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Potential of the Cardiovascular Drug Levosimendan in the Management of Amyotrophic Lateral Sclerosis: An Overview of a Working Hypothesis

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Abstract: Levosimendan is a calcium sensitizer that promotes myocyte contractility through its calcium-dependent interaction with cardiac troponin C. Administered intravenously, it has been used for nearly 2 decades to treat acute and advanced heart failure and to support the heart function in various therapy settings characterized by low cardiac output. Effects of levosimendan on noncardiac muscle suggest a possible new application in the treatment of people with amyotrophic lateral sclerosis (ALS), a neuromuscular disorder characterized by progressive weakness, and eventual paralysis. Previous attempts to improve the muscle response in ALS patients and thereby maintain respiratory function and delay progression of disability have produced some mixed results. Continuing this line of investigation, levosimendan has been shown to enhance in vitro the contractility of the diaphragm muscle fibers of non-ALS patients and to improve in vivo diaphragm neuromuscular efficiency in healthy subjects. Possible positive effects on respiratory function in people with ALS were seen in an exploratory phase 2 study, and a phase 3 clinical trial is now underway to evaluate the potential benefit of an oral form of levosimendan on both respiratory and overall functions in patients with ALS. Here, we will review the various known pharmacologic effects of levosimendan, considering their relevance to people living with ALS.

Key Words: levosimendan, ALS, diaphragm, muscle, cardiac troponin C, slow-twitch fibers

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A NEW WORKING HYPOTHESIS FOR A CARDIOVASCULAR DRUG

Levosimendan is an inodilator that, in intravenous formulation, has been used for nearly 20 years to treat acute heart failure and to support heart function in various therapy settings involving low cardiac output. In addition to an inotropic effect due to calcium sensitization of cardiac troponin C (cTnC)[1], the drug has a number of other well-documented effects, including vasodilation and cardioprotection.[2] More recently, effects of levosimendan on skeletal muscle have attracted interest and suggest a possible clinical value of levosimendan in managing people with amyotrophic lateral sclerosis (ALS), a devastating neuromuscular disorder, characterized by progressive weakness and eventual paralysis. An oral formulation of levosimendan is currently in advanced clinical development for the treatment of ALS. We will review the various known actions of levosimendan, considering their relevance to people living with ALS.

INTRODUCTION TO ALS

ALS is an adult-onset condition characterized by a progressive muscular paralysis attributable to degeneration of motor neurons in the brain and spinal cord.[3] Initial focal weakness spreads to involve most skeletal muscles, including the diaphragm and other respiratory muscles and results in progressive weakness and loss of functional independence. Death typically occurs within a few years of diagnosis, frequently from respiratory failure or complications secondary to degeneration of the motor neurons supplying the diaphragm and other respiratory muscles.[4,5]

A defining aspect of ALS is the involvement of both upper and lower motor neurons, although there may be a predominance of one type during the early stages of the disease.[6] Spinal onset is the most common (~60%), symptoms first emerging in one or more of the limbs, manifested by problems such as weakness, foot-drop, or deterioration of manual dexterity. Bulbar-onset ALS accounts for some one-third of cases and is associated with slurring and hoarseness of speech and swallowing difficulties. Occasional cases of respiratory-onset ALS are also encountered (~3%–5% of all diagnoses).[7–10] Behavioral changes are common in patients with ALS: some 30% of patients have evidence of

executive dysfunction at presentation with up to 80% affected by stage 4 disease,[11] and frontotemporal dementia has a close association with ALS.[12–19] Irrespective of the initial presentation, the relentless spread of the disease results in progressive disability,[20] with increasing difficulty in walking, handling or lifting objects, speaking, and swallowing, including dyspnea because of respiratory failure, leading ultimately to death.

ALS is the most frequent neurodegenerative disorder of midlife. In Europe and the United States, the incidence is 1–2/100,000 person-years, with an overall prevalence of 3–5 patients/100,000 at any one time. The lifetime risk of ALS is 1 in 300 by age 80.[21] The incidence and prevalence of ALS increase with age,[22,23] and, consequently, the incidence will nearly double over the next 100 years as the population ages.[24]

The causes of ALS are unclear. About 5% of cases are familial, with a first-degree relative affected, although familial ALS is not well defined among neurologists. Causative gene variants are found in up to 80% of those with a family history and about 14% of those without.[3,25,26] Even in those not carrying a large effect Mendelian gene, the heritability of ALS is about 60%, suggesting a significant genetic component. No environmental factor has been consistently identified as greatly increasing ALS risk. Although a number of associations (such as athleticism, serving in the armed forces etc.) have been proposed, the importance of these factors in precipitating the disease is not clear. Irrespective of the cause of the disease, various pathophysiological abnormalities (Fig. 1) can be identified in ALS (Box 1).

BOX 1.

Pathophysiological Abnormalities Identified in ALS

Disturbances in protein quality control and aggregation of abnormal proteins.
Endoplasmic reticulum stress.
Disturbance of multiple aspects of RNA metabolism.
Microglial activation and production of extracellular superoxide.
Reduced energy supply from oligodendrocytes to motor axons.
Release of toxins from astrocytes that target motor neurons.
Disruption of the cytoskeleton and impaired axonal transport.
Glutamate excitotoxicity.

Prion-like spread of ALS is also a possible mechanism, with cell-to-cell transmission of one or more misfolded proteins within the motor neuron network.[27–29]

Although reinnervation of denervated motor units may delay the onset of symptoms in the early course of ALS, later in the disease, these larger motor units are also lost leading to permanent weakness and muscle atrophy. The first neurons to die off in ALS are those associated with the fast-fatigable motor units.[30,31]

Management of ALS

There is no cure for ALS at present. The focus of medical care is toward supportive and palliative measures intended to preserve or maintain quality of life for patients and to ease the burden of care for the family and others; these interventions are often delivered through specialist multidisciplinary clinics.[32–34]

The medical repertoire is limited. Riluzole, which modulates glutamatergic neurotransmission (and is thus believed to attenuate glutamate excitotoxicity) and is a noncompetitive antagonist at N-methyl-D-aspartate receptors, has been shown to modestly improve 1-year survival, to delay progression from early to intermediate stages of ALS and to prolong the late stage.[35–37]

The free-radical scavenger edaravone has also been shown to slow the rate of progression of ALS, but this effect has been robustly demonstrated only for a small proportion of the ALS patient population, defined by very strict selection/status criteria.[37,38] It is administered by repeated intravenous infusion (10 days per 28-day cycle) and, although approved in the United States and Canada, is not available in the European Union. Currently, no treatment is approved to enhance motor function in ALS.

Noninvasive ventilation (NIV) has become the standard treatment for the management of respiratory insufficiency in ALS, with evidence for both preservation of quality of life (including a reduced rate of decline of respiratory function) and increased survival time.[39]

Invasive (tracheostomized) ventilation is an option selected by only a small proportion of patients with ALS.[40]

Notwithstanding the benefits of noninvasive and invasive mechanical ventilation, poor respiratory function remains a major source of disability, fatigue, morbidity, and mortality in ALS patients, and new therapies to support respiratory muscles, either alone or in association with NIV, could be of great clinical value.

RATIONALE FOR IMPROVING MUSCLE RESPONSE IN ALS

Amelioration of symptoms of ALS by improving the muscle response to the diminished motor nerve activity, to maintain respiratory function and delay progression of disability is a clearly attractive objective but has yielded mixed results.

Tirasemtiv is a fast-skeletal muscle fiber activator reported to sensitize the sarcomere to calcium. Enhancement of muscle contractile force and functional indices was recorded in isolated nerve-muscle preparations in human volunteer studies[41,42] and in an experimental model of ALS [superoxide dismutase 1 (SOD1) transgenic mouse]. A meta-analysis of 3 small studies in a total of 143 patients with ALS demonstrated significant, concentration-dependent improvements in maximum voluntary ventilation, sniff nasal inspiratory pressure, and muscle strength using handheld dynamometry.[43]

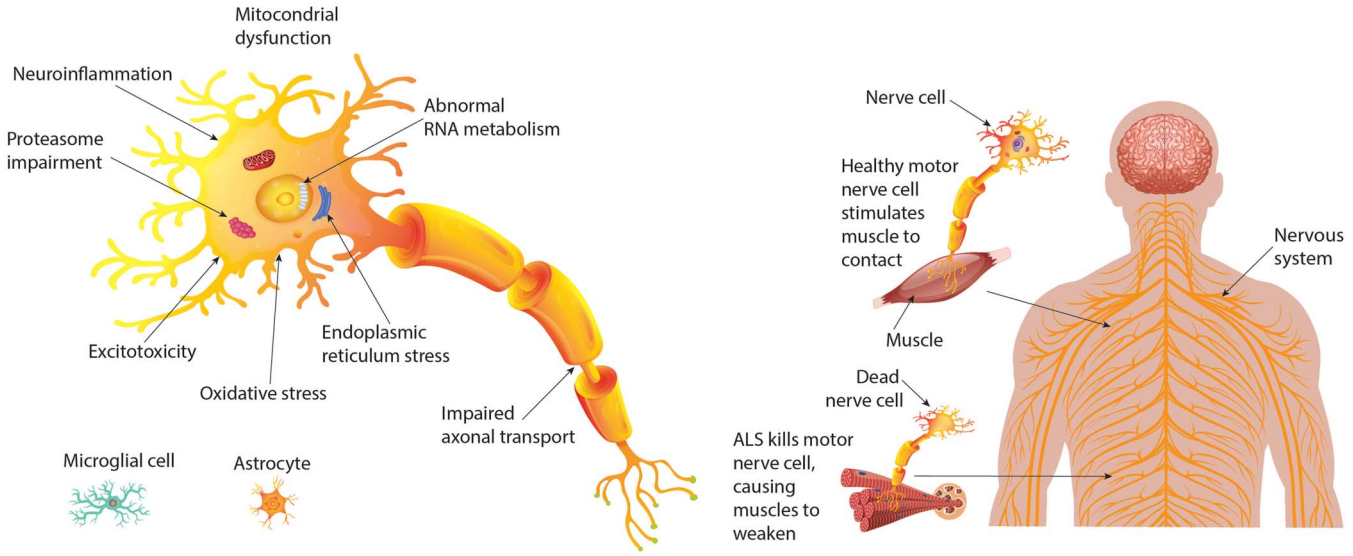

FIGURE 1. The dysfunction and death of motor neurons that is the core feature of ALS is believed to arise from multiple underlying pathophysiological processes. See text for further discussion.

In a placebo-controlled phase 2 study (BENEFIT-ALS), which randomized 596 patients with ALS and slow vital capacity (SVC) >50% predicted, a 12-week course of tirasemtiv therapy did not affect the primary endpoint of functional measures [ALS Functional Rating Scale-Revised (ALSFRS-R)[44]] but was associated with a significantly slower decline in SVC (mean difference 5.54 ± 1.19%; P = 0.0006) and muscle strength (P = 0.0158). A treatment effect on SVC was still apparent 4 weeks after cessation of therapy (Δ4.91%; P = 0.0002).[45]

These encouraging findings were not reproduced, however, in the subsequent phase 3 study VITALITY-ALS (ClinicalTrials.gov identifier: NCT02496767). That study, conducted in patients with possible, probable, or definite ALS, diagnosed within 24 months and with SVC at baseline ≥70% predicted, randomized participants to placebo or to tirasemtiv at doses of 250, 375, or 500 mg/d for 48 weeks. No statistically significant effect of therapy was identified on the study primary endpoint of change from baseline in SVC after 24 weeks or on any secondary endpoints evaluated at 48 weeks.[46] Full analysis of VITALITY-ALS is ongoing, but the investigators have proposed that poor tolerability of the target doses, in particular central nervous system adverse events, may have contributed to the study failure. Subgroup analysis of VITALITY-ALS restricted to patients who are able to tolerate the target doses of tirasemtiv produced indications of a beneficial effect on SVC.[47]

The development of reldesemtiv (CK-2127107), a follow-up molecule to tirasemtiv with the same mode of action, but which is reported not to cross the blood brain barrier, is ongoing. Reldesemtiv had been previously studied in a phase 2 clinical trial designed to assess its potential effect versus placebo on exercise tolerance, assessed as change from baseline in constant work rate endurance time over 2 weeks, in approximately 40 patients with chronic obstructive pulmonary disease (COPD). In October 2018, it was announced that the trial had recorded no statistically significant treatment differences on either its primary or any secondary endpoints.[48] At the same time, it was also announced that a phase 1b clinical trial designed to assess the effect of reldesemtiv versus placebo on skeletal muscle fatigue in approximately 60 patients aged 70–89 years, with limited mobility, had met its predefined criteria for lack of efficacy of reldesemtiv and that patients enrolment had been halted.[48]

The phase 2 clinical trial FORTITUDE-ALS compared the effects of 3 dose levels of reldesemtiv versus placebo in 458 patients living with ALS during 12 weeks of treatment. The primary and secondary endpoints of dose response in SVC and ALSFRS-R compared with placebo at 12 weeks were not met although there were promising trends reported on both endpoints, as well as a measure of muscle strength, when the dose groups were combined in post hoc analyses.[49] At the moment, a regulatory phase 3 clinical trial has not yet started.

PHARMACOLOGY AND MECHANISMS OF ACTION OF LEVOSIMENDAN

The calcium sensitizer levosimendan[50] was initially developed for intravenous use as an inotrope in patients with acute heart failure; it is now used in a wider range of cardiac-related situations in which inotropic therapy is considered appropriate.[51–58]

The principal pharmacologically relevant action of levosimendan is its inotropic effect, attributable to a novel mechanism of action distinctly different from those of conventional adrenergic agents.[1] In brief, levosimendan is a calcium sensitizer that promotes contractility through its calcium-dependent interaction with cTnC. Levosimendan

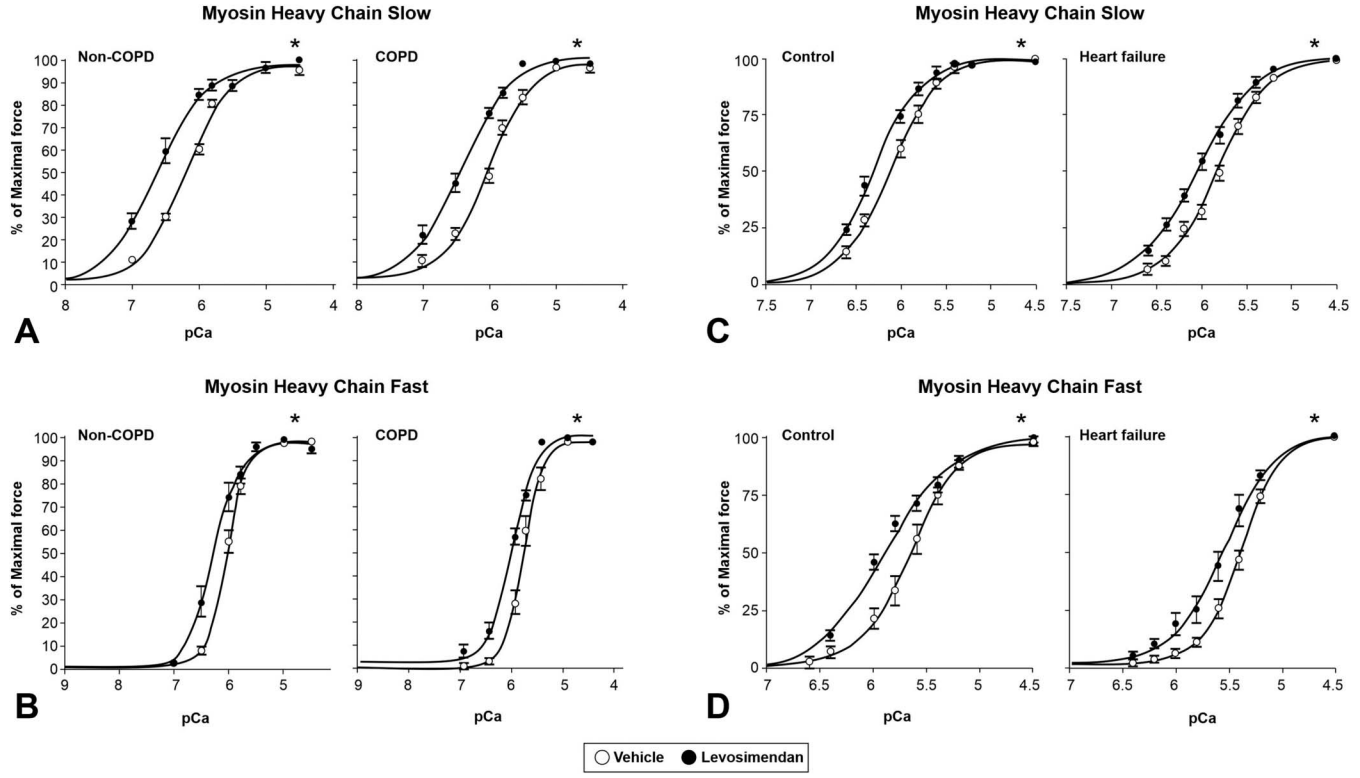

FIGURE 2. Levosimendan increased the in vitro calcium sensitivity of force generation ($P < 0.01$) in diaphragm fibers from patients with or without COPD, without affecting maximal force generation. This effect was apparent in both slow muscle fibers (panels A and C) and fast muscle fibers (panels B and D). Reproduced from van Hees et al[92,99] with permission.

targets the hydrophobic pocket in the tertiary structure of cTnC[59–64]: its effective binding site and the locus of its calcium-sensitizing effect are in the regulatory or N domain of cTnC and seem to be strongly predicated on the presence of a chiral methyl group and a hydrazine moiety in the drug's own molecular structure.[65–68] The binding of levosimendan to its target is calcium-dependent and reversible[69] and, thus, does not disturb relaxation.[70–72]

Levosimendan has additional pharmacological effects mediated by the opening of ATP-dependent potassium channels (K_{ATP} channels) in vascular smooth muscle cells[73–76] and cardiomyocytes.[77–80] Owing to this, levosimendan causes vasodilatation,[76] reduction of preload and afterload,[81] increase in peripheral perfusion,[82] reduction of pulmonary capillary wedge pressure,[83] and a selective dilation of the afferent arterioles in the renal glomeruli causing an increase in glomerular filtration.[84]

Levosimendan also opens the K_{ATP} channels in mitochondria in cardiomyocytes,[85] which has been associated with cardioprotection, infarct size reduction, and mitigation of ischemia/reperfusion injuries in a range of experimental and clinical studies.[86] In addition, levosimendan inhibits the phosphodiesterase (PDE)-III isoform, with a great selectivity against all other isoforms including PDE-IV.[87]

Levosimendan has been linked to a range of pleiotropic actions, including antiapoptotic and anti-inflammatory properties (see Farmakis et al[2] for a review) and has also been shown to increase cerebral blood flow.[88–90] Interestingly, levosimendan has been shown to enhance the contractility of both slow and fast muscle fibers in the isolated diaphragm from patients with COPD,[91] at least at high concentrations. Such pleiotropic effects are considered to be relevant to the overall therapeutic action of the drug.[1,92]

In animal studies on primary and secondary stroke, levosimendan significantly reduced stroke-induced mortality and morbidity, and its vasodilatory effects seemed to have a role in increasing blood volume in cerebral microvessels and large vessels in various zones of the brain.[88]

Levosimendan has an extensively documented safety profile in its cardiovascular-approved indications.[51,52,56,93] The most frequently recorded adverse events are hypotension, headache, atrial fibrillation, hypokalemia, and tachycardia.[50] In clinical use, short-term treatment with i.v. levosimendan exhibits sustained efficacy because of the formation of an active metabolite.[94]

RATIONALE FOR THE USE OF LEVOSIMENDAN IN ALS

Respiratory Muscle Weakness and Dysfunction

Two isoforms of the contraction-regulatory protein troponin C (TnC) are expressed in muscular tissues, the fast-twitch

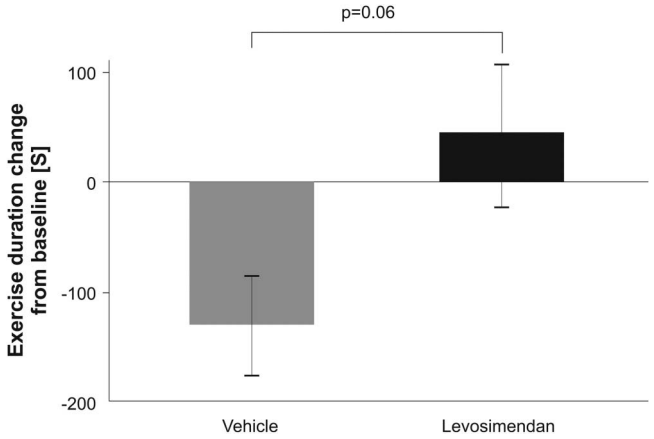

FIGURE 3. In rats with an antibody-induced form of myasthenia gravis, treatment with oral levosimendan (0.25 μg/kg; n = 4) was associated with enhanced exercise time (vs. baseline) in a treadmill test performed 2 hours after dosing.[101]

and slow-twitch (or cardiac) TnC.[95] The 2 proteins have distinctive calcium-binding properties that affect their actions as subunits of the troponin complexes. In adult muscle, the fast-twitch isoform gene is expressed exclusively in fast-twitch skeletal muscle, whereas the cardiac isoform gene (cTnC) is expressed both in the myocardium and in slow-twitch skeletal muscle.[96] The diaphragm is normally composed of a substantial proportion of slow-twitch fibers (approximately 50%), but other skeletal muscle also contains a proportion of slow-twitch fibers and thus also a proportion of cTnC.[97]

Levosimendan, which has been described as a cTnC-specific binder,[98] can thus also have an effect on the diaphragm and skeletal muscle. In addition, levosimendan has been suggested to have a direct effect also on fast-twitch fibers, at least at high concentration.[92]

Preclinical Experience With Levosimendan on the Diaphragm and Skeletal Muscle

Levosimendan has been shown to enhance the contractility of muscle fibers in the isolated diaphragm from COPD patients by improving calcium sensitivity (Fig. 2).[92] Similar findings have been reported from use of levosimendan in ex vivo diaphragm samples in a coronary ligation model of heart failure in rats.[99] In addition, levosimendan has also been shown to attenuate oxidative tissue damage in the diaphragms of mechanically ventilated mice with septic shock.[100]

In rats with an antibody-induced form of myasthenia gravis, treatment with oral levosimendan (0.25 mg/kg; n = 4) was associated with enhanced exercise time, compared with baseline, in a treadmill test performed 2 hours after dosing (Fig. 3; $P = 0.06$).[101]

Other Effects of Levosimendan Potentially Relevant in ALS

In addition to promotion or preservation of respiratory muscle contractility, the multifaceted pharmacology of levosimendan may also provide supplementary clinical impact in patients with ALS through a range of pharmacological effects (see Farmakis et al[2] and Papp et al[86] for reviews). These possibilities require detailed investigation before any conclusions can be reached about their clinical relevance in ALS.

Brain Circulation

Evidence has been assembled for correlations between diminished cerebral perfusion, grey matter atrophy, and aspects of ALS, notably those associated with decline in cognition.[102–104] In addition, it has been reported that low oxygen tension is associated with increased instability of the SOD1 protein and, by implication, a greater risk of aggregation of dysfunctional forms of that protein, leading to the development of ALS.[105]

Levosimendan has been shown to increase blood flow in the brain in situations of stroke in Dahl salt-sensitive rats or subarachnoid hemorrhage[89–91] in modified double-hemorrhage,[106] endothelin-1 (ET-1)–dependent vasoconstriction after experimental-induced subarachnoid hemorrhage[107] and injection of autologous blood into the cisterna magna model in rabbits.[108] Cerebral blood flow velocity was also increased

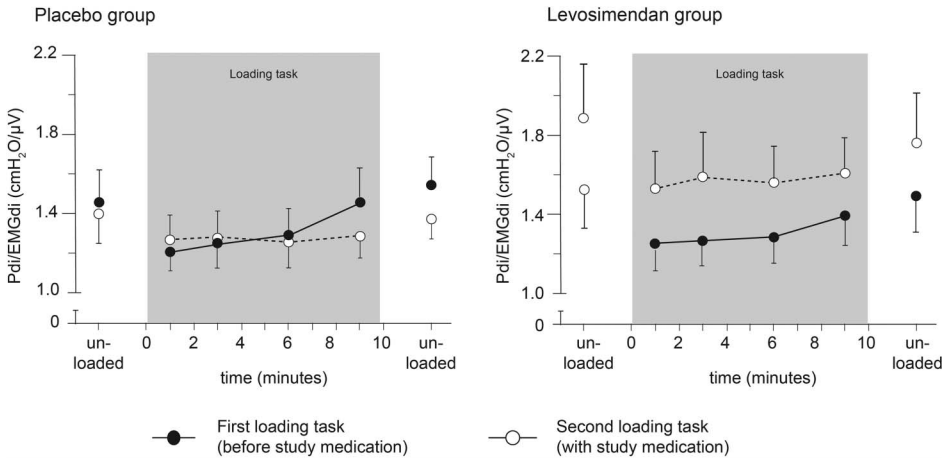

FIGURE 4. In a study of diaphragm function in healthy volunteers, administration of levosimendan, but not placebo, resulted in an increase in the neuromechanical efficiency of the diaphragm (defined as Pdi/EMGdi) during loaded and unloaded breathing ($P < 0.05$). Data are mean ± SEM. Levosimendan EMGdi, diaphragm electromyography; Pdi, transdiaphragmatic pressure. After Doorduin et al.[138] See text for further discussion.

in patients with a recent ischemic stroke or TIA receiving oral levosimendan up to 2 mg daily.[91] Similar possible effects in ALS would be a matter of interest.

Endoplasmic Reticulum Stress Relief

Endoplasmic reticulum (ER) stress seems to play a prominent role in the pathogenesis of ALS.[109] Long-term ER stress leads to cell death through apoptotic signaling cascades. This process provides a link to neurodegeneration.[110]

Observations in vitro on human cardiomyocyte progenitor cell-derived cardiomyocytes indicate that levosimendan attenuates the ischemia/reperfusion–induced ER stress mechanism.[111]

Prevention of Programmed Cell Death

During research into the mechanisms of ALS, it was discovered that transfected neuronal cells expressing mutant SOD1 cDNA were dying by apoptosis, a form of programmed cell death. A role for mutant SOD1 genes in apoptosis of neuronal cells is supported by various lines of experimental evidence.[110,112,113]

Levosimendan has been reported to display antiapoptotic effects in a range of in vitro (in H9C2 cells), ex vivo, and in vivo (in rats and pigs) experimental studies.[114–118] Multiple mechanisms of antiapoptosis have been identified, including the activation of survival signaling through opening of mitochondrial K_{ATP} channels, the modulation of nitric oxide release,[119–121] reduction in the expression and activity of caspase-3, and modulation of nuclear factor kappa-B (NF-κB). Cardioprotective effects explained at least in part by an antiapoptotic effect of levosimendan have been also described also in humans.[122,123]

Antioxidative and Anti-inflammatory Effects

Neuronal damage and death in ALS are caused by a combination of excitotoxic, inflammatory, and oxidative insults (see Redler and Dokholyhan[124] for a survey of the many factors that may be implicated and the role of cytosolic calcium overload as a possible prime mover in the emergence of inflammation and a prooxidative state).

Levosimendan has been shown to have both anti-inflammatory effects[125–129] and antioxidative properties.[2,130] Given the complex pathophysiology of ALS, these properties may give levosimendan a potential to influence these pathological processes, although their final role in disease progression is not completely understood.

Mitochondria-Protective Effects

Pathological changes in ALS are closely associated with pronounced and progressive changes in mitochondrial morphology, bioenergetics, and calcium homeostasis.[128] Levosimendan has been shown in experimental investigations to exert a range of effects by opening ATP-dependent (K_{ATP})[86,131–134] and calcium-dependent (BK) potassium channels[135] that may mitigate mitochondrial damage and dysfunction and that may be relevant to its use in ALS.[114,117,118,136,137]

HUMAN EXPERIENCE WITH LEVOSIMENDAN RELEVANT TO ALS

Healthy Volunteer Data

The effects of levosimendan on diaphragm function have been studied in healthy volunteers (ClinicalTrials.gov identifier: NCT01101620).[138] Thirty subjects were randomized to placebo or levosimendan infusion for 40 minutes with an inspiratory loading test before and after treatment. An inspiratory loading test resulted in significant loss of diaphragm contractility during placebo treatment but not during treatment with levosimendan, suggesting that the drug preserved diaphragm contractility. That finding was associated with improved neuromechanical efficiency of the diaphragm during levosimendan infusion (Fig. 4).

The mean neuromechanical efficiency of the diaphragms of participants during levosimendan treatment was improved by 21% ($P < 0.05$) during unloaded breathing and during the second loading task compared with the first loading task, whereas no change was observed in the placebo group. This improved neuromechanical efficiency in people receiving levosimendan was sustained throughout the loading task.

In addition, stimulation of the phrenic nerves revealed a diminished contractile response of the diaphragm after the first loading task with placebo but no diminution with levosimendan. Neither levosimendan nor placebo altered subjective sensations of respiratory effort.

Levosimendan Clinical Trials in ALS Patients

Some preliminary possible positive effects of short-term orally administered levosimendan in patients with ALS were seen in a post hoc analysis of the LEVALS study (ClinicalTrials.gov identifier: NCT02487407).[139] This phase II trial, based on a randomized, double-blind, placebo-controlled, crossover design, evaluated the efficacy and safety of oral levosimendan in 66 patients with definite or probable ALS. Patients had symptoms of ALS for between 12 and 48 months before the study and were required to have early respiratory decline [defined as baseline seated SVC between 60% and 90% (mean 75.3%) of that predicted for age, height, and sex]. Participants were allowed to use riluzole but not assisted ventilation or gastrostomy of any type.

The patients received 2 weeks of treatment with oral levosimendan 2 mg/d (1 mg twice daily), levosimendan 1 mg/d, and placebo in a random order during 3 study periods separated by a 2- to 3-week washout period.

The primary endpoint was the percentage change from baseline in SVC (measured in the sitting position) after 14 days of treatment. A statistically significant treatment effect on this endpoint was not recorded. However, poststudy analysis of outcomes revealed significant and dose-dependent treatment effects of levosimendan on supine SVC after a 14-day treatment period, with average increments in supine SVC of +0.77% and 2.38% for 1 mg and 2 mg/d levosimendan, respectively, compared with an average 3.62% decrement in the placebo group ($P = 0.018$ and 0.001, respectively).

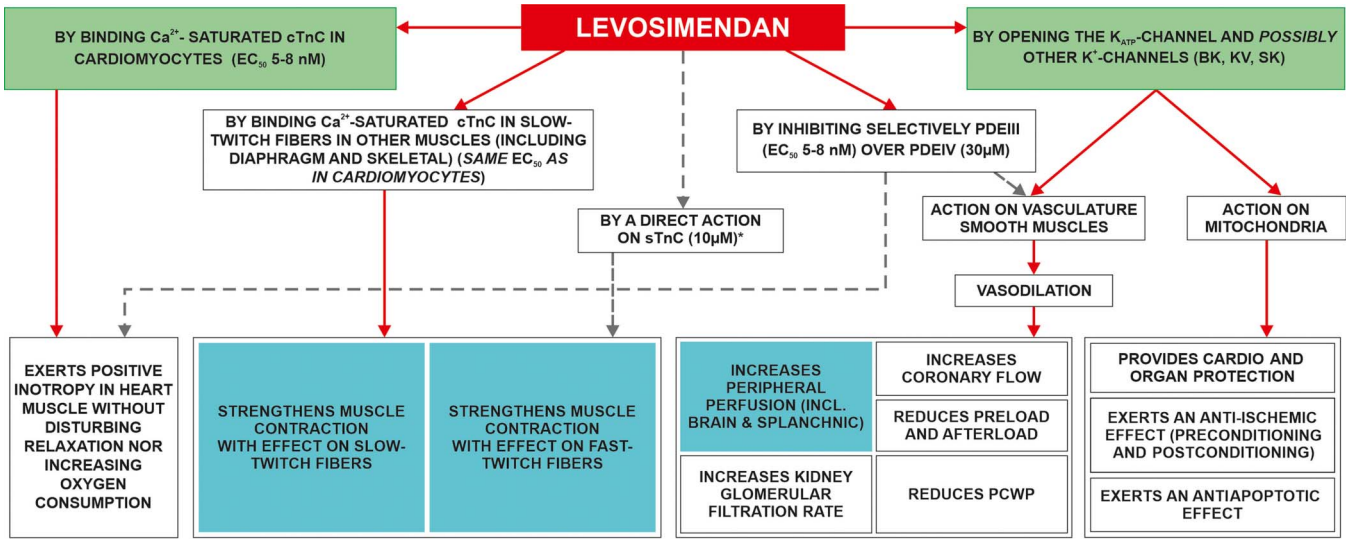

FIGURE 5. Scheme of the mode of actions and pharmacologic effects of levosimendan. The actions in the green boxes underlie the cardiovascular effects of the drug. In the blue boxes are pharmacologic effects of levosimendan that may be considered particularly beneficial in ALS. Grey dotted lines identify interplays that are still not fully elucidated. *An alternative explanation of these data is the putative presence of cTnC in fast-twitch fibers in the animal model used. cTnC and sTnC, cardiac and skeletal isoforms of troponin C, respectively; PDE III and IV, phosphodiesterase isoforms in cardiac tissue; PCWP, pulmonary capillary wedge pressure.

The observation of a treatment effect of levosimendan in the supine position is clinically relevant. Orthopnea, and the consequent interruption of sleep, is a common early indication of respiratory dysfunction in ALS, presumably because of splinting of the weakened diaphragm by abdominal organs, and changes in pulmonary function in the supine position may be a better predictor of progression of ALS than those detected while sitting.

Levosimendan seemed well tolerated by patients with ALS. Headache (levosimendan 2 mg, 28.8%; levosimendan 1 mg, 16.9%; placebo, 3.4%) and an increased heart rate (levosimendan 2 mg, 18.6%; levosimendan 1 mg, 5.1%; placebo, 1.7%) were more common with levosimendan than placebo and showed a dose-dependent increase in frequency, although the hypotension that has been associated with intravenous use of levosimendan was not reported during blinded treatment. The administration of the drug did not result in any increase of supraventricular and ventricular tachyarrhythmias.[139]

The LEVALS study provided, with qualifications, the first clinical evidence that levosimendan might preserve or slow the rate of decline of respiratory function in patients with ALS. A necessary next step is to demonstrate that the effect of levosimendan on SVC (which is essentially a laboratory test) is translated into clinically relevant benefits on patients' daily function. This information should come from the REFALS phase 3 trial [Effects of Oral levosimendan (ODM-109) on Respiratory Function in Patients With ALS; NCT03505021] that is ongoing in North America, Europe, and Australia.

REFALS will evaluate the effects of levosimendan (target dose 2 mg), compared with placebo, in 450 patients with ALS during 48 weeks of treatment. The primary endpoint will be supine SVC at 12 weeks, but key secondary endpoints include the ALSFRS-R through 48 weeks (determined as the Combined Assessment of Function and Survival) and the time to respiratory event (eg, the initiation of NIV treatment). In addition, reflecting the common challenge with orthopnea in these patients, the study is also applying scales of sleep quality and sleepiness as an alternative approach to understanding the potential clinical benefit of levosimendan to people with ALS.

Although much is already known about safety of both the IV and oral forms of levosimendan in heart failure, the REFALS study is also essential to characterize the safety and tolerability of levosimendan in this unique patient population. If effective, treatment with levosimendan may be relatively prolonged and in patients with typically rather less comorbidity than those with heart failure. The extensive safety assessments in REFALS are key to defining the benefit-to-risk profile of levosimendan in the treatment of ALS. A long-term open-extension study (NCT03948178) will provide further insights into the long-term safety and efficacy of oral levosimendan.

PERSPECTIVES ON LEVOSIMENDAN IN ALS

Although most researchers are understandably focused on strategies to slow or stop the progression of ALS, such options are not yet in sight for most patients. Treatments that can improve symptoms or maintain daily function for longer are clearly of great potential value for patients suffering from this devastating disease. The declining respiratory function alone is a major cause of disability, fatigue, morbidity, and mortality in ALS, quite apart from the loss of function in other skeletal muscles. The prospect of new treatments (Box 2) that might bring some symptomatic relief to patients living with ALS, even if the overall course of the disease is not altered, is thus very welcome.

BOX 2.

Prospect of New Treatments for Symptomatic Relief to Patients Living With ALS

Reldesemtiv (Cytokinetics, USA): phase II concluded.
Levosimendan (Orion Pharma, Finland): phase III running.

Whether drugs that directly enhance muscle function will have sufficient effect to bring significant benefit in ALS remains to be seen. Encouraging early hints were seen with tirasemtiv, only to be disappointed in the ensuing phase 3 trial. As regards reldesemtiv, a phase III has still to be initiated.

Although tirasemtiv and reldesemtiv are selective activators of fast skeletal muscle fibers, levosimendan primarily acts on slow fibers through cTnC. This distinction may be clinically important, not least considering that fast muscle fibers seem to be the first to die as muscle atrophies in ALS[140]; this hints at an additional potential effect later in the disease course and perhaps a different profile of clinical activity than a purely fast skeletal muscle activator. Of importance is the fact that because of its unique mechanism of action, levosimendan does not increase oxygen consumption.[55,141,142]

Although the direct activity of levosimendan on skeletal muscle is clearly the main effect of interest in relation to ALS, a number of the other activities of the drug raise some intriguing possibilities in the context of this disease (Fig. 5). There are not only well-documented beneficial effects of levosimendan on peripheral (and brain) circulation but also on autophagy, ER stress, apoptosis, inflammation, and mitochondrial function, all of which could also be of value in the progression of ALS if they also occur in neurons and/or muscle cells. Although the clinical value of drugs with these actions remains unproven in ALS, levosimendan may yet prove to be more than a skeletal muscle activator in ALS.

There remains much to learn before the effects of levosimendan in ALS are clear. Most of the data related to mode of action discussed in this article were generated in models quite distinct from those used in ALS, and it is a moot point whether such activities will also be evident and significant in more relevant models to ALS. The relative effects and contribution of levosimendan active metabolite when the drug is administered p.o. also need to be clarified further.

There is also much to learn about the safety profile of oral levosimendan in patients with ALS. The broad collection of safety data on the use of the drug during the last 2 decades (mostly during short-term use) has been largely reassuring, but that has been mainly in the context of patients with heart failure who were generally hospitalized. The emergence of new, unsuspected adverse reactions seems unlikely after all this time, but the significance of headache and an increased heart rate especially in people living with ALS is still to be understood.

Above all though, is the question of whether this collection of intriguing and promising actions will lead to measurable benefits for people with ALS: the improvement in supine SVC seen in a post hoc analysis in the LEVALS study is an encouraging first step. In addition to replicating that finding, we need to see that the effect is prolonged and leads to a meaningful improvement in patients' symptoms or an ability of people with ALS to function day-to-day: the results of the REFALS study will be eagerly awaited.

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