New approaches in the treatment of IBD

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Objectives

• Understand some of the basic immunologic pathways targeted by modern day IBD therapeutics.

• Understand current treatments, their efficacy and limitations.

• Detail the various mechanisms of action for emerging therapeutic agents in IBD.
Where we are now …
and where we want to be

Diagnosis
(usually endoscopy)

Disease prognosis
(clinical parameters)

Treatment based on
symptoms +/- endoscopic
inflammation

First visit:
IBD panel

Serotype
Genotype
Phenotype

IBD subtype
Disease prognosis
Patient-specific treatment plan
Integrated target-specific therapy

IBD
MULTIFACTORIAL PATHOGENESIS

Luminal Antigens
Diet
Microbes

Immuno-
genetics

Immune
Response

Environment

~ 80% Environmental

~ 20% Genetics

Slides courtesy of Neil Nandi. Drexel University

Oriana M. Damas, MD
Treating IBD
Our current biologic armamentarium in IBD

- **Infliximab**
  - Chimeric monoclonal antibody (75% human IgG1 isotype)
  - Mouse Human

- **Adalimumab**
  - Human recombinant antibody (100% human IgG1 isotype)
  - Human recombinant antibody (100% human IgG1 isotype)

- **Certolizumab Pegol**
  - Humanized Fab' fragment (95% human IgG1 isotype)
  - PEG, polyethylene glycol.

- **Vedolizumab**
  - Humanized IgG1

Impact of Therapy Will Depend on Degree of Structural Damage and Speed of Progression

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244-250.
Combination therapy is better

**Immunomodulators:**
- Thiopurines
  - MTX
- High inflammatory burden
- Moderate-to-severe disease
- Steroid-refractory disease
- Severe prognostic markers

**Anti-TNFs**
- Mechanistic synergy
- Higher levels of biologic

**SONIC**

Combination therapy with infliximab and azathioprine works better than either alone in Crohn’s disease

Mucosal Healing at Week 26

![Graph showing mucosal healing at week 26](image)

**UC SUCCESS**

Combination therapy with infliximab and azathioprine works better than either alone in UC


**Other anti-TNFs in the pipeline**

- **Biosimilars (many in development)**
  - Copy versions of currently approved biologic agents
  - Remsisa/ CTP-13
  - Reduction in price 30% and increase access to therapy
  - Last week Remsisa got FDA advisory committee endorsement

An Oral Anti-TNF (Avx-470)

Anti-TNF activity in colon mucosal tissue in UC patients treated with AVX-470 also corresponds with clinical response


Are anti-TNFs the best option? How come they don’t work 100%

• Dose not high enough:
  – Dose of anti-TNF proportional to extent and severity of inflammation
  – Tissue versus serum levels of drug

• Different mechanism driving inflammation:
  – Could be different cytokines
  – Could be epithelial dysfunction
  – Microbial dysbiosis

UNMET NEED TO FIND ALTERNATIVE THERAPIES
Anti-TNF Efficacy

- **Infliximab, ACCENT I**
  - Response, Wk 2: 68.5%
  - Remission, Wk 30: 39%
  - Overall, Wk 30: 22%

- **Adalimumab, CHARM**
  - Response, Wk 4: 60%
  - Remission, Wk 26: 40%
  - Overall, Wk 26: 24%

- **Certolizumab, PRECISE 2**
  - Response, Wk 4: 84.1%
  - Remission, Wk 26: 17.9%
  - Overall, Wk 26: 30.7%

  - ⅔ Responders lose response over 1 year
  - ⅓ Responders lose response more slowly

* Data here for Moderate-Severe Crohn's

Multiple Mechanisms of Action

**Lymphocytic Trafficking Blockade to Vascular Endothelium**
- Anti-Adhesion Molecules
- Anti-Integrins
- Anti-Addressins

**Cytokine Blockade**
- Anti-TNF
- Anti-IL-12/23

**Lymphocyte Circulation**
- S1P Modulators

**Intracellular Blockade**
- JAK Inhibitors
- SMAD Anti-sense Oligonucleotides
Minimizing Leukocyte traffic with anti-integrins

α₄β₇: GEMINI I - Vedolizumab in UC

Vedolizumab 300 mg IV at Weeks 0, 2, 6, then q8 weeks, Wk 6

New insights in 2016 about Vedo

- Gemini Long term extension study:
  - Clinical remission at 61% and 74% at weeks 52 and 104 weeks in CD.
  - Certain patients may benefit from a decrease in interval from q 8 to q 4 weeks.
  - Adverse events remain similar to induction studies and no PML!
  - Similar rates of antibodies were seen in the vedo monotherapy (3%) vs vedo plus imuno. (4%)

No response at week 10 of induction an added 300 mg infusion dose at week 10 can be considered.
Key Adhesion Molecule Interactions

**MAdCAM-1** = mucosal addressin cell adhesion molecule-1; **VCAM-1** = vascular cell adhesion molecule-1


Natalizumab

Vedolizumab

Upregulated by cytokines

PF-00547,659 (Anti-MAdCAM)

Leukocyte

**α4-Integrins:** required for firm adhesion to and migration across endothelium

E-Selectin

P-Selectin

MAdCAM-1

VCAM-1

α4β7

α4β1

Endothelial Cell

**MAdCAM-1** = mucosal addressin cell adhesion molecule-1; **VCAM-1** = vascular cell adhesion molecule-1


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PF-00547,659 (Anti-MAdCAM)
**Anti-Adhesion Evolution: Targeted Therapy**

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Endothelium

α4-β7

VCAM

E-cadherin

MAdCAM

Integrins α4-β1

Addressins

Leukocyte

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**β7: Etrolizumab in UC**

**A** Remission

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<th>Placebo</th>
<th>Etrolizumab 100 mg</th>
<th>Etrolizumab 300 mg+CD</th>
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**B** Response

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<td>10</td>
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**C** Mucosa Healing

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<tr>
<td>10</td>
<td>8%</td>
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Positive UC data (as above)

No available CD data yet, Active trial underway

**Slides courtesy of Neil Nandi, Drexel University**

**Anti-Adhesion Evolution: Targeted Therapy**


Endothelium

\[ \alpha_4 \beta_1 \]
\[ \alpha_4 \beta_7 \]
\[ \alpha_4 \beta_1 \]

Integrins

Addressins

VCAM

\[ \alpha_E \beta_7 \]

E-cadherin

MAdCAM

Leukocyte

**Anti-MAdCAM: PF-00547659**


Data promising in UC

Trial ongoing in CD
Novel Small Molecules

- Orally active small molecules interfere with intracellular signaling.

- Compared to therapeutic antibodies, small molecules have lower production costs and are orally administered.

- Janus kinase (JAK) inhibitors are best known.

Janus Kinase Pathway

- Jak-STAT pathway genes highly associated with IBD

- Janus kinase inhibitor
  - Tofacitinib is Jak 1/3 inhibitor used for psoriasis and RA.
  - Tofacitinib ultimately prevents cytokine production.

TNF, tumor necrosis factor; RA, rheumatoid arthritis

JAK-1/3 INHIBITOR: TOFACITINIB FOR UC

As of Sep 2015, announced having met their primary & secondary endpoints

Final data release May 2016

Two, Phase 3 trials - UC
OCTAVE 1
OCTAVE 2

One, Phase 2 trial - CD

ANTI-SMAD7 : MONGERSEN

Normal intestine

Suppression of pro-inflammatory genes

Mongerse et al Curr Drug Targets 2013 Nov;14(12):1400-4
**Anti-SMAD7: Mongersen**

**Normal intestine**
- TGFβ
- Smad2/3
- Suppression of pro-inflammatory genes

**CD**
- TGFβRI
- Smad7
- Amplification of pro-inflammatory genes

**CD + Mongersen**
- TGFβRI
- Smad7
- Suppression of pro-inflammatory genes

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**Mongersen**

Phase 2, 166 patients

Response @ 15 d x 2 weeks

Remission @ 28 d

Small study

Significant results

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IL-17 pathway extremely important and effective in psoriasis. However, mAb directed to IL-17 (secukinumab) or IL-17 Receptor (AMG 827) result in worsening IBD.


Anti-p40 Mechanism of Action

IL-12

IL-23

Ustekinumab

Briakinumab

No Signal


Ustekinumab for Crohn’s Disease: Blocks IL-12/IL-23

Clinical Response and Remission at Weeks 6 and 8


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Anti-P19: IL-23 Inhibition

MEDI2070 (Anti-p19 Ab) in CD (Week 8, mITT population)

Sands BE, et al. ECCO, Barcelona 2015
Some effector lymphocytes express CCR7+ which guides them into LN's.

Efferent lymphatic endothelium has an S1P gradient that attracts the CCR7+ lymphocytes to guide them out of the LN.

Ozanimod causes the S1P to become internalized.

Net Effect: Lymphocytes do not leave the LN to traffic to inflamed areas.

Effector memory T-cells (CCR7-) do not pass through these LN's. Hence protect immunity is intact.

Sphingosine-1Phosphate (S1P) Modulators: Ozanimod

Week 32 Clinical Remission

![Bar chart showing clinical remission at Week 32 for Placebo (20%), Ozanimod 0.5 mg (35.4%), and Ozanimod 1.0 mg (50.7%) with p = 0.0002.]

Ozanimod 0.5 mg and 1.0 mg showed significantly higher clinical remission compared to Placebo.
Patients with clinical symptoms on an anti-TNF*

- Detectable anti-drug antibodies
  - High antibodies: Change to different Anti-TNF or anti-integrin
  - Low antibodies: Add antimetabolite, recheck in 2-3 mos OR Change to anti-TNF or anti-integrin
- Undetectable anti-drug antibodies
  - Low trough: Increase dose or decrease dosing interval of anti-TNF
  - High trough: Switch to drug with alternate mechanism or action

Adapted from Scott, et al. Curr Treat Opinions 2016

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**Positioning New and Established Medications for IBD**

**Induction of Remission/Active Disease**
- Cyclosporine
- Ustekinumab (CD)
- Tofacitinib (UC)
- Vedolizumab (rapidity of response)
- Anti-TNFs
- Corticosteroids
- Budesonide
- 5-ASA

**Maintenance of Remission**
- Ustekinumab (CD)
- Vedolizumab
- Anti-TNFs
- Methotrexate (CD)
- 6-MP/Azathioprine
New proposed algorithms
Crohn’s  UC

Rogler. Where are we heading in pharmacologic IBD therapy? Pharmacologic research. 2015

<table>
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<th>Specific Target</th>
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Slides courtesy of Neil Nandi, Drexel University
Unmet need: what have we filled in so far

- UC
  - Vedolizumab big advance
  - Jak inhibitors
- CD
  - Ustekinumab (modest)
  - Vedolizumab better than clinical trial data belies
  - Jak inhibitors need another chance

The IBD Pipeline

**Take Home Points**

Multiple pathways contribute to the pathogenesis of IBD

IBD treatment is *more than just* anti-TNF’s

Available **Now:** Anti-α₄-β₇ Vedolizumab  
Anti-IL-12/23 Ustekinumab

Multiple other, mAb’s likely available in next 2-5 years

Patients finally have options!