Individualizing IBD therapy according to disease mechanism

3rd Annual Baylor University Medical Center IBD Conference
Dallas, TX
April 14, 2018
Peter Mannon, MD
University of Alabama at Birmingham

The ability to individualize IBD therapy according to mechanisms assumes that:
• We have characterized different pathways to disease (the same phenotype)
• The different pathways have unique nodes for intervention
• There exist effective therapeutic agents that can moderate the different pathways
• We can identify which pathways are dominant in the disease in individual patients and be able to do this before treatment

Individualizing IBD therapy according to disease mechanism

Precision medicine provides care designed to optimize efficiency or therapeutic benefit for particular groups of patients, especially by using genetic or molecular profiling.

Optimized versus precision medicine for IBD?
We cannot individualize IBD therapy according to disease mechanism at this time

Current approaches to fulfilling individualized therapy in IBD

Predicting non-response to anti-TNFs
Lessons from targeting specific molecules
Determining Endophenotypes of Disease: Hope for Improving Response to Therapy

Individualizing Therapy in IBD: anti-TNFα drugs

Pharmacokinetics: response related to tissue drug level
• TNF:anti-TNF Ab ratio different between inflamed and non-inflamed mucosa (Yao, A., et al. 2016. 264:201–205)
• Optimized trough serum levels associated with increased CD remission (Vanlo, C., et al. 2012. Gastroenterology 142:1230–1238)
• Higher rates of anti-TNF Ab cleavage due to increased MMP expression (Biancheri, P., et al. Gastroenterology 2015 149:1564–1574)
• Pharmacodynamics: is the signaling effect the same?
• Seems that R and NR to IFX can have same profile for many TNF-responsive genes but other changes in IL1β and IL-17 supporting importance of “non-TNF-driven inflammation” (Leal, et al. Gut 2015 64:233–242)
• We have many examples of molecular profiles of gene expression that change differentially in R and NR but no pre-treatment discriminators
Individualizing Therapy in IBD: anti-TNFα drugs

- Pre-treatment molecular signatures of cell subsets in LP showed NRs had higher plasma and activated macrophages (Gaujoux et al Gut 2018;0:1–11)
- NRs had lower expression of surface TNF in LP immunocytes
- Pre-treatment genotype IL17F (G/G) and the IL17R adaptor protein TRAF3IP2 (C/C or C/A) gene polymorphisms (Urabe et al Biomed Res Int 2015:416838)

Mucosal biopsy-based, pre and post IFX induction
CD: fecal calprotectin heterodimeric complex of S100A9/S100A8, a lymphocyte cell cycle protein
UC: genes involved in adaptive immune response, TNF pathway
IL-11: hematopoetic sten cell and megakaryocyte growth factor
These results have not been validated in larger studies

Therapy Based on Disease Mechanism: Highlighted Experiences

- Can we identify subjects who will do better with one targeted drug over another?
- Targeted mechanisms
  - IL-12/INFα and IL-23/IL-17 dominant in Crohn’s disease
  - Anti-IL-17A and anti-IL-17RA trials
  - Anti-p40 (IL-12/23): briakinumab, ustekinumab (Stelara)
  - IL-13 associated with ulcerative colitis (Th2-like)
  - Inhibited TGFβ signaling by excess SMAD7 (Mongersen) (no apparent regulatory defect in CD and UC despite the VEO-IBD and checkpoint inhibitor IBDs not withstanding)

The Origins of IL-23/IL-17 Contributions to Crohn’s disease

The IL-23/IL-17 Association with IBD

Elevated IL-17 in Active IBD

The Origins of IL-23/IL-17 Contributions to Crohn’s Disease

Role of IL-23 in Transfer Colitis Model

<table>
<thead>
<tr>
<th>Recipient genotype</th>
<th>IL-12/23</th>
<th>IL-12</th>
<th>IL-23</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAG, no IL-12/23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAG, no IL-12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAG, no IL-23</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P<0.0001

Hui et al. JIM 2009;22:24-27
Targeting IL-17 in IL-10-/- Colitis Model Does not Fully Inhibit Inflammation

Yen et al., JCI 2006 116: 1310

Targeting IL-17 in TNBS Colitis Model Worsens Outcome in IL-23 Deficiency (p19 KO)

Becker et al. J Immunol 2006; 177:2760-2764

Experience with anti-IL-17 Agents in Crohn’s Disease

- Secukinumab performed worse than placebo, especially in patients with higher CRPs
- 43% infection rate vs 0% placebo; 4 with severe mucocutaneous Candidiasis

Brodalumab (anti-IL-17AR) clinical trial results have not been published but this study was stopped early due to significantly more adverse events in the study drug arm.

IL-13 Is the Effector Cytokine in Experimental Oxazolone Colitis

Fuss, JCI 2004

Results of Interferon-beta Trial in UC

Fusaro et al., 2013

High IL-17 Production Accompanies Non-response to Interferon-β in Multiple Sclerosis

Burt et al., 2015
Individualizing Therapy in IBD: Insights from Monogenic diseases associated with IBD

- Subsets of IBD pts with NADPH oxidase hypomorphic phenotype and treatment with G-CSF or GM-CSF
- Subsets of IBD pts with hyper-inflammatory phenotypes may resemble mevalonate kinase deficiency or FMF pts with IBD who respond well to IL-1β antagonists
- Endophenotype of high IL-17 production

Individualizing Therapy in IBD Based on Mechanism of Disease

- Optimizing therapy versus individualizing for now
- Working to establish endophenotypes of disease that expand beyond excess cytokine production
- Continued focus on conventional and experimental therapies with comprehensive study of pre-treatment and post-treatment genetic, epigenetic, and molecular measures linked to robust outcomes
- Paying attention to the extremes of outcomes to differentiate dominant effects for robust predictors of outcomes to highly targeted therapies

Individualizing Therapy in IBD: Insights from Monogenic diseases associated with IBD

- Subsets of IBD pts with NADPH oxidase hypomorphic phenotype and treatment with G-CSF or GM-CSF
- Subsets of IBD pts with hyper-inflammatory phenotypes may resemble mevalonate kinase deficiency or FMF pts with IBD who respond well to IL-1β antagonists
- Endophenotype of high IL-17 production