Chronisch-entzündliche Darmerkrankungen

Gerd Kullak-Ublick

Division of Gastroenterology and Hepatology
University Hospital Zurich

Gastro Highlights USZ, 2. Juli 2005
Adacolumn: extracorporeal leukocyte apheresis

- cellulose acetate beads
- removes granulocytes and monocytes by FcγR and complement receptors
- used as adjunctive therapy
- steroid sparing
- response in 60-80%
- controlled trials underway

Adsorption efficiency (%)

- Granulocyte
- Monocyte
- Lymphocyte
- Platelet
- Erythrocyte

mean ± SE (n=216)
23-year old female with severe steroid-refractory ulcerative colitis:

10 days high-dose prednisolone

19-year old male with Crohn’s disease

after 6 Adacolumn sessions

after 10 Adacolumn sessions

Saniabadi AR et al., J Clin Apheresis 2005; May 12
Overview of leukocytapheresis trials

- 37 trials/case reports in ulcerative colitis – 1 controlled trial
  - all with 60-80% efficacy in reducing Disease Activity Index (DAI)
  - 20-60% induction of remission

- 7 trials/case reports in Crohn’s disease – no controlled trials
  - largely similar responses to those seen in UC in published data
  - leukocytapheresis appears to be less effective in CD than in UC
Morphologic changes in human leukocytes that adhere to Adacolumn

- Neutrophils and monocytes (400 x)
- An activated monocyte/macrophage with disappearing microvilli (12′000 x)
- Neutrophils firmly adsorbed to the carrier and surface microvilli have disappeared (10′000 x)
- Neutrophils with long pseudopodia and fully shed microvilli (12′000 x)

Saniabadi AR et al., J Clin Apheresis 2005; May 12
Possible mechanisms of leukocytapheresis

Effects on inflammatory cells

- Reduction of activated peripheral blood leukocytes
- Induction of immature leukocytes (granulocytes and monocytes) – activate Tregs?
- Reduction in oxidative stress
- Decrease in IL-1, IL-6, and TNF (decreased CRP and ESR)
- Increase in IL-4 production by PBMC
- Reduction of chemokine receptors on monocytes

Acceleration of epithelial regeneration

- Regeneration by bone marrow-derived epithelial cells
Adacolumn vs. Prednisolone in steroid-dependent ulcerative colitis

261 patients with exacerbated UC symptoms

153 worsened or unchanged
Steroid therapy

108 cases improved

5-ASA or sulfasalazine

261 patients with exacerbated UC symptoms

Steroid unresponders, 62 cases*

Steroid responders, 91 cases

69 cases relapsed during steroid tapering (steroid-dependent patients)

22 cases achieved stable remission

Adacolumn, 46 cases

Prednisolone, 23 cases

Remission 38 cases

Improved 5 cases

Unresponders 2 cases

Surgery 1 case

Remission 15 cases

Improved 3 cases

Unresponders 3 cases

Surgery 2 cases

n.s.

Hanai et al., Digestion 2004;70:36
Adacolumn vs. Prednisolone in steroid-dependent ulcerative colitis

Clinical activity index

Disease activity index

Hanai et al., Digestion 2004;70:36
Effect of Adacolumn on endoscopic findings in corticosteroid-dependent ulcerative colitis

at entry  6 weeks  20 weeks

Hanai et al., Digestion 2004;70:36
• Pathogenesis

• Treatment
NOD2

TLRs

LPS, flagellin
dsRNA, BLP

Gm⁺ and Gm⁻ Bacteria

Muramyl dipeptide (MDP)

hPEPT1

intestinal lumen

cell membrane

intracellular

NOD2

NFκB

cytokine release

Vavricka SR et al., Gastroenterology 2004; 127: 1401
Mutant NOD2 cannot block Toll-like receptor 2

IBD linkage areas

Ahmad et al., GASTROENTEROLOGY 2004;126:1533
Organic Cation Transporter OCTN1

Blood

Enterocyte

Gut lumen

OCTN1

Organic cations
Drugs
Carnitine
The Organic Cation Transporter OCTN1 is mutated in Crohn’s disease

<table>
<thead>
<tr>
<th>OCTN1</th>
<th>Carnitine uptake (pmol/mg protein)</th>
</tr>
</thead>
</table>

hOCTN1  hOCTN2  hOCTN3  mOCTN1  mOCTN2  mOCTN3

V  503L  503F | V  503L  503F

HeLa | GM 10665

Peltekova VD et al., Nature Genetics 2004; 36: 471
Gm⁺ and Gm⁻ Bacteria

Muramyl dipeptide (MDP)

hPEPT1

OCTN1

NOD2

antiiinflammatory effect

NFκB

Vavricka SR et al., Gastroenterology 2004; 127: 1401
NOD2
Organic cations
NFκB
Gm+ and Gm- Bacteria
Muramyl dipeptide (MDP)
hPEPT1
intestinal lumen
OCTN1
antinflammatory effect
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intracellular

Vavricka SR et al., Gastroenterology 2004; 127: 1401
NOD2

Organic cations

NFκB

Gm⁺ and Gm⁻ Bacteria

Muramyl dipeptide (MDP)

hPEPT1

intestine

lumen

cell

membrane

intracellular

OCTN1

inflammation

Vavricka SR et al., Gastroenterology 2004; 127: 1401
Inflammatory Bowel Diseases 2005

- Pathogenesis
- Treatment
<table>
<thead>
<tr>
<th></th>
<th>Infliximab: Chimeric MAB</th>
<th>CDP571: Humanized MAB</th>
<th>Adalimumab (D2E7): Human MAB</th>
<th>CDP870: PEGylated humanized Fab</th>
<th>Etanercept: Human fusion protein</th>
<th>Onercept: Human p55 receptor</th>
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<tbody>
<tr>
<td>Binds soluble TNF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Binds membrane TNF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
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<tr>
<td>Fixes complement + ADDC</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
<td>?</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>T-cell apoptosis</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>?</td>
</tr>
</tbody>
</table>

**ADDC**, antibody-dependent cellular cytotoxicity; **MAB**, monoclonal antibody
Adalimumab in patients with prior loss of response or intolerance to infliximab for Crohn’s disease

- an open-label study -

- 24 patients who had lost responsiveness (n=12) or developed intolerance (acute or delayed hypersensitivity, n=20) to infliximab
- 80 mg s.c. adalimumab at week 0 followed by 40 mg s.c. every 2 weeks
- assessment at week 12

Adalimumab in patients with prior loss of response or intolerance to infliximab for Crohn’s disease

% of patients

Week

<table>
<thead>
<tr>
<th>Week</th>
<th>Response</th>
<th>Remission</th>
<th>Fistula improvement</th>
<th>Fistula closure</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>29</td>
<td>18</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>12</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>12</td>
<td>59</td>
<td>29</td>
<td>56</td>
<td>33</td>
</tr>
</tbody>
</table>
Of the 11 patients receiving corticosteroid therapy ...

- 45% (5) discontinued steroid use within 14 weeks of initiation of adalimumab
- 27% (4) were able to decrease the dose of steroids at the time of their last follow-up

Papadakis KA et al., Am J Gastroenterol 2005; 100: 75
Response to adalimumab in infliximab-allergic patients (8 weeks)

- 80 mg s.c. followed by 40 mg s.c. every 2 weeks -

Harvey-Bradshaw-Index

ESR (mm/h)

Youdim et al., Inflamm Bowel Dis 2004; 10: 333
CDP571 in active Crohn’s disease (phase III)

1° endpoint: clinical response at week 28 (defined as a decrease in CDAI of ≥100 points or remission (CDAI ≤150 points))

2° endpoint: clinical response at week 2 (using the same definition)

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2° endpoint: clinical response at week 2 (using the same definition)

Sandborn WJ et al., Gut 2004; 53: 1485-93
CDP571 in active Crohn’s disease (phase III)

Intent-to-Treat Population: CRP ≥10 mg/L at baseline (40% of patients)

Sandborn WJ et al., Gut 2004; 53: 1485-93
292 patients with active CD
Randomized to receive SQ doses of CDP870 at Weeks 0, 4, 8
- placebo (n=73)
- 100 mg (n=74)
- 200 mg (n=72)
- 400 mg (n=72)
Endpoint: Clinical response (%) at Week 12 (decrease in CDAI of ≥100 points or CDAI ≤150 points)

* Preliminary data
† p < 0.05
‡ p = NS

CDP870: Phase II Study in Active Crohn’s Disease: Sensitivity Analysis of Response According to Baseline CRP

Baseline CRP (mg/L)

% Clinical Response

CRP>5, p<0.05
CRP>6, p<0.05
CRP>7, p<0.01
CRP>8, p<0.01
CRP>9, p<0.05
CRP>10, p<0.05

Placebo
CDP870 400 mg

Autologous Hematopoietic Stem Cell Transplantation in Patients With Refractory Crohn’s Disease

- phase 1 study, 12 patients with refractory CD
- peripheral blood stem cells mobilized with cyclophosphamide and G-CSF and CD34+ enriched
- immune ablative regimen: 200 mg/kg cyclophosphamide and 90 mg/kg equine antithymocyte globulin

CDAI

Crohn’s Severity Index

Oyama et al., Gastroenterology 2005;128:552
Sargramostim (*Leukine*, Berlex) for Active Crohn’s Disease

6 µg/kg/d sargramostim s.c. vs. placebo for 56 days (2:1, n = 124)

- Sargramostim (granulocyte-macrophage colony stimulating factor) is most commonly used for myeloid cell recovery after chemotherapy

- CD results from defective intestinal immune defense

- GM-CSF may improve intestinal mucosal barrier function and host defense

Sargramostim (*Leukine*, Berlex) for Active Crohn’s Disease

Anti-Interleukin-12 Antibody for Active Crohn’s Disease

Anti-Interleukin-12 Antibody for Active Crohn’s Disease

**Cohort 1**

<table>
<thead>
<tr>
<th>1 mg</th>
<th>3 mg</th>
<th>placebo</th>
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<tbody>
<tr>
<td>n=8</td>
<td>n=16</td>
<td>n=16</td>
</tr>
</tbody>
</table>

1 injection

4 weeks

1 mg 3 mg placebo

1 injection per week for 6 weeks

**Cohort 2**

<table>
<thead>
<tr>
<th>1 mg</th>
<th>3 mg</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=8</td>
<td>n=15</td>
<td>n=16</td>
</tr>
</tbody>
</table>

1 injection per week for 7 weeks

end of treatment: day 43

end of treatment: day 64


Cohort 1

Cohort 2

Response

Remission

p = 0.03

n.s.
Colitis ulcerosa
Infliximab for acute, non-steroid-refractory ulcerative colitis

**Infliximab**

Clinical activity score (Truelove & Witts)

- **n = 6**

**Prednisolone**

- **n = 7**

Ochsenkühn et al., Eur J Gastroenterol Hepatol 2004; 16: 1167
ACT 2

A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the **Safety** and **Efficacy** of Infliximab in Patients with Active Ulcerative Colitis

Centocor Protocol C0168T46
ACT 2 Study design

• Phase III, multicenter, randomized, placebo-controlled, double-blind, 3-arm, parallel trial

• Population: 360 pts with active Ulcerative Colitis

• 60 sites (worldwide)
<table>
<thead>
<tr>
<th></th>
<th>wk 0</th>
<th>wk 2</th>
<th>wk 6</th>
<th>wk 8</th>
<th>wk 14</th>
<th>wk 22</th>
<th>wk 30</th>
<th>wk 42</th>
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<tr>
<td><strong>Group I:</strong></td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>–</td>
<td>P</td>
<td>P</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Placebo</td>
<td>(n = 120)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Group II:</strong></td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>–</td>
<td>5</td>
<td>5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5 mg/kg infliximab</td>
<td>(n = 120)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group III:</strong></td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>–</td>
<td>10</td>
<td>10</td>
<td>–</td>
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**Primary endpoint**
ACT 2: Objectives and endpoint

To evaluate safety and efficacy of infliximab in patients with active UC

• Primary endpoint at Week 8 is proportion of patients in clinical response defined as
  – Decrease from baseline Mayo Score of $\geq 30\%$ and $\geq 3$ points
  – Decrease in the rectal bleeding subscore of $\geq 1$ OR
  – Rectal bleeding subscore of 0 or 1 if baseline subscore is $\leq 1$ at baseline
Major *inclusion* criteria

- Men or women $\geq$ 18 years of age at screening
- Have had ulcerative colitis of at least 3 months’ duration at screening, confirmed by the biopsy taken at screening
- Have active colitis confirmed during the screening sigmoidscopy by a score of $\geq 2$ on the endoscopy subscore of the Mayo score
- Have active disease, as defined as a baseline Mayo score of 6 to 12 inclusive
- Either have *concurrent* treatment with at least 1 of the following: oral corticosteroids, 6-MP, azathioprine or oral aminosalicylates

**OR**

Have failed to successfully taper, tolerate or respond to corticosteroids within the previous 18 months OR failed to tolerate or respond to oral aminosalicylates within the previous 18 months OR failed to tolerate or respond to 6-MP or azathioprine within the previous 5 years (all in dosages according to the protocol)
Infliximab for Colitis ulcerosa?

ACT2 trial

- 55 centers

- Placebo: n = 123
- Infliximab: n = 121
- Infliximab: n = 120

Infliximab 5 mg/kg
Infliximab 10 mg/kg
Infliximab for UC: Response at 8 weeks and 30 weeks

ACT 2 Investigators' Meeting 2005

unpublished data

* P < 0.001 vs. placebo
Infliximab for UC:

*Remission* at 8 weeks and 30 weeks

unpublished data, ACT2 Investigators’ Meeting 2005
Infliximab for UC:

**Mucosal healing** at 8 weeks and 30 weeks

![Bar diagram showing mucosal healing at 8 weeks and 30 weeks for placebo, 5 mg/kg, and 10 mg/kg doses of infliximab.]

Unpublished data, ACT2 Investigators’ Meeting 2005

* P < 0.001 vs. placebo
Summary (1)

• The organic cation transporter OCTN1 is a newly identified Crohn’s disease gene identified within the IBD5 locus

• Leukocyte apheresis (e.g. Adacolumn) is effective in ulcerative colitis > Crohn’s disease, but controlled trials are needed

• The humanized anti-TNFα antibody adalimumab is effective in Crohn’s disease, potentially due to multiple mechanisms of action (TNF inhibition, T-cell apoptosis, ADDC, complement fixation)

• A benefit of CDP571 and CDP870 is seen primarily in patients with elevated baseline CRP concentrations
Summary (2)

- New therapies in Crohn’s disease include **hematopoietic stem cell transplantation**, **anti-interleukin 12** and **sargramostim**

- **Infliximab** is effective not only in Crohn’s disease, but also in ulcerative colitis as shown in the ACT1 and ACT2 trials
Colitis ulcerosa: OPC-6535 Studie

- Phase III, multizentrisch, randomisierte, doppelblinde Dosisvergleichsstudie, 52-wöchig, mit Parallelarm zur Wirksamkeit und Sicherheit von 25 mg OPC-6535 täglich und 50 mg OPC-6535 täglich als orale Tabletten und 800 mg Asacol® zweimal täglich

- Ziel: Remissionserhaltung

- Einschlusskriterien: Colitis ulcerosa in Remission (< 52 Wochen), welche keine der folgenden Medikamente nehmen:
  - Corticosteroide (seit 6 Wochen vor dem Screening),
  - topische Medikamente (Corticosteroid- oder 5-ASA-Einläufe, Zäpfchen, Schaum),
  - Azathioprin, 6-Mercaptopurin
  - Methotrexat
Morbus Crohn: Everolimus (RAD001) Studie

- Phase II, multizentrische, randomisierte, doppelblinde, Placebo-kontrollierte Pilotstudie zur Untersuchung der Wirksamkeit von RAD001 (6 mg/Tag p.o.) im Vergleich zu Azathioprin (2,5 mg/kg/Tag, orale Gabe) und Placebo

- Einschlusskriterien:
  - Diagnose eines Morbus Crohn (klinische und entweder radiologisch, endoskopisch oder histologisch gesichert innerhalb der letzten 5 Jahre)
  - kein 6-MP, AZA, MTX, CyA, anti-TNFα AK während der letzten 3 Monate
  - CDAI > 220 and < 450
  - keine Steroidbehandlung in den letzten 14 Tagen (p.o., i.v. oder rektal)