Inflammatory Bowel Disease: Updates in Therapy

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ULCERATIVE COLITIS AND CROHN’S DISEASE:
THERAPEUTIC SIMILARITIES AND DIFFERENCES
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Therapeutic Agents
Crohn’s Only; UC Only

5 ASA Compounds
- Sulfasalazine
- Oral 5-ASA formulations
- Rectal 5-ASA

Biological Therapies
- PPD/HBV
  - Infliximab
  - Adlimumab
  - Certolizumab pegol
  - Golimumab
  - Natalizumab (JCV Ab)
  - Vedolizumab

Glucocorticosteroids
- Systemic steroids
- Topically acting steroids (budesonide)

PPD
HBV

Glucocorticosteroids
Systemic steroids
Topically acting steroids (budesonide)

Antibiotics
- Metronidazole
- Quinolones

Natalizumab

Immunosuppressives
- Azathioprine or 6-mercaptopurine/TPMT
- Methotrexate

Nutritional Therapies
- Elemental and polymeric formulas
- Pre- and probiotics

Symptomatic Agents
- Anti-diarrheals
- Anti-spasmodics

Antibiotics
- dl/Infliximab
- Adlimumab
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Nutritional Therapies
- Elemental and polymeric formulas
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Symptomatic Agents
- Anti-diarrheals
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Evolving Goals of Therapy for IBD: Sustained Deep Remission and Better Long-term Outcomes

<table>
<thead>
<tr>
<th>Goal</th>
<th>Clinical Parameters</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Response</td>
<td>Symptoms</td>
<td>Improved Quality of life</td>
</tr>
<tr>
<td>Remission</td>
<td>Endoscopy</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>Deep Remission</td>
<td>Mucosal healing</td>
<td>Avoidance of surgery</td>
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SUSTAINED DISEASE CONTROL
Sequential Therapy for UC

Disease Severity at Presentation

- Severe
- Moderate
- Mild

Therapy is stepped up according to severity at presentation or failure at prior step

Corticosteroids: Short- and Long-term Efficacy

1-Month Outcomes* (n=63)

- Complete Remission 54% (n=34)
- Partial Remission 30% (n=19)
- No Response 16% (n=10)

1-Year Outcomes (n=63)

- Prolonged Response 49% (n=31)
- Steroid Dependent 22% (n=14)
- Surgery 29% (n=18)

*30 days after initiating corticosteroid therapy.

**Infliximab in UC: The ACT1 and ACT2 Trials**

- **ACT 1**
  - Placebo: 23.1%
  - 5 mg of infliximab: 48.8%
  - 10 mg of infliximab: 45.9%

- **ACT 2**
  - Placebo: 14.0%
  - 5 mg of infliximab: 38.3%
  - 10 mg of infliximab: 36.9%

*P < .001 vs placebo


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**UC Success: Combination Therapy for UC**

- **IFX+AZA (n=78)**
  - Steroid-free remission: 40%
  - Response: 22%
  - Mucosal healing: 24%

- **IFX (n=77)**
  - Steroid-free remission: 77%
  - Response: 69%
  - Mucosal healing: 50%

- **AZA (n=66)**
  - Steroid-free remission: 63%
  - Response: 55%
  - Mucosal healing: 37%

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

Perricone R, et al. *DDW 2011; Abstract 835*
Mucosal Healing and Time to Colectomy in Infliximab-treated Patients


Accelerated Infliximab Rescue Reduces Early Colectomy Rate in Acute Severe UC

- Retrospective study of induction IFX 5mg/kg in patients who required hospitalization for acute severe, steroid-refractory UC
- No difference in colectomy rate during IFX maintenance

Proportion of Patients Colectomy-Free

Accelerated dosing protects against early colectomy in acute severe UC

Cyclosporine Versus Infliximab In Severe Acute Ulcerative Colitis Refractory To Intravenous Steroids: A Randomized Trial

**Primary Objectives**

- Difference Cys vs. IFX failure rates: -6.4% (95% CI: -24.8 to 12.0%)
- Difference Cys vs. IFX: -0.3% (95% CI: -13.3 to 12.8%)

**Response: Lichtiger score < 10 and decrease ≥ 3 points as compared to baseline**

Vedolizumab for Ulcerative Colitis: Gemini
Clinical Response, Remission, Mucosal Healing at 6 Weeks

- Clinical Response: Δ 21.7
- Clinical Remission: Δ 11.5
- Mucosal Healing: Δ 16.1

95% CI: 11.6, 31.7, 4.7, 18.3, 6.4, 25.9

- Δ 21.7
- Δ 11.5
- Δ 16.1

- 25.5 ± 5.4 ± 24.8 ± 40.9
- 47.1 ± 16.9 ± 40.9 ± 40.9

- p < 0.0001
- p = 0.0009
- p = 0.0012

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UC Patients Failed to Show Significant Improvement after Fecal Microbiota Therapy (FMT)

• Prospective, double blind RCT
  – 53 active UC patients (Mayo score ≥ 4 with endoscopic Mayo subscore ≥ 1)
  – Negative for C. difficile
  – 42% on steroids, 19% on immunomodulators, and 29% on biologics
  – 6 weeks of once-weekly fecal microbiota therapy delivered by retention enemas (n = 27) vs placebo delivered by water enemas (n=26)

• Results
  – No difference in remission between groups at week 6 (assessed by Mayo score, IBDQ and EQ-5D)
  – No adverse events related to FMT

• Limitations
  – Short duration (6 weeks)
  – Small sample size


Summary of UC Therapies

Mild to Moderate disease:
  Mesalamine (oral ± topical) induction and maintenance for mild-moderate disease (2.4-4.8 gm induction and maintenance)
  Topical Therapy

Moderate to Severe disease:
  Corticosteroid induction for moderate-severe disease
  Thiopurines maintain steroid-induced remission
  Anti-TNF agents for moderate to severe disease, steroid-refractory induction or steroid-dependent maintenance (± thiopurine)
  Vedolizumab: same indications as anti-TNF. Can be first line biologic

Severe Disease:
  Intravenous steroids
  ? High dose infliximab
  ? Cyclosporine
**Biologic Agents in Crohn’s Disease: Dosing Recommendations**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Induction</th>
<th>Maintenance</th>
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<tbody>
<tr>
<td>Infliximab</td>
<td>IV</td>
<td>5 mg/kg at weeks 0, 2, and 6</td>
<td>5 mg/kg every 8 weeks</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg/kg in lost response</td>
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<tr>
<td>Adalimumab</td>
<td>SC</td>
<td>160 mg week 0, 80 mg week 2, 40 mg week 4</td>
<td>40 mg every 2 weeks</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>SC</td>
<td>400 mg at weeks 0, 2, and 4</td>
<td>400 mg every 4 weeks</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>IV</td>
<td>300 mg at weeks 0, 2, 6</td>
<td>300 mg every 8 weeks</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>IV</td>
<td>***</td>
<td>300 mg every 4 weeks</td>
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**Safety of Starting Full Weight-Based Dosing vs Low-Dose Thiopurines in Normal Metabolizers (TPMT >25)**

- Retrospective study of 134 adult CD patients with TPMT > 25 (normal metabolizers) and > 1 year follow-up
  - Dose initiation at 2-2.5mg/kg AZA or 1-1.5 mg/kg 6MP (therapy) compared with gradual increase (control)
- Results
  - Overall similar rates of AEs
  - 90% of complications in both groups occurred in first 3 months

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Starting thiopurines at full weight-based dosing in patients with TPMT > 25 appears safe

Risk of Lymphoma Returns to Normal after Stopping Thiopurines

- 36,891 VA patients with UC with a median follow-up of 6.7 years and a median age of 60 years at inclusion
- 4,734 patients using thiopurines; median duration of exposure: 0.97 years

<table>
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<tr>
<th>Thiopurine use</th>
<th>Incidence Rate (per 1000 py)</th>
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<tr>
<td>Unexposed</td>
<td>0.6</td>
</tr>
<tr>
<td>During</td>
<td>2.3</td>
</tr>
<tr>
<td>After stopping</td>
<td>0.3</td>
</tr>
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- 142 confirmed lymphoma cases

Methotrexate

- 25 mg SQ weekly, shorter onset of efficacy
  - 39% MTX vs 19% placebo CR (p=.025)
- Monitor CBC, liver enzymes, liver biopsy
- Folic Acid 1 mg QD
  - 15 mg maintenance, 65% vs 39% (p=.04)
  - Maintain with 15-25 mg q week
- Avoid use in obese, ETOH, DM, conception
- **12.5 mg orally weekly as concomitant immunomodulator (UC or CD)**

Induction and Maintenance of Response and Remission

**SONIC: Corticosteroid-Free Clinical Remission at Week 26**

**Primary Endpoint**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of Patients (%)</th>
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<tr>
<td>AZA + placebo</td>
<td>52/170 30.6</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>75/169 44.4</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>96/169 56.8</td>
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Calculation of overall remission rate equals remission x response
Gemini 2 and 3: Vedolizumab for Maintenance of CD

- Responders randomized 1:1:1
  VDZ Q4W, Q8W, placebo from 6–52 weeks
  - Open-label VDZ Q4W if no clinical response at 6 weeks compared to placebo
  - Extension of induction trial for 6-week responders
- Maintenance at week 52
  - Cohorts 1+ 2
  - Among those with Clin Rem at week 6, still in Clin Rem at week 52

**VDZ is effective as maintenance therapy in Crohn’s disease. Induction therapy may take longer than 6 weeks.**


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Anti-TNF Antibody-Induced Psoriasiform Skin Lesions Respond to Ustekinumab

- 21 patients with anti-TNF antibody-induced psoriasis prospectively recruited from 434 anti-TNF treated IBD patients; Genotyping for IL23R and IL12B variants performed
- Results:
  - 19/331 CD – 5.7%, 2/103 UC patients – 1.3%
  - Predictors of skin lesions using multivariate analysis:
    - Smoking (OR 4.24, 95%CI 1.55-13.6; \( P=0.007 \))
    - Increased BMI (OR 1.12, CI 1.01-1.24; \( P=0.029 \))
  - 7/21 with severe skin lesions and/or alopecia treated with ustekinumab – 100% response
- Conclusions:
  - Anti-TNF antibody-induced psoriasiform skin lesions are not uncommon
  - Smoking and increased BMI are predictors
  - Ustekinumab can be used to successfully treat severe cases
  - Dose effect in development of psoriasiform lesions were not analyzed, and no dose or frequency reduction was attempted
  - Genetic factors predict severe cases – IL23R and IL12B variants

Treatment Algorithm in IBD Patients With Clinical Symptoms (Infliximab and HACA Concentrations)

- **Positive HACA**
  - Change to another anti-TNF agent
- **Therapeutic IFX concentration**
  - Active disease on endoscopy/radiology?
    - yes
      - Increase infliximab dose or frequency
    - no
      - Change to different anti-TNF agent
- **Subtherapeutic IFX concentration**
  - Change to different anti-TNF agent
  - Change to non-anti-TNF agent

Slide Courtesy of Dr. EVL

Do you need to use full dose azathioprine for immunogenicity prevention?

- Cross-sectional study of IBD patients (N=72, 63% CD) receiving IFX in combination with a thiopurine for ≥4 months

**Correlation Between 6-TGN and IFX Concentrations**

Higher 6-TGN levels correlate with higher IFX trough concentrations but levels of 125 may maximize IFX levels

**Comparison Between Groups With and Without Detectable Antibodies to IFX (ATI)**

Patients with detectable IFX abs had significantly lower 6TGN levels

**Can you stop anti-TNF? The STORI Trial**

- 115 Crohn’s disease patients on combination therapy
- Steroid-free remission for at least 6 months
- Infliximab therapy stopped, immunomodulator continued

**Deleterious factors included:** steroids within the year; no prior surgery; male; hemoglobin ≤ 14.5; white blood cell count > 6.0; any endoscopic activity; hsCRP ≥ 5; infliximab trough ≥ 2; fecal calprotectin ≥ 300μg/g

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**Close Monitoring of CRP and Fecal Calprotectin is Able to Predict Clinical Relapse in Patients with CD in Remission after Infliximab Withdrawal: A Sub-Analysis of the STORI Study**

- 113 patients with luminal CD treated with > 1 year IFX/IS combination in stable steroid-free remission for > 6 months (STORI), with discontinuation of IFX
- 51 (45%) with relapse at median of 10 months
- In relapers, higher median CRP and calprotectin during follow-up but also a sudden and pronounced increase in CRP and calprotectin during 4 months prior to relapse
- CRP of 6.1mg/L and calprotectin of 305mcg/g best for prediction of relapse
Can you switch the anti-TNF?

- **Aim:** Assessing efficacy and tolerability of adalimumab (ADA) therapy after an elective switch from infliximab (IFX) in CD patients in remission. (Open-label single-center study)
- **Primary endpoint:** Dose intensification or termination of ADA therapy

An elective switch from IFX to ADA carries the risk of losing response to IFX in a subset of patients.

- 21/29 (72%) remained in remission (1 patient needed dose intensification)
- 8/29 (28%) discontinued ADA therapy (50% due to AE and 50% lost response)
- 4 patients were re-started on IFX (2 patients lost response; 1 patient needed dose intensification)


Summary of Crohn’s Therapy

- **Mesalamine** does not work for CD (mild colonic ok)
- **Steroids/Budesonide:** induction
- **Azathioprine/Methotrexate:** steroid sparing and concomitant immunomodulator
  - Full dose Aza (?), 12.5 weekly MTX
- **Anti-TNF** (infliximab, adalimumab, certolizumab) induction and maintenance of remission in moderate to severe disease (+/- immunomodulator)
- **Vedolizumab** for induction/maintenance of remission in moderate-severe Crohn’s (+/- immunomodulator)
- **Natalizumab** in JCV (-) patients failing anti-TNF/Vedo
- **Ustekinumab** anecdotal evidence
THANK YOU!