Postmarketing Surveillance of Tocilizumab for Rheumatoid Arthritis in Japan – Full Analysis Report of 7,901 Patients –

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Disclosure of conflict of interest
- This PMS study was supported by Chugai Pharmaceutical Co
- HY received research grant from Chugai Pharmaceutical Co, Takeda Pharmaceutical Co, Abbott Japan, Eisai, Tanabe-Mitsubishi Pharma, Pfizer, Bristol-Meyers, Janssen Pharma, Otsuka Pharmaceutical
- HY received speaker fee from Chugai Pharmaceutical Co, Takeda Pharmaceutical Co, Abbott Japan, Eisai, Tanabe-Mitsubishi Pharma, Pfizer, Bristol-Meyers, Janssen Pharma

All case PMS for Biologics in Japan

• Infliximab
  - PMS 2003-
  - n=5,000†

• Etanercept
  - PMS 2005-
  - n=13,894‡

• Adalimumab
  - PMS 2008-
  - n=3,000§

• Tocilizumab
  - PMS 2008-
  - n=7,901

• Abatacept
  - PMS 2010-
  - ongoing

• Government instructed clinical study.
• All cases with biologics must be registered.
• Safety in the first 6 months must be actively monitored.
• Efficacy is also evaluated.

†; Takeuchi et al., Ann Rheum Dis 2008 67: 189-194
‡; T Koike et al., Mod Rheumatol 2011 21: 343-351
§; T Koike et al., Mod Rheumatol 2011 Oct 13. [Epub ahead of print] (Interim analysis)

Objectives and methods

Objectives
- Post-marketing surveillance of patients with RA treated with tocilizumab (TCZ) in Japan was conducted to investigate its safety and effectiveness in routine clinical practice

Methods
- Patients received TCZ 8 mg/kg q4w and were observed for 28 weeks
- Assessments included:
  - Baseline characteristics
  - DAS28-ESR
  - Boolean remission criteria (tender joint count ≤1, swollen joint count ≤1, patient global assessment [on 0–10 scale] ≤1 and serum CRP concentration [mg/dl] ≤1)
  - All Adverse events

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Patient background

<table>
<thead>
<tr>
<th></th>
<th>n=7,901</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years old)</td>
<td>58.7 ± 12.9*</td>
</tr>
<tr>
<td>≥70 years old (%)</td>
<td>20.7</td>
</tr>
<tr>
<td>Gender (% of females)</td>
<td>81.6</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>53.3 ± 10.2*</td>
</tr>
<tr>
<td>&lt;40kg (%)</td>
<td>5.4</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>10.4 ± 9.2*</td>
</tr>
<tr>
<td>≥10 years (%)</td>
<td>37.6</td>
</tr>
<tr>
<td>Class (3+4) (%)</td>
<td>26.1</td>
</tr>
<tr>
<td>Stage (III+IV) (%)</td>
<td>64.7</td>
</tr>
<tr>
<td>Prior use of Biologics DMARDs (%)</td>
<td>62.8</td>
</tr>
<tr>
<td>Concomitant use of DMARDs (%)</td>
<td>72.4</td>
</tr>
<tr>
<td>Concomitant use of MTX (%)</td>
<td>55.8</td>
</tr>
<tr>
<td>Concomitant use of corticosteroid (%)</td>
<td>74.0</td>
</tr>
</tbody>
</table>

* Mean ± SD

Efficacy

Disease activity (DAS28-ESR)

Changes in DAS28-ESR components

DAS28-ESR remission rate - by disease duration (week 28 LOCF)

Remission rate by Boolean definition - by disease duration (week 24 LOCF)

Remission rates in patients with early-stage disease were significantly higher than in patients with established disease.
Effect of prior use of anti-TNF drugs on DAS28/Boolean remission rate

- Remission rate in patients naïve to anti-TNF was significantly higher than in patients treated previously with anti-TNF.
- n=2071 vs 3833
- \( \chi^2 \) test, p<0.0001

Safety

Incidence of adverse events (n=7,901)
- Incidence of adverse events = 43.9% (3468pts., 6460 events)
- Incidence of serious adverse events = 9.6% (762pts., 1050 events)

Incidence of infections by disease duration
- The incidence of total infections in patients with established disease was significantly higher than in patients with early-stage disease.

Incidence of serious adverse events by previous anti-TNF treatment and concomitant MTX
- The incidence of serious AEs in MTX patients was significantly higher than in MTX+ patients.
Table: Incidence of adverse events

<table>
<thead>
<tr>
<th>AEs</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>874 (11.1)</td>
</tr>
<tr>
<td>Serious infection</td>
<td>298 (3.8)</td>
</tr>
<tr>
<td>Serious pneumonia</td>
<td>90 (1.1)</td>
</tr>
<tr>
<td>Serious cellulitis</td>
<td>31 (0.4)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>5 (0.06)</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>13 (0.2)</td>
</tr>
<tr>
<td>Cardiac function disturbance</td>
<td>59 (0.8)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>39 (0.5)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>775 (9.8)</td>
</tr>
<tr>
<td>Lipid metabolism abnormalities</td>
<td>167 (2.3)</td>
</tr>
</tbody>
</table>

Table: Incidence of Infection - compared with other Biologics in Japan

<table>
<thead>
<tr>
<th>ADRs</th>
<th>Tocilizumab</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients analyzed</td>
<td>7,901</td>
<td>5,000</td>
<td>13,894</td>
<td>3,000</td>
</tr>
<tr>
<td>Serious infection (%)</td>
<td>3.6</td>
<td>N.D.*</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Serious infection (/100PY)</td>
<td>8.51</td>
<td>8.56</td>
<td>N.D.*</td>
<td>N.D.*</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>1.49</td>
<td>2.16</td>
<td>1.25</td>
<td>1.17</td>
</tr>
<tr>
<td>Tuberculosis** (%)</td>
<td>0.06</td>
<td>0.28</td>
<td>0.09</td>
<td>0.13</td>
</tr>
</tbody>
</table>

* N.D.: No Data
** Including Extrapulmonary tuberculosis
† Takeuchi et al., Ann Rheum Dis 2008 67: 189-194
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Table: Standardized mortality ratio (SMR)

<table>
<thead>
<tr>
<th>Source</th>
<th>Deaths observed</th>
<th>Deaths expected</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actemra PMS interim report†</td>
<td>1.56</td>
<td>25</td>
<td>1.9 (1.1-2.5)</td>
</tr>
<tr>
<td>Actemra PMS full analysis report</td>
<td>1.15</td>
<td>35</td>
<td>1.4 (0.8-1.8)</td>
</tr>
<tr>
<td>Etanercept All-patient surveillance‡</td>
<td>1.40</td>
<td>72</td>
<td>1.2 (1.0-1.4)</td>
</tr>
<tr>
<td>IORRA Japanese cohort</td>
<td>1.46-1.90</td>
<td>7926</td>
<td>35,443</td>
</tr>
</tbody>
</table>

† PMS report www.enbrel.jp/member/report/kansetsu_7.html

Conclusions

- **Efficacy**
  - Tocilizumab was most effective in patients with RA at an early-stage and naïve to anti-TNF therapy.

- **Safety**
  - The most common AE and serious AE were laboratory test abnormalities and infections, a finding similar to other studies of anti-TNF.
  - The incidence of serious AE was higher in patients with longer disease and without MTX therapy.
  - SMR in this analysis was 1.15 (95% CI=0.8-1.6).

Acknowledgement

Co-authors

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