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AN OVERVIEW ON “SYMPTOMS AND SOME NOVEL DRUG TREATMENT FOR ALPORT SYNDROME”

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ABSTRACT

The cause of this Alport syndrome is inherited defect in type IV collagens. Type IV collagen is located or found in the ears, eyes, and kidneys. Alport syndrome affects ears, eyes, kidneys, etc. These descriptions refer to 'classic' Alport syndrome. It found in young adult or late childhood life. Alport syndrome is more severe in men than in women. Alport syndrome is an example of inherited disease that affects the glomeruli. These glomeruli were found in the tiny blood vessels within the kidney. It affects around 1 in 50,000 children. It was characterized by end-stage kidney disease, and hearing loss. This syndrome can also affect the eyes. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) should be administered to patients with Alport syndrome. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) classes of drugs apparently help to reduce Proteinuria by decreasing intraglomerular pressure.

KEYWORDS

Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin-receptor blockers (ARBs), Type IV collagen and Nephritis.

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INTRODUCTON

Alport syndrome was characterized by a genetic disorder. It affects around 1 in 50,000 children. It was characterized by end-stage kidney disease, and hearing loss. This syndrome can also affect the eyes, but do not usually affect sight except when changes to the lens occur in later life. This disorder was first identified in a British family by the scientist Cecil A. Alport in 1927. Alport Syndrome also had the label hereditary nephritis¹. Alport syndrome is caused by an inherited defect in type IV collagens. Type IV collagen is found in the ears,

eyes, and kidneys. Alport syndrome affects ears, eyes, kidneys, etc. These descriptions refer to 'classic' Alport syndrome. It found in young adult or late childhood life. Alport syndrome is more severe in men than in women. Alport syndrome is an example of inherited disease that affects the glomeruli. These glomeruli were found in the tiny blood vessels within the kidney. The gene for this syndrome is located or found in the X chromosome². This X chromosome determines individual sex. The disease is less severe in women because they have two X chromosomes. A normal gene on one of the X chromosomes limits the effects of the Alport gene.

Sign and Symptoms⁴⁻⁵

The main symptoms of this syndrome are the presence of blood in the urine. Boys with Alport Syndrome develop this symptom in infancy. Another important symptom of Alport Syndrome is hearing loss. In boys with the disease hearing loss is usually detectable by 8-10 years of age. Hearing loss in girls tends to be much milder than men. Alport Syndrome loses large amounts of protein in the urine that may result in retention of fluid and body swelling. This condition is called "the nephrotic syndrome". The boys with Alport Syndrome develop the typical signs and symptoms of kidney failure with high blood pressure, swelling. However, in some patients, hearing loss is only noted after kidney function has been lost. It reduced ability to hear high-frequency sounds i.e. 'high-tone hearing loss'.

Diagnosis⁶⁻⁸

The diagnosis can usually be made on a combination of clinical, family history and biopsy of the skin and kidney. Skin biopsies have been used to show absence of the *COL4A5* gene product, but these techniques are not straight forward, only apply to patients with severe *COL4A5* mutations. Electron microscopy also gives an idea of thinning of the glomerular basement membrane (GBM). The use of eye examinations and ear examination for screening has been proposed.

Medication⁹⁻¹³

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) should be

administered to patients with Alport syndrome. Both classes of drugs apparently help to reduce Proteinuria by decreasing intraglomerular pressure. The long-term uses of Losartan (an ARB) with that of Enalapril (an ACE inhibitor) are used for the treatment of Proteinuria in children with Alport syndrome. Some of the ACE inhibitors are given below;

ACE inhibitors

ACE inhibitors are used to inhibit angiotensin converting enzyme i.e. ACE. This enzyme is essential and necessary for conversion of angiotensin I into angiotensin II. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) should be administered to patients with Alport syndrome. They are as follows,

1. Captopril
2. Enalapril
3. Fosinopril
4. Lisinopril
5. Perindopril
6. Quinapril
7. Ramipril
8. Trandolapril
9. Benazepril

Captopril

This drug is an example of angiotensin-converting enzyme inhibitors. It is used in the treatment of hypertension and congestive heart failure. This drug was discovered and developed by Squibb and Son Pharmaceuticals Company. This drug is marketed by Bristol-Myers Squibb Company and sold under the trade name Capoten. This drug is used in the treatment of Alport syndrome.

Uses

- This drug is used in the treatment of hypertension and in congestive heart failure.
- It also used to treat myocardial infarction and preservation of kidney function.
- Currently, it is used in the treatment of cancer.

History

This drug was discovered in 1975 by the three scientists i.e. Miguel Ondetti, Bernard Rubin, and David Cushman at the United State. This drug was

approved by the United State of Food and Drug Administration on 6th April, 1981.

Enalapril

Enalapril is available in the form of Vasotec in the United State, Enaladex in other Countries. This drug is also used as veterinary drug. This drug is an example of angiotensin-converting enzyme inhibitors. This drug is used in the treatment of hypertension and in diabetic neuropathy. This drug is also used in the treatment of chronic heart failure. Angiotensin-converting enzyme is essential for converting peptide hormone angiotensin I to angiotensin II. Actions of angiotensin II is the vasoconstriction of blood vessels, and it also increase blood pressure. ACE inhibitors prevent these types of effect. This drug is used in the treatment of Alport syndrome.

History

This drug was discovered by Merck Company. This drug is available in the market in 1981.

Uses

- This drug is used in the treatment of hypertension, symptomatic heart failure.
- It is also used in the treatment of asymptomatic left ventricular dysfunction.
- This drug protects the function of kidney during hypertension.
- This drug is also used in the treatment of chronic kidney failure.

Mechanism of action

It inhibits the conversion of angiotensin I to angiotensin II by inhibiting the angiotensin-converting enzyme. Angiotensin II constricts the blood vessels and it increases the blood pressure. This drug inhibits or decreases the level of angiotensin II. This drug gives vasoconstriction and decreases the blood pressure.

Fosinopril

This drug is an example of angiotensin-converting enzyme inhibitors. This drug is used in the treatment of hypertension and chronic heart failure. This drug was developed or discovered by Bristol-Myers Squibb Company and sold in the form of trade name like Monopril. This drug is used in the treatment of Alport syndrome.

Lisinopril

Lisinopril is an example of angiotensin converting enzyme i.e. ACE inhibitors. This drug is used in the treatment of high blood pressure and heart failure. This drug is also used after heart attacks. This drug is a third example of angiotensin converting enzyme i.e. ACE inhibitors i.e. after Captopril and Enalapril. This drug was discovered or developed in early 1990s. It is hydrophilic drug. This drug is available in the form of brand names like Prinivil, Zestril and Tensopril. This drug was developed by Merck Company. The brand name Zestril was manufactured by Astra Zeneca in India. This drug is also marketed by Micro Labs as Hipril. This drug is used in the treatment of Alport syndrome.

Uses

- This drug is used in the treatment of hypertension and in congestive heart failure.
- It is also used in the treatment of myocardial infarction and diabetic neuropathy.

Side effect

The common side effect of this drug is headache, dizziness, and cough, difficulty in breathing and in swallowing, allergic reaction, hyperkalaemia, fatigue, and diarrhea. Other side effect of this drug is hypotension, chest pain, and Stevens-Johnson syndrome.

Mechanism of action

This drug blocks or inhibits the action of angiotensin converting enzyme i.e. ACE in the rennin-angiotensin-Aldosterone system i.e. RAAS. It inhibits the conversion of angiotensin I to angiotensin II by inhibiting the angiotensin-converting enzyme. Angiotensin II constricts the blood vessels and it increases the blood pressure. This drug inhibits or decreases the level of angiotensin II. This drug gives vasoconstriction and decreases the blood pressure.

Perindopril

Perindopril is an example of long acting ACE inhibitors. This drug is used in the treatment of high blood pressure, heart failure. This drug is also used in the treatment of coronary artery diseases. This drug is available in the form of trade name like Coversyl, Coversum and Aceon. The dose of this drug is 5 mg once daily. This drug is

contraindicated for children, pregnant women, during lactation, patient having renal failure problem. This drug is available in the form of tablet with dose of 2, 4, 8 mg. this drug is available in the form of brand names like Aceon, Acertil, Actiprex, Armix, Coverene, Coverex, Coversum, Prenessa, Prestarium, Prexanil, Prexum, Procaptan, Provinace and Covinace. This drug is used in the treatment of Alport syndrome.

Uses

- This drug is used in the treatment of essential hypertension and stable coronary artery disease.
- This drug is also used in the treatment of symptomatic heart disease or heart failure.
- This drug is used in the treatment of myocardial infarction.
- It reduces the risk of stroke in both hypertensive patient and non hypertensive patient.

Side effect

The most common side effect of this drug is cough, fatigue, headache, mood disturbances. The less common side effect of this drug is change in taste, nausea, skin rash, abdominal pain, and abdominal discomfort.

Quinapril

Quinapril is available in the form of brand name like Accupril. The brand name Accupril was marketed by Pfizer Pharmaceutical Company. This drug is an example of angiotensin-converting enzyme inhibitor i.e. ACE inhibitor. This drug is used in the treatment of hypertension and congestive heart failure. This drug is converted into quinaprilat in the liver after metabolism. This drug is used in the treatment of Alport syndrome.

Mechanism of action

This drug inhibits the angiotensin converting enzyme. This enzyme is essential for conversion of angiotensin I to angiotensin II. Angiotensin II acts as powerful vasoconstrictor and it increases the blood pressure. This drug inhibits the angiotensin converting enzyme and due to reduction of angiotensin production, plasma concentration of Aldosterone is also reduced. It increases the

excretion of sodium ion in the urine and increases the potassium in the blood.

Side effect

The common side effect of this drug is cough, vomiting, abdominal pain, dizziness and fatigue.

Ramipril

Ramipril is an example of angiotensin converting enzyme inhibitors i.e. ACE inhibitors. It is used in the treatment of high blood pressure i.e. hypertension and congestive heart failure. This drug inhibits the angiotensin converting enzyme and it gives relaxation to the muscles around the arteries or arterioles. After relaxation, arterioles expand and allow blood to flow through more easily. It reduces the blood pressure. This drug is available in the form of brand names like Prilace, Ramipro, Tritace and Altace. The brand name Prilace is marketed by Arrow Pharmaceuticals Company in Australia; Ramipro is marketed by Westfield Pharmaceuticals Company in Philippines; Tritace is marketed by Sanofi Aventis Pharmaceuticals Company and Altace is marketed by King Pharmaceuticals Company in United States. This drug is also available in India and sold under the brand names like Cardace, Zigpril, Ramistar and Zorem. This drug is used in the treatment of Alport syndrome.

Uses

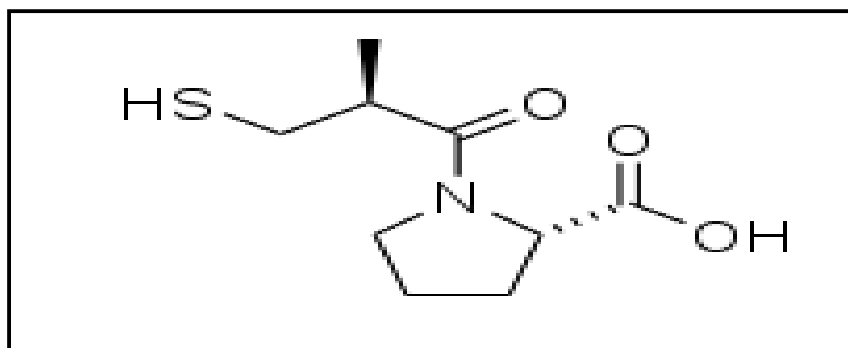
- This drug is used in the treatment of high blood pressure and in congestive heart failure.
- This drug is used in the treatment and prevention of heart attacks, stroke and cardiovascular death.

Trandolapril

Trandolapril is an example of ACE inhibitors. This drug is used in the treatment of high blood pressure. This drug is marketed by Abbott Laboratories and sold under the brand name Mavik. This drug acts as Pro-drug and half-life of this drug is 6 hours. This drug is converted into trandolaprilat. The half-life of this trandolaprilat metabolite is 10 hours. This trandolaprilat metabolite is more potent and 8 times more active than Trandolapril drug. About 25 % drug is excreted into the urine. About 80% of this drug is bound to serum protein. This drug is used in the treatment of Alport syndrome.

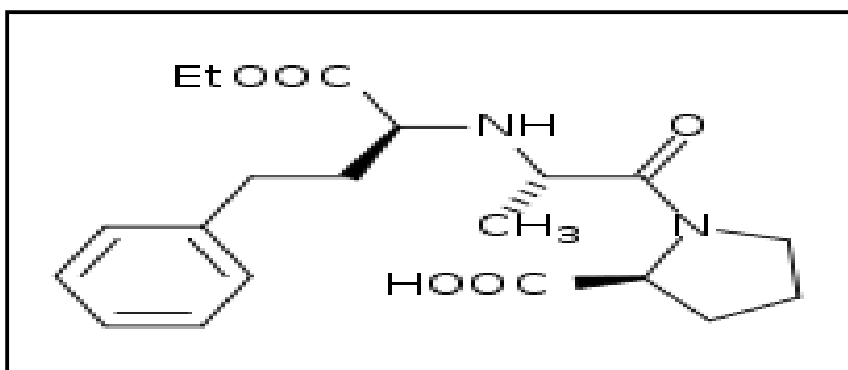
Benazepril

This drug is available in the form of brand name like Lotensin. This drug is an example of ACE inhibitors. This drug is used in the treatment of hypertension, congestive heart failure and preventions of heart attacks. This drug acts as pro-drug and it converted into active metabolite i.e. benazeprilat in the liver. This drug is commonly used in the form of combination with hydrochlorothiazide and sold under the trade name like Lotensin and Lotrel. This drug is also used as veterinary drug and used in the treatment of congestive heart failure in dogs and chronic renal failure in dogs and cats. This drug is used in the treatment of Alport syndrome.



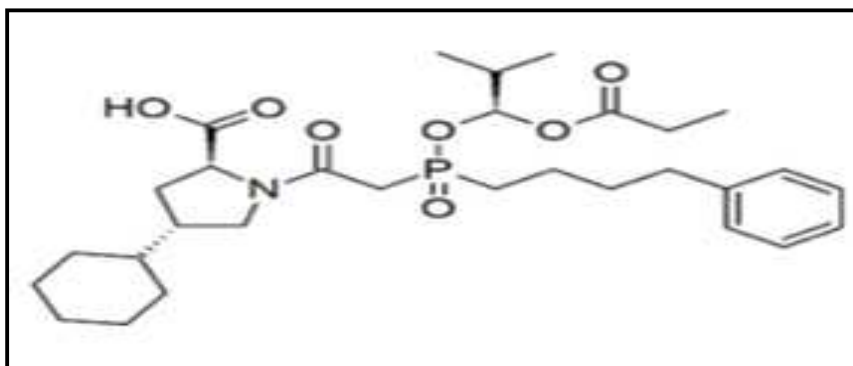
Systematic (IUPAC) name

(2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl] pyrrolidine-2-carboxylic acid



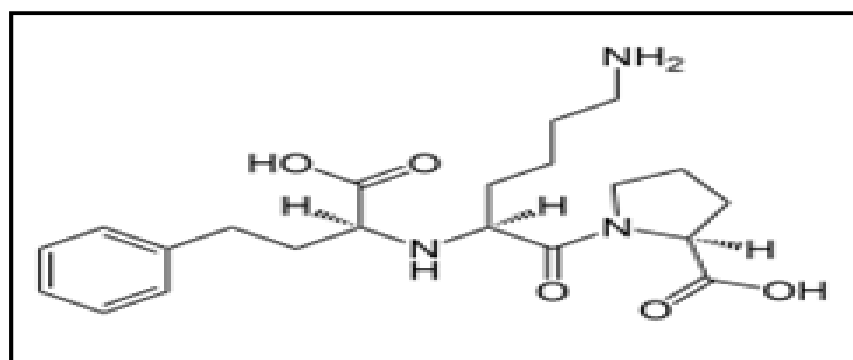
Systematic (IUPAC) name

(2S)-1-[(2S)-2-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]pyrrolidine-2-carboxylic acid



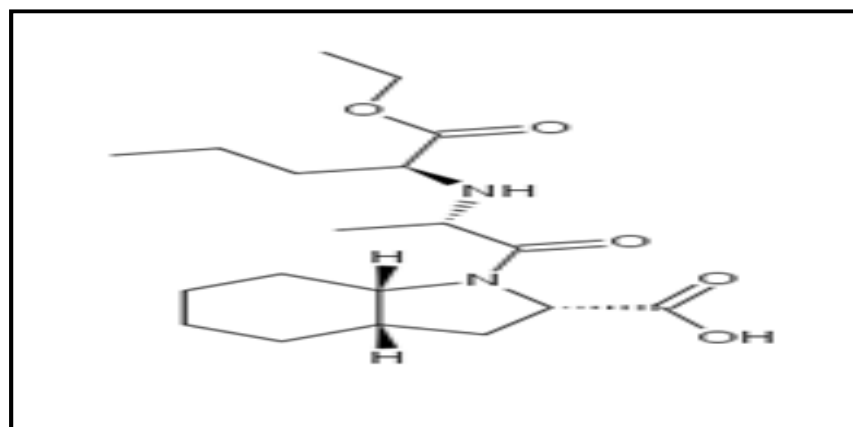
Systematic (IUPAC) name

(2*S*, 4*S*)-4-cyclohexyl-1-(2-([2-methyl-1-(propanoyloxy)propoxy](4-phenylbutyl) phosphoryl)acetyl) pyrrolidine-2-carboxylic acid



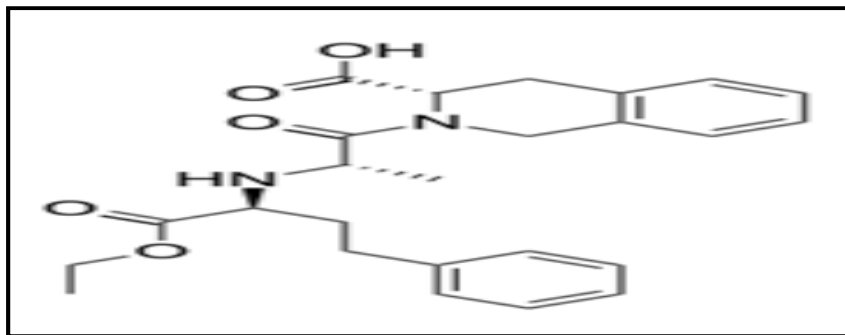
Systematic (IUPAC) name

*N*2-[(1*S*)-1-carboxy-3-phenylpropyl]-L-lysyl-L-proline



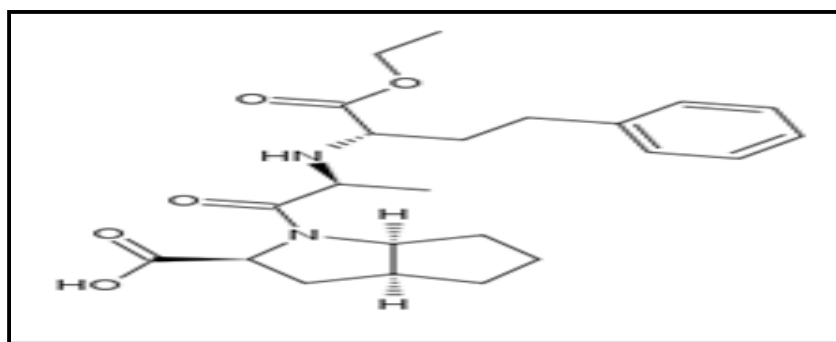
Systematic (IUPAC) name

(2*S*, 3*aS*, 7*aS*)-1-[(2*S*)-2-([(2*S*)-1-ethoxy-1-oxopentan-2-yl]amino)propanoyl]-octahydro-1*H*-indole-2-carboxylic acid



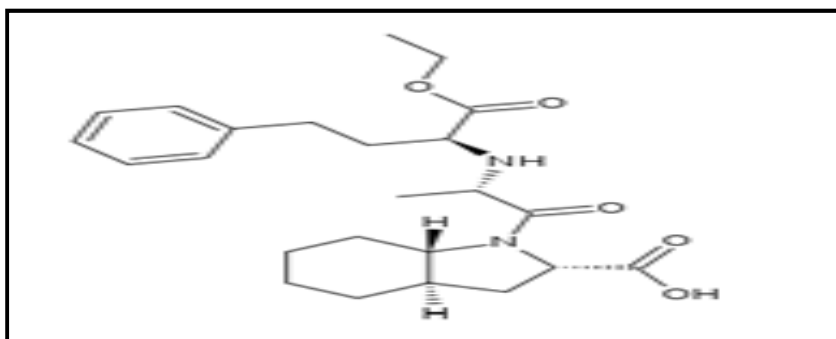
Systematic (IUPAC) name

(3*S*)-2-[(2*S*)-2-[[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-1, 2, 3, 4-tetrahydroisoquinoline-3-carboxylic acid



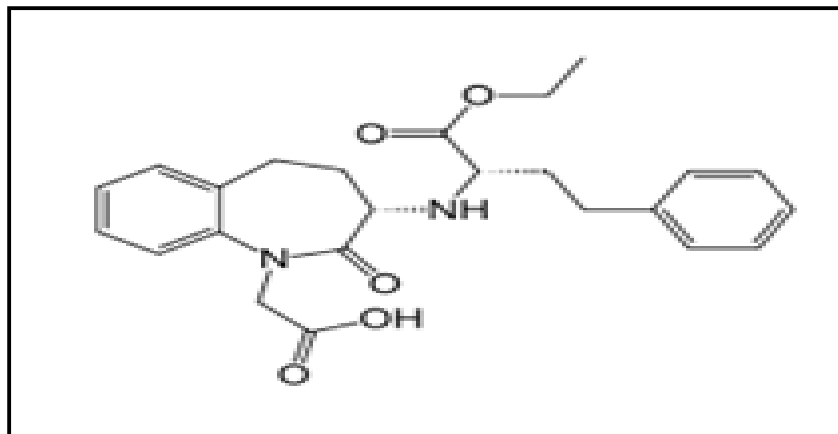
Systematic (IUPAC) name

(2*S*, 3*aS*, 6*aS*)-1-[(2*S*)-2-[[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-octahydrocyclopenta [*b*] pyrrole-2-carboxylic acid



Systematic (IUPAC) name

(2*S*, 3*aR*, 7*aS*)-1-[(2*S*)-2-[[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-octahydro-1*H*-indole-2-carboxylic acid



Systematic (IUPAC) name

2-[(3S)-3-[[[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]-propanoyl]-octahydro-1H-indole-2-carboxylic acid

CONCLUSION

The cause of this Alport syndrome is inherited defect in type IV collagens. Type IV collagen is located or found in the ears, eyes, and kidneys. Alport syndrome affects ears, eyes, kidneys, etc. These descriptions refer to 'classic' Alport syndrome. It found in young adult or late childhood life. Alport syndrome is more severe in men than in women. The gene for this syndrome is located or found in the X chromosome. This X chromosome determines individual sex. The disease is less severe in women because they have two X chromosomes.. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) are used to treat Alport syndrome.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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