Biologic sequences in IBD: The what, when and why of drug selection

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IBD in 2019 – how did we get here?

First UC series:
- 1875

First CD series:
- 1870

Red text indicates publication of RCT level evidence.
Success and failure in IBD drug development
### Selected emerging therapeutic options in IBD: Current evidence base by class¹

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Induction</td>
<td>Maintenance</td>
</tr>
<tr>
<td>Anti-integrin:</td>
<td>Ph2✓</td>
<td>✓</td>
</tr>
<tr>
<td>Etrolizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-adhesion:</td>
<td>Ph2✓</td>
<td>Ph2✓</td>
</tr>
<tr>
<td>Anti-MAdCAM1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-IL12/23</td>
<td>Ph3 – UEGW2018</td>
<td>Ph3✓</td>
</tr>
<tr>
<td>Anti-IL23p19¹</td>
<td>Ph2✓</td>
<td></td>
</tr>
<tr>
<td>JAK/STAT inhib¹</td>
<td>Ph3✓</td>
<td>Ph3✓</td>
</tr>
<tr>
<td>S1PR modulator</td>
<td>Ph2✓</td>
<td>Ph2✓</td>
</tr>
<tr>
<td>Discontinued</td>
<td>Apremilast Ph2✓</td>
<td></td>
</tr>
</tbody>
</table>

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¹ Data summary for most advanced agent(s) in class; OLE: open label extension; RWE: real world evidence
Personalised therapy ... a glimpse into the future?

Early diagnosis

- Phenotype (imaging)
  - Location
  - Severity
  - Complications

Early surgery?

- Genomics
- Proteomics
- Microbiome

Early precision treatment

- Optimised PK
  - Full mucosal healing
  - No symptoms No steroids
  - No complications
Back to 2019...
Most treatment decisions occur in the context of failure.
Why has failure occurred?

Compliance?

Primary loss of response?

Secondary loss of response?
  • Anti-drug antibodies?
  • Evolution of unfavourable PK?
  • Treatment-resistant disease?

Robust evaluation of induction

Can TDM help?

PK, pharmacokinetics; TDM, therapeutic drug monitoring
When can we decide on primary non-response?

Infliximab treatment for Crohn’s disease

CDAI <150 remission

Proportion of patients (%)

Weeks from the initial infusion

Episodic strategy
5 mg/kg scheduled strategy
10 mg/kg scheduled strategy
Combined scheduled strategy

CDAI, Crohn’s disease activity index

When can we decide on primary non-response?

**Week 56 CDAI remission among week 4 responders and non-responders to adalimumab (CHARM)**

- **Week 4 responders**:
  - Placebo: 12%
  - ADA 40 mg EOW: 36%
  - ADA 40 mg EW: 41%

- **Week 56 non-responders**:
  - Placebo: 8%
  - ADA 40 mg EOW: 16%
  - ADA 40 mg EW: 13%

**p < 0.001**

ADA, adalimumab; CDAI, Crohn’s disease activity index

When can we decide on primary non-response?

**CDAI-100 response among week 6 non-responders**
(GEMINI 2)

<table>
<thead>
<tr>
<th>Week 10</th>
<th>Week 14</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=69)</td>
<td>VDZ combined (n=351)</td>
<td>Placebo (n=69)</td>
</tr>
<tr>
<td>7.2 (1.1–13.4)</td>
<td>16.0 (12.1–19.8)</td>
<td>16.0 (17.3–26.0)</td>
</tr>
</tbody>
</table>

**Response among week 8 non-responders**
(UNITI)

<table>
<thead>
<tr>
<th>Week 8 (16 weeks after first dose; N=467)</th>
<th>Week 44 90 mg q8w (N=251)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI-100 response</td>
<td>Remission (CDAI&lt;150)</td>
</tr>
<tr>
<td>50.5</td>
<td>68.1</td>
</tr>
<tr>
<td>28.9</td>
<td>50.2</td>
</tr>
</tbody>
</table>

VDZ: vedolizumab

Declaring primary non-response?
Know when to make the call

Timing?

Modality of assessment?

Acceptable response?
Why has failure occurred?

Compliance?

Primary loss of response?

Secondary loss of response?
  • Anti-drug antibodies?
  • Evolution of unfavourable PK?
  • Treatment-resistant disease?
IBD patients receiving anti-TNF maintenance therapy on relapse

Supra therapeutic or therapeutic TC

Stop drug
- Swapping to a non-anti-TNF drug
- Surgery

Undetectable or subtherapeutic TC

Confirm IBD inflammation
- Endoscopy / imaging / biomarkers (CRP, FC)
- Exclude IBS, infections, malignancies, BOG, strictures, BSD, etc.
- Verify drug adherence

ADA (–)

ADA low

- Increase dose
- Shorten interval
- Add IMM

ADA (+) Measure ADA at consecutive time points

ADA high

Stop drug
- Switch to another anti-TNF
- Swapping to a non anti-TNF drug
- Surgery

ADA, antidrug antibody; BOG, bacterial overgrowth; BSD, bile salt diarrhoea; CRP, C-reactive protein; eq, equivalent; FC, faecal calprotectin; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IMM, immunomodulators; TC, trough concentrations; TNF, tumour necrosis factor.
Can immunogenicity be reversed?

**Patient 1**

- Start MTX
- Infliximab
- ATI

**Patient 3**

- Start AZA
- Infliximab
- ATI

**Graphs**

- Concentration (µg/mL) vs Weeks
- DG, HBI, CDAI concentrations over weeks

AAA, anti-adalimumab antibody; Ada, adalimumab; ATI, antibodies to infliximab

Can immunogenicity be predicted?

**Infliximab**

- Proportion of patients with no clearing anti-drug antibodies (%)

**Adalimumab**

- Proportion of patients with no clearing anti-drug antibodies (%)

- **Days**

- **Proportion of patients with no clearing anti-drug antibodies (%)**

Legend:

- No HLA-DQA1*05, immunosuppressants on visit 1
- No HLA-DQA1*05, no immunosuppressants on visit 1
- Has HLA-DQA1*05, immunosuppressants on visit 1
- Has HLA-DQA1*05, no immunosuppressants on visit 1
What data do we have to guide sequencing?
Systematic literature review: methods and publication flow

Systematic literature search for studies reporting efficacy outcomes associated with sequential biologic drug use:

- PubMed (Jan 2000 – May 2018)
- Key gastroenterology congresses (2013 – May 2018) in patients with IBD

Oxford Centre for Evidence-based Medicine levels

Aggregate response rates (total number of responders/total number of participants) extracted where clear definition of response evaluated over ≥ 12 weeks of treatment

149 records identified through database searching

363 records screened (after duplicates removed) abstracts assessed for eligibility

214 additional records identified through congress searching

232 full text articles / abstracts excluded (eg. sequencing not studied, insufficient data)

131 studies included in review
- 65 full papers
- 66 congress abstracts
Treatment sequencing data available

**Ulcerative colitis**
- Anti-TNF 3538
- Other anti-TNF 911
- Same anti-TNF 593
- Ustekinumab 122
- Golimumab 56
- Vedolizumab 1856

**Crohn’s disease**
- Anti-TNF 11,740
- Other anti-TNF 4355
- Vedolizumab 3480
- Ustekinumab 2064
- Same anti-TNF 1772
- Golimumab 69
- 21
Treatment sequencing data
Anti-TNF agent to anti-TNF agent

**Ulcerative colitis**
- Infliximab
  - 910 patients
- Adalimumab
  - 1 patient
- Infliximab or Adalimumab
  - 0 patients

**Crohn’s disease**
- Infliximab
  - 2765 patients
- Adalimumab
  - 141 patient
- Infliximab or Adalimumab
  - 1450 patients
- Certolizumab
Aggregate response rates across 47 studies after changing biologic therapy were 49%\(^a\)

<table>
<thead>
<tr>
<th>Biologic sequence</th>
<th>Crohn’s disease – Response rate in patients who received TDM (%)(^a)</th>
<th>Crohn’s disease – Response rate in patients who did not receive TDM (%)(^a)</th>
<th>Ulcerative colitis – Response rate in patients who received TDM (%)(^a)</th>
<th>Ulcerative colitis – Response rate in patients who did not receive TDM (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF → Ustekinumab</td>
<td>NA</td>
<td>56% (10 studies)</td>
<td>NA</td>
<td>65% (1 study)</td>
</tr>
<tr>
<td>Anti-TNF → Vedolizumab</td>
<td>34% (3 studies)</td>
<td>53% (7 studies)</td>
<td>55% (1 study)</td>
<td>56% (6 studies)</td>
</tr>
<tr>
<td>Anti-TNF → Anti-TNF</td>
<td>26% (3 studies)</td>
<td>54% (23 studies)</td>
<td>NA</td>
<td>42% (6 studies)</td>
</tr>
</tbody>
</table>

\(^a\) Response rates were defined differently across studies, including the use of the Harvey-Bradshaw Index (HBI) score, Crohn’s Disease Activity Index (CDAI) score, paediatric CDAI score, Mayo score, and physician’s global assessment, as well as endoscopic mucosal healing, complete resolution of inflammatory parameters on radiographic assessment, and others.
Why do 2nd line biologics appear to show weaker efficacy?  
Data from the CHARM study

- effect of prior monoclonal antibody exposure?

- effect of time / uncontrolled inflammation?

How *might* we make a choice?
Oncostatin M-expression may be associated with response to anti-TNF

Hierarchical clustering of chemokine and cytokine genes (n=2 IBD cohorts)

Identify consistently OSM-associated genes

Cytokines

IL1B, IL1A, IL6, IL11, IL1B, IL1A, IL6, IL11

Chemokines

CXCL1, CXCL2, CXCL3, CXCL5, CXCL6

Module low

15% Infliximab responsive
85% infliximab refractory

Module high

90% Relative risk = 5.0 (95% CI = 1.4–17.9), p=0.0006

OSM, oncostatin M
Anti-TNF non-responders show enhanced IL23 signalling?

Pre-treatment

On treatment

### Disease pathomorphism?

A randomised trial of ustekinumab in patients with moderate-to-severe Crohn’s disease

<table>
<thead>
<tr>
<th>Proportion of patients achieving clinical response at week 8</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Ustekinumab</strong></td>
<td><strong>Placebo better</strong></td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td>39.6</td>
<td>49.0</td>
</tr>
<tr>
<td><strong>Baseline weight (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>33.3</td>
<td>11</td>
</tr>
<tr>
<td>≥60 to &lt;75</td>
<td>286</td>
<td>17</td>
</tr>
<tr>
<td>≥75</td>
<td>48.1</td>
<td>23</td>
</tr>
<tr>
<td><strong>Baseline CRP (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.6</td>
<td>37.5</td>
<td>23</td>
</tr>
<tr>
<td>≥0.6</td>
<td>40.7</td>
<td>28</td>
</tr>
<tr>
<td><strong>Baseline CDAI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;302</td>
<td>50.0</td>
<td>22</td>
</tr>
<tr>
<td>≥302</td>
<td>26.0</td>
<td>29</td>
</tr>
<tr>
<td><strong>Previous use of corticosteroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never used</td>
<td>75.0</td>
<td>10</td>
</tr>
<tr>
<td>Ever used</td>
<td>36.7</td>
<td>41</td>
</tr>
<tr>
<td><strong>5 ASAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never used</td>
<td>16.7</td>
<td>9</td>
</tr>
<tr>
<td>Ever used</td>
<td>42.6</td>
<td>42</td>
</tr>
<tr>
<td><strong>Immodulators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never used</td>
<td>71.4</td>
<td>13</td>
</tr>
<tr>
<td>Ever used</td>
<td>28.2</td>
<td>38</td>
</tr>
<tr>
<td><strong>Anti-TNF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never used</td>
<td>53.8</td>
<td>26</td>
</tr>
<tr>
<td>Ever used</td>
<td>25.9</td>
<td>25</td>
</tr>
</tbody>
</table>
Anti-IL12/23 response stratified by baseline IL12/23

Peripheral blood:
- IL12 p40
  - Non-responder: n=8
  - Responder: n=6

Biopsies:
- IL12 p40
  - Non-responder: n=8
  - Responder: n=6
  - * indicates statistical significance

- IL23 p19
  - Non-responder: n=8
  - Responder: n=6
  - NS indicates no significant difference
Colonic $\alpha$E – etrolizumab response biomarker?

Etrolizumab in patients with moderately-to-severely active ulcerative colitis

Week 10 remission split by baseline colonic $\alpha$E expression

Gene expression at baseline

- Patients in clinical remission (%)

<table>
<thead>
<tr>
<th>Gene expression</th>
<th>Placebo</th>
<th>Etrolizumab 100 mg</th>
<th>Etrolizumab 300 mg+LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$E$^{\text{low}}$</td>
<td>13/18</td>
<td>0/16</td>
<td>0/19</td>
</tr>
<tr>
<td>$\alpha$E$^{\text{high}}$</td>
<td>38/20</td>
<td>6/16</td>
<td>0/17</td>
</tr>
<tr>
<td>$\alpha$E$^{\text{low}}$</td>
<td>17/16</td>
<td>0/16</td>
<td>0/10</td>
</tr>
<tr>
<td>$\alpha$E$^{\text{high}}$</td>
<td>67/20</td>
<td>50/16</td>
<td>0/9</td>
</tr>
</tbody>
</table>

Predictive signatures: a note of caution

ACT1: n=22
>90% sensitivity & specificity

PURSUIT: n=59
AUROC: 0.762

PROgECT: n=103
AUROC: 0.688

13 gene classifier

Back to the real-world again … with a bump

63% of patients initiated on a corticosteroid were only managed by this agent; some patients were on a corticosteroid for up to 10 cycles.

The Truven Health MarketScan database was used to assess treatment pathways in a large US insured population.

How do we make a choice?

**Efficacy data**
- Clinical symptoms
- Complications
- Other endpoints
- EIM efficacy
- Effects on fistulae

**Safety data**
- Special populations
- Need for combination therapy

**Cost**

**Infusion capacity**
Conclusions

- Treatment discussions in IBD typically take place in the context of prior failure
  - Minimise that period of failure through proactive monitoring
- Significant holes in the evidence base exist
- Patient characteristics may drive decisions
- Strategies should take account of:
  - Mode of failure
  - Trial data
  - Efficacy evidence from literature