Latest Treatment Updates for Crohn's Disease: Tailoring Therapy

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Heterogeneity of Inflammatory Bowel Disease

- Phenotypic: Montreal/Paris classification
- Genetic
- Serology
- Disease stage/course
- Previous treatment

- Fibrogenesis targets
- Epithelial-mesenchymal transition – fistulization
- PSC

GENOME-MICROBIOME-ENVIRONMENT
- SITE DEFINING
- SEVERITY DEFINING
- OUTCOME DEFINING
Why Assess Prognosis Initially?

• Assessing prognosis at an early stage is essential for the development of an appropriate management plan.
Risk Profiling in Crohn’s Disease

- Development of strictures
- Development of perianal fistulae
- Development of non-perianal fistulae
- Risk of IBD related surgery
- Development of microfistulae/abscess
- Uncomplicated course
# Predictors of Poor Outcomes in CD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Predictors</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munkholm PL. <em>Gastroenterology</em> 1993</td>
<td>Extensive (&gt;100cm), gastroduodenal or jejunal disease</td>
<td>Mortality</td>
</tr>
<tr>
<td>Franchimont D. <em>Eur J Gastroenterol Hepatol</em> 1998</td>
<td>Smoking, colitis, non-fibrostenotic type, young age at diagnosis</td>
<td>Corticodependency</td>
</tr>
<tr>
<td>Lichtenstein G. <em>Am J Gastroenterol</em> 2006</td>
<td>Disease severity, ileal disease, corticosteroid use</td>
<td>Stenosis or obstruction</td>
</tr>
<tr>
<td>Beaugerie L. <em>Gastroenterology</em> 2006</td>
<td>Need for steroids, perianal disease, age at diagnosis &lt;40 yrs</td>
<td>Disabling disease (&gt;2 steroids, IMs, hospitalisation, surgery within 5yr)</td>
</tr>
<tr>
<td>Loly C. <em>Scand J Gastroenterol</em> 2008</td>
<td>Age &lt;40, stricturing disease or intra-abdominal fistula, perianal disease, fever, weight loss &gt;5 kg, high platelet count</td>
<td>Severe disease (&gt;2 resections or &gt;70 cm, stoma, complex perianal disease 5 yr)</td>
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</table>
Predictors of Disabling Crohn’s Disease in the 5-year Period After Diagnosis

Score is based on the number of predictive factors at diagnosis: age <40 years, steroid treatment, perianal lesions

*Disabling Crohn’s disease predictive score
Beaugerie L et al. Gastroenterol 2006;130:650–656
Predicting Severe Crohn’s Disease: Deep Ulcers at Colonoscopy

Probability of colectomy in patients with or without deep ulcers covering >10% of at least 1 colonic segment

Bars represent 95% confidence intervals. In univariate analysis, presence of deep ulcers at index colonoscopy were associated with a significantly higher risk of colectomy ($p<0.0001$)

Adapted from Allez M et al. *Am J Gastroenterol* 2002;97:947–953
Which Prognostic Factors to Use?

- **Clinical** (age, extent, behaviour, symptoms)
- **Endoscopic** (mucosal healing)
- **Imaging**
- **Serological and laboratory markers** (CRP, ASCA, ANCA, OmpC)
- **Fecal** (calprotectin)
- **Genetic** (>100, primarily NOD2/CARD15)

ANCA: anti-neutrophil cytoplasmic antibodies; ASCA: anti-Saccharomyces cerevisiae antibodies; OmpC, outer membrane protein C precursor
What’s the Latest: Altering the Immune System to Suppress Inflammation-targeted Therapies

- **Signaling modulation:** JAK inhibition (tofacitinib)
- **Immune cell trafficking:** α4β7 inhibition (vedolizumab)
- **Cytokine modulation:** anti-IL12p40, anti-IL-23p19
- **Immune cell modulation**
- **TGF-beta:** Smad7 anti-sense (GED-0301)
Cytokine Signaling via Janus Kinases

IFN related cytokines
Common gamma chain
gp130 family cytokines

Tofacitinib in Crohn’s Disease

Phase 2 trial in UC was positive

Leukocyte Trafficking Mechanisms

Natalizumab
Vedolizumab
Etrolizumab
Anti-MAdCAM

Ghosh & Panaccione 2010
Vedolizumab in CD-GEMINI 2

- Placebo (N=153)
- Vedolizumab, every 8 wk (N=154)
- Vedolizumab, every 4 wk (N=154)

P<0.001 at wk 52, placebo vs. vedolizumab every 8 wk
P=0.004 at wk 52, placebo vs. vedolizumab every 4 wk

Sandborn WJ et. al. NEJM 2013:369;711
IL-12/IL-23 Pathway and Signaling
Ustekinumab: Response & Remission at Week 22: CERTIFI Study

Subjects who discontinued study agent due to lack of efficacy, had a prohibited CD-related surgery, or had prohibited concomitant medication changes after Week 8 are considered not to be in clinical response/remission, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical response/remission.
Latest on Known Drugs: Early Azathioprine in Crohn’s Disease: AZTEC Study

Probability of survival free of relapse

Panes J et. al. 2013; 145: 766
Early Azathioprine in Crohn’s Disease: RAPID GETAID Study
Diagnosis of IBD

Stratify by risk

Favorable outlook

Conventional Rx

Poor prognosis

Profile pathways for targeted molecules

AntiTNF, Anti Integrin, JAK blocker, Anti-p40

How Will We Practice in 2020?
Molecular Profiling: Epithelial Gene Expression: Anti-TNF Responders and Non Responders
Biomarkers of Anti-TNF Response in CD Tissues

CXCL6 (GCP2)

CXCL10 (IP-10)

Min-Max whiskers; + denotes Mean; 1-way ANOVA, Bonferroni post-test

Hirota C et. al. UEGW 2012
Smoking: Kaplan Meier Curves – Smokers and Non Smokers

Grey = smokers  Black = non-smokers

Nunes T et. al. APT 2013;38:752.
Plasma Vitamin D Status Prior to Anti-TNF Initiation

Zator ZA et. al. JPEN 2013 ePub ahead of print
Cumulative Probability of Abdominal Surgery

Crohn’s Disease Phenotype at Anti-TNF Start

B1 = inflammatory; B2 = stricturing; B3 = penetrating; L1 = terminal ileal
Predictive factors

- Non-colonic disease
- Penetrating disease
- Smoking, High BMI
- Male gender
- Early steroid use
- Severe endoscopic lesions
- NOD2/CARD15, ASCA, I2, OmpC, CBir1

Predictors of Surgery in Crohn’s Disease

Dubinsky MC. World J Gastroenterol 2010;16:2604–2608
Frøslie KF, Gastroenterol 2007;133:412–422
IBD Treatment Goals Are Evolving

- Change course of disease
- Deep remission
- Mucosal healing
- Steroid-free remission
- Clinical remission
- Improved symptoms

Treatment strategies need to evolve as treatment goals evolve

Adapted from IOIBD
Symptoms and Inflammatory Load: The Concept of Treat to Target (T-T)

We currently underestimate treatment need
Paradigm shift

Symptoms
Tissue damage

Inflammation

Overt inflammation

Treatment threshold

Aim to keep your patients in this health state

Asthma: PEFR
RA: low DAS, Sharp score
IBD: Lemann score, Mucosa
Tailoring Therapies in CD

- Azathioprine
  - TPMT
  - Metabolites
-Tacrolimus
  - Drug levels
- Ciclosporin
  - Drug levels

Other strategies are evolving
Managing Loss of Response

- Primary non-responder
- Secondary loss of response
- Pharmacokinetic failure
- Pharmacodynamic failure
- Immunogenicity failure

Optimize biologic – dose escalation

Measuring drug levels is more cost effective than empiric dose escalation
STORI Relapse Rate

Kaplan-Meier curve of relapse

Proportion

Months since inclusion

(n=45/115 – 7 relapses censored)
Median follow up 12 ± 1 months (IQR: 8–18 months)

N= 100 74 55 31

Louis E et al. Gastroenterol 2009;136:A146
STORI enrolled 115 Crohn’s disease patients who were treated with infliximab plus an immunomodulator for at least 1 year, and who were in stable remission for at least 6 months. Infliximab was discontinued, and 39% of patients relapsed within 1 year.

De Suray N. ECCO 2012: P274
POCER Study: Postoperative Crohn’s Disease Endoscopic Recurrence

Methods: Multicentre RCT

RISK Stratification: Low or High
(High risk: smoker, ≥ second operation, perforating disease)

SURGERY: Curative resection

Randomization

1/3 of patients

No Endoscopy (“Standard”)
Risk driven best drug therapy

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”)

6 Month Colonoscopy
Step up Rx if ≥2 on Rutgeerts scale

18 Month Colonoscopy

POCER Study: Postoperative Crohn’s Disease Endoscopic Recurrence

• Results (ITT):
  - 32% dropout rate; no difference between both study arms
  - 174 randomized: 122 Active/ 52 Standard

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<tr>
<th>Group</th>
<th>Rutgeerts (\leq i^2) at 18 months</th>
<th>(P)</th>
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<tbody>
<tr>
<td>Active Care (n=122)</td>
<td>62/122 (51%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Standard Care (n=52)</td>
<td>17/52 (33%)</td>
<td></td>
</tr>
<tr>
<td>Adalimumab Immediately Postop (n=28)</td>
<td>16/28 (57%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Adalimumab Initiated if (i^2) at 6 Months (n=32)</td>
<td>13/32 (41%)</td>
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  - 6-month endoscopic recurrence: ADA better than thiopurine in high-risk patients (\(P=0.028\))
  - Stepping up at 6 months if \(i^2\) brought 39% into endoscopic remission at 18 months
  - Remission at 6 months colonoscopy, 39% endoscopic recurrence at 18 months

• Conclusions:
  - Treatment according to risk of recurrence at 6 month colonoscopy, is superior to drug therapy alone
  - Step-up with anti-TNF therapy, based on colonoscopy findings at 6 months, is a viable strategy in high-risk patients

How to Manage Post-operative Recurrence

• High risk of recurrence
  – Smoker, penetrating disease, multiple surgeries
    • Use immunomodulators and anti-TNF

• Low risk of recurrence
  – Colonoscopy at 6-12 months
  – If significant recurrence, use immunomodulators and anti-TNF
Proposed Algorithm for Treatment of Early Crohn’s Disease

Early CD = disease duration <2 years and no previous use of IMS or TNF antagonists

High risk for rapid progression to bowel damage and disability

Potential predictors from literature
- Early onset (<40 years)
- Small bowel involvement
- Perianal disease at diagnosis
- Endoscopic severe lesions (ulcers)

Predictors that the authors apply in clinical practice
- Diagnosis at age <40 years
- Extensive small bowel involvement
- Perianal or severe rectal disease
- Deep ulcers at index colonoscopy
- Prior surgical resection
- Stricture and/or penetrating behaviour

Early top-down
IMS + TNF antagonist

Accelerated step-care
CS + IMS

Fail to respond
IMS + TNF antagonist

CD = Crohn’s disease; CS = corticosteroids; IMS = immunosuppressive; TNF = tumour necrosis factor

## Optimal Treatment Strategy Elements

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<th>Patient profiling</th>
<th>Treatment goal</th>
<th>Therapy</th>
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<tbody>
<tr>
<td>● Prognostic factors</td>
<td>● Measurable</td>
<td>● Early use to achieve optimum patient outcomes such as mucosal healing</td>
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<tr>
<td></td>
<td>● Acceptable benefit / risk</td>
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- Do not delay effective therapy until a time when it will be less effective…