National Institute for Health Research

NIHR Innovation Observatory
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Ronopterin for moderate to severe traumatic brain injury

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LAY SUMMARY

Traumatic brain injury is a form of brain injury that results from damage to the head or brain from an external force. This can affect cognitive, physical and psychosocial functioning temporarily or permanently. Long-term impairment of these factors can lead to disability and loss of independence. The majority of people with head injuries are diagnosed with mild head injuries, however one fifth have features that suggest a more severe outcome of skull fracture or brain damage.

Ronopterin is being developed as a continuous infusion that can be used individually or in combination with the current standard treatments for traumatic brain injury. The current medications available are only used to treat the symptoms of traumatic brain injury. If licensed ronopterin has the potential to reduce the pressure build up in the skull and reduce brain inflammation. Therefore this could be the first medication licensed for the treatment of traumatic brain injury.

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TARGET GROUP

Traumatic brain injury (moderate to severe)

TECHNOLOGY

DESCRIPTION

Ronopterin (VAS203) is an allosteric nitric oxide (NO) synthase inhibitor interacting with the tetrahydrobiopterin binding site of the enzyme. High levels of NO are produced in the brain after injury in the course of neuro-inflammation. Increased production of NO results in cytotoxicity in the brain as NO is metabolized to peroxynitrite. This results in damage to the vasculature and tissue of the brain. Inhibiting the action of NO synthase may reduce NO production following trauma. [1, 3]

Ronopterin is currently in development for the treatment of traumatic brain injury. In the phase III clinical trial, ronopterin is administered as a 17 mg/kg intravenous infusion over 48 hours (daily dose of 8.5 mg/kg).[2]

Ronopterin does not currently have Marketing Authorization in the EU for any indication.

INNOVATION and/or ADVANTAGES

Currently there are no proven effective pharmaceutical treatments for those who sustain acute closed head injuries, however, there are numerous drugs in clinical trial development. Pre-clinical studies indicate that ronopterin has positive effects on elevated intracranial pressure, which contributes to the detrimental impact of traumatic brain injury, and subsequent neurological outcomes measured by behavioural tests.[3]

Ronopterin offers a novel approach to the treatment of traumatic brain injury as it targets both cerebral blood vessels and cerebral tissue in a region-specific manner. It can also be administered in addition to best standard of care. Therefore, ronopterin has the potential to improve effectiveness by addressing post-traumatic inflammatory damage to the blood brain barrier and brain tissue.[3]

DEVELOPER

Vasopharm GmbH

AVAILABILITY, LAUNCH or MARKETING

Ronopterin was designated EU Orphan Drug Status by the EMA in 2006.[1]

PATIENT GROUP

BACKGROUND

Traumatic brain injury is a form of acquired brain injury that results from damage to the head or brain from an external mechanical force. This can possibly lead to permanent or temporary impairment of cognitive, physical, and psychosocial functions, with an associated diminished or altered state of consciousness.[4,5] Primary brain injury occurs at the moment of injury; the main mechanisms are categorised based on impact loading (e.g. collision of the head with a solid object at a tangible speed), impulsive loading (e.g. sudden motion without significant physical contact) and static or quasistatic loading (e.g. loading in which the effect of speed of occurrence may not be significant). Contact or inertial forces may disrupt the brain tissue by tissue compression, stretching and shearing. Secondary types of brain injury are not mechanically induced, therefore may be delayed from the moment of impact, and may superimpose injury on a brain already affected by a mechanical injury.[4]

Head injuries are assessed by healthcare professionals using the Glasgow Coma Scale (GCS). The GCS is a 3- to 15-point scale used to assess a patient's level of consciousness and neurological functioning. Scoring is based on best motor response, best verbal response, and eye opening with 3 being most severe and 15 least severe.[6] A head injury is usually classed as being severe if someone has a GCS score of 8 or less. Severe head injury is usually defined as being a condition where the patient has been in an unconscious state for 6 hours or more, or a post-traumatic amnesia of 24 hours or more. These patients are likely to be hospitalised and receive rehabilitation once the acute phase has passed. Depending on the length of time in coma, these patients tend to have more serious physical deficits.[7] Furthermore, a vast proportion of those with traumatic brain injury die as a result of an uncontrolled increase in intracranial pressure, within the first 48 hours of injury.[8] Long-term physical, cognitive, and behavioural impairments are the factors that most commonly limit a patient's return to independent living and his/her return to employment. These include insomnia, cognitive decline, post-traumatic headache (tension-type headaches are the most common form, but exacerbations of migraine-like headaches are also frequent) and posttraumatic depression. Depression after traumatic brain injury is further associated with cognitive decline, anxiety disorders, substance abuse, dysregulation of emotional expression, and aggressive outbursts.[4]

CLINICAL NEED and BURDEN OF DISEASE

Each year 1.4 million people attend hospitals in England and Wales with a recent head injury. Between 33% and 50% of these are children under 15 years of age. The majority, around 80%, are diagnosed with ‘mild’ head injury and do not require hospital admission. Annually, around 200,000 people are admitted to hospital with head injury. Of these, one-fifth have features suggesting that their injury may have been sufficient to cause a skull fracture, or have evidence of brain damage. Approximately 2% of children with head injuries and 7% of adults with head injuries experience impaired consciousness and around 4000 patients a year undergo a neurosurgical operation for an intracranial complication. Most patients recover without specific or specialist intervention but in others, long-term disability or even death result from the effects of complications, which can potentially be minimised or avoided with early detection and appropriate treatment.[9]

In the UK the annual incidence of attendance at the emergency department with a head injury is 6.6% and around 1% of all patients attending the emergency department are admitted as an inpatient with a head injury. Although case fatality is low, trauma is the leading cause of death under the age of 45

and up to 50% of these are due to a head injury. Up to half of all inpatient adults with a head injury experience long term psychological and/or physical disability.[10]

In 2016-17, there were 172,441 admissions for injuries of the head (ICD-10 code S00.0- S09.0) in England resulting in 207,122 finished consultant episodes and 567,060 bed days. Of those admissions, 153,567 were emergency cases.[11]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guidelines. Head injury: assessment and early management (CG176). January 2014.
- NICE quality standard. Head injury (QS74). October 2014.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Major Trauma Service (All Ages). D15/S/a.

OTHER GUIDANCE

Brain Trauma Foundation. *Guidelines for the Management of Severe Traumatic Brain Injury (4th Edition).* 2016

Scottish Intercollegiate Guidelines Network. *Brain injury rehabilitation in adults*. 2013

CURRENT TREATMENT OPTIONS

Currently pharmacological agents are used to treat the symptoms of traumatic brain injury and to reduce some of the risks associated with the condition. These include the use of:[12]

- Anxiolytics to reduce fear and nervousness
- Anticoagulants to prevent blood clots
- Anticonvulsants to prevent seizures
- Antidepressants to help stabilise mood and treat depressive symptoms
- Diuretics to help reduce the fluid in the brain as this can build up and increase the intracranial pressure
- Muscle relaxants to reduce muscle spasms
- Stimulants to increase attention and alertness
- Osmotherapy (mannitol or sodium chloride) to reduce brain oedema

Additionally surgery may be used in emergency cases to remove blood clotting, repair skull fractures and to relieve pressure in the skull.[12]

EFFICACY and SAFETY

Trial	NOSTRA-III; NCT02794168; ronopterin vs placebo; phase III
Sponsor	Vasopharm GmbH
Status	Ongoing
Source of Information	Trial registry[2]
Location	5 EU countries incl UK
Design	Randomised, placebo-controlled, double-blind study
Participants	n=220 (planned); aged 18-60 years; moderate to severe traumatic brain injury within the last 6-18 hours.
Schedule	Randomised to receive ronopterin intravenous infusion of 17 mg/kg over 48 hours (with a daily dose of 8.5 mg/kg) or placebo intravenous infusion of physiological saline over 48 hours.
Follow-up	Active treatment for 48 hours with various physiological measures and clinical outcome questionnaires assessed at 5 days, 14 days, 3 months and 6 months.
Primary Outcomes	Extended Glasgow Outcome Scale - 6 months
Secondary Outcomes	Quality of life after brain injury (QOLIBRI) - 6 months QOLIBRI overall scale - 6 months extended Glasgow Outcome Scale - 3 months QOLIBRI overall scale - 3 months Therapy Intensity Level - 14 days Number of decompressive craniectomies - 14 days
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Completion date reported as Aug 2019

ESTIMATED COST and IMPACT

COST

The cost of ronopterin is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *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: *reduced use of secondary care/specialist services, reduced need for interventional procedures*

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

Information was received from Vasopharm GmbH

Vasopharm GmbH 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.

REFERENCES

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