National Institute for Health Research

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Cethrin for traumatic spinal cord injury

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LAY SUMMARY

A traumatic cervical spinal cord injury results from trauma (such as a fall or car crash, rather than from a disease), and affects the spinal cord in the upper part of the spine (known as the cervical spine). The spinal cord is the bundle of nerves that runs down the middle of the back, and damage to these nerves disrupts how the brain and body communicate. This can result in a variety of complications including death, paralysis (loss of the ability to move one or more muscles) and breathing issues. Spinal cord injuries to the cervical spinal cord are the most severe of all spinal cord injuries. The risk of death is highest within the first year of injury.

Cethrin is being developed to treat traumatic cervical spinal cord injuries in adolescents and adults. The current treatment option for traumatic spinal cord injuries is methylprednisolone (a steroid) used to reduce inflammation. Surgery is an option in cases when the spinal fluid or tissue presses on the spinal cord. If marketed, Cethrin may help repair damaged nerve cells, allowing the brain and body to better communicate. This could help restore movement in patients with traumatic spinal cord injuries.

TARGET GROUP

Spinal cord injury; acute and traumatic; cervical.

TECHNOLOGY

DESCRIPTION

Cethrin is a recombinant derivative of C3 transferase (a natural enzyme that inhibits the activation of Rho kinase) formulated in a fibrin sealant to optimise its delivery in spinal surgery. When a spinal cord injury occurs, myelin debris at the injury site sends signals to neurons to regenerate their broken axons, but Rho kinase blocks these signals. By inhibiting Rho kinase, Cethrin promotes regeneration of cut axons and remodelling.[1]

Cethrin is delivered by a single intraoperative epidural administration to the injured region of the spinal cord.[1]

Cethrin is currently in phase II/III for the treatment of acute traumatic cervical spinal cord injury in adolescents and adults. In this trial patients received a single 9mg dose of VX-210.[1]

Cethrin does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

Cethrin may provide a potential significant benefit for the treatment of traumatic spinal cord injury mainly because it has a new mechanism of action. Recombinant derivative of C3 transferase is expected to work by inactivating a group of proteins called 'Rho proteins', which are believed to play a key role in preventing nerve cells from re-growing after they have been damaged. By blocking the activity of Rho proteins, this medicine may allow the nerve cells to repair themselves and regrow their damaged axons (the long processes of nerve cells along which nerve impulses pass). There is also some evidence that blocking Rho proteins may also prevent the death of damaged nerve cells. Together, these effects may restore the flow of nerve impulses along the spinal cord in patients with traumatic spinal cord injury.[2]

DEVELOPER

Vertex Pharmaceuticals

AVAILABILITY, LAUNCH or MARKETING

Cethrin was designated orphan drug status in the USA in 2005[3] and in the EU in 2008 (although this was transferred to the current company in 2015).[3]

The company's current licensing plans were unavailable.

PATIENT GROUP

BACKGROUND

Spinal cord injuries refer to damage of the spinal cord resulting from trauma (such as a car crash) or as a result of an infection, disease or degeneration (as seen in cancer). This helps distinguish traumatic from non-traumatic injuries. When the nerves in the spinal cord become damaged, the signalling between the brain and the parts of the body that are innervated at or below the lesion becomes disrupted. The lesion may be complete (no nerve fibres are functioning below the level of injury) or incomplete (one or more nerve fibres is secure). The cord need not be completely severed to result in a complete injury; the nerve cells may be destroyed as a result of pressure, bruising, or loss of blood supply, and if they die they do not have the ability to regenerate. The amount of functional loss depends upon the level of injury (the higher the damage occurs, the more of the body that is affected) and on the neurological completeness of the injury.[4]

The most dramatic changes in function are apparent between adjacent neurological levels in the cervical area.[4] The higher up in the spine that the injury occurs, the more severe the potential outcome. Some cervical spinal cord injuries are severe enough to result in death. Injuries to C1 and C2 are very rare and most injuries to the cervical spinal column occur near the C4 / C5 levels. [5] Nerves that innervate the diaphragm are at cervical level 3-4, so many people with injuries at or above C3 require ventilator assistance to breathe. Most individuals with C4 injuries regain breathing capacity, but do not have usable function in their arms and hands. As a result, they need assistance with virtually all activities of daily living, including feeding and dressing.[4]

Individuals with injuries at the C5 level usually have function in the deltoid and bicep muscles, so they will be able to bend the arm at the elbow. Some have the ability to develop a weak pinch by using an automatic motion known as tenodesis (when the wrist is extended, the thumb and index finger come together). Most people with C5 and C6 injuries require the use of a wheelchair, although those with C6 tetraplegia can move more independently with the use of assistive devices, making activities of daily living possible. People who have C7 and C8 levels of injury are nearly independent in their daily lives. They have the use of tricep muscles (which allow them to straighten and lock their arms for transfers from wheelchair to car or chair) and finger extensors (which allow them to open their hands).[4] Though damage to the spinal cord at any portion of the neck has the potential to result in full paralysis of each of the four limbs, survivors of C5-C8 injuries may be able to breathe on their own and speak normally.[5]

Persons who have injuries at the cervical or thoracic level have sustained damage to all of the upper motor neurons that innervate the body at or below the point of injury. This results in loss of voluntary control of bowel and bladder functioning. Fortunately, an intact lower motor neuron reflex arc may be retained from these muscles to the synapse in the spinal cord and back. This enables the possibility of “retraining” the body to respond to direct stimulation (for example, tapping on the lower abdomen to trigger voiding) and provides some degree of control over bowel functions. [4]

Furthermore, spinal cord injuries are associated with a series of secondary conditions and possible avoidable complications, particularly pressure ulcers, urinary tract complications, autonomic problems and joint stiffness/contractures.[6,7] The avoidance of these complications requires a high level of input from a dedicated multidisciplinary team. The complications originate by a patho-biological cascade of secondary injury mechanisms that occur within seconds of the initial trauma in various phases.[8] Preventing and mitigating these secondary mechanisms is where opportunity for

neuroprotection lies and where most attempts at therapeutic intervention have been staged.[9] Additionally, patients with spinal cord injuries often face a high lifetime rate of anxiety and depression and an unemployment rate of more than 60%.[10]

CLINICAL NEED and BURDEN OF DISEASE

The incidence of spinal cord injury in the UK is estimated at between 12 and 16 per million people, a wide range in age from infants to the elderly and a majority of injuries caused by trauma.[11] This is equivalent to 600–900 people in England per year, with the majority of cases caused by trauma.[12] In 2014, traumatic spinal cord injury affected approximately 3 in 10,000 people in the European Union.[13]

The patterns of spinal cord injury vary slightly between country, ethnic origin, age, and gender. It is more common in men (80%) and occurs at an average age of 42 years old.[14] In the UK in 2015, 42% of these injuries were associated with falls, 37% were caused by road traffic accidents, 11% were sport-related and 6% were from trauma or assault.[15]

Difficulty arises for those with tetraplegia when attempting to return to work as there is an increased demand for personal care assistance. Generally quality of life is impaired following spinal cord injury due to financial burden following an interruption or absence from work and through the inability to participate in everyday activities. A loss of independence in daily life and psychological stress additionally impair quality of life in those with spinal cord injury.[4]

Associated higher mortality in age >60 years is attributable to poor cardiorespiratory function, increased risk of complications, and higher incidence of high cervical injury.[16] Mortality risk is highest in the first year after injury and remains high compared to the general population. People with spinal cord injury are 2 to 5 times more likely to die prematurely than people without. Mortality risk increases with injury level and severity and is strongly influenced by availability of timely, quality medical care. Transfer method to hospital after injury and time to hospital admission are important factors.[6]

Hospital episodes statistics (2015 to 2016) indicate that for other and unspecific injuries of the cervical spinal cord, there were 873 finished consultant episodes (FCE), 526 admissions and 28,646 FCE bed days.[17]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Neuropathic pain in adults: pharmacological management in non-specialist settings (CG173). February 2017.
- NICE clinical guideline. Urinary incontinence in neurological disease: assessment and management (CG148). August 2012.
- NICE guidelines. Spinal injury: assessment and initial management (NG41). February 2016.
- NICE guidelines. Major trauma: service delivery (NG41). February 2016.
- NICE interventional procedures guidance in development. Intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by high spinal cord injuries. TBC.

- NICE interventional procedures guidance. Prosthetic intervertebral disc replacement in the cervical spine (IPG341). May 2010.
- NICE interventional procedures guidance. Intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure due to neurological disease (IPG307). May 2009.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013 NHS Standard Contract for Spinal Cord Injuries (All Ages). D13/S/a
- NHS England. 2013 NHS Standard Contract for Complex Spinal Surgery (All ages). D14/S/a
- NHS England. 2013 Clinical Commissioning Policy: Phrenic Nerve Pacing Following Spinal Cord Injury. NHSCB/D13/P/a

OTHER GUIDANCE

- National Spinal Cord Injury Strategy Board. *The Initial Management of Adults with Spinal Cord Injuries Advice for Major Trauma Networks and SCI Centres on the Development of Joint Protocols with Advice for Clinicians in Acute Hospitals*. Available from: https://www.mascip.co.uk/wp-content/uploads/2015/03/The-Initial-Management-of-Adults-with-SCI.-NSCISB.pdf [Accessed 21 August 2017]

CURRENT TREATMENT OPTIONS

Initial assessment under the advanced trauma life support protocol is essential. The primary survey is of importance with airway, breathing and circulation being the priority, with protection of any potential unstable fracture. The secondary survey is of even greater importance in a patient with impaired sensation.[6]

Methylprednisolone treatment improves neurologic recovery but is unlikely to bring a return to normal function unless there is minimal initial deficit.[18] Furthermore, it has been disputed that it should not be routinely used in the treatment of patients with acute spinal cord injury due to the complications associated with high doses.[19] Recent research has examined sequential therapies which operate on different aspects of the secondary injury processes ranging from early neuron protection to nerve regeneration in the chronic patient.[18] However, no licensed treatment options for nerve regeneration exist, although studies have generated positive findings using stem cells to treat spinal cord injuries.[20] Additionally, determining the appropriate efficacy from clinical trials can be difficult due to the small patient groups without controls often included in such studies.[21]

During the acute period of hospitalization, physicians may determine that the spinal column is unstable and further neurological damage could ensue. In this case, surgery may be recommended to fuse the spine at the point of injury or otherwise stabilize it with rods or other surgical hardware. The individual may be fitted with a halo or body cast to enable them to maintain immobility of the fracture site without being confined to bed for excessive periods of time.[4]

Along with a spinal cord injury, a person may have an array of other complications including fractures, internal injuries, and brain injuries, all of which require treatment. When the need for acute medical services has passed, the individual is usually transferred to a rehabilitation unit for multidisciplinary services to help build strength, redevelop skills in activities of daily living, identify and obtain adaptive equipment, and prepare the individual and the family for return to home and

community. Several neuroprotective agents, most frequently methylprednisolone, are often administered soon after injury in an attempt to disrupt this cascade of events and prevent further cell death.[4]

EFFICACY and SAFETY

Trial	SPRING, NCT02669849. Cethrin vs placebo, phase II/III
Sponsor	Vertex Pharmaceutical Inc
Status	Ongoing
Source of Information	GlobalData[1] and Trial registry[2]
Location	USA and Canada
Design	Randomised, placebo-controlled, double-blind study
Participants	n=150 (planned); aged 14-75 years; spinal cord injury; acute trauma to cervical spine; scheduled and planned to undergo spinal decompression/stabilization surgery that commences within 72 hours after the initial injury
Schedule	Randomised to Cethrin as a single 9-mg dose in fibrin sealant or placebo as a buffer solution in fibrin sealant.
Follow-up	Primary outcome measures and secondary outcome measures (except pharmacokinetics) taken 6 months after treatment.
Primary Outcomes	Change from baseline in upper extremity motor score (UEMS) at 6 months after treatment
Secondary Outcomes	• Spinal Cord Independence Measure (SCIM) III self-care subscore at 6 months after treatment • Capabilities of Upper Extremity Test (CUE-T) score at 6 months after treatment • Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) Quantitative Prehension score at 6 months after treatment • American Spinal Injury Association Impairment Scale (AIS) grade conversion from baseline to 6 months after treatment • Motor level change using the ISNCSCI Exam from baseline to 6 months after treatment • Pharmacokinetic parameters of VX-210: tmax (time of the maximum concentration) 48 hrs after treatment • Pharmacokinetic parameters of VX-210: Cmax (maximum observed concentration) 48 hrs after treatment • Pharmacokinetic parameters of VX-210: AUC (Area Under plasma Concentration) 48 hrs after treatment
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as June 2018.

ESTIMATED COST and IMPACT

COST

The cost for Cethrin 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

☐ 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

No information was received from Vertex Pharmaceuticals

Vertex Pharmaceuticals did not enter information about this technology onto the *UK PharmaScan* database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. *UK PharmaScan* is an essential tool to support effective NHS forward planning; allowing more

effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use *UK PharmaScan* so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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