Present Situation and Problems of Clinical Trials for inflammatory bowel disease in Japan

Takayuki Matsumoto
Division of Gastroenterology, Iwate Medical University
Japan
Available or Provisionally Applicable Biologics for the Treatment of Crohn’s Disease

Chemokine receptors
- CCX282-B (GSK)
- CCX-025 (GSK)
- ZP1848 (Zealand)
- RDP 58 (Genzyme)
- Laquinimod (Teva / Active Biotech)
- Tofacitinib (Pfizer)

Immunomodulators
- NN8555 (Novo Nordisk)
- Rifaximin EIR (AlphaWessermann)
- Adalimumab (AbbVie)
- Certolizumab pegol (UCB)
- Natalizumab (Elan/Biogen Idec)
- Ustekinumab (Centocor)
- Vedolizumab (Millennium / Takeda)

JAK3 inhibitors
- Remestemcel-L (Osiris)
- PDA-001 (Celgene Cellular)
- Cellnex (Cellerix)
- Debiaerse (Neovacs)
- Tofacitinib (Pfizer)

Stem cell therapies
- Remestemcel-L (Osiris)
- PDA-001 (Celgene Cellular)
- Cellnex (Cellerix)
- Debiaerse (Neovacs)

IL inhibitors
- TNFK-005 (Neovacs)
- C326 (QPharm)
- SCH-900222 (Merck & Co)
- AMG 827 (Pfizer)
- PF-04236921 (Pfizer)

CAM inhibitors
- TNF-α inhibitors
- Stem cell therapies
- JAK3 inhibitors
- Chemokine receptors
- Immuno-modulators

Danese S: Gut 2012
1. Provisional differences in response to biologics between Western and Asian populations.

2. Differences in protocols and results of clinical trials between Western countries and Japan (i.e. Adalimumumab for Crohn’s disease).

3. Problems in objective assessment of efficacy.

4. Problems in practical management of clinical trials (subject enrollment, global trials, etc.) including clinician-orientated clinical trials.
Genome-wide Association Study of Japanese Patients with Crohn’s Disease

Comparison of Crohn’s Disease-Associated Genes between Western and Japanese Population

Innate immunity

- LRRK2
- CARD9
- NOD2
- ATG16L1
- IRGM

Aquired immunity

- IL23R
- IL12B
- JAK2
- TYK2
- STAT3
- CCR6
- TNFSF15
- IL2RA

Strong association in Jp
Weak association in Jp
No association in Jp
No SNP in Jp
Not enough power

Hirano A, Matsumoto T, et al. Inflammatory Bowel Dis 2013
Major Clinical Trials for Adalimumab in Crohn’s Disease

Western countries

CLASSIC I
M02-403 Induction
Infliximab naïve

GAIN
M04-691 Induction
Infliximab failure

CHARM
M02-404 Maintenance
Infliximab naïve + failure

Japan

M04-729 Induction
Infliximab naïve + failure

M06-837 Maintenance
Results of Induction Trial

*\( p < 0.05 \) vs. placebo (FAS population)

Comparison between Induction Trials (Patients Naive to Infliximab)

Western area (CLASSIC I)

12.2
25.0
36.8
24.0
40.0
58.6
35.5
50.0
59.5

Japan (M04-729)

0
20
40
60
80

No statistical test was conducted.

*\(p<0.05\) vs. placebo (FAS population)
**Comparison between Induction Trials**
(Patients with Prior Use of Infliximab)

**Western area (GAIN)**

- Placebo: n=166
- 160/80 mg: n=159

- Clinical Remission: 7.2 vs. 21.4
- Clinical Response (Δ100): 24.7 vs. 38.4
- Clinical Response (Δ70): 33.7 vs. 51.6

*\(p<0.05\) vs. placebo (FAS population)

**Japan (M04-729)**

- Placebo: n=13
- 80/40 mg: n=20
- 160/80 mg: n=19

- Clinical Remission: 7.7 vs. 10.0 vs. 38.5
- Clinical Response (Δ100): 26.3 vs. 45.0 vs. 50.0
- Clinical Response (Δ70): 63.2

No statistical test was conducted.
Comparison between Maintenance Trials

Western area (CHARM) vs. Japan (M06-837)

Patients in Remission (%)

<table>
<thead>
<tr>
<th></th>
<th>Week 4</th>
<th>Week 26</th>
<th>Week 56</th>
<th>Week 0x</th>
<th>Week 24x</th>
<th>Week 52x</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>42.4%</td>
<td>39.5%</td>
<td>36.0%</td>
<td>40.9%</td>
<td>33.3%</td>
<td>9.1%</td>
</tr>
<tr>
<td>40 mg EOW</td>
<td>47.1%</td>
<td>46.5%</td>
<td>41.4%</td>
<td>38.1%</td>
<td>38.1%</td>
<td></td>
</tr>
<tr>
<td>40 mg Weekly</td>
<td>17.1%</td>
<td>11.8%</td>
<td></td>
<td>18.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NRI (Non-responder imputation)
*p<0.05 vs. placebo (FAS population)
Current measures of Crohn’s disease activity

**Clinical activity**
- **CDAI**  Crohn’s disease activity index developed by the NCCDS
- **HBI**  Harvey–Bradshaw simple index

**Endoscopic activity**
- **CDEIS**  Crohn’s disease endoscopic index of severity developed and validated by the GETAID for ileocolonic or colonic disease
- **SES-CD**  Simplified version of CDEIS
- **Rutgeert’s Score**  dedicated to endoscopic post-operative recurrence in the neoterminal ileum after ileocolonic anastomosis

**Histologic activity**
- **D’Haens, Geboes, et al.**  Scoring system for histological abnormalities in Crohn’s disease mucosal biopsy specimens

Simple endoscopic score for Crohn’s disease (SES-CD)

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>A</th>
<th>T</th>
<th>D•S</th>
<th>R</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of ulcer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent of ulcerative surface</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent of affected surface</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narrowing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Even though simplified,
1. It is extremely complicated to calculate, and
2. It does not take jejunal and ileal lesions into account.

Size of ulcer
- 0; none
- 1; 0.1~0.5cm
- 2; 0.5cm~2cm
- 3; >2cm

Extent of ulcerative surface
- 0; nine
- 1; <10%
- 2; 10~30%
- 3; >30%

Extent of affected surface
- 0; none
- 1; <50%
- 2; 50~75%
- 3; >75%

Narrowing
- 0; none
- 1; single
- 2; multiple
- 3; scope not pass through
Example of SES-CD

I: 3+2+1+0=6
T: 0+0+0+0=0
D/S: 3+2+1+0=6
R: 2+1+1+0=4

SES-CD=20
Is SES-CD predictive of clinical course of CD under infliximab?

Subjects: 44 patients with Crohn’s disease.
Methods: The association between SES-CD and loss of response to infliximab was retrospectively investigated.

Anal fistula (p=0.001)

SES-CD (n.s.)

Fuyuno Y, Matsumoto T, et al.: Dig Endosc (under submission)
The Lémann score for the assessment of digestive damage in Crohn’s disease

Pariente B et al. Inflamm Bowel Dis 2011

Patient inclusion

Segment (CD location based on patient evaluation)

- Upper tract
- Small bowel
- Large bowel
- Anus

Required investigations

- MRI + Upper endoscopy
- MRI or CTE
- MRI + colonoscopy
- MRI + pelvic MRI + Clinical examination

Investigations

Digestive damage evaluation

Pariente B et al. Inflamm Bowel Dis 2011
### Lémann Score: small bowel example

#### Severity assessment for each 20 cm segment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Stricturing lesions (0–3)</th>
<th>Penetrating lesions (0–3)</th>
<th>History of surgery or other interventional procedure (0–3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null (0)</td>
<td>Normal</td>
<td>Normal</td>
<td>No procedure</td>
</tr>
<tr>
<td>Mild (1)</td>
<td>Wall thickening &lt;3 mm without prestenotic dilatation</td>
<td>-</td>
<td>Endoscopic dilatation</td>
</tr>
<tr>
<td>Moderate (2)</td>
<td>Wall thickening (\geq 3) mm without prestenotic dilatation</td>
<td>Transmural fissure with increased density in perienteric fat</td>
<td>By-pass diversion_stricturoplasty</td>
</tr>
<tr>
<td>Severe (3)</td>
<td>Stricture with pre-stenotic dilatation</td>
<td>Abscess or fistula</td>
<td>Resection</td>
</tr>
</tbody>
</table>
Procedures for CT enterography

• By multidetector CT (MDCT), patients undergo CT examination in supine and prone positions.

• Positive or neutral contrast agent is administered transorally (enterography) or through duodenal tube (enteroclysis) for adequate luminal distension. Intravenous contrast material is administered for cases of positive contrast agent in the GI tract.

• Images are usually assessed under multiplanar reconstruction (MPR).

CTE findings of active CD

Mural hyperenhancement
Mural stratification
Comb sign

Number of Patients with CD at Kyushu University Hospital

Patients diagnosed during 1970-2011: N=403

Lost to follow-up or transferred elsewhere: N=107

Under follow-up: N=296

Naïve to biologics N=139

Under biologics N=157例 (IFX :127 ADA:30)
Aim: To evaluate the efficacy of simultaneous AZA for active CD under ADA.

Study protocol: Multicenter, open-labelled, prospective study.

Primary endpoint: Remission rate at 26 wks.

Hypothesis: The combination of AZA and ADA is superior to ADA by an 15 points increase in remission rate.

Sample size: 100 patients in each arm.
症例の登録状況（最終）

エントリー症例：177例
Dose-escalation study of ADA for Crohn’s disease
• Inclusion and exclusion criteria are difficult to interpret.
• A certain proportion of candidates could not be enrolled because of minor lack in clinical demographics.
• Primary endpoint (efficacy at 8 wks) does not seem to be appropriate.

Induction and maintenance trial of ustekinumab
• Extremely strict regulation and overload under global protocol.
• This was especially the case for dropouts.
• Both analogue and electronic CRFs were required.

In general
• Many candidates could not be enrolled because of enteral nutrition.
• Strict regulation under global protocol does not seem to conform to the clinical management of CD in Japan.
• IVRS does not seem to be appropriate for the clinical trial.
Conclusion

There seems to be following problems in clinical trials for Crohn’s disease in Japan.

1. Effects of biologics may be different between Western and Asian populations.
2. Assessment of disease activity may not be objective.
3. There are difficulties in the assessment of actual intestinal damages.
4. Less number of CD patients in Japan disturbs the enrollment of study subjects.
5. Regulations in inclusion and exclusion are complicated.