ACTEMRA™ in Rheumatoid Arthritis

What is ACTEMRA?

ACTEMRA/RoACTEMRA (tocilizumab) is the first in a new class of treatments for rheumatoid arthritis (RA) which target interleukin-6 (IL-6),[1] a chemical messenger in the body responsible for the painful and persistent inflammation that people with RA suffer.[2]

Excess levels of IL-6 are produced in the joints of 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.[2,3,4,5] Early treatment of RA is vital to prevent irreversible joint damage and progression of the disease. ACTEMRA inhibits the activity of IL-6 and reduces its impact.[1] This prevents a worsening of RA, both in the joints and throughout the body.[1]

High remission rates across different patient types

The availability of new biologic therapies for RA, such as ACTEMRA, has made remission a realistic goal for patients. Remission (when the symptoms of a disease are either greatly reduced or no longer evident) is measured by the 'DAS28' scoring system - a widely accepted method of defining disease activity. A patient is considered to be in remission when they have a score of DAS28 <2.6.[6]

Across the pivotal Phase III studies 30 percent of people with RA treated with ACTEMRA, regardless of previous treatment, have been shown to achieve DAS28 remission at 24 weeks.[7,8,9,10]

Preventing joint damage and improving physical function

Data from the LITHE study showed patients receiving ACTEMRA in combination with methotrexate (MTX) had significantly less damage to their joints at two years, compared to patients who received MTX in the control group. The data showed that with long-term use, patients with RA treated with ACTEMRA 8mg/kg plus MTX suffered 81 percent less damage to their joints compared to those treated in the control group at week 104.[11]

Rapidly reducing symptoms

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 depressed mood. Therefore, it is important that treatments for RA are effective in reducing pain symptoms. The ROSE study showed that adding ACTEMRA 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.[12]

Increasing effectiveness over time

RA is a life-long condition and patients will usually take medication for all of their life. Data from two long-term extension studies[13] demonstrate that the percentage of ACTEMRA patients achieving remission from their disease (DAS28<2.6) increased steadily over a two-year period, from 27 percent at 24 weeks to 50 percent at 96 weeks. ACTEMRA was also shown to improve the patients' ability to perform normal daily activities, as assessed by the Health Assessment Questionnaire (HAQ).[14]

Proven superiority over methotrexate

ACTEMRA is the only therapy to have proven superiority to MTX in monotherapy, based on an improvement of symptoms of 20 percent, 50 percent and 70 percent (ACR20, ACR50 and ACR70)[15] at 6 months. Seventy per cent of patients receiving ACTEMRA (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 ACTEMRA (24 percent versus 10 percent for MTX patients), and it increased over time. In addition, almost three times as many ACTEMRA patients achieved disease remission compared to those on MTX alone (34 percent vs. 12 percent).[7]

ACTEMRA vs. other agents in achieving ACR70

A recent meta-analysis compared the patterns of ACR response rates between ACTEMRA and other biologic agents in patients with RA who have an inadequate response (IR) to DMARDs and suggests that there is a higher likelihood of DMARD-IR patients achieving an ACR70 outcome with ACTEMRA versus other biologic agents analysed.[16]

ACTEMRA rapid and effective in the treatment of systemic juvenile idiopathic arthritis

Recent data has demonstrated the efficacy of ACTEMRA's use in a severe children's disease, systemic juvenile idiopathic arthritis (sJIA), a life-threatening condition with systemic symptoms, growth retardation, and arthritis. There is an unmet need in the treatment of sJIA as it has a relatively poor response to traditional RA treatments and there is currently no licensed treatment for this patient population. Data from the Phase III TENDER study showed following three months of treatment 85 percent achieved 30 percent improvement (JIA ACR30) in the signs and symptoms of sJIA plus absence of fever, compared to 24 percent of patients receiving placebo. Further data showed 70 percent achieved JIA ACR70 and 37 percent achieved ACR90. In addition to the significant improvement in JIA ACR response, nearly two thirds were free of rash after three months.[17]

Approval of ACTEMRA

ACTEMRA 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 DMARDs or anti-tumour necrosis factors (anti-TNFs). It is also approved for use in several other countries, including India, Brazil, Switzerland, Australia and Canada. In June 2010 ACTEMRA received a license extension from the European Commission to extend its indication to reduce the rate of progression of joint damage and improve physical function in patients with RA, when given in combination with MTX.

ACTEMRA 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 RA, JIA and sJIA were also approved in Japan.

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

ACTEMRA Phase III clinical trials

The Phase III clinical trial programme for ACTEMRA consists of five trials, designed to investigate the safety, efficacy and tolerability of ACTEMRA.[7,8,9,10,11] More than 4,000 patients across 41 countries have been involved in the trials, and over 2,500 of those patients participating in the Phase III OPTION, TOWARD, RADIATE and AMBITION trials entered the long-term extension studies (GROWTH95;

GROWTH96). The Phase III multi-national ACTEMRA clinical trial programme is the most comprehensive trial programme for any biologic in RA.

ACTEMRA Phase III clinical trials

- **OPTION** (T**O**cilizumab **P**ivotal **T**rial in Methotrexate **I**nadequate resp**ON**ders)
- **TOWARD** (**T**ocilizumab in c**O**mbination **W**ith traditional DM**ARD** therapy)
- **AMBITION** (**A**CTEMRA versus **M**ethotrexate double-**B**lind **I**nvestigative **T**rial **I**n m**ON**otherapy)
- **RADIATE** (**R**esearch on **A**CTEMRA **D**etermining eff**I**cacy after **A**nti-**T**NF Failur**E**s)
- **LITHE** (Toci**LI**zumab safety and **THE** prevention of structural joint damage)
- **ROSE** (**R**apid **O**nset and **S**ystemic **E**fficacy)
- **TENDER** (Tocilizumab in patients with systemic juvenile idiopathic arthritis (sJIA))

References:

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[11] 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
[12] Y. Yazici *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
[13] 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

[14] HAQ, or the Health Assessment Questionnaire Disability Index, is a patient self-report functional status (disability) measurement used to assess the patient's functional ability and discomfort during the past week. It is a commonly used instrument in many disease areas, including RA

[15] The ACR response is a standard assessment used to measure patients' responses to anti-rheumatic therapies, devised by the American College of Rheumatology (ACR). It requires a patient to have a defined percentage reduction in a number of symptoms and measures of their disease. For example, a 20, 50, or 70% level of reduction (the percentage of reduction of RA symptoms) is represented as ACR20, ACR50 or ACR70. An ACR70 response is exceptional for existing treatments and represents a significant improvement in a patient's condition

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