New Strategies for Biologic Use in Inflammatory Bowel Disease

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Objectives

• Describe new insights into CD pathogenesis

• Discuss recent studies on optimizing current therapies

• Review translation of immune mechanisms into development of new therapies

• Summarize results of recent clinical trials with these agents
Crohn’s Disease

Crohn’s Disease\textsuperscript{1-3}

• Patchy inflammation
• Mouth to anus involvement
• Transmural inflammation
• Fistulas and strictures common
• Risk of cancer
• Extraintestinal manifestations
• Higher risk for smokers
• Can have granulomas

Contributors to IBD Pathogenesis

- Abnormal epithelial barrier
- Abnormal microflora
- Mucosal immune defect
Role of Bacteria in IBD

Non-IBD patient
- Heterologous stool
- Autologous stool

IBD patient
- Heterologous stool
- Autologous stool

Duchmann et al. 1995. Clinical and Experimental Immunology
Terminal Ileum-Normal Patient
Terminal Ileum-Crohn’s Patient
TNF Promotes CD Activity and Pathogenesis Through Multiple Pathways

Role of IL-23 and Th17 Cytokines in Intestinal Inflammation
Role of IL-23 and Th17 Cytokines in Intestinal Homeostasis
Long-standing Therapies

• Traditional therapies have included
  – Corticosteroid therapy
  – Mesalamine compounds
  – Azathioprine/6-mercaptopurine
  – Methotrexate

• Hampered by incomplete responses and side-effects (complications)
Outcome of Therapy With Corticosteroids* in Adult Patients With CD

1-Month Outcomes (n = 74)

- Complete Remission†: 58%
- Partial Remission: 26%
- No Response: 16%

12-Month Outcomes (n = 74)

- Prolonged Response±: 32%
- Steroid Dependent: 28%
- Surgical Resection: 38%
- Lost to Follow-up: 1%

*Most patients received oral prednisone with initial doses ranging from 40 to 60 mg (tapering attempted over 3-6 months); †Defined as total regression of clinical symptoms; ±Defined as maintenance of complete or partial remission after steroid therapy was complete.

Crohn’s Disease Downward Spiral

- Health
- Mod disease
- Fistulizing disease
- Surgery
- Death
- Hospitalization
- Severe disease
- Mild disease

Treatment
Cumulative Probability* of Surgery in Crohn’s Disease in the Pre-Biologic Era

Up to 80% of CD patients will require surgical intervention

*Kaplan-Meier analysis.
Progression of Crohn's Disease

- Occurrence of a stricturing and/or penetrating complication was assessed retrospectively in 2,002 consecutive CD patients (1974–2000)
- The estimated risks for penetrating CD at 5 and 20 years after diagnosis are 40% and 70%

Previous “Step-Up” Approach to Crohn’s Disease Therapy

- **Severe**
  - Surgery
  - Bowel rest
  - Cyclosporine
  - Tacrolimus
  - TNF antagonist

- **Moderate-Severe**
  - Azathioprine
  - 6-mercaptopurine
  - Methotrexate
  - Prednisone
  - Budesonide
  - TNF antagonist

- **Mild**
  - Aminosalicylate (mesalamine or sulfasalazine)
  - Antibiotics
  - Budesonide

Evolving Biologic Therapies

• Incomplete response to therapy is driving need to re-evaluate treatment practices

• Evolution of IBD therapy is occurring in two ways:
  – Improved regimens using current therapy
    • “Top-down” administration schedule
    • Early “aggressive” biologic therapy
    • Aggressive post-operative use of biological therapy
  – Targeting novel “upstream” aspects of the immune system
    • Anti-adhesion molecules
    • Novel cytokine targets
    • Cell mediated therapy
Evidence Supporting Early Use of Biological Therapy
PRECiSE 2: Week 26 Clinical Response or Remission by Duration of Crohn’s Disease

**Response**

- *P < 0.01
- †P < 0.05
- ‡P < 0.001 vs placebo.

- Decrease in CDAI ≥ 100 points
- CDAI score < 150 points.

<table>
<thead>
<tr>
<th>Duration of Crohn’s Disease (years)</th>
<th>Certolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>90%</td>
<td>37%</td>
</tr>
<tr>
<td>1 to &lt; 2</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>2 to &lt; 5</td>
<td>62%</td>
<td>36%</td>
</tr>
<tr>
<td>≥ 5</td>
<td>57%</td>
<td>33%</td>
</tr>
</tbody>
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<tr>
<td>&lt; 1</td>
<td>68%</td>
<td>37%</td>
</tr>
<tr>
<td>1 to &lt; 2</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>2 to &lt; 5</td>
<td>47%</td>
<td>29%</td>
</tr>
<tr>
<td>≥ 5</td>
<td>44%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Adalimumab: Remission by Disease Duration

Week 26

- Placebo
- Adalimumab 40 mg EOW
- Adalimumab 40 mg weekly

Week 56

- Placebo
- Adalimumab 40 mg EOW
- Adalimumab 40 mg weekly

*Disease Duration (years)*

<table>
<thead>
<tr>
<th>Disease Duration</th>
<th>Week 26</th>
<th>Week 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>2 to &gt; 5</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>≥ 5</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

*P < 0.05 vs placebo.

EOW = every other week

The Future: Top Down Therapy for Crohn’s Disease

Early

Biologics

Corticosteroids

5-ASA

Late

AZA/6-MP/MTX

Surgery
The Future: Rapidly Progressive Therapy for Crohn’s Disease

- Corticosteroids
- 5-ASA
- AZA/6-MP/MTX
- BIOLOGICS
- Surgery

Time

Weeks/Months
ACG Guidelines: Management Goals for CD

• Evaluate response to initial therapy over several weeks
  – Maximal improvement seen within 12-16 weeks

• Closely monitor adverse events throughout therapy

• Patients in remission stay on maintenance therapy

• If symptoms continue according to clinical status
  – Advance treatment for moderate/severe disease

SONIC:

A Randomized, Double-Blind, Controlled Trial Comparing Infliximab and Infliximab plus Azathioprine in Patients with Crohn’s Disease Naïve to Immunomodulators and Biologic Therapy
Study Objective

• Assess induction of steroid-free remission and safety of:
  – IFX monotherapy
  – Combination therapy with IFX and AZA
  – AZA monotherapy

in patients with moderate-to-severe CD

SONIC Study Design

N=508
IMM naïve & Biologic naive

IFX 5 mg/kg + PBO caps
N=169

IFX 5 mg/kg + AZA 2.5 mg/kg
N=169

AZA 2.5 mg/kg + PBO infusion
N=170

Week 26
Primary endpoint: Steroid-free Remission

IFX administered at weeks 0, 2, 6 and q8wks
Mucosal healing is a major secondary endpoint
<table>
<thead>
<tr>
<th>Baseline Characteristics*</th>
<th>AZA + placebo (n=170)</th>
<th>IFX + placebo (n=169)</th>
<th>IFX + AZA (n=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>90 (52.9%)</td>
<td>84 (49.7%)</td>
<td>88 (52.1%)</td>
</tr>
<tr>
<td>White race – n (%)</td>
<td>147 (91.3 %)</td>
<td>146 (93.0 %)</td>
<td>142 (94.0 %)</td>
</tr>
<tr>
<td>Age year (IQ Range)</td>
<td>35 (26,43)</td>
<td>35 (26,46)</td>
<td>34 (26,45)</td>
</tr>
<tr>
<td>Weight – kg (IQ Range)</td>
<td>69.6 (58.5, 81.6)</td>
<td>68.9 (60.0, 80.5)</td>
<td>72.0 (61.0, 85.0)</td>
</tr>
<tr>
<td>Duration of CD, yr (IQ Range)</td>
<td>2.4 (1,8)</td>
<td>2.2 (1,9)</td>
<td>2.2 (1,9)</td>
</tr>
<tr>
<td>CDAI, median (IQ range)</td>
<td>275 (247, 322)</td>
<td>272 (247, 322)</td>
<td>278 (248,327)</td>
</tr>
<tr>
<td>CRP, mg/dl– median (IQ Range)</td>
<td>1.0 (0.4, 3.1)</td>
<td>1.1 (0.4, 3.1)</td>
<td>1.0 (0.3, 2.3)</td>
</tr>
</tbody>
</table>

*41% were on steroids at baseline; 18% had history of fistulas; 21% had bowel resections; 49% had extra-intestinal manifestations; 27% were hospitalized at least once in the year prior to enrollment b/c of their CD
Research Methods

Patient Population:
• Moderate-severe CD (CDAI ≥220≤450)
• NAÏVE to IMM (AZA, 6MP) and biologics
• Steroid dependent (2 or more cycles in past year); Failed 5-ASA; Failed budesonide therapy
• Pts could be placed on corticosteroids (CS) at enrollment up to Wk 14; Mandatory taper at Wk 14
• Colonoscopy at baseline and Wk 26

Primary endpoint: Steroid-free remission at week 26 (CDAI<150). Off steroids / budesonide ≥ 3 wks at week 26

Secondary endpoint: Mucosal healing at week 26 (Endoscopic score=0; no ulcers)
Results: Clinical Remission Without Corticosteroids at Wk 26*

*Clinical Remission defined as CDAI < 150. Patients were considered steroid free if they had not received oral steroids (prednisone or equivalent) for ≥ 3 weeks and budesonide at a dose of >6 mg/day for ≥ 3 weeks at Wk 26.

Results: Mucosal Healing at Wk 26†‡

†Mucosal healing defined as the absence of mucosal ulceration at Wk 26; residual erythema and/or edema may be present

‡Includes subjects with evidence of ulceration at baseline that were eligible for the mucosal healing analysis at Wk 26.

Corticosteroid–Free Clinical Remission Through Week 26

Corticosteroid-Free Clinical Remission Through Week 26

Weeks

Proportion of Pts (%)

AZA + Placebo
IFX + Placebo
AZA + IFX

*p<0.05 IFX + AZA vs AZA + PBO, IFX + PBO vs AZA + PBO
†p<0.05 IFX + AZA vs IFX + PBO
Corticosteroid–Free Clinical Remission at Week 26 by Baseline CRP

![Graph showing the proportion of patients in remission by CRP level and treatment group.]

- **CRP < 0.8 mg/dL (n=207):**
  - AZA + PBO: 35.2%
  - IFX + PBO: 40.3%
  - IFX + AZA: 50.7%
  - Proportion: 25/71 (AZA + PBO), 27/67 (IFX + PBO), 35/69 (IFX + AZA)
  - P-values: P=0.121, P=0.314, P=0.503

- **CRP ≥ 0.8 mg/dL (n=295):**
  - AZA + PBO: 27.6%
  - IFX + PBO: 47.5%
  - IFX + AZA: 63.5%
  - Proportion: 27/98 (AZA + PBO), 48/101 (IFX + PBO), 61/96 (IFX + AZA)
  - P-values: P=0.00, P<0.001, P=0.027
Steroid Free Remission at Wk 26: Patients with CRP >0.8 mg/dL and Lesions on Baseline Endoscopy (n=204)

- AZA: 28% (21/75)
- IFX: 56.9% (37/65)
- IFX+AZA: 68.8% (44/64)

P ≤ 0.001 for AZA vs. IFX
P = 0.169 for IFX vs. IFX+AZA
Results: Mucosal Healing at Wk 26†‡

†Mucosal healing defined as the absence of mucosal ulceration at Wk 26; residual erythema and/or edema may be present

‡Includes subjects with evidence of ulceration at baseline that were eligible for the mucosal healing analysis at Wk 26.
Safety: Adverse Events (AE) through Wk 30

<table>
<thead>
<tr>
<th></th>
<th>AZA + PBO n(%)</th>
<th>IFX + PBO n(%)</th>
<th>IFX + AZA n(%)</th>
<th>Total n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with ≥1 AE</td>
<td>138 (85.7)</td>
<td>139 (85.3)</td>
<td>156 (87.2)</td>
<td>433 (86.1)</td>
</tr>
<tr>
<td>Pts with ≥1 SAE</td>
<td>39 (24.2)</td>
<td>26 (16)</td>
<td>25 (14)</td>
<td>90 (17.9)</td>
</tr>
<tr>
<td>Serious Infections</td>
<td>8 (5)</td>
<td>4 (2.5)</td>
<td>6 (3.4)</td>
<td>18 (3.6)</td>
</tr>
</tbody>
</table>

- 1 patients treated with IFX + AZA developed TB
- 2 patients treated with AZA monotherapy developed colon cancer
- 1 patient treated with AZA monotherapy died of sepsis following colectomy
Conclusions

- SONIC trial provides novel comparison of anti-TNF therapy with AZA in patients with moderate to severe Crohn’s disease previously failing 5-aminosalicylate (5-ASA) and/or steroids
- Combination Infliximab/AZA was superior to IFX or AZA alone
- IFX monotherapy was superior to AZA alone
- Patients with a high CRP and/or ulcers at baseline colonoscopy had a particularly strong benefit from infliximab therapy
- Safety among treatment groups was similar
SONIC Extension Trial

- 280 patients continued on with their assigned treatment regimen in blinded fashion
- Continued differences were noted between the combination group vs monotherapy AZA
- Final safety evaluation performed at week 50

Clinical Remission defined as CDAI < 150. Patients were considered steroid free if they had not received oral steroids (prednisone or equivalent) for ≥ 3 weeks and budesonide at a dose of >6 mg/day for ≥ 3 weeks at Wk 26.
Safety at Week 50

• Proportion of subjects with 1 or more serious events
  – Azathioprine: 27%
  – Infliximab: 24%
  – Combination: 15%

• No new serious adverse events were reported during wks 30-54

Targeting Patients For Early Therapy

• Who are the correct patients for early aggressive therapy?

• What is the optimal choice of therapy?

• If we use combination therapy, how long do we continue both medications?
## Risk of 5-Year Disabling Disease Course With Need for Early Corticosteroid Use

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nondisabling, % (n = 166)</th>
<th>Disabling, % (n = 957)</th>
<th>Statistical Univariate Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 40 years</td>
<td>77.1</td>
<td>87.7</td>
<td>( P = 0.0004 )</td>
</tr>
<tr>
<td>40 years or above</td>
<td>22.9</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Location of the disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel only</td>
<td>44.6</td>
<td>32.8</td>
<td>( P = 0.002 )</td>
</tr>
<tr>
<td>Small bowel and colon</td>
<td>25.9</td>
<td>39.4</td>
<td></td>
</tr>
<tr>
<td>Colon only</td>
<td>29.5</td>
<td>27.8</td>
<td></td>
</tr>
<tr>
<td>Perianal lesions at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17.5</td>
<td>26.4</td>
<td>( P = 0.01 )</td>
</tr>
<tr>
<td>No</td>
<td>82.5</td>
<td>73.6</td>
<td></td>
</tr>
<tr>
<td>Requirement for steroids for treating the first flare</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>37.3</td>
<td>65.2</td>
<td>( P = 0.0001 )</td>
</tr>
<tr>
<td>No</td>
<td>62.7</td>
<td>34.8</td>
<td></td>
</tr>
</tbody>
</table>

Prediction of a 5-Year Disabling Course in CD: Retrospective Study (n = 1122)

Prediction of a 5-Year Disabling Course in CD:
Prospective Validation Study (n = 302)

- Score 0 (0 factors of disabling disease)
- Score 1 (1 factor)
- Score 2 (2 factors)
- Score 3 (3 factors)

Medical Prevention of Relapse

• Despite advances in therapy
  – 75% of patients require intestinal resection\(^1,2\)
  – One year post op 70-90% have endoscopic recurrence
  – 33% have clinical recurrence at 3 years and 60% have clinical recurrence at 10 years\(^3\)

• Endoscopic surveillance at 6-12 months has been advocated to determine high risk patients\(^4\)

Medical Prevention of Relapse

• Nitroimidazole antibiotics mildly effective
  – Rate of endoscopic occurrence >50% at 1 year\textsuperscript{1,2}

• AZA and 6-MP have variable results
  – Majority have endoscopic recurrence at 1 year\textsuperscript{3,4}

• These agents also provide low rates of endoscopic healing with active therapy

Infliximab for Post Operative Recurrence

• RDBPC trial to evaluate infliximab for preventing postoperative recurrence

• 24 patients underwent ileocolonic resection

• Infliximab 5mg/kg or placebo administered within 4 weeks after surgery
  – 0, 2, 6 weeks then every 8 weeks
  – Concomitant meds were continued at stable doses

• Primary endpoint: proportion of pts with endoscopic recurrence after 1 year of therapy

Endoscopic Recurrence Score\(^1\)

- i0 – no lesions
- i1 – 5 or fewer apthous lesions
- i2 – more than 5 apthous ulcers with normal mucosa between, or skip areas of larger lesions
- i3 – diffuse apthous ileitis with diffusely inflamed mucosa
- i4 – diffuse inflammation with large ulcers, nodules or narrowing

Endoscopic Outcomes

Regueiro et al. Gastro 2009;136:441-450

Infliximab versus Placebo

P = .0006

Endoscopic evaluation at 1-year follow-up
Endoscopic Recurrence Distribution

Regueiro et al. Gastro 2009;136:441-450
Clinical and Histologic Recurrence

Recurrence rates at 1 year

- Clinical
  - Infliximab: 0%
  - Placebo: 38.5%

- Histologic
  - Infliximab: 27.3%
  - Placebo: 84.6%
Summary

• Earlier use of anti-TNF therapies may yield improved efficacy rates

• Appears to be safe

• Cost considerations may be balanced by reduction in surgeries/hospitalizations

• Need to risk stratify who needs this approach
Upcoming Therapies

• Potential new targets:
  – IL-12/23
  – IL-17
  – Adhesion molecules
  – Cell mediated immunity
    • Anti-CTLA-4
    • Anti-CD3
  – Immunoregulatory factors
Anti-IL-12/IL-23

![Diagram showing the interaction between IL-12 and IL-23 with their respective receptors and the effect of ABT-874 and Stelara.](image)
ABT-874

- Fully human antibody against IL-12/23
- Phase 2 clinical trial (RDBPC)
  - Two cohorts
- Cohort 1 - two injections four weeks apart
  - High dose response/remission 50%
  - Low dose response/remission 19%
  - Placebo response/remission 13% and 25%
- Cohort 2 - weekly injection for seven weeks
  - High dose response/remission 69% and 38%
  - Low dose response/remission 20% and 13%
  - Placebo 25% and 0%
- No serious adverse events attributed to study drug

Mannon et al. NEJM 2004;351(20):2069-79
Ustekinumab

- Phase 2a RDBPC trial of 202 mod/severe CD pts
  - Two cohorts
- Cohort 1-randomized 4:1 to subQ or IV drug or placebo
- Cohort 2-open label infusion for primary or secondary non-responders to infliximab
- Week 8 clinical response primary endpoint
  - Group 1 response/remission 49% and 26%
  - Placebo response/remission 40% and 17%
    - IV patients performed slightly better

Ustekinumab-Infliximab Experienced Patients

Selective Adhesion Molecule Therapy

LFA-1 – ICAM-1, VLA-4 – VCAM-1, $\alpha_\beta_7$ – MAdCAM-1

Selectins, PSGL-1, VLA-4
Selectin signaling
Chemokines

Src kinases, PI3kinases, VAV1,2,3

Mac-1
ICAM-1

PECAM-1
CD99
JAMs
ESAM

ICAM-1
PECAM-1

Capture → Activation → Rolling → Slow Rolling → Arrest

Endothelial cells
Basement membrane

Adhesion Strengthening, Spreading
Intravascular crawling
Paracellular Transmigration
Transcellular Transmigration
Natalizumab

- Monoclonal antibody against α-4 integrin
- Prevents activated T-cell trafficking to sites of inflammation in brain/gut
- Currently approved for MS and CD
- PML infection significant concern
ENCORE: Clinical Response and Remission of CD in Patients Receiving Natalizumab

Response (Δ70)

<table>
<thead>
<tr>
<th></th>
<th>Wk 8</th>
<th>Wk 12</th>
<th>Wks 8 + 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab (n = 259)</td>
<td>40</td>
<td>56</td>
<td>*</td>
</tr>
<tr>
<td>Placebo (n = 250)</td>
<td>44</td>
<td>60</td>
<td>*</td>
</tr>
</tbody>
</table>

Remission (CDAI < 150)

<table>
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<th>Wk 12</th>
<th>Wks 8 + 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab (n = 259)</td>
<td>21</td>
<td>32</td>
<td>*</td>
</tr>
<tr>
<td>Placebo (n = 250)</td>
<td>16</td>
<td>25</td>
<td>38</td>
</tr>
</tbody>
</table>

*P < 0.001 vs placebo; †P = 0.002 vs placebo.
Vedolizumab

- Humanized antibody specifically targeting \( \alpha_4\beta_7 \) integrin responsible for activated T-cell trafficking to the GI tract

- Recent study evaluated 0.5 and 2mg/kg in moderate to severely active Crohn’s disease

- Primary endpoint: clinical response on day 57 by CDAI drop of \( \geq 70 \) after two monthly infusions

Vedolizumab

Stem Cell Therapy for Crohn’s

I died waiting for embryonic stem cell research to find a cure. What about you?

I was the embryo.
Sources of Stem Cells for Crohn’s Therapy
Role of Stem Cell Therapy in Crohn’s

- Immunosuppression
- Inhibit activated immune cells
- Tissue regeneration
- Regulate tissue based stem cell renewal
- Differentiation into multiple tissue lineages
- Modulation of cell cycle
- Differentiation into stroma

Environmental Factors
MSC for Fistulizing Disease

- Phase I clinical trial evaluated MSC harvested from adipose tissue of participants
- Adipose tissue (80-100ml) was obtained by liposuction
- Tissue was washed, processed and plated for cell culture
- Adherent cells were cultured until ~80% confluent, then passaged

Fistula Preparation and Innoculation

- Prior to stem cell transplantation, the fistulous tracts were cored out and the internal defect was sutured closed
- Cells were transplanted between passages 1 and 3
  - direct injection into the tract
  - directly into the wall of the rectum in the case of rectovaginal fistulas
- All tracts were filled with fibrin glue after injection

Monitoring for Response

• Fistulas were monitored weekly up to 8 weeks

• Healing: complete epithelialization of the external opening noted

• Maintenance of healing was monitored monthly for 12 to 30 months

Representative Response

Results

• Eight fistulas were evaluable for the study

• 6 of 8 fistulas were completely healed

• No cases of sepsis or abscesses were noted

• No treatment related adverse events were noted

Phase 2 Study of MSC for Fistulas

- 49 pts with complex perianal fistulas (35 cryptoglandular, 14 Crohn’s related)
- Randomized to fibrin glue treatment alone or fibrin glue + 40 million adipose derived MSC injected into tract

Crohn’s Fistula Healing Rates

MSC plus glue vs glue alone

Complete fistula healing at 12 months

Stem Cell Tx for Luminal CD

- First description of stem cell therapy from retrospective review of BMT patients
- Six active CD, 4 active UC patients underwent BMT for hematologic malignancy
- All patients experienced resolution of their IBD symptoms

Ditschkowski et al. Transplantation. 2003;75(10):1745-47
Autologous Hematopoietic Stem Cell (HSC) Transplantation in Refractory CD

• Phase 1, open label study in 12 refractory CD patients

• After BM ablation therapy, expanded AHSC reinfused into subjects

• Six month followup period
  – 11 of 12 patients experienced remission

Autologous Hematopoietic Stem Cell (HSC) Transplantation in Refractory CD

Autologous Hematopoietic Stem Cell (HSC) Transplantation in Refractory CD

Autologous MSC Therapy in Patients With Refractory CD

- Seven patients with refractory moderate-severe CD enrolled in study
- Underwent BM aspiration, MSC expanded 1-3 passages
- MSC 1-2 million cells/kg BW administered IV
- Patients followed by CDAI for efficacy
- Median CDAI at enrollment 334 (254-350) and therapy was well tolerated

Duijvestein et al. JCC 2009;3(1):S46-47
Autologous MSC Therapy in Patients With Refractory CD

• One patient dropped out due to severe flare requiring surgery

• Four patients evaluated for response at 6 weeks
  – Median drop in CDAI of 107 points
  – Two patients with colonic involvement demonstrated endoscopic improvement
  – No improvement was seen in two patients with ileal disease

• Conclusion: autologous bone marrow derived MSC therapy is feasible and safe for refractory Crohn’s disease

Duijvestein et al. JCC 2009;3(1):S46-47
Phase 2 Open-label Study of Prochymal MSC in Crohn’s Disease

• Open-label, phase 2 pilot study evaluating the use of donor-derived pooled MSC
  – Low dose (2 million cells per kg)
  – High dose (8 million cells per kg)

• Patients with moderate to severe CD
  – Refractory to immunomodulators and anti-TNF therapy
  – All patients with evidence of active disease
  – Mean CDAI 351

• Primary endpoint: CDAI drop of ≥100 pts

Onken et al. 2006 ACG Final Program Book, p. 121
Phase 2 Open-label Study of Prochymal MSC in Crohn’s Disease

- Nine of 10 patients randomized completed study
  - Underwent two sequential infusions of donor stem cells
- All patients experienced symptom improvement by day 28
- Primary endpoint of CDAI reduction was achieved by 33% of subjects
  - At day 28, mean reduction in CDAI of 105 (from 341 to 236)
- Mean IBDQ scores improved from 133 to 146, with 33% achieving remission (score >170)

Onken et al. 2006 ACG Final Program Book, p.121
Stem Cell Conclusions

• Stem cell therapy for Crohn’s disease demonstrates potential for refractory patients

• Need to complete phase III trials for definitive answers

• Provide compelling evidence that effective, less toxic therapy may be available in the near future

• Potential for cure?
Safety Issues

- Infections
- Graft-versus host disease
- Tumor development
Conclusions

- Enhanced remission rates possible with currently available biologic therapies
  - Some additional evidence needed
- Effective anti-inflammatory therapy can reduce complications
  - Early therapy, post operative therapy
  - Any effect on colon cancer?
- May be cost effective
- Current therapy leaves some holes to fill
  - Future medications may fill these or supplant current therapies