Intestinal Helminths

A New Approach to Therapy of Inflammatory Bowel Disease

Douglas R. LaBrecque, MD
Professor, Internal Medicine
Director, Liver Service
Univ. of Iowa Carver College of Medicine
Zach Johnson---Masters Champion
New Color Commentator for U. Colorado Football Team
What is IBD?

- Chronic inflammation of the digestive tract
- The cause is unknown, but is largely due to an abnormal immune system
- Inflammation causes dysfunction of the bowel
- Treatment is generally aimed at suppressing the immune system and reducing inflammation
All Treatments Have Problems

- 5-aminosalicylates – not very effective
- Corticosteroids – Wt. gain, osteoporosis, psychologic effects, fluid retention, acne
- Azathioprine/6-MP – susceptible to infections
- Infliximab – loses efficacy with time, high cost
- Cyclosporine / tacrolimus – seizures, renal failure, hypertension
- Methotrexate – liver injury, infections
- Mycophenolate mofetil – diarrhea, infections
A New Approach is Needed

First, what about the cause?
What goes wrong in IBD?

Environmental triggers (infection, bacterial products)

Failure to down-regulate

Chronic uncontrolled inflammation = IBD

Down-regulate

Normal gut controlled inflammation
Environmental triggers (infection, bacterial products)

Moderate inflammation

Normal gut controlled inflammation
Environmental triggers (infection, bacterial products) → Moderately inflamed

Down-regulate

Normal gut controlled inflammation

Normal gut controlled inflammation
Environmental triggers (infection, bacterial products)

Failure to down-regulate

Chronic uncontrolled inflammation = IBD

Down-regulate

Moderately inflamed

Normal gut controlled inflammation

Normal gut controlled inflammation
What Causes IBD?

Genes (Family trait) or Environment (External influence)
Evidence for a Genetic Influence

- Family clustering: sibs : parents : off-spring
  Empiric risk - 9% : 4% : 9%
- MZ Twin concordance – CD~50%, UC~15%
- Spouse studies: = to population, < <siblings
- Genetic markers
  - HLA subtype markers
  - CARD 15 (NOD 2)
  - Other candidate genes
Global Prevalence of IBD
Environmental Influence?

Helminthic Parasites

- **Red**: High Incidence
- **Yellow**: Moderate Incidence
- **Light Blue**: Low Incidence
Rise in Crohn’s Disease Over Time
Emergence of Immune-Mediated Diseases

(adapted from Bach, N.E.J.M. 347:911)
Our Hypothesis

- Immune mediated disease occurs in genetically predisposed persons IF they are not exposed to helminths.
- Helminths help to tame an overactive, misdirected and destructive response to environmental influences.
Are all worms bad?
“Worms are our friends”
Where Have All the Good Worms Gone?
Colonization common in the 30’s
U.S. Hookworm Eradication
First National Public Health Intervention

Rockefeller Foundation
1909 - 1915

US PHS
1915-1940s
U.S. Helminth Eradication

WPA Flyer
Distributed 1936-1941
Reported Cases of Trichinellosis in US

(MMWR 53:1-79, 2006)
Our Lifestyle Has Changed
Hygiene Has a High Priority

ONLY IN TEXAS!
Things Are Different in Some Parts of the World
Sometimes Very Different
Children Raised Differently
Environment vs. Genes

Etiologic Interplay

Nature vs. Nurture

Genes vs. Environment

IBD

Eradication of Helminths
Supportive experimental evidence
Using Helminths to Treat IBD

From Bench to Bedside
Which Worm?
Helminths

🌟 Nematodes (round worms)
- Trichuris trichiura (whipworm)
- Enterobius vermicularis (pinworm)
- Necator americanus (hookworm)
- Ascaris lumbricoides

🌟 Platyhelminths (flat worms)
- Trematodes (flukes)
  - Schistosoma (venous system)
  - Clonorchis (biliary system)
  - Fasciolopsis (intestine)
- Cestodes (tapeworms)
  - Taenia saginata / solium
  - Hymenolepsis nana
The Ideal Worm Egg

- Should not persist or multiply in the host
- Should not invade or cause disease
- Should not be a public health risk
- Should be stable and easy to produce
Meet *Trichuris suis*
Trichuris suis life cycle

1. Ingestion
   Infective ova

2. Larvae released

3. Mucosal attachment

4. Maturation

5. Egg excretion (Non-infective)

6. Embryonation in soil
Trichuris suis
(Porcine whipworm)

- Colonization is self-limited
- Does not multiply in host
- No systemic phase
- No direct transmission
- Eggs stable and easy to produce
Trichuris suis Ova Therapy in Active Ulcerative Colitis

Response (↓ UCDAI ≥ 4)

### Intention-to-treat

- Placebo: 16.7%
- T. suis: 43.3%
- p = 0.04

### Per-protocol

- Placebo: 17.4%
- T. suis: 44.8%
- p = 0.04
Ulcerative colitis

Pre-treatment

Post-treatment
Change in Mean UCDAI

~Responders:

  Initial       8.8 ± 0.4
  Week 12       2.8 ± 0.4
                   Δ 6.0 ± 0.6

~No side effects, complications or lab changes
Time to Response

Composite score

Bleeding (0-3)
Stool frequency (0-3)

P<0.0001
Trichuris suis Ova Therapy

in

Active Crohn’s Disease

CD Open-Label Study

Administered 2500 *T. suis* ova every 3 weeks
Remission/Response Rates

- **Response (CDAI >100)**
- **Remission (CDAI <150)**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Week</td>
<td>62.1</td>
</tr>
<tr>
<td>24 Week</td>
<td>72.4</td>
</tr>
</tbody>
</table>

CDAI: Crohn's Disease Activity Index
*Trichuris suis* in the Human Colon
Change in Mean CDAI
-Responders-

<table>
<thead>
<tr>
<th>Week</th>
<th>Crohn's Disease Activity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>(286 ± 10)</td>
</tr>
<tr>
<td>12 Week</td>
<td>(117 ± 13)</td>
</tr>
<tr>
<td>24 Week</td>
<td>(109 ± 12)</td>
</tr>
</tbody>
</table>
Overall Summary

~ Studied effects of *Trichuris suis*: 54 UC and 29 CD
~ In UC, *T. suis* superior to placebo
~ In CD, 72% remission rate, 79% response rate
~ No side effects or complications

**Conclusion**

*T. suis* is safe and effective in IBD
So, *T. suis* off to work

Incidently
We give eggs, not worms
Hygiene Hypothesis
(The Restated Worm Version)

Helminth Exposure

Immune Regulatory Conditioning

Prevents Excessive Inflammation

Common Viral, Bacterial and Protozoan Infections

Modern Hygiene Lacks Helminths

Permits Immune Dysregulation

Emergence of IBD and other Immune-mediated Diseases
Home of the Helminths
Collaborators

**University of Iowa**
- David Elliott
- Joel Kline
- Robert Summers
- Joel Weinstock
- Robin Thompson
- Betty Musgrave
- Dan Berg
- Art Blum
- Ahmed Metwali
- Tommy Setiawan
- Bushra Sulieman
- Andy Arsenescu
- Nedim Ince

**USDA, Maryland**
- Joseph Urban

**University of Wisconsin**
- Zsuzsa Fabry
- Matyas Sandor
- John Fleming

**Royal Institute, Denmark**
- Darwin Murrel
- Allan Roepsdtorff
Who knows what the future holds