Alternative Therapies in IBD: What do we know

Palo Alto Patient and Family Education Symposium

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# Alternative therapies in IBD

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Definition of Alternative Medicine?

- Precise definition elusive...and dynamic
- National Center for Complementary and Alternative Medicine
  - Diverse medical and healthcare systems, practices, and products not considered as conventional medicine

References
1. Hilsden RJ et al. Use of Complementary and Alternative Medicine by Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2011; 17: 655-662
Patients seek alternative therapies for many reasons:

- Because we haven’t cured IBD yet!
- Existing therapies are not working
- Fear of side effects of current therapies
- “they make sense”
- Internet hype and misinformation
Acupuncture and Moxibustion

Moxibustion: the application of heat to the acupuncture points through burning of small bundle of tightly bound herbs (moxa)
Acupuncture and Moxibustion
Single-centre single blind randomized controlled trial

Ulcereative Colitis

- 29 Patients
  - 18-65 yo
  - >2 y hx of UC
  - Mild to mod dis (CAI 4-10)
  - Stable Con meds for 4wks and stable throughout trial

10 Acu/Mox sessions over 5 weeks
N=15

10 Sham sessions over 5 weeks
N=14

1<sup>st</sup> endpoint: change in CAI at 5 weeks

Joos et al Scand J of Gastro 2006; 41:1056-1063
Results

• Small differences in outcome (moxa/acupuncture vs sham acupuncture)
  – CAI: 8→4.2 vs 6.5→4.8 (p=0.048)
• Both groups improved general well-being and quality of life (no difference between groups)
• Both traditional and sham offer benefit
Acupuncture and Moxibustion
Single-centre single blind randomized controlled trial

Crohn’s Disease

51 Patients

10 Acu/Mox sessions over 4 weeks
N=27

10 Sham sessions over 4 weeks
N=24

1° endpoint: change in CDAI

• 18-65 yo
• >1 y hx of CD
• Mild to mod dis CDAI 150-350
• Prednisone allowed at <15mg/d, stable for 4 wks
• Stable 5-ASA allowed
• No AZA/6-MP/MTX allowed

Joos et al Digestion 2004, 69(3): 131-9
Results

• Both groups improved but moxa/acupuncture group more
  – CDAI: 250 → 163 vs 220 → 181 (p=0.003)
• Both groups improved general well-being and quality of life
• Both traditional and sham offer benefit, but moxa/acupuncture more
Aloe Vera Gel

- Has been used as a medicinal ingredient for over 5000 years
- Purported to have a number of biologically active compounds
- One of the most commonly used natural remedies by patients with IBD
Aloe Vera Gel

Single-centre single blind randomized controlled trial

Ulcerative Colitis

44 Patients

- 18-80 yo
- >2 y hx of UC
- Mild to mod dis (SCCAI ≥3)
- Stable Con meds for 4wks and stable throughout trial
- If on AZA/6-MP, stable for 3mo
- No topical therapy

100 ml Aloe Vera Gel BID for 4 weeks
N=30

100 ml Placebo BID for 4 weeks
N=14

1° endpoint: remission (SCCAI) at 4wks

Results

• Clinical remission: 30% vs 7% (p=0.09)
• Clinical response: 47% vs 14% (p<0.05)
• Histological scores improved with aloe vera but not placebo (p=0.03)
• Sigmoidoscopy scores no different
• Conclusion: mixed results but promising. Needs more study
Wormwood for Steroid Sparing in Crohn’s Disease

Contains a number of active ingredients
Absinthin
Anabsin
Anabsinthin

Known anti-HSV, VZV, EBV, HHV, CMV properties

Induces production of interferon

Artemisia absinthium

¹Omer et al, Phytomedicine 2007; 14:87-95
Wormwood for Steroid Sparing in Crohn’s Disease

Multi-centre double blind randomized placebo controlled trial

40 Patients

• 18-80 y
• CDAI > 170
• Stable 5-ASA for 4 weeks
• On prednisone 40mg or less for 3 weeks
• Stable AZA/6-MP/MTX allowed
• Infliximab treated pts excluded

Wormwood capsules 500mg TID
N=20

Placebo capsules 500mg TID
N=20

1° endpoint: steroid dose, CDAI at 10 weeks and after follow up

Omer et al Phytomedicine 2007; 14: 87-95
Clinical Response to Wormwood

CDAI

Placebo
Wormwood

(n=20)

(n=20)

P=0.01*

*proportion with 70 pt dec. in CDAI

Week
-2
2
6
10
16
20

Tapering of steroids
Resume steroids in exacerbation
Baseline
Double blind treatment
Follow up observation period

Omer et al. Phytomedicine 2007; 14: 87-95
Comments

- Lack of statistical comparisons
- Mechanism of action unclear
- Prolonged steroid sparing after cessation
- Improvement in CDAI and IBDQ
- ?Something there
- Needs and warrants further study
Curcumin

- Found in South Asian spice tumeric
- Potential anti-inflammatory effect
- Most clinical studies in a variety of disease states have been negative
Curcumin Maintenance Study in Ulcerative Colitis

Multi-centre double blind randomized controlled trial for quiescent UC

89 Patients

• 13-65 yo
• Quiescent disease (CAI ≤4)
• On no steroids at baseline
• No AZA/6-MP/CSA allowed

Curcumin 1g po BID + 5-ASA

N=45

Placebo 1g po BID + 5-ASA

N=44

1º endpoint: CAI and EI at 6 mo and post-follow up

5-ASA = 1.0-3.0g/d SZ or 1.5-3.0g/d mesalamine

Hanai et al Clin Gastro Hep 2006; 4:1502-1506
Curcumin in Ulcerative Colitis

Relapse = CAI ≥5, 7 protocol violators

Hanai et al Clin Gastro Hep 2006; 4: 1502-1506
What is FMT?

• Acquisition of fecal material from a healthy donor
• Preparation of diluent
• Delivery to recipient
  – N-G
  – Colonoscopy
  – Enema
  – Pill form (desiccant)
Fecal Microbiota Transplantation (FMT) in IBD patients

- Some promising case reports and case series in UC
- No controlled trials
- Heterogeneity of patient types and severity
- Variable outcomes
- Limited post-transplant assessment of microbiome
- 2 Categories of FMT studies in IBD patients:
  - FMT as primary therapy for IBD
  - FMT as therapy for Clostridium difficile infection in IBD patients
Efficacy of FMT in IBD

• No controlled trials
• Several case reports with high free disease activity rate post-FMT of 63% (up to 2012). \(^1\)
• 7 reported cohort studies (6/7 reported in 2013).
• Clinical remission rate of case studies + cohort studies: 54\% \(^2\)

• Meta-analysis of these 7 cohort studies demonstrates only an overall pooled estimate of 32\% (95\%CI 11\%-64\%). \(^2\)
  – Only 3 studies reported patients that achieved clinical remission.
  – 2 of the 3 studies included peds population (age 7-20).

\(^2\)Colman RJ and Rubin DT *Submitted.*
Safety of FMT in Inflammatory Bowel Disease

• Some safety concerns remain
  – Common to have transient fever and some non-specific GI symptoms after FMT
  – Reports of worsening IBD after FMT\(^1,2\)
  – Lack of efficacy is a safety concern
  – Other safety outcomes have been described in non-IBD: new immune conditions (ITP, RA, peripheral neuropathy, Sjogrens)\(^3\)

• Unknown consequences of patients doing this at home

IND through FDA Center for Biologic Evaluation & Research required in order to perform FMT in IBD

Current sponsors:
  David Rubin, University of Chicago (UC)
  Alan Moss, Beth Israel-Deaconess in Boston (CD)

Why Parasites Might be the Answer (or just the question)

Autoimmune disorders incidence

Countries with low rates of helminthic infections: have high autoimmune disease rates

Helminthes infestation incidence
Trichuris suis ova (worm eggs)
2 RCTs of Trichuris suis ova for IBD

Safety and Tolerability of Trichuris ova in CD\(^1\)

Results:
- 36 patients (2 to 6 mo F/U)

Adverse events:
- GI symptoms: 7 (25.9%) in ova vs 3 (33.3%) in placebo group.
- No dose dependent relationship.
- No clinically meaningful changes in GI signs and symptoms.

Trichuris suis therapy for active UC\(^2\)

Results:
- 54 pts (12 wk Tx)

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<th>TSO (n=30)</th>
<th>Placebo (n=24)</th>
<th>P-value</th>
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<tr>
<td>Clinical response (↓UCDAI ≥ 4)</td>
<td>43% (13/30)</td>
<td>16.7% (4/24)</td>
<td>0.04</td>
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Ongoing Study

• Phase II – RCT of Suis Ova Treatment in left-sided UC and its effects on Mucosal Immune State and Microbiota (NCT01953354)

Treatment arms:
• 7500 Trichuris suis ova every 2 weeks for 10 weeks versus placebo
Cannabis
Mechanism of Cannabinoid Derivatives in IBD

- Unknown
- Appetite stimulant
- Bowel relaxant/anticholinergic
- No evidence that it is anti-inflammatory

Cannabidiol (CBD) No More Effective Than Placebo Active Crohn’s Disease

- CBD one of 60 active substances in cannabis and thought to have greater scope medical applications than THC
- Evaluated 20 patients CDAI > 200
  - No prior marijuana use (per history)
- CBD 10mg BID vs. Placebo x 8 weeks
- No change vs placebo for CDAI
  - CBD 337 +/- 108 → 220 +/- 112
  - Placebo 308 +/- 96 → 216 +/- 121
  - Hemoglobin, albumin, kidney/liver function remained unchanged
- Cannabidiol does not produce psychotropic effect
- Cannabidiol does not seem to be effective compared to placebo in this small study
  - Dose?

Controlled Trial of THC in Crohn’s Disease

- Inclusion: IBD patients with CDAI>200 refractory to steroids, IMM or anti-TNFs.
- RCT of Δ9-tetrahydrocannabinol (THC) Cigarettes with 115mg THC vs no THC
- Primary endpoint complete remission

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<th>THC (n=11)</th>
<th>Placebo (n=10)</th>
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<tr>
<td>Clinical remission</td>
<td>45% (5/11)</td>
<td>10% (1/10)</td>
<td>0.43</td>
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<tr>
<td>Clinical response</td>
<td>90% (10/11)</td>
<td>40% (4/10)</td>
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CAM Therapy in IBD

“First Principles”

• First, do no harm;
• Ensure no opportunity cost (i.e., do not delay treating a serious illness for which there is known effective therapy);
• If the CAM therapy carries little risk of harm, then consider its use and follow the patient closely;
• If the CAM therapy carries serious risk of harm, advise the patient accordingly and follow the patient closely;
• Where possible, it is recommended to try to follow an evidence-based rationale for therapy; and
• Where the evidence is lacking, try to maintain an open mind and a balanced approach.

References