PRECISION MEDICINE IN IBD

Philippe Saniour, MD
LSGE 2019
Precision Medicine in IBD

The goal of precision medicine in IBD is to utilize specific clinical and biologic characteristics of *individual patients* to predict the disease course and tailor treatment to deliver optimal care, in other words try to *personalize* the treatment.
Natural History Crohn’s Disease

Patterns of severity of bowel symptoms in CD

IBSEN: disease course in Crohn's disease over 10 years

- 45% penetrative
- 19% stricturing
- 32% inflammatory
- 3% minor

The risk of developing severe disease increases over time.
Natural History Ulcerative Colitis

Curve 1: Remission or mild severity of intestinal symptoms after initial high activity

55% (n=208)

0 10 yrs

Curve 2: Increase in the severity of intestinal symptoms after initial low activity

1% (n=4)

0 10 yrs

Curve 3: Chronic continuous symptoms

6% (n=22)

0 10 yrs

Curve 4: Chronic intermittent symptoms

37% (n=139)

0 10 yrs

NATURAL HISTORY OF ULCERATIVE COLITIS

Risk of colectomy: 24% after 10 years
~ 30% after 20 years
Significant Increased risk of cancer

Adapted from Langholz E. et al. Gastroenterology 1994
Treatment of IBD

Ulcerative Colitis

Crohn’s Disease

J Buricsh, Dan Med J 2014
Biologics and Small Molecules in IBD
Efficacy of Biologics
Long Term Efficacy of Biologics

Ustekinumab

Vedolizumab
Long Term Efficacy of Biologics

Crohn's Disease Response to Primary TNF-alpha Blocker

- Clinical response to primary TNF-alpha blocker
- LOR to primary TNF-alpha blocker
- PNR to primary TNF-alpha blocker

- Respond to TNF-alpha blocker switch: 53%
- Respond to class switch to integrin blocker: 24%
- Incidence LOR to ADA: 24%
- Incidence LOR to IFX: 13%

45% Clinical Response
35% LOR
20% PNR
Improve Outcomes

• Predict the course of the disease
• Apply an adapted strategy
• Choose the most appropriate drug
• Optimize the use of the chosen medicine
Predictors of Outcomes CD

Vermeire S et al, Gut 2013
Park et al, Inflamm Bowel Dis 2017
## Predictors of Outcome CD

<table>
<thead>
<tr>
<th></th>
<th>Colonic or ileocolonic disease at diagnosis (L2 or L3)</th>
<th>Small bowel disease at diagnosis (L1 or L4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥30 years at diagnosis</td>
<td>&lt;30 years at diagnosis</td>
</tr>
<tr>
<td><strong>GCS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ASCA</strong>&lt;sup&gt;+&lt;/sup&gt; positive</td>
<td>49.0% (40.1–57.9)</td>
<td>76.7% (69.1–84.2)</td>
</tr>
<tr>
<td><strong>NO</strong></td>
<td>24.8% (17.1–32.5)</td>
<td>53.0% (44.0–61.9)</td>
</tr>
<tr>
<td><strong>ASCA</strong>&lt;sup&gt;+&lt;/sup&gt; negative</td>
<td>21.5% (14.1–28.8)</td>
<td>48.3% (39.4–57.2)</td>
</tr>
<tr>
<td><strong>NO</strong></td>
<td>8.6% (3.6–13.6)</td>
<td>24.3% (16.6–31.9)</td>
</tr>
</tbody>
</table>

*Solberg IC et al, Inflamm Bowel Dis 2014*
Predictors of Outcome UC

• IBSEN Cohort predictors of poor outcome:
  - Young age at diagnosis (<40 y)
  - Extensive disease
  - Need for systemic steroids
  - High CRP (>30 mg/l)

• ACT (Infliximab trial) predictors of poor outcome:
  - Recent diagnosis (<3 y)
  - Mayo score > 10
  - Need for steroids at inclusion
  - CRP > 20 mg/l at diagnosis

Solberg IC et al, Scand J Gastroenterol 2009
Sandnorn WJ et al, Gastroenterology 2009
Predictors of Outcome IBD

The use of a CD8 T cell gene expression signature that corresponds to differences in T cell exhaustion, detectable during active untreated disease (including at diagnosis) that can predicts disease course in IBD

Biasci D, Lee JC et al, Gut 2019
Treatment Strategy

The Earlier the Better

Starting Anti-TNF Therapy: The Importance of Timing

Graph showing the percentage of CD patients in remission over different disease durations with different trials.

References:
Treatment Strategy

Combination treatment

Corticosteroid free remission at week 26

Colombel JF et al, NEJM 2010
Treatment Strategy

Top Down

Treatment Strategy


CHARM subanalysis
Choose the Appropriate Medicine

- Pros and Cons of Anti-TNF
  - Most studied and experienced
  - Evidence for fistulizing disease treatment (Infliximab > Adalimumab)
  - Use for extra-intestinal manifestations
  - Data regarding decrease post-op recurrence
  - Use in Acute Severe UC (Infliximab)

  - Issues with safety, demyelinating disease and heart failure
  - High rate of antibodies formation with time (Infliximab > Adalimumab)
  - Need for combination with Azathioprine (Infliximab)
Choose the Appropriate Medicine

• Pros and Cons of Vedolizumab

- Cumulating data in UC and CD regarding clinical and endoscopic efficacy
- Safety, mainly regarding patients with h/o infections and cancers
  (caution re digestive cancers)

- No evidence on efficacy in extra-intestinal manifestations
  (except on arthralgias and arthritis thru decreasing intestinal activity),
  post op use and fistulizing disease
- Slow onset of action (CD)
Choose the Appropriate Medicine

• Pros and Cons of Ustekinumab

- Cumulating data in CD (and UC) regarding clinical and endoscopic efficacy
- Possible efficacy in fistulizing disease (Real world data and post hoc analysis)
- Safety

- No evidence based trials regarding post-op use, fistulizing disease and extra-intestinal manifestations (except anti-TNF induced psoriasis)
Choose the Appropriate Medicine

• Pros and Cons of Tofacitinib

- Non biologic, so lack of antibody formation
- Rapid onset and fast decision regarding efficacy
- Oral administration

- Safety (VZV and PE ?)
- Pregnancy
Chose the Appropriate Medicine

Usually it will come down to a discussion between the patient and the physician regarding the efficacy in the given disease setting, the safety and the route of administration of the medication.

The best results are always with the FIRST administered medication.
Predictors for Anti-TNFs

pANCA positivity and poor response

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate analysis (n = 184)</th>
<th>Multivariate analysis (n = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Log-rank P value</td>
<td>OR (95% CI) P value</td>
</tr>
<tr>
<td>Short-term complete</td>
<td>&lt;.001</td>
<td>3.75 (2.35–5.97) &lt;.001</td>
</tr>
<tr>
<td>clinical response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term CRP level</td>
<td>.014</td>
<td></td>
</tr>
<tr>
<td>normalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term mucosal</td>
<td>&lt;.001</td>
<td>1.87 (1.17–2.98) .009</td>
</tr>
<tr>
<td>healing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pANCA negative</td>
<td>.052</td>
<td>1.96 (1.23–3.12) .005</td>
</tr>
</tbody>
</table>

In a pooled analysis (N=415), pts with pANCA – had a near twofold higher response to Anti-TNFs compared to those who were pANCA +

Arias MT et al, Clin Gastroenterol Hepatol 2015
Nguyen DL et al, South Med J 2015
Predictors for Anti-TNFs

Oncostatin M predicts failure

Hierarchical clustering of chemokine and cytokine genes (n=2 IBD cohorts)

Identify consistently OSM-associated genes

Cytokines
- CSF2
- IL1B
- IL1A
- IFNG
- IL6
- IL17A
- IL11
- IL22

Chemokines
- CXCL1
- CCL2
- CXCL2
- CCL3
- CXCL3
- CCL4
- CXCL5
- CCL9
- CXCL6
- CCL10
- CXCL8
- CCL11

Module-low
- 85%
- Relative risk=5.0
- (95% CI=1.4–17.9)
- p=0.0006

Module-high
- 10%
- Relative risk=5.0
- (95% CI=1.4–17.9)
- p=0.0006

Infliximab responsive
- 15%

Infliximab refractory
- 85%

Nathaniel RW et al, Nat Med 2017
Predictors for Anti-TNFs

High intestinal plasma cells (Biopsy) and TREM-1 upregulation (Blood) predicts failure

Gaujoux R et al, Gut 2018
Predictors for Anti-TNFs

HLA-DQA1*05 predicts antibody formation

Sazonovs A et al, and the PANTS Consortium
Predictors for Vedolizumab

- Immunologic predictors:
  Increase circulating memory CXCR3+CCR6- T cells (Th1) at baseline associated with week 14 response and week 52 remission

- Microbiome:
  Community α-diversity was significantly higher, and Roseburia inulinivorans and a Burkholderiales species were more abundant at baseline among CD patients achieving week 14 remission

Coletta M et al, AGA 2018
Ananthakrishnan A et al, Cell Host Microbe 2017
Predictors for Ustekinumab

- Microbiota signature associated with better outcome:
  Two OTUs affiliated with *Faecalibacterium* (\(P \ 0.003\)) and *Bacteroides* (\(P \ 0.022\)) were significantly more abundant at baseline in subjects who were in remission 6 weeks after treatment than those with active CD.
Optimize the Treatment

- CALM: Treatment escalation decisions based on close monitoring of both clinical evaluation and biomarkers of inflammation (serum CRP and fecal Calprotectin)

CDEIS < 4 and no deep ulcers

(Clinical Management vs. Treat to Target)

Colombel JF et al, Lancet 2017
Optimize the Treatment

• PANTS:
  - 955 IFX, and 655 ADA
  - Primary non response at week 14: 23,8%
  - Non remission at week 54: 63,1%
  - Only factor associated with non response: Low drug concentration at week 14
  - Optimal week 14 drug levels for week 14 and 54 remission: 7 µg/ml for IFX and 12 µg/ml for ADA

Kennedy N et al, Lancet Gatroenterol Hepatol 2019
Optimize the Treatment

• PANTS:
  - 62.8% (IFX) and 28.5% (ADA) developed drug antibodies
  - Combination with an Immunomodulator (AZA or MTX) decreased the risk of antibodies formation (OR: 0.39 for IFX and 0.44 for ADA)
  - Conclusion: Clinical trials are required to investigate whether personalized induction regimens and T2T dose intensification improve outcome

Kennedy N et al, Lancet Gastroenterol hepatol 2019
The Future: The Omics

**Exposome**
- Environmental Rx:
  - Targets largely unknown
  - Selective efficacy (e.g., smoke cessation)
  - Hard to implement (behavioral modifications)
  - Lifetime implementation

**Genome**
- Genomic Rx:
  - Not yet available
  - Target selective
  - Unknown effectiveness
  - Unknown risks

**Immune Rx:**
- Reasonably effective
- Limited target selection
- Common side effects
- Loss of efficacy

**Gut microbiome**
- Microbial Rx:
  - Occasional efficacy
  - Not target selective
  - Predictable side effects
  - Limited time use

**Omens analysis**

**Personalized Rx:**
- Correct target identification
- Absolute specificity
- Potentially curative

**IBD Interactome**
- Multiomics Integration of IBD networks
The Future: Systems Biology
Conclusion

The Advent of Biologics improved the outcome of IBD patients in many aspects mainly regarding surgery and hospitalization

Despite that, in the era of deep remission, the target is reached in 30-40 % with any given drug

Patients stratification regarding disease severity, choosing the most appropriate medication and optimizing its use will probably help improve the outcomes

The era of personalized medicine is at its beginning, and the use of the Omics and Big Data will change our treatment paradigm in IBD