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Rexmyelocel-T for critical limb ischaemia in patients with diabetes mellitus

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LAY SUMMARY

Critical limb ischaemia (CLI) is a severe deterioration of the blood vessels, reducing blood flow to the limbs, most commonly the legs. This often results in severe pain, skin ulcers, and gangrene. Patients with diabetes mellitus (DM) have a higher risk of developing CLI. The main treatment for CLI is revascularisation, a surgical operation that usually involves using a balloon to open the blood vessel (angioplasty) or bypass surgery redirecting the blood flow by reconnecting blood vessels to bypass the damaged blood vessel (bypass surgery). A significant number of people with CLI, particularly those with DM, will not be able to have this surgery as there are too many risks. The only option for these patients is amputation.

The treatment, rexmyelocel-T, is being developed to relieve leg pain at rest and heal leg ulcers. The treatment uses cells from bone marrow which are injected into the damaged blood vessel, where they restore existing blood vessels and create new blood vessels. By improving the blood flow in the limb, this treatment aims to improve the patient's condition so that they do not require amputation.

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TARGET GROUP

Critical limb ischaemia (CLI) in patients with diabetes mellitus (DM) who are unsuitable for endovascular or surgical vascularisation – first line

TECHNOLOGY

DESCRIPTION

Rexmyelocel-T (REX-001) is a novel cell therapy that consists of autologous bone marrow-derived mononuclear cells (BM-MNCs) which, following administration to CLI patients, migrate to the ischaemic tissue.[1]

BM-MNCs are a rich source of progenitor cells, which directly contribute to vasculogenesis and indirectly stimulate angiogenesis through a paracrine mediated mechanism. The BM-MNCs potentially induce vasculogenesis by providing progenitor cells where circulating levels are low. The BM-MNCs also provide for cytokines at the site of ischemia (cells are injected directly into these areas) released from their constituent mesenchymal stromal cells (MSCs), monocytes, lymphocytes and other cells. Increased cytokine release results in both mobilization of additional endothelial progenitor cells (EPCs) from BM and recruitment of circulating EPCs to ischemic areas. The EPCs from whichever source integrate into the ischemic area and differentiate into mature endothelial cells (ECs) to form new capillaries. The BM-MNCS potentially induce angiogenesis through increasing the number of ECs in ischemic tissue and increasing activation of hypoxia inducible factor-1a (HIF-1a) and release of VEGF. The BM-MNCs may contribute to arteriogenesis through lumen enlargement of arteriolar anastomoses to form collateral vessels.[2]

Rexmyelocel-T is intended for use in patients with CLI Rutherford Category 4 and DM to provide relief of ischaemic rest pain in the legs, and for patients with CLI Rutherford Category 5 and DM to provide complete healing of ischaemic leg ulcers.[3]

In the phase III trials NCT03111238 and NCT03174522 rexmyelocel-T is administered in a single dose through an intra-arterial catheter.[4,5]

Rexmyelocel-T does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, rexmyelocel-T will offer a new treatment option for patients with CLI and DM who are unsuitable for endovascular or surgical vascularisation, who currently have few alternative therapies.

DEVELOPER

Rexgenero Ltd

AVAILABILITY, LAUNCH or MARKETING

Rexmyelocel-T was awarded PIM status for critical limb ischaemia by MHRA in April 2016.

In October 2016 Rexgenero Ltd received a Follow-up Scientific Advice letter from EMA that the design of the two phase III trials NCT03111238 and NCT03174522 was endorsed, and that if successful, these two trials would be sufficient for marking authorisation.[3]

PATIENT GROUP

BACKGROUND

Critical limb ischaemia (CLI), the end stage of peripheral arterial disease (PAD), is a severe obstruction of peripheral arteries, markedly reducing blood flow to the limbs. This often results in severe pain, skin ulcers, and gangrene leading to the requirement of limb amputation. Mortality rates can be as high as 40% within a year of diagnosis.[1]

Diabetes mellitus (DM) is a major risk factor for PAD, and patients with diabetes are twice as likely as those without diabetes to develop the condition. PAD also progresses more rapidly in those with diabetes, and these patients are five to 10 times more likely to need major amputation than patients without diabetes.[6]

PAD in patients with DM is often accompanied by peripheral neuropathy with sensory dysfunction. This means that patients may not be aware of the development of an ischaemic ulcer or gangrene, and the presentation of CLI in patients with diabetes is usually at a later stage than patients without diabetes, with more severe lesions.[7]

CLINICAL NEED and BURDEN OF DISEASE

Each year 50-100 per 100,000 population cases of CLI are diagnosed.[6]

The prognosis for CLI is poor. Within 1 year of onset, 25% of patients will have died, and 25% will have undergone major amputation.[8] Lower leg amputation is a high-risk procedure with a 30-day mortality of ±10% and less than 30% of surviving patients being ambulatory outdoors at 17 months of follow-up.[7]

Analysis of data from two trials found that patients with CLI and diabetes had an almost 20% risk of having major amputation in the first 6 months after inclusion in a trial, and within 5 years one in three patients with CLI and diabetes had a major amputation.[7]

It is not possible to identify hospital admissions for patients with a primary diagnosis of CLI. However, in England in 2015/16 there were 3,188 hospital admissions with primary procedure code (OPCS) X09 Amputation of leg, resulting in 110,394 FCE bed days. 1,364 admissions were coded with admission method of waiting list/planned/other (i.e. not emergency admissions), implying that these amputations were not following an immediate trauma.[9]

The population likely to be eligible to receive rexmyelocel-T could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Peripheral arterial disease: diagnosis and management (CG147). August 2012.
- NICE quality standard. Diabetes in adults (QS6). August 2016.
- NICE quality standard. Peripheral arterial disease (QS52). January 2014.
- NICE medical technologies guidance. The Debrisoft monofilament debridement pad for use in acute or chronic wounds (MTG17). March 2014.
- NICE medical technologies guidance. The MIST Therapy system for the promotion of wound healing (MTG5). July 2011.
- NICE guideline. Diabetic foot problems: prevention and management (NG19). January 2016.
- NICE guideline. Type 2 diabetes in adults: management (NG28). December 2015.
- NICE evidence summary. Critical limb ischaemia in peripheral vascular disease: intravenous iloprost (ESUOM24). December 2013.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Specialised Vascular Services (Adults). 170004/S.

OTHER GUIDANCE

- European Society for Vascular Surgery. Management of Critical Limb Ischaemia and Diabetic Foot: Clinical Practice Guidelines. December 2011.[10]

CURRENT TREATMENT OPTIONS

NICE guidance states that all people with CLI should be assessed by a vascular multidisciplinary team before treatment decisions are made. Revascularisation (angioplasty or bypass surgery) should be offered if necessary. [11] However, a significant proportion of patients are not suitable for revascularisation due to multiple conditions that lead to cardiovascular complications, or the absence of viable blood vessels.[1] Non-surgical treatments such as prostanoids, spinal cord stimulation and lumbar sympathectomy are generally thought to have little long-term benefit, so management of symptoms and amputation are recommended for patients who are unsuitable for revascularisation. In amputation the knee joint is preserved whenever possible for the sake of mobility, although this must be balanced with the need to ensure wound healing.[6]

EFFICACY and SAFETY

Trial	NCT03111238; Rexmyelocel-T vs placebo; phase III
Sponsor	Rexgenero Ltd
Status	Ongoing, recruiting
Source of Information	Trial registry[4]
Location	10 EU countries, incl UK
Design	Randomised, placebo-controlled
Participants	N=60 (planned); aged 18-85 yrs; critical limb ischaemia Rutherford category 4 and diabetes mellitus; first line
Schedule	Randomised to rexmyelocel-T or placebo in the index limb, given as a single intra-arterial administration
Follow-up	Follow-up 24 mths
Primary Outcomes	Complete relief from ischaemic rest pain without developing ischaemic lesions on the index leg at 12 mths
Secondary Outcomes	Not reported
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Anticipated completion date for primary endpoint reported as December 2019

Trial	NCT03174522; Rexmyelocel-T vs placebo; phase III
Sponsor	Rexgenero Ltd
Status	Ongoing, recruiting
Source of Information	Trial registry[5]
Location	10 EU countries, incl UK
Design	Randomised, placebo-controlled

Participants	N=78 (planned); aged 18-85 yrs; critical limb ischaemia Rutherford category 5 and diabetes mellitus; first line
Schedule	Randomised to rexmyelocel-T or placebo in the index limb, given as a single intra-arterial administration
Follow-up	Follow-up 24 mths
Primary Outcomes	Complete healing of all ischaemic ulcers on the index leg at 12 mths
Secondary Outcomes	Not reported
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Anticipated completion date for primary endpoint reported as December 2019

ESTIMATED IMPACT

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: improved quality of life for carers

☐ 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: additional costs due to bone marrow harvesting in an operating theatre under local/general anaesthesia, and infusion of the final product intra-arterially visualised by angiography[2]

☐ Other reduction in costs: social care costs, cost of treating ulcers, cost of amputation, cost of associated disabilities

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

[1] Cell and Gene Therapy Catapult. *Creating characterisation and potency assays for an autologous cell therapy product.* Available from: https://ct.catapult.org.uk/case-study/developing-characterisation-and-potency-assays [Accessed 27 September 2017]

[2] UKPharmaScan. *Technology Summary (641410).* Available from: https://www.ukpharmascan.org.uk/HS/technology/641410 [Accessed 27 September 2017] Login required

[3] Rexgenero. *Rexgenero receives confirmation from the EMA that the design of two confirmatory Phase III clinical trials for Rexmyelocel-T is acceptable.* Available from: http://www.rexgenero.com/rexgenero-receives-confirmation-from-the-ema-that-the-design-of-two-confirmatory-phase-iii-clinical-trials-for-rexmyelocel-t-is-acceptable/ [Accessed 27 September 2017]

[4] Clinical Trials.gov. *The Efficacy and Safety of Rexmyelocel-T to treat Ischaemic Rest Pain in subjects with CLI Rutherford Category 4 and DM: NCT03111238.* Available from: https://clinicaltrials.gov/ct2/show/study/NCT03111238?term=NCT03111238&rank=1&view=record [Accessed 27 September 2017]

[5] Clinical Trials.gov. *The Efficacy and Safety of Rexmyelocel-T to treat Ischaemic Ulcers in subjects with CLI Rutherford Category 5 and DM: NCT03174522.* Available from: https://clinicaltrials.gov/ct2/show/NCT03174522?term=NCT03174522&rank=1 [Accessed 27 September 2017]

[6] Peach G, Griffin M, Jones KG et al. Diagnosis and management of peripheral arterial disease. *British Medical Journal*. 2012;345:e5208. Available from: http://www.bmj.com/content/345/bmj.e5208 [Accessed 29 September 2017]

[7] Spreen MI, Gremmels H, Teraa M et al. Diabetes is associated with decreased limb survival in patients with critical limb ischaemia: pooled data from two randomized controlled trials. *Diabetes Care.* 2016 Nov; 39(11): 2058-2064.

[8] Wilson TR, Aldoori MI. Chronic critical limb ischaemia and the diabetic foot. In: Baker Q, Aldoori MI, editors. Clinical Surgery: A Practical Guide. Florida: CRC Press; 2009. p.230-250.

[9] NHS Digital. *Hospital Admitted Patient Care Activity, 2015-16*. Available from: http://www.content.digital.nhs.uk/catalogue/PUB22378 [Accessed 26 September 2017]

[10] European Society for Vascular Surgery. Management of Critical Limb Ischaemia and Diabetic Foot: Clinical Practice Guidelines. *European Journal of Vascular and Endovascular Surgery.* 2011;42(2):S1-S90. Available from: http://www.ejves.com/issue/S1078-5884(11)X0013-8 [Accessed 27 September 2017]

[11] National Institute for Health and Care Excellence. Peripheral arterial disease: diagnosis and management (CG147). 2012.