Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Edaravone

Evidence Summary

Edaravone may be clinically effective in treating ischemic stroke, intracerebral hemorrhage, and ALS, but evidence for prevention of vascular diseases or cognitive decline is limited to rodent studies.

Neuroprotective Benefit: Strong Aβ- and free radical- scavenging properties of edaravone offer promise as a neuroprotective agent, but evidence for cognitive protection is limited to preclinical studies with severe pathology or invasive manipulations.

Aging and related health concerns: Ample clinical data exist showing edaravone is effective in treating ischemic stroke, intracerebral hemorrhage, and amyotrophic lateral sclerosis (ALS), but no studies have tested whether it prevents age-related diseases.

Safety: Several meta-analyses in stroke and intracerebral hemorrhage patients have shown that adverse events with edaravone are common but mild; however, no clinical data exist for long-term treatment.

What is it? Edaravone is a synthetic free radical scavenger marketed for treating acute ischemic stroke in Japan and China. In 2015, it was also approved for amyotrophic lateral sclerosis (ALS) treatment in Japan. It has been marketed as Radicut® (MCI-186) in Japan by Mitsubishi Tanabe Pharma since 2001 and by Edinburgh Pharmaceuticals in India by the brand name Arone®. In February 2016, Mitsubishi Tanabe Pharma America Inc. was established to accelerate approval of edaravone (Radicut) for treating ALS in the US. On May 5, 2017, MT Pharma America announced FDA approval of edaravone (Radicava™) to treat ALS. It is the first new drug to treat ALS in 22 years. It will be sold under the brand name Radicava™ and the drug should be available in the US by August 2017.

Neuroprotective Benefit: Strong Aβ- and free radical- scavenging properties of edaravone offer promise as a neuroprotective agent, but evidence for cognitive protection is limited to preclinical studies with severe pathology or invasive manipulations.

Types of evidence:

- 0 meta-analyses or systematic reviews
- 1 clinical trial examining postoperative cognitive impairment in patients undergoing carotid artery surgery
- 0 observational studies
- 13 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function: None available.

Human research to suggest benefits to patients with dementia: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research: The vast majority of studies testing the effects of edaravone are in models of significant brain pathology or insult, and it is currently unknown whether similar benefits can be expected in healthy people with normal oxidative stress levels. While some controversies remain for efficacies of antioxidants in general, edaravone has several additional advantages, such as its ability to readily cross the blood-brain-barrier, reduce inflammation, and inhibit apoptosis (Jiao et al., 2015).

In a clinical trial of patients undergoing carotid endarterectomy (surgery to remove plaque buildup to reduce the risk of stroke), the incidence of postoperative cognitive impairment was lower in people

receiving edaravone pretreatment (2%; 1 out of 55 patients) than controls (12%; 11 out of 92 patients) (Ogasawara et al., 2005).

The most extensive study on edaravone in the context of Alzheimer's disease pathology was carried out by Jiao and colleagues (Jiao et al., 2015). In an *in vitro* experiment, edaravone bound to the 13-18 amino acid sequence of Aβ42, inhibited Aβ aggregation, and disaggregated already-formed Aβ fibrils. In human neuroblastoma cells, edaravone dose-dependently protected neurons from cell death. *In vivo* experiments in a mouse model of Alzheimer's disease (APPswe/PS1) showed that edaravone prevented cognitive deficits and reduced Aβ levels, cerebral amyloid angiopathy, neuronal and dendritic loss, inflammation, and tau-phosphorylation. Notably, a 3 month-treatment of edaravone (from 9-12 months old) was effective in protecting against cognitive deficits even after the onset of Aβ deposition. Other than its free radical scavenging properties, edaravone suppressed BACE1 (involved in amyloidogenesis) and GSK3β (involved in tau phosphorylation), decreased inflammation, and inhibited apoptotic mechanisms by suppressing the Fas/FasL signaling pathway, cytochrome c release, and caspase 3 activation (Jiao et al., 2015).

Other studies in cell culture and rodent models of Alzheimer's have also shown that edaravone improves cognitive function (Zhou et al., 2013; He et al., 2014; Yang et al., 2015), cell viability (Yan et al., 2012), and mitochondrial function (Yan et al., 2012), while reducing Aβ levels (Shen et al., 2013) and oxidative stress (Yan et al., 2012; Zhou et al., 2013).

Cognitive benefits of edaravone have also been demonstrated in rodent models of postoperative cognitive dysfunction (Wang et al., 2016), ischemic stroke (Sun et al., 2015), traumatic brain injury (Ohta et al., 2013), and chronic stress (Jangra et al., 2016).

In a rat model of vascular dementia (chronic cerebral hypoperfusion; CCH), edaravone (5 mg/kg, i.p.) reversed both spatial and fear-memory deficits (Li et al., 2017). Edaravone significantly reduced the level of oxidative stress in the brain by increasing superoxide dismutase (SOD) activity and decreasing levels of reactive oxygen species. Edaravone treatment also restored levels of multiple synaptic proteins in the hippocampi. In rats that did not undergo CCH, behavioral performance was comparable between edaravone-treated and placebo-treated, suggesting that edaravone may not improve learning and memory in healthy animals with good cognitive function.

In a rat model of chemotherapy (cisplatin)-induced cognitive impairment, edaravone treatment (10 mg/kg/week, i.p.) for 7 weeks inhibited cognitive deficits, increased expression of Nrf2 (which regulates

expression of antioxidant proteins), and reduced mortality by half (Jangra et al., 2016). Like the study above, the control and edaravone groups without cisplatin had equivalent cognitive scores, suggesting that edaravone may not improve cognitive function in healthy animals.

In a rat model of cognitive impairment (i.c.v. injection of streptozotocin), edaravone treatment (10 mg/kg, orally, once daily) for 28 days ameliorated cognitive impairment, oxidative stress, and inflammatory responses (TNFα, IL1β) (Reeta et al., 2017). Edaravone prevented the streptozotocin-induced increased activity of cholinesterases while normalizing expression of choline acetyltransferase (ChAT) in the cortex and hippocampus, suggesting the treatment may increase acetylcholine levels.

APOE4 interactions: Unknown.

Aging and related health concerns: Ample clinical data exist for the effectiveness of edaravone as a treatment for ischemic stroke, intracerebral hemorrhage, and ALS, but no studies have tested whether it prevents age-related diseases.

Types of evidence:

- 2 Cochrane meta-analyses, 1 in ischemic stroke (3 RCTs) and 1 in intracerebral hemorrhage (10 RCTs)
- 2 other meta-analyses in acute ischemic stroke and intracerebral hemorrhage (total of 30 RCTs) and in heart surgery patients (7 trials)
- 1 clinical trial in ischemic stroke patients over 80 years old
- 3 laboratory studies, 2 in ischemia-reperfusion injury model and 1 in human neural stem cells

It is unknown whether edaravone prevents age-related diseases, but it has been used extensively for treatment of ischemic stroke and intracerebral hemorrhage. Mechanisms of action, as in studies above, likely include its free radical scavenging properties as well as its ability to inhibit inflammation and apoptosis (Jiao et al., 2015).

Stroke: Meta-analyses of up to 16 RCTs have shown that edaravone improves neurological symptoms in patients with acute ischemic stroke or intracerebral hemorrhage (Feng et al., 2011; Yang et al., 2011; Yang et al., 2015). However, the quality of trials in these analyses was generally poor. Higher quality, larger-scale randomized controlled trials are required to confirm these findings.

In ischemic stroke patients over 80 years old, treatment with edaravone in combination with recombinant tissue plasminogen activator (tPA) improved clinical outcomes 3 months after the stroke (Kono et al., 2013).

Coronary artery bypass surgery: A meta-analysis of 7 clinical trials in patients undergoing coronary artery bypass surgery showed that edaravone treatment (60 mg/day for 14 days) decreased the proportion of patients with marked heart damage compared to controls (Zheng et al., 2015). Edaravone-treated patients had decreased markers of myocardial damage (i.e., creatine kinase-MB, cardiac troponin 1, and MDA, an oxidative stress marker).

Preclinical studies: In rodent models of ischemia-reperfusion injury, edaravone reduced neuronal (Wen et al., 2006) and cardiomyocyte death (Watanabe et al., 2007). Edaravone also protected human neural stem cells from irradiation (Ishii et al., 2007).

In a rat model of intracerebral hemorrhage, a combination of pharmacologically-induced hypothermia (with neurotensin receptor agonist HPI-201) and edaravone (10 mg/kg) significantly prevented brain edema, blood-brain-barrier permeability, and expression of inflammatory cytokines (IL1β, IL6, TNFα) (Zhu et al., 2015).

In a strain of mice (EL mice) that is highly susceptible to convulsive seizures, edaravone treatment (10 mg/kg/day, i.p.) for 7 days significantly increased antioxidant potency (GSH/GSSG ratio) and reduced seizure susceptibility (Baba et al., 2016).

Safety: Several meta-analyses in stroke and intracerebral hemorrhage patients have shown that adverse events with edaravone are common but mild; however, no clinical data exist for long-term treatment.

Types of evidence:

- 3 meta-analyses or systematic reviews based on 3-16 RCTs in patients with ischemic stroke or intracerebral hemorrhage
- 2 double-blind RCTs, 1 in ALS patients and 1 in acute ischemic stroke patients
- 1 retrospective study in patients with carbon monoxide poisoning
- 1 small study in pediatric cerebral ischemia patients
- 1 phase I clinical study in healthy volunteers

Three meta-analyses in patients with acute ischemic stroke or intracerebral hemorrhage have reported that adverse events with edaravone are common (9%) but mild. In two Cochrane meta-analyses, one in acute ischemic stroke patients (Feng et al., 2011) and the other in patients with intracerebral hemorrhage (Yang et al., 2011), no differences in adverse events were found between edaravone-treated versus non-treated groups. Edaravone treatment was also not associated with increased or decreased numbers of death during treatment (RR 0.62, 95% CI 0.11-3.50) or at 3-month follow-up (RR 0.93, 95% CI 0.20-4.32). In another meta-analysis, which included patients with acute ischemic stroke (16 RCTs) and intracerebral hemorrhage (14 RCTs), the most common adverse event was mild impairment of kidney function, reported in 3.25% of patients receiving edaravone versus 1.49% in controls (Yang et al., 2015). One patient receiving edaravone had acute renal failure so edaravone may not be recommended for people with renal dysfunction. The incidence of mild impairment of liver function was similar in edaravone-treated (3.18%) versus controls (3.23%)(Yang et al., 2015).

Other smaller studies including one in carbon monoxide poisoning (Mori et al., 2015) and another in pediatric cerebral ischemia (Nakamoto et al., 2015) reported that no patients presented with complications from edaravone treatment. A double-blind randomized controlled trial in ALS patients also showed that the incidence of adverse events in edaravone-treated (89.2%) versus placebo-treated (88.5%) groups were comparable (Abe et al., 2014).

In a phase I clinical study in healthy volunteers (n=30), edaravone doses of up to 60 mg/day for 5 days were well-tolerated and no symptomatic adverse events were observed (Li et al., 2012). However, some abnormalities in laboratory test results were reported, including increased alanine transaminase (liver function) and triglyceride levels, and decreased white blood cell counts and creatinine levels (kidney function). These changes were judged to be small in magnitude and tolerable, and all abnormal indices returned to normal levels within 7 days.

Edaravone was approved in the US based on results from a phase III study in ALS patients that were published in May 2017. In a phase III double-blind RCT, 137 early-stage ALS patients were recruited and received edaravone (60 mg, i.v.) or saline for 24 weeks (6 cycles of 2 weeks on and 2 weeks off) (Writing Group, Edaravone ALS 19 Study Group, 2017). Edaravone-treated patients experienced a significantly smaller decline in functional impairment (ALSFRS-R score) compared to those receiving placebo. It is currently unknown whether edaravone may be effective in a wider population of patients at later stages of ALS.

The number of patients reporting at least one adverse event did not differ between edaravone and control groups. Incidents of adverse events and severe adverse events (SAEs) were also comparable between the two groups. Adverse events were reported in 58 (84%) patients receiving edaravone and 57 (84%) patients receiving placebo. Eleven (16%) patients taking edaravone and 16 (24%) taking placebo had SAEs, which included dysphagia (difficulty swallowing; 12% in edaravone, 12% in placebo) and respiratory disorder (3% in edaravone and 3% in placebo). One (1%) patient receiving edaravone and 4 (6%) patients receiving placebo had adverse events (1 dysphagia in edaravone group and 1 dyspnea, 2 respiratory disorder, and 1 rash in the placebo group) that led to withdrawal from the trial. No deaths were reported during the study. Adverse events with incidence of 10% or more were contusion, constipation, and dysphagia in both groups, and dermatitis in the edaravone group. The only SAE with incidence of over 5% was dysphagia (difficulty swallowing) observed in both groups. No changes in laboratory and sensory tests were observed between groups. Two (3%) of 69 patients receiving edaravone had adverse drug reactions (abdominal discomfort, eczema, and abnormal liver function test) and 7% of controls had adverse reactions (dizziness, constipation, rash, chondrocalcinosis pyrophosphate, increased blood bilirubin, increased blood creatine phosphokinase, and abnormal liver function test).

No information on drug interactions is available on drugs.com or WebMD.

Sources and dosing: Edaravone is used for treating acute ischemic stroke and ALS in Japan. Sources of edaravone include Radicut® (MCI-186) by Mitsubishi Tanabe Pharma in Japan and Arone® by Edinburgh Pharmaceuticals in India.

As of August 2017, Edaravone is also approved in the US for ALS and is sold under the brand name Radicava™.

Edaravone is currently administered intravenously. The most commonly used dose is 30 mg twice daily in adults. Treatment duration in clinical studies range from 3-28 days for acute ischemic stroke, hemorrhagic stroke, and heart surgery, and for up to 24 weeks for ALS patients. Oral formulations of edaravone are being tested (e.g., TW001, discussed below). In AD model mice, bioavailability of oral edaravone was 38% of intravenous delivery (Jiao et al., 2015).

Research underway: There are no ongoing clinical trials that are testing the effects of edaravone on cognitive function or dementia risk. One clinical trial examined the effects of edaravone injection for treatment of acute ischemic stroke (NCT 02430350). This study was completed in January 2017 but the

results are not published yet. Another trial is testing whether edaravone protects from ischemia-reperfusion injury in kidney transplantation patients (NCT 02644915). This study is not yet open for participant recruitment.

A biotech company Treeway has developed an oral formulation of edaravone (TW001). They have tested this formulation in a phase 1 study including ALS patients and healthy volunteers, and are planning to start a phase 2/3 study.

Search terms:

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- Radicut
- MCI-186
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