What's New in the Management of IBD?

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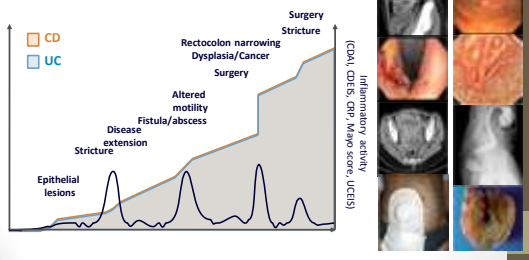
Disclosures

- Speaker's bureau – Abbvie, Janssen, Shire, Takeda
- Advisory Board – Abbvie, Janssen, Shire, Takeda

Objectives

- Review conventional IBD therapies
- Review of biological therapy
- Review of probiotic and alternative therapies

Crohn's disease (CD) and ulcerative colitis (UC) are progressive diseases



CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein; UCEIS, Ulcerative Colitis Endoscopic Index of Severity

Adapted from Pariente B *et al. Inflamm Bowel Dis* 2011 Jun;17(6):1415–22 and Torres J *et al. Inflamm Bowel Dis* 2012;18:1356–63

Paradigm shift

- Goals of therapy
  - Symptom improvement; response
  - Clinical remission
  - Endoscopic remission; mucosal healing
  - Complete remission

Therapeutic pyramid

5-ASA therapy is not effective management of Crohn's disease

- First line agents for UC
  - Effective induction and maintenance therapy
  - Favorable side-effect profile
- Cochrane reviews and metanalyses show 5-ASA is no better then placebo in CD

Immunomodulator therapy

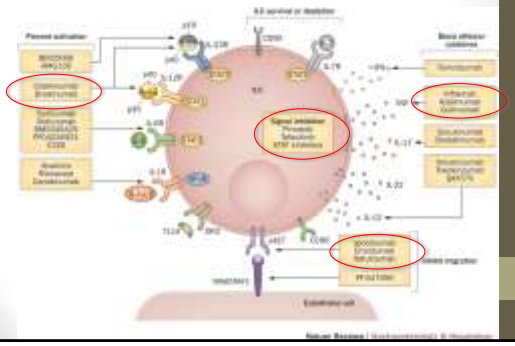
- Azathioprine/6MP
  - Frequently used in UC and CD
  - Shown to increase remission rates in patients on anti-TNF (combo therapy)
  - Now questionable benefit as monotherapy
  - Important potential adverse event profile
    - Pancreatitis, hepatitis, leukopenia
    - Lymphoma (Health Canada warning)

Canadian data support MTX in Crohn's disease

- Used in adult and pediatric CD (parenteral vs oral)
- Also used in combination with anti-TNF therapy
- Potential side-effects include: hepatitis, leukopenia, pneumonitis and nausea
- Teratogen
- No proven benefit in UC

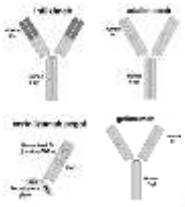
Feagan B NEMJ 1995

There are many biologic targets

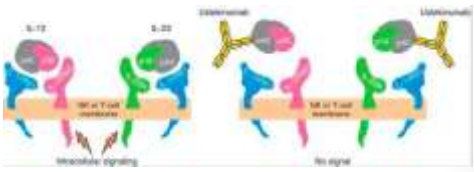


New and old biologic agents

- The anti-TNF agents
  - Infliximab, adalimumab and certolizumab pegol antibodies with affinity for tumor necrosis factor (TNF)
  - Effective in inducing an maintating remission in CD and UC
  - Effective in fistulizing CD and preventing postop recurrence



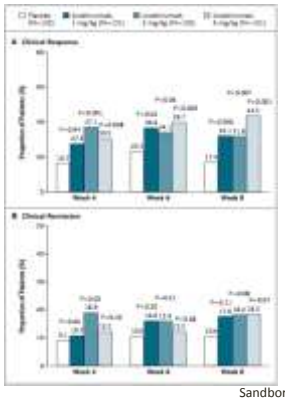
Ustekinemab is effective in antiTNF refractory CD



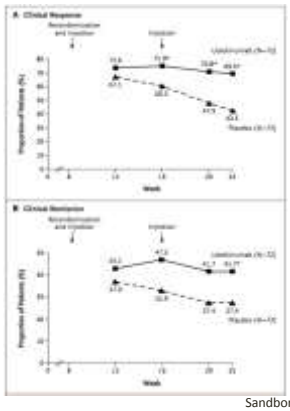
CERTIFI

- 526 patients with moderate to severe CD randomized to 3 different doses of ustekinemab vs placebo
- 1e endpoint – clinical response at 6 weeks
- Responders were re-randomized to ustekinemab vs placebo at 8 and 16 weeks and assessed at 22 weeks
- ALL patients were antiTNF experienced

Sandborn W NEJM 2012

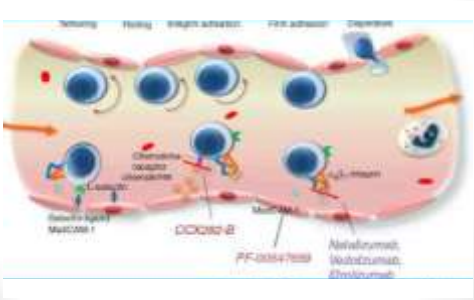


Sandborn W NEJM 2012



Sandborn W NEJM 2012

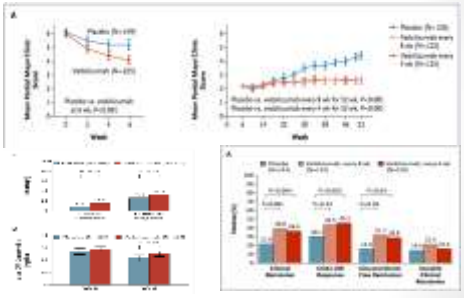
On a roll – the story of the ….lizumab's



Vedolizumab has been assessed in CD and UC

- Studied in medically experienced groups
  - High proportion of antiTNF non-responders
- GEMINI 1 – UC
  - 1e outcomes
    - Induction phase – clinical response at week 6
    - Maintenance phase – clinical remission at week 52
- GEMINI 2 –CD
  - 1e outcomes
    - Induction phase – clinical remission and CDAI 100 response at week 6
    - Maintenance phase – clinical remission at week 52

Vedolizumab is effective and safe in UC and CD



Sandborn NEJM 2013

Feagan NEJM 2013

Vedolizumab has few side effects

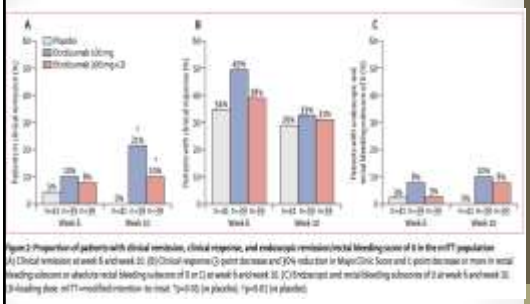
Table 2. Adverse Events Affecting at Least 5% of Patients Who Received Vedolizumab.*

Event	Placebo (N = 301)	Vedolizumab (N = 814)
	no. (%)	
Adverse event		
Crohn's disease exacerbation	65 (21.6)	164 (20.1)
Arthralgia	40 (13.3)	110 (13.5)
Pyrexia	40 (13.3)	103 (12.7)
Nasopharyngitis	24 (8.0)	100 (12.3)
Headache	47 (15.6)	97 (11.9)
Nausea	30 (10.0)	90 (11.1)
Abdominal pain	39 (13.0)	79 (9.7)
Upper respiratory tract infection	17 (5.6)	54 (6.6)
Fatigue	14 (4.7)	53 (6.5)
Vomiting	23 (7.6)	49 (6.0)
Back pain	12 (4.0)	38 (4.7)
Any serious adverse event	46 (15.3)	199 (24.4)
Any serious infection†	9 (3.0)	45 (5.5)
Any cancer‡	1 (0.3)	4 (0.5)

Etrolizumab promising anti-adhesion agent in some patients with moderate to severe UC

- DBPCT – 11 countries, 40 centres
- 124 patients randomized to either 2 different doses of SC etrolizumab or placebo for 8 weeks
- 1e endpoint clinical remission (Mayo score) at 10 weeks

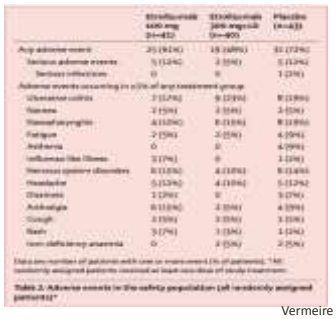
Vermeire S Lancet 2014



Sub-group analysis showed most benefit in alphaE + patients

Vermeire S Lancet 2014

Similar safety profile to placebo

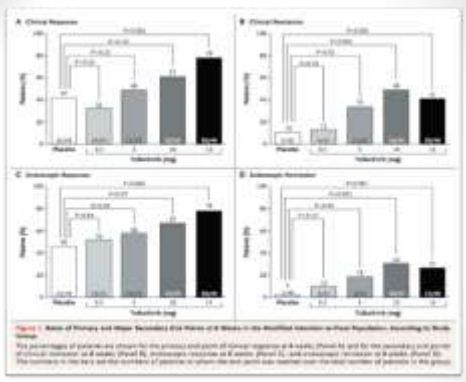


Vermeire S Lancet 2014

Tofacitinib

- Exciting oral agent
- Inhibits Janus family of kinases
  - Results in manipulation of cytokines and lymphocyte function
- Sandborn et al evaluated tofacitinib in moderate to severe UC
- 194 patients were randomized to three different drug doses or placebo
- 1e response – clinical response at 8 weeks

Sandborn NEJM 2012



Sandborn NEJM 2012

Safety profile

Sandborn NEJM 2012

Is marijuana effective in treating IBD?

- Marijuana use is common in the IBD population
- Patients report relief of GI symptoms and may request medical marijuana
  - Symptom relief or disease control?
- Some evidence to support potential anti-inflammatory mechanisms of action within the GI tract

Marijuana use is more common in individuals with IBD

- Allegretti et al found that current use was 12% and previous use was 39%
  - 16% of current or previous users, used marijuana to control symptoms and most stated that is was 'very helpful'
  - Those who had never used marijuana expressed an interest in using it if it were legally available

Allegretti Inflamm Bowel Dis 2013

Few studies assess THC in IBD

- Small (N=21) Israeli study
  - Patients were medically refractory to many others agents
- Randomized to 115 mg THC (cigarettes) BID vs placebo for 8 weeks
- 1e outcome was clinical remission (CDAI) at 8 weeks

Allegretti J Inflamm Bowel Dis 2013

Medically experienced group

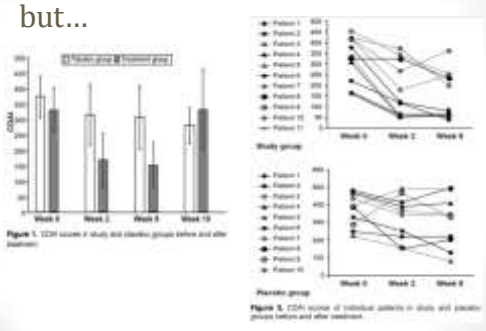
Table 2. Past and Current Medical Treatment:

Medication	Past medication, n (%)			Concomitant medication, n (%)		
	Study (N = 11)	Placebo (N = 10)	P value	Study (N = 11)	Placebo (N = 10)	P value
Mesalamine	11 (100)	10 (100)	NS	3 (27.3)	2 (20)	.7
Steroids	11 (100)	9 (90)	.4	4 (36) (3 steroid dependent)	2 (20) (1 steroid dependent)	.3
Purine analog	10 (90)	10 (100)	NS	3 (27)	6 (60)	.3
Methotrexate	3 (27)	1 (10)	.3	1 (9)	0	1
Anti-TNF-α	9 (82)	8 (80)	.7	1 (9)	4 (40)	.3

NS, not significant.

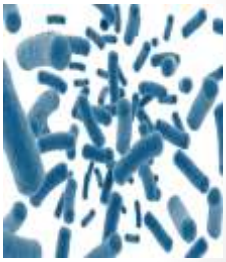
Allegretti J Inflamm Bowel Dis 2013

THC failed to induce remission but…



Allegretti J Inflamm Bowel Dis 2013

The new frontier – the microbiome



Mouse microbiota study

Many patients are very keen on probiotic therapy

- Data show that VSL#3 and Nissle 1917 are superior to placebo for maintenance remission in mild to moderate ulcerative
- VSL#3 is effective in preventing recurrent pouchitis
- No good evidence supporting probiotic use in inducing remission or in Crohn's disease

Matsuoka Seminol Immunopathol 2015

FMT in IBD – the process

- Variable
  - Donor selection - healthy family/household member vs study specified donors vs "poop bank"
  - Donor screening – enteric pathogens, HIV, viral hepatitis, syphilis, HTLV I/II, VRE and MRSA, no recent Abx exposure
  - Graft preparation – fresh vs frozen, whole stool slurry vs supernatant
  - Mode of delivery – NG tube vs colonoscopy/sigmoidoscopy vs enema

Canada wins the race to RCT data in FMT for management of ulcerative colitis!

- Moayyedi et al assessed FMT's effect on UC disease activity
- Mayo > 3 (endo Mayo >0)
- DBRCT - 50 cc FMT or 50 cc water retention enemas weekly for 6 weeks (partly blinded)
- Evaluated at baseline and 7 weeks assessment post intervention
  - Mayo score, IBDQ and sigmoidoscopy (baseline and exit)
  - CBC, CRP, ESR
  - Stool for microbiota assessment
- 1e outcome – remission (Mayo <3 and complete mucosal healing)
- 2 e outcomes – improvement , IBDQ

Moayyedi Gastro 2015

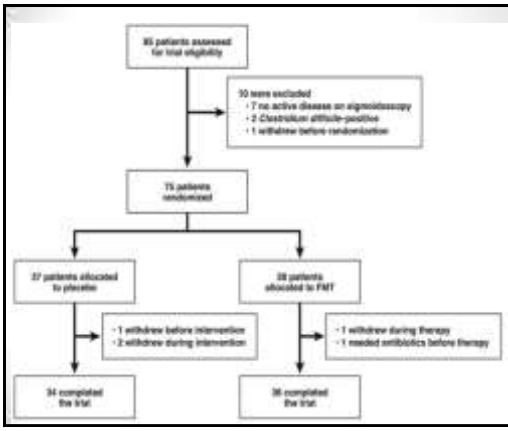


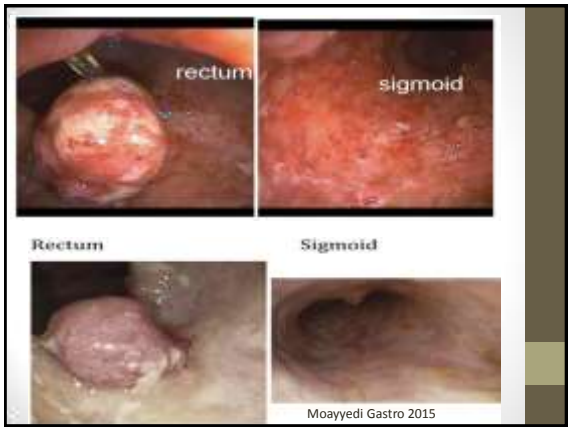
Table 1. Baseline Characteristics of Patients in the Trial

Variable (denominator: placebo or FMT)	Placebo (n = 37)	FMT (n = 38)
Age, y (37, 38)	35.8 ± 12.1	42.2 ± 15.0*
Male sex, n (%) (37, 38)	26 (70)	18 (47)*
White race, n (%) (37, 38)	29 (78)	36 (95)
Nonsmoker, n (%) (37, 38)	21 (57)	19 (50)
UC <1 year, n (%) (37, 38)	4 (11)	4 (11)
Pancolitis, n (%) (30, 36)	12 (37.5)	20 (62.5)
Concomitant medications, n (%)		
Mesalamine therapy (37, 38)	20 (54)	21 (55)
Glucocorticoids (37, 38)	13 (35)	15 (39)
Immunosuppressants (37, 38)	6 (16)	11 (29)
Anti-TNF therapy (37, 38)	2 (5)	5 (13)
Years had UC (37, 38)	7.0 ± 6.6	7.9 ± 5.6
Hemoglobin concentration, g/L (37, 37)	128.8 ± 22.4	129.3 ± 17.3
White cell count, $\times 10^9$/L (37, 37)	8.8 ± 2.8	8.0 ± 2.5
ESR, *mm/h* (27, 26)	21.1 ± 16.3	18.9 ± 15.6
CRP, *mg/L* (27, 26)	7.2 ± 7.7	10.6 ± 16.6
High ESR, n (%) (27, 26)	14 (52)	8 (31)
High CRP, n (%) (27, 26)	13 (48)	11 (42)
Full Mayo Clinic score (37, 38)	7.86 ± 2.28	8.24 ± 2.61
IBDQ score (37, 37)	134.4 ± 32.3	130.3 ± 36.3
EQ-5D score (37, 36)	78.2 ± 15.4	75.7 ± 20.4

Table 2. Outcome Measures Comparing Fecal Microbial Transplantation With Placebo

Outcome	Placebo (n = 37)	FMT (n = 38)	*P* value
Clinical remission,[a] n (%)	2 (5)	9 (24)	.03
Clinical response,[b] n (%)	9 (24)	15 (39)	.16
Full Mayo score	6.34	6.09	.42
IBDQ score	149.38	152.13	.44
EQ-5D score	70.07	68.52	.99
CRP, *mg/L* (n = 17 placebo, n = 15 FMT)	3.3 ± 3.4	4.9 ± 5.9	.38
ESR, *mm/h* (n = 17 placebo, n = 15 FMT)	13.1 ± 11.2	15.9 ± 17.0	.59
Proportion with high ESR, n (%)	4 (24)	3 (20)	1.0
Proportion with high CRP, n (%)	5 (29)	2 (13)	.40
Patients with serious adverse events n (%)	2[c] (5)	3[d] (8)	1.0

Moayyedi Gastro 2015

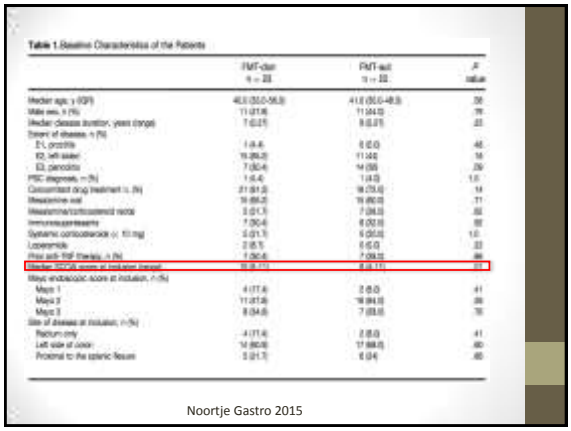


Moayyedi Gastro 2015

A Dutch study shows a contrary outcome

- DBRCT of mild to moderate UC patients
- Exclusion criteria included recent antiTNF or MTX use
- Intervention: FMT(D) or FMT(A) at week 0 and week 3
- 1e outcome: clinical remission (SCCAI) and endoscopic Mayo score improvement at week 12

Noortje Gastro 2015



Noortje Gastro 2015

FMT failed to induce remission at week 12

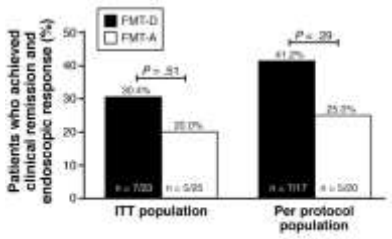


Figure 2. Proportion of patients who achieved the primary end point at 12 weeks after treatment. FMT-D, FMT donor feces; FMT-A, FMT autologous; ITT, intention-to-treat.

Noortje Gastro 2015

Fecal microbiota transplant for IBD needs fine tuning

- Small studies with variable results but
  - Promising and likely effective option
- Need to optimize the process, delivery of FMT
  - Identification of optimal donor/recipient
  - Mode of delivery
  - How do we prolong engraftment?

Summary

- Many emerging therapies for IBD
  - Most promising are biologics with novel mechanisms of action
  - Manipulation of microbiome may revolutionize IBD management and offer a parallel treatments to pharmaceutical agents
    - FMT not currently recommended for IBD management outside of a clinical trial
  - Jury is still out on the benefit of marijuana in IBD
    - Seems to mediate symptoms but doe sit decrease GI tract inflammation?

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