Does Medical Therapy for Crohn’s Help to Avoid Anorectal Surgery?

Andrew A. Shelton, MD, FACS, FASCRS
Clinical Professor of Surgery
Stanford University Department of Surgery
Division of General Surgery
Section of Colon & Rectal Surgery

Perianal Crohn’s Disease

- Skin tags
- Hemorrhoids
- Fissures
- Ulcers
- Stenosis/stricture
- Abscess
- Fistula
Perianal Crohn’s Disease

Crohn’s Disease — Incidence of Fistulas

Fistulas in Crohn’s Disease

Anal Fistulas — Classification

Schwartz DA, Gastroenterology, 2002
Anal Fistulas — Classification

Subcutaneous
“Simple”

Intersphincteric
“Complex”

Trans sphincteric
“Complex”

Supra sphincteric
“Complex”
**Anal Fistulas — Classification**

Extra sphincteric “Complex”

---

**IBD — Medical Management and Treatment Goals**

- Induce rapid response
- Maintain remission without steroids
- Achieve and maintain complete mucosal healing
- Avoid complications, hospitalizations and minimize extent of any required surgery
- Prevent disease related mortality
- Improve quality of life

---

**IBD — Medical Treatment Options**

**Anti-inflammatories**
- 5-ASA
- Sulfasalazine
- Steroids

**Immunomodulators**
- 6-mercaptopurine/Azathioprine
- Methotrexate

**Biologics**
- Infliximab
- Adalimumab
- Certolizumab
- Golimumab
- Natalizumab
Antibiotics for Perianal Disease

- Metronidazole (Flagyl)
- Ciprofloxacin (Cipro)
- Rifaximin

Recurrence when Abx stopped

Immunomodulators for Perianal Disease

- 6-Mercaptopurine (“6-MP”)
- Purinethol®
- Azathioprine (Imuran®)
- Methotrexate (Trexall®)
- Cyclacosphorine (Sandimmune®)

83% Success
50% Success

IBD — Biologics

- Anti-TNFα
  - Infliximab
  - Adalimumab
  - Certolizumab
  - Golimumab
- Anti-Adhesion
  - Natalizumab

Pearson DC, Ann Internal Med, 1995

**Decreased drainage or complete healing**
**IBD — Biologics**

Monoclonal Antibodies, Fusion Proteins and Fc-Free Fab’ Fragments Against TNFα

- Chimeric monoclonal antibody
- Human monoclonal antibody
- Human recombinant receptor/Fc fusion protein
- Humanized Fc-Free Fab’ fragment

**IBD — TNF Inhibitors**

- TNFα (inflammatory mediator)-increased in serum and mucosa, gut lumen in IBD patients
- These agents antibodies against TNFα
- Side Effects: Infusion or injection site reaction, delayed reaction, infection, hep B reactivation, worsens heart failure, lupus-like reaction, formation of antibodies to drug (infliximab), hepatotoxicity, hematologic events, neurologic event, malignancy

**The New England Journal of Medicine**

INFLIXIMAB FOR THE TREATMENT OF FISTULAS IN PATIENTS WITH CROHN’S DISEASE


Present et al, NEJM, 1999
“The primary endpoint was based on the investigators physical evaluation of the patient; a fistula was considered closed when it no longer drained despite gentle finger compression…”

Present et al, NEJM, 1999

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>5mg/kg</th>
<th>10 mg/kg</th>
<th>5 or 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>26.00%</td>
<td>68%</td>
<td>56%</td>
<td>62%</td>
</tr>
<tr>
<td>(p=0.002)</td>
<td>(p=0.02)</td>
<td>(p=0.002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>13.00%</td>
<td>55%</td>
<td>38%</td>
<td>46%</td>
</tr>
<tr>
<td>(p=0.001)</td>
<td>(p=0.04)</td>
<td>(p=0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to response</td>
<td>42 days</td>
<td>14 days</td>
<td>14 days</td>
<td>14 days</td>
</tr>
<tr>
<td>Duration</td>
<td>86 days</td>
<td>84 days</td>
<td>99 days</td>
<td>86 days</td>
</tr>
</tbody>
</table>

Present et al, NEJM, 1999

% Patients with complete closure of all fistulas

Present et al, NEJM, 1999

Median Duration of Fistula Closure (Weeks)

Present et al, NEJM, 1999
**Maintenance infliximab (ACCENT II)**

**RESPONSE = 50% REDUCTION IN DRAINING FISTULAS**

- 196 Patients enrolled and given 1 mg of infliximab/kg at weeks 0, 2, and 6
- 24 Excluded: 9 for adverse events, 6 for withdrawal consent, 6 for lack of efficacy, 3 for noncompliance
- 283 Assessed for response and underwent randomization at week 16
- 195 Had a response
- 87 Had no response
- 46 Assigned to infliximab (0 mg/kg) maintenance
- 59 Assigned to placebo maintenance
- 45 Assigned to infliximab (5 mg/kg) maintenance
- 44 Assigned to placebo maintenance
- 282 Included in safety analysis through week 54

**Figure 1. Enrollment and Treatment of Patients.**

Sands et al, NEJM, 2004

---

**IBD — Maintenance infliximab (ACCENT II)**

**ACCENT II — NEED FOR SURGERY?**

<table>
<thead>
<tr>
<th></th>
<th>All Randomized</th>
<th>Randomized as Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo 143</td>
<td>Infliximab 139</td>
</tr>
<tr>
<td></td>
<td>Placebo 99</td>
<td>Infliximab 96</td>
</tr>
<tr>
<td>All OR</td>
<td>118 (169)</td>
<td>60 (83) p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>126 (125)</td>
<td>65 (62) p&lt;0.05</td>
</tr>
<tr>
<td>Inpatient OR</td>
<td>45 (65)</td>
<td>10 (14) p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>41 (41)</td>
<td>7 (7) p&lt;0.01</td>
</tr>
<tr>
<td>Major OR</td>
<td>13 (18)</td>
<td>2 (3) p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>11 (11)</td>
<td>2 (2) p&lt;0.05</td>
</tr>
</tbody>
</table>

Lichtenstein, Gastroenterology, 2005

---

**IBD — Maintenance infliximab (ACCENT II)**

**A**

- Patients with Response (%)
- 100
- 50
- 25
- 12
- 6
- 3
- 2
- 1
- 0

Week

- P<0.001

Sands et al, NEJM, 2004

---

**B**

- Patients with Complete Response (%)
- 100
- 60
- 40
- 20
- 10
- 5
- 2
- 1
- 0

Week

- P=0.002
- P=0.009

Sands et al, NEJM, 2004

Saturday, March 8, 2014
**ACCENT II — NEED FOR SURGERY?**

Lichtenstein, Gastroenterology, 2005

**Surgery for Fistulas in Crohn’s Disease**

Jones, Annals of Surgery, 2010

**Rectal Resection for Crohn’s Disease**

Jones, Annals of Surgery, 2010

**Incision and drainage of abscess in Crohn’s Disease**

Jones, Annals of Surgery, 2010

---

3X INCREASE

p=0.03
Infliximab and Need for Surgery

% patients with complete response vs need for surgery after treatment with infliximab

- Complete Response
- Surgical Treatment
- Persistent fistula

Poritz, DCR, 2002

Perianal Crohn’s Disease

Multidisciplinary Approach

Regueiro, Inflammatory Bowel Disease, 2003

Mean Time to Recurrence (Months)

Regueiro, Inflammatory Bowel Disease, 2003
Multidisciplinary Approach

Sagar P, Colorectal Disease, 2011

Fistula Response %

Complete (n=22) | Partial (n=23) | None (n=7) | Total (n=52)
---|---|---|---
Number of infusions | 12.5 | 16.0 | 3.0 | 12.0
Follow up (Months) | 40.0 | 41.0 | 17.0 | 36.0
Time to relapse | 21.0 | 14.0 | NA | 13.0
% having surgery | 22.700% | 65.000% | 57.000% | 46.000%

Multidisciplinary Approach

Sagar P, Colorectal Disease, 2011

Need for Proctectomy and Biologics

Topstad, DCR, 2003

Perianal Fistula (n=21) | RVF (n=8)
---|---
Complete Response | Partial Response | No response
---|---|---
Prebiologic Era | Biolgic Era
Permanent Ileostomy | Ileorectal
60.8 | 19.2 | 39.2 | 80.8

Coscia, Colorectal Disease, 2013
Infliximab for Nonfistulizing Perianal Disease

Does Medical Therapy for Crohn’s Help to Avoid Anorectal Surgery?
Congenital Anorectal Disorders

Lan Vu, MD
Assistant Professor of Surgery
Division of Pediatric Surgery
University of California, San Francisco

I have nothing to disclose

Anorectal malformation

Epidemiology:
1 in 5,000 live births
More common in Asians, boys >> girls

Associated Birth Defects:
Vertebral anomalies: tethered cord
Anorectal malformation
Cardiac defects
Tracheoesophageal fistula or esophageal atresia
Renal anomalies
Limb anomalies: missing radial bone
Key points for colostomy:

1. At the level of descending colon: allow for enough length for future pull-through procedure
2. Double barrel stomas: prevent stool spillage into the blind-ending rectum or into urinary fistula
Posterior Sagittal Anorectoplasty (PSARP), Alberto Pena (1980)

Laparoscopic assisted anorectal pull-through (LAARP), K Georgeson (2000)

Refocus:
From changing surgical techniques to defining markers of clinical postoperative outcomes and improving postoperative management

Fecal Incontinence

- Definition: “repetitive (voluntary or involuntary) passage of stool in inappropriate places by children four years of age and older, at which time a child may be reasonably expected to have completed toilet training and to exercise bowel control”
Postoperative function and Quality of Life

- Poor for high ARM, good for low ARM
- QOL correlates with fecal continence
- Distinguishing “pseudoincontinence” from constipation from “true incontinence”

Diagnostic studies to evaluate anatomy and function

- 34 ARM patients (fecal incontinence)
  - feasibility study to evaluate pelvic anatomy
  - no correlation with clinical management
- Limitations:
  - Need MRI standards for normal pelvic anatomy
  - Justification of cost

Long-term function

- Australia, 2007: series of 167 patients with ARM from 1982 to 2000 (only 84 patients responded to questionnaires)
  - Soiling problems in 86%, 79%, and 43% (high, intermediate, and low malformation)
  - Constipation 62%, abdominal pain 49%
  - Behavioral problems 80% (15% suicidal ideation)
- Pena et al, 2000: series of 1192 patients over 19 years
  - only 38% totally continent
  - 25% suffered fecal incontinence
  - bowel management program to improve quality of life (95% success)
  1. Daily enemas to clean patients with constipation
  2. Constipating diet or medication for those with fecal incontinence
- Continence dependent on level of malformation
- Stooling problems continue into adolescence
- Importance of follow-up and bowel management program

• 17 ARM patients
  - IAS disruption and pressure > 20 mm Hg → biofeedback and laxatives
  - absence of IAS and pressure < 20 mm Hg → daily enemas
- Limitations: feasibility of study at young age
175 patients with ARM (4-17 years)
- 12%: did not know level of anomaly
- 33% had bowel management program
  - started at mean age of 3.5 yrs
  - 50% improved QOL
  - 35% small improvements
  - 10% no improvement

Take-home points
- VACTERL association
- Colostomy needs to leave adequate distal length for future pull-through procedure
- Long-term quality of life correlates with fecal continence
- Early education and initiation of bowel management program: distinguishing pseudo-incontinence from true incontinence.