Should Deep Remission Be A Treatment Goal?

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Mayo Clinic
Rochester, MN, USA

Should Deep Remission Be A Treatment Goal?

• No, not until we have convincing data that it makes a difference.

Deep Remission: Cohn’s Disease Evolution

Top Down versus Step Up Therapy for Crohn’s Disease

Top-Down vs Step-Up Treatment for Crohn’s: Final Data

- Top Down: 59 pt
- Step Up: 60 pt
- 16 semester follow-up past the original 2 yr study
- At 2 years:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Top Down (pt)</th>
<th>Step Up (pt)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA</td>
<td>60%</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>22%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>IFX</td>
<td>20%</td>
<td>15%</td>
<td></td>
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</table>

Time in remission: 67% vs 68% (NS)

# of flares: 13% vs 20% (p<0.01)

Time to hospitalization (semesters): 14 vs 13 (NS)

Time to surgery (semesters): 15 vs 14 (NS)

No ulcers at endoscopy: 64% vs 56% (NS)

Hoekman DR et al. Amsterdam, Leuven DDW 2015
Abstract # 924
Mucosal Healing in Crohn’s Predictor of Sustained Remission?

- Subgroup analysis
  - Top-Down vs Step-Up study 133 pt
- Colonoscopy at 2 years
  - 46 patients
    - Mucosal healing +
      - SES = 0
    - Mucosal healing –
      - SES 1-9
- Reassessed at 3-4 years

\[
\begin{array}{|c|c|}
\hline
& \text{Proportion of patients in remission} \\
\hline
\text{Colonoscopy at 2 yrs} & \text{MH+} \quad 0 \quad 10 \quad 20 \quad 30 \quad 40 \quad 50 \quad 60 \quad 70 \quad 80 \quad 90 \quad 100 \\
\text{SES} = 0 & 17/24 pt \\
\text{SES 1-9} & 6/22 pt \\
\hline
\end{array}
\]

Baert F et al Gastro 2010; 138:463-68

Crohn’s Disease: SONIC Infliximab, Azathioprine, or Combination

Background

- Crohn’s 169 pt
  - Infliximab
  - Azathioprine
  - Infliximab + Azathioprine
- 26 wk
- CDAI <150 off steroids

\[
\begin{array}{|c|c|}
\hline
\text{Clinical Remission} & P=0.02 \\
\hline
\text{P<.001} & P=0.036 \\
\hline
\end{array}
\]

Colombel JF NEJM April 2010: 362(15): 1383-95

Higher Levels of Infliximab May Alleviate the Need of Azathioprine Co-medication for Crohn’s Disease: A Sonic Post-Hoc Analysis

- Sonic Study 2010 post hoc
  - 206 patients with Crohn’s 97 IFX only
    - 109 IFX + Azathioprine
  - Serum Infliximab concentration
  - Clinical steroid-free remission at week 26
  - Conclusion: Benefit of combination Rx only with low IFX concentrations

\[
\begin{array}{|c|c|}
\hline
\text{IFX Concentrations} & \text{Steroid-free Remission at 26 wk} \\
\hline
\text{Q1} & \text{Q2} & \text{Q3} & \text{Q4} \\
\hline
\text{IFX AZA} & \text{IFX} & \text{NS} & \text{NS} \\
\hline
\end{array}
\]

Colombel JF et al Mt Sinai NYC DDW 2017 oral # 134

Deep Remission: Cohn’s Disease Evolution

- Definition: A state with little or no risk of disease progression

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<td>1. Resolution of inflammation by endoscopy, imaging, or markers</td>
<td>Clinical remission</td>
<td></td>
</tr>
<tr>
<td>2. Resolution of symptoms</td>
<td>“No data that endoscopic remission yields a better long-term outcome”</td>
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Colombel JF et al Digestive Dis 2012 sup 3: 107-11
Selecting Therapeutic Targets in IBD

• Treat to Target
• 28 IBD Experts, 75% of those who voted

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<td>• Biomarker remission CrP, Fecal Calprotectin</td>
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<tr>
<td>• Histologic remission</td>
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Deep Remission: Cohn’s Disease

Evolution

Mucosal Healing 2008
Deep Remission 2010
Sonic

Stride 2012
Calm 2015
2017

Deep Remission: Cohn’s Disease

CALM Study
Tight Control Management of Crohn’s

• 244 patients, multi-national, Open-label
• Entry Criteria
  • CDAI 200-450
  • CDEIS >6 with ulcers in > 1 segment
  • High CrP and/or Fecal Calprotectin
• Primary Endpoint
  • CDEIS < 4 and no deep ulcers at 48 weeks

Colombel JF et al The Lancet 2017; 390: 2779-2789

CALM Study
Design

Baseline: Prednisone ≤ 40 mg daily tapered over 9 weeks, time shortened at treating physician’s discretion

Clinical Management
Tight Control
Treatment escalated at 12, 24, 36 wk if:
CDAI decreased <100 pt or CDAI ≥200 Still on prednisone
Treatment escalated at 12, 24, 36 wk if:
CDAI ≥ 150 CRP High
Fecal calprotectin high
Still on prednisone

Colombel JF et al The Lancet 2017; 390: 2779-2789

CALM Study Primary Endpoint Achieved: 48 wks

P=0.01

37/122
56/122

Colombel JF et al The Lancet 2017; 390: 2779-2789
**Course of Crohn’s Disease in Eastern Compared to Western Europe**

- Prospective 488 pt
- Enrolled in 2010
- 14 West Euro countries
  - Pop 7.1 million
- 8 East Euro countries
  - Pop 2.6 million
- Aim: compare the 5 year outcome and disease course

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<th>E Euro</th>
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<tr>
<td>5-ASA</td>
<td>56%</td>
<td>90%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Immuno</td>
<td>66%</td>
<td>54%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Biologic</td>
<td>33%</td>
<td>14%</td>
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**Probability of progressing from non-penetrating, non-stricturing**

- East
- West

Ps0.41

0 1 2 3 4 5 Years


**Probability of hospitalization**

- East
- West

Ps0.95

0 1 2 3 4 5 Years

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Surgery for Crohn’s Disease Declining Rates Prior to Biologic Use

- Published data from:
  - Europe
  - Canada
  - U.S.
  - Korea
  - Japan
  - Hong Kong

Bernstein CN et al GUT 2012; 61: 622-9

Deep Remission: Ulcerative Colitis Evolution

- Norway
- Diagnosis 1990-94
- 353 UC pts
  - Endoscopy within 0.5 and 2 yrs after diagnosis
- 150 patients
  - Endoscopy 5 yrs after diagnosis
- Colectomy
  - MH+ 3pts
  - MH- 13pts

Frøslie KF et al Gastro 2007;133: 412-22

Mucosal Healing Ulcerative Colitis

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Predictors of Mucosal Healing

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2007

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2007

Deep Remission

2012

Stride

2015

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IBS in UC Patients in Deep Remission

• Southeast Norway
• 260 UC patients for ≥20 years
• Colonoscopy and/or fecal calprotectin
• Prospective assessment of Rome III criteria
• Comparison: % IBS symptoms


Deep Remission Conclusions

• Deep Remission—relief of symptoms and endoscopic healing—makes sense
• Evidence that achievement of Deep Remission changes the natural history of disease is lacking for Crohn’s Disease and Ulcerative Colitis
• Deep remission isn’t a mandatory goal until we have convincing data that it makes a difference.