Treating to Achieve a Target and Disease Monitoring in 2015: State of the Art

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Evolving Treatment Strategies in IBD

• Traditional:
  – “Failure” of conventional therapy (optimized? AEs?)
  – Perianal disease

• Evolving:
  – Based on prognosis (smoking, young age of diagnosis, severe endoscopic lesions)
  – As a result of treat to target
A Proposed Definition of “Optimal Use Therapies in IBD”

_The best result obtainable under specific conditions_

- The right time: not too early, not too late
- The right dose: not too much, not too little
- The right interval: no breakthrough between infusions
- The right duration: not too short, not too long?
- The right efficacy:safety: disease control, no AEs
Evolving Endpoints and Treatment Strategies
Historical Treatment Strategies are Flawed

“Step-Up”

“Dirty Therapy”

<table>
<thead>
<tr>
<th>Disease severity at presentation?</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Aminosalicylate</td>
<td>Aminosalicylate</td>
<td>Aminosalicylate</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Anti-TNF (UC)/Thiopurine/MTX (CD)</td>
<td>Anti-TNF</td>
<td>Anti-integrin</td>
</tr>
</tbody>
</table>

- Prednisone
- Budesonide-MMX
- 5-Aminosalicylates
- Methotrexate
- AZA/6-MP
- Anti-Adhesion
- Aminosalicylate (UC)/Thiopurine/MTX (CD)
- Anti-TNF
- Anti-integrin
- Corticosteroids
Problems with Existing Treatment Strategies

• Don’t accurately reflect heterogeneity of patient types.
• Require failure of one step or class before moving onto another.
• “Reactive” rather than “proactive.”
• Historically symptom-based or complication-based rather than based on objective markers.
• Imply static treatment levels and do not address changes over time.
• New therapies tend to be added to the end of the line rather than positioned earlier or more thoughtfully.
How Can We Do This Better?

- Choosing therapies based on prognosis as well as severity
- Utilizing validated objective endpoints of disease control
- Understanding therapy risk in the context of disease risk
- Adjusting therapies serially until endpoints are achieved
- Optimizing therapies to match disease severity and inflammatory burden
How Can We Do This Better?

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Movement to Objective Measures of Control and Chronic Care Model of IBD: Improved Outcomes

**Goal**
- Response
- Remission
- Deep remission

**Clinical parameters**
- Improved symptoms
  - No symptoms
  - Normal labs
- Normal endoscopy
- Mucosal healing

**Outcomes**
- Improved QoL
- Decreased hospitalization
- Avoidance of surgery
- Minimal/no disability

**SUSTAINED DISEASE CONTROL**
What is Treat to Target? Example from Rheumatology

- Shared decision-making between RA patient and doctor
- Focus on higher risk groups
- Primary goal: maximize health-related quality of life
  - Control of symptoms
  - Normalization of function and social participation
  - Prevention of progressive structural damage
- Abrogation of inflammation is the most important mean to achieve goals
- *Treatment to target by measuring disease activity and adjusting therapy accordingly optimizes outcomes in RA*

What Might Be the Target in IBD?

- Symptoms
- Growth and Development
- Laboratory values
- Mucosal healing
  - How to measure? (SES-CD, UCEIS)
  - What about histology?
- Surrogate markers
STRIDE: Selecting Therapeutic TaRgets in Inflammatory Bowel Disease Endpoints

• **Methods:** 28 IBD specialists developed recommendations based on a systematic literature review and expert opinion.

• **Results:** 12 recommendations for UC and CD.

• **UC TARGET:**
  – **PRO:** resolution of rectal bleeding and diarrhea/altered bowel habit *and*
  – **endoscopic remission:** Mayo endoscopic subscore of 0-1. Histological remission is an *adjunctive goal*.

• **CD TARGET:**
  – **PRO:** resolution of abdominal pain and diarrhea/altered bowel habit; *and*
  – **endoscopic remission:**
    • resolution of ulceration at ileocolonoscopy, *or*
    • resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy.

• **Biomarker remission (normal CRP and calprotectin) was considered an adjunctive target.**

Studying Treat to Target in IBD

Can it be done?
Does it work?
Retrospective Analysis of Patients Having Colonoscopy for UC: Treatment Adjustments to Achieve Targets

1. Treated to target of mucosal healing: Dose adjustments in therapy.
2. Not treated to target of mucosal healing: No change in therapy.

Prospective REACT Trial:
Algorithm based treatment with early combined immunosuppression reduced complications in Crohn’s Disease

- Center-level cluster randomisation to early combined immunosuppression algorithm (ECI) or current best practice (CM)
- 1982 patients recruited from 40 centres
- Regular clinical review every 4 or 12 weeks
- Used algorithm to treat to target
- Primary end-point: **Clinical Remission** (HBI <5 & no steroids)

**Therapeutic Algorithm for Crohn’s Disease**

Prospective REACT Trial:
Algorithm based treatment with early combined immunosuppression reduced complications in Crohn’s Disease

Conclusions:

• There was no difference in clinical remission (primary endpoint).
• There were significantly reduced rates of surgery and serious complications in the ECI group (secondary endpoints).

Hospitalization, Surgery or Serious Disease-Related Complication

HR = 0.73 (0.62, 0.86)

Using Treat to Target to Aid Patient Discussions
Getting Your Patient on Effective Therapy
Shared Decision Making

• Discuss the risk of untreated or *ineffectively treated* disease
• Agreement in goals (improved quality of life, avoidance of surgery and hospitalization, etc)
• Negotiate trial of therapy and plan of follow-up
  – Perception of risk changes with efficacy
  – Individualize risk
• Use of objective disease monitoring tools to assess and to communicate disease activity (Treat to Target)

• Negotiated follow-up (short-term) to reassess disease activity OBJECTIVELY

Monitoring: How and When?
The Five Phases of Disease Monitoring

<table>
<thead>
<tr>
<th>Phase</th>
<th>Monitoring objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>Check need for treatment</td>
</tr>
<tr>
<td></td>
<td>Establish a baseline for determining response and change</td>
</tr>
<tr>
<td>Initial titration</td>
<td>Assess individual response to treatment</td>
</tr>
<tr>
<td></td>
<td>Assess immediate adverse effects</td>
</tr>
<tr>
<td></td>
<td>Achieve control</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Detect drift from control limits</td>
</tr>
<tr>
<td></td>
<td>Detect long term harms</td>
</tr>
<tr>
<td>Re-establish control</td>
<td>Bring level back within control limits</td>
</tr>
<tr>
<td>Cessation</td>
<td>Check safety of cessation</td>
</tr>
</tbody>
</table>

In IBD, Many Faces of Monitoring
Individualized Approaches
Patients, Providers or Both

• **Pre-treatment:** what markers correlate with disease activity?
  • Scope?
  • Symptoms/PRO?
  • CRP/fecal calprotectin

• **Initial titration:**
  – what markers can be used to address or predict response to therapy?
  – Disease-related and therapy-related
    • CRP/fecal calprotectin
    • Metabolites, serum drug levels

• **Maintenance:** what markers can monitor for disease drift or relapse (and distinguish from patient-described “flare”)?
• **Cessation or de-escalation:** how to monitor for relapse or breakthrough after de-escalation
Evolution of Disease Monitoring

Fecal Calprotectin
calcium and zinc-binding protein derived from neutrophils
and monocytes

Endoscopic Activity (Modified Baron Score)

Fecal Calprotectin (µg/g)

Patient Reported Outcomes and Monitoring
The “GI Monitor”


Mesalamine Dose Escalation for Clinically Quiescent UC Decreases Fecal Calprotectin (FC)

- Multicenter open-label RCT in UC patients in remission on 5-ASA <3 g/day (N=119)
  - 58 patients with fecal calprotectin<50 µg/g continued on current therapy
  - 52 patients with fecal calprotectin>50 µg/g randomized to stable or increased dose of MMX mesalamine†
- Results
  - More patients in dose escalation group achieved primary and secondary outcomes than stable-dose mesalamine
  - No serious AEs

In clinically quiescent UC, increasing mesalamine may lower fecal calprotectin to levels associated with lower relapse rates

†26 patients on alternative 5-ASA switched to MMX mesalamine for 6 weeks and 17/26 proceeded to randomization (3 flares, 4 non-adherent).

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)
Use of Therapeutic Drug Monitoring in IBD

Titration Phase
Maintenance Phase
Stopping/De-escalation Phase
Early Assessment of Drug Levels Correlates with Longer Term Response

• Crohn’s disease:
  – detectable week 14 infliximab trough levels are associated with week 54 efficacy outcomes¹
  – adalimumab trough levels predict sustained clinical response²

• Ulcerative colitis:
  – higher infliximab concentration at week 8 associated with higher weeks 30 and 54 clinical remission rates³
  – rapid clearance of infliximab leads to ATI, non-response⁴

Trough Levels of Drug Correlate with Clinical Response

• Higher levels assoc with mucosal healing with infliximab\(^1\), adalimumab\(^2\), certolizumab pegol\(^3\)

• Associated with response, remission\(^4\)

• But “optimal” levels are in a range\(^5\)

Dose Optimization Increases Probability of Remaining on Infliximab Up to 5 years

Retrospective cohort of patients in clinical remission, single physician practice

- Infliximab dose optimisation to trough concentrations 5–10 µg/mL (n=48)
- No infliximab dose optimisation (n=78)

Probability on infliximab

Weeks on infliximab

\[ p = 0.0006 \]
Therapy Adjustments Over Time
The Concept of Disease Burden

Induction therapy continues at same dose as maintenance

Maintenance therapy decreased/de-escalated

Inflammatory burden

Therapy intensity

Time

Drug

Drug

How long?
Examples of De-escalation of Therapy

• Steroid induction $\rightarrow$ steroid-sparing maintenance therapy
  – Steroids withdrawn

• Therapeutic drug monitoring of infliximab $\rightarrow$ dose reduction?

• Concomitant IMM + anti-TNF therapy $\rightarrow$
  – Maintained on combo therapy
  – Possibility of withdrawing IMM (IMM experienced)$^1$
  – Possibility of withdrawing anti-TNF (Crohn’s disease)$^2$

• 5-ASA?
  – MOMENTUM study shows 4.8 g/d $\rightarrow$ 2.4 g/d IF complete response$^3$

Optimized Infliximab Levels (3-7 mcg/mL) Associated with Stable Maintenance (TAXIT study)

Clinically based (CB) and trough level based (LB) groups

TAXIT: Prospective controlled Trough level Adapted infliximab Treatment

Monitoring of CRP and Fecal Calprotectin Predicts Clinical Relapse in CD Patients after Infliximab Withdrawal: A Sub-Analysis of the STORI Study

- Lead clinical relapse by 4 mo
- CRP of 6.1mg/L and calprotectin of 305mcg/g best for prediction of relapse
A Proposed Algorithm for Treatment of IBD Focused on Target Goal

Treatment Escalated Until Goal Met, Patient Refuses, or Run out of Options

Baseline assessment of disease activity by endoscopy paired with surrogate marker

3-6 months

Choice of initial therapy based on severity and prognosis of patient

Re-assessment of disease activity directly or with surrogate marker

TARGET ACHIEVED?

No

Discussion with patient treatment options

Is patient willing to proceed with your recommendations?

No

Clinical follow-up

Yes

Adjust therapy

Yes

6-12 months

De-escalation?

Clinical follow-up that includes assessment of disease stability

3-6 months

“Treat to Target”

“No

3-6 months

“Disease Monitoring”
Optimizing Therapies for IBD: Therapy-Specific Approaches

• **5-ASA**: maximize dose and delivery
  – Delivery may be impaired in distal colitis
  – Dosing

• **Steroids**: don’t over treat
  – too long, especially when they aren’t working

• **Thiopurines**: metabolites can show adherence, shunting profiles
  – allopurinol

• **Anti-TNF**: therapeutic drug monitoring
  – immunogenicity, rapid clearance, predict likelihood of response

• **Additional mechanisms to consider:**
  – Diversion and bowel rest
  – Calcineurin inhibitors
  – Novel therapies
Future of Patient Disease Monitoring: Home Fecal Calprotectin (FC)

Comparison* of Home FC (CalproSmart, n=638) with FC Analyzed in Lab (ELISA, n=894) in IBD Patients (N=221)

<table>
<thead>
<tr>
<th>CalproSmart</th>
<th>&gt;600 μg/g</th>
<th>200-600 μg/g</th>
<th>&lt;200 μg/g</th>
</tr>
</thead>
</table>
| Total test time: 25 minutes

Diagnostic Performance of CalproSmart

- AUC=0.856
- rho=0.685, P<0.0001
- 4.4% inter-assay variability
- 10.9% intra-assay variability
- 150 ug/g FC cut-off

*Measured monthly for 6 months.
Summary: Treating to Achieve Target and Disease Monitoring

• Movement to objective endpoints of management
• Precision medicine approaches may include a treat to a target using a systematic assessment and serial adjustments of therapy to achieve validated endpoints
• Monitoring is key to achieving goals and keeping patients well
  – Monitor for response to therapy, adherence, and disease drift
  – De-escalation is possible