New treatment options in UC

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Talk Outline

1. Raising expectations
2. Optimising UC therapy
3. Clinical trials
4. What’s new on the PBS?
5. Questions
1. Raising expectations...

- We are entering a new era of therapy in IBD:
  - The goal of therapy in IBD: Get back to normal life!
    - Stop disease progression
    - Improve quality of life
    - Avoid disability
  - Tailored therapy
  - ‘Treat to target’
    - Beyond symptoms, treat inflammation
  - Manage the person, not just the disease
2. Optimising standard therapy in UC

5-aminosalicylic acid therapy

<table>
<thead>
<tr>
<th>Preparations</th>
<th>Oral</th>
<th>Enemas</th>
<th>Suppositories</th>
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<tbody>
<tr>
<td>Active ingredient</td>
<td>Sulfasalazine (salazopyrine)</td>
<td>Pentasa Mesalazine</td>
<td>Colazide Balsalazide</td>
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<td>Colonic delivery</td>
<td>Sulfasalazine</td>
<td>Salofalk Mesalazine</td>
<td>Dipentum Olsalazine</td>
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<td>Preparations</td>
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<td>Oral</td>
<td>Tablets</td>
<td>Granules</td>
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The facts...

Oral 5-ASA therapy

- No difference in efficacy between oral 5-ASA’s for UC
  - Tolerance may differ

- Higher oral doses (≥2g/day) more effective for flares of UC

- Minimum oral maintenance dose in UC is 2g/day

- Once daily oral dosing is as good as split daily dosing
  - *Except for sulfasalazine

- Adherence to tablets is most important!
  - MORE IMPORTANT THAN DOSE
Key point...

**Topical 5-ASA therapy**

- COMBINATION of oral and rectal 5ASA therapy in UC is BETTER than either alone
  - Even in extensive colitis!
  - Can use topical in the event of a flare

- Topical therapy is as effective as oral 5ASA therapy for rectal disease

- Suppositories...
  - Salofalk

- Enemas
  - Foam
  - Liquid
    - Volume
    - Applicator
Optimising standard therapy in UC

Thiopurines

- Azathioprine and Mercaptopurine...

- Good for remission maintenance in both UC and CD
- Less steroids (60%)
- Less surgery (50%)

Safety

- Around 20% of patients have a side-effect (80% don't!)
- 2/3 of patients who don't tolerate AZA can tolerate MP

Possible side-effects

- Nausea, aches and pains
- Liver function derangement
- Bone marrow suppression
- Pancreatitis
- Skin cancer
- Lymphoma...
Safe use...

**Thiopurines**

- Involve local doctor
- Regular blood tests
  - Weekly, monthly, 3-monthly
- Vaccinations
  - Fluvax (yearly), Pneumovax (5 yearly)
  - AVOID live vaccines*
- Pap smears
  - Annually
- Skin check
  - Annually
- Safe in pregnancy and breast feeding
Optimising use...
Thiopurines AND allopurinol

- Dose is important
  - Azathioprine $\geq 2\text{mg/kg}$
  - Mercaptopurine $\geq 1\text{mg/kg}$

- ‘Shunters’
  - Too much 6-MMP (side-effects)
  - Too little 6-TG (effective)

- Allopurinol and thiopurine therapy
  - LOWER dose thiopurine
  - ADD allopurinol
  - Favourable metabolites
  - Careful monitoring
3. Clinical trials

- Clinical trials are a great opportunity!
  - Access to exciting new therapies
  - Personalised care and close follow-up and monitoring
  - Dedicated and available team

- RAH IBD Service is actively involved in multiple international trials...
Clinical trials in UC

Etrolizumab

**HIBISCUS I & HIBISCUS II**

Etrolizumab vs Adalimumab

Eligibility:
- Moderate to severe ulcerative colitis
- Failing or intolerance of standard therapy
- No prior anti-TNF therapy
Clinical trials in UC
Faecal Transplant Study

Faecal Transplant Study
(Dr Sam Costello, Consultant Gastroenterologist)

Eligibility:
- Active UC
- Clinical (diarrhoea or blood in stool) and
- Endoscopy

Entry
- Flexible sigmoidoscopy, stool test, dietary analysis

Follow-up
- Until 12 months

Study protocol:
Faecal transplant via colonoscopy and enema
Randomised and double blinded study
- 50% receive FMT at colonoscopy at week 0
- 50% receive FMT at colonoscopy at week 8
- Own stool is used as placebo
Clinical trials in UC
Dietary intervention trial

IBD Dietetics Group

Aiming to begin group education evenings on diet in IBD!

Please let us know if you may be interested on the form...
Clinical trials in IBD

Psychological care study

• Evaluation of whether psychological care provided alongside IBD services improves outcomes in IBD

• All patients attending IBD clinic invited to participate (UC and Crohn’s disease)

• Participants will be given:
  • Mental health, medication adherence, and quality of life questionnaires

• Opportunity to engage with a psychologist at the time of your visit to the IBD clinic
Upcoming trials in IBD...

- **Crohn’s disease**
  - Antibiotic therapy (RHB-104)
  - Gilead study (highly-selective monoclonal antibody for MMP9)
  - Vedolizumab (maintenance therapy for CD)
  - Celgene study (GED0301, oral SMAD7 antisense drug)

- **Ulcerative colitis**
  - Vedolizumab (maintenance therapy for UC)
  - Vedolizumab vs. adalimumab in severe active UC
  - Receptos (small molecule (S1P1 and S1P5 receptors))
New treatment options for UC

Vedolizumab (VDZ)

- VDZ is a humanised monoclonal antibody (mAb) that bind to gut-specific white blood cells (α4β7)
  - Stops migration of immune cells into the gut
- PBS Approved on 1st August 2015!
How does VDZ work?

Migration of gut-homing lymphocytes blocked with vedolizumab

Vedolizumab prevents lymphocyte migration into the gut, without affecting other lymphocyte subtypes

How effective is **VDZ** in UC?

**GEMINI I: Vedolizumab in UC. Induction phase: Outcomes at week 6**

**Induction ITT Population**

**Primary Outcome**
- **Clinical Response**
  - PBO (n=149): 25.5%
  - VDZ (n=225): 47.1%
  - **p<0.001**
- **Clinical Remission**
  - PBO (n=149): 5.4%
  - VDZ (n=225): 16.9%
  - **p<0.001**
- **Mucosal Healing**
  - PBO (n=149): 24.8%
  - VDZ (n=225): 40.9%
  - **p<0.001**

**Secondary Outcomes**


ITT, intent-to-treat; PBO, placebo; VDZ, vedolizumab; Mean Δ% (95% CI) = mean percentage point difference VDZ vs PBO (95% confidence interval)
GEMINI I: Vedolizumab in UC: Maintenance phase: Outcomes at week 52

Primary Outcome: Maintenance ITT Population

Adjusted difference, percentage points (95% CI)

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical Remission</th>
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<tbody>
<tr>
<td>VDZ Q8W vs PBO (n=126)</td>
<td>26.1 (14.9, 37.2)</td>
</tr>
<tr>
<td>VDZ Q4W vs PBO (n=125)</td>
<td>29.1 (17.9, 40.4)</td>
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How effective is VDZ in UC?

CI, confidence interval; ITT, intent-to-treat; PBO, placebo; VDZ, vedolizumab
How effective is VDZ in CD?

Clinical remission in CD at week 6 GEMINI II and weeks 6 & 10 in GEMINI III

Overall Population 100% patients

- C13007 Week 6: 15%, Δ=8%, p=0.206
- C13011 Week 6: 12%, Δ=16%, p=0.0001
- C13011 Week 10: 3%, Δ=7%, p=0.0478

*48% in C13007 & 75% in C13011

TNFα Failure Population

- C13007* Week 6: 11%, Δ=6%, Not tested
- C13011* Week 6: 12%, Δ=3%, p=0.4332
- C13011* Week 10: 12%, Δ=3%, p=0.4332

CI, confidence interval; PBO, placebo; TNF, tumour necrosis factor; VDZ, vedolizumab

How effective is VDZ in CD?

GEMINI II: Vedolizumab in CD: Maintenance phase: Outcomes at week 52

Clinical Remission: 17.4% vs. 14.7%
CDAI-100 Response: 13.4% vs. 15.3%
GC-Free Remission: 15.9% vs. 12.9%
Durable Remission: 7.2% vs. 2.0%

VDZ/PBO (n=153)
VDZ Q8W (n=154)
VDZ Q4W (n=154)

CDAI, Crohn’s Disease Activity Index; GC, glucocorticoid; ITT, intention-to-treat; PBO, placebo; VDZ, vedolizumab
Is VDZ safe?

- VDZ is gut-specific
- No significant differences in adverse reactions between VDZ and placebo in GEMINI trials
  - Serious infection <1%
  - Malignancy <1%
  - Slight increase in rates of gastroenteritis and perianal abscess formation
- VDZ predecessor drug natalizumab was associated with risk of PML (progressive multifocal leucoencephalopathy)
  - NO cases of PML with VDZ so far (>3000 patients, many long-term treatment)
VDZ summary and PBS criteria

- VDZ is effective and available for treating flares and maintaining remission in patients with moderate to severe UC or Crohn’s disease
  - Failed to respond to, or intolerant of, conventional therapy
  - Naïve or failed anti-TNF therapy
- Injections at 0,2,6 weeks and then 8 weekly
- Limited systemic immunosuppression and few side-effects
  - Good if risk of infection is high or prior cancer
- Practice points
  - Likely for use WITH immunosuppressant (azathioprine)
  - Onset of action of VDZ takes 2-3 months
  - ‘Monitor’ for PML
New treatment options for UC
Infliximab on PBS

- Infliximab for treating a flare of UC (0, 2, 6 weeks)
  - PBS approved April 2014
  - Moderate to severe UC
  - Failed conventional therapy

- Infliximab for maintenance of remission (8 weekly)
  - PBS approved November 2014
Conclusions

- Raise expectations!
- Optimise standard therapies
- Exciting new therapeutic options and clinical trials
  - Please fill out forms to declare your interest
- THANK YOU!
Questions?