Integrating research evidence into clinical practice

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<table>
<thead>
<tr>
<th>Disclosures</th>
<th>Subrata Ghosh</th>
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<tbody>
<tr>
<td>Receipt of grants/research supports</td>
<td>Abbvie, GSK, Vertex</td>
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<td>Receipt of honoraria or consultation fees</td>
<td>Janssen, Abbvie, Pfizer, Receptos, Celgene, BMS, Takeda, Ferring, Falk, Boehringer-Ingelheim</td>
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<td>Participation in a company sponsored speaker’s bureau</td>
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<td>Stock shareholder</td>
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<td>Other support (please specify)</td>
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</tbody>
</table>
Immunopathogenesis of Crohn’s disease

Conventional therapy is defined as corticosteroids (CS) and/or immunomodulators (IMM).

IV, intravenous; LTE, long-term extension; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; TNF, tumour necrosis factor; UST, ustekinumab.

Uniti 1 & 2: Proportion of patients with a 100 point clinical response

Uniti 1 & 2: proportion of patients in clinical remission

IM-UNITI: Clinical Remission and Changes in CRP Levels During Maintenance Therapy through Week 44

Patients who had insufficient data at the designated analysis time point had their last value carried forward. 

Colombel JF. Poster presented at ECCO 2018. P281
1. What is the efficacy of ustekinumab when more stringent composite response criteria are used?
UNITI-1 and UNITI-2: Clinical and Biological Response at Week 6

*Clinical Response (CDAI decreased ≥100 points from baseline or CDAI <150)
†Biological Response (Clinical response with ≥50% reduction from baseline in CRP or FeCa)
‡All comparisons vs. placebo

Colombel JF. Poster presented at ECCO 2018. P281
Among randomized patients in IM-UNITI with an elevated CRP or FeCa at induction baseline

*Induction-only patients, †Clinical response (CDAI decreased ≥100 points from baseline or CDAI <150)
‡Biological response (Clinical response with ≥50% reduction from induction baseline in CRP or FeCa)
**All comparisons vs. placebo

Colombel JF. Et al. Poster presented at ECCO 2018. P281
Number Needed to Treat to Achieve Clinical Response at Week 8 along with Response or Remission at Week 52

**Figure 3.** Induction Efficacy in Combined UNITI-1 and UNITI-2, Then Followed Through Maintenance (As If Treat Through): Response-Response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Induction at Week 8 (%)</th>
<th>Response Maintenance at 1 Year (%)</th>
<th>Response at Week 8 and Remission at 1 Year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo*</td>
<td>26.0</td>
<td>47.0</td>
<td>47.0</td>
</tr>
<tr>
<td>Placebo*</td>
<td></td>
<td>56.0</td>
<td>59.0</td>
</tr>
<tr>
<td>UST -8 mg/kg IV → 90 mg SC q8weeks*</td>
<td>53.0</td>
<td>57.0</td>
<td></td>
</tr>
<tr>
<td>UST -6 mg/kg IV → 90 mg SC q12weeks*</td>
<td>14.4</td>
<td>27.9</td>
<td>26.6</td>
</tr>
</tbody>
</table>

**Figure 4.** Induction Efficacy in Combined UNITI-1 and UNITI-2, Then Followed Through Maintenance (As If Treat Through): Response-Remission

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Induction at Week 8 (%)</th>
<th>Remission Maintenance at 1 Year (%)</th>
<th>Response at Week 8 and Remission at 1 Year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo*</td>
<td>26.0</td>
<td>47.0</td>
<td>47.0</td>
</tr>
<tr>
<td>Placebo*</td>
<td></td>
<td>48.0</td>
<td>53.0</td>
</tr>
<tr>
<td>UST -8 mg/kg IV → 90 mg SC q8weeks*</td>
<td>53.0</td>
<td>49.0</td>
<td></td>
</tr>
<tr>
<td>UST -6 mg/kg IV → 90 mg SC q12weeks*</td>
<td>12.2</td>
<td>24.9</td>
<td>22.9</td>
</tr>
</tbody>
</table>

NNT:
- UST -5 mg/kg IV → 90 mg SC q8weeks: 7.5
- UST -6 mg/kg IV → 90 mg SC q12weeks: 8.2

NNT:
- UST -6 mg/kg IV → 90 mg SC q8weeks: 7.9
- UST -6 mg/kg IV → 90 mg SC q12weeks: 8.3

*IV-Induction—Maintenance (SC)
Number Needed to Treat to Achieve Clinical Response at Week 8 along with Response or Remission at Week 52 (conventional therapy failures)

Figure 5. UNITI-2 Induction Efficacy Then Followed Through Maintenance (As If Treat Through): Response-Response

Figure 6. UNITI-2 Induction Efficacy Then Followed Through Maintenance (As If Treat Through): Response-Remission

*IV-Induction→Maintenance (SC)

NNT:
- UST 6 mg/kg IV → 90 mg SC q6weeks: 5.2
- UST 6 mg/kg IV → 90 mg SC q12weeks: 5.5

NNT:
- UST 6 mg/kg IV → 90 mg SC q6weeks: 5.1
- UST 6 mg/kg IV → 90 mg SC q12weeks: 6.1

Ghosh S. et al. Poster presented at ECCO 2018. P672
Number Needed to Treat to Achieve Clinical Response at Week 8 along with Response or Remission at Week 52 (antiTNF failures)
2. Maintenance with ustekinumab SC q12w or q8w?
Ustekinumab dose adjustment

- Ustekinumab 90mg SC every 8 weeks
  - A. May be more suitable for patients with high disease burden
  - B. Is similarly effective to UST 90mg SC every 12 weeks in most patients
  - C. It is best to start with UST 90mg SC every 12 weeks and increase if necessary
  - D. UST 90mg SC every 8 weeks has more adverse effects than every 12 weeks.
Clinical Endpoints at Week 44 of IM-UNITI, Stratified by CRP at Maintenance Baseline

A CRP >10 mg/L at maintenance baseline (i.e. before the first SC dose) discriminates a high inflammatory burden population that benefited from UST 90 mg SC q8 week dosing versus q12 week dosing.
Randomized Patients in Clinical Remission through Week 44

A. Patients with Maintenance Baseline CRP ≤5 mg/L
   - N=72
   - N=63
   - N=69
   - Proportion of Patients at Week 44 (%)
   - p=0.055

B. Patients with Maintenance Baseline CRP >10 mg/L
   - N=29
   - N=33
   - N=38
   - Proportion of Patients at Week 44 (%)
   - p=0.034
   - p=0.522

- Placebo SC
- UST 90 mg SC q12w
- UST 90 mg SC q8w

Ghosh S. Poster presented at ECCO 2018. P186
Endoscopic Endpoints in the Pooled Maintenance Population

*Subjects with eligible SES-CD and ulcerations at baseline

Clinical Endpoints at Week 44 of IM-UNITI, Stratified by Fecal Calprotectin at Maintenance Baseline

A) Patients with Maintenance Baseline Fecal Calprotectin >250 µg/g

- Clinical Remission
  - Placebo SC (n=68): 33.8%
  - UST 90 mg SC q12w (n=76): 46.1%
  - UST 90 mg SC q8w (n=55): 56.4%

- Clinical Response
  - Placebo SC (n=68): 55.3%
  - UST 90 mg SC q12w (n=76): 51.8%
  - UST 90 mg SC q8w (n=55): 61.8%

B) Patients with Maintenance Baseline Fecal Calprotectin ≤250 µg/g

- Clinical Remission
  - Placebo SC (n=60): 38.3%
  - UST 90 mg SC q12w (n=48): 50.0%
  - UST 90 mg SC q8w (n=66): 53.0%

- Clinical Response
  - Placebo SC (n=60): 51.7%
  - UST 90 mg SC q12w (n=48): 51.7%
  - UST 90 mg SC q8w (n=66): 60.4%

*All comparisons versus placebo*

Ghosh S. Poster presented at ECCO 2018. P186
Clinical Remission Over Time By Induction Study: ITT of Randomized Patients Entering LTE

UNITI - 1: TNF antagonist failure
- Patients in Clinical Remission (%)
- Weeks
- UST 90 mg q12w (N=32)
- UST 90 mg q8w (N=27)

UNITI - 2: Conventional therapy failure
- Patients in Clinical Remission (%)
- Weeks
- UST 90 mg q12w (N=52)
- UST 90 mg q8w (N=55)

ITT, intent to treat population; LTE, long-term extension; q8w, every 8 weeks; q12w, every 12 weeks; TNF, tumor necrosis factor; UST, ustekinumab

3. Is corticosteroid discontinuation an option with ustekinumab in CD?
Corticosteroid-Free Remission and Response at 44 Weeks – Patients Receiving Corticosteroids at Baseline

**Abbreviations:** CS=corticosteroid(s); N=number of patients in treatment group; q8w=every 8 weeks; q12w=every 12 weeks; UST=ustekinumab

*Versus placebo

Real World Data: Steroid and Opioid Use Among Crohn's Patients Before and After Initiation of Ustekinumab

There was a statistically significant decline in the percent of patients with opioid claims, and percent with steroid claims within 60-days of initiating the first dose of ustekinumab subcutaneous for the treatment of CD.

McNemar's tests for dependent measures using Pre-induction period as the reference level.

Obando C et al. Presented at ECCO 2018. P313
4. When should patients’ response to treatment with ustekinumab be evaluated? Is dose adjustment feasible?
Ustekinumab delayed responders: non-responders to 130 mg\textsuperscript{a} or ~6 mg/kg IV induction

\textsuperscript{a} 130 mg dose is not approved in Europe.
\textsuperscript{b} Based on 100-point decrease in CDAI.

R, randomization; SC, subcutaneous.

Response and remission after 16 weeks of ustekinumab

Of 467 patients given induction treatment at week 0, 251 were not in clinical response and continued to receive 90 mg SC q8w in the maintenance study.

Clinical remission through Week 44: delayed responders group from induction who received UST 90 mg SC q8w vs randomized patients who received 90 mg SC q8w

Adapted from Colombel J-F, et al. Presented at ACG 2017; P2133.

SmPC, summary of product characteristics.
IM-UNITI: Efficacy in patients who increased their study dose in the randomized population

Proportion of patients achieving clinical response or clinical remission 16 weeks after dose adjustment from UST q12w to UST q8w

- Clinical response: 55.20% (n=29)
- Clinical remission: 41.40% (n=29)

IM-UNITI: Clinical remission among randomized patients who entered the LTE at week 44 and 92

5. What is the effect of co-medication with immunomodulators in terms of efficacy, drug levels, safety and immunogenicity?
Combination therapy with UST in clinical practice

- Combination therapy with immunosuppressant drugs
  - A. Ustekinumab has better efficacy if combined with immunosuppressants
  - B. Ustekinumab is better pharmacokinetics if combined with immunosuppressants
  - C. Ustekinumab may be used as monotherapy without loss of efficacy
  - D. Induction efficacy is better with Ustekinumab if combined with immunosuppressants
IM-UNITI: Concomitant immunomodulators in patients receiving ustekinumab SC 90mg q8w

- P<0.05, but only nominally significant, as the endpoint is not among the Type 1 error-controlled endpoints (therefore interpret with caution).
- Key: AZA, azathiopurine; MTX, methotrexate; CDAI, Crohn’s disease activity index; 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; SC, subcutaneous; CI, confidence interval; q12w, every 12 weeks

Mixed population, from UNITI-1 and UNITI-2 trails
6-MP, 6-mercaptopurine; AZA, azathioprine; MTX, methotrexate.

Exposure–response to SC ustekinumab in IM-UNITI maintenance study

Median serum UST concentrations over time through the maintenance study IM-UNITI in those receiving or not receiving concomitant immunomodulators

UST 6 mg/kg IV → 90 mg SC q8w

Receiving AZA, 6-MP, or MTX
Not receiving AZA, 6-MP, or MTX

Serious infection rate in clinical practice

• Serious infection rates are

  • A. Higher with anti-TNF therapy than Ustekinumab
  • B. Same with anti-TNF therapy and Ustekinumab
  • C. Higher with Ustekinumab than anti-TNF
  • D. SAE with opportunistic infection is higher with Ustekinumab than anti-TNF
### Adverse events in UNITI-1, UNITI-2, and IM-UNITI

<table>
<thead>
<tr>
<th>Event</th>
<th>UNITI-1</th>
<th>UNITI-2</th>
<th>IM-UNITI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Ustekinumab</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n = 245)</td>
<td>(n = 246)</td>
<td>(n = 208)</td>
</tr>
<tr>
<td>Any AE</td>
<td>159 (64.9)</td>
<td>159 (64.6)</td>
<td>164 (65.9)</td>
</tr>
<tr>
<td>Common AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18 (7.3)</td>
<td>26 (10.6)</td>
<td>15 (6.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (9.0)</td>
<td>20 (8.1)</td>
<td>20 (8.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (7.3)</td>
<td>20 (8.1)</td>
<td>13 (5.2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15 (6.1)</td>
<td>14 (5.7)</td>
<td>16 (6.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13 (5.3)</td>
<td>12 (4.9)</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (5.3)</td>
<td>9 (3.7)</td>
<td>13 (5.2)</td>
</tr>
<tr>
<td>CD event</td>
<td>24 (9.8)</td>
<td>13 (5.3)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (5.3)</td>
<td>6 (2.4)</td>
<td>9 (3.6)</td>
</tr>
<tr>
<td>Infections&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>58 (23.7)</td>
<td>57 (23.2)</td>
<td>64 (25.7)</td>
</tr>
<tr>
<td>Serious</td>
<td>3 (1.2)</td>
<td>3 (1.2)</td>
<td>7 (2.8)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>15 (6.1)</td>
<td>12 (4.9)</td>
<td>18 (7.2)</td>
</tr>
<tr>
<td>AEs associated with infusion or injection-site reactions&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 (2.0)</td>
<td>11 (4.5)</td>
<td>9 (3.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The listed adverse events were reported by at least 5% of the patients in any group.

<sup>b</sup> Infections were assessed by the investigator.

<sup>c</sup> AEs associated with infusions in UNITI-1 and UNITI-2 refer to events that occurred within 1 hour after infusion. AEs summarized for IM-UNITI refer to injection-site reactions. AE, adverse event; CD, Crohn’s disease.
### Safety Summary Through 1 Year of Treatment of PsO, PsA and CD Patients With & Without Baseline MTX (Event Rates per 100 PYs)

<table>
<thead>
<tr>
<th></th>
<th>Psoriatic Arthritis</th>
<th>Crohn's Disease</th>
<th>Psoriasis**</th>
<th>All Disease Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO</td>
<td>UST</td>
<td>PBO</td>
<td>UST^-^</td>
</tr>
<tr>
<td>Pts treated</td>
<td>+MTX</td>
<td>-MTX</td>
<td>+MTX</td>
<td>-MTX</td>
</tr>
<tr>
<td>160</td>
<td>219</td>
<td>465</td>
<td>553</td>
<td>76</td>
</tr>
<tr>
<td>Pt years of follow-up</td>
<td>64</td>
<td>81</td>
<td>396</td>
<td>454</td>
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<tr>
<td>PTs D/C due to AE (%)</td>
<td>5.0</td>
<td>6.4</td>
<td>3.4</td>
<td>2.7</td>
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<tr>
<td>Event rate per 100 PY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAEs</td>
<td>0.303</td>
<td>0.648</td>
<td>0.628</td>
<td>1.146</td>
</tr>
<tr>
<td>Serious infections</td>
<td>1.56</td>
<td>0.00</td>
<td>0.00</td>
<td>1.76</td>
</tr>
<tr>
<td>MACE*</td>
<td>0.00</td>
<td>1.23</td>
<td>0.25</td>
<td>1.10</td>
</tr>
<tr>
<td>Malignancies (excluding NMSC)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.22</td>
</tr>
<tr>
<td>Deaths</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*MACE adjudicated events includes CV death, non-fatal MI, or non-fatal stroke; **In the psoriasis studies, no concomitant DMARD therapy (including MTX) was permitted. ^includes data from the time of crossover, ^^includes data from the first UST dose onward for patients who crossed over from PBO

Gensler LS et al. Presented at EULAR 2017, SAT0465
6. Are drug levels important?
Proportions of Patients Achieving Clinical Remission By Serum UST Concentration Quartiles at Week 24 in IM-UNITI (Maintenance)

Clinical Remission at Week 44 of IM-UNITI by Average Trough Serum UST Concentration Quartiles

Percent of Patients in Remission (%)

Average Trough Serum UST Concentration (μg/mL)

- PBO
- n=131
- Q1 ≤0.5: 35.9%
- Q2 >0.5 to ≤1.2: 70.8%
- Q3 >1.2 to ≤2.3: 77.1%
- Q4 >2.3: 75.0%

- UST SC q12w
- n=48
- UST SC q8w
- n=48

p=0.003

Proportions of Patients Achieving Clinical Remission By Serum UST Concentration Quartiles at Week 24 in IM-UNITI per Dose

**UST 90 mg SC q12w**

- **Q1** ≤0.3: 62.5%
- **Q2** >0.3 to ≤0.6: 62.5%
- **Q3** >0.6 to ≤1.2: 70.8%
- **Q4** >1.2: 79.2%

**UST 90 mg SC q8w**

- **Q1** ≤0.3: 47.8%
- **Q2** >0.3 to ≤0.6: 83.3%
- **Q3** >0.6 to ≤1.2: 79.2%
- **Q4** >1.2: 83.3%

Proportions of Patients Achieving Endoscopic Endpoints By Serum UST Concentration Quartiles at Week 44

Endoscopic response (SES-CD reduction ≥50% from induction BL)
Endoscopic remission (SES-CD total score ≤2)
### UST Concentrations and Selected Safety Events

#### Induction: UNITI-1 and UNITI-2

<table>
<thead>
<tr>
<th>Safety event</th>
<th>Incidence through week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=452)</td>
</tr>
<tr>
<td>Infections, (%)</td>
<td>23.5</td>
</tr>
<tr>
<td>Serious infections, (%)</td>
<td>1.3</td>
</tr>
<tr>
<td>SAEs, (%)</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Serum UST concentration at Week 8 was used as the systemic exposure metric; Q1: ≤ 1.6 μg/mL, Q2: >1.6 to ≤3.5 μg/mL, Q3: >3.5 to ≤6.8 μg/mL, Q4: >6.8 μg/mL.

#### Maintenance: IM-UNITI

<table>
<thead>
<tr>
<th>Safety event</th>
<th>Incidence through week 44</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=131)</td>
</tr>
<tr>
<td>Infections, (%)</td>
<td>67.2</td>
</tr>
<tr>
<td>Serious infections, (%)</td>
<td>3.1</td>
</tr>
<tr>
<td>SAEs, (%)</td>
<td>21.4</td>
</tr>
</tbody>
</table>

Average steady-state serum UST concentration was used as the systemic exposure metric; Q1: ≤ 0.5 μg/mL, Q2: >0.5 to ≤1.1 μg/mL, Q3: >1.1 to ≤2.3 μg/mL, Q4: >2.3 μg/mL.

7. Long-term extension?
Subject to local regulatory review prior to external use.

Clinical Remission Over Time
ITT of Randomized Subjects Entering LTE

LTE, long-term extension; q8w, every 8 weeks; q12w, every 12 weeks; UST, ustekinumab

Long-term management of disease: Issues and strategies

Choice of Therapy
New therapies, new mechanisms of action

Efficacy
- Induction and maintenance
- Optimisation
- Adherence

Safety
- Side effects
- Screening
- Proactive prevention

Biomarkers

Disease modification

Anti-TNF Exposed population
- Role of UST

Anti-TNF naïve population
- Role of UST