Medical Management of Intestinal Strictures

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Stricturing Crohn’s Disease

- Up to one third of patients with CD develop strictures within 10 years of diagnosis and most commonly affect the distal ileum or the surgical anastomotic site (Cosnes et al. 2002).

- Small bowel CD is an independent predictor of a shorter time to complications (2.12 (1.05–4.29) (Siegel et al 2016).

- A number of risk factors have been identified for stricture development, such as disease duration, smoking, ileal disease and NOD2/CARD15 genetic mutations, though only a limited number have been robustly replicated.
Treating Biologic Refractory Crohn’s disease

- The traditional paradigms are getting challenged.

- The concept of optimum Therapeutic Drug levels are getting challenged.

- The transition to out of class therapeutic agents (with reference to anti-TNF) is getting challenged.

- We need more studies in stenotic CD – concepts are evolving
Genetic factors conferring an increased susceptibility to develop Crohn’s disease (CD) also influence disease phenotype:

Results from the IBDchip European project

OR of association and 95% CI for single nucleotide polymorphisms (SNPs) that passed Bonferroni correction for each outcome
Kaplan Meier Curves – smokers and non-smokers

Grey = smokers    Black = non-smokers

Nunes T et. al. APT 2013;38:752.
Assessing disease modification in IBD:
Lémann Index (LI)

LI is a quantitative tool to assess cumulative structural bowel damage in CD

- Entire GI tract evaluated for damage (stricturing, penetrating lesions, surgery)
  - Divided into 4 regions, and subdivided into segments
  - Lesions and surgery in each segment scored 0-3 according to severity
  - Composite region and overall index score calculated

- LI used to assess damage progression, and to evaluate treatment strategy

- Potential endpoint for disease-modification trials

<table>
<thead>
<tr>
<th>Region</th>
<th>Segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper GI tract</td>
<td>Oesophagus</td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
</tr>
<tr>
<td></td>
<td>Duodenum</td>
</tr>
<tr>
<td>Small bowel</td>
<td>n segments of 20 cm (up to 20)</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>Caecum</td>
</tr>
<tr>
<td></td>
<td>Ascending colon</td>
</tr>
<tr>
<td></td>
<td>Transverse colon</td>
</tr>
<tr>
<td></td>
<td>Descending colon</td>
</tr>
<tr>
<td></td>
<td>Sigmoid colon</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
</tr>
<tr>
<td>Anus</td>
<td>Anus</td>
</tr>
</tbody>
</table>
Pro or Anti-fibrogenic effect on Myofibroblasts

Lawrence, Rogler et al. JCC 2015
Process of tissue repair and fibrosis

- Innate and Adaptive Immune Response
- Epithelial Injury
- Mesenchymal cell
- Activated Myofibroblast
- Post-transcriptional or post-translational regulation of ECM
- Reversal of phenotype
- Reduced Apoptosis
- Normal healing
- Proliferation
- Apoptosis
- ECM deposition
- ECM degradation

Lawrence, Rogler et al. JCC 2015
Cellular Immune Response and Fibrosis
Paediatric Inception Cohort: Development of Stricturing or Penetrating Complications at FU

Kugathasan et al. Lancet 2017
Increased Effectiveness of Early Therapy With Anti–Tumor Necrosis Factor-α vs an Immunomodulator in Children With Crohn’s Disease


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Cumulative Probability of Abdominal Surgery

Crohn’s disease Phenotype at anti-TNF start

B1 = inflammatory; B2 = stricturing; B3 = penetrating. L1 = terminal ileal

LPL GATA3 expression and anti-TNF response in CD

Sa1969 DDW Gene Expression of Matrix Metalloproteinase-3 in Lamina Propria Mononuclear Cells Predicts Response to TNF Inhibitors in Colonic Inflammatory Bowel Disease
Christina Hirota, Ji Li, Miriam Fort Gasia, Mailin Deane, Aito Ueno, Paul L. Beck, Marietta Iacucci, Xianyong Gui, Subrata Ghosh

Gata3

% CD4+ T cells

Responders Non-responders

p=0.002**

Ji Li et al. IBD 2016;22:1179-1792
Paediatric Inception Cohort: Ileal Gene Signatures Associated With Disease Complications

Kugathasan S et al. Lancet 2017

Ileal Gene Signatures predict B2 > B3
Anti-TNF use within 90 days reduces internal penetrating complication-free survival

<table>
<thead>
<tr>
<th></th>
<th>Stricturing behaviour (B2)</th>
<th>Penetrating behavior (B3)</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>p value</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.13 (0.97–1.31)</td>
<td>0.11</td>
</tr>
<tr>
<td>Race</td>
<td>1.25 (0.43–3.63)</td>
<td>0.68</td>
</tr>
<tr>
<td>Isolated ileal location (L1)</td>
<td>1.66 (0.65–4.26)</td>
<td>0.29</td>
</tr>
<tr>
<td>ASCA IgA+</td>
<td>2.87 (1.21–6.82)</td>
<td>0.0165</td>
</tr>
<tr>
<td>CBir1+</td>
<td>1.52 (0.63–3.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Early anti-TNF</td>
<td>1.13 (0.51–2.51)</td>
<td>0.76</td>
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BUT NOT STRICTURING DISEASE

<table>
<thead>
<tr>
<th></th>
<th>Ileal (n = 37)</th>
<th></th>
<th>Colonic (n = 11)</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
<td>SEM</td>
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<tr>
<td><strong>I. Mucosa</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Active inflammation</td>
<td>35.14</td>
<td>2.45</td>
<td>44.85</td>
<td>7.25</td>
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<tr>
<td>Chronic inflammation</td>
<td>54.28</td>
<td>3.16</td>
<td>62.12</td>
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<tr>
<td>Fibrosis</td>
<td>26.13</td>
<td>3.90</td>
<td>15.15</td>
<td>5.25</td>
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<tr>
<td>Muscular Hyperplasia</td>
<td>83.33***</td>
<td>3.03</td>
<td>59.09***</td>
<td>8.52</td>
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<tr>
<td>Space volume expansion</td>
<td>17.12</td>
<td>4.01</td>
<td>9.09</td>
<td>4.69</td>
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<tr>
<td><strong>II. Submucosa</strong></td>
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<tr>
<td>Active inflammation</td>
<td>12.61</td>
<td>2.07</td>
<td>20.20</td>
<td>4.45</td>
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<tr>
<td>Chronic inflammation</td>
<td>61.56</td>
<td>2.60</td>
<td>64.65</td>
<td>3.91</td>
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<tr>
<td>Fibrosis</td>
<td>40.09**</td>
<td>1.99</td>
<td>53.03**</td>
<td>7.04</td>
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<tr>
<td>Muscular Hyperplasia</td>
<td>75.23**</td>
<td>3.27</td>
<td>56.06**</td>
<td>7.87</td>
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<tr>
<td>Adipocyte proliferation</td>
<td>29.73</td>
<td>3.60</td>
<td>21.21</td>
<td>5.07</td>
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<tr>
<td>Neuronal hypertrophy</td>
<td>37.84</td>
<td>5.80</td>
<td>33.33</td>
<td>12.71</td>
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<tr>
<td>Space volume expansion</td>
<td>39.64</td>
<td>5.14</td>
<td>42.42</td>
<td>10.14</td>
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<tr>
<td><strong>III. Muscularis propria</strong></td>
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<tr>
<td>Active inflammation</td>
<td>5.71</td>
<td>1.59</td>
<td>9.09</td>
<td>4.45</td>
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<tr>
<td>Chronic inflammation</td>
<td>42.04</td>
<td>4.31</td>
<td>26.26</td>
<td>6.75</td>
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<tr>
<td>Fibrosis</td>
<td>0.90*</td>
<td>0.90</td>
<td>3.03*</td>
<td>3.03</td>
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<tr>
<td>Muscular Hypertrophy</td>
<td>78.83*</td>
<td>3.86</td>
<td>60.61*</td>
<td>9.87</td>
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<tr>
<td>Neuronal hypertrophy</td>
<td>79.28</td>
<td>4.16</td>
<td>69.70</td>
<td>8.35</td>
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<tr>
<td>Adipocyte proliferation</td>
<td>14.41</td>
<td>3.99</td>
<td>18.18</td>
<td>6.91</td>
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<tr>
<td>Space volume expansion</td>
<td>81.08</td>
<td>3.55</td>
<td>63.64</td>
<td>10.50</td>
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</tbody>
</table>
Contrast Enhanced Ultrasound

Reduced Blood Volume and Blood Flow in Patients with Fibrotic Disease

Nylund K et al. Ultrasound in Med & Biol 2013;39:1197
Severe CD NTI – Incomplete mechanical bowel obstruction

NTI, neo-terminal ileum
Stricture
localised perforation with inflammatory mass
MR-Enterography: extent of disease

Thickened narrowed terminal ileum

Assessment of extent/severity of disease
Assessment of complications
Assessment of treatment response
Model to predict complications of CD

16-year-old girl, small bowel and perianal disease, QSS group=4

Risk of complication

No treatment

Early IM treatment

Early anti-TNF treatment

Years from presentation

Overall HR
Benefits of therapy
196.08
0.18

Personal Characteristics

Disease Location

Serological Inputs

Genetic Inputs

Input age at Dx
Gender input
SB input
LB input
UT input
PA input
Months since Dx

ASCA A input
ASCA G input
CBir1 input
OmpC input
pANCA input

Genetic information
SNP8 input
SNP12 input
SNP13 input

Immunomodulators
Anti-TNF
Corticosteroids

Treatment option=1: treatment within 90 days from diagnosis.
Treatment option=2: treatment after 90 days from diagnosis.

Dx, diagnosis; SB, small bowel; LB, large bowel; UT, upper tract; PA, perianal; anti-CBir1, anti-flagellin; OmpC, anti-outer-membrane porin C of E. coli; pANCA, perinuclear antineutrophil antibody; QSS, quartile sum score; SNP, single nucleotide polymorphism.

Siegel CA, et al. Inflamm Bowel Dis 2011;17:30–38
POCER
Postoperative Crohn’s Endoscopic Recurrence
Randomised, multicentre study in Australia and New Zealand
Standard care with best drug therapy versus endoscopic monitoring with treatment step up in postoperative CD

**POCER: study design**

**High/low risk stratification**
(High risk: smoker, ≥2 surgeries, perforating disease)

**Randomisation 1:2**

1/3 of patients

**All patients:** Metronidazole: 0–3 months

Low risk: No further treatment
High risk: Thiopurine or adalimumab if thiopurine intolerant

2/3 of patients

**Endoscopic intervention (Active arm)**

6-month colonoscopy
Step up treatment if ≥i2 on Rutgeerts scale*

**No endoscopy (Standard arm)**

Risk driven by best drug therapy

18 month colonoscopy

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*To thiopurine (low-risk patients), adalimumab 40 mg eow (high-risk patients on thiopurine), or adalimumab 40 mg ew (high-risk thiopurine-intolerant patients)
POCER: endoscopic outcomes at 18 months

**Remission** (Rutgeerts i0–i1) and **recurrence** (Rutgeerts i2–i4)

<table>
<thead>
<tr>
<th></th>
<th>Active arm (n=122)</th>
<th>Standard arm (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remission</strong></td>
<td>51%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>49%</td>
<td>67%</td>
</tr>
</tbody>
</table>

Primary endpoint: p=0.03
POCER: mucosal healing at 18 months

Complete mucosal healing (Rutgeerts i0) and mucosal lesions (Rutgeerts i1–i4)

<table>
<thead>
<tr>
<th></th>
<th>Active arm (n=122)</th>
<th>Standard arm (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete healing</td>
<td>22%</td>
<td>8%</td>
</tr>
<tr>
<td>Lesions</td>
<td>79%</td>
<td>92%</td>
</tr>
</tbody>
</table>

p=0.03
PREVENT Study Clinical Endpoints

![Graph showing clinical recurrence rates](image)

- Clinical recurrence prior to or at Week 76:
  - Placebo (N = 150): 20.0%
  - Infliximab 5 mg/kg (N = 147): 12.9%
  - P = .097

- Clinical recurrence prior to or at Week 104:
  - Placebo (N = 150): 25.3%
  - Infliximab 5 mg/kg (N = 147): 17.7%
  - P = .098

Regueiro M et al. Gastroenterology 2016;150: 1568-78
PREVENT Study endoscopic recurrence

![Bar chart showing endoscopic recurrence rates in placebo and infliximab groups.](chart.png)

- Endoscopic recurrence defined by Rutgeerts score ≥ i2, fistula/abscess criteria, and treatment failure rules:
  - Placebo: 60.0%
  - Infliximab 5 mg/kg: 30.6%
  - *P < .001*

- Endoscopic recurrence only based on endoscopic criteria (i.e., Rutgeerts score ≥ i2):
  - Placebo: 51.3%
  - Infliximab 5 mg/kg: 22.4%
  - *P < .001*

Regueiro M et al. Gastroenterology 2016;150: 1568-78
Colonoscopy 6-12 months after resection and introduction of TNFi in patients with endoscopic recurrence with or without immunosuppressive drugs would appear to be a pragmatic therapeutic strategy in most patients. Risk attenuation such as cessation of smoking should always be encouraged.

Ghosh S, D’Haens G. Editorial  Gastroenterology 2016;150:1521-1524
RESECTION

IMMUNOHISTOLOGICAL RECURRENCE

COLONOSCOPIC RECURRENCE

SYMPTOMATIC RECURRENCE

TIME
Stages of Postoperative Recurrence

- Immunohistological recurrence
- Endoscopic recurrence
- Symptomatic recurrence
- Complications
- Surgery

INDEX SURGERY

TIME SINCE SURGERY

Ghosh S, D’Haens G. Gastroenterology 2016;150:1521
Anti-fibrotic strategies in Crohn’s disease

• Early effective treatment before fibrosis happens.

• Arrest stenosis by anti-inflammatory therapy

• Use specific targeted therapies in development:
  • Anti-MMP9
  • Anti-IL36
  • Small molecule oral kinase inhibitors
  • Inhibit TGF-beta mediated collagen deposition
Filgotinib: JAK 1 inhibitor in CD

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (n=44) %</th>
<th>Filgotinib 200mg (n=128) %</th>
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</thead>
<tbody>
<tr>
<td>Clinical remission (CDAI&lt;150)</td>
<td>23</td>
<td>48</td>
</tr>
<tr>
<td>Clinical response (100 point CDAI)</td>
<td>41</td>
<td>60</td>
</tr>
<tr>
<td>IBDQ</td>
<td>17.6</td>
<td>33.8</td>
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</table>

All endpoints statistically significant

Lancet 2017;389:266-275
Nintedanib

Fibrosis
(liver cells and myofibroblasts)

Angiogenesis
(endothelial cells, pericytes and vascular smooth muscle cells)

Cell membrane

FGF

VEGF

FGFR

POGF

PDGFR

Pip2

Pip3

Pip3

Pip3

Pip3

PKC

PKA

Nucleus

Proliferation, migration, survival and angiogenesis
Pirfenidone - MoA
Medical Management of Intestinal Strictures

Pre-stricture

- Assess risk factors
- Commence on Disease modification
- Objectively assess Resolution of inflammation
- Aim to resolve inflammation Within 6 months

Established stricture

- Assessment for inflammation Micropenetrating disease etc
- Effective therapy for inflammation
- Assess for residual stenosis
T2T recommendations in CD

Composite endpoint

**Clinical/PRO remission**
- Defined as resolution of abdominal pain and normalisation of bowel habit
  - Assessed at minimum of 3 months during active disease
  - Patients’ individual goals should also be addressed

**AND**

**Endoscopic remission**
- Defined as resolution of ulceration
  - Should be assessed within 6–9 months after start of therapy
  - When endoscopy cannot adequately evaluate inflammation, assess resolution of inflammation by cross-sectional imaging

**Adjunctive measures**
- **Biomarkers**: CRP and faecal calprotectin are adjunctive measures of inflammation, not targets, for monitoring CD
- **Histology**: histologic remission is not considered a target

CRP, C-reactive protein; PRO, patient-reported outcome