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Tocilizumab (RoActemra) for adults with systemic sclerosis – second line

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LAY SUMMARY

Systemic sclerosis is a condition where the body becomes overactive causing the immune system to attack the layers of cells under the skin and around internal organs and blood vessels. The most common symptom is the thickening and hardening of the skin. Other common symptoms include Raynaud's phenomenon (poor blood circulation causing numbness and coldness in the fingers and toes), and muscle and joint pain. It can be further subdivided into limited systemic sclerosis where scarring of the skin is confined to below the elbows and knees and the face, and diffuse systemic sclerosis, where scarring is more widespread on the body and affects internal organs. Systemic sclerosis affects women four times more than men, however, the disease develops more severely in men.

There is currently no cure for systemic sclerosis and treatment options focus on the management of symptoms. Tocilizumab is intended for the treatment of systemic sclerosis in adults. It is currently in development and early research indicates that it is able to target the key mechanisms thought to be responsible for the disease. If licensed, it could provide a new treatment option for adults with systemic sclerosis.

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TARGET GROUP

Systemic sclerosis in adults - second line

TECHNOLOGY

DESCRIPTION

Tocilizumab (RoActemra) is the first interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody developed for the treatment of rheumatoid arthritis 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 under development for the treatment of systemic sclerosis in adults and is administered subcutaneously via a pre-filled syringe, at 162 mg weekly, in two phase III clinical trials.[3,4]

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 rheumatoid arthritis in adults not previously treated with MTX, and also for moderate to severe active rheumatoid arthritis in adult 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) 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 (20 mg/ml concentrate for solution for infusion) is already licensed for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with nonsteroidal anti-inflammatory drugs and systemic corticosteroids. It can also be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. Tocilizumab in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. It can also 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]

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

- Uveitis

INNOVATION and/or ADVANTAGES

The complex pathophysiology of systemic sclerosis is not fully understood. Current treatment options do not target the underlying disease mechanism, but instead focus on only one of the systems affected by the condition. Key opinion leaders emphasise that it would be ideal for one therapy to target all of the disease manifestations, and that the development of biologics will offer an improvement in the standard of care surrounding systemic sclerosis.[6]

Recent evidence indicates that tocilizumab has the ability to modify inflammation, vasculopathy and tissue fibrosis, which are considered the three primary pathological features of systemic sclerosis.[7] Therefore if licenced, tocilizumab will offer a novel treatment option for systemic sclerosis.

DEVELOPER

Roche Products Ltd and Chugai Pharma UK Ltd

AVAILABILITY, LAUNCH or MARKETING

Tocilizumab was designated Breakthrough Therapy in 2015 and Orphan Drug Designation in 2013 in the USA for systemic sclerosis (scleroderma).[1]

PATIENT GROUP

BACKGROUND

Systemic sclerosis is a complex disease of the connective tissue which affects skin, blood vessels, heart, lungs, kidneys, gastrointestinal (GI) tract and musculoskeletal system. When this affects the internal organs, significant mortality and morbidity arises.[8] The primary pathological features of systemic sclerosis are excessive collagen production and deposition, vascular damage and immune system activation via autoantibody production and cell-mediated autoimmune mechanisms.[9] It can be further subdivided into limited cutaneous systemic sclerosis where fibrosis is confined to below the elbows and knees and the face, and diffuse cutaneous systemic sclerosis, where fibrosis is more widespread on the body and affects internal organs.[6]

The initial symptom presented in most cases of systemic sclerosis is Raynaud's phenomenon.[10] This is caused by the constriction of the blood vessels, which reduces the blood supply to the fingers and toes. Additional symptoms found in most people are hardening of the skin and swelling of the hands and feet, resulting in joint pain. Systemic sclerosis can further affect the digestive system and lead to difficulties in swallowing or oesophageal dysmotility, which provokes gastroesophageal reflux and sometimes dysphagia.[10,11]

The pathogenesis of systemic sclerosis remains unclear, however numerous risk factors have been identified.[6] Several risk factors have been determined for the disease, such as sex, genetics, ethnicity, and to some extent, exposure to environmental contaminants.[7] It is thought that environmental triggers and risk factors may lead to the development of the disease in genetically susceptible people.[12] Women are four times more likely than men to develop systemic sclerosis,[10] however men have a worse prognosis. Pregnancy also increases scleroderma risk by 2.8 times when compared to

those who have never been pregnant.[7] In addition, several small genetic changes and certain human leukocyte antigen alleles (gene responsible for encoding the major histocompatibility complex cell surface protein, which regulates the immune system) have been associated with increased risk of systemic sclerosis.[13]

Systemic sclerosis can further lead to life-threatening complications of the lung such as pulmonary fibrosis and, less frequently, pulmonary arterial hypertension.[10] Survival is dependent on the involvement of the visceral organs.[14]

CLINICAL NEED and BURDEN OF DISEASE

For the UK in 2014, the prevalence of systemic sclerosis in adults above 18 years was 4,948. The prevalence of Raynaud's phenomenon in those with systemic sclerosis was 4,765 (96% of the systemic sclerosis population).[5] In 2016, there were 3,654 admissions for systemic sclerosis (ICD-10 M34) in England, resulting in 3,849 bed days and 3,842 finished consultant episodes.[15]

The prognosis for those with systemic sclerosis depends largely on the sub-type. For those with limited cutaneous systemic sclerosis there is an estimated 10-year survival rate of 80-90%, although, pulmonary arterial hypertension, which occurs in about 10% of cases, and severe lung fibrosis, may lead to a more severe prognosis. The prognosis for diffuse cutaneous systemic sclerosis is more severe due to the increased risk of life-threatening complications such as renal crisis, severe digestive involvement, severe lung fibrosis, and, sometimes, severe heart involvement and pulmonary arterial hypertension. This sub-type has an estimated 10-year survival rate of 60-80%.[10] According to a systematic review of worldwide data, survival rates in systemic sclerosis from diagnosis to 5 years was 75% and from diagnosis to 10 years was 63%.[16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Evidence Summary. Skin Involvement in systemic sclerosis: rituximab (ES7). March 2017.
- NICE Evidence Summary. Digital Ulcers: sildenafil (ESUOM42). March 2015.
- NICE Evidence Summary. Scleroderma: oral mycophenolate (ESUOM32). July 2014.

NHS ENGLAND and POLICY GUIDANCE

- NHS Clinical Commissioning Policy in development. Rituximab in Connective Tissue Disease associated Interstitial Lung Disease (adults) A/14/X01.
- NHS England. 2013/14 NHS Standard Contract for Specialised Dermatology Services (All Ages). A12/S/a.
- NHS England. Clinical Commissioning Policy: Sildenafil and Bosentan for the Treatment of Digital Ulceration in Systemic Sclerosis.

OTHER GUIDANCE

Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, Distler O, Clements P, Cutolo M, Czirjak L, Damjanov N. Update of EULAR recommendations for the treatment of systemic sclerosis. *Annals of the Rheumatic Diseases*. 2017; 0:1-12.

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CURRENT TREATMENT OPTIONS

There is no cure for systemic sclerosis and treatment focuses mainly on managing and preventing organ related complications. Recommendations provided by the European League against Rheumatism recommend treatment options for the following complications: Raynaud's phenomenon, digital ulcers, pulmonary arterial hypertension, skin and lung disease, scleroderma renal crisis and gastrointestinal involvement. For those with rapidly progressive systemic sclerosis, haematopoietic stem cell transplantation has been newly recommended as a viable treatment option.[8]

Non-pharmacological strategies may also be used to relieve symptoms including moisturising the skin (to keep it supple and relieve itching), physiotherapy (to keep muscle supple and loosen tight skin), keeping hands and feet warm (for those with Raynaud's phenomenon), eating healthily, exercising and stopping smoking (to control blood pressure and improve circulation).[17]

EFFICACY and SAFETY

Trial	faSScinate NCT01532869; tocilizumab vs placebo; phase II/III
Sponsor	Roche Products Ltd
Status	Published
Source of Information	Trial registry[3] and publication[18]
Location	EU (incl UK), USA and Canada
Design	Randomised, placebo-controlled, double blind study
Participants	n=87; aged ≥18 years; active systemic sclerosis
Schedule	Randomised to receive tocilizumab (162 mg) by subcutaneous injection per week for week 0 to week 48 (blinded-treatment period) and then in the open-label period for week 48 to week 96; or receive tocilizumab matched placebo by subcutaneous injection per week for week 0 to week 48 (blinded-treatment period) and then received tocilizumab (162 mg) subcutaneous injection per week in the open-label period for week 48 to week 96.
Follow-up	Active treatment for 96 weeks
Primary Outcomes	Change from baseline in modified Rodnan Skin Score at week 24 Percentage of participants with treatment-emergent adverse events and serious adverse events [time frame: week 48]

Secondary Outcomes	Change from baseline in physical function assessed by Scleroderma Health Assessment Questionnaire Disability Index (SHAQ-DI) Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score Change from baseline in clinician's Global Assessment Change from baseline in patient's Global Assessment Change from baseline in functional assessment of Chronic Illness Therapy−Fatigue (FACIT-Fatigue) score Change From baseline in 5-D Itch scale Change from baseline in mRSS Percentage of participants who maintained or improved in mRSS Change from baseline in Tender Joint Count 28 (TJC28) Area Under the Concentration-Time Curve (AUC) Mean serum concentrations of Interleukin (IL)-6 Mean serum concentrations of Soluble IL-6 Receptor Percentage of participants with anti-tocilizumab antibody
Key Results	The least squares mean change in modified Rodnan skin score at 24 weeks was −3·92 in the tocilizumab group and −1·22 in the placebo group (difference −2·70, 95% CI −5·85 to 0·45; p=0·0915). The least squares mean change at 48 weeks was −6·33 in the tocilizumab group and −2·77 in the placebo group (treatment difference −3·55, 95% CI −7·23 to 0·12; p=0·0579). In one of several exploratory analyses, fewer patients in the tocilizumab group than in the placebo group had a decline in percent predicted forced vital capacity at 48 weeks (p=0·0373). However, we detected no significant difference in disability, fatigue, itching, or patient or clinician global disease severity. 42 (98%) of 43 patients in the tocilizumab group versus 40 (91%) of 44 in the placebo group had adverse events. 14 (33%) versus 15 (34%) had serious adverse events.[18]
Adverse effects (AEs)	Serious infections were more common in the tocilizumab group (seven [16%] of 43 patients) than in the placebo group (two [5%] of 44).[18]
Expected reporting date	-

Trial	focuSSced; NCT02453256; tocilizumab vs placebo; phase III
Sponsor	Roche Products Ltd
Status	Ongoing
Source of Information	Trial registry[4]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled, double blind study
Participants	n=212 (planned); aged ≥18 years; active systemic sclerosis
Schedule	Randomised to receive tocilizumab (162 mg) by subcutaneous injection per week for week 0 to week 47 (blinded-treatment period) and then in the open-label period for week 48 to week 96; or receive tocilizumab matched placebo by subcutaneous injection per week for week 0 to week 47 (blinded-treatment period) and then received tocilizumab (162 mg) subcutaneous injection per week in the open-label period for week 48 to week 96.
Follow-up	Active treatment for 96 weeks
Primary Outcomes	Change in Modified Rodnan Skin Score (mRSS)
Secondary Outcomes	Percentage of participants with ≥20%, 40%, or 60% improvement in mRSS Change in Forced Vital Capacity (FVC) Change in Health Assessment Questionnaire Disability Index (HAQ-DI) score Change in Patient Global Assessment Score Change in Physician Global Assessment Score Time to treatment failure according to mRSS, FVC, or Protocol-Specified Event Percentage of participants with adverse events Change in digital ulcer count Percentage of participants with anti-tocilizumab antibodies Correlation between anti-Tocilizumab antibody status and outcome measures pertaining to the efficacy, safety, and pharmacokinetics of Tocilizumab Erythrocyte sedimentation rate (ESR) Serum interleukin (IL)-6 level Serum soluble IL-6 receptor (sIL-6R) level Serum C-Reactive protein (CRP) level

	Serum tocilizumab concentration Correlation between serum tocilizumab concentration and outcome measures pertaining to the efficacy, safety, and immunogenicity of tocilizumab
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date February 2019

ESTIMATED COST and IMPACT

COST

Tocilizumab is already marketed in the UK for the treatment of rheumatoid arthritis; 4 pre-filled syringes with 162mg/0.9ml solution, for subcutaneous use, have an NHS Indicative Price of £913.12.[19]

The drug cost range (per patient per year or patient per episode if less than one year) using the NHS Indicative Price is likely to be between £5,000 and £10,000.[a] Various Patient Access Schemes are also available for tocilizumab.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ 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

[a] Company confidential information

☒ Increased drug treatment costs	☐ Reduced drug treatment costs
☐ Other increase in costs	☒ Other reduction in costs: *reduced use of secondary care/specialist services*
☐ Other	☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified	☒ None identified

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