The Evolving Role of Biologics in IBD: 2012

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Treatment Goals c. 2012

- Induce and maintain response/remission
- *Mucosal Healing/Deep Remission*
- Prevent complications
- Improve quality of life
- Restore and maintain nutrition
- Limit surgery
Conventional “Therapeutic Pyramid” for Crohn’s disease

- **Budesonide**
- **Antibiotics**
- **5-ASA**
- **MTX**
- **AZA/6-MP**
- **Systemic Steroids**
- **Biologics**
- **Surgery**

Severity levels:
- **Mild**
- **Moderate**
- **Severe**
Sequential Therapies for IBD

Step-Up according to severity at presentation or failure at prior step.

Disease Severity at Presentation

- Severe
  - Aminosalicylate
  - Anti-TNF
  - Natalizumab

- Moderate
  - Corticosteroid
  - Aminosalicylate
  - Anti-TNF (UC)/Thiopurine/MTX (CD)

- Mild
  - Aminosalicylate (UC)/Thiopurine/MTX (CD)
  - Induction
  - Maintenance

Natalizumab

Anti-TNF (UC)/Thiopurine/MTX (CD)
Step-up management approach

Advantages

- Patients attain remission with less toxic therapies
- Potentially more toxic therapies reserved for more severe or refractory disease
- Minimizes risk of adverse events
- Cost sparing (short-term?)

Disadvantages

- Patients have to “earn” most effective treatments
- Decrease in quality-of-life before patients obtain optimal therapy
- Likelihood of surgery is high
- Disease is not modified
Longitudinal Course of CD

Preclinical phase:
Subclinical inflammation (immune response and histologic lesions)

Early Crohn’s disease:
Inflammation (clinical, biological, endoscopic, radiologic evidence of disease activity)
No fistula, abscess, or stricture
Inflammatory Activity and Progression of Damage in a Theoretical Patient with CD

Disease onset

Diagnosis

Early disease

Stricture

Fistula/abscess

Surgery

Stricture

(CDAI, CDEIS, CRP)

Digestive damage

Impact of Therapy will Depend on Degree of Structural Damage & Velocity of Progression

Cumulative Probability (%)

Patients at risk:
N = 2002

Months
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240

High Potential

Low Potential

Penetrating

Inflammatory

Stricturing

Cosnes J et al. Inflamm Bowel Dis 2002;8:244-250.
Probability of Surgical Intervention in CD

Rate of Surgery for CD and the Use of Immunosuppressives in Paris over 3 Decades

Use of Immunosuppressives

Need for Surgery

60% exposed to IS therapy

No Change in Surgery Rates
Immunosuppressives used too late in course!
Rationale for Early Intervention in CD

- Immunopathology supports concept of early intervention in CD

- Subgroup analyses of large clinical trials suggests TNFα antagonists may be more effective in patients with disease duration ≤ 1-2 years

- AEs occur less often in early rheumatoid arthritis patients treated with TNFα antagonists

- Potential for disease modification to prevent transmural complications (surgery/hospitalization)

EXTEND: disease duration and deep remission* rates

Patients in deep remission* at Week 52 (%)

<table>
<thead>
<tr>
<th>Disease duration</th>
<th>Placebo</th>
<th>Adalimumab 40 mg eow</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years</td>
<td>0/9</td>
<td>3/9</td>
</tr>
<tr>
<td>2 to &lt;5 years</td>
<td>0/15</td>
<td>2/11</td>
</tr>
<tr>
<td>≥5 years</td>
<td>0/41</td>
<td>7/44</td>
</tr>
</tbody>
</table>

*Deep remission defined as clinical remission (CDAI <150) and complete mucosal healing in EXTEND
p<0.001 for adalimumab vs placebo, adjusted for baseline disease duration (Cochran-Mantel-Haenszel test)
All patients (n=135) received adalimumab 160/80mg induction therapy, before randomisation (n=129) to
adalimumab 40mg eow or to placebo
CDAI: Crohn’s disease activity index; eow: every other week

Rationale for Early Intervention in CD

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Rheumatoid Arthritis Progression

Graph: Adapted from Kirwan JR. J Rheumatol 2001;28:881-6
Photo: Copyright © American College of Rheumatology
Treatment of Early RA Prevents Progression of Structural Damage

Baseline

102 Weeks

Infliximab: $\triangle$ Total Sharp Score = -10.5
Evidence for Biologics & “Disease Modification”
Infliximab: Endoscopic Healing and Reduced Hospitalizations and Surgeries

Rate of Hospitalizations and Surgeries (%)

- Patients with no healing (n=74)
- Patients with healing at 1 visit (10 or 54 wk) (n=16)
- Patients with healing at both visits (10 and 54 wk)

*Number per 100 patients

EXTEND: deep remission* rates with adalimumab at 1 year

*Deep remission defined as clinical remission (CDAI <150) and complete mucosal healing in EXTEND
All patients (n=135) received adalimumab 160/80mg induction therapy, before randomisation (n=129) to adalimumab 40mg eow or to placebo
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**EXTEND**: patients who achieved deep remission* with adalimumab at Week 12 and hospitalization rates

**All-cause hospitalization through Week 52**

- Deep remission* (Week 12): 0/11
- Non-deep remission* (Week 12): 9/53

**CD-related hospitalization through Week 52**

- Deep remission* (Week 12): 0/11
- Non-deep remission* (Week 12): 5/53

*Deep remission defined as clinical remission (CDAI <150) and complete mucosal healing in EXTEND
CD: Crohn’s disease; CDAI: Crohn’s disease activity index

Can we predict patients who will have a “progressive” course?
Clinical Predictors of Risk of Progressive/Aggressive Crohn’s Disease at Diagnosis

• Young age
• Fistulae
• Need for steroids
• Deep ulcerations
• High serologic titers
• Smoking
What do we mean by “top down” therapy?

- Early intervention with immunosuppressive
- Early intervention with biologic
- Giving our most effective therapy at diagnosis (combination biologic + IS)
Efficacy of AZA as Crohn’s Disease Maintenance Therapy After Steroids in Adults*

*Remission induced by prednisolone tapered over 12 wk

Inclusion: Patients were not steroid dependent

Efficacy of 6-MP as Crohn’s Disease Maintenance Therapy After Steroids in Steroid-naïve Children

\[ P < .007 \]

At baseline, patients received prednisone plus either 6-MP or placebo. Steroids were tapered after induction of remission.

Comparing ACCENT I, CHARM, and PRECiSE 2

Results

- **ACCENT I**: (infliximab) 5 mg/kg dose.
- **CHARM**: (adalimumab) Maintenance trial with 80/40 mg induction dosing. Randomized responders = CR-70 at week 4. Week 26 remission among randomized responders on 40 mg every other week dosing.
- **PRECiSE 2**: (certolizumab pegol)

In Patients Failing Therapy Including Steroids & Immunosuppressants

- Week 2 Response: 58.5%
- Week 30 Remission: 39.0%
- Overall Remission Week 30: 22.8%

**CHARM** (adalimumab)
- Week 4 Response: 60%
- Week 26 Remission: 40%
- Overall Remission Week 26: 24%

**PRECiSE 2** (certolizumab pegol)
- Week 6 Response: 64.1%
- Week 26 Remission: 47.9%
- Overall Remission Week 26: 30.7%

*5 mg/kg dose.

**Maintenance trial with 80/40 mg induction dosing. Randomized responders = CR-70 at week 4. Week 26 remission among randomized responders on 40 mg every other week dosing.*
Infliximab Induction and Maintenance Therapy in Patients with Ulcerative Colitis:

- Clinical Remission

\[ P \leq 0.003 \text{ vs placebo} \]

\[ P < 0.001 \text{ vs placebo} \]

In Patients Failing Therapy Including Steroids & Immunosuppressants

ACT 1

- Placebo
- IFX 5 mg/kg
- IFX 10 mg/kg

ACT 2

- Placebo
- IFX 5 mg/kg
- IFX 10 mg/kg

In Patients Failing Therapy Including Steroids & Immunosuppressants

Early Aggressive Biologic Therapy vs Conventional Management of Crohn’s Disease

Newly diagnosed, antimetabolite, anti-TNF, or steroid-naïve CD patients (n=133)

Conventional therapy (n=66)
- Steroids
- + AZA
- + MTX
- Steroids

Early aggressive (n=67)
- + IFX
- IFX (0,2,6 weeks) + AZA
- + (episodic) IFX
- Steroids

Complete Ulcer Disappearance (Mucosal Healing)

- "Top-Down": 73% (P=0.003)
- Step Up: 30%

SONIC: Mucosal Healing at Week 26

Primary Endpoint

Proportion of Patients (%)

- **AZA + placebo**: 16.5 (18/109)
- **IFX + placebo**: 30.1 (28/93)
- **IFX + AZA**: 43.9 (47/107)

Significant differences:
- AZA + placebo vs. IFX + placebo: $P<.001$
- AZA + placebo vs. IFX + AZA: $P=.023$
- IFX + placebo vs. IFX + AZA: $P=.055$

Comparison of Infliximab Trials: Immunosuppressive Experienced vs. Naïve Patients: ACCENT I vs. SONIC

Clinical Remissions

ACCENT I             SONIC

p=NS             p<0.02
So What is the Risk of Early-Aggressive Intervention?
**SONIC: Summary of Adverse Events Through Week 50: All Randomized Patients**

<table>
<thead>
<tr>
<th></th>
<th>AZA + placebo (n=161)</th>
<th>IFX + placebo (n=163)</th>
<th>IFX + AZA (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 AE, n (%)</td>
<td>144 (89.4%)</td>
<td>145 (89.0%)</td>
<td>161 (89.9%)</td>
</tr>
<tr>
<td>Patients with ≥1 SAE, n (%)</td>
<td>43 (26.7%)</td>
<td>39 (23.9%)</td>
<td>27 (15.1%)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>9 (5.6%)</td>
<td>8 (4.9%)</td>
<td>7 (3.9%)</td>
</tr>
</tbody>
</table>

TB - 1 patient treated with infliximab and azathioprine
Colon cancer - 2 patients treated with azathioprine monotherapy
Death - Post colectomy, in a patient treated with azathioprine monotherapy

Who are the patients who are most at risk for serious infections?

• Older
  – average age = 63 (systematic review); 67 (Mayo)
  – OR 3.0 (95%CI 1.2–7.2) for >50 years vs ≤24 years

• Multiple co-morbidities

• Concomitant steroids and/or narcotics

Young “healthy” patients are not in the clear, but probably less at risk

Siegel et al, Clin Gastroenterol Hepatol 2006;4:1017–24
Colombel et al, Gastroenterology 2004;126:19–31
Safety of Biologic Therapies

- Consider risks of underlying condition
  - Lymphoma in RA or IBD
- Consider risks of concomitant medications
  - Corticosteroids
  - Immune suppressants
The problem with confounding factors

• Severity of the disease
• Age
• Malnutrition
• Surgery
• Leucopenia
• Concomitant use of other medications
When to Introduce Early-Aggressive Therapies?

The “Tipping Point” may be need for Corticosteroids?
Corticosteroids: Short & Long Term Efficacy in Crohn’s Disease


30-Day Responses (n=74)
- Complete: 58% (n=43)
- Partial: 26% (n=19)
- None: 16% (n=12)

1-Year Responses (n=74)*
- Prolonged Response: 28% (n=21)
- Steroid Dependent: 32% (n=24)
- Surgery: 38% (n=28)

*One patient lost to follow-up
Cumulative Incidence of Surgical Resection Over 1 Year in CD Patients Starting Corticosteroids

N=77

So what are the real issues regarding “early aggressive” therapies?

• If biologics cost $1.00 we would not be having these discussions
  – Cost of therapy is the overriding issue for all parties

• Fear of infections/neoplasia
  – Primarily risk of lymphoma in young patients

• Fear of “running out” of options
  – Reserving therapy for refractory patients
Conflict Resolution: Does One Size Fit All?

NO!
So What Should We Do?

• Assess prognosis at diagnosis
  – Initiate therapy according to disease severity and risk of progression
  – Steroids are a “tipping point” for complications and poor prognosis

• Prepare patients for immune suppression
  – PPD, Chest x-ray, vaccinations

• Monitor patients for risks
  – Early assessment of disease progression &/or complications
Current and Future Therapeutic Paradigms

**Current**
- Bottom-up approach
- Conservative use of immunomodulators
- Goals
  - Induce remission
    - Mucosal healing*
  - Maintain remission
  - Prevent complications
  - Optimize surgical outcomes & post-op prophylaxis

**Future**
- Initiate therapy ~ to prognosis
- Early-aggressive therapy if bad prognosis
- Additional goals
  - Disease modification
  - Pharmacoeconomics
- Disease prevention!