Anti-TNF and cyclosporine are identical choices for severe ulcerative colitis refractory to steroid therapy

CON

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**Anti-TNF and cyclosporine are identical choices for severe ulcerative colitis refractory to steroid therapy**

- Con

**Disclosure of Potential Conflict of Interest**

<table>
<thead>
<tr>
<th>Consultant</th>
<th>Abbott Hungary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MSD Hungary</td>
</tr>
<tr>
<td></td>
<td>Ferring</td>
</tr>
<tr>
<td>Lecture</td>
<td>Ferring</td>
</tr>
<tr>
<td></td>
<td>Abbott</td>
</tr>
</tbody>
</table>
Defining the severe attack

- Diarrhoea ≥6 with visible blood and
- Pulse rate >90bpm, or
- Temperature >37.8°C, or
- Haemoglobin <10.5g/dL, or
- ESR >30mm/hr

Truelove & Witts *BMJ* 1955;ii:1041
BSG Guidelines on IBD Gut 2004; **53 Suppl IV**:v1-16
Kornbluth & Sachar ACG Guidelines on UC *Am J Gastro* 2004;100:1371-85
ACPGBI Position on Acute Severe Colitis *Colorectal Dis* 2008;10 **Suppl 3**:8-29

- The number of criteria in addition to a bloody stool frequency ≥6/day correlate with outcome
**What is the long-term outcome of ASC?**

**Complete response:** no visible blood, frequency ≤3 on day 7 of intensive treatment (same cohort as *Gut* 1996; **38**: 905-10)

**Incomplete response:** visible blood or frequency >3/day on day 7

<table>
<thead>
<tr>
<th></th>
<th>Complete n = 19</th>
<th>Incomplete n = 13</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colectomy rate in 12 mo</td>
<td>1/19 (6%)</td>
<td>7/13 (54%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Colectomy rate over 15yr</td>
<td>6/19 (32%)</td>
<td>10/13 (77%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Median time from index admission to colectomy (range, mo)</td>
<td>28 (6-99)</td>
<td>8 (3-72)</td>
<td>0.006</td>
</tr>
<tr>
<td>Longest period of remission (range, mo)</td>
<td>42 (0-120)</td>
<td>9 (1-35)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Bojic et al *IBD* 2009;15:823-8
Colectomy is related to the number of T&W criteria of severity on admission

<table>
<thead>
<tr>
<th>T and W criteria</th>
<th>Colectomy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloody stools $\geq$ 6/day and Pulse rate $&gt;90$ bpm, or Temperature $&gt;37.8^\circ$C, or Haemoglobin $&lt;10.5$ g/dL, or ESR $&gt;30$ mm/hr</td>
<td>(n = 294 admissions)</td>
</tr>
<tr>
<td>+ 1</td>
<td>9% (11/129)</td>
</tr>
<tr>
<td>+ 2</td>
<td>31% (29/94)</td>
</tr>
<tr>
<td>+ 3</td>
<td>48% (29/60)</td>
</tr>
<tr>
<td>+ 4</td>
<td>45% (5/11)</td>
</tr>
</tbody>
</table>

Dinesen et al J Crohn’s Colitis 2010;4:431-7
Active disease ECCO statement

Intravenous-steroid resistant ulcerative colitis of any extent

ECCO Statement

… Second line therapy with either ciclosporin [EL1b, RG B], or infliximab [EL1b, RG B] or tacrolimus [EL1b, RG B] will often be appropriate. If there is clinical deterioration colectomy is recommended. If there is no improvement within a further 4-7 days, colectomy should usually be recommended [EL5, RG D]. Third line therapy may be considered at a specialist centre

Dignass A JCC 2012

BUT: Are they really equal?
What should be considered when planning the rescue therapy

• Discuss medical strategy and patient’s views
• Consider pattern of disease
  • First presentation?
  • Relapse of established disease?
  • Relapse despite immunomodulators?
• Request Consultant colorectal surgeon’s opinion
  • About day 3: or refer to another centre
Which drug to chose?

Treatment success
Short and long-term efficacy
Ciclosporin (CSA) A for Induction of Remission in Acute Severe UC

Severe UC unresponsive to 7 days IV steroid therapy

Ciclosporin A 4 mg/kg per day for up to 14 days and IV steroids every 8 h

N=20; ** Improvement in clinical activity score at 14 days
Study terminated early for ethical reasons

What is the right dose of CsA?

- Start 2mg/kg iv
  - For approx. 4 days
  - Check [CsA] day 2 (aim >200, <400ng/mL)
  - Then convert to oral CsA 5mg/kg for 3 months
  - Monitor BP, creatinine, LFTs & [CsA] at 2 weeks, then monthly
  - Start azathioprine when prednisolone <20mg/d

ECCO guidelines on UC *JCC* 2012 [www.ecco-ibd.eu](http://www.ecco-ibd.eu)

<table>
<thead>
<tr>
<th></th>
<th>2mg/kg</th>
<th>4mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response @ 8d</td>
<td>86%</td>
<td>84%</td>
</tr>
<tr>
<td>Colectomy @ 2wk</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>[CsA] day 4</td>
<td>246 ± 65 ng/ml</td>
<td>345±146 ng/ml</td>
</tr>
</tbody>
</table>

Van Assche et al *Gastroenterology* 2003;125:1025
Problems with CSA therapy

• **Need for drug monitoring:**
  • ciclosporin use is restricted to centres that can regularly monitor concentrations and have sufficient clinical experience in the use of drugs not routinely used in outpatient practices

• **A bridge therapy: to where?**

• **Not suitable for non-IS naive patients**

• **Long term side-effects**
  • nephrotoxic effects, hypertrichosis, opportunistic infection, and 1–2% mortality

Levesque Lancet 2012
Arts J Inflamm Bowel Dis 2004
Long-term outcome of CsA treatment of severe ulcerative colitis: Leuven

IFX: effective for ASC
Colectomy after the first 90 days

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Placebo</th>
<th>p (Fisher)</th>
<th>analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colectomy</td>
<td>7/24 (29%)</td>
<td>14/21 (67%)</td>
<td>0.017</td>
<td>0.029</td>
</tr>
<tr>
<td>Colectomy in patients included on Sweden-index</td>
<td>7/15 (47%)</td>
<td>9/13 (69%)</td>
<td>0.276</td>
<td>0.476</td>
</tr>
<tr>
<td>Colectomy in patients included on Seo-index</td>
<td>0/9 (0%)</td>
<td>5/8 (63%)</td>
<td>0.009</td>
<td>0.016</td>
</tr>
<tr>
<td>Colectomy in patients with severe endoscopy</td>
<td>2/9 (22%)</td>
<td>4/6 (67%)</td>
<td>0.136</td>
<td>0.234</td>
</tr>
<tr>
<td>Colectomy in patients with a moderately severe endoscopy</td>
<td>5/15 (33%)</td>
<td>10/15 (67%)</td>
<td>0.143</td>
<td>0.246</td>
</tr>
</tbody>
</table>
Infliximab rescue for severe colitis?

Longterm outcome

- **Colectomy @ 90 days**
  - IFX 7/24 (29%)
  - Placebo 14/21 (67%)
  
  Järnerot et al Gastroenterology 2005;128:180

- **Single infusion IFX**
- **75% on AZA**

- **Colectomy at 3 yrs**
  - IFX 12/24 (50%)
  - Placebo 16/21 (76%, p=0.012)
  - AZA in 75% IFX group, 57% placebo

Gustavsson et al APT 2010.
SUCCESS Primary Endpoint: Patients in Remission

FAS population Week 16

IFX/AZA Combination (N=78)

Δ = -1.61; P = 0.813

Δ = 16.06; P = 0.032

Δ = 17.67; P = 0.017

SUCCESS Primary Endpoint:
Patients in Remission

FAS population Week 16

Δ = -1.61; P = 0.813

Δ = 16.06; P = 0.032

Δ = 17.67; P = 0.017

IFX (N=77)

IFX/AZA Combination (N=78)

CSA and IFX: metaanalysis

But:
- retrospective
- low pts numbers
- different study designs
- all open label
- different definitions

Chang KH Int J Colorectal Dis 2013
(accepted before CySIF)
CSA and IFX head to head: CySIF

Study period

-5 0 7 14 42 98 days

Screening

CsA

IFX

R

i.v. oral

+ azathioprine

+ azathioprine

Laharie Lancet 2012
## CSA and IFX head to head: CySIF

<table>
<thead>
<tr>
<th></th>
<th>Ciclosporin (n=58)</th>
<th>Infliximab (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female sex</strong></td>
<td>28 (48%)</td>
<td>27 (47%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>39 (26–50)</td>
<td>36 (26–52)</td>
</tr>
<tr>
<td><strong>Disease duration (years)</strong></td>
<td>2.4 (0.4–7.1)</td>
<td>1.0 (0.2–4.4)</td>
</tr>
<tr>
<td><strong>First attack of ulcerative colitis</strong></td>
<td>10 (17%)</td>
<td>16 (28%)</td>
</tr>
<tr>
<td><strong>Disease located in E3</strong></td>
<td>34 (59%)</td>
<td>31 (54%)</td>
</tr>
<tr>
<td><strong>Patient naive to azathioprine</strong></td>
<td>54 (93%)</td>
<td>53 (93%)</td>
</tr>
<tr>
<td><strong>Duration of intravenous steroid treatment (days)</strong></td>
<td>8 (6–9)</td>
<td>7.5 (6–9%)</td>
</tr>
<tr>
<td><strong>Lichtiger score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>27 (47%)</td>
<td>12 (21%)</td>
</tr>
<tr>
<td><strong>12–13</strong></td>
<td>19 (33%)</td>
<td>24 (42%)</td>
</tr>
<tr>
<td><strong>≥14</strong></td>
<td>12 (21%)</td>
<td>21 (37%)</td>
</tr>
<tr>
<td><strong>Mayo disease activity index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>30 (52%)</td>
<td>25 (44%)</td>
</tr>
<tr>
<td>11</td>
<td>17 (29%)</td>
<td>20 (35%)</td>
</tr>
<tr>
<td>12</td>
<td>11 (19%)</td>
<td>12 (21%)</td>
</tr>
<tr>
<td><strong>Mayo endoscopic score of 0</strong></td>
<td>55 (95%)</td>
<td>55 (96%)</td>
</tr>
<tr>
<td><strong>IBDQ score</strong></td>
<td>103 (89–118)†</td>
<td>96 (84–113%)‡</td>
</tr>
<tr>
<td><strong>Haemoglobin (g/L)</strong></td>
<td>105 (95–124)$$</td>
<td>115 (96–124)$$</td>
</tr>
<tr>
<td><strong>C-reactive protein (mg/L)</strong></td>
<td>30 (16–67)$$</td>
<td>46 (28–73)$$</td>
</tr>
<tr>
<td><strong>Albumin (g/L)</strong></td>
<td>28 (24–32)¶</td>
<td>27 (23–33)‡</td>
</tr>
</tbody>
</table>

Table 1: Demographic and clinical characteristics of patients

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*Ulcerative colitis location according to the Montreal classification—ie, pancolitis defined by an ulcerative colitis extended above the splenic flexure.*

†n=52. ‡n=50. §n=56. ¶n=55.
Primary end point: treatment failure

Definitions of failure
- Non response at D7
- Relapse at D7-D98
- Lack of remission at D98
- Colectomy
- SAE
- Death

Difference CsA vs IFX failure rates:
-6.4% (95%CI: -12.0 to 24.8%)

CsA (n=55) 60%  IFX (n=56) 54%

Laharie Lancet 2012
Response rate at D7

Difference CsA vs IFX response rates:
-0.3% (95%CI: -13.3 to 12.8%)

Response: Lichtiger score < 10 and decrease ≥ 3 points as compared to baseline

Laharie Lancet 2012
CSA and IFX head to head: CySIF

- BUT, there are problems with the interpretation:
  - Short term!
  - Superiority design (underpowered to detect non-inferiority)
    - only 80% power to detect a Δ30%
      Kevans D GE 2012 DDW
  - IFX therapy was not optimised:
    - ASC with IFX may have increased clearance (half life of IFX in ASC is 2.8 days vs. 9.5 days in typical IBD pts)
    - ACT1/2 pts with higher trough had better response, remission, and mucosal healing

Colectomy rate
Cys: 18 ± 5%
IFX: 21± 5%

Laharie Lancet 2012
Reinisch W GE 2012 DDW
What is real life?
UK Audit in Severe UC

6135 IBD patients hospitalized

2981 UC

2444 Acute

863 Severe

471 High risk of colectomy

83% received steroids IV in first line

<table>
<thead>
<tr>
<th></th>
<th># of patients</th>
<th>Response</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>108</td>
<td></td>
<td>2.5%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>98</td>
<td>75%</td>
<td>0%</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>52</td>
<td>46%</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

Arnott I et al., Gut 2010; 59: Abstract# A19
IFX salvage after CsA failure

- **47 pts failing CsA after iv corticosteroids**
  - Mean duration of CsA = 6d

- **Then given IFX**
  - 13% remission after 1st infusion
  - 60% remission in those who achieved 3 infusions (n=21/47)

- **Steroid free remission over 30 months (2.5y)**
  - 33%

- **Colectomy**
  - 14/47 (30%)

- **AEs**
  - 23% (11/47 - Listeriosis, Candidiasis, death)

- **Deaths**
  - 1/47, aged 40, 10d after IFX, followed by colectomy: nosocomial pneumonia

Chaparro et al *Aliment Pharmacol Ther* 2012;**35**:275-83
Consider ALSO!
Side effect profile and contraindications
Long term side effects of CSA therapy

- Long term side-effects
  - nephrotoxic effects, hypertrichosis, opportunistic infection, and 1–2% mortality

<table>
<thead>
<tr>
<th>TABLE 3. Adverse Reactions Occurring During CSA Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections: 16 (18.6%)</td>
</tr>
<tr>
<td>Arterial hypertension: 6 (7.0%)</td>
</tr>
<tr>
<td>Hypertrichosis: 5 (5.8%)</td>
</tr>
<tr>
<td>Headache: 3 (3.5%)</td>
</tr>
<tr>
<td>Elevated liver tests (&gt;2×): 2 (2.4%)</td>
</tr>
<tr>
<td>Seizure: 0 (0.0%)</td>
</tr>
</tbody>
</table>

Follow-up: 773 days
Consider contraindications

• **CSA**
  - Cholesterol, magnesium levels (Mg<0.5mM, chol <3.0mM), seizure history
  - Active infection
  - Renal infussicieny
  - Expertise available

• **IFX**
  - Sepsis
  - TBC
  - Optic neuritis
  - Infusion reaction (hypersensitivity)
  - Cancer
## Side effects in comparative trials

<table>
<thead>
<tr>
<th></th>
<th>Ciclosporin (n=58)</th>
<th>Infliximab (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>0*</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiovascular event</strong></td>
<td>1*</td>
<td>1†</td>
</tr>
<tr>
<td><strong>Severe infections</strong></td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Cytomegalovirus colitis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Septicaemia</td>
<td>2†</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anal abscess</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Renal event</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hepatic event</strong></td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td><strong>Pulmonary event</strong></td>
<td>1‡</td>
<td>0</td>
</tr>
<tr>
<td>Worsening of ulcerative colitis</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Degenerative arthrosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td><strong>Total patients (%)</strong></td>
<td>9 (16%)</td>
<td>14 (25%)</td>
</tr>
</tbody>
</table>

* A 66-year-old man developed myocardial ischaemia during the study and died during follow-up (day 137) from a myocardial infarction. † Venous thromboembolism. ‡ Central-venous-catheter-related septicaemia with non-aureus Staphylococcus. § Increased aminotransferases leading to treatment withdrawal (at least two cases related to azathioprine). ¶ Suspected pneumonia (unconfirmed).

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Chang KH Int J Colorectal Dis 2013
Lahaire Lancet 2012
Postoperative complications?
Results from a metaanalysis

Norgard APT 2012 (Danish National Data n=1226, 199 exposed, OR: 1.07 (95%CI: 0.71-1.59))
Zhang APT 2012, Chang KH Int J Colorectal Dis 2013
Summary: CSA or IFX

- Discuss available medical strategies and patient’s views,
- Consider pattern of disease
  - Relapse despite immunomodulators?
- **Differences between CSA and IFX**
  - CSA use is limited to expert centers
  - CSA: bridge therapy, not suitable for non-IS naive patients, IFX can be used as maintenance therapy
  - Drug half life may be important for patients with high risk for surgery
  - Consider contraindications
  - Need for drug monitoring for CSA
    - (maybe trough levels? for IFX)
  - Sequential salvage therapy is an option only in expert centers and should be evaluated on a case-by-case
- **Timely surgery! And treatment modifications**