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Newcastle University

Health Technology Briefing
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Adalimumab for Dupuytren's disease

Company/Developer	Celltrion Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 34999	NICE ID: 11870	UKPS ID: 669345

Licensing and Market Availability Plans

Currently in phase II clinical trials.

Summary

Adalimumab is in clinical development for the treatment of early-stage Dupuytren's disease (DD). DD is a condition which causes the connective tissue in the hand or fingers to become thicker and less flexible over time. These start with nodules that progress to fibrous cords over time. This results in a contracture, which is the bending of fingers towards the palm. The specific cause of DD is unknown, but it more likely to affect men, particularly of northern European descent. DD can be uncomfortable, painful or limit the use of the hand. There are no recommended treatment options for early-stage DD, with treatment focused on surgical interventions to straighten the fingers affected by the disease progression. There is no cure for DD and current treatment options may not completely straighten the finger(s), can result in loss of strength and flexibility, and the contracture may come back.

Adalimumab is administered by injection into the affected tissue. It works by targeting part of the immune response that is related to DD progression called tumour necrosis factor (TNF). By reducing TNF, adalimumab reduces nodule hardness and the size of the nodule, which could be a potential way to control disease progression. If licensed adalimumab would be the first pharmacological treatment option for people with early-stage DD.

Proposed Indication

Early-stage Dupuytren's disease (DD), also known as Dupuytren's contracture.[1]

Technology

Description

Adalimumab (Humira) is an immunosuppressant that binds specifically to tumour necrosis factor (TNF) and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. It is a therapeutic target for DD and modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.[2,3]

Adalimumab is in clinical development for adults with early-stage DD (NCT03180957, RIDD).[1] In the phase IIa clinical trial patients were randomised to receive intra-nodular injection of adalimumab on one occasion in dose cohorts of 15mg in 0.3ml, 35mg in 0.7ml, or 40mg in 0.4ml, or an equivalent volume of placebo in a 3:1 ratio.[4] In the phase IIb clinical trial the most active nodule as reported by the participant was selected for inclusion in the study and participants were randomly assigned 1:1 to receive either an intra-nodular injection of 40mg adalimumab in 0.4ml or an equal volume of saline at baseline, 3, 6, and 9 months after randomisation, and followed up at 12 and 18 month timepoints.[3]

Key Innovation

Intranodular adalimumab injections reduced nodule hardness and size in patients with early-stage DD, indicating the potential to control disease progression.[5]

Current recommended treatment cannot usually help in the early stages.[6] There is no approved therapy for the treatment of early DD, as such there is a need to develop therapy to retard progression of DD and prevent the development of recurrent disease following, surgery, needle fasciotomy or collagenase injection in patients with established finger contractures.[7]

Regulatory & Development Status

Adalimumab is licensed in the UK for:[8]

- Plaque psoriasis
- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Axial spondyloarthritis
- Crohn's disease
- Ulcerative colitis
- Hidradenitis suppurativa
- Uveitis
- Polyarticular juvenile idiopathic arthritis
- Enthesitis-related arthritis

Adalimumab is in phase II and III clinical trials for a number of conditions including mild to moderate COVID-19, inflammatory bowel disease, and pyoderma gangrenosum.[9]

Patient Group

Disease Area and Clinical Need

DD affects the connective tissue under the skin of the palm or fingers called fascia.[10] Over time this causes the fascia to become thicker and less flexible, causing one or more fingers to bend towards the palm, this is called a contracture.[6,10] Early-stage DD begins with nodules that progress to fibrous cords.[3] The contracture can be uncomfortable, painful and/or limit the use of the hand.[10] The exact cause of DD is unknown, but it has been linked to family history (inheritance), smoking, alcohol consumption, diabetes and epilepsy.[6] Main treatment include surgical interventions using local or general anaesthetic, with recovery times of 2-12 weeks depending on the procedure. After treatment the finger may not be completely straight, lose strength and flexibility, and the contracture may come back over time.[6] DD is six times more common in men than women, and more likely to affect people of northern European descent.[11]

4% of general UK population may develop DD, 40% of these may be suitable for adalimumab therapy.[1] The prevalence of DD increases to about 20% in those aged over 65 years old. In the UK there are approximately 2 million people with DD.[11] In England, 2021-22, there were 14,297 finished consultant episodes (FCE) for DD (ICD-10 code M72.0) with 13,555 day cases and 632 FCE bed days.[12]

Recommended Treatment Options

There is currently no recommended pharmacological treatment for early-stage DD, however NICE recommends the following interventional procedures:[13,14]

- Needle fasciotomy
- Radiation therapy

Clinical Trial Information

Trial	**RIDD; NCT03180957; EudraCT 2015-001780-40; A Multi-centre, Double Blind, Randomised, Placebo-controlled, Parallel Group, Phase II Trial to Determine the Efficacy of Intra-nodular Injection of Anti-TNF to Control Disease Progression in Early Dupuytren's Disease, With a Dose Response** **Phase II –** Completed **Location(s):** Netherlands and UK **Study completion date:** December 2020
Trial Design	Randomised, quadruple-masked (participant, care provider, investigator, outcomes assessor) parallel assignment.
Population	N=209, all sexes, aged 18 years and older, with early-stage DD.
Intervention(s)	**Phase IIa:** Patients were randomised to receive intra-nodular injection of adalimumab on one occasion in dose cohorts of 15mg in 0.3ml, 35mg in 0.7ml, or 40mg in 0.4ml, or an equivalent volume of placebo in a 3:1 ratio. Two weeks later the injected tissue was surgically excised and analysed.[4] **Phase IIb:** The most active nodule as reported by the participant was selected for inclusion in the study and participants were randomly assigned 1:1 to receive either an intra-nodular injection of 40mg adalimumab in 0.4ml or an equal volume of saline at baseline, 3, 6, and 9 months after randomisation, and followed up at 12 and 18 month timepoints.[3]
Comparator(s)	Matched placebo.

Outcome(s)	**Primary outcome measures:** • Dose Response: expression of mRNA for α-SMA [Time Frame: Analysis of tissue removed at 12-18 days post-treatment] • Early Disease: change in nodule hardness between baseline at 12 months [Time Frame: 12 months] See trial record for full list of other outcomes.
Results (efficacy)	**Phase IIa:** There was no change in mRNA levels for ACTA2, COL1A1, COL3A1 and CDH11. Levels of α-SMA protein expression in patients treated with 40mg adalimumab (1.09 ± 0.09ng per µg of total protein) were significantly lower (p = 0.006) compared to placebo treated patients (1.51 ± 0.09 ng/µg). The levels of procollagen type I protein expression were also significantly lower (p < 0.019) in the sub group treated with 40mg adalimumab (474 ± 84 pg/µg total protein) compared with placebo (817 ± 78 pg/µg).[4] **Phase IIb:** Primary outcome data were available from 113 participants. Nodule hardness was lower (−4·6 AU [95% CI −7·1 to −2·2], p=0·0002) in the adalimumab compared with the saline group at 12 months.[3]
Results (safety)	**Phase IIa:** There were two serious adverse events, both considered unrelated to the study drug.[4] **Phase IIb:** There were no related serious adverse events; the most common adverse events were minor injection site reactions.[3]

Estimated Cost

The cost of adalimumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE Interventional procedures guidance. Radiation therapy for early Dupuytren's disease (IPG573). December 2016.
- NICE Interventional procedures guidance. Needle fasciotomy for Dupuytren's contracture (IPG43) February 2004.

NHS England (Policy/Commissioning) Guidance

No relevant guidance found.

Other Guidance

- British Medical Journal (BMJ) Best Practice. Dupuytren's contracture. December 2019.[15]

Additional Information

References

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