Vedolizumab Use in IBD

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Disclosures

Genetech/Hoffman LaRoche
Outline

Mechanism of Action

Gemini I Trial in UC

Gemini II and III Trials in CD

Safety Profile
Case 1

45 year old male with diagnosed with Pan-UC one year ago. He continues to have progressive diarrhea and rectal bleeding after 1 year of treatment. He is unable to taper off steroids and remains on mesalamine 4.8g and prednisone 15mg.

Colonoscopy shows Mayo subscore 2 disease

Past Medical History: HTN

Family History: Mother died of lymphoma at age 50
Sequential Therapies for Ulcerative Colitis

Disease Severity at Presentation

- Severe
- Moderate
- Mild

Adalimumab 9/28/2012
Golimumab 5/15/2013
Vedolizumab 5/20/2014

Colectomy

Infliximab Cyclosporine
Infliximab Thiopurine

Corticosteroid
Aminosalicylate
Aminosalicylate

Therapy is stepped up according to severity at presentation or failure at prior step.
IBD Therapeutic Targets

1: Maladaptive response to intestinal injury & the enteric flora
CD: defective innate antimicrobial response
UC: defective epithelial response

2: T-cell activation including enteric flora antigens

3: Cytokines & chemokines

1: Leukocyte adhesion & recruitment
Selectins
PMN
Integrins
ICAM-1
MAdCAM-1
Lympocyte

Activated Mφ
Activated T cell
Naive T cell
Resting Mφ

FUT2

TNF
IL-10
Th1
Th2
Th17
Treg
IL-17
IL-4
IL-5
IL-13
IL-12
IL-23
IFNγ

GM-CSF auto-antibodies
Anti-flagellin antibodies

B cell

CD4 T cell
MHC Class II
TCR
CD4
CD28
CTLA4
B7
Leukocyte Trafficking as a Target in Inflammatory Bowel Disease

Rutgeerts P. Gastroenterology 2009;136:1182–1197

Vedolizumab
α4β7 Integrin–MAdCAM-1 Interaction Contributes to Inflammation

Vedolizumab

The Rest Of the Body

Colon
Trials for Vedolizumab

Gemini I
Gemini II
Gemini III

Approved in May 2014 in US and European Union

Dosing
• Induction 300mg IV at week 0, 2, and 6
• Maintenance dose 300mg IV every 8 weeks
• 30 minute infusion
## Vedolizumab in UC: GEMINI 1

### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=149)</th>
<th>Vedolizumab (n=746)</th>
<th>Total (n=895)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease Location</strong></td>
<td></td>
<td></td>
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<tr>
<td>Pan-ulcerative colitis</td>
<td>33.6%</td>
<td>37.9%</td>
<td>37.0%</td>
</tr>
<tr>
<td>Prox to Splenic Flex</td>
<td>12.1%</td>
<td>12.2%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Descending</td>
<td>39.6%</td>
<td>37.5%</td>
<td>37.9%</td>
</tr>
<tr>
<td>Rectum &amp; Sigmoid</td>
<td>14.8%</td>
<td>12.6%</td>
<td>13.0%</td>
</tr>
<tr>
<td><strong>Mayo Score, mean</strong></td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
</tr>
<tr>
<td><strong>Concomitant Med</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>38.9%</td>
<td>36.7%</td>
<td>37.1%</td>
</tr>
<tr>
<td>6MP/AZA</td>
<td>12.1%</td>
<td>18.9%</td>
<td>17.8%</td>
</tr>
<tr>
<td>6MP/AZA + CS</td>
<td>17.4%</td>
<td>16.5%</td>
<td>16.6%</td>
</tr>
<tr>
<td>Prior Anti-TNF</td>
<td>49.0%</td>
<td>48.0%</td>
<td>48.2%</td>
</tr>
</tbody>
</table>

Clinical Response, Remission, Mucosal Healing at 6 Weeks

Induction ITT Population

- Clinical Response: Δ 21.7, 95% CI: 11.6, 31.7, P<0.0001
- Clinical Remission: Δ 11.5, 95% CI: 4.7, 18.3, P=0.0009
- Mucosal Healing: Δ 16.1, 95% CI: 6.4, 25.9, P=0.0012

Fegan et al NEJM 2013
GEMINI I: Vedolizumab in UC
Primary and secondary outcomes through 52 Weeks, maintenance ITT population

- **Clinical Response**
  - Δ26.1 Δ29.1
  - Placebo: 15.9%
  - VDZ Q8 wks: 41.8%
  - VDZ Q4 wks: 44.8%

- **Durable Clinical Response**
  - Δ32.8 Δ28.5
  - Placebo: 23.8%
  - VDZ Q8 wks: 52.0%
  - VDZ Q4 wks: 56.6%

- **Mucosal Healing**
  - Δ32.0 Δ36.3
  - Placebo: 19.8%
  - VDZ Q8 wks: 51.6%
  - VDZ Q4 wks: 56.0%

- **Durable Clinical Remission**
  - Δ11.8 Δ15.3
  - Placebo: 8.7%
  - VDZ Q8 wks: 20.5%
  - VDZ Q4 wks: 24.0%

- **CS-Free Remissions**
  - Δ17.6 Δ31.4
  - Placebo: 13.9%
  - VDZ Q8 wks: 31.4%
  - VDZ Q4 wks: 45.2%

*P<0.05  **P<0.01  ***P<0.0001

Clinical Response and Remission at 6 Weeks: Prior Anti-TNFα Failure vs No Anti-TNFα Exposure

**Induction ITT Population**

Patients with Prior Anti-TNF Failure ($n = 145$)

- Clinical Response: 20.6%
  - Δ 18.4
  - 95% CI: 3.9, 32.9
- Clinical Remission: 3.2%
  - Δ 3.2
  - 95% CI: -9.8, 22.8

Patients Without Anti-TNF Exposure ($n = 206$)

- Clinical Response: 53.1%
  - Δ 26.8
  - 95% CI: 13.7, 39.9
- Clinical Remission: 6.6%
  - Δ 6.6
  - 95% CI: 2.4, 30.2

Sources:

- Fegan et al NEJM 2013

*Note: Δ values indicate change from baseline.*
Clinical Remission, Durable Clinical Response at 52 Weeks: Prior Anti-TNFα Failure vs No Anti-TNFα Exposure

<table>
<thead>
<tr>
<th>Maintenance ITT Population</th>
<th>Patients with Prior Anti-TNF Failure (n = 121)</th>
<th>Patients Without Anti-TNF Exposure (n = 224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Remission</td>
<td>Placebo: 5.3% (Δ31.9, 95% CI Q8Wks: 10.3, 51.4)</td>
<td>Placebo: 19.0% (Δ26.8, 95% CI Q8Wks: 12.4, 41.2)</td>
</tr>
<tr>
<td>Durable Clinical Response</td>
<td>Placebo: 37.2% (Δ29.7, 95% CI Q8Wks: 11.8, 49.6)</td>
<td>Placebo: 26.6% (Δ38.7, 95% CI Q8Wks: 24.0, 53.4)</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>VDZ Q8 wks: 35.0% (Δ26.7, 95% CI Q8Wks: 7.5, 45.9)</td>
<td>VDZ Q8 wks: 45.8% (Δ29.0, 95% CI Q8Wks: 14.6, 43.3)</td>
</tr>
<tr>
<td>Durable Clinical Response</td>
<td>VDZ Q8 wks: 42.5% (Δ29.0, 95% CI Q8Wks: 14.6, 43.3)</td>
<td>VDZ Q8 wks: 56.2% (Δ29.6, 95% CI Q8Wks: 14.6, 44.6)</td>
</tr>
</tbody>
</table>

Legend: Placebo, VDZ Q8 wks, VDZ Q4 wks

* gemini
Case 1

45 year old with steroid dependent pan-UC and family history of lymphoma.

He was started on Vedolizumab 300mg IV at week 0, 2 and 6.

After completing induction dosing, he was able to taper off steroids and has remained off steroids for 1 year with maintenance therapy of 300mg IV every 8 weeks.
Case 2

23 year old female diagnosed with Crohn’s disease at age 12. She was initially treated with azathioprine. At age 17 underwent ileocectomy for ileal stricture.

At age 18, flared with colonoscopy showing moderated active disease in transverse colon and ileal. Treated with Infliximab with azathioprine. On 4th infusion developed infusion reaction.

Placed on Adalimumab and azathioprine to which she responded.
Case 2

Three years later, she flares. Placed on steroids. Drug levels were checked:

Adalimumab level: undetectable, antibody to adalimumab >100, 6tgn 122, 6mmpn 10,231

Tried on combination certolizumab with methotrexate. LFTs went up to 200 with methotrexate. She did not respond to certolizumab.

Currently on prednisone 30mg daily with symptoms of 8 to 10 loose bowel movements daily with blood. Colonoscopy shows moderately active disease in rectum, sigmoid colon and ileocolonic anastomosis.
Vedolizumab (Anti-α4β7 Integron) For Response in Moderately-to-Severely Active Crohn’s Disease: Results at week 6, Gemini II
Vedolizumab (Anti-4 Integrin) For Maintenance of Response in Moderately-to-Severely Active Crohn’s Disease: Results at Week 52 in 461 Patients

Maintenance ITT Population

- Clinical Remission
  - Δ17.4: 21.6%
  - Δ14.7: 39.0%
  - Δ14.7: 36.4%

- CDAI-100 Response
  - Δ13.4: 30.1%
  - Δ15.3: 43.5%
  - Δ15.3: 45.5%

- CS-Free Remission
  - Δ15.9: 15.9%
  - Δ12.9: 31.7%
  - Δ12.9: 28.8%

- Durable Remission
  - Δ7.2: 14.4%
  - Δ2.0: 21.4%
  - Δ2.0: 16.2%

*P<0.05  **P<0.01

†CS tapering began in responders at 6 weeks; for others, as soon as a clinical response was achieved.

Sandborn W.
N Engl J Med 2013
Gemini II Study

Modest effect on induction of clinical remission, maintenance data better.

Possible explanations:

Severity of disease in the study population

- 50% had treatment failure with one or more anti-TNFs
- 30% had treatment failure with two or more anti-TNFs

Pharmacologic action could be slower due to transmural inflammation seen in Crohn’s disease
Gemini III Study

Randomized, double blinded, placebo controlled trial to assess efficacy of vedolizumab for induction of clinical response and remission in patients with prior anti-TNF exposure

Study Population: 416 Crohn’s disease patients who previously failed other treatments; 101 patients who were anti-TNF naive

Endpoints: Clinical remission and response rates at week6 based on CDAI
Effects of Vedolizumab Induction Therapy for Patients With Crohn’s Disease in Whom Tumor Necrosis Factor Antagonist Treatment Failed

A

Patients in clinical remission at week 6, %

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<tr>
<th></th>
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<tr>
<td>TNF antagonist-failure population</td>
<td>n=157</td>
<td>n=159</td>
</tr>
<tr>
<td>Overall population</td>
<td>n=50</td>
<td>n=51</td>
</tr>
<tr>
<td>TNF antagonist-naive subgroup</td>
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B

Patients in clinical remission at week 0, %

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<tbody>
<tr>
<td>TNF antagonist-failure population</td>
<td>n=197</td>
<td>n=201</td>
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<tr>
<td>Overall population</td>
<td>n=50</td>
<td>n=51</td>
</tr>
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<td>TNF antagonist-naive subgroup</td>
<td>n=197</td>
<td>n=201</td>
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C

Patients with clinical remission at both weeks 6 and 10, %

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<tbody>
<tr>
<td>TNF antagonist-failure population</td>
<td>n=8.3</td>
<td>n=12.0</td>
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<td>n=0</td>
<td>n=10</td>
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<tr>
<td>TNF antagonist-naive subgroup</td>
<td>n=8.2</td>
<td>n=15.3</td>
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D

Patients with a CDAD-100 response at week 6, %

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E

Patients with a CDAD-100 response at week 10, %

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Safety: Is Vedolizumab Gut Selective?

No peripheral blood lymphocytosis

No protective effect in primate model of MS (EAE)

No inversion of CD4/CD8 ratio in CSF of humans

Clinical data – no cases of PML observed

Preservation of systemic humoral responses to T cell dependent antigens with modest impairment to oral antigen (vaccine study)
# Vedolizumab: Safety

## Infusion-related Reactions
- 4% (vs. 3% placebo)
- <1% “severe”
- <1% required discontinued therapy
- Anaphylaxis: 
  - 1 / 1434 (0.07%)

## Immunogenicity
- 4% anti-vedolizumab antibodies at any time during 52 weeks of study
  - 16% persistently “+”
  - 59% neutralizing

## PML*
- No cases

## Tuberculosis
- GEMINI 1 - 895 pts: 0 cases
- GEMINI 2 - 1115 pts: 1 pt

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*Progressive multifocal leukoencephalopathy

Entyvio [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; May 2014.
Adverse Events With Vedolizumab

- Rare infusion-related reactions and hypersensitivity
  - 30-minute infusion and no postinfusion monitoring
- Not recommended in patients with active, severe infection until the infection is controlled
- No cases of PML have been observed
- Rare reports of elevations of transaminase and/or bilirubin
- Most common adverse reactions (incidence $\geq 3\%$ and $\geq 1\%$ higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities
Immunogenicity

It is a monoclonal antibody

Experts recommending dual therapy

Duration of dual therapy between 12 to 24 months of combination therapy
Pregnancy Classification

Class B

Expect it to cross placenta in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester

Breastmilk: unknown
Case 2

24 year old female with steroid refractory Crohn’s disease who no longer is responding to anti-TNF agents.

Placed on Vedolizumab. She started to see a response at week 14 and has started to taper off steroids.
Final thoughts

Vedolizumab (VDZ) is more effective than placebo as induction and maintenance therapy in patients with moderate to severely active ulcerative colitis (anti-TNF exposed and naïve patients)

Vedolizumab is approved for moderately active CD, response less robust then UC

Safety profile is favorable

Maybe better option for older patients

Give concurrent immunomodulator therapy to decrease immunogenicity
Final Thought

Questions that exist:

Role of Vedolizumab for patients with EIM and perianal disease

First line versus second line therapy in UC and CD

Role for hospitalized severe UC patients

Pregnancy and breastfeeding

Synergistic use with anti-TNF
Thank You