BEST OF DDW 2019: IBD

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Lenox Hill Hospital
Northwell Health™
Disclosures

Abbvie/Takeda/Pfizer/Janssen/Gilead/Prometheus
-Research Support/Advisory Board/Fellowship Support/Educational Grants
Vedolizumab Shows Superior Efficacy Versus Adalimumab: Results of VARSITY—The First Head-to-Head Study of Biologic Therapy for Moderate-to-Severe Ulcerative Colitis

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1Icahn School of Medicine at Mount Sinai, New York, New York, USA; 2Nancy University Hospital, Nancy, France; 3Mayo Clinic College of Medicine, Rochester, Minnesota, USA; 4Humanitas University, Milan, Italy; 5Formerly Takeda Development Centre Europe Ltd, London, UK; 6Takeda Development Center Americas, Inc, Cambridge, Massachusetts, USA; 7University-Hospital Schleswig-Holstein, Kiel, Germany.

*Denotes equal contributions; †Note: Brihad Abhyankar was an employee of Takeda at the time of this research.

Digestive Disease Week® 2019
May 19, 2019
Phase 3b randomized, double-blind, double-dummy, multicenter, active-controlled study

Endoscopies at Baseline, Week 14, and Week 52

Wk 0

18-Week Follow-up Period (Weeks 50-68)

Wk 52

Long-term Follow-up by Telephone

(6 months after last dose)

Wk 88

N=385

 Screening Phase
(Minimum 28 Days)

Randomize 1:1

N=386

Vedolizumab IV
300 mg at Weeks 0, 2, 6, and every 8 weeks thereafter until Week 46

Placebo SC
Week 0 and Q2W until Week 50

Adalimumab SC
160 mg at Week 0,
80 mg at Week 2, and 40 mg Q2W
until Week 50

Placebo IV
Weeks 0, 2, 6, and every 8 weeks thereafter until Week 46

Randomization stratification factors were concomitant use of oral corticosteroids and previous exposure/failure of TNFi therapy or naïve to TNFi therapy.

Intravenous; Q2W, every 2 weeks; RBS, rectal bleeding score; SC, subcutaneous; TNFi, tumor necrosis factor inhibitor.

Includes 2 patients who were randomized but did not receive a dose of vedolizumab.
Patient Disposition

224 study sites in 34 countries

Assessed for eligibility N=1,285

Excluded\(^a\) n=514

Randomized n=771

<table>
<thead>
<tr>
<th>Discontinued</th>
<th>n=147</th>
<th>38.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment/AE</td>
<td>n=25</td>
<td>17.0%</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>n=82</td>
<td>55.8%</td>
</tr>
<tr>
<td>Voluntary withdrawal</td>
<td>n=26</td>
<td>17.7%</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>n=4</td>
<td>2.7%</td>
</tr>
<tr>
<td>Significant protocol deviation</td>
<td>n=4</td>
<td>2.7%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>n=1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Other</td>
<td>n=5</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

Adalimumab SC n=386

Completed treatment n=239 (61.9%)

Vedolizumab IV n=385\(^b\)

Completed treatment n=287 (74.5%)

Discontinued n=96 24.9%

<table>
<thead>
<tr>
<th>Discontinued</th>
<th>n=96</th>
<th>24.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment/AE</td>
<td>n=17</td>
<td>17.7%</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>n=41</td>
<td>42.7%</td>
</tr>
<tr>
<td>Voluntary withdrawal</td>
<td>n=28</td>
<td>29.2%</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>n=0</td>
<td>0</td>
</tr>
<tr>
<td>Significant protocol deviation</td>
<td>n=4</td>
<td>4.2%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>n=1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Other</td>
<td>n=5</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

AE, adverse event; IV, intravenous; SC, subcutaneous.

Most common reasons for exclusion were not meeting entrance criteria (81.3%), voluntary withdrawal (6.8%), and pretreatment/AE (3.7%).

Includes 2 patients who were randomized but did not receive a dose of vedolizumab.
Primary Efficacy Endpoint: Overall Clinical Remission\textsuperscript{a} at Week 52\textsuperscript{b}

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients, %</th>
<th>n/N:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab SC 40 mg Q2W</td>
<td></td>
<td>87/386</td>
</tr>
<tr>
<td></td>
<td>22.5%</td>
<td>120/383</td>
</tr>
<tr>
<td>Vedolizumab IV 300 mg Q8W</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31.3%</td>
<td>74/305</td>
</tr>
<tr>
<td></td>
<td></td>
<td>104/304</td>
</tr>
<tr>
<td></td>
<td>24.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13/81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16/79</td>
</tr>
<tr>
<td></td>
<td>16.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20.3%</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Clinical remission was defined as a complete Mayo score of \(\leq 2\) points and no individual subscore \(>1\) point.

\textsuperscript{b}Prespecified Subgroup Analysis

CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous; TNFi, tumor necrosis factor inhibitor.
Key Secondary Efficacy Endpoint: Overall Endoscopic Improvement (Mucosal Healing) at Week 52

Δ=11.9% (95% CI: 5.3%, 18.5%) p=0.0005

Δ=13.6% (95% CI: 6.0%, 21.2%) p=0.0005

Δ=5.5% (95% CI: −7.7%, 18.8%) p=0.4136

CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous; TNFi, tumor necrosis factor inhibitor.

*Endoscopic improvement was defined as a Mayo endoscopic subscore of ≤1 point.

*Full analysis set includes all randomized patients who received at least 1 dose of study drug.

*NI subgroup analysis was prespecified and produced nominal p values.
## Efficacy Outcomes at Week 52 by Baseline Use of Corticosteroids or Immunomodulators

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Adalimumab SC n/N (%)</th>
<th>Vedolizumab IV n/N (%)</th>
<th>Δ</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without baseline corticosteroid use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical remission</td>
<td>50/246 (20.3)</td>
<td>83/245 (33.9)</td>
<td>13.6</td>
<td>(5.8, 21.3)</td>
</tr>
<tr>
<td>Endoscopic improvement</td>
<td>62/246 (25.2)</td>
<td>104/245 (42.4)</td>
<td>17.2</td>
<td>(9.0, 25.5)</td>
</tr>
<tr>
<td><strong>Without baseline immunomodulator use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical remission</td>
<td>61/286 (21.3)</td>
<td>96/282 (34.0)</td>
<td>12.7</td>
<td>(5.4, 20.0)</td>
</tr>
<tr>
<td>Endoscopic improvement</td>
<td>75/286 (26.2)</td>
<td>119/282 (42.2)</td>
<td>16.0</td>
<td>(8.3, 23.7)</td>
</tr>
<tr>
<td><strong>With baseline corticosteroid use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical remission</td>
<td>37/140 (26.4)</td>
<td>37/138 (26.8)</td>
<td>0.4</td>
<td>(−10.0, 10.8)</td>
</tr>
<tr>
<td>Endoscopic improvement</td>
<td>45/140 (32.1)</td>
<td>48/138 (34.8)</td>
<td>2.6</td>
<td>(−8.5, 13.7)</td>
</tr>
<tr>
<td><strong>With baseline immunomodulator use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical remission</td>
<td>26/100 (26.0)</td>
<td>24/101 (23.8)</td>
<td>−2.2</td>
<td>(−14.2, 9.7)</td>
</tr>
<tr>
<td>Endoscopic improvement</td>
<td>32/100 (32.0)</td>
<td>33/101 (32.7)</td>
<td>0.7</td>
<td>(−12.3, 13.6)</td>
</tr>
</tbody>
</table>

*Post hoc analyses.

Cl, confidence interval; IV, intravenous; SC, subcutaneous.

Baseline corticosteroids recorded by interactive web response system, and baseline immunomodulators by electronic case report forms.

Complete Mayo score of ≤2 points and no individual subscore >1 point.

Mayo score endoscopic subscore of ≤1 point.
Clinical Response\textsuperscript{a,b} by Visit Based on Change in Partial Mayo Score From Baseline\textsuperscript{c,d}

![Graph showing clinical response over time for different treatments.]

- **Clinical Response**\textsuperscript{a,b} by Visit Based on Change in Partial Mayo Score From Baseline\textsuperscript{c,d}

CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; RBS, rectal bleeding score; SC, subcutaneous.

\textsuperscript{a}Clinical response based on partial Mayo score is defined as a reduction in partial Mayo score of ≥2 points and ≥25% from Baseline, with an accompanying decrease in RBS of ≥1 point or absolute RBS of ≤1 point.

\textsuperscript{b}Patients with missing clinical response status were considered nonresponders.

\textsuperscript{c}Full analysis set includes all randomized patients who received at least 1 dose of study drug.

\textsuperscript{d}Prespecified analysis.

The 95\% CI of the percentage is based on the Clopper-Pearson method.
Conclusions

- Vedolizumab showed superior clinical and endoscopic efficacy over adalimumab in the treatment of moderately to severely active UC
- Treatment effects were most pronounced in the TNFi–naïve subpopulation (subgroup analysis)
- Corticosteroid-free remission rates were numerically higher with adalimumab than with vedolizumab (p=NS)
- Regardless of concomitant CS or immunomodulator use at Baseline, vedolizumab demonstrated a consistent advantage over adalimumab; the two drugs seemed to perform equally well in the presence of these concomitant medications
- Histologic efficacy at Week 52 favored vedolizumab over adalimumab
- Improvements in clinical response with vedolizumab versus adalimumab emerged between Weeks 6 and 14
- Both drugs were generally safe and well tolerated, consistent with known profiles
- These results provide the most direct evidence to date on the comparative efficacy of biologics to support clinical decision making in the management of moderately to severely active UC

corticosteroid; UC, ulcerative colitis; TNFi, tumor necrosis factor inhibitor.
Vagus Nerve Stimulation Reduces Disease Activity and Modulates Serum and Autonomic Biomarkers in Biologic-Refractory Crohn’s Disease

Geert D’Haens, Amsterdam, Netherlands; Zeljko Cabrijan, Osijek, Croatia; Michael Eberhardson, Stockholm, Sweden; Remco van den Bergh, Amsterdam, Netherlands, Mark Lowenberg, Amsterdam, Netherlands, Silvio Danese, Milan, Italy; Gionata Fiorino, Milan, Italy; Rik Schuerman, Amsterdam, Netherlands; Yaakov Levine, Valencia, CA; David Chernoff, Valencia, CA.

This study was sponsored by SetPoint Medical
THE INFLAMMATORY REFLEX IN THE GUT

Figure adapted from Gut 2013;62:1214-1222

Neurogastroenterol Motil 2012;24(2):191
Am J Physiol 2007;293(3):G560

The Spring Course
BEST OF DDW 2019

June 1, 2019

Lenox Hill Hospital
Northwell Health
CLINICAL EPILEPSY DEVICE WAS USED FOR PROOF-OF-CONCEPT STUDY

1. Lead
2. Tie-Downs
3. Vagus Nerve
4. Helical Electrodes
5. Anchor Tether
6. Strain Relief Bend
7. Strain Relief Loop
8. Coiled Extra Lead
STUDY DESIGN: SINGLE-ARM OPEN LABEL TWO COHORTS

Subject Cohorts
I. **VNS Monotherapy, n=8**: 8 week washout of TNF alpha inhibitors, vedolizumab or natalizumab
II. **Adjunctive Therapy, n=8**: Subjects remain on biologic to which they have insufficient response

- 4 centers: Amsterdam, Stockholm, Zagreb, Milan
- Standard disease endpoints: CDAI, SES-CD, biomarkers
MAJOR INCLUSION / EXCLUSION CRITERIA

• Major Inclusion Criteria
  ▪ M/F subjects age 18-75
  ▪ Moderately-to-severely active Crohn’s disease
    ▪ CDAI: 220-450, SES-CD ulcer score ≥ 2 in at least 1 segment
  ▪ Fecal Calprotectin ≥ 200μg/g
  ▪ Inadequate response and/or intolerance to one or more TNF inhibitors

• Major Exclusion Criteria
  ▪ Celiac disease, ulcerative colitis, pelvic fistulae, bowel surgery within 4 months, extensive colonic resection
  ▪ Use of prohibited medications without washout
    ▪ TNF inhibitors; Glucocorticoids >10 mg prednisone (or equivalent) QD
    ▪ Azathioprine, 6-mercaptopurine, methotrexate allowed on stable dose
  ▪ History of vagotomy, recurrent vaso-vagal syncope
  ▪ Previously implanted active electrical device (e.g. cardiac pacemaker)
SERUM C-REACTIVE PROTEIN

VNS Monotherapy

Adjunctive Therapy

Median hsCRP

hsCRP (mg/dL)

Baseline 12 16 Study Week

hsCRP (mg/dL)

Baseline 12 16 Study Week

hsCRP (mg/dL)

Baseline 12 16 Study Week

hsCRP (mg/dL)

VNS Monotherapy
Adjunctive Therapy
All Subjects
# Safety

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>SAEs in Subjects</th>
<th>Early Terminations</th>
<th>Disease Related</th>
<th>Implantation Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNS Monotherapy</td>
<td>8 in 5/9</td>
<td>1</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Adjunctive Therapy</td>
<td>4 in 3/8</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

**Disease Related**
- Crohn's Disease
- Gastroenteritis
- Ileus
- Dehydration
- Prerenal failure
- Inflammation
- Cachexia

**Implantation Related**
- Postoperative surgical wound infection
  (This patient had device removed before therapy was initiated)
CONCLUSIONS

- The inflammatory reflex maintains immunologic homeostasis and can be driven non-pharmacologically with electrical vagus nerve stimulation (VNS).
- 16 weeks of VNS in 16 patients with extremely refractory Crohn’s disease led to:
  - CDAI-70 response > 50%
  - CDAI remission in 3/8 VNS monotherapy patients and 1/8 adjunctive therapy patients
- Centrally read SES-CDs showed >25% reductions in 5/15 patients, with 1/15 in endoscopic remission; longer treatment may result in more complete healing.
- Improvements were observed in biomarkers of disease activity:
  - Fecal calprotectin levels reduced in 14/16 patients, median reduction -63%
  - Serum CRP (not elevated at baseline in many patients) declined on average
  - Reductions in circulating proinflammatory cytokines
- Improvements in patient reported outcome (QoL) metrics (IBDQ, SHS).
- Improvements in autonomic tone as assessed by heart rate variability.
- SAEs occurred in a number of patients, all related to severe Crohn’s disease and one patient had surgical infection.
LONG-TERM MULTIDONOR FECAL MICROBIOTA TRANSFER (FMT) BY ORAL CAPSULES FOR ACTIVE ULCERATIVE COLITIS

Microbiome as Therapy in IBD and CDI

50th Digestive Disease Week
San Diego, 21st of May 2019
**Fecal Microbiota Transfer (FMT) for Treatment of Ulcerative Colitis**

**Clinical Remission**

- Meta Analysis: 4 RCT, n=277
- FMT 28% vs. Placebo 9% (OR: 3.67 95% CI: 1.82-7.39; P<.01)

**Endoscopic Remission**

- FMT 14% vs. Placebo 5% (OR: 2.69 95% CI: 1.07-6.74; P=.04)

Costello SP et al. Aliment Pharmacol Ther 2017;46
# Fecal Microbiota Transfer (FMT) – Intensity

<table>
<thead>
<tr>
<th>Disease</th>
<th>CDI</th>
<th>UC</th>
<th>UC</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>van Nodd et al. 2012</td>
<td>Rossen et al. 2015</td>
<td>Moayyedi et al. 2015</td>
<td>Paramsothy et al. 2017</td>
</tr>
<tr>
<td>Trial</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td>Donor</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3-7</td>
</tr>
<tr>
<td>FMT Intensity</td>
<td>1x enema</td>
<td>2x nasoduodenal tube</td>
<td>6x enemas</td>
<td>40x (1 colonoscopy, 39 enemas)</td>
</tr>
<tr>
<td>Remission FMT vs. control</td>
<td>81% vs. 23%</td>
<td>30% vs. 20% ns</td>
<td>24% vs. 5%</td>
<td>44% vs. 20% *steroid free</td>
</tr>
</tbody>
</table>

Rossen NG et al. Gastroenterology 2015;149  
Moayyedi P et al. Gastroenterology 2015;149  
Paramsothy et al. Lancet 2017;389
Mode of Application

Enema

Nasogastric/duodenal tube

Oral intake - Capsule

Health care utilization, potential complications, costs

Picture: creative commons + https://www.fpv.org.au
Materials and Methods: FMT Capsules

FMT Capsule Preparation

1. Fresh donated stool (75-100g)
2. Homogenization + Filtration
   - 200ml 0.9% sodium chloride w/ 10% glycerol

3. Double encapsulation
   - acid-resistant hypromellose capsules (DRcaps Capsugel, Cambridge, MA)
## Eligibility Criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active UC despite treatment with</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>- corticosteroids (&lt;30 mg prednisone/day),</td>
<td></td>
</tr>
<tr>
<td>- immunosuppressive and/or</td>
<td></td>
</tr>
<tr>
<td>- TNF or integrin antibody treatment agents</td>
<td></td>
</tr>
<tr>
<td>Active UC (Mayo ≥ 4)</td>
<td>Unable to give written consent</td>
</tr>
<tr>
<td>Endoscopic Subscore ≥ 1</td>
<td></td>
</tr>
</tbody>
</table>
Materials and Methods: Diagnostics

Treatment Protocol - Diagnostic Assessment

Clinical Assessment
+ AE + pMayo
+ Fecal Calpro

Colonoscopy

| BL | d1 | w4 | w8 | w12 |

12 weeks

Baseline -14d

Vancomycin
125mg qid p.o
Metronidazol
400mg bid p.o.

5d/week
5 Capsules bid
(4 donors)
### Results – Patient Characteristics

<table>
<thead>
<tr>
<th>Number of patients enrolled</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Mean age</td>
<td>37 ±7</td>
</tr>
<tr>
<td><strong>Disease location</strong></td>
<td></td>
</tr>
<tr>
<td>Pancolitis</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Proctosigmoiditis</td>
<td>2 (20%)</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Concomitant corticosteroids</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Biologic experienced</td>
<td>7 (70%)</td>
</tr>
</tbody>
</table>
Clinical Outcomes

Stool Frequency

Partial Mayo Score

Mayo Endoscopic Subscore

Mayo Score

Serious Adverse Events: 2 – worsening of colitis, discontinuation within 5 days of study

Adverse Events: minor bloating/flatulence within first week
Fecal Microbiota Diversity and Community Structure

- Lower diversity of UC patients at BL
- Antibiotics decreased diversity
- Capsule FMT increased diversity
First study to evaluate clinical and microbial impact of capsule based long-term FMT

Capsule stability sufficient to facilitate intestinal release

Safe and effective to rapidly modulate microbial diversity

Engraftment of multidonor community structure with Prevotellaceae becoming dominant members

Beneficial clinical response with significant reduction of Mayo Score

Limitations: single-center, small sample size, no control group
Thank You