Withdrawal of drug therapy in patients with quiescent Crohn’s disease

DR. JEAN-FRÉDÉRIC COLOMBEL

DIRECTOR OF THE IBD CENTER, ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI, NEW YORK, USA
Withdrawal of drug therapy (IS and biologics) in CD

• The feasibility of de-escalation of therapy once remission is achieved is a common question encountered in clinical practice, driven by patient and clinician concerns around safety, adverse events, cost and national regulations.

• Withdrawal of immunosuppressive and biologic drugs in patients with quiescent CD could limit adverse events and reduce healthcare costs.

• Alternatively, ceasing these drug therapies may result in negative outcomes such as disease relapse, drug desensitization, bowel damage and need for surgery.
What are the consequences of stopping a drug (IS or biologics) once remission is achieved?
Stopping therapy: possible scenarios

Monotherapy
- Stop IS
- Stop Anti-TNF-α

Combination therapy
- Stop IS
- Stop Anti-TNF-α
Cochrane Review: Withdrawal of drug therapy for patients with quiescent Crohn's disease

**Inclusion criteria**

- Adults (age >18 years) with CD who achieved remission (as defined by the study) while receiving immunosuppressive or biologic drugs administered alone or in combination
- Minimum duration of six months after drug discontinuation
- Received a minimum treatment duration of 6 months
Types of studies

• Randomized controlled trials (RCTs)
• Controlled clinical trials
• Prospective cohort studies

Primary outcome

• Proportion of patients who relapse following discontinuation of immunosuppressive or biologic drugs, administered alone or in combination

• The comparison was usual care (continuing therapy)
9103 records identified

5414 records after duplicates removed

5414 records screened

5341 records excluded

73 full text articles assessed

68 records excluded with reasons

5 studies included in meta-analysis
Stopping Immunosuppressives (monotherapy)
Immunosuppressive withdrawal after monotherapy vs usual care

Relapse at 12-24 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Continue azathioprine</th>
<th>Discontinue azathioprine</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lernann 2005</td>
<td>3</td>
<td>9</td>
<td>43</td>
<td>25.6%</td>
<td>0.36 [0.10, 1.23]</td>
<td></td>
</tr>
<tr>
<td>O'Donoghue 1978</td>
<td>4</td>
<td>11</td>
<td>27</td>
<td>29.8%</td>
<td>0.41 [0.15, 1.12]</td>
<td></td>
</tr>
<tr>
<td>Villet 2004</td>
<td>3</td>
<td>8</td>
<td>16</td>
<td>22.2%</td>
<td>0.40 [0.13, 1.22]</td>
<td></td>
</tr>
<tr>
<td>Wenzl 2014</td>
<td>4</td>
<td>8</td>
<td>26</td>
<td>23.0%</td>
<td>0.50 [0.17, 1.46]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 104 111 100.0% 0.42 [0.24, 0.72]

Total events 14 36

Heterogeneity: Chi² = 0.17, df = 3 (P = 0.98); I² = 0%
Test for overall effect Z = 3.13 (P = 0.002)

Adverse Events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Continue azathioprine</th>
<th>Discontinue azathioprine</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lernann 2005</td>
<td>2</td>
<td>1</td>
<td>43</td>
<td>1.4%</td>
<td>2.15 [0.20, 22.81]</td>
</tr>
<tr>
<td>O'Donoghue 1978</td>
<td>1</td>
<td>0</td>
<td>27</td>
<td>0.8%</td>
<td>3.36 [0.14, 78.79]</td>
</tr>
<tr>
<td>Wenzl 2014</td>
<td>19</td>
<td>22</td>
<td>26</td>
<td>97.9%</td>
<td>0.96 [0.65, 1.15]</td>
</tr>
</tbody>
</table>

Total (95% CI) 90 96 100.0% 0.88 [0.67, 1.17]

Total events 22 23

Heterogeneity: Tau² = 0.00; Chi² = 1.64, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.39)
Stopping Immunossupressives (combination therapy)
Immunosuppressive withdrawal after combination therapy vs usual care

Relapse at 24 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Assche 2008</td>
<td>24/40</td>
<td>22/40</td>
<td>1.09 [0.75, 1.59]</td>
</tr>
</tbody>
</table>

Risk Ratio

0.5 1 1.5 2
Favours continuing AZA  Favours withdrawing AZA

Adverse Events

<table>
<thead>
<tr>
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<td>Van Assche 2008</td>
<td>24/40</td>
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<td>0.96 [0.68, 1.36]</td>
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Risk Ratio

0.5 1 1.5 2
Favours continuing AZA  Favours withdrawing AZA

Stopping biologics
Stopping biologics in CD

• There are no prospective controlled studies or randomized controlled studies on stopping biologics in CD

• There are no studies specifically assessing anti-TNF-α withdrawal after a period of monotherapy (variable rates of combination therapy among studies)
STORI: Infliximab diSconTinuation in Crohn's disease patients in stable Remission on combined therapy

Prospective, multicentre cohort study in 20 centres

N=115 CD patients in remission on IFX and AZA, 6-MP or MTX

- At least 1 year on IFX/AZA and ≥6 months steroid-free remission

IFX stopped and patients followed every 2 months for ≥1 year (median: 28 months)

Primary endpoint: time to relapse after withdrawal of IFX
Time to relapse after IFX withdrawal (STORI trial)

43.9% of patients relapsed after 1 year

52.2% of patients relapsed over 2 years

Number at risk:

<table>
<thead>
<tr>
<th>Months since infliximab withdrawn</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>115</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>79</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
</tr>
<tr>
<td>12</td>
<td>49</td>
</tr>
<tr>
<td>15</td>
<td>47</td>
</tr>
<tr>
<td>18</td>
<td>38</td>
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<tr>
<td>21</td>
<td>32</td>
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<td>32</td>
</tr>
<tr>
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<td>29</td>
</tr>
<tr>
<td>30</td>
<td>15</td>
</tr>
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</table>
Long-term outcomes after infliximab withdrawal in CD

Median follow up 7 years of the STORI cohort (n=102)

Cumulative incidence of starting or restarting a biologic
- Cumulative incidence of anti-TNF resumption: 34.3(±9.3)%, 56.0(±9.7)% and 64.4(±9.5)% respectively 1, 3 and 5 years after IFX withdrawal
- 29.0% (95%CI: 20.7-39.6) of the patients were still without biologic treatment 7 years after IFX withdrawal

Time-to-major complication
- 18/102 experienced a severe failure after a median follow-up of 83.3 months (IQR: 71.1-92.9)
- 18.5% (95%CI: 10.2-26.8) major complications 7 years after IFX withdrawal
Stopping anti-TNF-α agents in CD: qualitative data – prospective studies

<table>
<thead>
<tr>
<th>Type of remission</th>
<th>Relapse rates at 6 months (% average)</th>
<th>Relapse rates at 12 months (% average)</th>
<th>Relapse rates at 24 months (% average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>19.9%</td>
<td>36%</td>
<td>46.4%</td>
</tr>
<tr>
<td>Deep</td>
<td>16.7%</td>
<td>31.7%</td>
<td>49.2%</td>
</tr>
</tbody>
</table>

Deep: Clinical remission and endoscopic or radiological or analytical (CRP and/or FC)
### FACTORS PREDICTIVE OF RELAPSE

**Reflective of disease activity at de-escalation or during follow-up**

- Elevated inflammatory markers (leucocyte count, CRP, FC)
- Laboratorial markers suggestive of ongoing inflammation (low hemoglobin)
- Absence of mucosal healing

**Factors reflective of disease poor prognostic features**

- Smoking
- Perianal disease
- Disease location (Ileocolonic disease; colonic vs ileal or ileocolonic disease, extensive colitis vs limited)
- Young age at diagnosis

**Previous disease course**

- Prior disease course marked by higher therapeutic requirements (higher steroid use, prior anti-TNF-α course, need for dose-escalation prior to discontinuation, prior immunosuppressive failure)

**Other**

- Male sex (HR 3.7 [1.9-7.4])
- Elevated/detectable IFX trough levels

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Torres J, Boypati R. et al. Gastroenterology 2015
Conclusions

• Withdrawal of thiopurines in patients with CD in clinical remission is associated with a higher chance of relapse but a potentially lower chance of adverse events

• There is no difference in relapses rates for patients on combination therapy that stop or continue IS

• No studies have assessed anti-TNF-α discontinuation in CD patients in remission in a controlled way

• Data from uncontrolled studies on anti-TNF-α withdrawal suggest that roughly 50% of patients will relapse after 2 year follow-up
The ‘Biocycle’ project

Ongoing study

<table>
<thead>
<tr>
<th>Combo therapy</th>
<th>Anti-TNF-α</th>
<th>Antimetabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A control</td>
<td>Anti-TNF-α</td>
<td>Antimetabolites</td>
</tr>
</tbody>
</table>

Arm B

Anti-TNF-α withdrawal → New treatment cycle if needed

Arm C

Antimetabolites withdrawal → New treatment cycle if needed

CCFA

GETAID

Sweden