Technology evaluation: MRA, Chugai
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Chugai, the Japanese subsidiary of Roche, is developing a humanized anti-interleukin (IL)-6 receptor monoclonal antibody MRA for the potential treatment of multiple myeloma, rheumatoid arthritis, Crohn’s disease and other IL-6-related disorders. MRA is currently undergoing phase II clinical trials for these indications.

Introduction
Interleukin (IL)-6 is a pleiotropic cytokine with a wide range of biological activities, including regulation of immune responses, support of hematopoiesis and generation of acute-phase reactions [475335]. Deregulation of IL-6 production has been implicated in the pathogenesis of a variety of diseases. Chronic inflammation of the joint in rheumatoid arthritis (RA) induces IL-6 production by synovial cells, macrophages and lymphocytes in the affected synovium. Overproduction of IL-6 appears to be involved in the pathogenesis of pannus formation, angiogenesis, infiltration of mononuclear cells and destruction of cartilage and bone [475335], [475553], [475555]. IL-6 is also present at very high levels in the serum and/or related tissue from patients with Crohn’s disease (CD) [475336], Castleman’s disease [475337], multiple myeloma (MM) [475338] and systemic lupus erythematosus (SLE) [475341]; it may, therefore, play a crucial role in the pathogenesis of these diseases. As a result, therapy involving blockade of IL-6 functions may constitute a new therapeutic strategy.

The functions of IL-6 are mediated through a receptor system comprising two cell-surface molecules, a signal transducer and a binding molecule (the IL-6 receptor, IL-6R). Blockade of IL-6 binding to its receptor seems to be specific and effectively inhibits IL-6 functions. Chugai is therefore developing MRA, a humanized anti-IL-6R monoclonal antibody for potential use in the treatment of IL-6-related disorders, including RA, CD and Castleman’s disease [459399], [469916], [469932].

Synthesis and SAR
PM-1, a mouse monoclonal antibody against human recombinant IL-6R, was generated from a mouse immunized with IL-6R partially purified from the human myeloma cell line U266 [475342]. In humans, the production of neutralizing antibodies to mouse antibodies can be clinically problematic, and cause the effects of administered antibodies to be transient [154800]. To prevent the induction of such antibodies against the anti-IL-6R antibody, the PM-1 antibody was reshaped to create MRA [154800].

Complementarity-determining regions of the mouse PM-1 light and heavy chain variable regions were grafted to human REI and NEW framework regions (FRs), respectively. Template DNA was prepared using Ncol-BamHI fragments containing DNA sequences coding for the reshaped human light and heavy chain variable regions, which have FRs from human REI and NEW, respectively. These were then subcloned into the HindIII-BamHI site of pUC19 vector using a HindIII-Ncol adaptor. Using appropriate mutagenic PCR primers and template DNA, several versions were constructed. After DNA sequencing, the HindIII-BamHI fragments coding for reshaped human PM-1 variable regions were excised from pUC19 vectors and inserted in the HindIII-BamHI sites in human elongation factor expression vectors. Plasmid DNAs were transfected into COS cells for production of MRA and this antibody was purified. The ability to bind to IL-6R and the inhibitory effect of IL-6 function of the original PM-1 were conserved in the MRA molecule [154800]. Thus, the administration of MRA induces hardly any anti-MRA antibodies and it can be repeatedly administered [154800].

Pharmacology

In vitro and in vivo data have shown that MRA blocks IL-6 functions in the cynomolgus monkey. MRA inhibited two functional parameters in vitro in this animal; T-cell proliferation stimulated by phytohemagglutinin and human IL-6, and IgG production evoked by Staphylococcus aureus Cowan-1- and human IL-6-stimulated B-lymphocytes [472428]. MRA (5 mg/kg iv) completely inhibited IL-6-induced typical responses (such as elevation of blood platelet counts and serum C-reactive protein (CRP) levels) in cynomolgus monkeys [472418], [472427].

The in vivo effect of MRA on the development of collagen-induced arthritis was examined in cynomolgus monkeys. MRA (10 mg/kg iv) given once weekly for 13 weeks significantly inhibited arthritis symptoms. The elevation of serum CRP and fibrinogen levels was also inhibited, as was erythrocyte sedimentation rate (ESR). Furthermore, radiographic and histological examination showed that MRA treatment suppressed joint destruction [472418]. In severe combined immunodeficiency (SCID) mice in which human RA
synovial tissue was grafted, MRA (100 µg ip) administered once weekly for 4 weeks significantly decreased the number of inflammatory cells and metalloprotease-positive cells in the implanted tissues [475344]. These results suggest that MRA may be an attractive agent for the treatment of RA.

In SCID mice subcutaneously inoculated with solid tumors of the S6B45 myeloma cell line, PM-1 (100 µg ip) administered 24 h after tumor inoculation, with ten subsequent injections at 48 h intervals, strongly inhibited the growth of myeloma cells [248634]. MRA (2 mg as a single iv injection administered on the day after tumor transplantation) substantially suppressed the elevation of serum M-protein and development of tumor-associated abnormalities, and significantly increased the lifespan in a SCID mouse xenograft MM model induced by iv injection of the human MM cell line KPM2 [475345]. These in vivo results suggest that MRA may be effective in the treatment of MM.

Further preclinical studies suggest a therapeutic potential of MRA in the treatment of human SLE and CD. MR16-1, a rat anti-mouse IL-6R antibody, potently suppressed the development of autoimmune disease in BWF1 mice, as a model of human SLE, and this was attributed to its effect on the specific suppression of IgG class antibody production [475341]. In the murine colitis model induced by transfer of CD45RB<sup>+</sup> CD4<sup>+</sup> T-cells from BALB/c mice, ip injection of rat anti-murine IL-6R antibody (2 mg at the time of colitis induction and 1 mg weekly for up to 8 weeks) significantly inhibited the average colitis score. T-cell expansion in treated mice was less remarkable than in the control mice and expression of the adhesion molecules ICAM-1 and VCAM-1 were inhibited [475336].

Metabolism
To investigate the kinetic properties of MRA, cynomolgus monkeys were administered MRA (4 or 40 mg/kg iv) once weekly for 13 weeks. Serum MRA concentrations showed linearity between the two doses. When the first doses of 4 and 40 mg/kg were infused into two monkeys, for each dose, serum concentrations of MRA reached maximum levels of 93 and 138 µg/ml at 2, 4, 8 and 12 weeks. Concentrations of MRA in bone marrow were almost equal to those in serum [472429]. Similar changes in MRA serum concentrations were also observed at 2, 4, 8 and 12 weeks. Concentrations of MRA in bone marrow were almost equal to those in serum [472429]. Serum concentrations of MRA were maintained for a long period; in some cases, there was a sufficient level of MRA to inhibit IL-6 functions 1 week after administration [472427].

Toxicity
In order to investigate the toxicological properties of MRA, cynomolgus monkeys were administered MRA (0, 4 or 40 mg/kg iv) once weekly for 13 weeks. During the period of treatment, no changes in clinical signs or symptoms of anaphylaxis were observed. Food consumption of each monkey was normal and there were no differences in body weight between control and treated animals. Hematological and biochemical parameters, including blood platelet counts and serum IgG levels, were also unaffected. Urinalyses, electrocardiograms and body temperatures were not affected, and pathological examination revealed no treatment-related alterations [472429].

Clinical Development
Phase I
RA
In a pilot study, patients (n = 11) with refractory RA received MRA in saline (50 or 100 mg iv) administered once or twice weekly. The treatment was well tolerated and no major side effects were observed except for the appearance of anti-idiotypic antibody in one case, resulting in withdrawal from the trial. A transient decrease in neutrophil counts, mostly within the normal range, was observed in most of the cases on the day following MRA administration. In the eight patients who received MRA treatment for more than 8 weeks, swollen joints, pain, tenderness and morning stiffness in the joint was reduced and anemia, thrombocytosis, hypoalbuminemia and polyclonal hyper-γ-globulinemia all improved within 2 months in every patient. At 8 weeks, clinical response was 88%, as assessed by the American College of Rheumatology 20% response (ACR20) criteria, and 50%, as assessed by ACR50 criteria. The therapeutic effects of the treatment were maintained throughout the 6-month treatment period [475384].

An open-label trial evaluated the safety and efficacy of repetitive MRA treatment in 15 patients with active RA. MRA (2, 4 or 8 mg/kg iv) was administered three-times over a period of 2 h every other week. All patients tolerated MRA treatment, showed improvement and were allowed to remain on MRA treatment for 24 weeks. Patients were further assessed for safety (4 weeks after the last dose) and efficacy. The treatment was well tolerated at all doses and no serious adverse events were observed. CRP, serum amyloid A protein levels and ESR were completely normalized in 12 out of 15 patients (80%) within 6 weeks. Hemoglobin and serum albumin levels were normalized in all patients. In addition, decreases in tender or swollen joint counts were also noted. Production of antibodies to MRA was not observed in any patients [475346].

Castleman's disease
MRA (50 or 100 mg) was administered either once or twice weekly to patients with multicentric plasma-cell-type or mixed-type Castleman's disease (n = 7). The trough level of serum MRA was 10 µg/ml during maintenance treatment using 50 mg of MRA twice weekly, and decreased to 5 µg/ml using a treatment of 100 mg of MRA once weekly. Treatment was well tolerated except for a transient and mild decrease in granulocyte counts on the day after MRA administration in two patients who spontaneously recovered within 2 days. No decrease in T-cell function was observed. Fever and fatigue disappeared, and anemia, as well as serum levels of CRP, fibrinogen and albumin, began to improve immediately after MRA administration. After 3 months of treatment, hyper-γ-globulinemia and lymphadenopathy were also remarkably alleviated, as were renal function abnormalities in patients with amyloidosis. Autoantibodies such as antinuclear antibody and anti-DNA antibody disappeared. Histopathological examination of lymph nodes revealed a reduction in follicular hyperplasia and vascularity after MRA treatment. These data showed that MRA could achieve marked responses in the refractory
form of this disease without significant adverse reactions or development of neutralizing antibodies [475337], [475384].

**Phase II RA**

Registered RA patients (n = 164) were entered into a double-blind, placebo-controlled trial in which either placebo or MRA (4 or 8 mg/kg iv) were infused every 4 weeks for 3 months without the use of disease-modifying antirheumatic drugs. Patients were permitted to take corticosteroids (10 mg/day or less) and non-steroidal anti-inflammatory drugs. The average rates of reduction of joint pain and joint swelling for the placebo group were 7.7 and 2.6%, respectively, compared with reductions of 63.1 and 63.4%, respectively, in the 8 mg/kg MRA group. Furthermore, this treatment group exhibited improvement in inflammatory markers and increased bone formation markers, as well as a reduction in bone absorption markers. The ACR20 responses for the placebo, 4 and 8 mg/kg groups were 11.3, 57.4 and 78.2%, respectively, and the ACR50 responses of the three groups were 1.9, 25.9 and 40.0%, respectively [459399], [468323].

In a double-blind, randomized trial, patients (n = 54) with active RA were allocated to four treatment groups and received a single dose of MRA (0.1, 1.0, 5.0 or 10.0 mg/kg iv) or placebo. A significant difference was observed between the 5.0 mg/kg and placebo group at week 2 (p = 0.011). Five out of nine patients (55.6%) in the 5 mg/kg group and none in the placebo group demonstrated ACR20 responses. Baseline disease activity (DAS) ranged from 6.5 to 6.9. At week 2, the DAS for the 5.0 and 10.0 mg/kg groups was 4.8 and 4.7, respectively. ESR and CRP levels in the 5 and 10 mg/kg groups normalized 1 week after treatment and remained normal for 3 weeks [475348].

**Side Effects and Contraindications**

The phase II trial of MRA showed the overall incidences of adverse events were 72.2, 81.5 and 89.1% (serious events: 3.7, 1.8 and 3.6%) in the placebo, 4 and 8 mg/kg MRA groups, respectively, and the incidences of infection were 16.7, 22.2 and 20.0%, respectively; by May 2002, phase II trials for RA in Japan had been completed [459399], [468323]. By November 2002, phase II trials in Japan for Castleman's disease had been completed [469932], and phase I trials for this indication were ongoing in the US by October 2002. By this time, phase II trials in juvenile idiopathic arthritis were ongoing in Japan and the UK, and phase II trials had been initiated in Japan for CD. Also by October 2002, MRA was in phase II trials in France and phase I trials in the UK for the treatment of MM [466457], [468323]. By November 2002, a phase I trial for SLE had been initiated in the US [469932]. In May 2001, Chugai predicted launch in 2003/2006 [409785]. By October 2002, Chugai anticipated moving the drug candidate into phase III studies as quickly as possible [466737].

As part of the merger agreement between Chugai and Roche in December 2001, Roche gained opt-in rights on MRA in the US [434295]. In October 2002, Chugai reported that it would closely cooperate with Roche for joint development, production and marketing on a worldwide basis, except in Japan and South Korea [466737]. In November 2000, MRA was granted orphan drug status in Japan for the target indication of Castleman's disease [391361]. In May 2000, Chugai signed multiple patent license agreements with Protein Design Laboratories whereby Chugai was to receive non-exclusive worldwide licenses under PDL's antibody humanization patents for an undisclosed number of Chugai antibody targets. Chugai was to pay PDL upfront signing and licensing fees totalling US $6.04 million [366951]. In July 1996, Chugai filed patent application WO-09620728 for the use of IL-6 receptor mAbs to increase the sensitivity of tumor cells to antitumor agents.

**Commercial Opinion**

In August 1999, Lehman Brothers gave MRA a 10% probability of reaching the market with an expected launch in 2003. Sales were predicted to peak in 2010 at US $75 million [349228].
<table>
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<tr>
<th>Developer</th>
<th>Country</th>
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</table>

**Literature classifications**

Key references relating to the technology are classified according to a set of standard headings to provide a quick guide to the bibliography. These are as follows:

**Chemistry**: References which discuss synthesis and structure-activity relationships.

**Biology**: References which disclose aspects of the drug’s pharmacology in animals.

**Metabolism**: References which discuss metabolism, pharmacokinetics and toxicity.

**Clinical**: Reports of clinical phase studies in volunteers providing, where available, data on the following: whether the experiment is placebo-controlled or double- or single-blind; number of patients; dosage.

### Chemistry

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<tr>
<th>Study Type</th>
<th>Result</th>
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<tr>
<td>Synthesis and SAR.</td>
<td>MRA was constructed by grafting the complementarity-determining regions from mouse PM-1, a specific monoclonal antibody against human IL-6R, into human IgG to recreate a functional antigen-binding site in a reshaped human antibody.</td>
<td>154800</td>
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### Biology

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<tr>
<td>In vivo</td>
<td>Anti-inflammatory effects.</td>
<td>Collagen-induced arthritis in the cynomolgus monkey.</td>
<td>MRA (10 mg/kg iv) administered once weekly for 13 weeks inhibited arthritis symptoms, CRP level and ESR. Joint destruction was suppressed.</td>
<td>472418</td>
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<tr>
<td>In vivo</td>
<td>Anti-inflammatory effects.</td>
<td>SCID mice xenograft with human RA synovial tissue.</td>
<td>MRA (100 µg ip) administered once weekly for 4 weeks decreased the number of inflammatory cells in the implanted tissues.</td>
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<tr>
<td>In vivo</td>
<td>Anti-inflammatory effects.</td>
<td>Murine colitis model induced by transfer with CD45Rb&lt;sup&gt;+&lt;/sup&gt; CD4&lt;sup&gt;+&lt;/sup&gt; T-cells from BALB/c mice.</td>
<td>Rat anti-murine IL-6R antibody administered by ip injection (2 mg at the time of colitis induction and 1 mg weekly up to 8 weeks) significantly inhibited the average colitis score and T-cell expansion.</td>
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<td>In vivo</td>
<td>Antimyeloma activity.</td>
<td>SCID mice xenograft MM model induced by iv injection of the human MM cell line, KPMM2.</td>
<td>A single iv injection of MRA (2 mg) on the day after tumor transplantation suppressed the elevation of serum M-protein and development of the tumor-associated abnormalities, and significantly increased lifespan.</td>
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<tr>
<td>In vivo</td>
<td>Immunosuppressive ability.</td>
<td>BWF1 mice as a model of human SLE.</td>
<td>Administration of rat anti-mouse IL-6R antibody suppressed the development of the autoimmune disease.</td>
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### Metabolism

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<tr>
<td>In vivo</td>
<td>Kinetic properties.</td>
<td>Normal cynomolgus monkeys to which MRA was administered (4 or 40 mg/kg iv) once weekly for 13 weeks.</td>
<td>Serum concentrations of MRA showed linearity between the two doses.</td>
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Clinic

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<tr>
<td>Safety and efficacy in RA patients.</td>
<td>In a phase I open-label trial, MRA (2, 4 or 8 mg/kg) was administered three times by iv infusion over a period of 2 h every other week in patients (n = 15) with RA.</td>
<td>The treatment was well tolerated at all doses without any serious adverse events. CRP levels, ESR and clinical symptoms were decreased or normalized.</td>
<td>475346</td>
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<tr>
<td>Safety and efficacy in RA patients.</td>
<td>In a phase II double-blind, placebo-controlled trial, either placebo or MRA (4 or 8 mg/kg) were infused iv every 4 weeks for 3 months to RA patients (n = 164).</td>
<td>The ACR20 responses of the placebo, 4 and 8 mg/kg groups were 11.3, 57.4 and 78.2%, respectively. Overall incidences of adverse events were 72.2, 81.5 and 89.1% (serious events were 3.7, 1.8 and 3.6%), respectively, in the three groups.</td>
<td>468323</td>
</tr>
<tr>
<td>Safety and efficacy in RA patients.</td>
<td>In a phase I double-blind, randomized trial, a single iv dose of placebo or MRA (0.1, 1.0, 5.0 or 10.0 mg/kg) was administered to RA patients (n = 45).</td>
<td>Five of nine (55.6%) patients in the 5.0 mg/kg group and none in the placebo group demonstrated ACR20 responses. ESR and CRP levels in the 5 and 10 mg/kg groups normalized. The most common adverse effect reported was diarrhea, occurring in 17.8% of the patients.</td>
<td>475384</td>
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<tr>
<td>Safety and clinical response in RA patients.</td>
<td>In a phase I pilot study of refractory RA, patients (n = 11) received 50 or 100 mg MRA iv in saline once or twice weekly.</td>
<td>The treatment was well tolerated and no major side effects were observed. There was improvement in the level of swollen joints, pain, tenderness and morning stiffness in the joints, anemia, thrombocytosis, hypoalbuminemia, and polycythaemic hypergamma globulinemia. Clinical response was 88% as assessed by ACR20 criteria at 8 weeks.</td>
<td>475384</td>
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<tr>
<td>Safety and efficacy in Castleman's disease patients.</td>
<td>A phase I trial in which MRA (50 or 100 mg) was administered either once or twice weekly to treat Castleman's disease patients (n = 7).</td>
<td>Treatment was well tolerated except for a transient and mild decrease in granulocyte counts. Fever and fatigue disappeared, and laboratory index improved.</td>
<td>475337</td>
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