Product Overview of Actemra

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# Major Biologics for Rheumatoid Arthritis (RA)

<table>
<thead>
<tr>
<th>Type</th>
<th>Generic Name (Brand Name)</th>
<th>Japan</th>
<th>Overseas</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF inhibitor</td>
<td>Chimeric anti-TNF-α antibody</td>
<td>infliximab (Remicade)</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>Human anti-TNF-α antibody</td>
<td>adalimumab (Humira)</td>
<td>Approved</td>
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<tr>
<td></td>
<td>TNF receptor-Fc fusion protein</td>
<td>etanercept (Enbrel)</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>Human anti-TNF-α antibody</td>
<td>Golimumab</td>
<td>Under development</td>
</tr>
<tr>
<td>IL-6 inhibitor</td>
<td>Humanized anti-IL-6 receptor antibody</td>
<td>tocilizumab (Actemra)</td>
<td>Approved</td>
</tr>
<tr>
<td>IL-1 inhibitor</td>
<td>IL-1 receptor antagonist</td>
<td>anakinra (Kineret)</td>
<td>-</td>
</tr>
<tr>
<td>B-cell inhibitor</td>
<td>Chimeric anti-CD20 antibody</td>
<td>rituximab (Rituxan)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Humanized anti-CD20 antibody</td>
<td>ocrelizumab</td>
<td>Under development</td>
</tr>
<tr>
<td>T-cell inhibitor</td>
<td>CTLA-4-Fc fusion protein</td>
<td>abatacept (Orencia)</td>
<td>Under development</td>
</tr>
</tbody>
</table>
History of Development

- **1986** Cloning of IL-6 (Osaka University, Kishimoto and others)
  Joint development started with Osaka University
- **1988** Cloning of IL-6 receptor
- **1990** gp130 structure elucidation
- **1997** Initiation of clinical development for RA
- **2001** Initiation of clinical development for Castleman’s disease
- **2002** Initiation of clinical trial for systemic juvenile idiopathic arthritis (sJIA)
- **2003** License agreement of MRA with Roche
- **2005** Approval for indication of Castleman’s disease in Japan
- **2006** Application for additional indications of RA and JIA
- **2007** Biological License Application for RA in the US and Europe
- **2008** Approval in Japan for additional indications of RA, polyarticular-course JIA and sJIA
Overview of Clinical Studies Conducted in Japan (RA)

Total number of Actemra-treated patients: 601 (1891.3 patient-years)

Administration period: 0.1 to 8.1 years
Median: 2.9 years

* Extension studies were conducted for every trial in Japan
Structure of Actemra

Antigen

Variable region

Constant region

Fab region

Fc region

VH : Heavy chain variable region

VL : Light chain variable region

CH : Heavy chain constant region

CL : Light chain constant region

CDR : Complementary determining region

VH : Heavy chain variable region

VL : Light chain variable region

CH : Heavy chain constant region

CL : Light chain constant region

Mouse variable region

Humanized region

CDR : Complementary determining region

VH : Heavy chain variable region

VL : Light chain variable region

CH : Heavy chain constant region

CL : Light chain constant region
Signal Transduction by IL-6

- **IL-6**
- **[Membrane-bound IL-6 receptor (IL-6R)]**
- **[Soluble IL-6 receptor (sIL-6R)]**
- **gp130**
- **Outside of cell membrane**
- **Cell membrane**
- **Inside of cell membrane**
- **DNA**
- **Cell nucleus**

Signal transduction to nucleus → Transcription to genetic information
Inhibition of Signal Transduction of IL-6 by Actemra

- [Membrane-bound IL-6 receptor (IL-6R)]
- [Soluble IL-6 receptor (sIL-6R)]
- IL-6
- gp130
- Outside of cell membrane
- Cell membrane
- Inside of cell membrane

Signal transduction to nucleus
Biological Activities of Interleukin-6 (IL-6)

- Angiogenesis
- Induction of differentiation of osteoclast
- VEGF production
- Cytotoxic T-cell differentiation
- Antibody production
- Cellular differentiation
- CRP production
- Production of Amyloid A protein
- Production of hepaticin
- Reduction in albumin production
- Increase in blood platelet
- Myeloma cell
- Multifunctional colony formation
- Skin keratinocyte
- Proliferation
- Neuron-like cell differentiation
- PC-12 cells
- Kidney mesangium cell
- Proliferation
Activities of Actemra on Suppression of Osteoclastic Cell Formation

Actemra suppresses synovial cell formation through its action of suppressing RANKL expression by synovial fibroblasts. (in vitro)
Indications

- The following diseases which do not show sufficient response to the existing therapies
  - Rheumatoid arthritis\(^1\)
    (including inhibition of progression of structural joint damage)
  - Polyarticular-course juvenile idiopathic arthritis \(^1\)
  - Systemic juvenile idiopathic arthritis \(^2\)

1) Actemra should be administered to patients who have failed to show sufficient response in the past despite receiving appropriate treatment with one or more anti-rheumatic drugs.

2) Actemra should be administered to patients who have failed to show sufficient response in the past despite receiving appropriate treatment with corticosteroids.
Dosage and Administration

○ RA and polyarticular-course JIA

The recommended dose of tocilizumab (genetical recombination) is 8mg/kg as a single intravenous drip infusion administered at 4-week intervals.

○ Systemic JIA and Castleman’s disease

The recommended dose of tocilizumab (genetical recombination) is 8mg/kg as a single intravenous drip infusion administered at 2-week intervals.

The dosing interval can be shortened to a minimum of 1 week depending on the patient’s disease condition.
Safety

Out of 783 cases, adverse events were reported in 751 cases (95.9%)

● Major adverse events
  – Nasopharyngitis 421 cases (53.8%)
  – Cholesterol increased 292 cases (37.3%)
  – LDL increased 148 cases (18.9%)
  – Triglycerides increased 126 cases (16.1%)
  – ALT(GPT) increased 119 cases (15.2%)

● Serious adverse events
  – Infection, anaphylactic shock, anaphylactoid symptoms, digestive tract rupture, neutropenia, heart failure

※Breakdown of 783 cases: Castleman’s disease--35 cases; RA--601 cases; polyarticular-course JIA--19 cases; sJIA--128 cases.
Product Characteristics

1. Actemra is an original product from Japan and the first humanized anti-IL-6 receptor monoclonal antibody in the world.

2. Rheumatoid arthritis
   - Demonstrated high efficacy by monotherapy in active RA patients taking methotrexate. (24 weeks Japanese phase III clinical study: SATORI study)
   - Demonstrated high efficacy by monotherapy in RA patients who had inadequate response to DMARDs. (52 weeks Japanese phase III clinical study: SAMURAI study)
   - Improved anemia, serum amyloidosis and laboratory parameters of MMP-3.

3. To demonstrate significant efficacy in polyarticular-course juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis. (Japanese phase III clinical studies)
Conditions for Approval  
- Post-Marketing Surveillance -

For RA, polyarticular-course JIA, systemic JIA

1. In post-marketing, until data is gathered for a fixed number of patients, safety and efficacy data for Actemra should be collected by conducting a drug use-results survey of all cases and necessary measures should be taken for the proper use of Actemra.

2. A large-scale post-marketing surveillance should be conducted with a comprehensive investigation of the safety of Actemra including the safety of long-term treatment and occurrence of infections, etc.
Website

アクテムラの治療を受ける患者さんへ

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