ARE WE READY TO CHANGE THE COURSE OF DISEASE IN IBD

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Session objectives

• Build upon the foundation of progression in Crohn’s disease and increase acceptance of the progressive nature of ulcerative colitis

• Increase acceptance of the importance of treating early, setting treatment goals, and using enhanced clinical monitoring
Lémann Index score significantly increased with disease duration in a prospective, cross-sectional, observational study in patients with CD

Median Lémann index score

- <2 years (n=45)
  - 6.3

- ≥2 to <10 years (n=46)
  - 14.3

- ≥10 years (n=47)
  - 19.0

138 patients with CD
Age (median): 34 years
CDAI (median): 187
CDAI <150 (n): 50

Median Lémann Index score increased with duration of disease

P<0.001

Bowel damage assessed by cross sectional imaging at diagnosis increases the risk of hospitalisation and surgery

Complicated CD classified as patients with complications at diagnosis, such as strictures, fistulas and abscesses

Almost 40% of patients already had bowel damage at diagnosis
Crohn’s disease and ulcerative colitis are progressive diseases that reduce patient quality of life.

Progression of digestive damage and inflammatory activity in a theoretical patient with CD
CDAI, Crohn’s disease activity index; CDEIS, Crohn’s disease endoscopic index of severity; CRP, C-reactive protein

Is there a window of opportunity for timely intervention before bowel damage and complications develop?

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**REACT: Algorithm for early therapy in CD**

**CORTICOSTEROID THERAPY (BUDESONIDE OR PREDNISONE DEPENDING ON DISEASE LOCALIZATION)**

**REMISSION**
- **TAPE CORTICOSTEROID**
- **RE-EVALUATE IN 12 WEEKS – REMISSION?**
  - **REMISSION**
    - **NO MAINTENANCE THERAPY**
    - **CONTINUE COMBINATION MAINTENANCE THERAPY**
  - **NO REMISSION**
    - **ADALIMUMAB AND AZATHIOPRINE or METHOTREXATE**
      - Corticosteroid as needed
      - **INCREASE ADALIMUMAB to weekly dose**
      - **SWITCH ANTIMETABOLITE**
      - **SWITCH TNF-ANTAGONIST**
      - **RE-EVALUATE IN 12 WEEKS**
  - **RE-EVALUATE IN 12 WEEKS – REMISSION?**

**NO REMISSION**
- **ADD ADALIMUMAB AND AZATHIOPRINE OR METHOTREXATE**
- **TAPER CORTICOSTEROID**
- **RE-EVALUATE IN 12 WEEKS REMISSION?**
- **RE-EVALUATE IN 12 WEEKS**
- **CONSIDER RESECTION**

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A4 weeks at Canadian sites, 12 weeks at Belgian sites
Patients could enter the algorithm receiving any baseline treatment

Khanna R, et al. ECCO 2014, Copenhagen; OP004
REACT: Complications over 24 months

Nominally significant differences in favour of early treatment

**Hospital admission**
HR (95% CI) = 0.84 (0.56, 1.08)

**Surgery**
HR (95% CI) = 0.69 (0.50, 0.97)

**Serious complication**
HR (95% CI) = 0.73 (0.61, 0.87)

**Hospital admission, surgery, or serious disease-related complication**
HR (95% CI) = 0.73 (0.62, 0.86)

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<thead>
<tr>
<th>Time (months)</th>
<th>CM</th>
<th>ECI</th>
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<tbody>
<tr>
<td>0</td>
<td>1084</td>
<td>897</td>
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<td>3</td>
<td>811</td>
<td>782</td>
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<td>6</td>
<td>741</td>
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<td>9</td>
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<td>24</td>
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<td>472</td>
<td>406</td>
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<tr>
<td>21</td>
<td>406</td>
<td>472</td>
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<tr>
<td>24</td>
<td>472</td>
<td>490</td>
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CM, conventional management; ECI, early combined immunosuppression; HR, hazard ratio
Cumulative probability of abdominal surgery in Calgary: Effect of phenotype and damage: complications mean delayed treatment

Crohn’s disease phenotype at anti-TNF start

- B1 = Inflammatory
- B2 = Stricturing
- B3 = Penetrating
- L1 = Terminal ileal

Follow-up (years)

Cumulative probability of major abdominal surgery

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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR</strong></td>
<td>p value</td>
<td><strong>HR</strong></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.13 (0.97–1.31)</td>
<td>1.37 (1.03–1.81)</td>
</tr>
<tr>
<td>Race</td>
<td>1.25 (0.43–3.63)</td>
<td>3.02 (0.97–9.39)</td>
</tr>
<tr>
<td>Isolated ileal location (L1)</td>
<td>1.66 (0.65–4.26)</td>
<td>1.26 (0.36–4.43)</td>
</tr>
<tr>
<td>ASCA IgA+</td>
<td>2.87 (1.21–6.82)</td>
<td>2.09 (0.71–6.12)</td>
</tr>
<tr>
<td>CBir1+</td>
<td>1.52 (0.63–3.7)</td>
<td>4.82 (1.53–15.2)</td>
</tr>
<tr>
<td>Early anti-TNF</td>
<td>1.13 (0.51–2.51)</td>
<td>0.30 (0.10–0.89)</td>
</tr>
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</table>

**BUT NOT STRICTURING DISEASE**

The primary endpoint was success at week 24, defined as adalimumab continuation without prohibited treatment (corticosteroids after the eight week following inclusion, other anti-TNFs), endoscopic dilation or bowel resection.

At week 24, 62/97 (64%) patients had achieved success.

Among the whole cohort, 50.7% ± 5.3% of patients did not undergo bowel resection 4 years after inclusion.
Potential impact associated with timely treatment

Retrospective analysis of Korean patients with poor prognostic factors (N=670; CD): 365 in the ‘early therapy’ group (79 anti-TNF therapy, 286 immunomodulator therapy), 305 in the ‘late therapy’ group

Patients with Crohn’s disease naïve to both intestinal surgery and intestinal complications with at least 2 risk factors for progression, treated with anti-TNF/IMM therapy.

*Behavioural progression defined as the development of stricturing or penetrating complications in patients with non-stricturing, non-penetrating behaviour.

Since licensing anti-TNFs for Crohn’s disease, hospitalisation and surgical resection rates have substantially reduced

Medical management in IBD patients in a population-based cohort study in the Netherlands (N=1,162)

Hospitalisations

Surgical resection

Decreasing surgical rates in Crohn’s disease
Calgary Health Region
Early anti-TNF therapy could prevent digestive damage in Crohn’s disease

130 CD outpatients with prospective evaluation of the Lémann Index
- Mean global Lémann Index = 11.9 ± 14.1; range 0 to 72.5

Farre C, et al. UEG Week 2017

![Diagram showing Lémann Index with disease duration and anti-TNF therapy status.]
Treat-to-target approach has been explored in IBD clinical studies: Tight Control Changes Outcomes and Progression

In algorithm-driven, prospective treatment studies, the treat-to-target approach was associated with a:

- **Lower rate of hospitalisation, surgery and complications** in patients with established Crohn’s disease\(^1\)
  - Combined immunosuppression algorithmic approach, treating to the target of clinical remission, compared with a conventional approach

- **Lower rate of endoscopic recurrence** in postoperative Crohn’s disease\(^2\)
  - Colonoscopy and treatment step-up for endoscopic recurrence, compared with risk-stratified drug therapy alone

- **Higher rate of mucosal healing** with absence of deep ulcers in early Crohn’s disease\(^3\)
  - Treatment optimisation driven by biomarker levels (CRP and FCP) and clinical symptoms, compared with clinical symptoms alone

CRP, C-reactive protein; FCP: faecal calprotectin

UC is a progressive disease with long-term physical impacts

Disease extension
• Colorectal inflammation extent changing over time

Structural changes
• Strictures also associated with UC
• Pseudopolyposis and bridging fibrosis

Functional abnormalities
• Decreased contractility and motility
• Impaired colonic permeability

Anorectal dysfunction
• ‘Lead pipe’ colon
• Rectal narrowing and widening of presacral space

UC as a progressive disease: Disease extension
Global meta-analysis

- Risk of extension higher in patients from America (37.8%) vs Europe (19.6%) (p<0.0001)
- Rate of extension higher in patients <18 years vs older patients (p<0.0001)

UC as a progressive disease: Functional abnormalities

UC characterised by:

• Decreased contractility
• Reduction in the pressure or amplitude of segmental contractions
• Variability in the behaviour of propulsive pressure waves

Pathophysiological mechanisms responsible for these abnormalities remain unclear

Colorectal cancer and UC: Population-based studies

Meta-analysis comparing frequencies of colorectal cancer in referral centres and population-based studies

Cumulative colorectal cancer (%)

- Referral centres
- Referral centres + population
- Population-based studies

Years

0 10 20 30

0 5 10 15 20 25 30 35 40 45 50

1% at 10 years

4% at 20 years

14% at 30 years

Colonic strictures in UC should raise concerns about the risk of cancer

Frequency of dysplasia and cancer among patients undergoing surgery for colorectal stricture without preoperative evidence of dysplasia or cancer

<table>
<thead>
<tr>
<th></th>
<th>CD (n=248)</th>
<th>UC (n=39)</th>
</tr>
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<tbody>
<tr>
<td>Low-grade dysplasia, % (n)</td>
<td>1.2% (3)</td>
<td>2.5% (1)</td>
</tr>
<tr>
<td>High-grade dysplasia, % (n)</td>
<td>0.4% (1)</td>
<td>2.5% (1)</td>
</tr>
<tr>
<td>Cancer, % (n)</td>
<td>0.8% (2)</td>
<td>5.0% (2)</td>
</tr>
<tr>
<td>Overall, % (n)</td>
<td>2.4% (6)</td>
<td>10.0% (4)</td>
</tr>
</tbody>
</table>

A nationwide study from GETAID: 12,013 patients who underwent surgery for colonic strictures between 1992 and 2014 were screened
Colectomy rates have been decreasing since biologics have been introduced.

Temporal trend analysis of colectomy rates – Alberta data (1997–2009)\(^1\)

- Total
- Elective
- Emergent

Risk of surgery in UC Systematic review (2009–2012)\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>1-year</th>
<th>5-year</th>
<th>10-year</th>
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<tbody>
<tr>
<td>Risk</td>
<td>4.9%</td>
<td>11.6%</td>
<td>15.6%</td>
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10-year predicted and observed colectomy rates – Swiss cohort\(^3\)

Anti-TNF successfully treats many of the common EIMS of IBD

Treatment of IBD with anti-TNF agents results in the improvement of EIM

<table>
<thead>
<tr>
<th>EIM</th>
<th>Prevalence in IBD patients</th>
<th>Parallel course of IBD</th>
<th>Anti-TNF treatment response</th>
<th>Anti-TNF agent</th>
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<tbody>
<tr>
<td>Musculoskeletal</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>3 – 10%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Not necessarily</td>
<td>Yes</td>
<td>Infliximab&lt;sup&gt;2&lt;/sup&gt;; adalimumab&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>10 – 20%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Infliximab&lt;sup&gt;4,5&lt;/sup&gt;; adalimumab&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>20 – 25%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Not necessarily</td>
<td>Yes</td>
<td>adalimumab&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dermatologic</td>
<td></td>
<td></td>
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<tr>
<td>Erythema nodosum</td>
<td>3 – 20%</td>
<td>Yes</td>
<td>Yes</td>
<td>Adalimumab&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>0.5 – 20%</td>
<td>No</td>
<td>Yes</td>
<td>Infliximab&lt;sup&gt;6&lt;/sup&gt;</td>
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<tr>
<td>Ocular</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Uveitis</td>
<td>6%</td>
<td>No</td>
<td>Yes</td>
<td>Adalimumab&lt;sup&gt;7&lt;/sup&gt; infliximab&lt;sup&gt;8&lt;/sup&gt;</td>
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<tr>
<td>Episcleritis</td>
<td>2 – 6%</td>
<td>Yes</td>
<td>Yes</td>
<td>Infliximab&lt;sup&gt;8&lt;/sup&gt;</td>
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<tr>
<td>Hepatobiliary disease</td>
<td></td>
<td></td>
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<tr>
<td>Primary sclerosing cholangitis</td>
<td>7.5 – 18%</td>
<td>No</td>
<td>No</td>
<td>but no worsening of condition in IBD patients treated with adalimumab&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

IBD extends beyond the gut: so should our therapeutic goals

Adalimumab in ulcerative colitis
INSPIRADA: single-arm, multi-country, open-label study in a clinical practice setting

EIMs over time (ITT, LOCF)

Note: Adalimumab is not licenced for use in all conditions listed

EIM, extra-intestinal manifestations; ITT, intent to treat; NRI, non-responder imputation; LOCF, last observation carried forward
Change from baseline over time in percentage of patients with any EIM, p<0.001 (McNemars test). *p<0.01 compared with baseline using McNemar’s test
Strategy to change the course of the disease

Early diagnosis; effective therapy; risk stratify; monitor closely; objective markers; assess change