National Institute for Health Research

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Tonogenchoncel-L (Invossa) gene therapy for regeneration of cartilage in patients with degenerative arthritis or osteoarthritis of the knee

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LAY SUMMARY

Osteoarthritis is a common condition causing pain and swelling in the joints, most commonly the hands, knee and hips. Osteoarthritis causes the destruction of the cartilage (a tough layer which covers the end of the bones) and inflammation of the joint. The exact cause of osteoarthritis is unknown, but it is thought that being female, increasing age and weight and knee injuries increase the risk of getting knee osteoarthritis. Current treatments for knee osteoarthritis focus on easing the symptoms, e.g. painkillers for pain and walking sticks to help people move around. However there are no treatments at the moment which can stop the cartilage in the joint from breaking down and therefore no treatment which can stop osteoarthritis getting worse.

Tonogenchoncel-L is a type of treatment which involves taking cells which make up the cartilage and altering them genetically to help stimulate the growth of the cartilage. These modified cells are injected directly into the knee joint with the intention of helping the lost cartilage regrow. If tonogenchoncel-L was licenced in the UK it could provide a unique treatment for people with knee osteoarthritis which has the potential to help cartilage regrow and improve symptoms.

TARGET GROUP

Degenerative arthritis or osteoarthritis of the knee

TECHNOLOGY

DESCRIPTION

Tonogenchoncel-L (Invossa; TissueGene-C) is an allogenic cell therapy involving the injection of a mix of human chondrocytes which are genetically modified to produce Transforming Growth Factor β1 (TGF-β1) (shown to play a role in the formation and maintenance of articular cartilage by regulating the homeostasis of the hyaline cartilage matrix) and unmodified chondrocytes. It is intended to stimulate regeneration of cartilage and treat symptoms (e.g. pain and inflammation) in people with osteoarthritis of the knee.[1]

In the planned phase III clinical trial, Tonogenchoncel-L will be administered by a single 2ml intra-articular injection containing 3 x 10*7 allogeneic human chondrocytes at a ratio of 3:1 of unmodified chondrocytes to genetically modified chondrocytes expressing TGF-β1 cells.[2]

Tonogenchoncel-L does not currently have Marketing Authorisation in the EU for any indication.

A phase III trial (NCT03203330) for Tonogenchoncel-L is currently being planned for the treatment of knee osteoarthritis.[2]

INNOVATION and/or ADVANTAGES

If licensed, tonogenchoncel-L will offer an additional treatment option for knee osteoarthritis. This treatment is novel in that it is regenerative in nature, encouraging the growth of new cartilage in the joint, and thereby may offer advantages over already approved treatments by addressing and treating disease progression and symptoms rather than symptoms alone. The need for regenerative treatment has been highlighted as an important future focus for knee OA treatment.

"The unmet need is to try to alter the course of the disease pharmacologically and of course those other things I mentioned, weight loss, cane, braces will do that to a degree, but the real key is finding something that will inhibit the progression of cartilage loss and possibly even repair." – EU Key Opinion Leader[3]

DEVELOPER

TissueGene, Inc.

PATIENT GROUP

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis which affects the joints, most commonly the knees, hips and hands. OA affects the tissues of the joint, causing the breakdown of the cartilage (the tough, flexible tissue which covers the ends of bones in articular joints), thickening of the underlying bones, and the thickening and inflammation of the synovium and ligaments.[4, 5]

The main symptoms of osteoarthritis is pain and stiffness in the joint which usually gets worse when you use the joint and in the morning (although if the OA is severe it may be there all the time). Other symptoms of knee OA include, joint tenderness, knee pain and stiffness after inactivity, larger 'bumpier' looking knee, grating/cracking sound and sensation (crepitus) in the knee, limited range of movement in the knee, weakness and muscle wasting and knees 'giving way' beneath you or making it hard to straighten the legs. The severity of symptoms can vary greatly from mild symptoms which come and go to continuous and severe problems.[5, 6, 7]

The exact causes of knee osteoarthritis are not known but there are several factors thought to increase risk of knee OA, including joint injury (overuse, possibly as a result of a physically demanding job, or injury to the joint), as a result of another condition (e.g. rheumatoid arthritis or gout), increasing age, family history, obesity and female gender.[8, 9] There is no single diagnostic test for knee OA so diagnosis is usually made by presence of symptoms, physical examination (checking for body growth, swelling and crepitus in the joint) and x-ray (to check if there is loss of cartilage or joint space).[5]

Living with knee OA can affect various aspects of daily living, including increased levels of depression, problems with sleep due to joint pain and difficulty continuing work (especially if it is a physically demanding job).[10] OA contributes greatly to disability, accounting for 2.4% of all years lived with disability (TLD) and being ranked 10th in the leading contributors to global YLDs.[11]

CLINICAL NEED and BURDEN OF DISEASE

Estimating incidence and prevalence of Knee OA is difficult due to the potential variation in the definition of Knee OA used (e.g. based on radiographic and/or symptomatic criteria). However based on data from Arthritis UK, the prevalence of UK adults over 45 years who have sought treatment for OA is approximately 8.75 million. Of these 4.11 million people (18.2% of the adult UK population over 45 years old) has OA of the knee, with 6.1% of these having a severe form of OA.

OA risk increases substantially with age, with approximately a third of women and a quarter of men in the UK between 45 and 64 years seeking treatment for OA, rising to almost half in those ages 75 years and older. Prevalence of OA is also higher in women compared to men, with women accounting for approximately 60% of hip and knee replacement operations (with the majority of these conducted due to osteoarthritis).[12]

Living with Knee OA can impact quality of life and present with comorbidities which impact on general health and wellbeing. Common comorbidities with OA include cardiovascular disease (with men and women over 65 years old at 17% and 15% respectively higher risk of hospitalization for cardiovascular disease), metabolic syndrome (which occurs in 59% people with OA compared to 23% of people without OA) and depression and anxiety (affecting approximately 20% people with OA).

The impact of OA on activities of daily living can be substantial, with pain being a common problem, with nearly three quarters of people with OA reporting constant pain and 1 in 8 describing their pain as unbearable. Impacts on work have also been documented, with a third of people with OA retiring early, giving up work or reducing working hours due to their condition. Ultimately, Knee OA can lead to joint replacement surgery, with 98% of primary knee replacements in 2015 attributed damage due to Knee OA.[12]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance. Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee (TA477). October 2017.
- NICE Quality Standard. Osteoarthritis (QS87). June 2015.
- NICE Clinical Guideline. Osteoarthritis: care and management (CG177). February 2014.
- NICE Interventional procedures guidance. Microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects (IPG560). June 2016.
- NICE Interventional procedures guidance. Implantation of a shock or load absorber for mild to moderate symptomatic medial knee osteoarthritis (IPG512). January 2015.
- NICE Interventional procedures guidance. Platelet-rich plasma injections for osteoarthritis of the knee (IPG491). May 2014.
- NICE Interventional procedure guidance. Arthroscopic radiofrequency chondroplasty for discrete chondral defects of the knee (IPG493). May 2014.
- NICE Interventional procedure guidance. Partial replacement of the meniscus of the knee using a biodegradable scaffold. July 2012.
- NICE Intervention procedure guidance. Individually magnetic resonance imaging-designed unicompartmental interpositional implant insertion for osteoarthritis of the knee (IPG317). September 2009.
- NICE Interventional procedures guidance. Arthroscopic knee washout, with or without debridement, for the treatment of osteoarthritis (IPG230). August 2007.

NHS ENGLAND and POLICY GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- Osteoarthritis Research Society International. Background to and outline of the OARSI treatment guidelines. 2013.
- American Academy of Orthopaedic Surgeons. Treatment of Osteoarthritis of the Knee. Evidence Based Guideline. 2nd Edition. May 2013.
- American College of Rheumatology. American College of Rheumatology 2012 Recommendations for the use if nonpharmacological and pharmacologic therapies in osteoarthritis of the hand, hip and knee. 2012.

CURRENT TREATMENT OPTIONS

OA cannot be cured and the currently available treatments for Knee OA mainly aims to address the symptoms of Knee OA. NICE recommend a holistic approach to assessing and managing OA, considering the effect of OA on the persons function, quality of life, occupation, mood, relationships and leisure activities. There are a range of treatments recommended for use by NICE, including;[13]

- First line ‘core treatments’ – offered in the first instance to everyone with OA.

    - Patient information – verbal and written information to enhance understanding of OA and its management
    - Exercise – encourage local muscle strengthening and aerobic exercise irrespective or age, comorbidity, pain severity or disability
    - Weight loss – offer interventions to achieve weight loss if obese or overweight
- Non-Pharmacological treatment
    - Thermotherapy - local application of heat or cold to joint
    - Electrotherapy – specifically TENS as an adjunct therapy to pain relief
    - Aids and devices
        - Bracing, joint supports and instability – as adjunct to core treatments for people with biomechanical joint pain and instability and OA.
        - Assistive devices (e.g. walking sticks and tap turners) – as adjunct to core treatments for people with OA with specific problems with activities of daily living.
    - Manual therapy (manipulation and stretching) - as adjunct to core treatments
- Pharmacological treatment
    - Offer paracetamol/topical NSAIDs for pain relief in addition to core treatments for knee OA before any other analgesic medication.
    - Topic capsaicin as an adjunct to core treatments for knee OA
    - Offer oral NSAIDs or COX-2 inhibitors (at the lowest effective dose for the shortest possible time) co-prescribed with paracetamol and a proton pump inhibitor (PPI) if topical NSAIDs are ineffective
    - Intra-articular corticosteroid injection – as an adjunction to core treatments for the relief of moderate to severe pain in people with osteoarthritis
- Surgical treatment – people should only be referred for surgery if they have received at least the core treatments. Referrals should be based on symptoms (e.g. prolonged and established functional limitation or severe pain), quality of life and for those who are refractory to non-surgical treatments. Surgical procedures recommended by NICE for treatment of Knee OA include:
    - Mini-incision surgery for total knee replacement
    - Platelet- rich plasma injections for osteoarthritis of the knee
    - Joint distraction for knee osteoarthritis without alignment correction
    - Implantation of a shock and load absorber for mild to moderate symptomatic medial knee osteoarthritis
    - Individually magnetic resonance imaging-designed unicompartmental interpositional implant insertion for osteoarthritis of the knee

NICE do not recommend the use of intra-articular hyaluronan injections for the treatment of knee OA. NICE also intend to undertake a full review of the evidence on pharmacological management of osteoarthritis and the Guidance Development Group (GDG) draw attention to the evidence review of the effectiveness of paracetamol which identified reduced effectiveness of paracetamol in the management of osteoarthritis compared to what was previously thought. NICE also recommend not to refer patients for arthroscopic lavage and debridement as treatment for knee OA unless the person has a clear history of mechanical locking.[13]

EFFICACY and SAFETY

Trial	NCT03203330; adults aged 40 years and older; tonogenchoncel-L vs placebo, phase III (planned)	NCT01221441; adults 18 to 70 years; tonogenchoncel-L vs placebo, phase II
Sponsor	TissueGene Inc.	TissueGene Inc.
Status	Planned	Published
Source of Information	trial registry[14]	trial registry[15]
Location	Not reported	USA
Design	Randomised, placebo-controlled, parallel assignment	Randomised, placebo-controlled, parallel assignment
Participants	n=510 (planned); aged 40 years and older; osteoarthritis of the knee; Kellgren & Lawrence Grade 2 and 3; OARSI Grade 1 or 2 medial JSN; Pain >40mm on VAS; WOMAC Score <70 points for target knee	n=102; aged 18-70 years; osteoarthritis of the knee; Kellgren & Lawrence Grade 3; symptomatic (>4 months of consecutive pain)
Schedule	Randomised to single intra-articular injection to the knee of 2ml (containing 3 x 10^7) TG-C cells or 2ml placebo (containing normal saline).	Randomised to single intra-articular injection to the knee of (containing 3 x 10^7) TG-C cells or placebo (containing 0.9% saline).
Follow-up	Single active treatment with a follow-up 2 years.	Single active treatment with a follow-up 2 years.
Primary Outcomes	Knee function as assessed by WOMAC – baseline to 12 months Knee pain as assessed by VAS – baseline to 12 months	Change from baseline in the International Knee Documentation Committee (IKDC) subjective knee evaluation score at 1 year Change from baseline in Visual Analog Scale (VAS) score at 1 year
Secondary Outcomes	International Knee Documentation Committee (IKDC) scoring of knee symptoms, pain and function – baseline, 12 and 24 months Change in joint space width – baseline to 12 and 24 months Evaluation of the change from baseline in physical component score (PCS) of the SF-12v2 questionnaire – baseline to 12 and 24 months Change from baseline in the disability index of the Health Assessment	Change from baseline in Knee Injury and Osteoarthritis Outcome Score (KOOS) at 2 years Change from baseline in articular cartilage damage in the knee as determined by the Lysholm Knee Score at 2 years Comparative evaluation of knee Magnetic Resonance Images (MRIs) from baseline to 1 year

	Questionnaire (HAQ-DI) – baseline to 24 months	Change in pain severity from baseline to 2 years as assessed by questionnaire Number of participants with change in pain severity measured by incidence and dose of analgesia – baseline to 2 years Change from baseline in knee function as determined by the Lower Extremity Functional Scale at 2 years Incidence of total knee arthroplasty at 2 years Number of patients experiencing injection site reactions related to treatment Incidence and severity of adverse events in treated patients Number of participants with adverse events due to clinically significant changes in haematology and urinalysis tests -2 Years Change in SF-36 General Health Assessment Questionnaire (Overall Score) from baseline to 2 years
Key Results	-	The results of 38 participants from the TG-C group and 20 participants of the placebo group were analysed. Change from baseline to 24 months in IKDC subjective knee evaluation score was 23.3 (range: 17.3 to 29.3) in the TG-C group and 9.9 (range: 1.7 to 18.1) in the placebo group.
Adverse effects (AEs)	-	The most common AEs in the active treatment group was musculoskeletal and connective tissue disorders (2/67 [2.99%] vs 0% in placebo group), gastrointestinal disorder (1/67 [1.49%] vs 0% in placebo group), abdominal pain (1/67 [1.49%] vs 0% in placebo group), radius fracture (1/67 [1.49%] vs 0% in placebo group). The number of total adverse events in the TG-C

		group was 7/67 (10.45%) and 4/35 (11.43%) in the placebo group.
Expected reporting date	Estimated completion date 30 June 2021	-

ESTIMATED COST and IMPACT

COST

The cost of tonogenchoncel-L is not yet known.

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: potential reduced need for future treatment

☐ Re-organisation of existing services

☐ Need for new services

☒ Other: new staff training requirements, requirement for new facilities, specialist laboratory resources for preparation of cells

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other increase in costs: new specialist clinics required, additional staff training required

☐ Other reduction in costs: reduced use of secondary care/specialist services, reduced need for interventional procedures

☒ Other: *specify, e.g. uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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