A vedolizumab specific four-gene colonic signature accurately predicting future endoscopic remission in patients with inflammatory bowel disease

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Disclosures

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- Consultancy fees Janssen.
- Research grant Pfizer.
Introduction

- **Vedolizumab**, targeting the $\alpha 4\beta 7$ integrin, has proven **efficacy** in both Crohn’s disease and ulcerative colitis during the GEMINI phase III program\(^1,2\)

- **Real-life endoscopic remission** data are **encouraging**, though we still face a **therapeutic gap**\(^3\)

- With the increased therapeutic armamentarium, **predictive biomarkers** are urgently **awaited**.

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**UC** = Mayo endoscopic subscore 0-1
**CD** = absence of ulcerations
Aims

To identify baseline transcriptomic profiles predicting future endoscopic remission in inflamed colonic biopsies of IBD patients initiating vedolizumab
Methods

Inflamed colonic biopsies → Total RNA → RNA Sequencing Illumina HiSeq 4000 NGS

- UC: Mayo endoscopic score 0-1
- CD: absence of ulcerations

Anti-TNF therapy

Vedolizumab therapy

w0 w2 w6 w14 w22
Differential gene expression

Endoscopic remission

No
Yes

Number of genes differentially expressed

<table>
<thead>
<tr>
<th></th>
<th>Nominal p-value 0.01</th>
<th>FDR correct p-value &lt; 0.25</th>
<th>FDR correct p-value &lt; 0.10</th>
<th>FDR correct p-value &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of genes</td>
<td>327</td>
<td>44</td>
<td>10</td>
<td>5</td>
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</tbody>
</table>
Predictive modelling

31 colonic biopsies

20 discovery
9 NH, 11 MH

11 validation
3 NH, 8 MH

44 diff expressed genes
(FDR 0.25)

Random generalized
linear modelling

4 gene signature

Accuracy | 80.0%
Sensitivity | 81.8%
Specificity | 77.8%
PPV | 81.8%
NPV | 77.8%
LR + | 3.7
LR - | 0.23

Accuracy | 100.0%
Sensitivity | 100.0%
Specificity | 100.0%
PPV | 100.0%
NPV | 100.0%
LR + | ∞
LR - | 0

MH = endoscopic remission
NH = no remission
# Predictive modelling – independent validation

**RNA-seq validation**

- **n = 16**
- **11 NH, 5 MH**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>81.3%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>66.7%</td>
</tr>
<tr>
<td>Specificity</td>
<td>90.0%</td>
</tr>
<tr>
<td>PPV</td>
<td>80.0%</td>
</tr>
<tr>
<td>NPV</td>
<td>81.8%</td>
</tr>
<tr>
<td>LR +</td>
<td>6.67</td>
</tr>
<tr>
<td>LR -</td>
<td>0.37</td>
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</tbody>
</table>

**Microarray validation**

- **n = 13 (MILLENIUM)**
- **10 NH, 3 MH**

<table>
<thead>
<tr>
<th>Metric</th>
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<tbody>
<tr>
<td>Accuracy</td>
<td>76.9%</td>
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<tr>
<td>Sensitivity</td>
<td>100.0%</td>
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<tr>
<td>Specificity</td>
<td>70.0%</td>
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<tr>
<td>PPV</td>
<td>50.0%</td>
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<tr>
<td>NPV</td>
<td>100.0%</td>
</tr>
<tr>
<td>LR +</td>
<td>3.3</td>
</tr>
<tr>
<td>LR -</td>
<td>0</td>
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</table>

MH = endoscopic remission
NH = no remission
Predictive modelling – a vedolizumab specific signal

RNA-seq anti-TNF cohort
n = 24
16 NH, 8 MH

<table>
<thead>
<tr>
<th>Metric</th>
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<tbody>
<tr>
<td>Accuracy</td>
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<tr>
<td>Sensitivity</td>
<td>75.0%</td>
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<tr>
<td>Specificity</td>
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<td>PPV</td>
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<tr>
<td>NPV</td>
<td>80.0%</td>
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<tr>
<td>LR +</td>
<td>1.5</td>
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<tr>
<td>LR -</td>
<td>0.5</td>
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</table>

MH = endoscopic remission
NH = no remission
Conclusions

• We identified and validated the first vedolizumab-specific predictive 4-gene expression signature

• Allowing treatment guidance in IBD patients with colonic involvement

• Further validation in bigger independent cohorts
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Séverine Vermeire. MD. PhD.
Marc Ferrante. MD. PhD.
Back up
<table>
<thead>
<tr>
<th>Diagnosis, n, %</th>
<th>VEDOLIZUMAB (n=31)</th>
<th>ANTI-TNF COHORT (n=24)</th>
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</thead>
<tbody>
<tr>
<td>Ulcerative colitis</td>
<td>20 (64.5)</td>
<td>16 (66.7)</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>11 (35.5)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Age, years, (median, IQR)</td>
<td>45.3 (29.6 – 56.3)</td>
<td>36.0 (22.0 – 54.9)</td>
</tr>
<tr>
<td>Gender, n women, %</td>
<td>17 (54.8)</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Disease duration, years, (median, IQR)</td>
<td>8.4 (4.0-15.3)</td>
<td>1.9 (0.5 – 7.0)</td>
</tr>
<tr>
<td>Disease location, n, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td>0 (0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>L2</td>
<td>2 (18.2)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>L3</td>
<td>9 (81.8)</td>
<td>6 (75.0)</td>
</tr>
<tr>
<td>L4</td>
<td>2 (18.2)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>E1</td>
<td>3 (15.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>E2</td>
<td>10 (50.0)</td>
<td>13 (81.3)</td>
</tr>
<tr>
<td>E3</td>
<td>7 (35.0)</td>
<td>3 (18.7)</td>
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</table>
**Included patients**

<table>
<thead>
<tr>
<th>Disease behaviour, $n$, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- B1</td>
<td>6 (54.5)</td>
<td>4 (50.0)</td>
</tr>
<tr>
<td>- B2</td>
<td>3 (27.3)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>- B3</td>
<td>2 (18.2)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>- Perianal</td>
<td>5 (45.5)</td>
<td>2 (45.5)</td>
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</table>

<table>
<thead>
<tr>
<th>Steroid use during induction, $n$, %</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>- Topical</td>
<td>10 (32.3)</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>- Systemic</td>
<td>8 (25.8)</td>
<td>7 (22.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous anti-TNF exposure, $n$, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Naïve</td>
<td>10 (32.3)</td>
<td>NA</td>
</tr>
<tr>
<td>- exposed</td>
<td>21 (67.7)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>C-reactive protein, $mg/L$, (median, IQR)</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>2.0 (0.9 – 6.7)</td>
<td>6.3 (1.8 – 17.0)</td>
</tr>
</tbody>
</table>
Differential gene expression – some top hit examples

**Claudin 8 expression**
in colonic biopsies of IBD patients initiating vedolizumab therapy

Nominal p-value $5.0 \times 10^{-6}$
FDR correct p-value 0.02

**Grazyme B expression**
in colonic biopsies of IBD patients initiating vedolizumab therapy

Nominal p-value $1.0 \times 10^{-4}$
FDR correct p-value 0.12
Pathway analysis

- Granulocyte adhesion and diapedesis
- Agranulocyte adhesion and diapedesis

Leukocyte migration
- Leukocyte adhesion to vascular endothelial cell
- Cellular extravasation