Optimizing AntiTNF Therapy in Patients with IBD

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We’ve come a long way…
We've come a long way…


IBD is recognized

We've come a long way…


Sir Samuel Wilks - Ulcerative Colitis is Described - 1875
1932
Crohn Ginzburg and Oppenheimer describe 14 cases of Crohn's in JAMA

Prednisone
We've come a long way…


Prednisone

Mesalamine

We've come a long way…


Prednisone

Azathioprine / 6-MP

Methotrexate

Mesalamine
We’ve come a long way…


Prednisone  Azathioprine / 6-MP  Methotrexate
Mesalazine

Infliximab approved for CD- 1998
Adalimumab for CD- 2002
Certolizumab Pegol for CD -2008
Natalizumab for CD- 2008
Vedolizumab for UC & CD - 2014

Infliximab for UC- 2005 Adalimumab for UC- 2012 Golimumab for UC- 2013

What Do We Know: Guiding Principles

- Early therapy is better than late therapy especially Crohn’s disease
**Early intervention with biologics enhances efficacy: PRECiSE 2**

<table>
<thead>
<tr>
<th>CD duration (yr)</th>
<th>Patients (%)</th>
<th><strong>Certolizumab pegol 3 inj, placebo maintenance, SC</strong></th>
<th><strong>Certolizumab pegol 3 inj, 400 mg q-4weekly, SC</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>n= 210</td>
<td>36.2</td>
<td>37.1</td>
<td>89.5</td>
</tr>
<tr>
<td>215</td>
<td>62.8</td>
<td>50</td>
<td>62.2</td>
</tr>
<tr>
<td>Any</td>
<td>35</td>
<td>22</td>
<td>55</td>
</tr>
<tr>
<td>&lt;1</td>
<td>***</td>
<td>**</td>
<td>*</td>
</tr>
<tr>
<td>1–&lt;2</td>
<td>68.4</td>
<td>55</td>
<td>46.7</td>
</tr>
<tr>
<td>2–&lt;5</td>
<td>29.1</td>
<td>23.5</td>
<td>44.3</td>
</tr>
<tr>
<td>≥5</td>
<td>55</td>
<td>45</td>
<td>98</td>
</tr>
</tbody>
</table>

*Response (≥100 pt Decrease CDAI)*

<table>
<thead>
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<th>CD duration (yr)</th>
<th>Patients (%)</th>
<th><strong>Certolizumab pegol 3 inj, placebo maintenance, SC</strong></th>
<th><strong>Certolizumab pegol 3 inj, 400 mg q-4weekly, SC</strong></th>
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<td>n= 210</td>
<td>28.6</td>
<td>37.1</td>
<td>68.4</td>
</tr>
<tr>
<td>215</td>
<td>47.9</td>
<td>50</td>
<td>46.7</td>
</tr>
<tr>
<td>An</td>
<td>35</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>&lt;1</td>
<td>***</td>
<td>**</td>
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</tr>
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<td>1–&lt;2</td>
<td>68.4</td>
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<td>44.3</td>
</tr>
<tr>
<td>≥5</td>
<td>55</td>
<td>45</td>
<td>98</td>
</tr>
</tbody>
</table>

*Remission (CDAI ≤150)*

**Sandborn et al, NEJM 2007**

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**CHARM: Adalimumab in early Crohn’s disease**

<table>
<thead>
<tr>
<th>Disease duration</th>
<th>Patients in remission CDAI &lt;150 (%)</th>
<th><strong>Placebo (n=170)</strong></th>
<th><strong>Adalimumab 40 mg q-weekly SC (n=157)</strong></th>
<th><strong>Adalimimab 40 mg EOW SC (n=172)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 26</td>
<td></td>
<td>17</td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 to &lt;5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 56</td>
<td></td>
<td>17</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 to &lt;5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Preliminary Data Schreiber et al, Gastroenterology 2007; 132: A147 (Abstract 985)*

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* *p<0.001  **p<0.01  *p<0.05
What Do We Know: Guiding Principles

- Treat Often
  Maintenance versus Episodic

ATI Formation Is Higher When Treatment Is Episodic vs Scheduled

Incidence of ATI According to Treatment Regimen

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Incidence of ATI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance</td>
<td>8.0</td>
</tr>
<tr>
<td>Episodic</td>
<td>30.0</td>
</tr>
<tr>
<td>Maintenance</td>
<td>16.0</td>
</tr>
<tr>
<td>Episodic</td>
<td>39.0</td>
</tr>
</tbody>
</table>

*The incidence of ATI was measured at week 72 in the ACCENT 1 subanalysis.

Maintenance Infliximab Decreases Long-term Need for Bowel Surgery


What Do We Know: Guiding Principles

- Try to Achieve Mucosal Healing
Early Aggressive Biologic Therapy versus Conventional Management of Crohn’s Disease

Newly diagnosed* - AntiTNF, Antimetabolite and Steroid Naive Crohn’s disease (n=133)

Early Aggressive (n=67)
- IFX (0/2/6) + AZA
- MTX

Conventional Therapy (n=66)
- Steroids
- IFX + AZA

*within 4 years  

STEP UP - "Conventional"

TOP DOWN

Glucocorticosteroids

Antimetabolites

Infliximab

Remission: CDAI <150 & No Corticosteroid Therapy

<table>
<thead>
<tr>
<th>Week 14</th>
<th>Week 26</th>
<th>Week 52</th>
<th>Week 78</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>P=0.001</td>
<td>P=0.006</td>
<td>P=0.03</td>
<td>P=0.80</td>
<td>P=0.43</td>
</tr>
</tbody>
</table>


Complete Ulcer Disappearance

<table>
<thead>
<tr>
<th>Early Aggressive (AZA + IFX)</th>
<th>Step Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>73%</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Early Aggressive Therapy**

**Mucosal Healing Predicts Sustained Clinical Remission In Early Crohn’s Disease**

![Graph showing mucosal healing and remission rates](image)

* *p<0.05; **p<0.01 (Fisher’s exact)

**EXTEND:** patients with Crohn’s disease who achieved deep remission* with adalimumab at Week 12 and hospitalization rates

<table>
<thead>
<tr>
<th>All-cause hospitalization through Week 52</th>
<th>CD-related hospitalization through Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep remission* (Week 12)</td>
<td>Deep remission* (Week 12)</td>
</tr>
<tr>
<td>0/11</td>
<td>0/11</td>
</tr>
<tr>
<td>Non-deep remission* (Week 12)</td>
<td>Non-deep remission* (Week 12)</td>
</tr>
<tr>
<td>9/53</td>
<td>5/53</td>
</tr>
</tbody>
</table>

* Deep remission defined as clinical remission (CDAI <150) and complete mucosal healing in EXTEND
  CD: Crohn’s disease; CDAI: Crohn’s disease activity index

What Do We Know: Guiding Principles

- Is Monotherapy with Biologics Adequate or is Combination therapy with an Immunomodulator necessary?

What Do We Know: Guiding Principles

- The Concern
  SAFETY OF COMBINATION THERAPY
### Meta Analysis: Lymphoma with Anti-TNF Use

- 8905 patients representing 20,602 patient-years
- 13 non-Hodgkin lymphomas (mean age 52, 62% male)
- 10/13 exposed to immunomodulator (IM)*
- ½ died as a result of non-Hodgkin lymphomas (NHL)

<table>
<thead>
<tr>
<th>Group</th>
<th>NHL rate per 10,000</th>
<th>IRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEER all ages</td>
<td>1.9</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>IM alone</td>
<td>3.6</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Anti-TNF vs SEER</td>
<td>6.1</td>
<td>3.23</td>
<td>1.5–6.9</td>
</tr>
<tr>
<td>Anti-TNF vs IM alone</td>
<td>6.1</td>
<td>1.7</td>
<td>0.5–7.1</td>
</tr>
</tbody>
</table>

*Not reported in 2


### Incidence Rates of LD According to Thiopurine Exposure Grouped by Age at Entry in Cohort

- **<50 years**
  - Continuing: 0.37 per 1000 patient-years
  - Discontinued: 0
  - Never received: 0

- **50 - 65 years**
  - Continuing: 0
  - Discontinued: 0.66
  - Never received: 0.40

- **>65 years**
  - Continuing: 5.41
  - Discontinued: 1.88
  - Never received: 1.68

Risk of Lymphoma in Patients with Inflammatory Bowel Disease Treated with Azathioprine and 6-Mercaptopurine: a Meta-Analysis

- 18 studies (among 4383 citations) met inclusion criteria.
- The SIR for lymphoma was
  - Overall- 4.49 (95% CI, 2.81–7.17),
  - 2.43 (95% CI, 1.50–3.92) in 8 population studies
  - 9.16 (95% CI, 5.03–16.7) in 10 referral studies.
- Population studies demonstrated an
  - Increased risk among current users (SIR=5.71; 95% CI, 3.72–10.1) but
  - No increased risk in former users (SIR=1.42; 95% CI, 0.86–2.34).


Risk of Lymphoma in Patients with Inflammatory Bowel Disease Treated with Azathioprine and 6-Mercaptopurine: a Meta-Analysis

- Sex
  - Men have a greater risk than women (RR=2.05; P<.05)
  - Both sexes were at increased risk for lymphoma
  - Men: SIR for men = 3.60 (95% CI, 2.68–4.83)
  - Women: SIR for women = 1.76 (95% CI, 1.08–2.87)

- Age
  - Patients < 30 years had the highest RR
    - SIR=6.99; CI, 2.99–16.4
  - Younger men had the highest risk
  - The absolute risk was highest in patients > 50 years
    1:377 cases per patient–year

Could it improve the safety of infliximab?

SONIC
Azathioprine + IFX Combination Therapy

Patients (%)

Infusion reactions
Antibodies to IFX
Serious infection


What Do We Know: Guiding Principles

- The Benefit of Concomitant Immunomodulator with anti-TNF Therapy
ATI Formation Is Lower in Patients on Concomitant IM Therapy

ACCENT 1 Subanalysis
Percent ATI(+) Patients According to Treatment Regimen

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>ATI(+) Patients (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No immunomodulators</td>
<td>38</td>
<td>0.003</td>
</tr>
<tr>
<td>With immunomodulators</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Episodic strategy</td>
<td>11</td>
<td>0.42</td>
</tr>
<tr>
<td>5 mg/kg Maintenance</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg Maintenance</td>
<td>8</td>
<td>0.42</td>
</tr>
</tbody>
</table>


SONIC
IFX 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

<table>
<thead>
<tr>
<th>IFX Trough Levels (μg/ml)</th>
<th>IFX + placebo</th>
<th>IFX + AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med (n=97)</td>
<td>1.6</td>
<td>3.5</td>
</tr>
<tr>
<td>(n=109)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In Patients Failing Immunomodulator Therapy: Concomitant Immunomodulator Use Does not Impact Outcome (Clinical Remission) of Maintenance IFX in CD

![Bar chart showing clinical remission outcomes for patients with and without concomitant immunomodulator use.](chart1.png)

*Clinical response: ACT III = decrease in Mayo score (≥30%, and ≥3 points) and a decrease in rectal bleeding score (≥1 or a score of 0 or 1 at Week 8); ACCENT I = improvement of ≤70 points in CDAI score and 22% improvement in CDAI score.*


CHARM: Effect of concomitant Immunosuppressant Use on Remission at Weeks 26 and 52 Responders

![Bar charts showing patients in remission for different treatment groups at Weeks 26 and 52.](chart2.png)

There was no significant difference between the response of patients receiving concomitant immunosuppressants vs those who were not at either dose of adalimumab and at either time point (Breslow-Day Test).

IMM = immunomodulator

But Wait.............
It’s Different in Early Disease

SONIC

Patient Population

• Subjects 21 years of age or older with:
  – Moderate-to-Severe Crohn’s disease (CD)
    • CDAI ≥220 and ≤450
  – No prior exposure to biologic agents or immunomodulators
  – Normal thiopurine methyltransferase (TPMT)

**SONIC Study Design**

**Randomization of patients**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine 2.5 mg/kg + placebo infusions</td>
<td>Week 0*, 2, 6, 10, 14, 18, 22, 26*, 30, 34, 38, 42, 46, 50, 54</td>
</tr>
<tr>
<td>Infliximab 5 mg/kg + placebo capsules</td>
<td></td>
</tr>
<tr>
<td>Infliximab 5 mg/kg + Azathioprine 2.5 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

**Primary Endpoint (Corticosteroid-free Remission at Week 26)**

**Secondary Endpoint (Week 50)**

*Endoscopy performed at Weeks 0 & 26*

**SONIC Clinical Remission Without Corticosteroids at Week 26**

**Primary Endpoint**

![Graph showing clinical remission](image)

Mucosal Healing at Week 26


UC SUCCESS

- Moderate-to-severe UC (Mayo score ≥6)
- Failing corticosteroids
- No prior exposure to biologic agents; no current immunomodulators

AZA 2.5mg/kg
IFX 5mg/kg
IFX + AZA

- 1° endpoint: Steroid-free remission at week 16 (total Mayo score ≤2)

UC SUCCESS study

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>IFX+AZA (n=78)</th>
<th>IFX (n=77)</th>
<th>AZA (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid-free remission</td>
<td><em>40</em></td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Response</td>
<td>77</td>
<td>69</td>
<td>50</td>
</tr>
<tr>
<td>Mucosal Healing</td>
<td>63</td>
<td>55</td>
<td>37</td>
</tr>
</tbody>
</table>

*P*.05 compared to IFX; #P*.05 compared to AZA


What Do We Know: Guiding Principles

- **The Benefit of Concomitant Immunomodulator Use with anti-TNF Therapy**
  - Higher Drug Levels
  - Fewer Acute AE’s
    - Infusion Reactions
    - Serious Infections
  - Better Efficacy
What Do We Know: Guiding Principles

Treat Patients With Active Disease

SONIC: Infliximab in Active CD (Naïve) Corticosteroid-Free Clinical Remission at Week 26 by Baseline Endoscopy Status

<table>
<thead>
<tr>
<th>Proportion of Patients (%)</th>
<th>Lesions (n=325)</th>
<th>No Lesions (n=93)</th>
<th>No Endoscopy or UTD* (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33/115</td>
<td>40.7</td>
<td>21.4</td>
</tr>
<tr>
<td></td>
<td>50/99</td>
<td>33.3</td>
<td>13/34</td>
</tr>
<tr>
<td></td>
<td>61.3</td>
<td>40.0</td>
<td>38.2</td>
</tr>
<tr>
<td></td>
<td>11/27</td>
<td>12/36</td>
<td>6/28</td>
</tr>
<tr>
<td></td>
<td>50.5</td>
<td>57.1</td>
<td>57.1</td>
</tr>
</tbody>
</table>

AZA = azathioprine; IFX = infliximab. *Unable to determine.
What Do We Know: Guiding Principles

Assessing and Managing Loss of Response to TNF Inhibitors

Defining Primary and Secondary Failure
Assessing Loss of Response to a Biologic

- Assess for inflammation

  - Inflammation present
    - Consider immunogenicity
  - No inflammation
    - Treat underlying mechanisms

Loss of Response

Dose Escalation or Rescue?
PRECISE 4: Re-induction of Certolizumab Pegol in Patients Losing Initial Response After Induction

- Week 4: 57% Response, 29% Remission
- Week 24: 43% Response, 35% Remission
- Week 52: 39% Response, 35% Remission

One re-induction only allowed


CHARM: Benefit of Weekly Dosing with Adalimumab for Flare

- At any time for all patients who moved to weekly dosing (n=71): 37% Response, 58% Remission
- At week 56 for patients who completed the study (n=36): 47% Response, 69% Remission

78% Remission

Loss of Response

Switching to Another Agent

GAIN: Clinical Response and Remission to Adalimumab - Week 4
In Patients with Moderate to Severe CD and Secondary Failure to Infliximab

- Placebo
- Adalimumab 160/80 mg EOW, SC

Patients, %

- Response (CR70)
- Response (CR100)
- Remission CDAI <150

n= 166 159 166 159 166 159

***p<0.001, **p<0.01, both vs placebo
Full analysis population

Optimizing AntiTNF Therapy

Approaches

• Treat Early Disease
  – But, not in all patients: attempt to prognosticate - fistula, early steroid users, smokers, severe endoscopic lesions, age < 40, high risk anatomy - rectum, foregut, extensive disease.

• Treat Actual Active Disease

• Benefit of Concomitant Immunomodulator Use with anti-TNF Therapy
  • Higher Drug Levels
  • Fewer Acute AE's
    ▪ Infusion Reactions
    ▪ Serious Infections
  • Better Efficacy

• Evaluate Secondary Nonresponse
  • CMV, C. diff, Fibrotic Stricture, Fistula...
  • Dose Escalation
  • Switch Drug Mechanisms

Elevating Infliximab Concentration From Subtherapeutic Levels Is Effective in Regaining Response in ATI (-) Patients

<table>
<thead>
<tr>
<th>Clinical Outcomes of Patients with Detectable Antibodies to Infliximab or Subtherapeutic Infliximab Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response to Test</strong></td>
</tr>
<tr>
<td>Detectable ATI</td>
</tr>
<tr>
<td>Change anti-TNF</td>
</tr>
<tr>
<td>Subtherapeutic concentration</td>
</tr>
<tr>
<td>Change anti-TNF</td>
</tr>
</tbody>
</table>

HACA, human antichimeric antibody

Addition of an Immunomodulator to IFX Therapy Eliminates Antidrug Antibodies in Serum and Restores Clinical Response of Patients With IBD


Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, age</th>
<th>Disease location</th>
<th>Duration</th>
<th>Prior treatments</th>
<th>No. infusions until LOR</th>
<th>Immuno-modulator introduced</th>
<th>Subsequent course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 26</td>
<td>CD</td>
<td>8 years</td>
<td>AZA, MTX, ADA</td>
<td>5 infusions 5 mg/kg/6 wk</td>
<td>MTX</td>
<td>Clinical remission 12 months</td>
</tr>
<tr>
<td>2</td>
<td>F, 18</td>
<td>CD</td>
<td>3 years</td>
<td>AZA, MTX</td>
<td>7 infusions 5 mg/kg/4 wk</td>
<td>6-MP</td>
<td>Clinical remission 10 months</td>
</tr>
<tr>
<td>3</td>
<td>M, 22</td>
<td>CD</td>
<td>2 years</td>
<td>None</td>
<td>14 infusions 5 mg/kg/4 wk</td>
<td>AZA</td>
<td>Clinical response 8 months</td>
</tr>
<tr>
<td>4</td>
<td>M, 37</td>
<td>UC Left-sided</td>
<td>2 years</td>
<td>AZA</td>
<td>9 infusions 5mg/kg/6 wk</td>
<td>AZA</td>
<td>Clinical remission 13 months</td>
</tr>
<tr>
<td>5</td>
<td>F, 34</td>
<td>UC Left-sided</td>
<td>3 years</td>
<td>AZA</td>
<td>3 infusions, induction regimen</td>
<td>MTX</td>
<td>Clinical remission 10 months</td>
</tr>
</tbody>
</table>

Concentration of IFX and ATI Levels Before and After Immunomodulator Treatment

IFX levels closed squares
ATI open squares


Factors that Influence the PK of TNF Antagonists

<table>
<thead>
<tr>
<th>Impact on TNF antagonist PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of ADAs</td>
</tr>
<tr>
<td>Decreases drug concentration</td>
</tr>
<tr>
<td>Increases clearance</td>
</tr>
<tr>
<td>Worse clinical outcomes</td>
</tr>
<tr>
<td>Concomitant use of Immunosuppressives</td>
</tr>
<tr>
<td>Reduces ADA formation</td>
</tr>
<tr>
<td>Increases drug concentration</td>
</tr>
<tr>
<td>Decreases drug clearance</td>
</tr>
<tr>
<td>Better clinical outcomes</td>
</tr>
<tr>
<td>Low serum albumin concentration</td>
</tr>
<tr>
<td>Increases drug clearance</td>
</tr>
<tr>
<td>Worse clinical outcome</td>
</tr>
<tr>
<td>High baseline CRP concentration</td>
</tr>
<tr>
<td>Increase drug clearance</td>
</tr>
<tr>
<td>High baseline TNF concentration</td>
</tr>
<tr>
<td>May decrease drug concentration by increasing clearance</td>
</tr>
<tr>
<td>High body size</td>
</tr>
<tr>
<td>May increase drug clearance</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Males have higher clearance</td>
</tr>
</tbody>
</table>

Gary R. Lichtenstein, MD, FACG

Management Algorithm for Loss of Response to Anti-TNF Agents

Loss of response to 1st anti-TNF agent

Evaluate for:
- Objective evidence of inflammation
- Exclusion of complications, such as stricture, abscess, infection

Inflammation present
- No complication

Inflammation absent
- No complication

Symptomatic therapy for presumed irritable bowel-like symptoms

Inflammation absent
- Complication

Specific treatment for complication

1st agent = infliximab: Consider checking infliximab and antibody to infliximab levels

1st agent = adalimumab or certolizumab pegol

ATI Low
- Low serum infliximab
- Increase dose and/or decrease interval

ATI High
- Low serum infliximab
- Switch to 2nd anti-TNF

ATI Low
- Adequate serum infliximab
- Switch to 2nd anti-TNF
OR
- Switch to agent from a different class