Managing loss of response to immunomodulators and biologics in IBD

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Loss of response to immunomodulator is an indication for biologic therapy.
Define “Response”

- Clinical
  - CDAI?
- Inflammation
  - CRP?
- Mucosal Healing

“Loss of Response”

- Implies initial response according to whichever criteria
- Hence, Loss of Response is “loss of maintenance of response”
Key Points

- Goals of Maintenance Therapy
- Defining Maintenance of Response/Remission
- Defining Loss of Response
- Factors Associated with Loss of Response
- Assessing Loss of Response
- Impact of Combination Therapy with Immunosuppressives
- Adherence

Definition of Maintenance of Remission in IBD

- Defining “maintenance of remission”: in ideal world
  - All clinical trials agree upon the definition of remission
  - The determination of remission is made using standard, objective evaluation tools
  - All trials have standard inclusion/exclusion criteria and a standard design
- Defining “maintenance of remission”: the reality
  - The definition of “remission” varies by trial
  - Designs and patient populations vary by trial
  - Follow-up time varies by trial (from 6 months to 5+ years)

Comparing agents across trials is therefore a challenge
Defining Maintenance Treatment

• Simply: A maintenance therapy prevents “relapse”
  – In contrast to episodic therapy or re-treatment

• Levels of Maintenance
  – Maintenance of Response
  – Maintenance of Clinical (or Post-operative) Remission
    • Maintenance of Steroid-free remission
  – Maintenance of Mucosal Healing
  – Disease Modification
  – Prevention of Hospitalizations/Surgery

Inherent Nature of IBD

• Natural history is relapse for majority of patients after
  – Induction therapy in CD or UC or
  – Surgical resection (Crohn’s disease)
Maintenance Therapy with Biologics

• Relapse=Loss of Response (LOR)
  – Pertains to primary end-point
    • Remission, response, etc.

• Considerations regarding biologics
  – Is dose change a LOR?
  – Immunogenicity
  – Serum Levels
  – Role of concomitant medications
  – Long-term combination vs. mono-therapy
  – Adherence

Relapse is Anticipated after Biologic Induction without Maintenance Therapy
Re-Treatment Benefit With Infliximab

Clinical response defined as a ≥ 70-point decrease in CDAI score from baseline.

* Patients responding to an initial infusion.


Even with Maintenance Therapy LOR is Common
ACCENT I: Infliximab Maintenance in CD*

Infliximab groups vs. placebo: \( P < .0001 \)

- Placebo
- Infliximab 5 mg/kg q 8 wk
- Infliximab 10 mg/kg q 8 wk

*Among 335 patients responding at Week 2


CHARM
Kaplan-Meier analysis of time in steroid-free remission

PRECiSE 3: Remission rates over 3.5 years of continuous Certolizumab pegol exposure

Remission defined as HBI ≤ 4

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>1 yr*</th>
<th>1.5 yrs*</th>
<th>2.5 yrs*</th>
<th>3.5 yrs*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>74.3%</td>
<td>61%</td>
<td>41%</td>
<td>36.2%</td>
</tr>
<tr>
<td>78/105</td>
<td>64/105</td>
<td>43/105</td>
<td>38/105</td>
<td></td>
</tr>
</tbody>
</table>

*from start of P2

Lichtenstein et al, ACG 2009, Abstract 716

ACT 1 and ACT 2: Maintenance of Clinical Remission in Ulcerative Colitis

N=364 in each trial

Comparing ACCENT I, CHARM, and PRECiSE 2 Results

Factors Associated with Loss of Response

- Serum Levels
  - Recovery with increased doses/decreased frequency
- Immunogenicity
  - Immunogenicity is associated with decreased serum levels
- Loss of Mechanism
- Duration of Disease
- Prior Anti-TNF therapy
Adalimumab Dose Intensification in Crohn's Disease: A Systematic Review

- 39 studies
- Loss of response for Primary responders 18.2%
  - Annual risk was 20.3% per patient-year
- 37% Primary responders required dose increase
  - Annual risk was 24.8% per patient-year.
- Pooled analysis showed dose escalation permitted
  - Response to be regained in 71.4%
  - Remission in 39.9%


Predictors for Adalimumab Loss of Response and Dose Escalation

- **Demographic characteristics**
  - Male
  - Current/former smoker
  - Family history of IBD

- **Disease characteristics**
  - Isolated colonic CD
  - Extra-intestinal manifestations
  - Non-stricturing phenotype
  - Longer disease duration
  - Greater baseline CDAI

- **Previous therapy**
  - Anti-TNF-non-naive
  - Previous infliximab non-response

- **Concomitant therapy**
  - Corticosteroid use

- **Adalimumab therapy**
  - 80/40 mg Induction therapy
  - Low serum trough concentration
  - No deep remission at week 12

Immunogenicity of TNF Antagonists

Patients With Detectable Antibodies to a TNF Antagonist

<table>
<thead>
<tr>
<th>Patients, %</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)</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>Infliximab¹ (CD 10 mg/kg)</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Infliximab² (UC 5 mg/kg)</td>
<td>No data</td>
<td>19%</td>
</tr>
<tr>
<td>Infliximab² (UC 10 mg/kg)</td>
<td>No data</td>
<td>9%</td>
</tr>
<tr>
<td>Certolizumab³ (PRECISE I)</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Certolizumab⁴ (PRECISE II)</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>Adalimumab⁵ (RA, all doses)</td>
<td>No data</td>
<td>12%</td>
</tr>
<tr>
<td>Adalimumab⁵ (CLASSIC II)</td>
<td>No data</td>
<td>4%</td>
</tr>
</tbody>
</table>

IMS = immunosuppressant.


Influence of Immunogenicity on long-term efficacy of infliximab in Crohn’s disease

- 125 consecutive refractory CD patients
- On-demand / episodic IFX treatment, mean 3.9 infusions (range 1–17)
- ATI in 61% patients
- Relative risk of infusion reaction with higher ATI titer: 2.4 (95% CI 1.65–3.66; p<0.001)

Antibodies to Infliximab are Reduced by Immunomodulators during Episodic Therapy

\[ P < 0.01 \]

\[ 43\% \] \quad \[ 75\% \]

Taking Immunomodulators \( n=56 \)
Not Taking Immunomodulators \( n=69 \)

ACCENT I: Antibodies to Infliximab Reduced by Induction & Maintenance

\[ 38 \] \quad \[ 11 \] \quad \[ 8 \]

Episodic Strategy Maintenance q 8 wk Maintenance q 8 wk

No immunomodulators

ACCENT I: Antibodies to Infliximab Reduced Further by Induction & Maintenance + Immunomodulator Therapy

SONIC: Immunogenicity Results at Week 30*
SONIC: Clinical Remission at Week 26 Without Corticosteroids by Immunogenicity

*IFX and IFX+AZA patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis.

Adalimumab Immunogenicity Reduced by Induction/Maintenance & Immunomodulator

- Rates in RA trials
  - Overall: 5%
  - (-) methotrexate: 12%
  - (+) methotrexate: 1%

- Rates in CD trials
  - CLASSIC I²: 2 of 299 (0.7%)
  - GAIN7: 0 of 325 patients (0%)
  - Induction + Maintenance
    - CLASSIC II randomized3-5: 2 of 54 patients (3.7%)
    - CLASSIC II open-label3-5: 6 of 215 patients (2.8%)
    - CHARM6: not measured

Factors Associated with Immunogenicity

- Low-Dose Induction
- Episodic Therapy
- No Concomitant Immunosuppressive

Impact of Trough Levels
SONIC: Infliximab Trough Levels at Week 30*

- Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis.


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High Infliximab Levels are Associated with Mucosal Healing in Crohn’s Disease

- Serum samples in 210 CD patients undergoing treatment with infliximab
- Infliximab trough levels were correlated with endoscopic healing (complete, partial or none)

Van Moerkercke W. et al. DDW 2010. Abs #405
SONIC: Clinical Remission Without Corticosteroids by Trough IFX Concentration at Week 26

Primary Endpoint

<table>
<thead>
<tr>
<th>IFX Concentration (µg/ml) at Week 30</th>
<th>Proportion of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19/32</td>
</tr>
<tr>
<td>&gt;0-1</td>
<td>13/23</td>
</tr>
<tr>
<td>&gt;1-3</td>
<td>43/69</td>
</tr>
<tr>
<td>&gt;3-6</td>
<td>36/49</td>
</tr>
<tr>
<td>&gt;6</td>
<td>31/43</td>
</tr>
</tbody>
</table>

* IFX and IFX+AZA patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis.


Recovery with Increased Dose or Decreased Dosing Interval
Dosing with Certolizumab 200 mg q 2 Wks Provides Higher Plasma Trough Concentrations than 400 mg Every 4 Weeks

- PK modeling shows that certolizumab pegol dosed as 200 mg Q2weeks may result in higher trough plasma concentrations than 400 mg Q4

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapeutic area</th>
<th>Predicted concentration via Pharmacokinetic (CD POPPK) model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimzia Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRECISE 1 (n = 98)</td>
<td>Crohn’s disease</td>
<td>200 mg Q2W: 16.5, 400 mg Q4W: 10.0</td>
</tr>
<tr>
<td>PRECISE 2 (n = 81)</td>
<td>Crohn’s disease</td>
<td>--</td>
</tr>
<tr>
<td>Study 005 (n = 54)</td>
<td>Crohn’s disease</td>
<td>--</td>
</tr>
<tr>
<td>RAPID 1 (n = 329)</td>
<td>Rheumatoid arthritis</td>
<td>200 mg Q2W: 17.4, 400 mg Q4W: --</td>
</tr>
<tr>
<td>RAPID 2 (n = 229)</td>
<td>Rheumatoid arthritis</td>
<td>200 mg Q2W: 15.7, 400 mg Q4W: --</td>
</tr>
</tbody>
</table>

- CD patients may benefit from certolizumab pegol 200 mg Q2W
- 65% higher plasma trough concentrations in RA patients with 200 mg q2wks compared with certolizumab pegol 400 mg Q4W treatment in CD patients

Lacroix et al. DDW 2010, S1029
Interactions Between Antibodies and Serum Levels

Antibodies to Infliximab shorten Duration of Response

Clinical Outcomes and Duration of Response in Infliximab-Treated Patients Differ by ATI Status

- **ATI negative (n = 28)**
- **ATI positive (n = 16)**

<table>
<thead>
<tr>
<th>Complete Response Achieved</th>
<th>Mean Duration of Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients</td>
<td>Days</td>
</tr>
<tr>
<td>ATI negative</td>
<td>70</td>
</tr>
<tr>
<td>ATI positive</td>
<td>0</td>
</tr>
</tbody>
</table>

*Farrell RJ et al. Gastroenterology. 2003;124:917-924*

ATI Levels for Discriminating Response Types in Infliximab Treated Crohn’s Patients

- **Patients with CD on maintenance IFX treatment**
- **Patients who maintained response (n = 48)**
  - had higher mean serum trough IFX (2.4mcg/mL)
  - than those with secondary loss of response (n = 24) (0mcg/mL) and
  - had lower antibodies to infliximab (ATI) (0U/mL vs. 34 U/mL) levels.
- **Primary non-responders (n = 15) had undetectable ATI levels and higher s-IFX than the other groups.**

*Steenholdt C et al. DDW 2010. Abs #W1270*
Anti-TNF Therapy for CD: Dose Escalation and Early Discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Infliximab (n=199)</th>
<th>Adalimumab (n=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean disease duration</td>
<td>10.9 yrs</td>
<td>15 yrs</td>
</tr>
<tr>
<td>% on combined IS</td>
<td>64%</td>
<td>93%</td>
</tr>
<tr>
<td>1st anti-TNF used</td>
<td>--</td>
<td>37.5%</td>
</tr>
<tr>
<td>Required dose escalation</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td>Required dose escalation by 1 yr</td>
<td>14%</td>
<td>32%</td>
</tr>
<tr>
<td>Predictors for dose escalation</td>
<td>↓ by longer disease duration</td>
<td>↓ by stricturing phenotype; ↑ by prior anti-TNF exposure</td>
</tr>
<tr>
<td>Stopped therapy by 1 yr*</td>
<td>29%</td>
<td>13%</td>
</tr>
<tr>
<td>Reasons for stopping therapy</td>
<td>Treatment failure, ADRs/drug allergy</td>
<td>Treatment failure, ADRs/drug allergy</td>
</tr>
</tbody>
</table>

*Patients on combined IS therapy were less likely to stop therapy at 1 yr.

Loss of Response to Adalimumab Dose Increase – CHARM Study

27 % over 1 year

Approximately half of these maintain benefit and continue at the increased dose

Colombel JF et al. Gastroenterology. 2007;132:52
EMEA website
WELCOME: Regain of response after switch to open label from time of switch

Cumulative number of patients regaining response through Week 26 = 66


Trough Levels of Infliximab May Be a Better Predictor of Continued Response Than ATI

Clinical Utility of Measuring Serum Infliximab and Human Anti-Chimeric Antibody Levels in IBD Patients

- Chart review of 151 IBD patients who underwent IFX level and HACA status
- Indications for testing were:
  - Loss of response: 50%
  - Partial response after initiation: 23%
  - Possible autoimmune/delayed hypersensitivity reaction: 15%
- Median time to initial testing was 50 wks

<table>
<thead>
<tr>
<th>Results</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HACAs identified</td>
<td>23%</td>
</tr>
<tr>
<td>Therapeutic IFX levels</td>
<td>33%</td>
</tr>
<tr>
<td>Patients in whom test results impacted treatment</td>
<td>73%</td>
</tr>
<tr>
<td>If positive HACA, % having complete or partial response with:</td>
<td></td>
</tr>
<tr>
<td>- Change to another anti-TNF</td>
<td>92%</td>
</tr>
<tr>
<td>- Increasing dose</td>
<td>17%</td>
</tr>
<tr>
<td>If sub-therapeutic levels, % having complete or partial response with:</td>
<td></td>
</tr>
<tr>
<td>- Change to another anti-TNF</td>
<td>40%</td>
</tr>
<tr>
<td>- Increasing dose</td>
<td>86%</td>
</tr>
</tbody>
</table>

Afif, W., E. V. Loftus, Jr., et al. (2010). Am J Gastroenterol

Efficacy of 3rd anti-TNF monoclonal antibody in CD after failure of two others

Patients:
- CD patients (n=67) who received ADA or CZP as 3rd anti-TNF after loss of response and/or intolerance to 2 prior anti-TNF

Methods:
- Clinical response assessed by questionnaire at Weeks 6 and 20 (HBI or benefit appreciated by clinician)
- 1st drug exposure:
  - IFX (n=65)
  - ADA (n=1)
  - CZP (n=3)
- 3rd drug exposure:
  - ADA (n=27)
  - CZP (n=40)

Results:
- In responders at Week 6, probability to be on treatment at 6 months is 80%

Allez M, et al. DDW 2008: #W1244
Crohn's Disease: Infliximab Trough Levels and CRP During Infliximab-Immunomodulator Combination Treatment Are Associated With Clinical Outcome After Immunomodulator Withdrawal

Drobne D et al. DDW 2011
Abstract 279

Design

- **Objective**
  - To study the influence of immunomodulator (IMM) withdrawal on IFX trough levels and to identify predictors of disease flare and loss of response to IFX after withdrawal of IMM

- **Patients (N=223)**
  - On IFX maintenance therapy for CD, of whom 155 were cotreated with IMMs

- **Treatments**
  - IMMs discontinued in 117 patients when durable clinical remission was achieved after >6 months of cotreatment
**Key Results**

*Loss of response after IMM withdrawal*

- TLS detectable & CRP<5
- TLS detectable & CRP>5
- TLS undetectable & CRP>5

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**Conclusions**

- Undetectable IFX trough levels and CRP>5 mg/l during IFX-IMM combination therapy are associated with an increased loss of response to IFX after IMM withdrawal
To optimize response—Patients must have active disease!

Mucosal Ulcerations
Elevated CRP/ESR

SONIC: Corticosteroid-Free Clinical Remission at Week 26 by Baseline Endoscopy Status

Absence of mucosal ulceration predicts non-response!

Assessing Loss of Response to a Biologic

- Assess for Inflammation
  - Inflammation Present
  - Consider Immunogenicity
  - No Inflammation
  - Treat underlying mechanisms

Assessing Loss of Response to Infliximab

- Antibodies to infliximab
  - (+)
    - Alternative anti-TNF
  - (-)
    - No infliximab
    - Reduce infusion interval or increase dose (10 mg/kg)
  - (-)
    - Infliximab present
    - Natalizumab
Drug Level/Antibody Assay Not Available

Assess Response to Infusion/Injection

- Short duration or Abrogated Response
  - Intensify Dose/Decrease Dosing Interval or Switch to Alternative Anti-TNF
- No Response
  - Switch to Different Class