindications

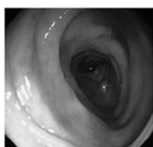
Ulcerative Colitis

- Chronic inflammatory bowel disease – only affects the colon (starts “bum up”)
 - proctitis,
 - proctosigmoiditis,
 - L-sided,
 - pancolitis
- Severity:
 - mild,
 - moderate,
 - severe
 - fulminant

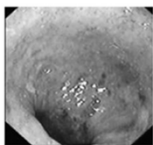




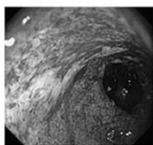
0 Normal or inactive disease



1 Mild disease (erythema, decreased vascular pattern, mild friability)

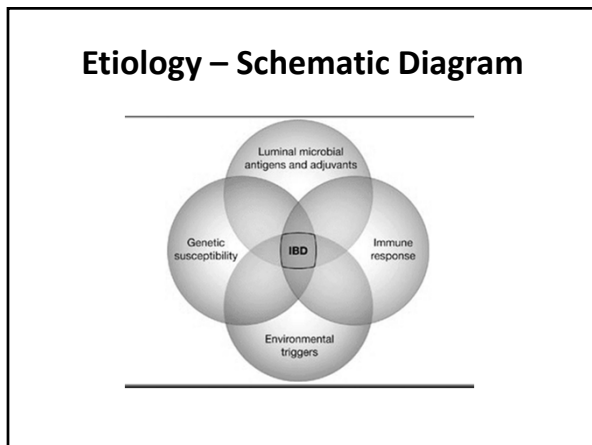


2 Moderate disease (marked erythema, absent vascular pattern, friability, erosions)



3 Severe disease (spontaneous bleeding, ulcerations)

Table 1. Mayo Scoring System for Assessment of Ulcerative Colitis Activity. ^a
Stool frequency[†] 0 = Normal no. of stools for this patient 1 = 1 to 2 stools more than normal 2 = 3 to 4 stools more than normal 3 = 5 or more stools more than normal Subscore, 0 to 3
Rectal bleeding[‡] 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes Subscore, 0 to 3
Findings on endoscopy 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration) Subscore, 0 to 3
Physician's global assessment[§] 0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease Subscore, 0 to 3



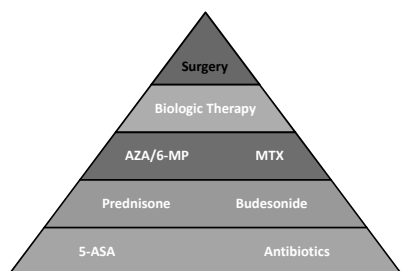
- ### What are the goals of therapy?
1. Induce and maintain remission
 - - Steroid-free remission
 2. Prevent complications
 3. Improve QOL
 4. Avoid surgery
 5. ? Mucosal healing

Treatment of IBD

TWO PHASES:

- INDUCTION of Remission
 - 5-ASA
 - Corticosteroids
 - MTX
 - Anti-TNF
 - Surgery
- MAINTENANCE of Remission
 - 5-ASA
 - Imuran/6-MP, MTX
 - Anti-TNF

IBD Treatment Pyramid



Aminosalicylates (5-ASA)

TWO TYPES:

- Sulfasalazine: sulfapyridine + mesalamine
- Mesalamine: mesalamine + mesalamine
 - Pentasa, Asacol, Salofalk, MMX
 - Different release characteristics...

Side Effects – 5-ASA

Sulfasalazine

- Anorexia
- N/V
- Neutropenia, agranulocytosis
- Hemolysis
- Macrocytosis (folate deficiency)
- Reversible male infertility
- Plus mesalamine SE

Mesalamine

- Headache
- Drug fever, rash
- Paradoxical exacerbation of diarrhea
- Pancreatitis
- Hepatitis
- Pericarditis
- Nephritis

Generally well tolerated

5-ASA in Ulcerative Colitis

IBD Treatment Pyramid

- **Mainstay of treatment** in mild-moderate UC
- Effective for induction & maintenance
- No need more more than daily or BID therapy
- Combination oral & rectal therapy improves remission rates

Glucocorticoids for Ulcerative Colitis

VERY EFFECTIVE FOR INDUCTION OF REMISSION:

- Prednisone 40-60mg/day plus taper
 - Effective for inducing remission
- Budesonide - *Not effective*

FOR IN-PATIENTS:

- Solumedrol (methylprednisone) 20-30mg IV BID

Side Effects - Prednisone

- **Sleep & mood disturbance**
- **Acne**, alopecia
- Striae, central obesity
- Hirsutism
- **Adrenal suppression**
- Proximal myopathy
- Glucose intolerance
- Hypertension
- Weight gain
- Glaucoma
- Cataracts
- **Infection**
- Pseudotumor cerebri
- Edema
- Impaired wound healing
- Growth retardation
- **Osteopenia/osteoporosis**
- **Avascular necrosis**

Immunosuppressives

- Azathioprine – 2.5 mg/kg/d
- 6-mercaptopurine – 1.5 mg/kg/d
- (Methotrexate – 15-25mg/week (PO/SC))

AZA/6-MP – Crohn's Disease & UC

- Azathioprine 2.5mg/kg/d
- 6-mercaptopurine 1.5mg/kg/d
- Not effective in inducing remission
- 70% effective in maintaining remission
- Need to follow bloodwork (CBC, liver enzymes for side effects)

Side Effects – AZA/6-MP

- Nausea
- Drug fever
- Rash
- Arthralgias
- Leukopenia
- Thrombocytopenia
- Bone marrow suppression
- Pancreatitis
- Hepatitis
- Infection
- Lymphoma

Anti-TNF: Biologic Therapy

- Anti-TNF α
 - **Infliximab** (Remicade®)
 - **Adalimumab** (Humira®)
 - Certolizumab
 - **Golimumab**(Simponi®) (New)

Why anti-TNF?

- Pts with UC have high levels of TNF- α in the colon mucosa, produced by lamina propria mononuclear cells
- TNF- α key player in the inflammatory cascade
- Shut it off and decrease inflammation

Anti-TNF α (available in Canada)

- **Infliximab** (intravenous)
 - Chimeric monoclonal antibody to soluble and membrane-bound TNF α
- **Adalimumab** (subcutaneous)
 - Human monoclonal antibody to soluble TNF α but not to lymphotoxin
- **Golimumab** (subcutaneous)
 - IgG1 monoclonal antibody against TNF
 - Subcutaneous administration
 - (also tested IV – data not published)
 - AKA: CANTO 148
 - Binds membrane bound and soluble TNF

Who we use it on?

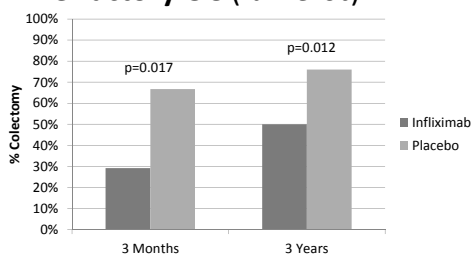
- Outpatients failing other therapies
- Fulminant/severe not responding to steroids
 - Oxford rule

“Oxford Rule” In-patient Severe/Fulminant Colitis

- Day 3
 - 8 BM/day or 3-8 BM/day and CRP > 45
 - 85% chance of colectomy
- Day 7
 - > 3 BM/day or visible blood
 - 60% chance of continuing Sx and 40% of requiring colectomy

(Gut 1996; 38: 905-910)

Evidence for Infliximab in Steroid-Refractory UC (*Jarnerot*)



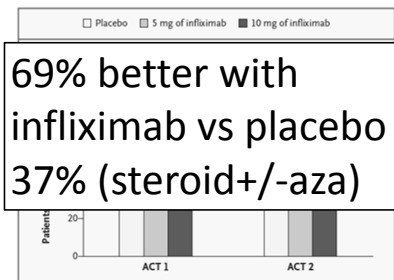
None of the pts in endoscopic remission at 3months had a colectomy; versus 50% who were not in remission (p=0.02)

GASTROENTEROLOGY 2005;128:1805-1811 Aliment Pharmacol Ther 2010; 32: 984-989

Infliximab – Ulcerative Colitis Outpatients

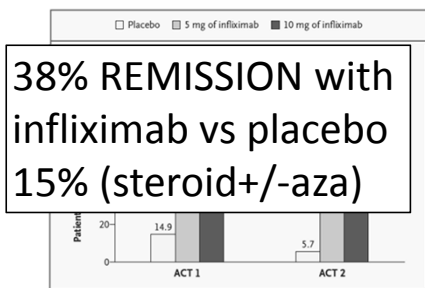
- ACT I&II (NEJM 2005; 353:2462)
 - **Outpatient trial**
 - 2 – DR, RCT of 364 pts with mod-severe UC (Mayo 6-12; with endo score 2+) randomized to placebo, 5, 10 mg/kg at 0, 2, 6 & q8wk
 - DEFINITIONS:
 - Response: decrease Mayo 3 (at least 50%) with bleeding decreasing by 1+ (absolute score 0-1)
 - Remission: Mayo ≤ 2, endo score 0-1
 - Mucosal healing: Absolute score 0-1

ACT I&II – Clinical Response 8 wks



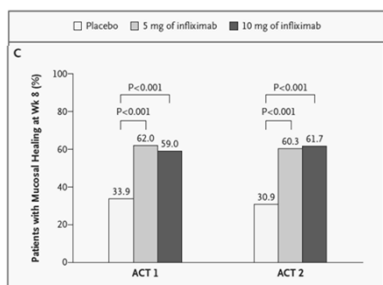
N Engl J Med 2005;353:2462-76.

ACT I&II – Remission 8 weeks



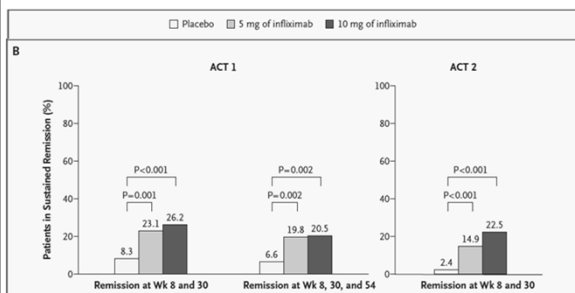
N Engl J Med 2005;353:2462-76.

ACT I&II – Mucosal Healing 8 wks



N Engl J Med 2005;353:2462-76.

ACT I&II – Sustained Remission

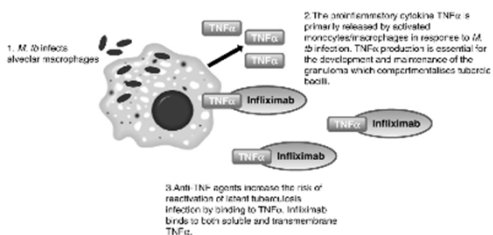


N Engl J Med 2005;353:2462-76.

Side Effects – Anti-TNF

- **Infusion reactions** (fever, headache, nausea, flushing, dyspnea, anaphylaxis)
- Serum sickness (myalgia, arthralgia, facial edema, urticaria)
- **Infection** – URTI, UTI, abscess
- **Re-activation of TB**
- CNS – optic neuritis, MS
- Malignancy – **lymphoma**, hepatosplenic T-cell lymphoma
- CHF – contraindicated in heart failure

Why we test for TB prior to starting anti-TNF



- Macrophages activated by TB need TNF- α which is needed to form granuloma and trap the TB bug and contain the infection

Anti-TNF Summary

- Anti-TNF therapy are useful for induction and maintenance of remission in both Crohn's Disease and UC
- No stopping rules
- Often used in combination therapy

Surgery in Ulcerative Colitis

- "Cure" for UC
- Indications:
 1. Refractory to medical therapy
 2. Toxic megacolon/fulminant
 3. Malignancy or dysplasia
 4. Patient preference



'AH - MUST BE MY OSTOMY SUPPLY

Goals of therapy

1. Induce and maintain remission
 - - Steroid-free remission
2. Prevent complications
3. Improve QOL
4. Avoid surgery
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Questions?????

What is Golimumab?

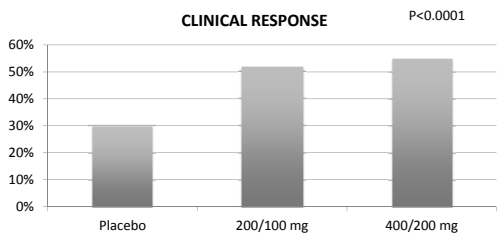
- IgG1 monoclonal antibody against TNF
- Subcutaneous administration
 - (also tested IV – data not published)
- AKA: CNTO 148
- Binds membrane bound and soluble TNF

Golimumab for UC

- INDUCTION (PURSUIT-SC)
 - Combined with Phase 2 dose-finding study 1064 pts
 - 4 dosing groups: 100/50, 200/100, 400/200, placebo
- P: 774 pts with mod-severe UC (Mayo 6-12, endo 2+)
- TNF-naïve
- I: 200/100, 400/200 at wks 0, 2
- C: placebo
- O: Wk 6 clinical response
 - 2ndary: clinical remission, mucosal healing, IBDQ

Gastro 2013; June E-pub

Golimumab - Induction



Gastro 2013; June E-pub

Golimumab Induction - 2ndary Outcomes

	Placebo N=256	200/100 N=257	400/200 N=258
Clinical Remission	6.3%	18.7% P<0.0001	17.8% P<0.0001
Mucosal Healing	28.5%	43.2% P=0.0005	45.3% P<0.0001
Change in IBDQ	14.6	27.4 P<0.0001	27.0 P<0.0001

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Golimumab for UC

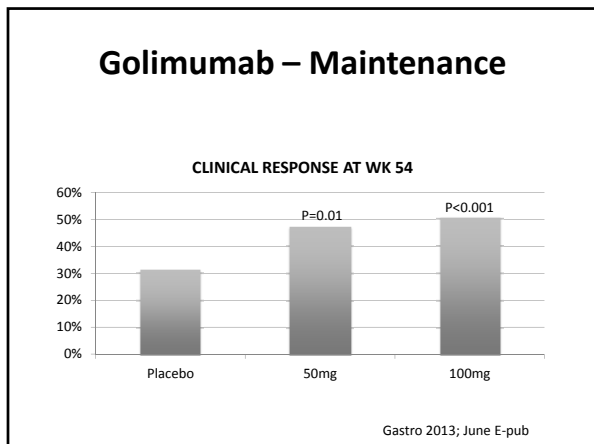
- MAINTENANCE
- P: 464 pts who responded to Induction Golimumab
- I: 50 or 100mg q4wks
- C: placebo
- O: Wk 54 clinical response
 - 2ndary: clinical remission, mucosal healing at wk 30 & 54

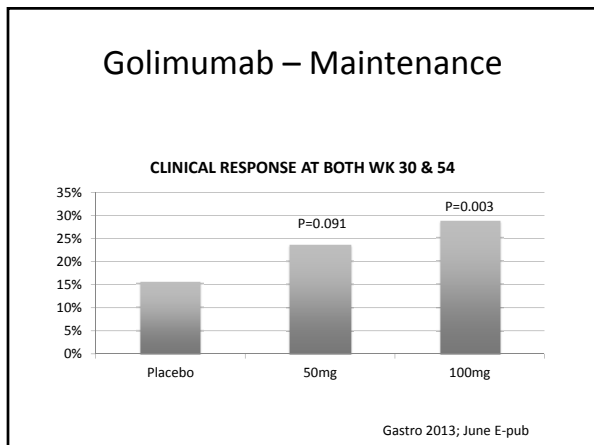
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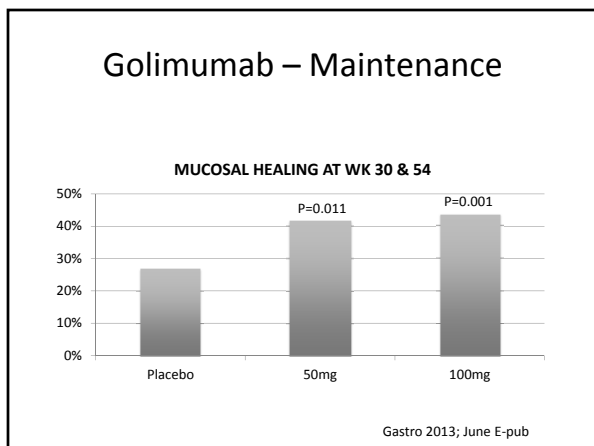
Golimumab for UC

- MAINTENANCE
- P: 464 pts who responded to Induction Golimumab
- I: 50 or 100mg q4wks
- C: placebo
- O: Wk 54 clinical response
 - 2ndary: clinical remission, mucosal healing at wk 30 & 54

Gastro 2013; June E-pub







Golimumab Maintenance - 2ndary Outcomes

	Placebo N=156	200/100 N=153	400/200 N=154
Clinical Remission at Wk 30	22.4%	35.9% P=0.009	40.9% P<0.001
Clinical Remission at Wk 54	22.4%	33.3% P=0.071	34.4% P=0.01
Steroid Use at Baseline	87	79	83
Steroid free at Wk 54	20.7%	38.0% P=0.031	31.3% P=0.112

Gastro 2013; June E-pub

Golimumab Maintenance – Adverse Reactions

- SAE: 7.7%, 8.4%, 14.3% (P, 50, 100)
- Serious infections: 1.9%, 3.2%, 3.2%
- 4 pts developed active TB
- 3 deaths: sepsis, TB, cardiac failure (all in 100mg group)

Gastro 2013; June E-pub

Golimumab Dosing

- **Ulcerative colitis:**
- **U.S. labeling: SubQ: Induction: 200 mg at week 0, then 100 mg at week 2, followed by maintenance therapy of 100 mg every 4 weeks**
- **Canadian labeling: SubQ: Induction: 200 mg at week 0, then 100 mg at week 2, followed by maintenance therapy of 50 mg every 4 weeks (maintenance dose may be increased to 100 mg every 4 weeks if needed)**

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