

RoACTEMRA in Rheumatoid Arthritis

What is RoACTEMRA?

RoACTEMRA/ACTEMRA (tocilizumab) is the first in a new class of treatments for rheumatoid arthritis (RA) which targets the interleukin-6 (IL-6) receptor.ⁱ IL-6 is a chemical messenger in the body responsible for the painful and persistent system-wide inflammation that people with RA suffer.ⁱⁱ

Excess levels of IL-6 are produced in people with RA. This not only leads to inflammation and long-term joint damage, but can also lead to a range of other complications that affect the whole body including anaemia, fatigue, weight loss, increased risk of cardiovascular disease and osteoporosis.^{2,iii,iv} Early treatment of RA is vital to prevent irreversible joint damage and progression of the disease.

RoACTEMRA inhibits the IL-6 receptor and reduces the impact of IL-6.¹ This prevents a worsening of RA, both in the joints and throughout the body.¹

Quality of Life

Every RA patient is likely to suffer from some degree of pain either from active inflammation in a joint or mechanical joint pain due to muscle weakness. The severity of pain will vary from person-to-person but can severely impact on a patient's quality of life and can be associated with poor sleep patterns and depression. Therefore, it is important that treatments for RA are effective in reducing pain. The ROSE study demonstrated that adding RoACTEMRA to existing disease-modifying-anti-rheumatic-drugs (DMARDs) can achieve rapid reductions in pain and disease activity as early as week one compared to treatment with DMARDs alone.^v

In the ACT-SURE open label study, in a setting closer to clinical practice than is typical of phase III studies, response to RoACTEMRA treatment was rapidly perceived by patients and increased over time. Improvements in Health Related Quality of Life (QoL) and disability (as assessed by patients' completing validated questionnaires) occurred as early as week four, and continued through week 24.^{vi}

High remission rates

RA is a lasting condition and patients will usually take medication for all of their life. Data from two long-term extension studies demonstrate that the percentage of RoACTEMRA patients achieving remission (the period during which the symptoms of a disease subside) from their disease increased steadily over a two-year period, from 27 percent at 24 weeks to 50 percent at 96 weeks.^{vii}

Preventing joint damage

Data from the LITHE study has previously shown that patients receiving RoACTEMRA in combination with methotrexate (MTX) had significantly less damage to their joints at two years, compared to patients who received MTX alone in the control group. Specifically, patients with RA treated with RoACTEMRA plus MTX suffered 81 percent less damage to their joints compared to those treated in the control group at week 104.^{viii}

Results from the recent ACT-RAY MRI substudy have shown that reductions in synovial membrane (the soft tissue that lines all synovial joints) and bone inflammation at week 12 were maintained through to week 52 with RoACTEMRA therapy.^{ix}

Efficacy in monotherapy

MTX is widely prescribed for people with RA. However, up to 40% of patients do not adequately respond to, and/or experience adverse events with MTX, and require other DMARDs and/or biologic agents to control inflammation and therefore may benefit from an alternative treatment approach for their RA.^x

Data from the AMBITION study demonstrated that RoACTEMRA is the only therapy to have proven superiority to MTX in monotherapy, based on an improvement of RA symptoms of 20 percent, 50 percent and 70 percent (ACR20, ACR50 and ACR70) at six months.^{xi}

- 70 percent of patients receiving RoACTEMRA (8mg/kg) monotherapy achieved a 20 percent improvement in their RA symptoms compared to 52 percent of patients receiving MTX alone. This improvement was seen as early as two weeks in those patients taking RoACTEMRA, and increased over time.
- Almost three times as many RoACTEMRA patients achieved disease remission compared to those on MTX alone.⁹

In addition, findings from a sub-analysis of the open-label ACT-SURE study previously showed that there was no apparent difference in clinical outcomes in patients treated with RoACTEMRA monotherapy versus RoACTEMRA combination treatment with DMARDs.^{xii}

Furthermore, results from the randomised controlled ACT-RAY study have now demonstrated that RoACTEMRA alone is as efficacious as RoACTEMRA plus MTX.^x

Highly effective in the treatment of systemic juvenile idiopathic arthritis (sJIA)

There is an unmet need in the treatment of sJIA, a life-threatening condition with systemic symptoms, growth retardation, and arthritis. sJIA has a relatively poor response to traditional RA treatments, however recent data has demonstrated the efficacy of RoACTEMRA in this severe childhood disease.

One year data from the Phase III TENDER study has shown that RoACTEMRA is highly effective and generally well tolerated in patients with sJIA. 88 percent of patients achieved a 30 percent reduction in symptoms (JIA ACR30^{**}) plus absence of fever, with 89 percent achieving JIA ACR70 and 65 percent achieving JIA ACR90^{**} at week 52.

RoACTEMRA was recently licensed in the US for treatment of this patient population.

*** The standard definition of improvement for use in clinical trials of JIA*

Improvement in systemic manifestations of RA

RA is a systemic disease, meaning that it can affect the whole body and internal organs.^{xiii} Whilst this is not true for everyone that has RA, it can lead to a range of other complications including fatigue, anaemia and an increased risk of cardiovascular disease.^{2,3,4}

Studies have shown that RoACTEMRA has the additional benefit of improving some of the systemic disease elements of RA. In particular, RoACTEMRA can:

- Help patients with anaemia by normalising haemoglobin levels^{xiv}
- Improve fatigue^{xv}

RoACTEMRA was first approved in Japan, and launched by Chugai in June 2005 as a therapy for Castleman's disease; in April 2008, additional indications for rheumatoid arthritis (RA), polyarticular

juvenile idiopathic arthritis and systemic-onset juvenile idiopathic arthritis were also approved in Japan. RoACTEMRA was approved in the European Union in January 2009 for the treatment of RA in patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) inhibitors. It is also approved for use in over 90 other countries, including India, Brazil, Switzerland, and Australia. RoACTEMRA was approved in the United States in January 2010 for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF inhibitors. In addition, RoACTEMRA is now approved in the United States for the treatment of active SJIA in patients two years of age and older.

RoACTEMRA is the result of research collaboration by Chugai and is also being co-developed globally with Chugai.

ⁱ Sebba A. Tocilizumab: The first interleukin-6-receptor inhibitor. *American Journal of Health-System Pharmacy* 2008;65(15):1413-1418

ⁱⁱ Lipsky P Interleukin-6 and rheumatic diseases. *Arthritis Res Ther* 2006; 8 (Suppl 2):S4

ⁱⁱⁱ Yoshizaki K *et al.*, Therapy of rheumatoid arthritis by blocking IL-6 signal transduction with a humanized anti-IL-6 receptor antibody. *Springer Semin Immunopathol* 1998;20:247–259

^{iv} Maggio M *et al.*, Interleukin-6 in Aging and Chronic Disease: A Magnificent Pathway. *Journal of Gerontology* 2006;61A(6):575-584

^v Yazici Yet *et al.*, Significant improvement in disease activity after one week of treatment with tocilizumab in patients with rheumatoid arthritis. The ROSE study. Abstract presented at EULAR 2009

^{vi} Bykerk VP *et al.*, Health-Related Quality of Life (HRQoL) in Tocilizumab (TCZ)-Treated Rheumatoid Arthritis (RA) Patients With Inadequate Response (IR) to Previous Treatments: ACT-SURE Results. Abstract presented at EULAR 2011.

^{vii} Smolen J *et al.*, Long-term efficacy of tocilizumab in rheumatoid arthritis for up to 3.5 years. Oral presentation at ACR, 18th October 2009

^{viii} Fleischmann R *et al.* LITHE: Tocilizumab inhibits radiographic progression and improves physical function in rheumatoid arthritis (RA) patients (Pts) at 2 years with increasing clinical efficacy over time. Oral presentation at ACR, 18th October 2009

^{ix} Troum O *et al.*, Early reductions in synovitis and osteitis with tocilizumab therapy are maintained through week 52: results from the ACT-RAY MRI substudy. Abstract presented at EULAR 2011

^x Pincus T, *et al.* *Clin Exp Rheumatol* 2010; 28(Suppl. 61):S68–S79.

^{xi} Jones G *et al.*, Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. *ARD Online First*, published 17 March 2009

^{xii} Bykerk *et al.* ACR 2010; Poster 1840

^{xiii} National Rheumatoid Arthritis Society. What is it? Available at

http://www.nras.org.uk/about_rheumatoid_arthritis/what_is_ra/what_is_ra.aspx. Accessed in April 2011

^{xiv} RoACTEMRA® (tocilizumab) Summary of Product Characteristics. Roche Registration Limited. June 2010.

^{xv} Genovese MC, *et al.* Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy (TOWARD) study. *Arthritis & Rheumatism* 2008;58(10):2968-2980