Why Do Patients With Crohn’s Disease Not Respond To Their Medications?

**Primary Nonresponse**
- Drug/mechanism just doesn’t work
- Wrong diagnosis
  - Infection
  - Ischemia
  - Crohn’s disease
- Wrong dose
  - Not enough
  - Too much?
  - Other pK issues
- Wrong delivery
  - Rationale
- Allergy/intolerance

**Secondary Nonresponse**
- Change in dose (by you)
- Change in delivery
- Change in physiology
  - Does disease change over time?
- Intentional nonadherence
  - Episodic dosing strategy
  - Denial
  - Fear of therapy
- Unintentional nonadherence
  - Can’t afford medication
  - Inconvenient dosing regimen
Practical Issues of the Refractory Crohn’s Patient

- Confirm that this is inflammation!
- Does the degree of inflammation explain the symptoms?
- Assess drug compliance and adherence
- Assess drug optimization otherwise—metabolism and pK issues
- Use combination therapy for biologics and add combination therapy when there are overlapping symptoms
- Don’t forget about surgery—it is the most effective treatment option

Symptoms after Crohn’s Surgery are Not Always Inflammatory!

<table>
<thead>
<tr>
<th>Symptom/Cause</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative pain</td>
<td>Limited analgesia, regional anesthesia when possible</td>
</tr>
<tr>
<td>Post-resection “diarrhesis” (rapid transit due to absence of obstruction and muscular hypertrophy)</td>
<td>Anti-diarrheals</td>
</tr>
<tr>
<td>Bile salts</td>
<td>Bile acid sequestrant</td>
</tr>
<tr>
<td>Narcotic bowel</td>
<td>NO narcotics!</td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
<td>antibiotics</td>
</tr>
</tbody>
</table>
The Patient Failing Thiopurine Therapy

Metabolism of Azathioprine and 6-Mercaptopurine

The Patient not Responding to Thiopurine

- Confirm adherence, consider metabolites:

<table>
<thead>
<tr>
<th>6-TG</th>
<th>6-MMP</th>
<th>Possible cause</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>undetectable</td>
<td>undetectable</td>
<td>Non-adherent or underdosed</td>
<td>Understand why pt not taking med or increase dose</td>
</tr>
<tr>
<td>Low (&lt;230)</td>
<td>Low or undetectable</td>
<td>Non-adherent or underdosed</td>
<td>Discuss adherence, increase dose</td>
</tr>
<tr>
<td>Low (&lt;230)</td>
<td>High (&gt;5700)</td>
<td>6-MMP shunter</td>
<td>1. Increase thiopurine, or 2. Consider allopurinol, or 3. Switch agents</td>
</tr>
<tr>
<td>“Therapeutic” (&gt;230-&lt;400) or High (&gt;400)</td>
<td>Normal range or high</td>
<td>Primary non-responder</td>
<td>1. Assess disease 2. Switch to different mechanism</td>
</tr>
</tbody>
</table>


Practical Approach to Allopurinol and Thiopurine Combination Therapy

- Not for everyone! Be aware of safety concerns.
- Choose patient (and MD) wisely:
  - Active disease
  - Adherence with thiopurines
  - Subtherapeutic 6-TGn, supratherapeutic 6-MMP
  - Elevated LFTs or nausea may be present but not necessary to consider this approach
- Drop thiopurine to 25 mg (6-MP) or 50 mg (Aza)
- Allopurinol 100 mg
- Notify pharmacist!
- CBC weekly for one month, then monthly...
- Metabolites at week 3
- Dose adjustment if necessary but in small increments

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Factors Affecting the Pharmacokinetics of Monoclonal Antibodies

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<th>Impact on Pharmacokinetics</th>
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<tr>
<td>Presence of ADAs</td>
</tr>
<tr>
<td>• Decreases serum mAbs</td>
</tr>
<tr>
<td>• Threefold-increased clearance</td>
</tr>
<tr>
<td>• Worse clinical outcomes</td>
</tr>
<tr>
<td>• Reduces formation</td>
</tr>
<tr>
<td>Concomitant use of IS</td>
</tr>
<tr>
<td>• Increases serum mAbs</td>
</tr>
<tr>
<td>• Decreases mAb clearance</td>
</tr>
<tr>
<td>• Better clinical outcomes</td>
</tr>
<tr>
<td>High baseline TNF-α</td>
</tr>
<tr>
<td>• May decrease mAbs by increasing clearance</td>
</tr>
<tr>
<td>Low albumin</td>
</tr>
<tr>
<td>• Increases clearance</td>
</tr>
<tr>
<td>• Worse clinical outcomes</td>
</tr>
<tr>
<td>High baseline CRP</td>
</tr>
<tr>
<td>• Increases clearance</td>
</tr>
<tr>
<td>Body size</td>
</tr>
<tr>
<td>• High BMI may increase clearance</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>• Males have higher clearance</td>
</tr>
</tbody>
</table>


mAB, monoclonal antibody; ADA, antidrug antibody
The Challenge of Immunogenicity

- All biologic therapies, regardless of humanization, induce immunogenicity
- Immunogenicity may result in hypersensitivity reactions and loss of response to therapy
  - Subtherapeutic drug concentrations lead to lack of efficacy
- Methods to reduce immunogenicity:
  - Maintenance therapy with drug
  - Loading dose of drug
  - Concomitant immune-modulatory therapy
- Emerging:
  - Appreciation for distinction between low titer and high titer antibodies
  - Treatment to overcome low titer antibodies.

### Immunogenicity of TNF Antagonists with and without Concomitant Immune Modulators (IMS) in CD

<table>
<thead>
<tr>
<th></th>
<th>Episodic Maintenance</th>
<th>Scheduled Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMS-</td>
<td>IMS+</td>
</tr>
<tr>
<td>Infliximab¹ (CD 5 mg/kg) (CD 10 mg/kg)</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>Certolizumab² (PRECISE I)</td>
<td>No data</td>
<td>10%</td>
</tr>
<tr>
<td>Certolizumab³ (PRECISE II)</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>Adalimumab⁴ (CLASSIC II)</td>
<td>No data</td>
<td>4%</td>
</tr>
</tbody>
</table>

Immunogenicity of TNF Antagonists with and without Concomitant Immune Modulators (IMS) in CD

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</tr>
</tbody>
</table>
| **Infliximab**
(CD 5 mg/kg) (CD 10 mg/kg)  | 38%  |   16% | 11%  | 7% |
| **Certolizumab**
(PRECISE I) | No data | 10% | No data | 4% |
| **Certolizumab**
(PRECISE II) | 24% | 8% | 12% | 2% |
| **Adalimumab**
(CLASSIC II) | No data | 4% | No data | 0% |


Who is at risk for anti-drug antibodies?

- The patient receiving episodic therapy
  - Intentional
  - Unintentional: break in therapy due to coverage issues or complication
- “Pseudo-episodic therapy”
  - Sub-therapeutic serum drug levels
  - The patient with drug clearance between doses
- The patient who developed anti-drug antibodies previously

1Vermeire S et al. Gut 2007;56(9);1226.
Switching to Another Biologic Therapy
What to choose and when to choose it?

- Evidence only exists in one direction (infliximab first), assumption is the opposite is true
- Primary non-responder: anti-TNFα loading dose with no response:
  - Where is the drug going?
  - Try a different mechanism (not a different anti-TNF therapy!)
- Primary responder now relapsing
  - Assess for inflammation
  - If suspect immunogenicity, switching to second anti-TNF is reasonable1-3
  - If not immunogenicity, consider a different mechanism of treatment

3. Rutgeerts Pi, et al. DDW 2008: #494

Interpretation of Infliximab Levels and Antibodies to Infliximab in a Patient Losing Response

<table>
<thead>
<tr>
<th>Infliximab Level</th>
<th>Antibodies to Infliximab</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated</td>
<td>Absent</td>
<td>Switch treatment mechanism</td>
</tr>
<tr>
<td>Elevated</td>
<td>Present</td>
<td>Unclear, consider switching to another TNF-inhibitor</td>
</tr>
<tr>
<td>Not elevated</td>
<td>Absent</td>
<td>Adjust dose, interval of infliximab</td>
</tr>
<tr>
<td>Not elevated</td>
<td>Present</td>
<td>Switch to another TNF-inhibitor</td>
</tr>
</tbody>
</table>

Switching Between TNF Inhibitors: Rheumatoid Arthritis Experience

- Response to a second inhibitor is lower relative to first \(^1\)

- Response to a second inhibitor will be comparable if initial discontinuation was due to adverse events \(^1, 2\)

- Patients who do not respond to 2 TNF inhibitors are not likely to respond to a third \(^2\)

1. Gomez-Reino et al. Arthritis Research & Therapy 2006;8:R29

Secondary Loss of Response to anti-TNF: Attenuation

The graph illustrates the activity of disease over time, showing cycles of remission and exacerbation with doses of anti-TNF and subsequent dose adjustments.
Secondary Loss of Response to anti-TNF: Relapse/Other Causes

Can we assess loss of response to anti-TNF more accurately?

- Update on Therapeutic Monitoring
Clinical utility of measuring IFX and ATI levels in patients with IBD

Clinical outcomes in patients with detectable ATI (n=35)*

<table>
<thead>
<tr>
<th>Complete / partial response (%)</th>
<th>Anti-TNF changed (11/12)</th>
<th>Infliximab increased (1/6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>92</td>
<td>17</td>
</tr>
</tbody>
</table>

P<0.004

Clinical outcomes in patients with sub-therapeutic concentrations (n=69)*

<table>
<thead>
<tr>
<th>Complete / partial response (%)</th>
<th>Anti-TNF changed (2/6)</th>
<th>Infliximab increased (25/29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40</td>
<td>86</td>
</tr>
</tbody>
</table>

P<0.016

* 6 discontinued IFX, 3 continued same dose 3, 3 proceeded to surgery, 5 patients could not be assessed

* 10 continued same dose, 9 discontinued IFX, 8 proceeded to surgery and 7 patients could not be assessed


Factors contributing to primary non-response or loss of response to TNF inhibitors

- No inflammation (IBS)
- Wrong endpoint
  - Structural damage, i.e. stricture
  - Bile-salt diarrhea, bacterial overgrowth, B12 deficient
  - Celiac disease
- Mechanism of inflammation not TNF dependent
  - Normal CRP (1)
  - pANCA positive? (2,3)
- Polymorphism in IgG Fc receptor IIIa (4)
- Smoking (5)
Poor Correlation Between Symptoms and Objective Markers of Inflammation

- Prospective follow-up of 188 patients enrolled in SONIC trial, with assessment of endoscopic activity at baseline and 26 weeks

<table>
<thead>
<tr>
<th></th>
<th>‘Clinical Remission’ (CDAI &lt;150, n= 136)</th>
<th>‘Moderate-Severely Active CD’ (CDAI ≥220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Mucosal Healing</td>
<td>56.9%</td>
<td>29.6%</td>
</tr>
<tr>
<td>CRP Normalization</td>
<td>64.7%</td>
<td>48.2%</td>
</tr>
<tr>
<td>Both, Complete Mucosal</td>
<td>39.7%</td>
<td>22.9%</td>
</tr>
<tr>
<td>Healing and CRP Normalization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Almost half the patients believed to be in clinical remission (asymptomatic) have active endoscopic disease
- Almost a third of patients believed to have symptoms due to CD, are in endoscopic remission

Therapeutic Drug Monitoring of Infliximab (IFX) Predicts Mucosal Healing Following Dose Intensification in IBD

- Enrolled 52 IBD patients (34 CD and 18 UC) with secondary failure to IFX. Dose escalation to 10mg/kg in all.
- IFX trough, ATI, CRP, and calprotectin measured before dose optimization and at Week 8
- Endpoint – Mucosal healing at Week 8
- Conclusion: The change in infliximab trough levels after dose intensification (delta IFX) predicts mucosal healing in IBD patients.

Non-Anti-TNF Mechanisms of Management for the Patient Failing anti-TNF Therapy

Confirm Inflammation First

- Natalizumab
- Methotrexate
- Surgery
  - Including staged approaches or diversion for induction of remission
- Bowel rest

- Less evidence:
  - Mycophenolate
  - Tacrolimus

Don’t Forget about Clinical Trials!

Leukocyte Trafficking Inhibition

Brain
Bone marrow

Gut

Integrins

Camels

Addressins

Endothelium

Leukocyte

Langerhans cell

Vascular endothelium

Vascular components

Vascular inflammation

Natalizumab

Vedolizumab, rhuMab-beta7

PF-00547659

MadCAM-1

VCAM-1

Supplemental materials

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Updated Utilization and Safety Results of Natalizumab in CD and MS
(TOUCH, CD INFORM, TYGRIS & Pregnancy Registry Studies)

- 118,100 patients have received globally (post-marketing) as of 6/30/2013
  - Predominantly MS patients

- PML (Progressive Multifocal Leukoencephalopathy)
  - Rare but serious – 410 cases reported globally as of 01-Oct-2013; 23% have died
  - Longer duration and prior immunosuppressant use increases risk
  - Risk for patients treated 24-36 months similar to rates seen in clinical trials
  - Limited safety data beyond 4 yrs of treatment
  - No known treatment or prevention interventions for PML

https://medinfo.elan.com (accessed 12-Dec-2013); PML Incidence according to Elan Pharmaceuticals at 04-Nov-2013.

Recommendations for JCV Antibody Testing

- Testing prior to treatment with natalizumab
  - If positive, consider retesting.
    - If confirmed, option is treatment with natalizumab for 9-12 months

- If negative, may treat with natalizumab, retest every 6 months
  - If converts to positive, stop therapy

- The benefit and safety of a drug holiday and restarting after “resetting” the exposure has not been tested in Crohn’s disease

- Vedolizumab (expected approval Q2 2014) does not have PML associated with it.
What to do when the patient loses response to anti-TNF therapy in IBD

- Optimize use in the first place: choose the right patients, treat early, monitor carefully
- Confirm inflammation
- Distinguish between primary and secondary loss of response
- Use therapeutic monitoring to assist with assessment
- Understand emerging and new therapies

What happens to the patients who receive natalizumab in the current post-TNF paradigm?

Chicago Experience

Recommendations for JCV Antibody Testing

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Vedolizumab for Crohn’s Disease
Primary Endpoints (Gemini II and III)

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>Placebo</th>
<th>VDZ Induction</th>
<th>VDZ Q8 Weeks</th>
<th>VDZ Q4 Weeks</th>
<th>P Value / 95% CIa</th>
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<td>Clinical remission at Week 6 (Gemini II)</td>
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<td>--</td>
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</tr>
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<td>Clinical remission at Week 6 in anti-TNF failures (Gemini III)</td>
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<td></td>
<td></td>
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<tr>
<td>Clinical remission at Week 52</td>
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<td>39%</td>
<td>36%</td>
<td>&lt;0.001 (&lt;0.01)</td>
</tr>
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<td>--</td>
<td>28%</td>
<td>27%</td>
<td>3.0, 27.5, 2.0, 26.9</td>
</tr>
</tbody>
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NS=not significant.
*a95% CI for difference from placebo. Although these endpoints were prespecified, P values are not provided because multiple testing adjustments were not made.

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Clinical Assessment of Disease Control

- Routine inquiry regarding stability of disease control (stable maintenance between doses)
- Strict adherence to maintenance regimen
- Ongoing laboratory assessment of clinical stability
- Increasing utilization of surrogate markers of inflammatory activity (fecal calprotectin)

Additional Approaches to the “Refractory” Crohn’s Patient

- Surgery- end ileostomy
- Temporary loop ileostomy/diversion and distal bowel rest as induction therapy
- Emerging (if you can get them):
  - Ustekinumab (does the patient have psoriasis?)
  - Vedolizumab (not available yet, but soon)
- Salvage therapies:
  - TPN and bowel rest (with or without surgery)
  - Tacrolimus/cyclosporine
  - Mycophenolate
  - Anti-mycobacterial therapy
Approach to the Refractory Crohn’s Patient

• Confirm the diagnosis of inflammation
• Confirm patient is taking current therapy
• Assess optimization of current therapy
• Consider symptom contributors like IBS, bacterial overgrowth or fibrostenosis
• Switch mechanism of therapy
• Don’t forget surgery!
• Don’t get burned more than once when it comes to anti-drug antibodies and approaches to prevent them

Vermeire S et al. Gut. 2007;56(9);1226.