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Tocilizumab (RoACTEMRA) [subcutaneous injection with an auto injector device] for adult patients with moderate to severe active rheumatoid arthritis - after DMARD failure

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LAY SUMMARY

Rheumatoid arthritis (RA) is a long-term condition that causes pain, swelling and stiffness in the joints. The condition occurs in women more often than men. The symptoms usually affect the hands, feet and wrists. There may be periods where symptoms become worse, known as flare-ups. Some people with RA also experience problems in other parts of the body, or more general symptoms such as tiredness and weight loss. RA is an autoimmune disease (the immune system attacks the cells that line the joints), resulting in the symptoms of RA. Over time, this can damage the joint itself, the cartilage and nearby bone.

There is currently no cure for rheumatoid arthritis. The most common treatment options are steroids to reduce inflammation, medications to reduce pain and inflammation and medications that slow the progression of joint damage from RA. Tocilizumab is already licensed for the treatment of RA as both intravenous and subcutaneous (pre-filled syringe) formulations, however its use, via an auto-injector device is being developed. This is expected to improve the ease of patients treating themselves, in those who have active moderate to severe RA who do not respond to some conventional treatments.

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TARGET GROUP

Rheumatoid arthritis (RA) in adults: active; moderate to severe - after failure of disease-modifying anti-rheumatic drugs (DMARD) or anti-tumour necrosis factor (TNF)

TECHNOLOGY

DESCRIPTION

Tocilizumab (RoACTEMRA) is the first interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody developed for the treatment of RA to help tackle this debilitating disease.[1]

It binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of immune cells including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haematopoiesis.[2]

Tocilizumab is administered subcutaneously via a pre-filled syringe, at 162 mg weekly, in the completed phase III clinical trial,[3] and is now being considered in conjunction with an auto-injector device.[4] Tocilizumab is also available as an intravenous formulation administered at doses of 8mg/kg.

Tocilizumab (162 mg subcutaneous injection) is already licensed by the EMA for the treatment of giant cell arteritis in adult patients. Tocilizumab, in combination with methotrexate (MTX), is indicated for severe, active and progressive RA in adults not previously treated with MTX, and also for moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more DMARDS or tumour necrosis factor (TNF) antagonists. In these patients, tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.[5]

Tocilizumab is in phase II and phase III clinical trial development for the following conditions[2]:

- Schnitzlers syndrome
- Cardiovascular disease
- Pulmonary arterial hypertension
- Amyotrophic lateral sclerosis
- Refractory adult polymyositis and dermatitis
- Takayasu arteritis
- Systemic sclerosis
- Osteoarthritis of the hand
- Uveitis

INNOVATION and/or ADVANTAGES

Tocilizumab administration via auto-injector is expected to improve patient convenience,[4] therefore, this would improve compliance with tocilizumab use in patients with moderate to severe RA after DMARD failure.

DEVELOPER

Roche Products Ltd

PATIENT GROUP

BACKGROUND

RA is a chronic, inflammatory, multi-system, progressive autoimmune disease affecting the synovial joints, typically the small joints of the hands and feet, which are often affected bilaterally and symmetrically. Clinical features of RA include joint pain (usually worse after periods of rest or inactivity), joint swelling, stiffness and loss of function. On palpation, affected joints are tender, warm and give a 'boggy' feel. Extra-articular presentations may include lymphadenopathy, rheumatoid nodule (occurring over extensor surfaces in 20-30% people with RA), cardiopulmonary disease (e.g. pleurisy, intrapulmonary nodules, diffuse interstitial fibrosis and atherosclerosis), eye disease (including keratoconjunctivitis, dry eyes/sicca, episcleritis and corneal ulcerations) and rheumatoid vasculitis (typically ischaemic mononeuropathy and progressive scleritis).[6] Systemic features include morning stiffness, malaise, fatigue, fever and weight loss. Symptoms may be insidious, palindromic (waxing and waning) or explosive in onset. Rarely, patients may present with fever, joint pain or weight loss. Risk factors for RA include a genetic predisposition, which is oligogenic including the shared epitope on chromosome 6), and environmental triggers, including smoking in susceptible individuals.[7]

The severity of the disease is measured using the composite disease activity score (DAS28), which consists of the assessment of 28 joints for swelling/tenderness, the patient's assessment of health and erythrocyte sedimentation rate or C-reactive protein. DAS28 <3.2 indicates low disease activity, DAS28 ≥3.2 and ≤5.1 indicates moderate activity, and DAS28 >5.1 indicates high activity.[8] Additionally the severity of RA can be defined by the stage of disease. As the disease progresses beyond the early stage (stage I), there is a spread of inflammation in synovial tissue, affecting joint cavity space across joint cartilage. This inflammation gradually results in cartilage destruction, accompanied by a narrowing of the joint, and characterises stage II or moderate RA. Severe RA (stage III) is marked by formation of pannus in the synovium and loss of joint cartilage which exposes bone beneath the cartilage. These joint changes and deformities become evident on x-ray. Stage IV is referred to as end stage RA during which the inflammatory process subsides and formation of fibrous tissue and/or deformity of the bone results in ceased joint function. This stage may be associated with formation of subcutaneous nodules.[9]

Without adequate treatment, at 20 years after diagnosis, more than 60% of patients with RA may develop significant functional impairment (stage III), including need of mobility aids, loss of ability for self-caring, and requirement of joint replacement.[7] The overall impact of RA is that it can lead to progressive disability and a decrease in quality of life and functional status,[10] resulting in overall impaired health-related quality of life, and loss of productivity and social functions.[11] Approximately one-third of people stop work within two years of onset, and after ten years, 30% of patients are

considered severely disabled.[12,13] People with RA have reduced life expectancy and excess cardiovascular mortality.[14]

CLINICAL NEED and BURDEN OF DISEASE

The estimated prevalence of RA in England is 0.86%, equivalent to around 346,000 people.[15] The annual incidence of RA is 1.5 per 10,000 in males and 3.6 per 10,000 in females, which equates to approximately 12,000 new diagnoses each year in the UK.[11] Peak age of onset is 40-70 years and the disease is severe in around 15% of patients.[10] Around 10% of patients with RA (approximately 34,600 people) are eligible to receive current available biological treatments after the failure of conventional DMARDs.[11] In 2015-16, there were 61,142 admissions for RA (ICD-10 M06) in England resulting in 62,315 finished consultant episodes and 19,021 bed days.[16]

There is a 47% increased risk of death compared to the general population in patients with RA. Additionally 31% of early deaths in those with RA are due to cardiovascular disease, and a further 29% of all deaths are caused by pulmonary problems.[17] In 2015, 858 deaths from RA (and juvenile arthritis) were registered in England and Wales.[18]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Baricitinib for moderate to severe rheumatoid arthritis (TA466). August 2017.
- NICE technology appraisal. Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor (TA415). October 2016.
- NICE technology appraisal. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (TA375) January 2016.
- NICE technology appraisal. Tocilizumab for the treatment of rheumatoid arthritis (TA247). February 2012.
- NICE technology appraisal. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs (TA225). June 2011.
- NICE technology appraisal. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (TA195). August 2010.
- NICE technology appraisal. Certolizumab pegol for the treatment of rheumatoid arthritis (TA186). February 2010.
- NICE quality standards. Quality standard for rheumatoid arthritis (QS33). June 2013.
- NICE clinical guidelines. Rheumatoid arthritis in adults (CG79). February 2009. [updated December 2015]

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.

OTHER GUIDANCE

- British Society of Rheumatology. Top ten quality standards for RA. 2012.
- Scottish Intercollegiate Guidelines Network. Management of early rheumatoid arthritis. (123). 2011.
- European League Against Rheumatism (EULAR). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. 2010
- American College of Rheumatology. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. 2015

CURRENT TREATMENT OPTIONS

RA is currently incurable; however, symptoms can usually be managed. The goal of management is to suppress disease, control pain, reduce functional limitation, reduce risk of permanent joint damage and achieve clinical remission. The clinical management of RA includes physical therapy, surgical interventions and a range of pharmacological treatments.[12] The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommend targeting inducement of remission or low disease activity. Joint damage, which may begin early in the disease course, is shown to have high correlation with impaired physical function and long-term disability. With a modern strategy of early treatment, slowing or halting the progression of underlying joint damage is usually achievable. Not all patients respond to current biologic or small molecule DMARDs and some patients may experience loss of efficacy or require discontinuation of therapy due to adverse events (AEs), which emphasises the need for additional or alternative treatment options. There is an unmet need for alternative treatment options for a subgroup of around 10-15% of patients who are unresponsive to, or intolerant of all existing treatment options.[19]

There are two main types of pharmacological therapies for RA, including;[11, 12, 13, 20]

1. Non-biologic therapies:

- Corticosteroids.
- Non-steroidal anti-inflammatory drugs (NSAIDs).
- Cyclo-oxygenase-2 (COX-2) inhibitors.
- Conventional DMARDs: e.g. methotrexate, sulfasalazine, leflunomide and azathioprine (first line treatment). Usually administered within three months of diagnosis, either as combination therapy (methotrexate and at least one other conventional DMARD) or as monotherapy (when combination therapy is deemed inappropriate).

2. Biologic DMARDs:

- TNF-α inhibitors: e.g. etanercept, infliximab, adalimumab, golimumab and certolizumab pegol. TNFα inhibitors work by modulating a key costimulatory signal required for full activation of T lymphocytes expressing CD28.
- IL-6 inhibitors: IL-6 inhibitor, tocilizumab, is currently recommended for use in combination with methotrexate for patients with RA with a DAS28 score >5.1 after failure of at least two conventional DMARDs, including methotrexate.
- Abatacept

If methotrexate is unsuitable, treatment with biologic DMARDs may be used as monotherapy. However, amongst patients who have responded to TNF-α inhibitors, a significant number of patients

discontinue therapy over time due to loss of efficacy, intolerance or AEs. In a systematic study of European registries, after 5-years pooled drug survival rates of TNF-α inhibitors were 37-52% depending on the TNF-α inhibitor. In patients receiving TNF-α inhibitors, switching to an IL-6 inhibitor may be more effective than switching to a second (or third) anti-TNF-α.

Rituximab in combination with methotrexate is recommended for patients with severe active RA who have had an inadequate response to, or are intolerant of other DMARDs, including at least one TNF-α inhibitor. Where rituximab is unsuitable or ineffective, biologic DMARDs may be used in combination with methotrexate or as monotherapies.

Baricitinib in combination with methotrexate, is recommended as an option for treating severe (DAS28 >5.1) active RA in adults whose disease has responded inadequately to intensive therapy with conventional DMARDS), if the company provides baricitinib with the discount agreed in the patient access scheme. Additionally baricitinib can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, with treatment continued only if there is a moderate response measured using EULAR criteria at 6 months after starting therapy.

EFFICACY and SAFETY	
Trial	SUMMACTA, NCT01194414, adults aged ≥18 years old; tocilizumab (subcutaneous) vs tocilizumab (intravenous) vs tocilizumab (subcutaneous then intravenous) vs tocilizumab (intravenous then subcutaneous); phase III
Sponsor	Roche Products Ltd
Status	Published[21]
Source of Information	Trial registry,[3] Publication[21]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active-controlled study
Participants	n=1262; aged ≥18 years old; active RA; moderate to severe; inadequate response to current DMARD therapy
Schedule	Subjects were randomised into four treatment arms: Arm 1: Subjects received tocilizumab at a dose of 162 mg subcutaneously, weekly plus intravenous placebo every 4 weeks during the double-blind period from baseline to week 24. Non-biologic DMARD at a stable dose continued throughout the study. Arm 2: Subjects received tocilizumab at a dose of 8 mg/kg intravenously every 4 weeks plus subcutaneous placebo weekly during the double-blind period from baseline to week 24. Non-biologic DMARDs at a stable dose continued throughout the study. Arm 3: Subjects who received tocilizumab 162 mg subcutaneous injection weekly plus placebo to tocilizumab intravenous infusion every 4 weeks for 24 weeks in double blind treatment period switched to tocilizumab 8 mg/kg intravenous infusion every 4 weeks for a total of 72 weeks in open label extension period. Non-biologic DMARDS at a stable dose continued throughout the study. Arm 4: Subjects who received tocilizumab 8 mg/kg infusion every 4 weeks plus placebo to tocilizumab SC injection weekly in double blind treatment period switched to tocilizumab 162 mg subcutaneous injection weekly for a total of 72 weeks in open label extension period. Non-biologic DMARDS at a stable dose continued throughout the study.
Follow-up	The study had a double-blind period of 24 weeks followed by an open-label period of 72 weeks.
Primary Outcomes	Percentage of participants achieving an American College of Rheumatology Criteria (ACR20) response at week 24 Percentage of participants with adverse events, serious adverse events and clinically significant laboratory assessments from baseline to up to 3 months after last dose of study drug (approximately up to 2 years)

Secondary Outcomes	Percentage of participants achieving an American College of Rheumatology Criteria (ACR50) response at week 24 Percentage of participants achieving an American College of Rheumatology Criteria (ACR70) response at week 24 Percentage of participants With American College of Rheumatology Criteria (ACR20, ACR50, ACR70) at week 97 Percentage of participants With DAS28 remission at week 24 and week 97 Percentage of participants achieving a decrease of ≥0.3 in the Health Assessment Questionnaire-Disability Index (HAQ-DI) from baseline to week 24 and from baseline to week 97 Percentage of participants who withdrew because of lack of therapeutic response at week 24 and week 97 Area under the serum concentration curve of tocilizumab after first subcutaneous injection or intravenous infusion at week 0: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after first dose Area under the serum concentration curve of tocilizumab at steady state for subcutaneous and intravenous treatment at week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose Minimum serum concentration (Cmin) of tocilizumab at week 0 and week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose Maximum serum concentration (Cmax) of tocilizumab at week 0 and week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose Time to maximum serum concentration (Tmax) of tocilizumab at week 0 and week 20: at 6 hours (hr), 24 hr, 48 hr, 96 hr, 120 hr and 168 hr after dose Change from baseline in serum interleukin-6 (IL-6) concentration to week 25 Change From baseline in serum soluble interleukin-6 receptor (sIL-6R) concentration to week 97 Percentage of participants who developed antibodies to tocilizumab at week 97

Key Results	At week 24, 69.4% (95% CI 65.5 to 73.2) of tocilizumab-SC-treated patients versus 73.4% (95% CI 69.6 to 77.1) of tocilizumab-IV-treated patients achieved an ACR20 response (weighted difference between groups −4.0%, 95% CI −9.2 to 1.2); the 12% NIM was met. ACR50/70 responses, DAS28 and physical function improvements were comparable between the tocilizumab-SC and tocilizumab-IV groups. The safety profiles of tocilizumab-SC and tocilizumab-IV were similar, and the most common adverse event was infection. Injection-site reactions (ISR) occurred more frequently in the tocilizumab-SC group than in the tocilizumab-IV (placebo-SC) group. No anaphylaxis was reported over the 24 weeks.[21]
Adverse effects (AEs)	Injection site reactions (ISRs), which occurred more frequently in patients receiving tocilizumab subcutaneously than in patients receiving tocilizumab intravenously; however, the overall frequency of ISRs decreased over 97 weeks. All ISRs were common terminology criteria for adverse events grade 1 or 2. The most common ISR symptom was erythema.[21]
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Tocilizumab is already marketed in the UK for the treatment of RA; 4 pre-filled syringes with 162mg/0.9ml solution, for subcutaneous use, have an NHS Indicative Price of £913.12.[22]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☒ Other: *improved patient convenience and compliance with medication use*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other ☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs ☐ Reduced drug treatment costs

☐ Other increase in costs ☐ Other reduction in costs

☐ Other ☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified ☒ None identified

INFORMATION FROM

Information was received by Roche Products Ltd

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