What’s New in the Management of IBD?

Dr. Chadwick Williams
Assistant Professor, Dalhousie University and Memorial University of Newfoundland
CSGNA 2015 – Moncton, NB

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

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 than 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

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 and maintaining remission in CD and UC
  - Effective in fistulizing CD and preventing postop recurrence

Ustekinumab is effective in anti-TNF refractory CD
CERTIFI

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

Sandborn W NEJM 2012

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

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

Sandborn W NEJM 2012

Sandborn W NEJM 2012

Sandborn W NEJM 2012
Vedolizumab has few side effects

Etrolizumab promoting 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

Similar safety profile to placebo

Sandborn NEJM 2012

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
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 it was ‘very helpful’
  - Those who had never used marijuana expressed an interest in using it if it were legally available

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

Medically experienced group

THC failed to induce remission but...
The new frontier – the microbiome

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

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, HSV 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

Mouse microbiota study

Matsuoka Seminol Immunopathol 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

FMT failed to induce remission at week 12
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 does sit decrease GI tract inflammation?

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