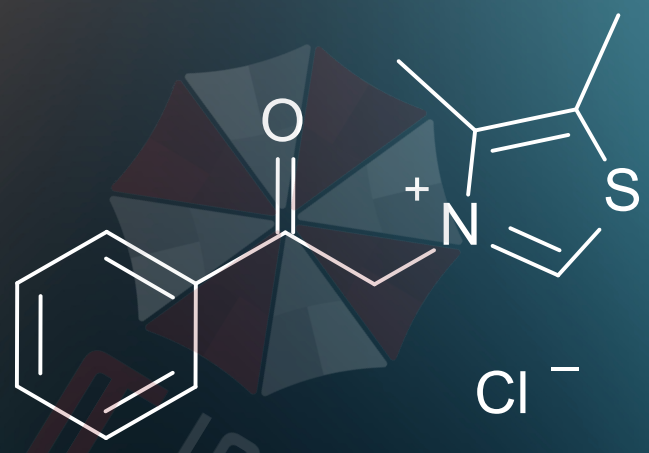

Alagebrium (ALT-711): Mechanisms, Clinical Insights, and Its Role in Reversing AGE-related Pathologies

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Alagebrium (also known as ALT-711) is a drug which was originally developed by Alteon. It was the first drug which was suggested to be used to reverse a process involved in aging, namely, to break crosslinks between advanced glycation end-products (AGEs). These products form in the body over time, as a result of the reaction between sugar, such as glucose and fructose, and other biomolecules. AGEs affect nearly every type of cell and molecule in the body and are thought to be a contributing factor in aging and some chronic diseases. These AGE`s are especially problematic with people suffering from diabetes mellitus, since these individuals have chronically elevated blood sugar levels. The rights to Alagebrium were later transformed to Synvista during clinical development. In 2009, the company announced that it was terminating clinical trials of alagebrium to focus on diagnostic tests and another clinical candidate SYI-2074 (formerly ALT-2074), which was also discontinued shortly after.

Mechanism of Action

The first step of the glycation reaction involves a sugar and side chains from amino acids in proteins. The thus formed intermediate product is then converted into so called “Amadori products” within days. The Amadori products then react to dicarbonyl compounds and finally to advanced glycation end products (AGEs) within weeks. While the part of the formation of Amadori products is recyclable, the later stages leading to AGEs are irreversible.

In a healthy state, AGEs are normally produced in a slow manner, but they are rapidly produced and accumulated in hyperglycemia, diabetes, atherosclerosis, hyperlipidemia, inflammation, renal failure, and neurodegenerative diseases such as Alzheimer’s disease. AGEs contribute to the aging process because most of their primary effects are seen on long-lasting proteins such as collagen and lens crystals in the eye.

The mechanism of action of alagebrium remains controversial. Alagebrium primarily results in the chemical cleavage of carbon-carbon bonds in the cross-linked structures, thereby removing newly formed AGEs.

Zinc, iron, and copper are required for normal function integrity but are abundantly present in diabetes and the related complications. Alagebrium is a potent inhibitor of copper-catalyzed ascorbic acid oxidation. Although alagebrium exerts an

antioxidant capacity in preclinical animal models and the in vitro hydrolyzed product shows a strong chelating activity, it is unclear whether it is a direct or indirect effect. Therefore, it is difficult to distinguish whether the effect of alagebrium is through metal chelation or AGEs destruction.

Also, it is unknown whether alagebrium has a direct link to receptors for AGEs (RAGE). The correlation of the reduction in RAGE protein expression with alagebrium was found in preclinical studies. In transgenic mice without RAGE, alagebrium treatment has still been shown to improve renal function and pathology and cardiovascular disease. Therefore, it is unknown whether the deterioration of AGE pathway is related to RAGE protein interaction, through direct feedback or the reduction of metal ions and oxidative stress.

Animal Trials

In a study by the Alton Ochsner Clinic on non-diabetic, spontaneous hypertensive rats, alagebrium treatment reversed aortic stiffness by regulating left ventricular elasticity. The oral administration of alagebrium improved diastolic heart parameters, decreased left ventricular stiffness, and improved cardiac function in aged dogs.[1] In another study on aged monkeys, the pulse wave velocity and augmentation index decreased significantly and aortic stiffness decreased continuously, which highlights alagebrium may have positive effects on the cardiovascular system in general.[2]

AGEs may also accumulate in the eye, more specially the retina , and lead to a progressive loss of eyesight. AGE-breakers, such as N-phenylacylthiazolium and alagebrium, have been proposed as therapeutic agents for reversing the increase in protein cross-linking. Epicatechin, a diet flavonoid, has also been discussed to serve a similar function in AGE breaking. In one study, the potential impact of epicatechin on reducing the burden of AGEs in vitro and in vivo was evaluated. It was observed that pre-formed AGEs which were incubated with epicatechin or alagebrium were broken down by epicatechin and alagebrium, but the effect strength of epicatechin was higher. It was also observed in this case that epicatechin was effective at lower concentrations than alagebrium.[3]

Diabetes

Cardiovascular complications associated with diabetes mellitus are one of the major causes morbidity and mortality worldwide. Diabetes affects 346 million people worldwide and the risk of cardiovascular diseases and cardiovascular deaths in diabetic individuals is 2-fold higher than in those without diabetes.

In a study, 4-week treatment of rats with methylglyoxal (a compound used to induce diabetes) significantly increased blood pressure, total cholesterol, and triglyceride levels and decreased HDL level. It has been observed that a novel alagebrium analog reduces MG-induced metabolic parameters significantly. Alagebrium itself had a protective effect against the harmful effects of high glucose and MG as well.[4,5] The administration of alagebrium for 4 weeks in a further study with diabetic rats improved their general response to high blood sugar levels.[6]

Additionally, in diabetic mice, a 20-week study was performed. They received either alagebrium or aminoguanidin, a compound that is supposed to reduce AGE formation, but not break them like alagebrium. Both compounds reduced the size of atherosclerotic plaques which formed in the diabetic mice by 30 and 40% respectively. Diabetes-associated accumulation of AGEs in aortas and plasma and decreases in skin collagen solubility were ameliorated by both treatments, in addition to reductions in the vascular receptor for AGE.[7] A similar study found that plaques of the wall of the aorta were not removed by a number of different anti-atherosclerotic drugs, including alagebrium, but alagebrium showed the highest potential in slowing down the progress to new plaque formation.[8]

As shown in some previous studies, a particularly interesting effect of alagebrium is its inhibiting effect on plaque formation in blood vessels. A large share of death`s in 1st world countries can be traced back to the formation of these plaques and blood vessel degeneration in general. AGE-induced collagen cross-linking (ARCC)

increases flow resistance in blood vessels and induces a thickening of the blood vessel wall. Abdominal aortic stents were implanted to lean, obese, and diabetic rats. Blood pressure, vessel diameter, and vessel wall stress were calculated after 21 days, and the amount of blood vessel wall thickening was measured. ARCC and RAGE expressions were determined in the arterial segments (the aorta, carotid, iliac, femoral, and arterioles). In the diabetic rats, the flow-direction resistance increased by 60%, but flow and wall shear stress decreased significantly (44% and 56%, respectively). In conclusion, alagebrium reduced ARCC and increased blood vessel function in diabetic rats.[9]

AGEs have recently shown to be associated with vascular calcification through a RAGE-mediated process. Despite the correlation between AGE levels and vascular calcification, there is no evidence that reducing in vivo AGEs or inhibiting the AGE- RAGE signaling pathway reduces this calcification. In a further study in rats, the effect of the inhibition of AGE formation by pyridoxamine and elimination of AGEs by alagebrium on diabetic blood vessel calcification was assessed. When the AGE- RAGE signaling pathway was inhibited by alagebrium, calcification was prevented.[10]

Heart Function

High blood glucose levels also affect proteins in heart muscle cells negatively. Hence, in diabetic patients a condition termed "diabetic heart disease" has been observed. is a clinical condition that can progress to heart failure and sudden death. However, the exact mechanisms responsible for the changes in excitation– contraction coupling leading to cardiac dysfunction during diabetes are unknown.

Thus, on study investigated whether an AGE cross-link breaker could prevent the changes certain cardiac proteins leading to in vivo cardiac dysfunction during diabetes. Diabetic rats were treated with alagebrium for 8 weeks and compared with age-matched placebo-treated diabetic rats and healthy rats. Diabetes resulted in in vivo cardiac dysfunction, and alagebrium treatment partially alleviated diastolic dysfunction. Collectively, that study showed that AGE accumulation in the type 1 diabetes model substantially impaired normal heart muscle cell metabolism and alagebrium was able to partially restore negative changes to the heart.[11]

Kidney Function

Similar to the heart, the kidneys are known to suffer from long-term elevated blood glucose levels, eventually leading to kidney failure in untreated diabetes. Diabetic rats were treated with alagebrium and divided into groups according to treatment periods of 16-32 weeks (early) and 24-32 weeks (late). Treatment with alagebrium significantly reduced diabetes-induced serum and AGE products. It also improved kidney filter function and reduced blood pressure and renal hypertrophy regardless of the treatment duration. However, it seems that the earlier treatment group had profited more from alagebrium treatment, as a number of metabolic parameters only improved only in this group.[12] A number similar studies in diabetic mice and rats also found positive effects on kidney function similar conclusions.[13]– [15]

Neurological Disorders

Diabetes also quite well known to damage small nerve fibers, beginning at the feet and slowly moving up the body towards the neck over years of time. Damage to the nerves also leads to blood vessel dysfunction in the affected areas.

A study in diabetic rats aimed at determining if there is a pressure-induced vasodilatation change in diabetic mice at 8 weeks. Control and diabetic mice were left untreated or treated with sorbinil (aldose reductase inhibitor) or alagebrium in the last 2 weeks. Blood vessel behavior was completely altered in diabetic animals. Alagebrium and sorbinil partially restored normal bloodvessel function.[16]

The death of neurons on the feet also leads to bad wound healing and hence chronic wounds. A mouse model of these diabetes induced wounds was administered alagebrium orally (10 mg/kg) per day for 14 days. This treatment accelerated the healing of diabetic wounds, improved sensory functions and gait, and ameliorated histological

changes in the treated mice.[17]

Testicular Function

A further study investigated the effects of alpha-lipoic acid (ALA) and alagebrium on testicular function in AGE animal models. AGE in the testes were found to lead to abnormal patterns in sperm parameters, testicular functional tests, as well as the expression of several important proteins. However, the administration of ALA or alagebrium helped mitigate these effects. While ALA demonstrated a slightly greater overall benefit compared to ALT, the difference was not statistically significant in either case.[18]

Human Clinical Trials

Several clinical studies sponsored by Synvista Therapeutics have been conducted between 2002 and 2010. In 2001, the data of 93 hypertensive patients randomized to receive placebo or alagebrium were recorded in a pilot study. After 2 weeks of treatment, the patients in the alagebrium group had decreased arterial pulse rate with increased bloodvessel compliance.[19]

A 2-year toxicity study of alagebrium on rats showed liver alterations. When the data were published in 2004 new patients in clinical trials until the preclinical work for alagebrium was completed, but trials were resumed later.

In a subsequent Phase I study, high-dose alagebrium was used to evaluate its effect on triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), and no harmful effects on function were detected. In the Phase I studies on healthy subjects, no side effects or deaths were observed after alagebrium treatment.

Between 2001 and 2003, Phase IIb clinical trials were conducted in many regions of North America. Individuals were divided into two cohorts based on left ventricular hypertrophy (LVH). Overall, in these studies, there was no significant change in systolic and pulse pressures when alagebrium therapy was compared with placebo. When individual basal measurements were compared with 3- and 6-month measurements, some changes were observed in the systolic blood pressure.[20]

In the DIAMOND Phase II study, the effect of alagebrium on many parameters, including exercise oxygen consumption (VO2), was measured. Compared with baseline, alagebrium reduced left ventricular mass and corrected diastolic function but did not alter blood pressure, VO2 , or aortic distensibility.[21]

The effect of 8-week alagebrium treatment on vascular inflammation, inflammation, and collagen turnover was assessed in a double-blind study on individuals with systolic hypertension. Alagebrium improved vascular function and inversely correlated with collagen turnover and serum markers of inflammation.[22]

In the BENEFICIAL study, diabetic and non-diabetic heart failure patients were treated with placebo or alagebrium to assess their aerobic capacity and diastolic/systolic function after 36 weeks. The primary (aerobic capacity) and secondary (diastolic/systolic function) results were unchanged. The analysis of diabetes subgroups also revealed no significant interaction.[23]

In 4 clinical studies (NCT00739687, NCT00557518, NCT00662116, NTC00089713), the effects of alagebrium on chronic heart disease and renal dysfunction in individuals with and without diabetes were evaluated by Synvista Therapeutics Inc. between 2004 and 2009. Unfortunately, these studies were terminated in the early period due to the bankruptcy of Synvista Therapeutics Inc. and global financial crisis. In 2013, a randomized, double-blind, placebo-controlled cardiovascular clinic trial aimed to evaluate the effect of multi-dose alagebrium with individual exercise on diastolic heart failure (NCT01913301). This study was also discontinued because of financial causes. In the last two randomized, double-blind, placebo-controlled studies, exercise was combined with 200 mg/day alagebrium for 1 year in the elderly population. Alagebrium was mostly well-tolerated except for the gastrointestinal symptoms observed in two individuals.[24] In this study, alagebrium showed a small but beneficial effect on heart function. Other studies were terminated early due to the financial in sufficiency. To date,

clinical trials with alagebrium have not been continued.

Conclusion

Alagebrium is the first compound in a new class of drugs, which is designed to break apart advanced glycation end products (AGEs). These AGEs occur everywhere in the body and are associated with aging. They occur especially often in those individuals suffering from high blood-glucose levels, particularly in those diagnosed with diabetes. Breaking apart AGEs in the body is theorized to reverse some processes which are impaired by AGE formation, such as reduced organ function and increased blood vessel stiffness.

In animal models alagebrium has shown positive effects quite often. In particular, diabetic mice and rats have shown improvements in a variety of health parameters, which seems to indicate alagebrium is indeed effective in treating the various negative processes associated with diabetes.

In humans, alagebrium has proven effective in reducing systolic blood pressure and providing therapeutic benefit for patients with heart failure. Unfortunately, most studies which were completed are Phase I and II studies, which do not provide a good assessment of effect strength. Phase III clinical trials were started, but aborted due to the bankruptcy of Synvista. Hence, the therapeutic potential of alagebrium in humans remains mostly unexplored. It is reasonable to assume that alagebrium is effective in slowing down progress in many diabetes associated diseases (e.g. renal, neural, cardiac), as shown in various animal models of such conditions.

Typical human doses in human studies range around 100-300 mg/day. Alagebrium is reported to be mostly well tolerated with only minor gastro-intestinal side effects.

Recently, a study was published looking for more active but related compounds of alagebrium. One of the molecules found exhibited “high effectiveness against all three examined mechanisms of glycation reaction inhibition in in vitro tests and was able to suppress capacity of methylglyoxal to form AGEs in vivo.” This molecule may be a candidate to improve upon alagebriums positive metabolic properties.

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