Biologics, Novel Therapeutic Approaches in Inflammatory Bowel Diseases

Walter Reinisch
Univ-Klinik für Innere Medizin III
Abt. Gastroenterologie & Hepatologie
AKH Wien
From availability-driven therapies using drugs of unspecific or unknown mode of action to (steroids, thiopurines, etc…) to Translational medicine
The Threats of the IBD Study Machinery

- Powered to reveal minor differences (clinically relevant?)
- Designs more sophisticated (complicated)
- Heterogeneous patient populations enrolled
- Results difficult to interpret (raises controversy)
- Necessitates new endpoints (e.g. AUC CDAI)
- Safety profiles of concern?
Add new risks to conventional drugs in IBD

Rate per 1,000 EIP Patients

TBC in IFX treated patients

Progressive multifocal leukencephalopathy in patients treated with Natalizumab
Add new formats of Postmarketing Patient’s monitoring: TREAT-Registry

Lichtenstein et al. Gastroenterology 2005;128 (suppl 2): A580
Treatment Goals in IBD

- Cure
- Decelerate Natural course of IBD
- Tissue Healing
- Maintenance of Steroid-Free Remission
- Steroid-free Remission
- Clinical Remission
- Clinical Response
Determined clinical relevance of new endpoints in CD

Rutgeerts P et al. Gastrointest Endo. 2005
Determined clinical relevance of new endpoints in UC

- **Percent of Patients Achieving Clinical Remission (%)**
  - Mucosal Healing at Week 8: 48.3%
  - No Mucosal Healing at Week 8: 9.5%

Reinisch W et al. *in prep*
The Role of Pro-inflammatory Cytokines in CD
Monoclonal Antibodies, Fusion Protein, and Fab’ fragment against TNF

- Chimaeric monoclonal antibody
- Human monoclonal antibody
- Human recombinant receptor/Fc fusion protein
- Humanized Fab’ fragment

Targets:
- infliximab
- adalimumab
- etanercept
- certolizumab pegol

Weir et al. Therapy 2006;3(4):535-545
Add Efficacy to conventional drugs in CD

Infliximab in human CD

Add Efficacy to conventional drugs in UC

Clinical Response

GAIN: Week 4 Remission to Adalimumab by Infliximab History

- % of Patients

Loss of response:
- PBO: 7/87
- 160/80: 15/77
- 8% in 160/80

Intolerant:
- PBO: 5/95
- 160/80: 21/95
- 22% in 160/80

Loss of response and intolerant:
- PBO: 0/21
- 160/80: 3/19
- 16% in 160/80
Certolizumab pegol – Maintenance of response and remission

Results
- Remission rates remained high after 1 year of treatment
  - Of 215 patients who responded at week 6, 104, 90 and 80 were in remission at 6, 12 and 18 months respectively

Remission by treatment duration

<table>
<thead>
<tr>
<th>Remission (%)</th>
<th>Week 26 (N = 215)</th>
<th>Week 52 (N = 215)</th>
<th>Week 80 (N = 215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48.4%</td>
<td>41.9%</td>
<td>37.2%</td>
<td></td>
</tr>
</tbody>
</table>
Patients with PGA Score of 0 or 1

All Patients Receiving Infliximab Who Participated in Extension

ACT Extension: Per-Protocol Analysis

Proportion of Patients (%)

PGA of 0
PGA of 1

Last Visit†
Week E56
Week E104

92%
75%

52%
61%

31%
31%

83%
97%

†Combined data from ACT 1 Week 54 & ACT 2 Week 30
Changed our view on IBD as progressive diseases

- Penetrating
- Inflammatory
- Stricturing

Patients: n = 2002 552 229 95 37

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.
Progression of ulcerative colitis

- Disease extension 16 % at 5 yrs
- and 31 % at 10 yrs
- Especially in patients with refractory disease or frequent relapses,
- Smoking is protective
Outcome of Steroid Treatment

Disease activity of CD

Initial prednisolone dose 50 mg/d

- Steroid-responsive: 29% at day 0, 29% at month 5
- Steroid-dependent: 31% at day 0, 29% at month 5
- Steroid-refractory: 21% at day 0, 21% at month 5

6-MP in adolescent CD

Response and remission at week 10 in comparison to ACCENT I

Response

Remission
Patients in the Top-Down arm more rapidly achieve remission than step-up patients.
T-cell directed therapies

Selectins, Integrins, and Chemokines Mediate Tissue-Specific Recruitment of Leukocytes in the GI Tract

α4β7hi expressed on a subset of human memory CD4+ T cell mediates selective traffic to gut mucosa and nodes via Mucosal Addressin Cell Adhesion Molecule (MadCAM1)
MLN-02: α4β7 blockade in UC: week 6

Overall p=0.030

% Remission

15% Placebo
33% 0.5 mg/kg
34% 2.0 mg/kg
Natalizumab adds longterm-efficacy on top of conventional medications

- Primary endpoint: \( p = 0.007 \) (\( \leq 0.001 \))
- Natalizumab 300mg (n=168):
  - 61% at primary endpoint
  - 54% at month 15
- Placebo (n=170):
  - 20% at primary endpoint
  - 28% at month 9

\( p = 0.244 \) at month 3

Graph shows patients who maintained response (%)

- Time (months): 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15
- Patients who maintained response (%): 100, 80, 60, 40, 20, 0

ENACT-2 Start
Add new risks to conventional drugs in IBD

TBC in IFX treated patients

Progressive multifocal leukencephalopathy in patients treated with Natalizumab
Baseline CDAI $\geq 250$ and CRP > 7.5 mg/L Show Clear Differentiation Between Traficet-EN® and Placebo Response in CDAI

Traficet-EN™ an Selective, Orally Active Inhibitor of CCR9: Phase 2 Trial – CDAI Scores Drop After 4 Weeks

Per Protocol % of Subjects

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Traficet-EN®</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>45%</td>
<td>49%</td>
</tr>
<tr>
<td>CDAI $\geq 250$</td>
<td>40%</td>
<td>56%</td>
</tr>
<tr>
<td>CRP &gt; 7.5 mg/L</td>
<td>35%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Rate of Decrease in CDAI
P=0.006

70 Point Drop

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Traficet-EN®</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI $\geq 250$, CRP &gt;7.5 mg/L</td>
<td>3/13</td>
<td>4/13</td>
</tr>
</tbody>
</table>

100 Point Drop

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Traficet-EN®</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI $\geq 250$, CRP &gt;7.5 mg/L</td>
<td>23%</td>
<td>42%</td>
</tr>
</tbody>
</table>
Biology of Interleukins 12 and 23

- CD4+ TCR
- Antigen Presenting Cell
- MHCII
- TLR?
- Stimulus
- IL-12
  - p40
  - p35
- IL-12Rβ1
- IFNg (Th1)
- IL-17 (Th17)
- IL-12Rβ1
- IL-23R
- IL-23
  - p40
  - p19
- IL-23R
- p40

CNTO 1275

- Fully human IgG1k monoclonal antibody
- Binds the p40 subunit of human and primate IL-12/23
- Prevents IL-12 and IL-23 from binding IL-12Rβ1
- Normalizes IL-12 and IL-23 mediated signaling, cellular activation, and cytokine production
- In development in Crohn’s disease and psoriasis (IV or SC)

Sandborn DDW 2007
Study Design

• Primary Population:
  – Subjects with moderately to severely active Crohn’s disease despite treatment with 5-ASA compounds, antibiotics, corticosteroids, and/or immunomodulators
  – 104 subjects randomized in a 1:1:1:1 ratio to treatment groups I-IV

• Secondary Population:
  – Subjects who failed to respond to infliximab at the maximum approved dose and treatment regimen for Crohn’s disease as defined in the US package insert
  – 27 subjects randomized in a 1:1 ratio to treatment groups V and VI (Open-label)
## Study Design Overview

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo SC</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td></td>
</tr>
<tr>
<td>CNTO 1275 90 mg SC</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td></td>
</tr>
<tr>
<td>Placebo IV</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNTO 1275 4.5 mg/kg IV</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Population 1
- Placebo SC
- CNTO 1275 90 mg SC
- Placebo IV
- CNTO 1275 4.5 mg/kg IV

### Population 2
- CNTO 1275 90 mg SC
- CNTO 1275 4.5 mg/kg IV
Clinical Response at Week 8

Primary Endpoint: ↓CDAI scores of ≥25% & ≥70 points

Population 1

<table>
<thead>
<tr>
<th>Response</th>
<th>Groups I &amp; III</th>
<th>Groups II &amp; IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined placebo</td>
<td>39.6</td>
<td></td>
</tr>
<tr>
<td>Combined CNTO 1275</td>
<td></td>
<td>49.0</td>
</tr>
</tbody>
</table>

p=0.34

DDW 2007
≥ 100-Point Response at Week 8

Response: ↓ CDAI scores ≥ 100 points

Population 1

<table>
<thead>
<tr>
<th>Groups I &amp; III</th>
<th>Groups II &amp; IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.2</td>
<td>49.0</td>
</tr>
</tbody>
</table>

Proportion of subjects (%)

- **Combined placebo**
- **Combined CNTO 1275**

p=0.05

DDW 2007
Clinical Response at Week 8 in Patients with Prior Infliximab Exposure

N=49

Population 1

<table>
<thead>
<tr>
<th>Response</th>
<th>Groups I &amp; III</th>
<th>Groups II &amp; IV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined placebo</td>
<td>25.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined CNTO 1275</td>
<td></td>
<td>59.1%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

DDW 2007
Unexpected High Response Rates from Placebo

Response = CDAI decrease by at least 70
Enhanced Response = CDAI decrease by at least 100
Remission = CDAI <=150

Percent of Patients (%)

N = 10
N = 6
N = 14
N = 15

Placebo 0.1 mg/kg 1.0 mg/kg* 4.0 mg/kg**

Anti-IFN-γ antibody (fontolizumab) in human CD

Visilizumab Background

Changes to Murine Parent anti-CD3

Non–FcR-Binding Humanized Anti-CD3 Antibody: Visilizumab

M291

Visilizumab

Mutations

Val → Ala

Gly → Ala
Visilizumab Background

MOA *In Vivo* Working Hypotheses

- Apoptosis of activated CXCR3+ T cells
- Altered migration of CXCR3+ T cells

Activated T cells

Resting T cells

Blood

Gut
Visilizumab in UC: Phase I/II (408)

Clinical Activity: Median Mayo Score

<table>
<thead>
<tr>
<th>Visilizumab Doses</th>
<th>Baseline</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mcg/kg</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>7.5 mcg/kg</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>10 mcg/kg</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>12.5 mcg/kg</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

n = 17, 14, 20, 15, 18, 13, 13, 11
Abatacept Selectively Modulates Co-stimulation via CD80/86:CD28 Pathway

- Abatacept inhibits full activation of CD28-dependent T-cells
- by blocking Signal 2
Change from Baseline in DAS28 (ESR) at 1 Year*

Error bars represent the standard error of the mean.
*ITT analysis.
Schiff et al. ACR 2006, L43.
Ongoing Phase III Abatacept Studies In CD and UC

- Placebo-controlled induction and maintenance studies
- N~650 in each study
- Adult subjects with moderate to severe CD/UC who have had insufficient response and/or intolerance to conventional therapy (including primary and secondary non-responders to anti-TNF)
MAP Kinase Inhibitoren

CNI-1493

Inhibits:
- Macrophage activation
- Proinflammatory cytokines
- NO
MAP Kinases in severe CD

IEL

Phospho JNK

PMN

Activated p38 MAPK

LPL
CNI-1493 (Semapimod) in severe CD

- CDAI: Decrease over weeks
- CRP: Decrease over weeks

- n = 12
- 8 or 25 mg/m² i.v. for 12 days
Oral p38 MAPK Inhibitor BIRB 796 in active CD: Randomised, double-blind, placebo-controlled trial

n = 284
CDAI 220 - 450
Studien Medikation
2x/d für 8 Wo

Conclusion

• IBD as a lifelong disease affecting patients from young adulthood
• IBD poses an attractive investment for the biotech industry
• Rich pipeline of new compounds
• Major achievements have been obtained
• Quest for the magic bullet still ongoing
• Cure of IBD, the goal of all our industrious efforts is still out of sight