Drug withdrawal IBD: few evidence, lots of strategies

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Why should we stop biologics/immunosuppressants in IBD? (... if they keep working on a patient)

- **Medical reasons (Benefit/Risk)**
  - Over-treatment of long-time remitters
  - Safety concerns (infections, malignancies: lymphoma, skin)
  - Specific situations (e.g. pregnancy, elderly, previous cancer)

- **Patients may ask for it**
  - Convenience
  - Patients do not like to take drugs
  - Patients may be afraid of complications

- **Payor push back/cost**
  - Medical costs
Drug withdrawal IBD

Few evidence

Lots of strategies (?)
Few evidences: 3 possible scenarios

1. Patients on immunomodulator monotherapy;
2. Patients on anti-TNFα monotherapy;
3. Patients on combo therapy.
Few evidences: 3 possible scenarios

1. Patients on immunomodulator monotherapy;
2. Patients on anti-TNFα monotherapy;
3. Patients on combo therapy
Controlled withdrawal trial in Crohn’s disease patients in long-term remission on azathioprine

83 patients in clinical remission with AZA for at least 3.5 years before randomisation

CRP >20 mg/L: RR 16.9 (95% CI 2.7-104.3), p<.0001
Haemoglobin <12 g/dL: RR 8.7 (95% CI 1.6-48.8), p=.0034
Time without steroids <50 months: RR 5.2 (95% CI 1.5-18.1), p=.004

Independent predictors of relapse

Azathioprine withdrawal in Crohn’s disease

66 patients in clinical remission with AZA for 63.6 months
Stop AZA and 54.5 months of median FU: 32 of 66 (48.5%) relapse

Cumulative probability of remaining in remission after AZA withdrawal

Relapse predicting classification according to the presence of risk factors (CRP, Hb, Neutrophils levels) after AZA withdrawal

23 out of the 32 relapsing patients were retreated with AZA and 22 were put into remission again
Azathioprine withdrawal in UC

36% 61%

67 patients on AZA for at least 6 months
Steroid-free clinical remission for at least 2 months

Kaplan-Meier survival plot of the rate of relapse over one year for 67 patients with ulcerative colitis in remission after taking azathioprine

Azathioprine withdrawal in UC

Median AZA treatment: 47 mo (3–105)
Median follow-up: 55 mo (1–182).

Cumulative relapse rate:
35 % at 1 year
65 % at 5 years

Cox regression

AZA duration: HR 2.8
No sustained remission: HR 2.3
Disease extent: HR 2

Predictors of relapse after withdrawal
Few evidences: 3 possible scenarios

1. Patients on immunomodulator monotherapy;

2. Patients on anti-TNFα monotherapy;

3. Patients on combo therapy
Evolution after anti-TNF drug discontinuation in IBD (multicenter retrospective observational study – Spain)

1055 IBD (69% CD) in which anti-TNFs had been withdrawn after clinical remission

1) **Relapse after discontinuation:**
Incidence rate: 19% per pts-yr (95%CI 17-20)

2) **Risk of relapse** (multivariate) in CD:
IM treatment after discontinuation (HR 0.7)
Colonic localization (HR=1.51)
Stricturing behavior (HR=1.5)
Ada (HR=1.29)

3) 69% of **relapsers retreated** with the same agent:
**75% remission** at FU, 11% mild adverse events
Discontinuation of IFX in Patients With UC Is Associated With Increased Risk of Relapse

A Multinational Retrospective Cohort Study

193 UC patients in remission (> 12 months) on IFX:
111 (57.5%) discontinued – 82 (42.5) continued

HR of relapse:
- IFX discontinuation
  HR 3.7 (95% CI 2.02-6.77); P< .001
- Concomitant thiopurines
  HR 0.61 (95% CI0.37-0.99); P= .048

A: thiopurines
B: aminosalicylates
C: combination

Few evidences: 3 possible scenarios

1. Patients on immunomodulator monotherapy;
2. Patients on anti-TNFα monotherapy;
3. Patients on combo therapy
Which drug can be stopped in a patient receiving combination therapy (anti-TNFs + AZA)?

1. Immunosuppressant
Withdrawal of Immunosuppression in CD Treated With Scheduled IFX Maintenance

- Open-label RCT

- n=80 CD in remission, treated with combo ≥6 months

- Randomisation: IS cessation vs. continuation

Withdrawal of IM in CD After Combination therapy and Trough Level of Infliximab at withdrawal
The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab

Prospective IBD cohort (n=125)

1) 90% of the patients who developed ATI did so within the first 12 months of therapy
2) transient ATI were detected throughout the duration of infliximab therapy

Combotherapy (IM+IFX) resulted in longer ATI-free survival compared with monotherapy

Which drug can be stopped in a patient receiving combination therapy (anti-TNFs + AZA)?

2. anti-TNF
IFX withdrawal in patients receiving prolonged combination (IFX+AZA) therapy in CD

115 CD patients in remission on IFX+AZA (CDAI<150 and steroid free ≥6 months)

<table>
<thead>
<tr>
<th>Deleterious Factor</th>
<th>HR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous surgery</td>
<td>4.0 (1.4-11.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Steroids (month -12 to -6)</td>
<td>3.5 (1.1-10.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemoglobin ≤ 14.5 (g/dl)</td>
<td>6.0 (2.2-16.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male Gender</td>
<td>3.7 (1.9-7.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fecal calpro ≥ 300 μg/g</td>
<td>2.5 (1.1-5.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Infliximab TL ≥ 2 mg/L</td>
<td>2.5 (1.1-5.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>WBC &gt; 6 (10³/ml)</td>
<td>2.2 (1.2-4.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>CRP hs &gt; 5 (mg/l)</td>
<td>3.2 (1.6-6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDEIS &gt; 0</td>
<td>2.3 (1.1-4.9)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Median follow up 28+/- 2 months

43.9% relapse
52.2% relapse

Louis E, et al. Gastroenterology 2012
STORI: long-term follow-up (retrospective)

- 102 CD patients receiving combotherapy
- Median FU duration: 78 months

**Survival without failure of the de-escalation strategy**

**Long-term outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of any anti-TNF</td>
<td>22%</td>
</tr>
<tr>
<td>Major complications</td>
<td>18.5%</td>
</tr>
<tr>
<td>Anti-TNF retreatment</td>
<td>71%</td>
</tr>
<tr>
<td>IFX retreatment</td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>66%</td>
</tr>
<tr>
<td>Failure (including 45% of severe relapse)</td>
<td>34%</td>
</tr>
</tbody>
</table>

*Ifx restart failure + major complications*
Drug withdrawal IBD

Few evidence

Lots of strategies (?)
Lots of strategies (?)

1. Assess the risk of relapse
2. TDM
3. Dose reduction
4. Biocycle
Lots of strategies (?)

1. Assess the risk of relapse
2. TDM
3. Dose reduction
4. Biocycle
Factors associated with relapse of IBD after discontinuation of thiopurines monotherapy

Table 1. Factors associated with higher relapse rates in CD [left column] and UC [right column] following withdrawal of thiopurine IM monotherapy. Based on Torres et al. 2015.\textsuperscript{87}

<table>
<thead>
<tr>
<th>Factors associated with higher CD relapse risk</th>
<th>Factors associated with higher UC relapse risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated C-reactive protein level\textsuperscript{23, 77, 89}</td>
<td>Increased leukocyte count\textsuperscript{23, 91}</td>
</tr>
<tr>
<td>Increased leukocyte or neutrophil count\textsuperscript{23, 89}</td>
<td></td>
</tr>
<tr>
<td>Low haemoglobin level\textsuperscript{77, 89}</td>
<td>Extensive disease [pancolonic/extensive]\textsuperscript{84}</td>
</tr>
<tr>
<td>High-risk disease [peri-anal involvement]</td>
<td>Younger age\textsuperscript{83}</td>
</tr>
<tr>
<td>Younger age\textsuperscript{76}</td>
<td>Male gender\textsuperscript{84}</td>
</tr>
<tr>
<td>Male gender\textsuperscript{76}</td>
<td>Number of relapses on azathioprine\textsuperscript{84, 91}</td>
</tr>
<tr>
<td>Short duration of remission\textsuperscript{76}</td>
<td>Shorter duration of azathioprine\textsuperscript{84, 91}</td>
</tr>
<tr>
<td>Shorter time since latest steroids\textsuperscript{77}</td>
<td>Longer time from diagnosis to azathioprine\textsuperscript{91}</td>
</tr>
<tr>
<td>Higher dose of azathioprine\textsuperscript{79}</td>
<td></td>
</tr>
<tr>
<td>Thiopurine tapering before de-escalation\textsuperscript{13}</td>
<td></td>
</tr>
<tr>
<td>Smoking cessation\textsuperscript{80}</td>
<td></td>
</tr>
</tbody>
</table>

Bold type identifies factors observed consistently.
Factors associated with relapse of IBD after discontinuation of anti-TNFs

<table>
<thead>
<tr>
<th>Factor</th>
<th>Risk of relapse</th>
<th>IBD type</th>
<th>Association (and corresponding references)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger age</td>
<td>Higher</td>
<td>CD</td>
<td>HR 1.83 (1.03–3.25) (age ≥25 years at diagnosis associated with remission)²⁹</td>
<td>Evidence based on few studies</td>
</tr>
<tr>
<td>Smoking</td>
<td>Higher</td>
<td>CD</td>
<td>OR 2.74 (0.99–7.59)²⁵, HR 1.91 (1.11–3.27)²⁷</td>
<td>Evidence based on few studies</td>
</tr>
<tr>
<td>Longer disease duration</td>
<td>Higher</td>
<td>CD</td>
<td>Early introduction of anti-TNF therapy is associated with less severe intestinal tissue impairment and restored mucosal immune homoeostasis²⁶</td>
<td>Evidence based on few studies</td>
</tr>
<tr>
<td>Fistulising perianal CD</td>
<td>Higher</td>
<td>CD</td>
<td>Incidence of relapse in perianal vs. luminal CD: 66% vs. 31%¹⁷, 65% vs. 42%³⁴</td>
<td>Stop anti-TNF not recommended unless radiological healing confirmed</td>
</tr>
<tr>
<td>Escalated anti-TNF doses</td>
<td>Higher</td>
<td>CD</td>
<td>Incidence of relapse in patients with escalated dose: 90%¹⁵ and 100%⁷⁸</td>
<td>Stop anti-TNF not recommended</td>
</tr>
<tr>
<td>Prevention of post-operative CD</td>
<td>Higher</td>
<td>CD</td>
<td>Incidence of relapse in patients with intestinal resection: 100%⁶¹ and 83%⁶²</td>
<td>Stop anti-TNF not recommended</td>
</tr>
<tr>
<td><strong>Laboratory markers</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low haemoglobin levels</td>
<td>Higher</td>
<td>CD</td>
<td>HR 6.0 (2.2–6.5) (haemoglobin level ≤145 g/L)²⁰</td>
<td>Evidence based on few studies</td>
</tr>
<tr>
<td>High leucocyte count</td>
<td>Higher</td>
<td>CD</td>
<td>HR 2.4 (1.2–4.7) (leucocyte count &gt;6 × 10⁹/L)³⁰</td>
<td>Evidence based on few studies</td>
</tr>
<tr>
<td>High CRP levels</td>
<td>Higher</td>
<td>CD</td>
<td>HR 3.2 (1.6–6.4) (hsCRP level ≥5 mg/L)²⁹, OR 2.38 (0.92–6.19)²²</td>
<td>Evidence based on few studies</td>
</tr>
<tr>
<td>High faecal calprotectin</td>
<td>Higher</td>
<td>CD</td>
<td>HR 4.2 (1.9–9.2) (CRP &gt; 5 mg/L)⁵⁸</td>
<td>False-negative results limit clinical application</td>
</tr>
<tr>
<td>High serum anti-TNF levels</td>
<td>Higher</td>
<td>CD</td>
<td>PPV for relapse 67% (FC &gt; 50 µg/g)¹⁵, HR 2.5 (1.1–5.8) (FC 300 µg/g)²⁰, HR 6.5 (2.7–15.6) (FC &gt; 250 µg/g)⁵⁸</td>
<td>Lack of validated cut-off point limits clinical application</td>
</tr>
<tr>
<td><strong>Endoscopic factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal healing</td>
<td>Lower</td>
<td>CD &amp; UC</td>
<td>When anti-TNFs were stopped based on achievement of clinical remission, 42% of CD patients relapsed during the following year.¹² However, if patients discontinued anti-TNFs after achieving also endoscopic remission, this figure decreased to 26%.¹² Similar differences were observed for UC at 12–24 months: relapse rates were 50% and 33% after therapy withdrawal based on clinical and endoscopic remission, respectively¹²</td>
<td>Lower risk not confirmed by some studies Degree of mucosal healing necessary unclear</td>
</tr>
</tbody>
</table>

The overall risk of relapse after discontinuation of anti-TNF:
- 44% for CD (FU range: 6–125 months)
- 38% for UC (FU range: 6–24 months).

What about our decision?
Lots of strategies (?)

1. Assess the risk of relapse
2. TDM
3. Dose reduction
4. Biocycle
Relapse Rate After Discontinuing anti-TNF in long-term deep remission is lower when nil drug levels

48 patients stopped IFX (n=35) or adalimumab (n=13) in deep endoscopic remission: 41% of relapse at 12 months
Long-Term Outcome of Patients With CD Who Discontinued Infliximab Therapy Upon Clinical Remission

52% of patients remained in Sustained Clinical Remission after a median FU of 9.7 years (IQR 8-11.5)
Proposed algorithm to guide drug discontinuation or de-escalation in patients with IBD who achieved sustained deep remission while on combotherapy

- **Sustained deep remission under combination therapy**
  - **TRI > 5 µg/mL**
    - **stop thiopurines**
  - **6-TGN > 250 with TRI > 3**
    - decrease AZA dose to obtain 6-TGN levels > 125 pmol
  - **6-TGN > 250 with TRI < 2**
    - discuss stopping IFX

Lots of strategies (?)

1. Assess the risk of relapse
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Azathioprine dose reduction in patients in deep remission receiving combination therapy (IFX + AZA)

Prospective monocentric study (Saint-Etienne)

n = 81 IBD on combotherapy and in deep remission for at least 6 months

IFX + AZA continued (n = 28)

IFX + AZA halved (n = 27)

IFX + AZA stopped (n = 26)

Clinical relapse within 1 yr

 ROC analysis (AUROC: 0.93), a threshold of 6-TGN < 105 pmoles was associated with unfavourable pharmacokinetic (sensitivity, 67%; specificity, 92%; likelihood ratio, 7.67).
TAXIT: optimisation phase

IFX Dose de-escalation in patients with high levels
(n=67, 26%: TL>7ug/ml)

| CD: Harvey-Bradshaw ≤4 / UC: Partial MAYO ≤2 | C-reactive protein (CRP) level |
|---------------------------------------------|---------------------------------
| Patients (%)                                | Mean CRP Concentration (mg/liter) |
| CD (N=48)                                   | CD (N=48)                       |
| Before optimisation                         | Before optimisation             |
| 81.4                                        | 9.0 ± 2.0                       |
| After optimisation                          | After optimisation              |
| 74.4                                        | 11.0 ± 2.3                      |
| P=0.60                                      | P=0.56                          |
|                                              |                                 |
| UC (N=19)                                   |                                 |
| Before optimisation                         |                                 |
| 94.4                                        |                                 |
| After optimisation                          |                                 |
| 88.9                                        |                                 |
| P=1.0                                       |                                 |

Successful dose de-escalation of patients with supra-therapeutic levels whilst retaining disease control

Vande Casteele et al, Gastroenterology 2015
De-escalation strategies

Deep remission
Every 10-week FC assessment
Cumulative probability of relapse at 12 months 14%

Ada every 3 weeks, median FUP 15.9 months
Failure in 35.7%
Lots of strategies (?)

1. Assess the risk of relapse
2. TDM
3. Dose reduction
4. Biocycle
Figure 1: New concept of intermittent anti-tumor necrosis factor α therapy in inflammatory bowel disease. Stopping anti-TNFα agents after achieving a deep remission may result in prolonged clinical remission. Close monitoring of these patients with fecal calprotectin and CRP measurements (arrows) will allow early re-initiation of anti-TNFα therapy, when inflammation is starting to rise, which may result in a sustained clinical benefit (dotted line) preventing a disease flare (red cross). These patients may be considered as treated periodically and not episodically. TNF: Tumor necrosis factor; CRP: C-reactive protein.
A prospective randomized controlled trial comparing infliximab-antimetabolites combination therapy to antimetabolites monotherapy and infliximab monotherapy in patients with Crohn’s disease in sustained steroid-free remission on combination therapy (SPARE)
Conclusions?

- Drug withdrawal may be an option in select IBD patients
- There is a lack of consistency across the studies in terms of individual prognostic markers
- TDM can offer a promising strategy to indentify candidates for drug withdrawal