Vedolizumab: policing leukocyte traffic

Dr Brian Feagan, London, Canada
Vedolizumab: Policing Lymphocyte Trafficking

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Overview and Goals

- Why alternatives to our current treatments for IBD are needed
- Review data regarding the currently available and developmental drugs in this class
- Future directions and conclusions
The Clinical Need: Net Remission at 6 Months with TNF Antagonists

Infection and TNF Antagonists

- TREAT registry n > 6,000, f/u > 5yrs
- Factors independently associated with serious infections (Descending order of risk):
  - Disease activity mod-severe (HR = 2.24, 95% CI = 1.57, 3.19; P < 0.001),
  - Narcotic analgesic treatment (HR = 1.98, 95% CI = 1.44, 2.73; P < 0.001)
  - Prednisone therapy (HR = 1.57, 95% CI = 1.17, 2.10; P = 0.002)
  - Infliximab treatment (HR = 1.43, 95% CI = 1.11, 1.84; P = 0.006).

Selective Leukocyte Adhesion Molecule Inhibitors
Recruitment of Neutrophils Into Inflamed Tissue

Van Deventer SJ. Gut
Consequences of Leukocyte Entry

• Cellular immunity

• Humoral immunity

• Cytokine/chemokine expression

• Phagocytic activity

• Antigen presentation

Role of Adhesion Molecules in Antigen Presentation

T cell

CD4

Immunologic synapse

Myelin cross-reactive antigen

TCR

LFA-1

VLA-4

CD28

CTLA-4

Ag/MHC

B7-1

B7-2

Signal One

Signal Two

VCAM-1

ICAM-1

Antigen presenting cell

Courtesy B. Cree, MD, PhD, MRC.
Therapeutic Targets

Leucocyte Adhesion

CD 11a/CD18

NATALIZUMAB

VEDOLIZUMAB

α4β1 (VLA-4)

α4β7

CCX282-B

CCR9

CCL-25

ISIS-2302

ICAM-1

MAdCAM mAb (PF-547659)

MadCAM-1

VCAM-1

ACTIVATED INTESTINAL MICROVASCULAR ENDOTHELIAL CELLS

Adapted from Danese S Gut 2011;60:998-1008
Endothelial and Leukocyte Adhesion: $\alpha_4$ Integrins

- Leukocyte membrane glycoproteins
- $\beta_1$ and $\beta_7$ subunits
- Interact with endothelial ligands VCAM-1, fibronectin, and MAdCAM-1
- Mediate leukocyte adhesion and trafficking

Rationale for $\alpha_4$ Integrins as Therapeutic Targets

- Increased VCAM-1 and MAdCAM-1 expression in mucosa of inflammatory bowel disease (IBD) patients
- Inflamed intestinal mucosa from IBD patients displays increased $\alpha_4$-dependent adhesiveness to leukocytes in vitro
- Human and animal studies suggest the $\alpha_4\beta_7$ MAdCAM-1 interaction mediates leukocyte homing to the intestine
- Anti-$\alpha_4$ and anti-$\alpha_4\beta_7$ antibodies ameliorate spontaneous colitis in the Cotton-top Tamarin animal model
Natalizumab: A Humanized Monoclonal Antibody against $\alpha_4$-Integrins

- $\alpha_4$-Integrin antagonist
- CDR grafted from murine antibody
- Human IgG4 subclass framework
- Non-complement fixing

Cumulative Number of New Gd+ Lesions *Miller et al., 2003 (1 Year)*

- **Placebo (n=71)**
- **3 mg/kg (n=68)**
- **6 mg/kg (n=74)**

*Mean no. of new Gd+ lesions vs placebo*

*P<0.001

Infusion given

Natalizumab Phase III Study in Active CD: Efficacy of Natalizumab as Active Crohn’s Therapy (ENACT-1)

- Patients with active CD (N = 906) randomized to receive IV infusions at weeks 0, 4, and 8
  - Natalizumab 300 mg (n = 181)
  - Placebo (n = 724)
- Primary endpoint was response (≥ 70 pt decrease in CDAI) at week 10

P = 0.018

ENACT-2: Maintenance of Sustained Clinical Response

Patients who maintained response (%)

Natalizumab 300 mg (n = 168)

Placebo (n = 170)

P = 0.005
P < 0.001
P < 0.001
P < 0.001
P < 0.001

61.3%
28.8%

Time (months)

Start ENACT-2

ENACT-2: Patients Removed from Concurrent Steroids

Patients not receiving steroids (%)

- Natalizumab 300 mg (n=67)
- Placebo (n=76)

* P < 0.05

Start ENACT-2

### ENACT-2: ITT Safety and Tolerability Profile

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 214)</th>
<th>Natalizumab (n = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with adverse events</td>
<td>203 (95%)</td>
<td>192 (90%)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>21 (10%)</td>
<td>19 (9%)</td>
</tr>
<tr>
<td>Discontinuations due to adverse events</td>
<td>53 (25%)</td>
<td>26 (12%)</td>
</tr>
<tr>
<td>Drug-related adverse events</td>
<td>53 (25%)</td>
<td>40 (19%)</td>
</tr>
<tr>
<td>Frequently occurring drug-related AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>16 (7%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (2%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (4%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Patients with serious infections</td>
<td>4 (2%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Patients with malignancies</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>(both were basal cell carcinomas)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute infusion reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As % of patients</td>
<td>16 (7%)</td>
<td>14 (7%)</td>
</tr>
<tr>
<td>As % of infusions</td>
<td>1.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td></td>
<td>7.2%</td>
</tr>
<tr>
<td>(primary analysis population)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sandborn WJ. et al. (ENACT-2)  
PML

- JCV- human papova virus
- Latent in renal tubuloepithelium; 60% of individuals
- Severe CNS disease in highly immunosuppressed patients (HIV\combination chemotherapy)
- Very high risk with natalizumab therapy (1:160 to 1:10,000 dependent on risk factors)
- “chilling” effect on anti-adhesion molecule Rx
Natalizumab and PML

• Diagnosis
  – Clinical impression
  – Brain MRI
  – CSF analysis for JCV DNA by PCR (has replaced brain biopsy)
  – Brain biopsy (gold standard)

• Safety study demonstrated risk of PML at 1:1,000 (95% CI 1:200 to 1:2,800) after a mean of 18 months of treatment in clinical trials

• Approved for multiple sclerosis and Crohn’s disease
• Restricted to patients for whom anti-TNF therapy failed
• Mandatory participation in the TOUCH risk management program
• ~ 180 additional cases reported in patients with multiple sclerosis, 100,000 patients under treatment
• Plasmapheresis is of benefit
• New antibody test highly accurate in identifying patients with prior exposure
PML Risk Reduction by JCV Serology

• ~40 % of patients do not acquire the virus
• No virus = No PML
• PCR of peripheral blood or urine not useful – low positive predictive value
• ELISA for JCV antibody detection highly sensitive and specific
• False-negative rate of 2.5 % (one sided UCL-95 of 4.4 %)
• All patients with PML were antibody positive
• Useful for risk stratification

Trampe A.K. et al Neurology 2012;78 (22); Gorelik L. et al Ann Neur 2010; 68(3)
Vedolizumab: Background

- Ligand for $\alpha_4\beta_7$ is MAdCAM
- Animal models show that ACT-1 selectively blocks trafficking of $\alpha_4\beta_7$ positive lymphocytes to the gut
- Raises possibility of gut specific immune modulation
- Striking benefit in cotton-top tamarin model

Hesterberg PE et al. *Gastroenterology* 1996;111:1373-80
Podolsky et al. *JCI* 1993;92:372-80
MLN-02 was created by grafting the complementarity determining regions of ACT-1 into a human IgG1 framework.

- Excellent safety/tolerability in Phase I studies.
- Clinical trial programs (Millennium) in both ulcerative colitis and Crohn’s disease.
Endothelial and Leukocyte Adhesion: $\alpha 4$ Integrins

- Leukocyte membrane glycoproteins
- $\beta 1$ and $\beta 7$ subunits
- Interact with endothelial ligands VCAM-1, fibronectin, and MAdCAM-1
- Mediate leukocyte adhesion and trafficking

MLN-02 in UC: Design of the Trial

249 Patients Screened

181 Randomized

2.0 mg/kg

60

55

0.5 mg/kg

58

57

Placebo

63

60

Completed week 6

172

68 Ineligible

Clinical Remission

Week 6

Overall $P = 0.030$

Placebo: 15%

0.5 mg/kg: 33%  $P = 0.021$

2.0 mg/kg: 34%  $P = 0.015$

**Vedolizumab Phase III: Study Design**

**Induction Phase**  
Week 0 – Week 6

- **Cohort 1**  
  - Blinded Induction  
  - N=374

  - **No**

  - **Cohort 1** complete?

  - **Yes**
    - **Cohort 2**  
      - Open-Label Induction  
      - N=521

  - **No**
    - Placebo  
      - N=149
    - VDZ  
      - N=225

**Maintenance Phase**  
Week 6 – Week 52

- Placebo  
  - N=149

- VDZ  
  - N=373

- **Week 6: Responder?**

  - **Yes**
    - Placebo  
      - N=126
    - VDZ  
      - Q8 wks  
        - N=122
    - VDZ  
      - Q4 wks  
        - N=125

  - **No**

**Corticosteroid Tapering**

*Responders began tapering regimen at 6 weeks; others, as soon as a clinical response was achieved.*

Clinical Response, Clinical Remission, Mucosal Healing at 6 Weeks, ITT Population

Clinical Response:
- Placebo: 25.5%
- Vedolizumab: 47.1%
- Δ: 21.7%
- 95% CI: 11.6, 31.7

Clinical Remission:
- Placebo: 5.4%
- Vedolizumab: 16.9%
- Δ: 11.5%
- 95% CI: 4.7, 18.3

Mucosal Healing:
- Placebo: 16.9%
- Vedolizumab: 40.9%
- Δ: 16.1%
- 95% CI: 6.4, 25.9

P < 0.0001
P = 0.0010

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

**ITT Population**

### Patients With Prior Anti-TNF Failure
- **Clinical Response:** Δ 18.4
  - 95% CI: 3.9, 32.9
  - Patients: 20.6
- **Clinical Remission:** Δ 6.6
  - 95% CI: -9.8, 22.8
  - Patients: 3.2
- **Clinical Response:** Δ 26.8
  - 95% CI: 13.7, 39.9
  - Patients: 9.8
- **Clinical Remission:** Δ 16.5
  - 95% CI: 2.4, 30.2
  - Patients: 6.6

### Patients Without Anti-TNF Exposure
- **Clinical Response:** Δ 53.1
  - Patients: 39.0
- **Clinical Remission:** Δ 23.1
  - Patients: 23.1

Primary and Secondary Outcomes Through 52 Weeks, ITT Population

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>VDZ Q8Wks</th>
<th>VDZ Q4Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Remission</td>
<td>15.9</td>
<td>23.8</td>
<td>19.8</td>
</tr>
<tr>
<td>Durable Clinical Response</td>
<td>8.7</td>
<td>13.9</td>
<td>41.8</td>
</tr>
<tr>
<td>Mucosal Healing</td>
<td>20.5</td>
<td>31.4</td>
<td>44.8</td>
</tr>
<tr>
<td>CS-Free Remission</td>
<td>45.2</td>
<td>45.2</td>
<td>20.5</td>
</tr>
</tbody>
</table>

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

Corticosteroid Use From Week 6*

Vedolizumab for CD Induction and Maintenance

**Induction Phase**
Week 0 – Week 6

- **Cohort 1**: Blinded Induction, N=368

  - Screening, Enrollment
  - **Cohort 1 complete?**
    - No
    - Placebo, N=148
    - VDZ, N=220

  - Yes
    - **Cohort 2**: Open-Label Induction, N=747
      - VDZ, N=747

**Maintenance Phase**
Week 6 – Week 52

- Placebo, N=148
- VDZ, N=506
- Placebo, N=153
- VDZ Q8 wks, N=154
- VDZ Q4 wks, N=154

**Week 52 Assessments**

*Corticosteroid Tapering*

*Responders began tapering regimen at 6 weeks; others, as soon as a clinical response was achieved.*
Clinical Remission and CDAI-100 Response at Week 6

- Clinical Remission
  - PBO: 6.8 (1.2, 14.3)
  - VDZ: 14.5
  - Mean Δ% vs PBO (95% CI)

- CDAI-100 Response
  - PBO: 25.7
  - VDZ: 31.4
  - P=0.23

*Mean Δ% vs PBO (95% CI): 7.8 (1.2, 14.3) for Clinical Remission, 5.7 (–3.6, 15.0) for CDAI-100 Response.

Primary and Secondary Outcomes at 52 Weeks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>VDZ/PBO</th>
<th>VDZ/VDZ Q8W</th>
<th>VDZ/VDZ Q4W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Remission (%)</td>
<td>21.6</td>
<td>39.0†</td>
<td>36.4†</td>
</tr>
<tr>
<td>CDAI-100 Response (%)</td>
<td>30.1</td>
<td>43.5‡</td>
<td>45.5‡</td>
</tr>
<tr>
<td>CS-Free Remission (%)</td>
<td>15.9</td>
<td>31.7‡</td>
<td>28.8‡</td>
</tr>
<tr>
<td>Durable Remission (%)</td>
<td>14.4</td>
<td>21.4</td>
<td>16.2</td>
</tr>
</tbody>
</table>

Mean Δ% vs VDZ/PBO: 17.4, 14.7

†P<0.01 vs placebo; ‡P<0.05 vs placebo

Study C13011: CD Design

- Randomized, placebo-controlled induction trial in Crohn’s disease
- Similar inclusion / exclusion criteria to C13007
- Main objectives: 2\textsuperscript{nd} Induction study to evaluate induction:
  - In TNF\(\alpha\) antagonist failure patients
  - At Week 6 (after 2 doses) and at Week 10 (after 3 doses)
- Patient population N = 416
  - TNF\(\alpha\) antagonist failures (75%); TNF\(\alpha\) naïve (25%)
  - Dosing at weeks 0, 2 and 6
  - Endpoint assessments at week 6 and 10

Sands et al, ECCO 2013
## Exposure-Adjusted Adverse Events Affecting >5% of Patients Through Week 52

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>PBO Rate (N=275)</th>
<th>VDZ Rate (N=620)</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>0.168</td>
<td>0.262</td>
<td>1.6039</td>
<td>0.9021, 2.8519</td>
</tr>
<tr>
<td>Colitis ulcerative</td>
<td>0.273</td>
<td>0.206</td>
<td>0.7543</td>
<td>0.5448, 1.0444</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0.137</td>
<td>0.187</td>
<td>1.3692</td>
<td>0.8677, 2.1605</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0.132</td>
<td>0.125</td>
<td>0.9432</td>
<td>0.5530, 1.6088</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0.115</td>
<td>0.113</td>
<td>0.9825</td>
<td>0.6069, 1.5907</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.101</td>
<td>0.095</td>
<td>0.9398</td>
<td>0.5166, 1.7099</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.044</td>
<td>0.075</td>
<td>1.6900</td>
<td>0.8253, 3.4605</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0.071</td>
<td>0.072</td>
<td>1.0317</td>
<td>0.5756, 1.8492</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.044</td>
<td>0.069</td>
<td>1.5721</td>
<td>0.7380, 3.3490</td>
</tr>
<tr>
<td>Cough</td>
<td>0.062</td>
<td>0.066</td>
<td>1.0668</td>
<td>0.5663, 2.0093</td>
</tr>
<tr>
<td>Influenza</td>
<td>0.031</td>
<td>0.057</td>
<td>1.8528</td>
<td>0.7463, 4.5996</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>0.234</td>
<td>0.179</td>
<td>0.8014</td>
<td>0.5083, 1.2636</td>
</tr>
<tr>
<td>Any infection</td>
<td>0.812</td>
<td>0.804</td>
<td>0.9932</td>
<td>0.7573, 1.3027</td>
</tr>
</tbody>
</table>
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)
Hepatitis B Surface Antibody (HbsAb) Concentration Through Day 74*

* Per Protocol Population

Parikh A. et al. ECCO 2013
Serum IgA Response to Oral Cholera Vaccine Through Day 74*

% responders (95% CI): PBO 50.0 (37.6, 62.4) 83.9 (74.7, 93.0) 74.2 (63.3, 85.1) 59.7 (47.5, 71.9)
VDZ 30.2 (18.8, 41.5) 63.5 (51.6, 75.4) 57.1 (44.9, 69.4) 50.8 (38.4, 63.1)

*Dukoral Population

Parikh A. et al. ECCO 2013
Therapeutic Targets

Leucocyte Adhesion

CD 11a/CD18

NATALIZUMAB

VEDOLIZUMAB

α4β1 (VLA-4)

α4β7

rhuMAb Beta 7

ACTIVATED INTESTINAL MICROVASCULAR ENDOTHELIAL CELLS

Adapted from Danese S Gut 2011;60:998-1008
Humanized Antibody to Beta - 7
[Rhumbeta7]

Stefanich E.G. et al Br J Pharmacol 2011 162 (8) :1855-70
Etrolizumab vs Placebo – Eucalyptus Phase II Randomized Induction Study in Active UC – Clinical Remission at Wk 10

- Humanized monoclonal antibody to the B7 subunit of the heterodimeric integrins $\alpha 4\beta 7$ and $\alpha E\beta 7$ in patients with mod-sev active UC
- N=124
- Randomized to 2 dose groups vs placebo

Vermiere S. et al. DDW 2013 Late Breaking Abstract.
Therapeutic Targets

Leucocyte Adhesion

LEUCOCYTE

CD 11a/CD18

NATALIZUMAB

LEUCOCYTE

CCR9

ISIS-2302

CCX282-B

CCR9

MAdCAM mAb (PF-547659)

ICAM-1

MAdCAM mAb

ACTIVATED INTESTINAL MICROVASCULAR ENDOTHELIAL CELLS

VEDOLIZUMAB

α4β7

rhuMAb Beta 7

VCAM-1

VCAM-1

Adapted from Danese S Gut 2011;60:998-1008
• Placebo controlled dose escalation RCT

• 3 doses against placebo

• Pooled analysis

• Total n=80

Vermiere S. et al. Gut 2011;60:1068-1075
Therapeutic Targets

Leucocyte Adhesion

LEUCOCYTE

CD 11a/CD18

NATALIZUMAB

VEDOLIZUMAB

α4β1 (VLA-4)

α4β7

rhuMAb Beta 7

VCAM-1

VCAM-1

MAdCAM mAb (PF-547659)

MAdCAM mAb

ACTIVATED INTESTINAL MICROVASCULAR ENDOTHELIAL CELLS

Adapted from Danese S Gut 2011;60:998-1008
GSK1605786: An Oral CCR9 Antagonist

- Potent and selective CCR9 receptor antagonist
- Orally administered
- No significant toxicity has been observed in pre-clinical studies
- Safety profile in Crohn’s patients is similar to placebo in > 500 subjects who have received GSK1605786 in clinical trials
- Gut-specific targeted therapy may avoid safety limitations of generalized immunosuppressants
CDAI 100 Response Achieved with 500 mg QD at Week 12

Maintenance of Remission Over 36 Weeks with 250 mg BID

Primary endpoint: Maintenance of response not achieved

Leucocyte Adhesion

Leucocyte

CD 11a/CD18

NATALIZUMAB

CCX282-B

CCR9

ISIS-2302

ISIC-25

VCAM-1

MAdCAM mAb (PF-547659)

ACTIVATED INTESTINAL MICROVASCULAR ENDOTHELIAL CELLS

Adapted from Danese S Gut 2011;60:998-1008
Sphingosine 1-Phosphate Receptor Modulation: Mechanism of Action

- S1P1R agonism induces receptor internalization; lymphocytes lose response to S1P gradient.
- Become trapped in lymph nodes, causing peripheral lymphopenia.
- Upon drug withdrawal, receptor expression is restored, and lymphocytes leave nodes, reversing lymphopenia.

Courtesy Dr. Alan Olsen
Fingolomod in MS

Adjusted Annualized Relapse Rate

- Interferon (N=431)
  - 0.33

- Fingolimod 0.5 mg (N=429)
  - 0.16
  - P<0.001

- Fingolimod 1.25 mg (N=420)
  - 0.20
  - P=0.16

Conclusions

• Anti-adhesion molecules remain a promising new class of drugs
• Multiple novel agents have either entered the clinic or are in an advanced stage of development
• The problem of PML with natalizumab should not constrain development of more selective agents
• Vedolizumab is likely to be the first “out of class” monoclonal for the treatment of UC
• Monoclonals are first generation drugs but oral agents are in development
• The precise role of these agents in comparison to standard treatments will require large scale, comparative efficacy trials