Frontiers in Intestinal and Colorectal Disease

Refractory Ulcerative Colitis – where to go...
Pharmacological strategies

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Pharmacological management of refractory Ulcerative Colitis
An evolution in progress

Ulcerative Colitis

5-ASA Steroids
Azathioprine
CSA

Methotrexate
Tacrolimus

Anti-TNFs

Vedolizumab

NICE Entyvio

1995
2000
2005
2010
2015
2020

Surgery

Refractory Ulcerative Colitis – where to go…

Pharmacological strategies

What we will cover

• Brief case to highlight optimization of conventional therapy

• Anti TNF agents in refractory UC

• Anti Integrin therapies in refractory UC

• What is left in the cupboard
Refractory Ulcerative Colitis – where to go...

Case history

- 18 year lady with 1 year history of extensive UC
- Enteropathic arthritis and erythema nodusum (ANCA +ve)
  - Non smoker / no relevant family history / no NSAID, antibiotics or travel
- Prednisolone at index presentation
- Steroid dependent despite Mezavant MMX 4.8g / day and 2g Salofalk enema
- Commenced 2mg/kg azathioprine (TPMT normal)
- Weaned off steroids and was well for approximately 6 months
  - Normal stool frequency / no rectal bleeding / CRP<5mg/l
- Started at University but continued in our adolescent IBD clinic

Call to telephone helpline:
- Increasing diarrhoea 8x per day
- Blood on most occasions
- Episode of incontinence
Refactory Ulcerative Colitis – where to go...

*Loss of response to medical therapy*

**Primary non response:** define correct timeline for assessment

**Secondary loss of response:** three key issues

1) Do they still have what you thought they had?
   Confirm active disease/exclude complications

2) Are they taking what you think they are?
   Check adherence / monitor TGN levels etc

3) Have you made the most of what you’ve got?
   Consider dose optimisation based upon therapeutic drug monitoring
When to measure? Non-response.

Low/Absent 6-TGN/ Low/Absent 6-MMP = Non-adherence
Education

Low 6-TGN/ Low 6-MMP = Under-dosing
Increase dose

Low 6-TGN/ High 6-MMP = Thiopurine resistance
Allopurinol

High 6-TGN/ High/N 6-MMP = Thiopurine refractory
Another drug

6-TGN, 6-thioguanine; 6-MMP, 6-mercaptopurine.
RefRACTORY ULCERATIVE COLITIS – WHERE TO GO...

Case History

1) Do they still have what you thought they had?
   - Had taken course of antibiotics with ibuprofen for a tooth abscess
   - Bloods: Hb 10.5g/dl, CRP 15mg/l / Albumin 34g/l
   - Stool: culture -ve/ CDT –ve, FCP 482µg/g
   - Apyrexial / not tachycardic
   - Flex sig: MAYO grade III

2) Are they taking what you think they are?
   - Confirms she takes 5ASA / azathioprine
   - TGN 357pMol / MMP 900pMol

3) Have you made the most of what you’ve got?
   - No real room for optimisation so....
Refactory Ulcerative Colitis – where to go...
what options are there?

1) Anti TNF therapy
   Infliximab / Adalimumab / Golimumab

2) Anti Integrin Therapy
   Vedolizumab

3) Alternative / conventional therapy
   Prednisolone then Methotrexate
   Tacrolimus

4) Clinical trial therapies
   Etrolizumab
   Ozanimod
   Tofacitinib
1) **Anti TNF therapy:** Infliximab / Adalimumab / Golimumab

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**UC SUCCESS study:** corticosteroid-free clinical remission and mucosal healing at Week 16

### Clinical remission

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (%)</th>
<th>( p )</th>
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</thead>
<tbody>
<tr>
<td>AZA + PBO</td>
<td>24/76</td>
<td>0.032</td>
</tr>
<tr>
<td>IFX + PBO</td>
<td>22/77</td>
<td>0.813</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>40/78</td>
<td>0.017</td>
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</table>

### Mucosal healing

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (%)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + PBO</td>
<td>18/76</td>
<td>0.028</td>
</tr>
<tr>
<td>IFX + PBO</td>
<td>22/77</td>
<td>0.295</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>31/78</td>
<td>0.001</td>
</tr>
</tbody>
</table>

AZA, 2.5 mg/kg, oral; IFX, 5 mg/kg, intravenous infusion; PBO, (oral capsule [+IFX] or intravenous infusion [+AZA] administered together with test drug)

\( p \) values were calculated with a two-sided Cochran-Mantel-Haenszel chi-square test.

Steroid-free clinical remission = total Mayo score ≤2

Mucosal healing = Mayo subscore of 0 or 1

Anti TNF therapy: Infliximab / Adalimumab / Golimumab

- **Patient received induction Infliximab** 5mg/kg weeks 0,2 & 6
- Reviewed in virtual biologics clinic
  - Partial response: BO 4 times per day with occ blood
  - Partial MAYO fell from 9 to 5
  - CRP = 7mg/l

Is this primary non response: Primary endpoint of ACT trials at week 8
Can you declare primary non response with no trough drug levels?

How can we assess whether she will continue to improve or deteriorate?
Endoscopic score of disease activity can predict response to therapy

Anti-TNF induced mucosal healing at week 8 predicts future colectomy: data from ACT I & II (728 patients)

Reducing endoscopy subscore to 0 or 1 reduces risk of colectomy

Colombel, Gastroenterology 2011
Refractory Ulcerative Colitis – where to go...

Optimal use of anti TNF therapy in UC

ACT 1 and ACT 2: infliximab concentration and clinical outcome in adult patients with moderate to severe UC

- Clinical response at Week 8
- Mucosal healing at Week 8

Factors that affect trough levels

- Dose / schedule
- Immunogenicity
- Disease burden
- Stool loss
- Serum albumin
- Patient weight

Serum albumin <30g/l:
66.6% vs 22.6% colectomy
OR 6.86 (1.03-45.6) p=0.05

Lees CW et al, APT 2007
Refactory Ulcerative Colitis – where to go...

Anti TNF agents in refractory UC?

**Anti TNF therapy:** Infliximab / Adalimumab / Golimumab

- **Induction Infliximab:** reviewed in virtual biologics clinic after week 6
  - Bowels open 4 x per day with occ blood
  - Partial MAYO fell from 9 to 5
  - CRP < 7mg/l

1) Do they still have what you thought they had?
   Stool: culture -ve/ CDT –ve
   Flex sig: MAYO grade I

2) Are they taking what you think they are?
   TGN 357 pMol / MMP 900 pMol

3) Have you made the most of what you’ve got?
   INF trough level 2.6μg/ml
   undetectable anti infliximab antibodies
Refractory Ulcerative Colitis – where to go...

Anti TNF agents in refractory UC?

Patient did not respond to escalated dosing of anti TNF despite adequate trough levels
Refractory Ulcerative Colitis – where to go...

Appropriate use of ‘rescue therapy’...

1) Anti TNF therapy
   - Infliximab / Adalimumab / Golimumab

2) Anti Integrin Therapy
   - Vedolizumab

3) Alternative / conventional therapy
   - Prednisolone then Methotrexate
   - Tacrolimus

4) Clinical trial therapies
   - Etrolizumab
   - Ozanimod
   - Tofacitinib
2) Anti Integrin Therapy: Vedolizumab

- **Screen:** HepBSAg –ve / HCV ab –ve / HIV –ve
  Quantiferon gold –ve / CXR NAD / Born in UK
  Stool cultures negative plus CDT
  We do not check JC virus ab

- **Consent:** Opportunistic infections
  Immunogenicity / GI infections
  Nasopharyngitis
  ?? malignancy

- **Induction:** Prednisolone 40mg 8 week course
  Vedolizumab 300mg weeks 0, 2 & 6

- **Maintain:** Vedolizumab 300mg 8 weekly
2) Anti Integrin Therapy: Vedolizumab

Induction Clinical Response and Remission at 6 Weeks in Patients with Prior Anti-TNF Failure or Naive – ITT
Refractory Ulcerative Colitis – where to go...

*what options are there?*

2) **Commenced vedolizumab with prednisolone.**
   - reviewed in virtual biologics clinic after week 6
     - Bowels open 1x per day with no blood
     - Partial MAYO fell to 1
     - CRP < 5mg/l
     - Continues well on 8 weekly vedolizumab
Refractory Ulcerative Colitis – where to go...

Choosing the right biologics for your patient

- **Disease related factors**
  - Diagnosis
  - Severity / Distribution / Phenotype

- **Patient related factors**
  - Age
  - Comorbidity
  - TB risk
  - Preference (infusion vs injection)

- **Previous therapies**
  - Naïve patients respond better to most drugs
  - ? Impact of azathioprine

- **Local issues**
  - NICE
1) Anti TNF therapy: Infliximab / Adalimumab / Golimumab
2) Anti Integrin Therapy: Vedolizumab
3) Alternative conventional therapy
   Methotrexate: Meteor trial did not meet its primary endpoint...

Franck Carbonnel, ECCO 2015
Refactory Ulcerative Colitis – where to go…

what options are there?

1) Anti TNF therapy: Infliximab / Adalimumab / Golimumab
2) Anti Integrin Therapy: Vedolizumab

3) Alternative conventional therapy

Methotrexate: Meteor trial did not meet its primary endpoint…

Tacrolimus

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**Efficacy of tacrolimus (RCT for 2 weeks)**

- Clinical response:
  - Placebo: 13.3%, Tacrolimus: 50.0%
  - *p* = 0.003

- Mucosal healing:
  - Placebo: 13.3%, Tacrolimus: 43.8%
  - *p* = 0.012

- Clinical remission:
  - Placebo: 0.0%, Tacrolimus: 9.4%

**Efficacy of tacrolimus (open-label continuous treatment)**

- Mucosal healing:
  - At week 2: 66.7%, At week 12: 85.7%

- Clinical remission:
  - At week 2: 14.3%, At week 12: 28.6%

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*Note: 0% at baseline*

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*CYP3A5 non-expressers more likely to achieve therapeutic levels at day 2 OR 40.5 (3.2-515.5; p=0.004)*

1) Anti TNF therapy: Infliximab / Adalimumab / Golimumab
2) Anti Integrin Therapy: Vedolizumab
3) Alternative conventional therapy: Methotrexate: Meteor trial did not meet its primary endpoint… Tacrolimus
4) Clinical trial therapies: Etrolizumab, Ozanimod, Tafacitinib

Refractory Ulcerative Colitis – where to go… what options are there?
ECCO’16 Amsterdam Congress
IBD innovations driving clinical decisions

11th Congress of ECCO
March 16-19, 2016

• Amsterdam RAI
• EACCME applied
The evolving pipeline of therapeutic options for IBD

Adapted from: Danese S. Gut 2012;61:918–932.