Inflammatory Bowel Disease
What’s new?

NIHR Nottingham Digestive Diseases Biomedical Research Centre

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Disclosures

➢ Educational support:
Abbvie, Janssen, NAPP, Takeda Pharmaceuticals, Merck Sharp & Dohme Ltd, Ferring and Dr Falk

➢ Speaker honoraria:
Merck Sharp & Dohme Ltd, Abbvie, Janssen, Ferring and Takeda Pharmaceuticals

➢ Advisory boards:
Abbvie, Takeda Pharmaceuticals, Janssen and Dr Falk
Agenda

• Disclosures
• Aetiology of IBD
• Incidence and Prevalence
• Symptoms
• Surgery
• Disease phenotypes
• Treatment Targets
• Present Treatments
• New treatments
• Nottingham IBD pathway
• Some clinical cases
• IBD occupational health resource information

Disease Burden
Complexity of the Disease
Perceived Outcomes

Why we need Occi health on Board!!
There are 2 main types of IBD
- Ulcerative Colitis (UC) and Crohn’s disease (CD)
- UC has a UK prevalence of 146,000
- CD has a UK prevalence of 115,000
IBD is emerging as a global disease: Incidence of IBD worldwide is increasing with time

- Low incidence areas report progressive rise in incidence\(^1,2\)
- High incidence areas report stable, increasing, or decreasing incidence\(^1,2\)
- Steady increase of paediatric-onset IBD (particularly CD) since the 1990s\(^2\)

\(^1\)Coloured lines represent data from different countries in Europe, North America and Asia.
Symptoms (depend on disease location)
Almost 1 in 2 stable patients have stated that IBD negatively affects their lives

Impact of IBD symptoms on life between flares
(European IMPACT survey 2010–11)

Based on responses to the question, ‘In between flares, my life is still significantly negatively impacted by symptoms of IBD compared to people without IBD’.


Ulcerative colitis (n=1,518)

- Significantly affected: 24%
- Somewhat affected: 23%
- Slightly unaffected: 39%
- Very unaffected: 14%

Crohn’s disease (n=2,888)

- Significantly affected: 25%
- Somewhat affected: 24%
- Slightly unaffected: 39%
- Very unaffected: 12%
Over 1 in 3 IBD patients were hospitalised for >5 days due to IBD symptoms in the last 5 years

Total hospitalised days due to IBD symptoms over the last 5 years
(European IMPACT survey 2010–11)

<table>
<thead>
<tr>
<th>Condition</th>
<th>11+ days</th>
<th>6–10 days</th>
<th>1–5 days</th>
<th>0 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative colitis (n=1,535)</td>
<td>64%</td>
<td>13%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease (n=2,914)</td>
<td>3%</td>
<td>34%</td>
<td>52%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Based on responses to the question, ‘Over the last 5 years, how many days in total have you been hospitalised because of IBD symptoms?’. Adapted from IMPACT Crohn’s & Colitis Patient Survey. Available at: http://efcca-solutions.net/media/european/EuropeanReport.pdf. Accessed: January 2017.
Colectomy rates in patients with IBD are decreasing

A systematic review of 30 population-based studies also showed that the 10-year risk of surgery has significantly decreased in patients with Crohn’s disease or ulcerative colitis ($P<0.05$)

Colectomy rates in patients with IBD are decreasing

Temporal trend analyses of colectomy rates in patients with ulcerative colitis (Calgary Health Zone, Canada; 2002–2010)

Adapted from Ma, C and Moran GW et al. Am J Gastroenterol. 2017. In press
Do the triggers for treatment escalation differ for ulcerative colitis and Crohn’s disease?

Distribution of patients within the highest treatment steps during the first year of disease in Europe

Aggressive treatment strategy has been associated with reduction in surgery rates in Crohn’s disease.

Are we waiting too long to initiate appropriate therapies in our ulcerative colitis patients?

How do the triggers for treatment escalation differ for ulcerative colitis and Crohn’s disease?

Therefore, timely treatment escalation and appropriate therapy selection is critical for steroid sparing.
Symptom and inflammatory disease progression

Cumulative intestinal damage + disease complications


CDAI, Crohn’s Disease Activity Index; CDEIS, Crohn’s Disease Index Of Severity.
Symptom and inflammatory disease progression

Cumulative intestinal damage + disease complications

Early effective treatment with disease-modifying agents

Better control inflammation

Fewer complications altering disease course

Early disease

Late disease

Disease Initiation; Expansion of Auto-inflammatory process

Sub-clinical inflammation

Disease diagnosis

Digestive damage (Lemann index)

Early effective treatment with disease-modifying agents

Better control inflammation

Fewer complications altering disease course

Tight control and monitoring (patient management program)

DISEASE PROGRESSION IN CD
Treat to Target goals in IBD

Our CHANGING goals....

<table>
<thead>
<tr>
<th>TREATMENT GOAL</th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historic treatment goals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction and maintenance of clinical response</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Induction and maintenance of clinical remission</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Current evolution of treatment goals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid-free remission</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Induction and maintenance of endoscopic healing</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Reduction in hospitalization</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Reduction in surgery</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Potential future treatment goals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in bowel damage</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Prevention of complications (stricture, fistula)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Prevention of colorectal dysplasia and cancer</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Maintain normal gastrointestinal physiology</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Reduce risk of serious infection and cancer</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Treatment goals</td>
<td>CD</td>
<td>UC</td>
</tr>
<tr>
<td>----------------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Resolution of symptoms (abdo pain/diarrhoea) is important but not sufficient</td>
<td>Resolution of symptoms (rectal bleeding/diarrhoea) is important but not sufficient</td>
</tr>
<tr>
<td><strong>Endoscopic</strong></td>
<td>Absence of ulceration</td>
<td>Mayo score of 0-1*</td>
</tr>
<tr>
<td><strong>Histological</strong></td>
<td>Histological remission is not a target</td>
<td>Histological remission is not a target*</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>Is a target in the absence of endoscopy</td>
<td>Not a target</td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td>CRP and FC are not targets but adjuncts</td>
<td>CRP and FC are not targets but adjuncts</td>
</tr>
<tr>
<td><strong>PRO</strong></td>
<td>Abdominal pain/frequency but also patient specific</td>
<td>Abdominal pain/frequency but also patient specific</td>
</tr>
<tr>
<td><strong>PRO frequency assessment</strong></td>
<td>3 months to 6-12 months</td>
<td>3 months to 6-12 months</td>
</tr>
</tbody>
</table>
Crohn’s disease is a disease of progressive phenotypes.


Cosnes J et al, Inflammatory bowel diseases 2002;8:244-250.

Some Old and New Treatments
Combination therapy: with azathioprine or methotrexate?

Ustekinumab Background

IL-12 & IL-23 are key cytokines in the pathogenic immune cascade of Crohn’s disease

Ustekinumab is a fully human IgG1k monoclonal antibody binding the p40 subunit of Interleukins-12 & 23

Inhibits IL-12- and IL-23-mediated signaling, cellular activation, and downstream cytokine production

Approved for moderate to severe psoriasis and psoriatic arthritis

Induction efficacy recently demonstrated in a broad CD population in UNITI-1\textsuperscript{1} and UNITI-2\textsuperscript{2}


Figure 1. Ustekinumab binds the shared p40 subunit of IL12/23 and neutralizes the effect of IL-12 and IL-23 binding the IL-12Rb1 T-cell receptor, thereby inhibiting differentiation of naïve CD4+ T cells into a Th1 or Th17 phenotype.

DC: Dendritic cell; IFNγ: Interferon gamma; IL: Interleukin; Th: T helper cell; TNFα: Tumor necrosis factor alpha.
Overall UNITI Phase 3 Crohn’s Program

**UNITI-1:** anti-TNF Failure Population
- Placebo IV*
- Stelara 130 mg IV*
- Stelara ~6 mg/kg IV*

**UNITI-2:** Failed Conventional Therapy
- Stelara 130 mg IV*
- Stelara ~6 mg/kg IV*
- Placebo IV*

**One Maintenance Study**

**IM-UNITI**
Randomized Withdrawal Maintenance Study

- Responders
  - 90 mg SC q8 wks
  - 90 mg SC q12 wks
  - Placebo SC

Objective: to evaluate the safety and efficacy of two subcutaneous (SC) ustekinumab regimens as maintenance therapy

* Subjects randomized to placebo and subjects who are non-responders to Stelara are eligible for non-randomized maintenance dosing after completion of the induction study.
Clinical Response and Remission Through Week 8

**Clinical Response**

UNITI-1 (anti-TNF Failure)
- Proportion of Subjects (%)
- Weeks 0, 3, 6, 8
- 30.10, 33.70, 37.80

UNITI-2 (Conv. Failure)
- Proportion of Subjects (%)
- Weeks 0, 3, 6, 8
- 38.8, 32.5, 28.7

All p-values < 0.05

**Clinical Remission**

UNITI-1 (anti-TNF Failure)
- Proportion of Subjects (%)
- Weeks 0, 3, 6, 8
- 12.9, 18.5, 20.9

UNITI-2 (Conv. Failure)
- Proportion of Subjects (%)
- Weeks 0, 3, 6, 8
- 23.0, 34.9, 40.2

Placebo 130 mg Ustekinumab 6 mg/kg Ustekinumab

All p-values <0.050 except 130 mg dose at Week 3 in both studies
Primary Endpoint: Clinical Remission at Week 44

<table>
<thead>
<tr>
<th>Ustekinumab</th>
<th>Proportion of Subjects (%)</th>
<th>p-Value</th>
<th>Δ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo SC* (N=131)</td>
<td>35.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 mg SC q12w (N=129)</td>
<td>48.8</td>
<td>0.040</td>
<td>12.9%</td>
</tr>
<tr>
<td>90 mg SC q8w (N=128)</td>
<td>53.1</td>
<td>0.005</td>
<td>17.2%</td>
</tr>
</tbody>
</table>

*Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry to this maintenance study

**Subjects who had a prohibited CD-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening CD prior to the designated analysis timepoint are considered not to be in clinical remission, regardless of their CDAI score

†Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission
Normal GI tract has a crucial role in immune response

Image developed by Takeda; adapted from Abraham C & Cho J N Engl J Med 200
Dysfunction of local gut immunity

Protective mucosal layer loss is a step on the inflammatory response cascade

Disrupted protective mucus layer

Dendritic cells present antigen

Proinflammatory cytokine release (e.g. TNF-α, interleukins)

Increase in adhesion molecules

Increase in vascular permeability

Tissue injury

Tissue injury can lead to disruption of gut physiology and activation of localised immune responses.

Inappropriate and sustained recruitment of inflammatory T cells

Infiltrating lymphocytes

Vascular permeability

Lymphocyte activation

Activated lymphocytes in vascular tissue track into the gut mucosa

α4β7 integrin/MAdCAM-1 adhesion facilitates local gut inflammation

α4β7-MAdCAM-1 interactions likely mediate selective lymphocyte trafficking to GI mucosa and gut-associated tissues.

Selective receptor blockade

Vedolizumab prevents transmigration of gut-homing lymphocytes into the gut submucosa

GEMINI I: Vedolizumab in Ulcerative Colitis
Induction Phase: Outcomes at Week 6

Induction ITT population

Primary Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PBO (n=149)</th>
<th>VDZ (n=225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Response</td>
<td>25.5%</td>
<td>47.1%</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>5.4%</td>
<td>16.9%</td>
</tr>
<tr>
<td>Mucosal Healing</td>
<td>24.8%</td>
<td>40.9%</td>
</tr>
</tbody>
</table>

Mean Δ% VDZ vs PBO (95% CI)

- Clinical Response: 21.7 (11.6 - 31.7)
- Clinical Remission: 11.5 (4.7, 18.3)
- Mucosal Healing: 16.1 (6.4, 25.9)

PBO, placebo; VDZ, vedolizumab; Mean Δ % (95% CI) = mean percentage point difference VDZ vs PBO (95% confidence interval).

GEMINI I: Vedolizumab in Ulcerative Colitis
Maintenance Phase: Outcomes at 52 Weeks

Maintenance ITT Population*

Primary Outcome

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Clinical Remission</th>
<th>Durable Clinical Response</th>
<th>Mucosal Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Δ% vs PBO</td>
<td>15.9</td>
<td>23.8</td>
<td>19.8</td>
</tr>
<tr>
<td>VDZ/PBO (n=126)</td>
<td>41.8^t</td>
<td>56.6^t</td>
<td>51.6^t</td>
</tr>
<tr>
<td>VDZ/VDZ Q8W (n=122)</td>
<td>44.8^t</td>
<td>52.0^t</td>
<td>20.5^t</td>
</tr>
<tr>
<td>VDZ/VDZ Q4W (n=125)</td>
<td></td>
<td></td>
<td>31.4^t</td>
</tr>
</tbody>
</table>

Secondary Outcomes

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Durable Clinical Remission</th>
<th>CS-Free Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Δ% vs PBO</td>
<td>26.1 29.1</td>
<td>17.6 31.4</td>
</tr>
<tr>
<td>VDZ/PBO (n=126)</td>
<td>32.8 28.5</td>
<td></td>
</tr>
<tr>
<td>VDZ/VDZ Q8W (n=122)</td>
<td>32.0 36.3</td>
<td></td>
</tr>
<tr>
<td>VDZ/VDZ Q4W (n=125)</td>
<td>11.8 15.3</td>
<td></td>
</tr>
</tbody>
</table>

* Included VDZ induction responders, further randomised to receive either study drug or placebo in maintenance; ^P<0.01 vs placebo; ‡P<0.05 vs placebo

GEMINI II & III: Vedolizumab in CD
Clinical Remission at Week 6

*Gemini II*¹
(ITT population)

<table>
<thead>
<tr>
<th>Group</th>
<th>% Achieving Remission (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, N=148</td>
<td>7 (0.5, 11.3)</td>
</tr>
<tr>
<td>VDZ (cohort 1), N=220</td>
<td>15 (12.0, 18.3)</td>
</tr>
<tr>
<td>VDZ (cohort 2), N=747</td>
<td>18 (14.0, 22.0)</td>
</tr>
</tbody>
</table>

\[ P = 0.02 \]

#Gemini III²
(Overall population)

<table>
<thead>
<tr>
<th>Group</th>
<th>% Achieving Remission (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, N=207</td>
<td>12 (9.0, 15.0)</td>
</tr>
<tr>
<td>Vedolizumab, N=209</td>
<td>19 (16.0, 22.0)</td>
</tr>
</tbody>
</table>

\[ P = 0.048 \]

*One of two primary endpoints. The other primary endpoint, CDAI-100 response was not met: 25.7% placebo vs 31.4% VDZ.

# Secondary endpoint. The primary endpoint for GEMINI III (Remission in anti-TNF failure population) was not met: 12.1% placebo vs 15.2% VDZ and therefore the \( P \) value is for descriptive purpose only (exploratory analysis).

1. Adapted from Sandborn WJ et al. NEJM 2013;369:711-721
2. Adapted from Sands BE et al. Gastroenterology 2014;147:618–627
GEMINI II: Vedolizumab in Crohn’s disease
Maintenance Phase: Outcomes at 52 Weeks

Maintenance ITT Population*

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VDZ/PBO (n=153)</td>
</tr>
<tr>
<td></td>
<td>VDZ/VDZ Q8W (n=154)</td>
</tr>
<tr>
<td></td>
<td>VDZ/VDZ Q4W (n=154)</td>
</tr>
</tbody>
</table>

- **Clinical Remission**
  - VDZ/PBO: 21.6%
  - VDZ/VDZ Q8W: 39.0%
  - VDZ/VDZ Q4W: 36.4%

- **CDAI-100 Response**
  - VDZ/PBO: 30.1%
  - VDZ/VDZ Q8W: 43.5%
  - VDZ/VDZ Q4W: 45.5%

- **CS-Free Remission**
  - VDZ/PBO: 15.9%
  - VDZ/VDZ Q8W: 31.7%
  - VDZ/VDZ Q4W: 28.8%

- **Durable Remission**
  - VDZ/PBO: 14.4%
  - VDZ/VDZ Q8W: 21.4%
  - VDZ/VDZ Q4W: 16.2%

*Included VDZ induction responders, further randomised to receive either study drug or placebo in maintenance

§CS tapering began in responders at 6 weeks; for others, as soon as a clinical response was achieved

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1. Adapted from Sandborn WJ et al. NEJM 2013;369:711-721
2. Adapted from Sands BE et al. Gastroenterology 2014;147:618–627
Nottingham IBD Pathways
Some clinical cases…
Spot the Defect!!

Case 1 - colovesical fistula
Case 2 - Enteroenteric fistula
• **Diagnoses:**
  • Crohn’s disease
    – Onset 13 years ago
    – Behaviour inflammatory with early stricturing disease in her sigmoid colon
    – Location ileocolonic

• **Medication:**
  • Infliximab loss of response
  • **Humira intolerant**
  • Mercaptopurine no response
  • Methotrexate intolerant with liver specific side effects
  • Mycophenolate no response
  • Prednisolone induced psychosis
  • Tacrolimus intolerant

Subtotal colectomy in November 2014 with an end ileostomy. This was complicated by wound dehiscence and mechanical obstruction (now resolved)

**Case 3**

A patient hard to convince...success story in the end
Case 4 – The heart sinking case...

Diagnoses:
1. Crohn's disease
   a. Location – ileocolonic, perianal
   b. Behaviour - perforating
   d. Humira September 2010 to June 2011 primary non responder.
2. Right hemicolecstomy in 2007 because of primary perforation.
3. Hartmann’s procedure with sigmoid and ileal resection November 2012 because of primary perforation leading to an end colostomy.
4. Recurrent flare in May 2013 with abdominal pain and diarrhoea.
5. Recurrent flare in May/June 2014 with evidence of colitis on CT – this is after nine months of Infliximab 5mg/kg q8.
6. Infliximab increased to 10 mg/kg in October 2014 due to a low trough level.

Azathioprine/Infliximab stopped in January 2015.

Medication:
Prednisolone 25mg – recently switched to Dexamethasone

* Recent diagnosis of EBV related high-grade B Cell Lymphoma in the brain.
Case 5 – When patients do not take ownership of the disease

- 35 year old lady
- Known case of perianal crohn’s disease
- Presenting to clinic with a perianal abscess
- Needs a) incision and drainage b) biological Rx
- Does not attend clinic repeatedly and attends her GP for recurrent courses of steroids
- Attends ER 12 months later with perianal sepsis
IBD key occupational facts

• 75% of Crohn’s are fully capable of work in the year after diagnosis, with 15% of people unable to work after 5–10 years of disease.

• In UC, after the first year approximately 90% of patients are fully capable of work (defined by less than 1 month off work per year), although UC causes significant employment problems for a minority.

• Patients want to work and are more productive than non-IBD patients. They need flexibility, an understanding and knowledgeable team, travel allowances and access to toilet facilities.

• They feel embarrassed about the condition although 8/10 patients have told their co-workers. 25% suffer from mental health issues.

• IBD is covered under the inequality act 2010
IBD key occupational facts

• Good place to start – CCUK

• [File Link]

• [File Link]

• [File Link]

Based on 2008 prices, the cost to per patient is in the range of £631 - £762 per patient per year. This suggests an overall annual cost to the NHS of up to £470 million. However, earlier research estimated the annual average cost per patient to be as high as £3,000.
Thanks

Questions....