Inflammatory Bowel Disease: All About Biologics

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Learning Objectives

• Review Immunology 101
• Understand current potential treatment targets
• Review current biologic treatments: how they work, safety/toxicity
• Discuss biosimilars
IBD is Characterized by Chronic Inflammation in the Gut

Activation of the immune system
What is the Immune System?

- Cells (T cells, B cells, macrophages) that defend the body against attack from infections
- To eradicate infection, the immune system causes inflammation
- Once an infection is eliminated, the immune system knows how to turn itself off

Photo courtesy of Scott Plevy, MD
Dysregulated Immune System

• In IBD, the “off” switch is broken
• Inflammation is a Key Aspect of IBD
Chronic Inflammation:
Proteins Called Cytokines Are the Light Switch

TNFα
IL-1β
IL-8
IL-12
IFNγ
IL-4/IL-13
IL-1Ra
TGFβ
IL-10

“On”

“Off”
IBD Treatment Strategy

“**Top-down**” Strategy
- Early, appropriate use of biologic as initial treatment
- Induces rapid clinical response
- May enhance quality of life

“**Bottom-up**” Strategy
- Standard, sequential treatment for remission and maintenance
- Cost-effective
- Minimal side effects
Treatment Approach Strategies

Low risk of disease progression

‘Top-down’: may over-treat and expose patients to costs, risks of immunosuppression

High risk of disease progression

‘Step-up’: may postpone adequate therapy in aggressive disease and results in disease progression, complications, morbidity
Early, Consistent IBD Treatment = Increased Chance of Staying Well

- Disease Prevention
  - Prevention of symptomatic disease
- Prevention of complications
- Prevention of relapse
THE EVOLUTION OF CROHN’S DISEASE: INFLAMMATION LEADS TO DAMAGE

Over a 20-year period, 88% risk of developing stricturing (18%) or penetrating (70%) disease

Cosnes J et al. Inflamm Bowel Dis. 2002
Natural History: Most Crohn’s Patients Will Require Surgery

Mekhjian HS et al. *Gastro* 1979
Risk of colectomy: 24% after 10 years
~ 30% after 20 years

Significant Increased risk of cancer

Adapted from Langholz E, et al. Gastroenterol 1994
Since introduction of biologic agents/anti-TNFs, decrease in total colectomy in UC patients
Update in the Evolution of Treatment Goals & Strategies

- Improved clinical symptoms
- Clinical remission
- Steroid free remission
- Mucosal healing
- Histologic remission

Adapted CCFA Canada Webinar 2015
IBD Medicine Cabinet

Over-the-Counter

Antibiotics

Aminosalicylates/Mesalamine

Corticosteroids, Budesonide

Immunomodulators – AZA/6MP, MTX

Biologics: Anti-TNFs/Anti-Adhesions/Anti-Interleukins
Biologics in IBD

- Infliximab approved for CD 1998
- Adalimumab for CD 2002
- Certolizumab pegol for CD 2008
- Natalizumab for CD 2008
- Vedolizumab for UC & CD 2014
- Infliximab approved for UC 2005
- Adalimumab for UC 2012
- Golimumab for UC 2013
- Ustekinumab for CD 2016
What are Biologic Drugs?

• Drugs are called “biologic” because they are produced by living cells, not manufactured.

• Immune cells in the body create proteins called antibodies that attach to specific targets (bacteria, viruses).

• Biologic drugs are antibodies designed to attach to specific proteins or hormones involved in inflammation that causes IBD.
Biologics

**Anti-TNF**
- Adalimumab (Humira®)
- Certolizumab pegol (Cimzia®)
- Infliximab (Remicade®)
- Golimumab (Simponi®)

**Selective adhesion molecule**
- Natalizumab (Tysabri®)
- Vedolizumab (Entyvio®)

**Anti-Interleukin**
- Ustekinumab (Stelara®)
WHAT’S NEW?
IBD DRUG PIPELINE

GY Melmed & SR Targan 2010
IBD Immunology 101

Taken with permission from RW Stidham
IBD Immunology 101

Mucosa

Submucosa

Blood Vessels

Taken with permission from RW Stidham
IBD Immunology 101

Taken with permission from RW Stidham
IBD Immunology 101

Mucosa

Submucosa

Blood Vessels

Taken with permission from RW Stidham
Biologic Drugs – Anti-TNF

• Infliximab (Remicade®)

• FDA Approval
  – Adult and pediatric moderate to severe Crohn’s
    • Induction and maintenance
  – Adult and pediatric moderate to severe UC
    • Induction and maintenance
  – Treatment of bowel to skin fistulas and rectovaginal fistulas
Biologic Drugs – Anti-TNF

• Remicade®

• Dosing
  – Intravenous infusion over ~2 hours
  – Based on weight
  – Induction: week 0, 2, and 6
  – Maintenance: every 8 weeks
Biologic Drugs – Anti-TNF

• Remicade®

• Advantages
  – Levels of the drug in the blood can be measured
  – Don’t need to inject self

• Disadvantages
  – Need to come to clinic/hospital for infusions
Biologic Drugs – Anti-TNF

• Adalimumab (Humira®)
• FDA Approval
  – Moderate to Severe Crohn’s in adults and pediatrics
    • Induction and maintenance
  – Moderate to Severe ulcerative colitis in adults
    • Induction and maintenance
• Dosing
  – Self administered injection under the skin
  – Induction: 160mg (4 syringes) on week 0, 80mg (2 syringes) on week 2, 40mg on week 4
  – Maintenance: 40mg (one syringe) every 2 weeks
Biologic Drugs – Anti-TNF

- **Humira®**

- **Advantages**
  - Medication given at home
  - Levels of the drug can be measured

- **Disadvantages**
  - You (or friend/family) must administer the shot
Biologic Drugs – Anti-TNF

• Certolizumab (Cimzia®)
• FDA Approval
  – Moderate to severe Crohn’s disease in adults
    • Induction and maintenance
• Dosing
  – Self administered injection under the skin
  – Induction: 400mg (two syringes) on week 0, 2, and 4
  – Maintenance: 400mg (two syringes) every 4 weeks
Biologic Drugs – Anti - TNF

• Cimzia®
• Advantages
  – Inject medication at home or receive in clinic (lyo)

• Disadvantages
  – Could not measure drug level in the blood – now you can

• ? Advantage
  – Large molecule that does not cross placenta
  – Safety for baby in pregnancy
Biologic Drugs – Anti - TNF

• Golimumab (Simponi®)

• FDA Approval
  – Moderate to severe ulcerative colitis in adults
    • Induction and maintenance

• Dosing
  – Self administered injection under the skin
  – Induction: 200mg (two syringes) on week 0, 100mg (one syringe) week 2.
  – Maintenance: 100mg every 4 weeks
Biologic Drugs – Anti-TNF

• Simponi®

• Advantages
  – Inject medication at home
  – Low total number of injections

• Disadvantages
  – Cannot measure drug level in the blood
Some IBD Definitions

• **Response**
  – Clinical: Improvements in abdominal pain, diarrhea and rectal bleeding, but not necessarily completely normal bowel function
  – Mucosal: Improvement in scope/imaging

• **Remission**
  – Clinical: Improvements in abdominal pain and diarrhea to essentially normal bowel function
  – Mucosal: No active disease on scope/imaging
Anti-TNF - Effectiveness

• No direct comparison between the anti-TNF drugs

• Crohn’s disease
  – Studied in patients that have already not responded to mesalamine, azathioprine/mercaptopurine
  – Approximately 60-70% respond to anti-TNF drugs within 6 weeks
  – Approximately 40% of responders will be in remission (symptom free) after one year
  – Approximately 65% of responders will maintain response after one year (symptom improvement, but not symptom free)
Anti-TNF - Effectiveness

- Ulcerative Colitis
  - Studied in patients that have already failed mesalamine, azathioprine/mercaptopurine
  - Approximately 50-65% will have a response after 8 weeks
  - Approximately 30-35% will have remission after 8 weeks
  - Approximately 30-50% will have continued response after one year, 20-30% remission after one year.
Combination Therapy: Steroid-Free Clinical Remission at Week 50

All Randomized Patients (N=508)*

- **AZA + placebo**: 24.1% (41/170)
- **IFX + placebo**: 34.9% (59/169)
- **IFX + AZA**: 46.2% (78/169)

*P* values:
- **AZA + placebo**: P < 0.001
- **IFX + placebo**: P = 0.028
- **IFX + AZA**: P = 0.035

*Patients who did not enter the Study Extension were treated as non-responders*

Colombel JF et al. NEJM 2010
Combination Therapy: Steroid-Free Clinical Remission at Week 16

SUCCESS

Panaccione R et al. Gastroenterology 2014
Safety/Toxicity of Anti-TNFs

**Stopped therapy due to adverse event**
10%

**Infusion or injection site reactions**
3% to 20%

**Drug-related lupus-like reaction**
1% (1/100)

**Non-Hodgkin’s lymphoma (combo)**
0.06% (6/10,000)

**Multiple sclerosis, heart failure, serious liver injury**
Case reports only

**Tuberculosis**
0.05% (5/10,000)

**Serious infections**
3% (3/100)

**Multiple sclerosis, heart failure, serious liver injury**
Case reports only

Risk for Cancer - Lymphoma
Safety/Toxicity of Anti-TNFs

• Serious Infections in Crohn’s disease
  – Anti-TNF increases risk 43%
  – Prednisone increases risk 57%
  – Opioid use doubles the risk
  – Active Crohn’s Disease - Moderate to severe more than doubles the risk
Blockade of Adhesion Molecules: Anti-Integrins

Taken with permission from RW Stidham
Anti-Integrin: Mailbox and Zip Code

• Vedolizumab (Entyvio®)

• FDA Approval
  – Moderate to Severe Crohn’s in adults
    • Achieving remission, mainly maintenance
  – Moderate to Severe ulcerative colitis in adults
    • Induction and maintenance

• Dosing
  – Given intravenously over a 30 minute infusion
  – Induction: 300mg on week 0, 2, and 6
  – Maintenance: 300mg every 8 weeks
Anti-Integrin

- **Entyvio®**

- **Advantages**
  - Minimal to no increased infection risk

- **Disadvantages**
  - Slow onset (especially Crohn’s)
  - Must be given in clinic/hospital
Entyvio® - Effectiveness

- Ulcerative colitis
  - Response by week 8 in 47%, Remission in 17%
  - Among responders, at one year durable response in 57%
  - Among responders, at one year remission in 42%
Entyvio® - Effectiveness

- Relatively quick onset in UC

![Graph showing comparison between Placebo (N=149) and Vedolizumab (N=225) with Mean Partial Mayo Clinic Score vs. Week. The graph indicates a statistically significant difference at 6 wk, P<0.001.](image-url)
Entyvio® - Effectiveness

- Crohn’s disease – week 6

![Graph showing effectiveness results for Placebo and Vedolizumab in Crohn's disease.](image)
Entyvio® - Effectiveness

- Crohn’s disease – one year among responders
- Onset of action much slower than in ulcerative colitis, up to 3 months
Entyvio® - Safety

- Crohn’s disease

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=301)</th>
<th>Vedolizumab (N=814)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease exacerbation</td>
<td>65 (21.6)</td>
<td>164 (20.1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>40 (13.3)</td>
<td>110 (13.5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>40 (13.3)</td>
<td>103 (12.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>24 (8.0)</td>
<td>100 (12.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>47 (15.6)</td>
<td>97 (11.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (10.0)</td>
<td>90 (11.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>39 (13.0)</td>
<td>79 (9.7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>17 (5.6)</td>
<td>54 (6.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (4.7)</td>
<td>53 (6.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23 (7.6)</td>
<td>49 (6.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>12 (4.0)</td>
<td>38 (4.7)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>46 (15.3)</td>
<td>199 (24.4)</td>
</tr>
<tr>
<td>Any serious infection†</td>
<td>9 (3.0)</td>
<td>45 (5.5)</td>
</tr>
<tr>
<td>Any cancer‡</td>
<td>1 (0.3)</td>
<td>4 (0.5)</td>
</tr>
</tbody>
</table>
Entyvio® - Safety

- Ulcerative Colitis
- Very little known in pregnancy

Table 4. Adverse Events Affecting at Least 5% of Patients Receiving Vedolizumab in the Safety Population.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N = 275)</th>
<th>Vedolizumab (N = 620)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>no. of patients (%)</td>
<td>no. of patients (%)</td>
</tr>
<tr>
<td>Headache</td>
<td>28 (10.2)</td>
<td>80 (12.9)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>58 (21.1)</td>
<td>97 (15.6)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>26 (9.5)</td>
<td>80 (12.9)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>21 (7.6)</td>
<td>52 (8.4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>25 (9.1)</td>
<td>56 (9.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (6.9)</td>
<td>38 (6.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (3.6)</td>
<td>35 (5.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (5.8)</td>
<td>35 (5.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (3.6)</td>
<td>33 (5.3)</td>
</tr>
<tr>
<td>Cough</td>
<td>13 (4.7)</td>
<td>36 (5.8)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>37 (13.5)</td>
<td>77 (12.4)</td>
</tr>
<tr>
<td>Any serious infection†</td>
<td>8 (2.9)</td>
<td>12 (1.9)</td>
</tr>
<tr>
<td>Any cancer</td>
<td>3 (1.1)‡</td>
<td>1 (0.2)§</td>
</tr>
</tbody>
</table>
Blockade of Cell-Activating Signals

[Diagram showing the blockade of IL-12/23 in dendritic cells to prevent T-cell activation.]

T-cells ACTIVATED
Interferon
IL-17

IL-12 Receptor

IL-12/23 Ligand

Dendritic cell

Taken with permission from RW Stidham
Anti-IL12/23: Key and Lock

• Ustekinumab (Stelara®)
• FDA Approval
  – Moderate to Severe Crohn’s disease

• Dosing
  – Induction: Single intravenous infusion based on weight
  – Maintenance: 90mg (one syringe) injection every 8 weeks
Anti-IL12/23

• Stelara®

• Advantages
  – Mainly given at home with infrequent injections (every 2 months, with initial infusion)

• Disadvantages
  – Your insurance may not want to pay for this
Stelara® - Effectiveness

A. Clinical Response

Prior Anti-TNF use

UNITI-1

Week 3: N=247, Week 6: N=245, Week 8: N=249

- Placebo: Week 3: 17.8%, Week 6: 25.3%, Week 8: 30.1%
- Ustekinumab, 130 mg: Week 3: 21.5%, Week 6: 34.3%, Week 8: 33.7%
- Ustekinumab, 6 mg/kg: Week 3: 20.2%, Week 6: 33.5%, Week 8: 37.8%

P-values:
- Placebo vs. Ustekinumab, 130 mg: P=0.001
- Placebo vs. Ustekinumab, 6 mg/kg: P=0.003
- Ustekinumab, 130 mg vs. Ustekinumab, 6 mg/kg: P<0.001

UNITI-2

Week 3: N=209, Week 6: N=209, Week 8: N=209

- Placebo: Week 3: 21.5%, Week 6: 32.5%, Week 8: 38.8%
- Ustekinumab, 130 mg: Week 3: 28.7%, Week 6: 51.7%, Week 8: 55.5%
- Ustekinumab, 6 mg/kg: Week 3: 32.1%, Week 6: 47.4%, Week 8: 57.9%

P-values:
- Placebo vs. Ustekinumab, 130 mg: P<0.001
- Placebo vs. Ustekinumab, 6 mg/kg: P<0.001
- Ustekinumab, 130 mg vs. Ustekinumab, 6 mg/kg: P<0.001
Stelara® - Effectiveness

Prior Anti-TNF use

No Prior Anti-TNF use
Stelara® - Effectiveness

• After one year among responders
Stelara®- Safety

• Must be tested for tuberculosis prior to starting

• No obvious increase in serious infections

• Slight increased risk of nasopharyngitis

• Very little known about pregnancy
Can Biologic Drugs Stop Working?

- Yes – Human cells are smart, can develop resistance or antibody to the biologic = *immunogenicity*
- Can measure biologic drug and antibody level
- May need to increase dose or frequency
- May also need to switch to another biologic
How can you prevent forming antibodies against a biologic?

• Take doses on schedule
  – Less likely to occur if the amount of drug in the bloodstream doesn’t reach zero

• Restart drug with full initial dosing when a break in dosing occurs

• Simultaneous use of azathioprine (or similar medications)
  – Often recommended when switching to new biologic
Biosimilars: New Hope or Nothing?

• For years, generic small molecule drugs introduced once patents expire on originator product
• Generic medicine is an *exact copy* of small molecule drug, identical to original product – structural and therapeutic identity
• Biosimilars = “biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product”
  – Similarity defined as “absence of relevant difference in the parameter of interest”
  – NOT exact copy of originator

WHO Expert Committee on Biological Standardization 2009
Biosimilar ≠ Generic

- Originator
- Reference
- Innovator
Small molecule
- Proof of quality (identical chemical structure)
- Pharmacokinetic bioequivalence
- Relies on clinical data from reference product

Biologic
- Proof of quality and similarity
- Pharmacokinetic bioequivalence
- Clinical data showing comparable safety and efficacy

Generics

Biosimilars

Taken from MedForum.medpagetoday.com/biosimilars
Snowflake Effect

Original biologic

Biosimilars

Taken from Amgenbiosimilars.com
Complexity of Biological Drugs

• Biological drugs are made in living cell lines and are intrinsically complex proteins
• Sensitive to changes in manufacturing process
• Differences in impurities and/or breakdown products can affect immunogenicity
• Originator products may also have manufacturing changes after approval
**Originator Biologics**

- Biologic developed and tested
  - FDA Application
  - Clinical Trials
  - FDA and Drug Sponsor Review Meeting
  - Biologic License Application
  - Drug Approval and Labeling

**Biosimilars**

- Biologic developed and tested
  - FDA Application
  - Clinical Trials
  - FDA and Drug Sponsor Review Meeting
  - Biologic License Application
  - Drug Approval and Labeling

- Thousands of participants for disease indications such as: Rheumatoid arthritis, Crohn’s, ulcerative colitis

- Must demonstrate safety and effectiveness
  - Example: Approval for IBD, RA, AS

- Clinical trials on one or more disease indication(s) from originator. Example: Rheumatoid arthritis

- Must demonstrate high similarity to reference drug. No clinically meaningful differences
  - Example: Approval for IBD, RA, AS
Biosimilars

Extrapolation
• Biosimilars can be extrapolated to other indications
• Comparison studies of a biosimilar that show equivalent efficacy/safety to originator for ONE INDICATION, may be extrapolated to ALL indications

Interchangeability
• Interchangeable designation of biosimilars may allow for free exchange with originator with no greater risk of AE or diminished effects
• Pharmacy substitution
• Subject to each state law
• FDA determines whether biosimilar interchangeable or not; ‘switch study’
What’s in the Pipeline for Biosimilars?

Inflectra – first FDA approved biosimilar for IBD
  – Has biosimilarity to infliximab
  – Studied in: Ankylosing spondylitis, RA
  – Extrapolated to: CD (adults, children) and UC (adults)
  – Not interchangeable with infliximab (no switch)
  – Now available in U.S.

Amjevita – recently approved
  – Biosimilarity to adalimumab
  – Studied in: plaque psoriasis, RA
Biosimilars in Development

• Over 650 biosimilars in development
• Nearly 50% are in pre-clinical trial stage
• Takes 7-8 years to develop a biosimilar
• Costs $100-250 million
• Adalimumab – 13 biosimilars under development
• Infliximab – 9 biosimilars

Radar RA et al. Bioproc Int 2013
Potential Issues with Biosimilars

• Risk of having originator therapy SWITCHED to biosimilar in stable patient

• Concern for immunogenicity or cross-reactivity
  – Anti drug antibodies will cross react
  – LOR or allergic reaction to originator and now biosimilar

• Confusion regarding names and branding:
  – “Remicade” vs “Remsima” – can accidentally be used interchangeability even though not approved for this
Potential Benefits with Biosimilars

• May decrease costs
  – Insurance - yes
  – Copay, premiums for patients?
• More availability of treatment options
• Insurances/payors may allow earlier appropriate start of treatments
• Increase research to help advance understanding of IBD
CCFA Position Statement on Biosimilars

Safety and Effectiveness:

Human testing
- Undergo thorough human testing and meet highest safety standards

Interchangeability
- Provide reasonable proof that switching would not incur immunogenicity or loss of response to innovator (vice versa)

Immunogenicity and cross reactivity
- Risk of cross reactivity of anti-drug antibodies from innovator agent to biosimilar must be clearly understood, defined and listed on the label and prescribing information

Unique name/identifier
- Each biosimilar should have unique identification number, name or else use international non-proprietary name standards to eliminate patient and provider confusion.

CCFA Position Statement on Biosimilars

Shared-Decision Making and Transparency:

Notification to Prescribing Provider

The prescribing provider should be notified of the substitution of the innovator agent with a biosimilar (or vice versa).

Prevention of Substitution

The prescriber should be able to prevent substitution by indicating “dispense as written” or “brand medically necessary.”

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UW Medicine Inflammatory Bowel Diseases Program
http://www.uwgi.org/ibd/

THANK YOU!

@IBD_Afzali