Biologics and New Medications

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Crohn’s & Colitis Foundation Patient Education Conference
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Disclosures

- None
Outline

- What is a biologic?
- Why do we use them?
- Which one should we use?
- When should we start them?
- What comes next?
Welcome to Biologics

- Biologic \(\rightarrow\) requires the use of a living system for manufacture
  - Vaccines
  - Blood/plasma products
  - Gene therapy
  - Monoclonal antibodies
Biologics Are Complex

Aspirin chemical structure

3D structure of immunoglobulin G (IgG)
Antibodies: Function

Effector region
Antibodies: Function

- Two principal mechanisms for therapeutic antibodies
  - **Block** one target from activating/binding to another target
  - **Mark** a target for destruction by other immune cells
  - Antibodies can only target other proteins
    - Anti-drug antibodies
Anti-Drug Antibodies

Baert et al., NEJM 2003
# Anti-Drug Antibodies (Risk Factors)

<table>
<thead>
<tr>
<th>Increase Risk</th>
<th>Decrease Risk</th>
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<tbody>
<tr>
<td>Sporadic dosing</td>
<td><strong>Maintenance therapy</strong></td>
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<td>Low drug level</td>
<td><strong>Concurrent immunomodulators</strong></td>
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<td>Prior formation of anti-drug antibodies</td>
<td>(azathioprine, methotrexate)</td>
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The “Perfect” Medication

- Universally effective
- Easy to take
- Minimal side effects
- Cheap/cost-effective
- Self-limited duration
The “Perfect” Medication

- Universally effective
- Easy to take
- Minimal side effects
- Cheap/cost-effective
- Self-limited duration
- So why do we recommend these?
Steroid-sparing Effect
IBD Natural History

Pariente B Inflamm Bowel Dis 2012
Top Down Therapy

MOST IMPORTANTLY:

At 104 weeks, ~70% of “top-down” individuals had no visible inflammation on colonoscopy compared to only 30% of the “conventional” group.

D’Haens et al., Lancet 371: 2008
Biologics Work Better

Colombel et al., NEJM 2010
UC: Decreasing Rate of Surgery

Figure 1. Rate of Colectomy During Emergent UC Admissions (blue line) Significantly Declined While IPAA During Elective Admissions (purple line) Was Stable

Ungaro et al., Gastroenterology (Suppl) 2018; 154(1)
Crohn’s: Change in Natural History

Combination therapy with anti-TNF and azathioprine before phenotype change

Yes
No
Yes-censored
No-censored

Duration of disease (months)

Magro et al., AJG 2014; 109(7)
Risks of Biologic Therapy: Infections

- Untreated moderate to severe Crohn’s disease itself increases risk of infection by a factor of **224%**
- Prednisone increases risk by **54%**
  - Also only medication that increases risk of death (2-fold increased risk)
- Infliximab increases risk by **43%**
  - Actual magnitude is about 2%/year
Risks of Biologic Therapy: Lymphoma

- Data are **mixed** as to whether biologics increase lymphoma risk
  - No association to date with vedolizumab or ustekinumab
  - Anti-TNF therapy (IFX, ADA, CTZ, GOL) unclear, but worst case scenario is about a 2-fold increased risk
Risk of Lymphoma: Context

Ten Thousand People
pictures to help you see your data

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The image shows a data table with placeholder text, indicating where the actual data would be inserted. This is a common feature in presentations to show how the data would look in a table format.
Risk of Lymphoma: Context

Ten Thousand People
— pictures to help you see your data
Risk of Lymphoma: Context

- Across entire lifespan, risk of death from lymphoma across US is about 1 in 119 in men and 1 in 152 in women
- This is equivalent to the lifetime risk of death due to motor vehicle accident
Biologics: Cost Considerations

- In both UC and CD, the use of currently available biologics in appropriately selected individuals does appear to be cost-effective
  - Versus the alternatives (e.g. hospitalization, surgery, lost productivity)
  - Still very expensive therapies at the payer level
    - Biosimilars?
Why Use Biologics?

- Less hospitalization (by 50%)
- Less surgery (by 40-70%)
- Less steroids (by 50-75%)

2% risk of infection/year

0.04% risk of lymphoma/year
Which One Should We Use?

- Currently FDA-approved biologic therapies approved for Crohn’s/UC
  - Anti TNF agents
    - Infliximab and biosimilars (Remicade, Inflectra, Renflexis)
    - Adalimumab (Humira)
    - Certolizumab (Cimzia)
    - Golimumab (Simponi)
  - Anti-integrin agents
    - Natalizumab (Tysabri)
    - Vedolizumab (Entyvio)
  - Anti-IL 12/23 agent
    - Ustekinumab (Stelara)
Mechanism of Action Matters

Bilsborough et al., AJG Suppl 2016
Mechanism of Action Matters

Bilsborough et al., AJG Suppl 2016
Which One to Start?

• To date, there have been no direct comparison trials between any currently available biologic agent
  ◦ Hard to compare head-to-head unless excluding prior treatment failures

• Initial consideration: route of administration
  ◦ IV versus subcutaneous
Effect of Prior Treatments

Effect of Prior Treatments

Special Scenarios

- **Crohn’s-related fistulas**
  - Consider infliximab or adalimumab

- **Pregnancy**
  - Certolizumab does not cross placenta
    - BUT safety of other anti-TNF agents appears to be good during pregnancy

- **History of lymphoma**
  - Vedolizumab or ustekinumab
Biosimilars: NOT Generics

- For older biologics that have come off patent, biosimilars are now available for use
- **Not** an exact copy of original drug **but**:
  - “...highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product.”
  - Translation: must have clinical trial evidence of efficacy akin to reference product
- **Not** the same as interchangeable
  - This would mean switches can happen without provider input
  - FDA has not approved biosimilars as interchangeable (yet)
Biosimilar Interchangeability

Jorgensen et al., Lancet 389: 2017
When Should We Start One?

- In general, earlier is better if one is necessary
  - Shorter duration of diagnosis = better likelihood of response
  - Top-down approach = better mucosal healing

- Compelling indications
  - **Frequent steroid usage**
  - Higher likelihood of disease progression
# Predictors of Disease Progression

<table>
<thead>
<tr>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger age at diagnosis (&lt; 40)</td>
<td>Younger age at diagnosis (&lt; 40)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Entire colon involved</td>
</tr>
<tr>
<td>Early need for steroids</td>
<td>Early need for steroids</td>
</tr>
<tr>
<td>Lack of mucosal healing (i.e ongoing inflammation)</td>
<td>Lack of mucosal healing (i.e ongoing inflammation)</td>
</tr>
<tr>
<td>Certain genetic mutations (NOD2)</td>
<td>Primary sclerosing cholangitis (PSC)</td>
</tr>
<tr>
<td>Fistulizing disease</td>
<td>Deep ulcerations in colon</td>
</tr>
<tr>
<td>Upper intestinal involvement or ileal involvement</td>
<td></td>
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<tr>
<td>Granulomas on biopsy</td>
<td></td>
</tr>
</tbody>
</table>
Start here
Too late?
Symptoms ≠ Outcome

ROC Curve for Predicting Mucosal Healing at Week 26
Using the Week 26 CDAI Score

No Mucosal Healing (N=98)  Mucosal Healing (N=90)

Week 26 CDAI Score AUC = 0.568

Peyrin-Biroulet et al., Gut 63: 2014
Monitoring Response

- Short-term goal = symptom improvement
- Long-term goal = alleviation/resolution of inflammation
  - Biomarkers (CRP, calprotectin)
  - Endoscopy
  - Imaging
  - Drug level monitoring (?)
Can Biologics Be Stopped?

- **Maybe**

- **Potential risks of doing so:**
  - Risk of flare (~50-60% at 2 years)
  - Risk of loss of response to therapy
    - **BUT** if carefully done, likelihood of restarting is ~70% or higher
  - Long-term “success” off biologics ~20% over 7 years
  - Remaining on oral therapy (such as azathioprine) likely important in this context
What Comes Next?

That's all Folks!
Progress Continues

- Universally effective
- Easy to take
- Minimal side effects
- Cheap/cost-effective
- Self limited duration
Next Generation Biologics

- **Second generation anti-integrin therapy**
  - Etrolizumab
    - Biomarkers may predict success with this class of therapy in the future

- **IL-23 blockers**
  - Multiple in development: already approved by FDA for psoriasis (guselkumab: Tremfya)
Pills Are Coming Back
Tofacitinib: JAK Inhibitors


A Remission

- OCTAVE Induction 1
  - Placebo (N=122) 8.2%
  - Tofacitinib, 10 mg (N=476) 18.5%
  - Difference, 10.3 percentage points P<0.007

- OCTAVE Induction 2
  - Placebo (N=112) 3.6%
  - Tofacitinib, 10 mg (N=429) 16.6%
  - Difference, 13.0 percentage points P<0.001

- OCTAVE Sustain
  - Placebo (N=198) 11.1%
  - Tofacitinib, 5 mg (N=198) 34.3%
  - Tofacitinib, 10 mg (N=197) 40.6%
  - Difference, 29.5 percentage points P<0.001

B Mucosal Healing

- OCTAVE Induction 1
  - Placebo (N=122) 15.6%
  - Tofacitinib, 10 mg (N=476) 31.3%
  - Difference, 15.7 percentage points P<0.001

- OCTAVE Induction 2
  - Placebo (N=112) 11.6%
  - Tofacitinib, 10 mg (N=429) 28.4%
  - Difference, 16.8 percentage points P<0.001

- OCTAVE Sustain
  - Placebo (N=198) 13.1%
  - Tofacitinib, 5 mg (N=198) 37.4%
  - Tofacitinib, 10 mg (N=197) 45.7%
  - Difference, 32.6 percentage points P<0.001
Tofacitinib: JAK Inhibitors

A. Remission

<table>
<thead>
<tr>
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<th>OCTAVE Induction 1</th>
<th>OCTAVE Induction 2</th>
<th>OCTAVE Sustain</th>
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</thead>
<tbody>
<tr>
<td>Placebo (N=122)</td>
<td>8.2</td>
<td>3.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Tofacitinib, 10 mg (N=476)</td>
<td>18.5</td>
<td>16.6</td>
<td>34.3</td>
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<tr>
<td>Difference, 10.3 percentage</td>
<td>P=0.007</td>
<td>Difference, 13.0</td>
<td>P&lt;0.001</td>
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<td>points</td>
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<tr>
<td>Difference, 23.2 percentage</td>
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<td>Difference, 29.5</td>
<td>P&lt;0.001</td>
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B. Mucosal Healing

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<td>15.6</td>
<td>11.6</td>
<td>13.1</td>
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<tr>
<td>Tofacitinib, 10 mg (N=476)</td>
<td>31.3</td>
<td>28.4</td>
<td>37.4</td>
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<td>Difference, 15.7 percentage</td>
<td>P&lt;0.001</td>
<td>Difference, 16.8</td>
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<td>Difference, 32.6</td>
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Oral Therapy Misconceptions

- Novel oral agents ≠ “safer” than biologics
  - Broader mechanism of action → unexpected side effects
    - Tofacitinib may lead to increased cholesterol levels of uncertain significance
- Novel oral agents ≠ cheaper than biologics
  - List price for tofacitinib = ~$5000/month
  - **BUT** generics will be available sooner than biologics and likely for much less cost
New Mechanisms of Actions
Oral Agents Pipeline

- **JAK inhibitors**
  - Multiple second generation in development
  - More targeted
  - Showing efficacy for both Crohn’s and UC

- **S1P inhibitors**
  - Ozanimod: late stage trials for UC right now
Novel Therapies

- Dietary approaches to management
  - Ongoing clinical trials regarding SCD (specific carbohydrate diet)

- Fecal microbiota
  - High quality work available re: UC and FMT (fecal transplant)
  - Novel probiotic formulations (i.e. “artificial FMT”)
$1,000,000 Question

- When we have more options (which is a good thing!), which one should we try first? Second?

- **Future needed research:**
  - Predictors of response
  - Novel combination therapies (e.g., mixing biologics with newer therapies? With each other?)
Thank You For Listening!