Inflammatory Bowel Disease: Current Treatment Strategies

Edward V. Loftus, Jr., M.D.
Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota, U.S.A.
Loftus Disclosures (last 12 months)

- **Research support**
  - AbbVie
  - UCB
  - Genentech
  - Janssen
  - Amgen
  - Pfizer
  - Takeda
  - Robarts Clinical Trials
  - Gilead
  - Receptos
  - Celgene
  - Seres Therapeutics
  - MedImmune

- **Consultant**
  - AbbVie
  - UCB
  - Janssen
  - Takeda
  - Bristol-Myers Squibb
  - Amgen
  - Salix
  - CVS Caremark
  - Eli Lilly
  - Pfizer
Overview

• Existing treatment paradigms for Crohn’s

• Evolving paradigms
  • Risk stratification
  • Treating earlier in disease course
  • Measuring objective inflammation to base treatment
  • Objective treatment endpoints
  • Therapeutic drug monitoring

• New therapies
Management of Crohn’s Disease

- **Induction**
  - Prednisone, Budesonide
  - AZA/6MP/MTX
  - Anti-TNF (Infliximab, Adalimumab, Certolizumab pegol)
  - Vedolizumab or Natalizumab

- **Maint**
  - AZA/MTX, Anti-TNF, Anti-Integrin

References:
Evolving Treatment Paradigm

Using Available Data for Risk Prognostication
### Risk Factors Associated With Intestinal Complications: Crohn’s, Olmsted County

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal ileum</td>
<td>7.8</td>
<td>3.5 – 17.4</td>
</tr>
<tr>
<td>Ileocolonic</td>
<td>5.6</td>
<td>2.3 – 13.9</td>
</tr>
<tr>
<td>Upper GI</td>
<td>9.5</td>
<td>3.0 – 30.1</td>
</tr>
<tr>
<td>Perianal fistula</td>
<td>1.7</td>
<td>0.99 – 2.86</td>
</tr>
</tbody>
</table>

# AGA Clinical Pathway for Crohn’s Disease: Characterizing Risk

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30 years</td>
<td>&lt;30 years</td>
</tr>
<tr>
<td>Limited</td>
<td>Extensive</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Superficial</td>
<td>Ulcers</td>
</tr>
<tr>
<td>No</td>
<td>Deep</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Sandborn WJ. Gastroenterology. 2014;147:702-705.**
AGA Clinical Pathway for Crohn’s Disease: Initial Treatment

Low-risk patient

Ileum and/or proximal colon, none to minimal symptoms
Options
- Budesonide 9 mg/day with or without AZA
- Tapering course of prednisone with or without AZA

Diffuse or left colon, none to minimal symptoms
Options
- Tapering course of prednisone with or without AZA

Moderate/high-risk patient

Options
- Anti-TNF monotherapy over no therapy or thiopurine monotherapy
- Anti-TNF + thiopurine over thiopurine monotherapy or anti-TNF monotherapy
- Methotrexate for patients who do not tolerate purine analog in combination with anti-TNF

Efficacy of biologics in CROHN’S DISEASE

Clinical remission with induction therapy – only biologic-naïve patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Remission with Induction Therapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targan</td>
<td>4</td>
</tr>
<tr>
<td>Infliximab</td>
<td>32.5</td>
</tr>
<tr>
<td>Lemann</td>
<td>74.5</td>
</tr>
<tr>
<td>CLINIC-1</td>
<td>12.2</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>29.8</td>
</tr>
<tr>
<td>Watanabe</td>
<td>20</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>29.2</td>
</tr>
<tr>
<td>PRECISE-1</td>
<td>39.7</td>
</tr>
<tr>
<td>Sandborn</td>
<td>31.6</td>
</tr>
</tbody>
</table>

Targan, Lemann, CLASSIC-1, Watanabe, Adalimumab, Certolizumab pegol, Sandborn
Crohn’s “Net Remission” at Six Months: Certolizumab, Adalimumab, Infliximab

Certolizumab Pegol – PRECISE 2

- Open-label Induction Week 6: Pbo 21.0, CzP 12.3
- Week 26 remission: Pbo 28.6, CzP 47.9
- Net remission week 26: Pbo 18.3, CzP 30.7

Infliximab – ACCENT I

- Open-label Induction Week 2: Pbo 58.5, IFX 21.0
- Week 30 remission: Pbo 39.0, IFX 12.3
- Net remission week 30: Pbo 17.0, IFX 22.8

Certolizumab Pegol – PRECISE 1

- Net remission week 26: Pbo 18.3, CzP 29.5

Adalimumab - CHARM

- Open Label Induction Week 4: Pbo 58.0, ADA 17.0
- Week 26 remission: Pbo 40.0, ADA 9.9
- Net remission week 26: ADA 23.2

References:
Mucosal Healing With Adalimumab in CD (EXTEND)

Primary End Point

Week 12 ITT

Week 52 ITT

ADA induction (160/80 mg)/placebo
ADA QOW (40 mg)

P=0.056, NS

P<0.001

13.1%
27.4%

8/61
17/62

0/61
15/62

ITT, intent-to-treat; NS, not significant

Infliximab Effect on Hospitalizations and Surgeries – ACCENT I

Crohn’s-related Hospitalizations

<table>
<thead>
<tr>
<th>Group</th>
<th>Hospitalizations Per 100 Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic</td>
<td>38</td>
</tr>
<tr>
<td>5 mg/kg</td>
<td>23</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>24</td>
</tr>
<tr>
<td>Combined</td>
<td>23.5</td>
</tr>
</tbody>
</table>

Intra-abdominal Surgeries

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients with Surgeries (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic</td>
<td>7.4</td>
</tr>
<tr>
<td>5 mg/kg</td>
<td>2.6</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>3.1</td>
</tr>
<tr>
<td>Combined</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Compare the efficacy of IFX with PBO in the prevention of clinical and endoscopic recurrence of CD following ileocolonic resection (randomized ≤45 days from surgery)

Clinical recurrence = composite of CDAI >200, >70 pt increase, and endoscopic recurrence (Rutgeerts ≥i2)

Regueiro M et al, Gastroenterology 2016;150:1568-78.
Technically a negative study since primary endpoint not met, but infliximab reduced endoscopic recurrence by ≥50%

Risk factors for clinical recurrence:
- Prior anti-TNF exposure
- >1 resection

Regueiro M et al, Gastroenterology 2016;150:1568-78.
SONIC: Corticosteroid-Free Clinical Remission at Week 26

Primary Endpoint

Infliximab vs Infliximab/MTX for Crohn’s-COMMIT Trial

- Crohn’s patients in flare on steroids
- Fixed steroid taper
- All pts IFX 5 mg/kg usual induction/maintenance
- Randomized to MTX or placebo (10 mg increased to 25 mg weekly)
- Primary endpoint: time to treatment failure (failure to achieve steroid-free remission at week 14 or failure to maintain this thru week 50

- Negative study
- Because all pts received steroids?

Indirect Treatment Comparison
Network Meta-analysis of Biologics in Biologic-Naïve Crohn’s Disease Patients

- Infliximab (IFX) may be superior to certolizumab pegol (CZP), but is comparable to adalimumab (ADA) for induction of remission
- All agents are comparable for maintenance of remission

Singh et al. Mayo Clin Proc 2014;89:1621
Limitations of Network Meta-analysis

- Differences in trial design – no trial of standard IFX induction therapy
- Differences in co-interventions
- Indirect comparisons with no head-to-head trials – decreases quality of evidence
- All short-term trials of induction and 1-year maintenance therapy
  - No data on long-term patient-relevant outcomes (hospitalization, surgery, etc.)
- Registration trials, with restrictive inclusion criteria – not real-world experience
Infliximab vs. Adalimumab for Crohn’s disease
U.S. Medicare Database

• Retrospective cohort, 2006-2010
• Biologic-naïve adults with CD, treated with IFX (n=1459) vs. ADA (n=871)

Limitations
• Older cohort – 44.2% >60y old
• In patients younger than 65y, IBD-related surgery

IFX vs. ADA – OR, 0.66 (0.47-0.93)

<table>
<thead>
<tr>
<th>Outcome of Interest</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>0.88 (0.72-1.07)</td>
</tr>
<tr>
<td>Surgery</td>
<td>0.79 (0.60-1.05)</td>
</tr>
</tbody>
</table>

Infliximab vs. Adalimumab-Crohn’s
Risk of IBD-RELATED HOSPITALIZATION

Adjusted HR (IFX vs. ADA): 0.80 (0.66-0.98)

Singh et al. Presented at DDW; May 19, 2015; Abstract 922
Infliximab vs. Adalimumab-Crohn’s
Risk of ABDOMINAL SURGERY

Adjusted HR (IFX vs. ADA): 0.76 (0.58-0.99)

Singh et al. Presented at DDW; May 19, 2015; Abstract 922
Infliximab for UC: ACT 1 and ACT 2
Clinical Remission

ACT 1

8 Weeks 30 Weeks 54 Weeks

Placebo IFX 5 mg/kg IFX 10 mg/kg

ACT 2

8 Weeks 30 Weeks

Placebo IFX 5 mg/kg IFX 10 mg/kg

‡ P ≤ 0.002 vs placebo
† P ≤ 0.003 vs placebo
§ P = 0.001 vs placebo

ACT1/2 Trials: Survival Free of Colectomy

Conclusion: IFX+AZA superior to both AZA and IFX monotherapy in inducing steroid-free remission

Panaccione R et al, Gastroenterology 2014;146:392-400.
Adalimumab for Moderate to Severe UC: Induction/Maintenance Trial (n=494)

Week 8 Endpoints

- Clinical remission: 9.3% (Placebo), 16.5% (ADA) vs. 10% (Placebo), 17.3% (ADA)
- Clinical response: 34.6% (Placebo), 41.1% (ADA) vs. 30% (Placebo), 38.3% (ADA)
- Mucosal healing: 31.7% (Placebo), 50.4% (ADA) vs. 15% (Placebo), 25% (ADA)

Week 52 Endpoints

- Clinical remission: 8.5% (Placebo), 17.3% (ADA) vs. 15% (Placebo), 25% (ADA)
- Clinical response: 8.3% (Placebo), 30.2% (ADA) vs. 10% (Placebo), 20% (ADA)
- Mucosal healing: 15.4% (Placebo), 25% (ADA) vs. 10% (Placebo), 15% (ADA)

* p<0.05
** p<0.005

Golimumab for Induction of Response in Moderate to Severe UC

- Subcutaneous fully human monoclonal antibody to TNF
- Approved for RA, AS, PsA
- Approved for UC in mid-2013
- Dose is 200 mg at week 0, 100 mg at week 2, then 100 mg every 4 wks

Efficacy of Anti-TNFs in Ulcerative Colitis

Clinical remission with induction therapy in registration trials – only biologic-naïve patients

- Infliximab
- Adalimumab
- Golimumab
Golimumab for Maintenance of Clinical Response in Moderate to Severe UC

Clinical Response Week 54

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N = 154)</td>
<td>31.2</td>
</tr>
<tr>
<td>Golimumab 50 mg (N = 151)</td>
<td>47.0</td>
</tr>
<tr>
<td>Golimumab 100 mg (N = 151)</td>
<td>49.7</td>
</tr>
</tbody>
</table>

Clinical Remission Week 54

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N = 154)</td>
<td>15.6</td>
</tr>
<tr>
<td>Golimumab 50 mg (N = 151)</td>
<td>23.2</td>
</tr>
<tr>
<td>Golimumab 100 mg (N = 151)</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Anti-TNF in UC Insurance Claims Study: Summary

• In biologic-naïve patients with ulcerative colitis, IFX is comparable to ADA for key patient-relevant outcomes
  – All-cause and IBD-related hospitalization
  – Steroid use
  – Serious infections

• Stable on analysis stratified by baseline anti-TNF mono- vs. combination immunosuppressive therapy

• Persistence on index anti-TNF therapy is modestly higher for IFX as compared to ADA

Singh et al. Presented at DDW; May 19, 2015; Abstract 923
Singh S et al, Aliment Pharmacol Ther 2016 (online early)
Evolving Treatment Paradigms

Treatment Endpoint Based on Objective Evidence Not Symptoms
Steroid Avoidance Had More Endoscopic Healing at 2 Years

Secondary End Point of the Top-Down/Step-Up Trial

\[ P = 0.0028 \]


\begin{itemize}
  \item Patients In Remission (%)
  \begin{itemize}
    \item Off Steroids
      \begin{itemize}
        \item Remission
        \begin{itemize}
          \item Simple endoscopic score 0: 70.8%
          \item Simple endoscopic score 1–9: 27.3%
        \end{itemize}
      \end{itemize}
    \item Off Steroids, No Anti-TNF
      \begin{itemize}
        \item Simple endoscopic score 0: 62.5%
        \item Simple endoscopic score 1–9: 18.2%
      \end{itemize}
  \end{itemize}
\end{itemize}

…and these patients did better in the next 2 yrs!
Radiographic Healing in Crohn’s Disease

Cumulative Probability of 1st Hospitalization for Active Disease

P = 0.04

P < 0.001

A Proposed Algorithm for Disease Monitoring in IBD

Baseline assessment of disease activity by endoscopy paired with surrogate marker

Choice of initial therapy based on severity and prognosis of patient

3-6 months

Re-assessment of disease activity directly or with surrogate marker

Healing Documented?

No

Discussion with patient treatment options

Yes

Clinical follow-up that includes assessment of disease stability

6-12 months

Is patient willing to proceed with your recommendations

No

Clinical follow-up

Yes

Adjust therapy

If no other treatment options left

3-6 months

Slide compliments of David T. Rubin, MD
Treat to Target in Clinical Practice – Crohn’s

- Retrospective analysis of UCSD practice 2011-12 – mostly WJS’ practice
- 110 CD patients had at least 2 endoscopies, and 67 patients had ulcers/erosions at baseline
- Median follow-up, 62 weeks
- Median interval between procedures, 24 weeks
- General plan was to use endoscopy to make decision about whether or therapy should be adjusted (e.g., add anti-TNF, optimize it, combo rx, etc)

Mucosal Healing Rates

### Predictors of Mucosal Healing

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration &lt; 2yrs</td>
<td>2.3 (1.1-4.7)</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.1 (1.1-4.4)</td>
</tr>
<tr>
<td>Previous IMM</td>
<td>0.4 (0.2-0.9)</td>
</tr>
<tr>
<td>Previous Surgery</td>
<td>0.3 (0.1-0.7)</td>
</tr>
<tr>
<td>Repeat scope within 26 wks</td>
<td>2.2 (1.2-4.3)</td>
</tr>
<tr>
<td>Med rx adjustment due to ulcers on scope</td>
<td>2.3 (1.2-4.9)</td>
</tr>
</tbody>
</table>

Challenges to Mucosal Healing in Crohn’s Disease

• It can’t be achieved in many/most patients

• Unclear how much healing is really needed to affect outcomes

• It is unknown what incremental healing can be achieved by dose escalation or switching therapies

• We don’t know the appropriate time interval between changes in therapy and subsequent reassessment

• Can surrogates of endoscopic healing be used?

REACT Trial: Algorithm-based Treatment with Early Combined Immunosuppression Reduced Complications in CD

- Center-level cluster randomisation to early combined immunosuppression algorithm or current best practice
- CD patients recruited from 40 centers (N=1982)
  - Regular clinical review at 4 weeks and then Q12 weeks
  - Used algorithm to treat to target
  - Followed for 24 months
- Primary endpoint: clinical remission (HBI <5 & no steroids) at 12 months

Khanna R et al, Lancet 2015
Lessons in Strategy from REACT: Proportion of Patients with Major Adverse Outcomes at 24 Months

A  Surgery

HR = 0.69 (0.50, 0.97)

P = 0.03

CM 9.5%
ECI 6.6%

B  Serious Complication

HR = 0.73 (0.61, 0.87)

CM 30.9%
ECI 24.3%

P < 0.001

C  Hospitalization

HR = 0.84 (0.65, 1.08)

P = 0.16

CM 15.6%
ECI 12.9%

D  Hospitalization, Surgery or Serious Disease-Related Complication

HR = 0.73 (0.62, 0.86)

CM 34.7%
ECI 27.4%

P < 0.001

Khanna R et al, Lancet 2015
Evolving Treatment Paradigm

Therapeutic Drug Monitoring
Effect of Trough Serum Infliximab Concentrations on Clinical Outcome at >52 Weeks

ADA Trough Above 0.33 µg/mL Predicts Clinical Response

Log Rank: \( P=0.01 \)

- ADA TR>0.33 µg/mL, n=104
- ADA TR<0.33 µg/mL, n=16

Variables Affecting TNF-α Inhibitor Levels

- Immunomodulator Usage
  - Antibody formation
  - Drug concentration
  - Drug clearance

- Anti-drug antibodies
  - Drug concentration
  - Drug clearance

- Male Gender
  - Drug clearance

- Low serum albumin (marker for protein losing colopathy?)
  - Drug clearance

- High BMI
  - Drug clearance

- High baseline CRP
  - Drug clearance

- High baseline TNF concentration
  - Drug clearance

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

Positive HACA
- Change to another anti-TNF agent
  - Persistent disease
- Change to non-anti-TNF agent

Therapeutic IFX concentration
- Active disease on endoscopy/radiology?
  - yes
  - Change to different anti-TNF agent
  - no
  - Investigate alternate etiologies

Subtherapeutic IFX concentration
- Increase infliximab dose or frequency
- Change to different anti-TNF agent
- Change to different anti-TNF agent
- Change to non-anti-TNF agent

Challenges with TDM in IBD

- Can’t be too concrete, otherwise you’ll ditch a good drug before you have fully optimized
  - E.g., adalimumab level of 8 mcg/mL in a patient on 40 mg Q 2 weeks—DON’T SWITCH
- Still haven’t defined what “therapeutic level” (upper limit) is for each drug, and it might vary for treatment goal
  - Adalimumab levels may need to be higher, for example in the teens
  - For fistula healings, infliximab levels may need to be in the teens

Yarur et al, Inflamm Bowel Dis 2016
Zittan et al, J Crohns Colitis 2016
Yarur et al, DDW presentation 2016
Newer Therapies: Vedolizumab and Ustekinumab
Vedolizumab in Moderate-severe UC
GEMINI 1

GEMINI I: Outcomes by Anti-TNF Exposure

Prior Anti-TNF Failure

Week 6

Anti-TNF Naive

Patients (%)

Clinical response
Clinical remission

Clinical response
Clinical remission

Placebo (N=63)
Vedolizumab (N=82)

Placebo (N=76)
Vedolizumab (N=130)

Vedolizumab Maintenance in UC
GEMINI I

Vedolizumab in Moderate to Severe Crohn’s Disease-GEMINI II

Vedolizumab in Moderate to Severe Crohn’s Disease-GEMINI II

Week 6

- Remission: Placebo = 6.8, Vedolizumab = 25.7, Vedolizumab (days 0, 15) = 31.4
- CR100 Response: Placebo = 14.5, Vedolizumab = 25.7

Week 52

- Clinical Remission: Placebo = 21.6, Vedolizumab Q8wks = 39, Vedolizumab Q4wks = 31.7
- CR 100: Placebo = 30.1, Vedolizumab Q8wks = 45.5, Vedolizumab Q4wks = 28.8
- Steroid-Free Remission: Placebo = 15.9, Vedolizumab Q4wks = 43.5

* Indicates statistical significance

GEMINI II (CD): Week 52 Outcomes Stratified by Prior Anti-TNF Exposure

Clinical Remission CDAI-100 Response

Anti-TNF Exposed

Anti-TNF Naïve

GEMINI 3: VDZ Induction in Crohn’s Patients Who Had Failed Anti-TNF Agents

- 315 moderate to severe CD who had failed anti-TNF
- Randomized 1:1 to PBO or VDZ 300 mg IV weeks 0, 2, and 6
- Missed primary endpoint of remission at week 6, but met same endpoint at week 10

Vedolizumab Safety

- Integrated safety analysis of GEMINI trials: rates of serious adverse events not significantly higher with vedolizumab compared to placebo
  - Rates of serious infections not significantly higher with vedo vs. placebo
  - No cases of PML
  - Risk factors for serious infections
    - Prior anti-TNF failure and opioid analgesic use in UC
    - Younger age, steroid use and opioid analgesic use in CD
  - No black boxed warnings for infection or cancer
  - Perioperative use before abdominal operations may be associated with higher rates of infection (53% vs 33% on anti-TNF vs 28% on non-biologics)

Colombel JF et al, Gut 2016 online early
Lightner AL et al, J Crohns Colitis 2016 online early
Anti-p40 vs anti-p19 mechanism of action

IL-12

IL-23

Ustekinumab

IL-12Rβ1
IL-12Rβ2
IL-23R
IL-12Rβ1

NK or T cell membrane

No Signal

UNITI-1 Trial
Ustekinumab in CD Patients Failing Anti-TNF Therapy

Clinical Response at Week 6
(≥100 point CDAI reduction)

Placebo 21.5%
130 mg 34.3%
~6 mg/kg* 33.7%

*Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight ≤55 kg), 390 mg (weight >55 mg and ≤85 kg), 520 mg (weight >85 kg).

Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to designated analysis time point are considered not to be in clinical response, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at designated analysis endpoint are considered not to be in clinical response.

UNITI-2 Trial
Ustekinumab in Anti-TNF-Naïve CD Patients

Clinical Response at Week 6
(≥100 point CDAI reduction)

Placebo
130 mg
~6 mg/kg*
Combined

Patients %

P<0.001
P<0.001

28.7
51.7
55.5
53.6

n=209
n=209
n=209
n=418

*Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight ≤55 kg), 390 mg (weight >55 mg and ≤85 kg), 520 mg (weight >85 kg). Subjects who had a prohibited Crohn’s disease-related surgery or had prohibited concomitant medication changes prior to designated analysis time point are considered not to be in clinical response, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score at designated analysis endpoint are considered not to be in clinical response.

Ustekinumab Induces Clinical Response (CR-100) Through Week 8

Clinical Response* (≥ 100 Point CDAI Reduction)

*All p-values < 0.05, any UST vs. PBO


Ustekinumab Maintenance: IM-UNITI

- Placebo (n=131)
- Ustekinumab 90 mg Q12W (n=129)
- Ustekinumab 90 mg Q8W (n=128)

**Clinical remission** (CDAI <150)
- Placebo: 35.9%
- UsteQ12W: 48.8%
- UsteQ8W: 59.4%
- P<0.01
- P<0.05

**Clinical response**
- Placebo: 44.3%
- UsteQ12W: 58.1%
- UsteQ8W: 59.4%
- P<0.05
- P<0.05

**Steroid-free remission**
- Placebo: 29.8%
- UsteQ12W: 42.6%
- UsteQ8W: 46.9%
- P<0.01

**Sustained clinical remission** (clinical remission at Week 36, 40, and 44)
- Placebo: 26%
- UsteQ12W: 40.3%
- UsteQ8W: 46.1%
- P<0.01

**Notes:**
### Ustekinumab—Summary of Key Safety Events Through Week 8

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ustekinumab</th>
<th>Ustekinumab</th>
<th>Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>130 mg</td>
<td>~6 mg/kg</td>
<td>Combined</td>
</tr>
<tr>
<td>Treated subjects in induction phase</td>
<td>245</td>
<td>246</td>
<td>249</td>
<td>495</td>
</tr>
<tr>
<td>Avg. duration of follow-up (weeks)</td>
<td>7.9</td>
<td>7.9</td>
<td>7.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Subjects with ≥1, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AE</td>
<td>159 (64.9)</td>
<td>159 (64.6)</td>
<td>164 (65.9)</td>
<td>323 (65.3)</td>
</tr>
<tr>
<td>SAE</td>
<td>15 (6.1)</td>
<td>12 (4.9)</td>
<td>18 (7.2)</td>
<td>30 (6.1)</td>
</tr>
<tr>
<td>Infection</td>
<td>58 (23.7)</td>
<td>57 (23.2)</td>
<td>64 (25.7)</td>
<td>121 (24.4)</td>
</tr>
<tr>
<td>Serious infection</td>
<td>3 (1.2)</td>
<td>3 (1.2)</td>
<td>7 (2.8)</td>
<td>10 (2.0)</td>
</tr>
<tr>
<td>AEs temporally related to infusion</td>
<td>5 (2.0)</td>
<td>11 (4.5)</td>
<td>9 (3.6)</td>
<td>20 (4.0)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
<td>0</td>
<td>0*</td>
<td>0</td>
</tr>
<tr>
<td>MACE**</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No anaphylaxis or serious infusion reactions reported

* Multiple myeloma following Week 20 safety f/u visit; ** Major Adverse Cardiovascular Events

Serious Infections with Ustekinumab—PSOLAR Safety Registry of Psoriasis

- Self-reported IBD cases within a psoriasis safety registry PSOLAR (n = 276)
- Overall prevalence of self-reported IBD was 2.3%
- Rate of serious infections was more than 2x higher in IBD (3.8 vs 1.6 per 100 PY)
- Rate of serious infection with UST was only 1.3 per 100 PY, vs. 5.75/100 with IFX, 4.3 with other biologics

MEDI2070 (Brazikumab), an anti-IL-23 Antibody, is Safe and Effective for Crohn’s Disease

Outcomes at 8 Weeks

- **CDAI response**
  - MEDI2070 700 mg IV at Weeks 0 and 4 (n=59): 49.2%
  - Placebo IV at Weeks 0 and 4 (n=60): 26.7%
  - Difference: 22.5% (90% CI: 8.3-36.8, P=0.010)

- **CDAI remission**
  - MEDI2070 700 mg IV at Weeks 0 and 4 (n=59): 27.1%
  - Placebo IV at Weeks 0 and 4 (n=60): 15.9%
  - Difference: 12.2% (90% CI: 0-24.3, P=0.102)

- **100-point improvement in CDAI**
  - MEDI2070 700 mg IV at Weeks 0 and 4 (n=59): 45.8%
  - Placebo IV at Weeks 0 and 4 (n=60): 25.9%
  - Difference: 20.8% (90% CI: 6.7-34.9, P=0.1017)

Sands B. Presentation 85 at DDW 2015.
Efficacy of BI 655066 (Risankizumab), a Selective IL-23 Inhibitor, in Moderate to Severe Crohn’s Disease

IV placebo, risankizumab 200 mg, or risankizumab 600 mg IV at weeks 0, 4, and 8

Week 12 Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Risankizumab 200 mg</th>
<th>Risankizumab 600 mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission</td>
<td>15.4%</td>
<td>24.4%</td>
<td>36.6%</td>
<td>0.025</td>
</tr>
<tr>
<td>Clinical response</td>
<td>20.5%</td>
<td>36.6%</td>
<td>41.5%</td>
<td>0.037</td>
</tr>
<tr>
<td>Endoscopic remission</td>
<td>2.6%</td>
<td>14.6%</td>
<td>19.5%</td>
<td>0.017</td>
</tr>
<tr>
<td>Deep remission</td>
<td>0%</td>
<td>2.4%</td>
<td>12.2%</td>
<td>0.062</td>
</tr>
</tbody>
</table>

New Horizons: Cytokine Signaling of Janus Kinase (JAK)

- Tofacitinib (CP-690,550) is a novel, small-molecule, oral JAK inhibitor that is being investigated as a targeted immunomodulator for several inflammatory diseases including ulcerative colitis (UC) and Crohn’s disease.1,2
- Tofacitinib inhibits JAK1, JAK2, and JAK3 in vitro with functional cellular specificity for JAK1 and JAK3 over JAK2.3 Importantly, tofacitinib directly or indirectly modulates signaling for an important subset of pro-inflammatory cytokines including IL-2, -4, -7, -9, -15, and -21.4

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Effects on the immune system</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>Stimulate the proliferation and differentiation of Th, Tc, B, and natural killer (NK) cells</td>
</tr>
<tr>
<td>IL-4</td>
<td>Induce the differentiation of Th0 to Th2 Induce immunoglobulin switching</td>
</tr>
<tr>
<td>IL-7</td>
<td>Promote the development, proliferation and survival of T, B, and NK cells</td>
</tr>
<tr>
<td>IL-9</td>
<td>Stimulate intrathymic T cell development</td>
</tr>
<tr>
<td>IL-15</td>
<td>Promote the proliferation, cytotoxicity and cytokine production of NK cells</td>
</tr>
<tr>
<td>IL-21</td>
<td>Enhance T and B cell function</td>
</tr>
</tbody>
</table>


Courtesy of Dr. William Sandborn
Tofacitinib for Moderately to Severely Active UC - Phase 2

- Janus kinase (JAK) antagonist
- Blocks downstream signaling of many pro-inflammatory interleukins
- Small molecule (oral)
- Recently approved for rheumatoid arthritis (Xeljanz)
- Increases LDL, HDL cholesterol

Week 8

Clinical Response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>42%</td>
</tr>
<tr>
<td>0.5mg BID</td>
<td>32%</td>
</tr>
<tr>
<td>3mg BID</td>
<td>48%</td>
</tr>
<tr>
<td>10mg BID</td>
<td>61%</td>
</tr>
<tr>
<td>15mg BID</td>
<td>78%</td>
</tr>
</tbody>
</table>

Clinical Remission

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10%</td>
</tr>
<tr>
<td>0.5mg BID</td>
<td>13%</td>
</tr>
<tr>
<td>3mg BID</td>
<td>33%</td>
</tr>
<tr>
<td>10mg BID</td>
<td>48%</td>
</tr>
<tr>
<td>15mg BID</td>
<td>41%</td>
</tr>
</tbody>
</table>

Tofacitinib for Induction of Remission in UC—2 Phase 3 Trials (n=1139)

- Mod-severe UC
- Randomized 4:1 to tofacitinib 10 mg BID or PBO
- Primary endpoint: remission at week (total Mayo ≤2, no subscore>1, rectal bleed 0)
- Results similar regardless of prior anti-TNF
- Rapid improvements, seen as early as week 2

Filgotinib Is Safe and Effective for Treatment of Moderate-to-Severe CD

Methods:
- Filgotinib is a selective once-daily oral JAK1 inhibitor
- The FITZROY study included 174 patients who were randomized to treatment with filgotinib 200 mg QD or placebo for 10 weeks
- All immunosuppressants were discontinued
- Primary endpoint: CDAI <150 at 10 weeks
- Endoscopic data not yet presented

Results:

Conclusions:
- Filgotinib has efficacy in moderate-to-severe CD patients
- During 10 weeks of treatment filgotinib was well tolerated; there were no unexpected safety findings

Sphingosine 1-Phosphate Receptor 1 Modulation: Mechanism of Action

- **S1P1R agonism induces receptor internalization** lymphocytes lose response to S1P gradient
- **Become trapped in lymph nodes** causing peripheral lymphopenia
- **Upon drug withdrawal** receptor expression is restored and lymphocytes leave nodes reversing lymphopenia
Efficacy Outcomes at Week 8 in the Trial of Ozanimod as Induction Therapy

- Phase 2 RCT, 8-week induction with oral SP1 receptor modulator in patients with moderate to severe UC (N=197)
- Comparable AEs between groups
  - Worsening of UC was most common (4.6%, 3.1%, and 1.5% with placebo, 0.5 mg, and 1 mg)
  - Modest effects on HR
  - No notable cardiac, pulmonary, ophthalmologic or malignancy AEs
Etrolizumab in Ulcerative Colitis - Phase 2

Clinical Remission at Week 10

Primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Etrolizumab 100 mg</th>
<th>Etrolizumab 300 mg + LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All comers</td>
<td>20.5</td>
<td>43.8</td>
<td>25.0</td>
</tr>
<tr>
<td>Anti-TNF-naive</td>
<td>10.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-TNF-IR</td>
<td>0.0</td>
<td>4.5</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Clinical remission = MCS ≤ 2 and all subscores ≤ 1.

Mongersen (GED-0301): Phase 2 Trial in Steroid-dependent or -resistant CD

Clinical Remission at Week 12

Endoscopic Response at Week 12: SES-CD Reduction by ≥25% and ≥50%

SES-CD Reduction by ≥25%

<table>
<thead>
<tr>
<th>Patients Achieving Endoscopic Response (%)</th>
<th>n/N=</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Evaluable Patients</td>
<td>19/52</td>
</tr>
<tr>
<td>Baseline SES-CD &gt;12</td>
<td>10/16</td>
</tr>
</tbody>
</table>

SES-CD Reduction by ≥50%

<table>
<thead>
<tr>
<th>Patients Achieving Endoscopic Response (%)</th>
<th>n/N=</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Evaluable Patients</td>
<td>8/52</td>
</tr>
<tr>
<td>Baseline SES-CD &gt;12</td>
<td>5/16</td>
</tr>
</tbody>
</table>

- Two patients had endoscopic remission (SES-CD ≤2) at Week 12
  - Both patients had SES-CD score of 0 at Week 12

Feagan BG et al, UEGW 2016 Presentation
Conclusions

• Crohn’s disease is a chronic inflammatory condition which can result in high morbidity

• Anti-TNF agents are effective for inducing and maintaining response/remission in Crohn’s

• Anti-TNF agents can reduce need for hospitalizations and surgeries in Crohn’s

• Natalizumab is an option for Crohn’s disease patients who are anti-TNF refractory, but carries a risk of PML
Conclusions

• Vedolizumab is a reasonable option for Crohn’s disease patients failing anti-TNF therapy

• Ustekinumab appears promising as a treatment for Crohn’s disease in both anti-TNF-naive and anti-TNF-exposed patients

• Many promising drugs in development
  • Tofacitinib for UC
  • Other JAK antagonists (e.g., filgotinib)
  • Anti-IL-23 drugs
  • Other anti-integrins (}