Biological Therapy for Inflammatory Bowel Disease

Dr. med. P. Juillerat, MSc
Oberarzt I
Head of IBD clinical studies

Wednesday Feb. 25th, 2015
9:15 – 10:00

Master's Course in Gastroenterology
Universitätsklinik für Viszerale Chirurgie und Medizin
Inselspital, Bern
TNF alpha Inhibitors

-1- Use:

„Therapeutical concepts“

-2- Limitation

-3- New biologics

Monoclonal Antibodies

- Biological characteristics
  - Antigen binding
  - Effector functions
    - complement interaction
    - Fc receptor interaction

- Physicochemical characteristics
  - N-terminal heterogeneity
  - Amino acid modifications
  - Hinge fragmentation
    - Glycosylation
      - fucosylation, sialylation...
  - Disulfide bond shuffling
  - C-terminal heterogeneity

Adapted from J. Windisch EAHP congress Milan, March 21-23, 2012
The TNF-alpha Blockade

Sands, Targan Gastroenterology 2002
Available TNF-Inhibitors

- **Infliximab**
  - IV week 0, 2, 6
  - Every 8 wks

- **Certolizumab Pegol**
  - SC week 0, 2
  - Every 4 wks

- **Adalimumab**
  - SC week 0, 2
  - Every 2 wks

- **Golimumab**
  - SC week 0, 2
  - Every 2 wks

References:


Evolution of Anti-TNF agents indications

Moderate to severe refractory and/or fistulizing Crohn’s disease

1999

INFLIXIMAB
June 2003

IBD.net.ch – Swiss Infliximab Study

Response in 32 CD patients

Initial Response W 6-12 W 14-18

55% = Fistula

Within 2 - 4 week: 
→ > 70% clinical response ! than half in remission

Gold standard: Steroids = 60% remission

European cooperative Crohn's disease study (ECCDS):

infliximab infusions, in the past ....


< 10 Infusions !
Infliximab for Crohn’s disease in the Swiss IBD Cohort Study: clinical management and appropriateness

Pascal Juillerat\textsuperscript{a,b}, Valérie Pittet\textsuperscript{b}, John-Paul Vader\textsuperscript{b}, Bernard Burnand\textsuperscript{b}, Jean-Jacques Gonvers\textsuperscript{a}, Philippe de Saussure\textsuperscript{c}, Christian Mottet\textsuperscript{a}, Frank Seibold\textsuperscript{d}, Gerhard Rogler\textsuperscript{e}, Markus Sagmeister\textsuperscript{f}, Christian Felley\textsuperscript{a}, Pierre Michetti\textsuperscript{a} and Florian Froehlich\textsuperscript{a,g}; the Swiss IBD Cohort Study Group*


**SWISSIBD cohort study**

Nov. 06 - Feb. 09
Feb. 09: treatment of about 1500 IBD patients

NB: 70% in university hospitals

Crohn's disease
ulcerative colitis

50%

20%

60%

33%

35%

25%

10%

3%

1%

5%

22%

7%

1%

3%

10%

35%

25%

50%

Anti-TNF

AZA/MTX

Steroids

5-ASA/SPS

5-ASA

ATB

CST

Thiop.

MTX

Anti-TNF

Feb. 09: treatment of about 1500 IBD patients

NB: 70% in university hospitals
Evolution of anti-TNF indication

1999
- INFLIXIMAB
- Moderate to severe refractory and/or fistulizing Crohn’s disease induction, then «on demand »

2003
- Moderate to severe Crohn’s disease – Maintenance or remission (infusion every 8 weeks)

2006
- Moderate to severe ulcerative colitis

2007
- Adalimumab = Humira ® (2003 in RA)

2007
- Certolizumab = Cimzia ®

2014
- Golimumab = Symponi®

New Players !
= New trends
“Early Disease”

- Previous drug exposure
  - AZA/6MP
  - Steroids
  - 5-ASA

- Disease duration (years)
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8
  - 10
  - 11
  - 12

- Studies:
  - SONIC 2010
  - GETAID
  - ACCENT 2002
  - SWISS IBD cohort study
  - Juillerat et al.
  - Targan et al. 1999

Adapted with courtesy from Prof. Colombel
Progression of digestive disease damage (Lémann score) and inflammation

Pre-clinical

Clinical

TREATMENT

Digestive Damage

Progression of digestive damage and inflammatory activity in a theoretical patient with CD

Inflammatory Activity (CDAI, CDEIS, PCR)

Disease onset

Diagnosis

Early disease

Stricture

Fistula/abscess

Surgery

CDAI : Crohn's disease activity index, indice d'activité de la maladie de Crohn ; CDEIS : Crohn's disease endoscopic index of severity, indice de gravité endoscopique de la maladie de Crohn ; PCR : protéine C réactive

Pariente B et al. Inflamm Bowel Dis 2011;17(6):1415-22
Progression of digestive disease damage (Lémann score) and inflammation

Progression of digestive damage and inflammatory activity in a theoretical patient with CD

Disease onset  Diagnosis  Early disease

Pre-clinical  Clinical

Inflammatory Activity (CDAI, CDEIS, PCR)

Digestive Damage

TREATMENT

Surgery

Stricture

Fistula/abscess

Stricture

Pariente B et al. Inflamm Bowel Dis 2011;17(6):1415-22
SUMMARY – Therapeutical concepts

- new indications (UC)
- more molecules

- Treat „early disease“

→ New objectives: „mucosal healing“ and «deep» Remission

Proportion (%) of patients On anti-TNF agents in Switzerland
all world sales of approved anti-TNF-α agents. 

Morbus Crohn
Colitis Ulcerosa
TNF alpha Inhibitors

Use:

Limitation / Loss of response
Before starting an immunosuppression (especially with anti-TNF)

- Hepatitis A, B, C, HIV – EXCLUSION

- Quantiferon test ( + chest Xray) :

    increased risk of reactivation

- update vaccines
- annual gynecological & dermatological controls

J.-F. Rahier et al, Jour Crohn Colitis 2009; ECCO Consensus
Adverse Events

71 Infusions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>urinary infection</td>
<td>9</td>
</tr>
<tr>
<td>fever</td>
<td>9</td>
</tr>
<tr>
<td>arthralgia</td>
<td>6</td>
</tr>
<tr>
<td>headache</td>
<td>4</td>
</tr>
<tr>
<td>thoracic pain</td>
<td>4</td>
</tr>
<tr>
<td>wheezing</td>
<td>4</td>
</tr>
<tr>
<td>abd. pain</td>
<td>3</td>
</tr>
<tr>
<td>myalgia</td>
<td>2</td>
</tr>
</tbody>
</table>

+ 43 delayed infusion reactions

41% OF ALL infusions
CASE 1 «Severe Adverse Event of Anti-TNF Therapy»
[prepared with Dr. A. Kugener]
S.M. 34yo

• Ileocolic and fistulizing Crohns disease

  – first diagnosed 10/2010, first manifestation 05/2010
  – Montreal classification L3 B3 + P
  – abdominal pain, diarrhea, hematochezia, weight loss
  – Osteopenia & vitamin D deficiency
  – iron deficiency anemia
Therapy & Personal history

• Steroid-dependent -> induced diabetes mellitus
• Azathioprin 02/2011 -> pankreatitis
• Methotrexate -> stopped, non adherence

• Personal history
  – Overweight (BMI 28.7)
  – H.pylori-associated gastritis 07/2011
  – Depression
  – Nicotin stopped 3y ago ~10py
Crohn’s disease: acute penetrating complications

- Perianal abscess, fistulectomy 2012 and seton-drainage 2013

Persistent activity:
3-4 x/d liquid diarrhea, diffuse abdominal pain

→ 11/2013
Referral for second opinion to the Inselspital
Colonoscopy 12/2013

- Anal fistula, high activity in the ileum and critical stenosis
- Lab values: CRP 16mg/l, Lc 10.5 G/l. Tc 435 G/l, Hb 105
Follow-up after infliximab-induction

• Very good response after initiating infliximab
• Returned to work (cleaning woman)

• Stool frequency 1x/d, formed, no blood, no mucus
**Infliximab**: 4th dose infliximab not given.

- After induction therapy (week 0, 4, 8) appearance of **severe psoriasis** (head, pubic area) and **palmoplantar pustulosis**
Follow-up

• Switch to Ustekinumab (Stelara®)
  → Induction at 3mg/Kg (180 mg)
  + metronidazole 500mg tid

Maintenance: 1 month later: 1.5 mg/Kg (90mg)

At 3 administration:

• Regression of psoriasis and palmoplantar pustulosis
  (hands and pubis: lesions have disappeared, feet: persistence of small lesions but no pus anymore and less painful).

• Fistulizing disease: inactiv, despite stopping Metronidazol (pat. did it by herself 6 weeks ago)
Tillack C, Brand S et al: (Gut. 2014 Apr;63(4):567-77)

Anti-TNF antibody-induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon-γ-expressing Th1 cells and IL-17A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment.

• first report on successful use of the anti-IL-12/IL-23 antibody ustekinumab for anti-TNF induced psoriasiform skin lesions

• all 9 patients treated with ustekinumab, psoriasiform skin lesions improved dramatically after the first two injections

• Crohn’s disease activity controlled with ustekinumab in majority of patients

Ustekinumab induction and maintenance therapy in refractory Crohn’s disease.

• Induction of ustekinumab (1mg, 3mg, 6mg/kg) in 526 patients
• 145 patients with clinical response (34.1-39.7%) at week 6 re-randomized to ustekinumab (90mg) vs. placebo

Response rate >69.4% after 22 Wo (p<0.001 vs. Placebo).
Loss of response to anti-TNF-α therapy

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Factors associated with loss of response to anti-TNF-α therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>Mechanism of action</td>
</tr>
<tr>
<td>ATI</td>
<td>IgG-mediated neutralisation of the anti-TNF-α therapy</td>
</tr>
<tr>
<td>Augmented clearance</td>
<td>Rapid elimination of drug from circulation leads to serum concentrations below its therapeutic level</td>
</tr>
<tr>
<td>Concomitant therapies</td>
<td>Interaction with drug metabolism</td>
</tr>
<tr>
<td>High baseline WBC count</td>
<td>Unknown</td>
</tr>
<tr>
<td>Anti-DNA, antihistone ANA</td>
<td>Unknown</td>
</tr>
<tr>
<td>Low CRP at baseline</td>
<td>Reduced clearance of material derived from anti-TNF-α induced apoptosis</td>
</tr>
<tr>
<td>Liver and renal function</td>
<td>Action on clearance of the drug</td>
</tr>
<tr>
<td>Gender, age, BMI</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
During the first year: **26% of patients** had to increase dosage (LOR) or **19%** stop for other reasons.
Adalimumab: CHARM:
Clinical Remission (responders)

Patients in Remission (%)

Weeks

Colombel JF et al. T686d, DDW 2006
...and what about the long term use!

Factors associated with durable response to infliximab, 5 years and beyond:

a multi center international cohort

P. Juillerat, H. Sokol, S. Fowler,
F. Froehlich, J–P. Vader
V. Yajnik, Vijay, L. Beaugerie,
A. Macpherson, J. Cosnes,
& J. R. Korzenik

ORIGINAL ARTICLE

Factors Associated with Durable Response to Infliximab in Crohn’s Disease 5 Years and Beyond: A Multicenter International Cohort

Pascal Juillerat, MD, MSc, Harry Sokol, MD, PhD, Florian Froehlich, MD, Vijay Yajnik, MD, PhD, Laurent Beaugerie, MD, Matthew Lucci, Bernard Burnand, MD, MPH, Andrew J. Macpherson, MD, Jacques Cosnes, MD, and Joshua R. Korzenik, MD

Inflamm Bowel Dis 2015;21:60–70
1014 CD patients : differences among centers

<table>
<thead>
<tr>
<th></th>
<th>MGH</th>
<th>St.-Antoine</th>
<th>Swiss IBD</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>348</td>
<td>267</td>
<td>399</td>
<td>1014</td>
</tr>
<tr>
<td></td>
<td>54%</td>
<td>63%</td>
<td>53%</td>
<td>56%</td>
</tr>
<tr>
<td><strong>Age (yrs +/-SD)</strong></td>
<td>43 (+/-14)</td>
<td>41(+/- 14)</td>
<td>42 (+/- 13.5)</td>
<td>42(+/-14)</td>
</tr>
<tr>
<td><strong>IFX duration</strong></td>
<td>19 (1-143)</td>
<td>18 (1-159)</td>
<td>6 (1-125)</td>
<td>13 (1-159)</td>
</tr>
<tr>
<td>(months, median ; range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age start IFX</strong></td>
<td>35 (+/- 14)</td>
<td>33 (+/- 12)</td>
<td>36 (+/- 13)</td>
<td>35 (+/- 13)</td>
</tr>
<tr>
<td>(yrs +/-SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median dis. duration, at start IFX</strong></td>
<td>7 (0- 44)</td>
<td>7 (0- 36)</td>
<td>7 (0- 44)</td>
<td>6 (0-44)</td>
</tr>
<tr>
<td>(yrs ; range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong># pts w/ IFX duration ≥7 y/ ≥ 10 years</strong></td>
<td>50/ 10</td>
<td>40/ 5</td>
<td>11/1</td>
<td>101/ 16</td>
</tr>
<tr>
<td><strong>MEDICATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>85%</td>
<td>88%</td>
<td>72%</td>
<td>75%</td>
</tr>
<tr>
<td>MTX</td>
<td>30%</td>
<td>N/A</td>
<td>16%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>Mean BMI (+/-SD)</strong></td>
<td>26 (+/-6)</td>
<td>22 (+/-5)</td>
<td>24 (+/-5)</td>
<td>24 (+/-5)</td>
</tr>
<tr>
<td>Smokers</td>
<td>10%</td>
<td>40%</td>
<td>38%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Juillerat *et al.* Inflamm Bowel Dis 2015;21:60–70
1014 Crohn’s disease patients representing 28’777 months of infliximab therapy.

Kaplan-Meier survival estimate 18% (first year)

3-5% / year

months

5y

10y

Juillerat et al. Inflamm Bowel Dis 2015;21:60–70
Current management of anti-TNF agents

Drug management:
-1- adapting dosages / intervals
-2- concomittant therapy
-3- Switch class

Tools:
-2- concomittant therapy

Efficacy
LOR

Trough levels and antibodies measurement
Functional blockade
Post hoc Analysis based on drug trough levels (before next administration)

> 3.5 μg/ml at week 14
And ↓ 60% CRP

Dosage increase to 10 mg/Kg
or concomittant IS : 4.6 vs. 1.7 (p=0.047)

Cornilie et al, Gut 2014; 63: 1721-7
LOR – Strategy

Afif et al. Sandborn W. Mayo clinic, Minnesota

AmJGastro 2010; 105:1133–1139;
DOSE INTENSIFICATION STRATEGY


Step 1: Reevaluation of the disease – Identify or confirm active IBD
Rule out: a fixed stenosis, superimposed infection (C. Difficile, CMV), or irritable bowel/functional symptoms.
  → Biological markers, stool toxin +/- endoscopy w/bx.

Step 2: Assessing drug trough level of Infliximab (IFX), before the next infusion and HACA (Human Anti-Chimeric Antibody).

A) Interpretation:

<table>
<thead>
<tr>
<th>HACA</th>
<th>IFX Detectable</th>
<th>Undetectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Unlikely</td>
<td>Immunogenicity</td>
</tr>
<tr>
<td></td>
<td>(limitations of the assay to identify antibodies in the presence of free drug)</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Failure of the drug to control inflammation (presumably because of a different dominant mechanism that drives inflammation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased drug clearance. (Individual rapid drug elimination AND/OR drug binding in serum or tissues based on disease activity level)</td>
<td></td>
</tr>
</tbody>
</table>

B) Attitude:

<table>
<thead>
<tr>
<th>IFX Detectable</th>
<th>Undetectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>HACA +</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>switching to adalimumab or certolizumab pegol</td>
</tr>
<tr>
<td>HACA -</td>
<td>Switching to an alternative drug</td>
</tr>
<tr>
<td></td>
<td>dose intensification</td>
</tr>
</tbody>
</table>
CASE 2 «Trough levels and anti-bodies against IFX»
[prepared with Dr. R. Oelsner]
54 year-old male

- Ulcerative pancolitis, first diagnosed 1993
- Montréal Classification: B3 S2

- In remission from 1993 till 1998


- No extraintestinal manifestation
Medication

- Multiple episodes of steroid therapy
- Long term 5 ASA (e.g. Asacol) : inefficient
- 2006 photodynamic therapy (Inselspital, Dr Ortner)
Comorbidities / complications

- 2007 steroid-induced **osteopenia**, 2008 **osteoporosis**
  - Bonviva 150 mg monthly, Calcimagon D3 2x/d

- Cutaneous **psoriasis** since 17 years old (single lesion at back)
  - treated with steroids at multiple occasions
Endoscopy (first contact)

- 05/2013 Colonoscopy: ulcerative pancolitis with mild inflammation in rectosigmoid (Mayo 1), strong activity up to proximal sigmoid (Mayo 3), moderate inflammation from descending colon to caecum (Mayo 2)

  ➔ re- started on steroids, outpatient clinic appointment in 2 weeks.

- 05/2013: Gastroscopy: Refluxoesophagitis LA Grade B
  - Pantoprazol
3 month later: first clinical visit (3x postponed by patient).

• 08/2013:
  – Bloody diarrhea 8 -10x/d, 3x/night, abdominal pain
  – Chronic fatigue
  – Concentration and memory problems
  – Depression → Citalopram

Chronic anaemia due to blood loss, severe iron deficiency & chronic inflammation (Calprotectin 934 mg/kg)

• Malnutrition- Hypoalbuminemia

<table>
<thead>
<tr>
<th>Albumin (BCP-Methode)</th>
<th>g/L</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactives Protein</td>
<td>mg/L</td>
<td>11</td>
</tr>
<tr>
<td>Bilirubin gesamt</td>
<td>μmol/L</td>
<td>3</td>
</tr>
<tr>
<td>Eisen</td>
<td>μmol/L</td>
<td>3</td>
</tr>
<tr>
<td>Transferrin Sättigung</td>
<td>%</td>
<td>4</td>
</tr>
<tr>
<td>Transferrin</td>
<td>g/L</td>
<td>2.90</td>
</tr>
<tr>
<td>Ferritin</td>
<td>μg/L</td>
<td>8</td>
</tr>
</tbody>
</table>

| Hämoglobin  | g/l  | 104   |
| Hämatokrit   | VI   | 0.33  |
| Erythrozyten | T/l  | 4.35  |
| MCV         | fl   | 76    |
| MCH         | pg   | 24    |
| MCHC        | g/l  | 313   |
| RDW (Ec-Grössenvarianz) | % | 15.2   |
| Thrombozyten | G/l  | 353   |
| MPV (mittleres Tc-Vol.) | fl | 6.3   |
| Leukozyten  | G/l  | 6.8   |
• 10/2013: **Treatment** start with **Infliximab** 400 mg iv
• Ferinject 1000 mg iv
• negative screening for TB, Hepatitis, HIV

• Infliximab scheme:

```
Start : 08.10.13  
Week: 22.10.13  
Week: 619.11.13  
Every 8 weeks
```

• 11/2013: diarrhea ↓ 6x/d, not nights and less blood.
  Weight gain

• 11/2013: Treatment **optimization**: Infliximab 500 mg  (>5 mg/kg)
Partial improvement

• 12/2013: persistent symptoms with night sweats, still frequent diarrhea, but less fatigue.
• combination therapy (infliximab/imurek) refused from patient

• 12/2013: reduce Infliximab interval

Start 0: 8.10.13
Week 2: 22.10.13
Week: 6 19.11.13
Week 10: 20.12.13
Week 14: 14.01.14
Week 18: 11.02.14
Every 8 weeks

• After 3rd Infusion: headache and flush symptoms -> Infliximab combined with pre-treatment: 80 mg prednisolon and Clemastin 2 mg iv
Presentation

• 02/2014: persistent bloody diarrhea 7-8 x/d, no abdominal pain, no nocturnal diarrhea. Calprotectin 350 mg /kg stool

• Follow up endoscopy 04/2014: moderate inflammation (Mayo 2), severe activity proximal colon
Summary of problems

• 8 mo. of *infliximab infusions* with slow, but visible improvement
  → *Dose increased and interval shorten to every 4 weeks*

However: persistent clinical complaints and bloody diarrhea

• Side effects of infusion: occasional vertigo

• Laboratory results: CRP 18 mg/l, Calprotectin 350 mg/kg
Infliximab laboratory results

• 06/2014: Infliximab serum level: >0,035 µg/ml
  (levels < 0,5µg/ml considered as too low)

• Infliximab antibodies: 354,2 AU/ml
**Development**

- **08/2014:** switch to **Golimumab (Simponi® 200 mg sc)**

- **Clinical improvement. No side effects**

  - **Start 0:** 200mg
    - 31.07.14
  - **Week 4:** 100mg
    - 27.08.14
  - **Every 4 weeks:** 50mg
Concomittant therapy reduces anti-TNF agents clearance

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Concomitant therapy</th>
<th>Mean IFX clearance (L/day)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>MTX</td>
<td>0.26</td>
<td>Kavanaugh et al, J Rheumatol 2000</td>
</tr>
<tr>
<td>Ankylosing spondylarthitis</td>
<td>Monotherapy</td>
<td>0.27</td>
<td>Xu et al, J Clin Pharmacol 2008</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>CS±AZA/6-MP (ACT-1) or 5-ASA (ACT-2)</td>
<td>0.41</td>
<td>Fassanmade et al, Eur J Clin Pharmacol 2009</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>CS±5-ASA, AZA/6-MP, MTX</td>
<td>0.38</td>
<td>Fassanmade et al, Clin Ther 2011</td>
</tr>
</tbody>
</table>

Monoclonal Antibodies and BIOSIMILARS

• Definition: *Biosimilar medicines* (‘biosimilars’) are *biological medicines similar to other, already authorized, biological medicines*, that are able to enter the market once the patent for the original product, the reference product, has expired.

• the monoclonal antibody infliximab is due to expire in the EU → Biosimilars:

  • **Infliximab**: *Remsima* (Celltrion) [North Korea, approval 2013, EU approval Sept. 2013 and Canada 2014], *Inflectra* (Hospira+Alvogen) [Hungary], *Flammegis* (Egis)

  **Similar clinical reauals**
Similar Pharmacokinetic and clinical results!

Mean serum concentration of Remsima™ vs Reference drug (Week 22)

ACR response rates at Week 30 (Per-protocol population)

But cross reaction to antibodies against IFX!

Yoo et al. Ann Rheum Dis. 2012; 71 (Suppl. 3) 359
Courtesy of Prof. P. Michetti
-3- Switch class

OR new biologics?
The new biologics

Crohn’s disease: beyond antagonists of tumour necrosis factor

Laurent Peyrin-Biroulet, Pierre Desreumaux, William Sandborn, Jean-Frédéric Colombel

“what is in the pipeline“
Drugs in the pipeline

Crohn’s disease

ulcerative colitis

S. Danese, Gut 2012;61:918-32.
S. Danese, Gut 2012;61:918-32.

Figure 1 Successful and unsuccessful therapeutic programs in inflammatory bowel disease. Green: programmes with a positive outcome. Orange: potentially effective or ongoing programmes. Red: programmes failed. IL, interleukin; TGF, transforming growth factor; INF, interferon; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; ICAM, intracellular cell adhesion molecule; MAAdCAM, mucosal addressin cell adhesion molecule.
Anti-adhesion molecules

• Blocade of the polymorphonuclear cells homing

C  Leucocyte migration and activation
Anti-adhesion molecules
• Blockade of the polymorphonuclear cells homing

Leucocyte migration and activation
Anti-adhesion molecules

- Blockade of the polymorphonuclear cells homing

C Leucocyte migration and activation
Natalizumab – Tysabri (früher Antegren)

• IgG 4 monoclonal Antikörper
• - zumab : humanisierter AK, (Ursprünglich von der Maus)
PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY – JC VIRUS

TYSABRI – „wirkt gleich wie Anti-TNF Inhibitoren“

2/3 der Patienten sprechen an

... und die Hälfte in Remission

Natalizumab ENACT-1: Subgroup Analysis of Clinical Response (CDAI ≥ 70) at Week 10

Analysis of Clinical Response

Proportion of patients in clinical remission

<table>
<thead>
<tr>
<th>Assessment time point</th>
<th>Placebo</th>
<th>Natalizumab</th>
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</thead>
<tbody>
<tr>
<td>11 Co-secondary end points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Week 8</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Week 12</td>
<td>25</td>
<td>38</td>
</tr>
<tr>
<td>Any Time</td>
<td>16</td>
<td>26</td>
</tr>
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P = .001

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Mecanism of Anti-integrin molecules

- **Etrolizumab** on β7 subunit only in the gut
- **Vedolizumab** (MLN 002) on α4 β7 subunits only in the gut
- **Etrolizumab** on β7 subunit only in the gut

Adapted from Lancet. 2008 372(9632):67-81
Vedolizumab (VDZ) Induction Therapy for UC: Results from the Phase 3 GEMINI I Trial

- N= 374 pts (ITT population); 39% were anti-TNFα failures
- Randomized 3:2, pts were treated with VDZ 300mg (IV) or PBO on days 1 & 15

- VDZ induction therapy was significantly more effective than PBO in achieving clinical response, clinical remission and MH in UC pts with a high rate of prior anti-TNF failure
- Through Wk 6 (S)AEs and serious infectious AEs were similar between treatment groups

VDZ Maintenance Therapy for UC: Results from the Phase 3 GEMINI I Trial

- N=373 induction responders at wk6 were randomized 1:1:1 to VDZ 300mg IV q4wks, q8wks or PBO for 46 wks
- 32% of ITT population had prior anti-TNFα failure

- Maintenance therapy with VDZ q4 or q8 was significantly more effective than PBO in achieving clinical remission, CS-free remission and enhanced response
- In safety population (N=895) rates of (S)AEs and serious infections were similar between VDZ and PBO

VDZ Induction Therapy for CD: Results from the Phase 3 GEMINI II Trial

- N= 368 pts (ITT population); 48% anti-TNFα failures of which 55% primary failures; 27% of total ITT pop. failed at least 2 anti-TNFs
- Randomized 3:2, pts were treated with VDZ 300mg (IV) or PBO on days 1 & 15

Secondary outcome:
In pts with elevated CRP at BL no significant differences (p=0.93) were observed for change in CRP at Wk 6 between treatment groups

VDZ induction therapy was significantly more effective than PBO in achieving clinical remission at Wk6

Through Wk 6 (S)AEs and serious infectious AEs were similar between treatment groups
VDZ Maintenance Therapy for CD: Results from the Phase 3 GEMINI II Trial

- N=461 induction responders* at wk6 were randomized 1:1:1 to VDZ 300mg IV q4wks, q8wks or PBO for 44 wks
- 51% of ITT pop. had prior anti-TNFα failure; 45% had no anti-TNFα exposure

- Safety: Exposure-adjusted rates for all AEs were comparable across treatment groups in safety pop. (N=1115)
- In ITT pop. exposure-adjusted rates of serious infections were comparable and rates of SAEs were higher with PBO than VDZ

ALICAFORSEN in left-sided UC: Metanalysis

• Anti-sense RNA to ICAM I
• Enema for 6 weeks
• Results week 30

<table>
<thead>
<tr>
<th>outcome</th>
<th>Alicaforsen</th>
<th>Placebo</th>
<th>5-ASA</th>
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</thead>
<tbody>
<tr>
<td>Decrease in DAI</td>
<td>41%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Remission</td>
<td>25%</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>Mucosal healing</td>
<td>25%</td>
<td>24%</td>
<td>6%</td>
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Anti-integrin: adverse events

• High risk of Infection: 31 vs. 22% (PBO)
  → In particular: upper resp. Tract infections and mucosa (e.g. Candidiasis)

• No severe infections

• No Neurological complications (NO PML)
• no Lymphoma, no cancer

• 3/286: Infusions reactions (also an antibody)
Conclusions

• **Anti-TNF agents** has dramatically changed the management of inflammatory bowel disease in the last 10 years.

• Therapy **optimization** with / without loss of response and/or intolerance (AE) is required.

• The switch to a new class of biologics: **anti-integrins** is awaited.
THANK YOU FOR YOUR ATTENTION!