PREDICTORS OF RESPONSE TO ANTI-TNFα TREATMENT IN CROHN’S DISEASE

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Background

• Infliximab (monoclonal IgG1 antibody against TNF-α) is effective in refractory and fistulizing Crohn’s disease

• Placebo-controlled double-blind randomised trials
  – Targan et al, NEJM 1997
  – Present et al, NEJM 1999

• Efficacy of re-treatment trials
  – Rutgeerts et al, Gastroenterology 1999
  – Hanauer et al, Lancet 2002 (ACCENT I)
  – Sands BE et al, NEJM in press (ACCENT II)

Overall response rates of 70-75%
Therapy refractoriness in ± 30% of patients
Importance of predictive factors

• Allows clear selection of patients likely to benefit from the drug and can prevent patients from undergoing unnecessary treatment

• Identification of modifiable factors associated with response leads to
  – optimization of response rates
  – optimization of duration of response

• Optimal cost-effectiveness: avoidance of unnecessary expensive infusions

• Identification of predictors of response to infliximab in Crohn's disease may also lead to direct implications in other diseases where infliximab is being used (rheumatoid arthritis, psoriasis, spondylarthropathy)
Predictive factors for response to infliximab

1. Clinical predictors

2. Genetic predictors

3. Serological predictors
Study population

• Patients followed at the IBD-unit of the University Hospital Gasthuisberg (Leuven, Belgium) and treated with infliximab for therapy-resistant luminal or fistulizing disease

• Demographic and clinical data available through clinical workstation (= electronic patients chart containing all visits, biochemistry, X-rays, endoscopy, biopsy results)

• Response to infliximab determined by changes in Crohn’s Disease Activity Index (luminal) or drainage assessment index (fistulising)

• Group of 200 healthy individuals used for control of allele frequencies in genetic studies
Predictive factors for response to infliximab

1. Clinical predictors

2. Genetic predictors

3. Serological predictors
### Table 1. Demographic and Baseline Clinical Characteristics of the Study Population (N = 240)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Refractory CD (n = 137)</th>
<th>Fistulizing CD (n = 103)</th>
<th>All Patients (N = 240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline CDAI (range)</td>
<td>294 (72–609)</td>
<td>200 (51–526)</td>
<td>261 (51–609)</td>
</tr>
<tr>
<td>Mean baseline CRP (mg/L)</td>
<td>24.5</td>
<td>24.9</td>
<td>24.7</td>
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<tr>
<td>Median age (yr) (IQR)</td>
<td>34 (28–44)</td>
<td>37 (30–46)</td>
<td>36 (28–44.75)</td>
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<tr>
<td>Female/male (%)</td>
<td>84/53 (61.3/38.7)</td>
<td>69/34 (67.0/33.0)</td>
<td>153/87 (63.8/36.2)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>68 (49.6)</td>
<td>39 (37.8)</td>
<td>107 (44.6)</td>
</tr>
<tr>
<td>Mean disease duration (yr)</td>
<td>10.7</td>
<td>13.0</td>
<td>11.7</td>
</tr>
<tr>
<td>Involved intestinal area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileitis (%)</td>
<td>23 (16.8)</td>
<td>17 (16.5)</td>
<td>40 (16.7)</td>
</tr>
<tr>
<td>Ileocolitis (%)</td>
<td>70 (51.1)</td>
<td>35 (34.0)</td>
<td>105 (43.8)</td>
</tr>
<tr>
<td>Colitis (%)</td>
<td>43 (31.4)</td>
<td>46 (44.7)</td>
<td>89 (37.1)</td>
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<tr>
<td>Localization of fistulas</td>
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<tr>
<td>Perianal</td>
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<td>Rectovaginal</td>
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<tr>
<td>Enterocutaneous</td>
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<td>Into bladder</td>
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<tr>
<td>Enterocolic</td>
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<tr>
<td>Concomitant treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminosalicylates (%) (%</td>
<td>59 (43.1)</td>
<td>47 (45.6)</td>
<td>106 (44.2)</td>
</tr>
<tr>
<td>Steroids (%)</td>
<td>75 (54.7)</td>
<td>33 (32.0)</td>
<td>108 (45.0)</td>
</tr>
<tr>
<td>6-MP/AZA/MTX (%)</td>
<td>76 (55.5)</td>
<td>64 (62.1)</td>
<td>140 (57.9)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>31 (22.6)</td>
<td>21 (20.4)</td>
<td>52 (21.7)</td>
</tr>
<tr>
<td>NSAIDs (%)</td>
<td>8 (5.8)</td>
<td>5 (4.9)</td>
<td>13 (5.4)</td>
</tr>
<tr>
<td>Previous abdominal surgery</td>
<td>51 (37.2)</td>
<td>31 (30.1)</td>
<td>82 (34.2)</td>
</tr>
</tbody>
</table>
Figure 1. Decision tree analysis (using SAS enterprise Miner; see text) on the total study population (n = 240). Absolute numbers as well as percentage of response (R) and nonresponse (NR) for the training data set (left column) and validation data set (right column) are given. Age was selected as the first splitting variable to predict the target, whereas use of azathioprine was selected as second splitting variable in the group of patients >39.5 yr.
Predictive factors for response to infliximab

1. Clinical predictors

2. Genetic predictors

3. Serological predictors
Inflammatory Mediators (TNFα)

Nucleus

TATA

p65
p50

NF-κB

I-κB

LPS or PGN

TLRs

Nod2/CARD15

I-κB

p65
p50

p65
p50

p65
p50

Inflammatory Mediators (TNFα)

Nucleus
NOD2/CARD15

N=245

Remission (n=132)
Partial Response (n=58)
No Response (n=55)

Wild Type CARD15
Heterozygous CARD15
Homozygous/Compound heterozygous

Gastroenterology 2002; 123:106-111
Infliximab and ADCC

- Infliximab binds mTNFα leading to complement activation and ADCC in vivo (Scallon et al cytokine 1995)
- ADCC important effector mechanism in eradication of intracellular pathogens and tumor cells and requires leukocyte receptors for IgGFc
  - FcGRIIIa, the gene coding for FcγRIIIa expressed on macrophages and NK cells carries functional polymorphism at aa position –158
  - FcGRIIIa-158 valine allotype higher affinity for IgG1 than FcγRIIIa-158 phenylalanine allotype
  - More affinity for IgG1 = more potent ADCC
- FcGRIIIa associated with response to rituximab in non-Hodgkin's lymphoma (Cartron G et al Blood 2002)
N=145
(all CRP>5mg/L)

FcGRIIIa-158

V/V
n=29
100%

V/F + F/F
n=116
69.8%

response
no response

P = 0.0002
RR=1.43 (95%CI: 1.27-1.61)

Aliment Pharmacol & Therap in press
**V/V patients**
Median variation $-80.1\%$
range: -31.0\% - -94.8\%

![Graph showing decrease in CRP from baseline to Week 4 for V/V patients]

**V/F and F/F patients**
median variation $-63.2\%$
range: +1100\% - -98.1\%

![Graph showing increase in CRP from baseline to Week 4 for V/F and F/F patients]

$P = 0.0078$
Predictive factors for response to infliximab

1. Clinical predictors
2. Genetic predictors
3. Serological predictors
ASCA+/pANCA+  n=9
ASCA+/pANCA-  n=90
ASCA-/pANCA+  n=11
ASCA-/pANCA-  n=98

N= 183

Am J Gastroenterology 2002; 97: 1458-1462
N=226

C-Reactive Protein

Response rate %

CRP >5mg/L: 76
CRP <5 mg/L: 46

p=0.004

Scand J Gastroenterol 2002; 37: 818-824
Conclusion:
Predictive factors for response to infliximab

1. **Clinical predictors of response**
   - Young age
   - Concomitant immunosuppression
   - Non-smoking
   - Crohn’s colitis

2. **Genetic predictors**
   - LTA Ncol-TNFc-aa13L-aa26 haplotype: non response
   - FcGRIIIa-158 Valine allotype: response

3. **Serological predictors**
   - ASCA-/pANCA+: non response
   - High baseline CRP
Acknowledgements

• IBD patients

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  – Mr and Mrs Broad
  – Prof Dr Daniel Hollander
  – Mrs Marciana Poland