National Institute for Health Research

NIHR Innovation Observatory
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Neridronic acid (Nerixia) for complex regional pain syndrome

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LAY SUMMARY

Complex regional pain syndrome (CRPS) is a poorly understood condition in which a person experiences persistent severe and debilitating pain. Although most cases of CRPS are triggered by an injury, the resulting pain is much more severe and long-lasting than normal. The pain is usually confined to one limb, but it can sometimes spread to other parts of the body. The skin of the affected body part can become so sensitive that just a slight touch, bump or even a change in temperature can provoke intense pain. Affected areas can also become swollen, stiff or undergo fluctuating changes in colour or temperature. Many cases of CRPS gradually improve to some degree over time, or get completely better. However, some cases of CRPS never go away, and the affected person will experience pain for many years.

The cause of CRPS is unknown, but it is generally thought to be the result of the body reacting abnormally to an injury. It is difficult to estimate exactly how common CRPS is, as many cases may go undiagnosed or misdiagnosed. Currently there are no approved treatments for CRPS. Neridronic acid administered by injection is currently being developed to treat CRPS and early results indicate that it has the possibility to control the condition. If approved neridronic acid will be a potential new treatment for CRPS.

TARGET GROUP

Complex regional pain syndrome (type I and II)

TECHNOLOGY

DESCRIPTION

Neridronic acid (Nerixia) is an investigational aminobisphosphonate and a new chemical entity in development for the treatment of complex regional pain syndrome (CRPS).[1,2]

Neridronic acid acts by binding and inhibiting the enzyme farnesyl diphosphate synthase (FPPS) in the HMG-CoA reductase pathway (also known as the mevalonate pathway). Inhibition of protein prenylation affects proteins found in an osteoclast, disruption to the lipid modification of Ras, Rho, Rac proteins. This ultimately leads to restore normal cytoskeletal dynamics, inhibition of osteoclastogenesis and stimulates cell survival.[2]

In the phase III clinical trial, NCT02972359, for the treatment of CRPS, neridronic acid was administered at a dose of 100 mg on day 1, 4, 7, 10, resulting in a total dose of neridronic acid 400 mg, intravenously.[3]

Neridronic acid is currently marketed in Italy for the treatment of osteogenesis imperfecta and Paget's disease of the bone.[4]

INNOVATION and/or ADVANTAGES

CRPS is a severely debilitating condition that currently has no EMA or FDA approved treatment options. It is evident that this issue requires addressing due to the significant clinical unmet need.[1]

Initial findings indicate that treatment with bisphosphonates are associated with permanent remission of type I CRPS.[5] Therefore if licensed, neridronic acid has the potential to be an effective new treatment option for patients with CRPS.

DEVELOPER

Grünenthal Ltd

AVAILABILITY, LAUNCH or MARKETING

Neridronic acid was designated US Orphan Drug status for complex regional pain syndrome from the FDA in March 2013. Neridronic acid also received FDA Fast Track Designation in August 2015 and US Breakthrough therapy in December 2016 for CRPS.[2]

No information on plans for Marketing Authorisation Application or UK licence/launch could be obtained.

PATIENT GROUP

BACKGROUND

CRPS is a poorly understood chronic neurological condition affecting the limbs. It is characterised by severe pain and is associated with sensory, motor, autonomic, skin and bone abnormalities.[6] This debilitating condition can be caused by minor injury, surgery or trauma and can range from being self-limiting to impairing daily living and quality of life.[7] Damage to the central nervous system and the peripheral system are believed to be the cause of CPRS,[8] and in approximately 90% of cases, a traumatic trigger can be identified.[9] The initial injury may result in hypoxia and the release of various inflammatory markers, neuropeptides and cytokines which can lead to neurogenic inflammation, allodynia and vasomotor dysfunction.[9]

The primary characteristic of CPRS is prolonged severe pain, often described as a 'burning' or 'pins and needles' sensation. Abnormal microcirculation caused by damage to the nerves that control blood flow and temperature, result in further complications including swelling of the affected limb and changes in skin temperature and skin colour.[8] Other symptoms confined to the affected limb include hyperalgesia, muscle weakness, and changes to the growth of hair and nails.[10,11] CRPS has two subtypes; type 1 known as reflex sympathetic dystrophy and type 2 referred to as causalgia.[9] In type 1 CPRS the symptoms presented are in the absence of any confirmed nerve injury and is the most common of two subtypes, whereas type 2 CPRS is associated with nerve injury.[9,12]

With the appropriate treatment, pain and swelling associated with CPRS can decrease and the range of motion at the affected joint can increase,[13] however, due to the multifactorial nature of the disease, it is extremely difficult to successfully combat CPRS.[7]

CLINICAL NEED and BURDEN OF DISEASE

CPRS is found more commonly in women than in men, although the overall incidence is unknown,[13] as many cases may go undiagnosed or are misdiagnosed.[17]

The age of developing the condition can vary, but it is rarely experienced by the elderly and those under the age of 10 years, and tends to peak at 40 years old.[8]

CPRS affects the arm in approximately 60% of all cases, whilst the leg is affected in 40% of cases.[14] The condition is often associated with substantial disability, loss of quality of life, and personal and societal economic burden.[14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (TA159). October 2008.
- NICE clinical guideline. Neuropathic pain in adults: pharmacological management in nonspecialist settings (CG173). February 2017.

- NICE interventional procedures guidance. Ultrasound-guided regional nerve block (IPG285). January 2009.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Pain: Specialised Services for Pain Management (Adult). D08/S/a.
- NHS England. Clinical Commissioning Policy: Intrathecal pumps for treatment of severe chronic pain. D08/P/a. July 2015.
- NHS England. Clinical Commissioning Policy: Deep brain stimulation for chronic neuropathic pain. D08/P/d. July 2015.

OTHER GUIDANCE

Royal College of Physicians. *Complex regional pain syndrome in adults UK guidelines for diagnosis, referral and management in primary and secondary care*. 2012. https://www.rcplondon.ac.uk/guidelines-policy/pain-complex-regional-pain-syndrome [Accessed 02 November 2017]

CURRENT TREATMENT OPTIONS

Management of pain is important to minimise suffering. This should be undertaken in parallel with any ongoing investigation and the specific management of potentially relevant pathology that may be contributing to the pain.[6] As the underlying biological mechanism for CRPS is not understood, it is recommended that a holistic approach to treatment is taken. Clinical experts suggest that any treatment should be given in parallel with psychological interventions as it is likely that a psychological associated mechanism exists.[15]

The aim of medication is to minimise pain and support physical rehabilitation. If simple analgesics do not reduce the patient's pain to a mild level after 3–4 weeks, medication for neuropathic pain may be considered.[6]

There is currently a lack of evidence to inform the best functional advice to offer patients with suspected CRPS, or CRPS for which concomitant pathology has not yet been ruled out. Pragmatically, encouragement of gentle limb use and an active lifestyle is recommended. This should include:[6]

- Gentle limb movement (unless contraindicated for orthopaedic reasons)
- Frequent attention to the affected limb (however experts suggest this may exacerbate the problem when considering the psychological mechanism underlying CRPS)
- 'Desensitisation' (gentle stroking of the affected limb with different textured fabrics while viewing the limb)
- Progressing to more active use when tolerated (e.g. weight bearing and stretching)

If there is any doubt about the safety of movement, the advice of an orthopaedic surgeon or rheumatologist should be sought.[6]

Mild cases of CRPS may be managed with simple and/or neuropathic pain medications such as non-steroidal anti-inflammatory drugs such as ibuprofen. Patients with CRPS should be encouraged to stay as active as possible and to not avoid using the affected body part. Physical rehabilitation and desensitisation exercises can improve strength and flexibility of the affected area.[16]

EFFICACY and SAFETY	
Trial	NCT02972359; EudraCT-2016-001164-11; neridronic acid (single arm); phase III
Sponsor	Grunenthal GmbH
Status	Ongoing
Source of Information	Trials registry[3]
Location	EU (not incl UK) and USA
Design	Non-randomised, uncontrolled, open-label study
Participants	n=220 (estimated); aged ≥18 years; complex regional pain syndrome
Schedule	Neridronic acid 100 mg administered intravenously on day 1, 4, 7, and 10, resulting in a total dose of neridronic acid 400 mg.
Follow-up	Follow-up period of approximately 50 wks (with visits at wk 2, 6, 12, 26, 39, and 52)
Primary Outcomes	Occurrence of any treatment emergent adverse event [time frame: day 1 to week 52]
Secondary Outcomes	Occurrence of permanent discontinuation from treatment due to an adverse event [time frame: day 1 to day 10] Change from baseline in the current pain intensity score [time frame: baseline to week 12 and week 26] Response to treatment, defined as at least 30% decrease from baseline in the current pain intensity score [time Frame: baseline, at week 12 and week 26] Response to treatment, defined as at least 50% decrease from baseline in the current pain intensity score [time frame: baseline, at week 12 and week 26] Patient Global Impression of Change (PGIC) [time frame: at week 12] Patient Global Impression of Change (PGIC) [time frame: at week 26] Change in the Pain Interference score of the Brief Pain Inventory (BPI) [time frame: baseline to week 12 and week 26]
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Estimated study completion date February 2019

ESTIMATED COST and IMPACT

COST

The cost of neridronic acid is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improved quality of life for carers and improved patient convenience*

☐ 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 from Grunenthal Ltd.

Grunenthal Ltd state that they are committed to using UK PharmaScan and that information regarding product rights and plans in Europe is commercially confidential.

REFERENCES

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