Emerging Biologic Therapies

- Anti-TNF therapies (adalimumab, certolizumab pegol, CDP571, etanercept, onercept)
- Anti-selective adhesion molecule therapies (natalizumab, MLN -02)
- Miscellaneous
  - Anti-interleukin 12 antibody
  - Sargramostim (GMCSF)
  - Visilizumab (anti-CD3 antibody)
Construct of anti-TNFα biologic agents

Murine
Chimeric
Infliximab
IgG₁ isotype
75% human

Humanized
Human Recombinant Receptor/Fc Fusion Protein

CDP571
Etanercept (p75)
Onercept (p55)
IgG₄ isotype
95% human
100% human

Pegylated Humanized

CDP870
Certolizumab
IgG₄ isotype
95% human

Human
D2E7

Adalimumab
IgG₁ isotype
100% human
## Characteristics of anti-TNFα agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mode of Action</th>
<th>Route</th>
<th>Half-life (days)</th>
<th>Interval Between Injections (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>+</td>
<td>IV</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>+</td>
<td>SC</td>
<td>12–14</td>
<td>2</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>+</td>
<td>SC</td>
<td>14</td>
<td>4</td>
</tr>
</tbody>
</table>

**Mode of Action:**
- **TNF neutralization**: Increases the half-life of the drug.
- **Apoptosis**: Causes cell death.
- **Others**: Includes ADCC and CF (Complement Fixation).

**Route:**
- **IV**: Intravenous injection.
- **SC**: Subcutaneous injection.
Design Characteristics for Trials with Biologic Agents in CD

**Short Term Induction** (Targan/CLASSIC I/ENCORE)
- Placebo-controlled induction
- Early endpoint (4 weeks, 12 weeks)
- Multiple doses of active drug
- 1:1:1:1 allocation
- 70-point or 100-point reduction in CDAI
- Remission

**Maintenance** (ACCENT/PRECiSE 2)
- Open Label induction
- Followed by maintenance of response in responders
- 70-point and 25% or 100-point reduction in CDAI
- Remission

**Induction and maintenance** (PRECiSE-1)
- Double-Blind, PLC induction
- DB-PLC Maintenance
- 100-point reduction in CDAI
- Remission
- Primary endpoint early and late response combined
Infliximab for Active CD: Remission at Week 4


Clinical remission defined as a CDAI score <150

*Clinical remission defined as a CDAI score <150*  

Adalimumab for Active CD: CLASSIC Results at Week 4

Clinical Remission
- Placebo/placebo: 12%
- 40 mg/20 mg: 18%
- 80 mg/40 mg: 24%
- 160 mg/80 mg: 36%

Clinical Response Δ 100
- Placebo/placebo: 25%
- 40 mg/20 mg: 34%
- 80 mg/40 mg: 40%
- 160 mg/80 mg: 50%

Clinical Response Δ 70
- Placebo/placebo: 37%
- 40 mg/20 mg: 54%
- 80 mg/40 mg: 59%
- 160 mg/80 mg: 59%

N=299
† P<.05

Remission=CDAI ≤150;
Response=reduction in CDAI of 70 or 100 points from baseline

Hanauer SB et al. Gastroenterology. 2006;130:323.
Phase II Study of Certolizumab pegol* in Active CD: Clinical Response

Clinical response = decrease CDAI ≥100 points or remission (CDAI ≤150)

*CDP 870, pegylated Anti–TNF antibody fragment

Phase II Study of Certolizumab pegol in Active CD: Remission

Remission = CDAI ≤ 150 points

Precise-1: induction therapy with certolizumab pegol in CD (response and remission at week 26)

- **Response (%):**
  - **Weeks 4:** Certolizumab pegol 28.7, Placebo 21.8; p ≤ 0.05
  - **Weeks 6:** Certolizumab pegol 35.2, Placebo 26.8; p ≤ 0.05
  - **Weeks 4 & 26:** Certolizumab pegol 23.1, Placebo 16.0; p ≤ 0.05

- **Remission:**
  - **Weeks 4:** Certolizumab pegol 19.5, Placebo 11.3; p ≤ 0.01
  - **Weeks 6:** Certolizumab pegol 21.6, Placebo 17.2; p = ns
  - **Weeks 6 & 26:** Certolizumab pegol 14.4, Placebo 9.8; p = ns

- **Sandborn Gastroenterology 2006 Abstract**

- **Post-hoc Analysis:**
  - **100-point Remission:** Certolizumab pegol 44.0, Placebo 46.2; p ≤ 0.01
  - **70-point Remission:** Certolizumab pegol 37.8, Placebo 32.0; p ≤ 0.01
  - **p = ns**
Clinical Remission at Week 4
IFX (Targan) – Certolizumab [TNF-Naïve] (Schreiber) – ADA (Hanauer) and PRECiSE 1 Certolizumab [TNF-Naïve]

Hanauer SB, Gastroenterology 2004 Vol. 127, No.1
Schreiber et al. Gastroenterology. 2005 Sep;129(3):807-18
Infliximab in ACCENT I: Maintenance of Clinical Response (70 points) in Week 2 Responders

*P<0.001, 10 mg vs. single
**P=0.002, 5 mg vs. single

Infliximab 5mg/kg  *P<0.001, 10 mg vs. single
Infliximab 10mg/kg  **P=0.001, 5 mg vs. single

N = 110  N = 113  N = 112

Infliximab in ACCENT I: Maintenance of Clinical Remission in Week 2 Responders

CHARM: maintenance therapy with adalimumab in CD

Clinical response

Week 26

Week 56

Clinical remission

p < 0.001

p = NS

p < 0.001

p = NS

p < 0.001

p = NS

Placebo

Adalimumab 40 mg EOW

Adalimumab 40 mg weekly

EOW = every other week.

CHARM: maintenance therapy with adalimumab in CD (steroid-free remission)

Patients in Remission and Off Steroids (%)

Off steroids, week 26
- PBO: 3% (2/66)
- 40 mg EOW: 35% (20/58)
- 40 mg weekly: 30% (22/74)

Off steroids, week 56
- PBO: 6% (4/66)
- 40 mg EOW: 29% (17/58)
- 40 mg weekly: 23% (17/74)

*\( p < 0.001 \); **\( p = 0.008 \)

EOW = every other week.
CHARM: maintenance therapy with adalimumab in CD (maintenance of healing of draining fistulas at weeks 26 and 56)

Healing = no draining fistulas
Patients with fistulas: draining fistulas at both screening and baseline

EOW = every other week.
Precise-2: maintenance therapy with certolizumab pegol in CD (response and remission at week 26)

Response

- All: 36.2% for 3 inj. + Placebo, 62.8% for Certolizumab
- CRP ≥ 10: 33.7% for 3 inj. + Placebo, 61.6% for Certolizumab

Remission

- All: 28.6% for 3 inj. + Placebo, 47.9% for Certolizumab
- CRP ≥ 10: 25.7% for 3 inj. + Placebo, 42% for Certolizumab

Schrieber Gut 2005 (Abstract)
Precise-1: induction therapy with certolizumab pegol in CD (response and remission at week 26)

**Response (%)**

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<thead>
<tr>
<th>Weeks</th>
<th>Certolizumab pegol</th>
<th>Placebo</th>
<th>Post-hoc Analysis</th>
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<tbody>
<tr>
<td>4</td>
<td>28.7</td>
<td>21.8</td>
<td>p ≤ 0.05</td>
</tr>
<tr>
<td>6</td>
<td>35.2</td>
<td>26.8</td>
<td>p ≤ 0.05</td>
</tr>
<tr>
<td>6 &amp; 26</td>
<td>23.1</td>
<td>16.0</td>
<td>p ≤ 0.05</td>
</tr>
<tr>
<td>4</td>
<td>19.5</td>
<td>11.3</td>
<td>p = ns</td>
</tr>
<tr>
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<td>6 &amp; 26</td>
<td>14.4</td>
<td>9.8</td>
<td>p = ns</td>
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</table>

**Remission**

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<th>Placebo</th>
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<td>33.7</td>
<td>p ≤ .01</td>
</tr>
<tr>
<td>6</td>
<td>46.2</td>
<td>37.8</td>
<td>p ≤ 0.05</td>
</tr>
<tr>
<td>6 &amp; 26</td>
<td>32.0</td>
<td>32.0</td>
<td>p ≤ .01</td>
</tr>
</tbody>
</table>

**Sandborn Gastroenterology 2006 Abstract**
Anchoring PRECiSE 2, ACCENT I, and CHARM Results Relative to PRECiSE 1

**PRECiSE 2**
- Week 6 Response: 64.1%
- Week 26 Remission: 28.6%
- Overall Remission Week 26: 18.3%

**ACCENT I**
- Week 2 Response: 58.5%
- Week 30 Remission: 21.0%
- Overall Remission Week 30: 12.3%

**PRECiSE 1**
- Overall Remission Week 26: 18.3% for Response, 29.5% for Remission

**CHARM**
- Week 4 Response: 58.0%
- Week 26 Remission: 17.0%
- Overall Remission Week 26: 9.9%

Calculation of overall remission rate equals Remission x Response
Anti-TNF Antibody Toxicity

- Immunogenicity (antibodies to infliximab, adalimumab, certolizumab pegol)
- Infusion reactions (infliximab)
- Delayed hypersensitivity reactions (infliximab)
- Injection site reactions (adalimumab, certolizumab pegol)
- Auto-antibody formation (predominantly infliximab)
- Drug-induced lupus
- Non-Hodgkin’s lymphoma (including γΔ hepatospleenic T cell lymphoma)
- ? Skin cancer
- ? Solid tumors
- Serious infections
- Opportunistic Infections (including tuberculosis, histoplasmosis, coccidiomycosis)
- Demyelination
Natalizumab: A Humanized, Monoclonal Antibody (mAb) Against $\alpha_4$ Integrins

Complementarity-Determining Regions (CDRs)

- CDR grafted from murine Ab
- Human IgG4 framework
- Retains full potency
Natalizumab (Anti-α4 Integrin Antibody) for Active CD

Clinical Remission (CDAI<150)

Placebo (n=63)
3 mg/kg+0 (n=68)
3+3 mg/kg (n=66)
6+6 mg/kg (n=51)

*P<0.05

ENACT-1: induction therapy with natalizumab in CD (response at week 10)

Natalizumab (n=724)
Placebo (n=181)

Time (weeks)
Patients (%)

Primary endpoint

P = 0.009

ENACT-1: induction therapy with natalizumab in CD (remission at week 10)

- Natalizumab (n=724)
- Placebo (n=181)

Patients (%)

Time (weeks)

*P ≤ 0.037

ENACT-1: induction therapy with natalizumab in CD (response at week 10 in patients with elevated CRP at baseline)

Placebo (N=134) 300 mg (N=526)

Week 2: Placebo 31, 300 mg 42, P = 0.020
Week 4: Placebo 44, 300 mg 44, P = 0.022
Week 6: Placebo 49, 300 mg 62, P = 0.006
Week 8: Placebo 47, 300 mg 60, P = 0.008
Week 10: Placebo 45, 300 mg 58, P = 0.007
Week 12: Placebo 48, 300 mg 63, P = 0.002
ENCORE: induction therapy with natalizumab in CD (response at weeks 8+12 in patients with elevated CRP at baseline)

Statistically significant for all comparisons

% Patients in Clinical Response

- Placebo (n=250)
- 300 mg (n=259)

Wk 4: Placebo 37%, 300 mg 40%
Wk 8: Placebo 51%, 300 mg 40%
Wk 12: Placebo 56%, 300 mg 44%
Wks 8 & 12: Placebo 60%, 300 mg 48%

*p=0.001
*p<0.001

Targan Gastro 2006 Abstract
ENCORE: induction therapy with natalizumab in CD (remission at weeks 8+12 in patients with elevated CRP at baseline)

Statistically significant for all comparisons

Placebo (n=250) 300 mg (n=259)

% Patients in Clinical Remission

- Wk 4: Placebo 16%, 300 mg 24%, p=0.009
- Wk 8: Placebo 21%, 300 mg 32%, p=0.002
- Wk 12: Placebo 25%, 300 mg 38%, p=0.001
- Wks 8 & 12: Placebo 16%, 300 mg 26%, p=0.002

Targan Gastro 2006 Abstract
Summary of Natalizumab Induction: Response at Week 4

Natalizumab 6+6 mg/kg (Ghosh) or 300 mg (Sandborn and Targan)

- Placebo
- Natalizumab 1 mg/kg
- Natalizumab 3+3 mg/kg
- Natalizumab 6+6 mg/kg (Ghosh) or 300 mg (Sandborn and Targan)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghosh (CD202)</td>
<td>30%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sandborn (ENACT-1)</td>
<td>47%</td>
<td>0.029</td>
</tr>
<tr>
<td>Targan (ENCORE)</td>
<td>37%</td>
<td>0.001</td>
</tr>
<tr>
<td>Sandborn (ENACT-1)</td>
<td>45%</td>
<td>0.006</td>
</tr>
<tr>
<td>Sandborn (ENACT-1)</td>
<td>44%</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Note: Percentages and P values reflect the response rates and statistical significance for each treatment group at Week 4.
Summary of Natalizumab Induction: Remission at Week 4

- Placebo: 14%
- Natalizumab 1 mg/kg: 29%
- Natalizumab 3+3 mg/kg: 29%
- Natalizumab 6+6 mg/kg (Ghosh) or 300 mg (Sandborn and Targan): 31%

<table>
<thead>
<tr>
<th>Study</th>
<th>Natalizumab 3+3 mg/kg</th>
<th>Natalizumab 1 mg/kg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghosh (CD202)</td>
<td>29%</td>
<td>29%</td>
<td>31%</td>
</tr>
<tr>
<td>Sandborn (ENACT-1)</td>
<td>23%</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Sandborn (ENACT-1 elevated CRP)</td>
<td>19%</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>Targan (ENCORE)</td>
<td>24%</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

P values:
- P = NS
- P = 0.009

Note: P < 0.028
ENACT-2: maintenance therapy with natalizumab in CD (landmark analyses)

At Week 36 At Week 60 At Week 36 At Week 60
Placebo Natalizumab

Response

*P ≤ 0.001

Sandborn NEJM 2005
ENACT-2: maintenance therapy with natalizumab in CD (sustained response)

Primary endpoint

Natalizumab 300mg (n=168)
Placebo (n=170)

Sandborn
NEJM 2005
ENACT-2: maintenance therapy with natalizumab in CD (sustained remission)

- Natalizumab 300mg (n=130) vs Placebo (n=120)
- Contingent primary endpoint: Time = 12 months
- Percent of patients in remission:
  - Natalizumab: 39% at 15 months
  - Placebo: 15% at 15 months
- Statistical significance:
  - P=0.217 at 3 months
  - P<0.05 at 4 months
  - P<0.001 at 6 months

Sandborn
NEJM 2005
ENACT-2: maintenance therapy with natalizumab in CD (steroid-free remission)

P = 0.014  P = 0.009  P ≤ 0.003

Sandborn
NEJM 2005
Natalizumab (Tysabri) PML

- Approved by the FDA in December 2004 for multiple sclerosis (MS)
- Withdrawn from market in February 2005: 3 cases of PML (progressive multifocal leukoencephalopathy)
- PML caused by the JC polyoma

Pathogenesis
- Infection is asymptomatic and occurs in childhood
- Virus remains latent
- Reactivation may results in PML in immunocompromised individuals

Clinical presentation
- Subacute progression of focal neurological deficits
  - Visual (retro-chiasmal)
  - Motor
  - Sensory
  - Cerebellar
- Cognitive impairment & behavioral abnormalities
Natalizumab (Tysabri) PML (continued)

- 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 1:1000 (95% CI 1:200 to 1:2800) after a mean of 18 months of treatment
- sBLA to return to market filed with FDA in September 2005, advisory committee March 2006, approved in June 2006
- Possible supplemental sBLA for Crohn’s disease in 2nd half 2006
- Possible FDA approval in 1st half 2007
MNL-02 (LDP-02): A Humanized Monoclonal Antibody Against α4β7 Integrins

- Complementarity-Determining Regions (CDRs)
  - CDR grafted from murine Ab
  - Human IgG1 framework
  - Fc receptor recognition and binding deleted, thus eliminating complement fixation and cytokine release
  - Administered intravenously every 4 weeks
MLN-02 (LDP-02) For Moderately Active Ulcerative Colitis

- 181 patients with active ulcerative colitis [ulcerative colitis clinical score (UCSS) ≥ 5 and modified Baron score (MBS) ≥ 2] receiving a stable dose of 5-ASA or no medical therapy
- Randomized to receive IV doses of placebo, 0.5 mg/kg, or 2.0 mg/kg MLN-02 on days 1 and 29
- The primary endpoint was % clinical remission (UCSS score 0 or 1, MBS 0 or 1, and no blood) at day 43

P=0.03

MLN-02 (LDP-02) For Moderately Active Ulcerative Colitis

- Secondary endpoint was % endoscopic remission (MBS 0) at day 43
- Secondary endpoint was % of patients with decrease ≥ 3 UCSS points from baseline
- Serious adverse events 8% for MLM-02 and 5% for placebo, one patient with angioedema after MLN-02

Anti–Interleukin-12 Monoclonal Antibody (J695, ABT-874) for Active Crohn’s Disease

**Phase II Trial**

- Cohort 1: n=40
- Cohort 2: n=39
- Active CD (CDAI 250-450)
- 7 weekly SQ injections of J695 1 or 3 mg/kg or placebo
- Clinical remission = CDAI <150 pts at week 7
- Clinical response = ↓ in CDAI ≥100 pts at week 7

Sargramostim (GMCSF) for Crohn’s Disease

- Gut inflammation phenotypically similar to Crohn’s disease occurs in chronic granulomatous disease, glycogen storage disease, and Chediak-Higashi syndrome
- 124 patients with active CD; concomitant treatment with steroids, immunosuppressives; infliximab not permitted
- Sargramostim 6 ug/kg or placebo SQ daily for 8 weeks

Rationale

**OKT3 and Immunosuppression**

- **Immunosuppression**
  - T-cell receptor modulation
  - T-cell clearance
  - Unresponsiveness

- **Activation**
  - Proliferation
  - Release of cytokines
  - Toxic effects:
    - Fever
    - Chills
    - Pulmonary distress, etc.

- Fc receptor-mediated T-cell activation contributes to toxicity but is not required for immunosuppression

Visilizumab: Severe Active Steroid-Refractory Ulcerative Colitis

Clinical Activity
Percent of Subjects in Response
MTWSI <10 with 3 point decline

Targan. Gastroenterology 2005 Abstract
Visilizumab: Severe Active Steroid-Refractory Ulcerative Colitis

Clinical Activity
Percent of Subjects in Remission
MTWSI ≤3

Targan. Gastroenterology 2005 Abstract