Using genetics to guide treatment of arterial hypertension with Rostafuroxin

Primary hypertension is a major health concern and can cause serious cardiac, renal and brain complications responsible for about 10% of worldwide health burden and costs. The development of hypertension is triggered by genetic factors that, in turn, are modulated by biological and environmental factors. Many drugs are available for the treatment of hypertension, but none target the underlying genetic mechanisms. During the past 40 years, the drugs used for hypertension (high blood pressure) have shown their limitations, partly due to their inability to target the causal genetic mechanisms of the condition. The majority of patients (50–85% globally) still do not reach the therapeutic target of blood pressure control. In 20–25% of patients, this control is still not achieved when a combination of multiple drugs is used. These patients are therefore considered carriers of ‘resistant hypertension’.

In the US, the control of blood pressure decreased by 20% in all hypertensive individuals within four years (from 2015 to 2018). This decrease is slightly greater in White patients compared to African American patients. Alongside this, many drugs may fail to fully protect other organs from the damage that hypertension can cause. Dr Giuseppe Bianchi, Professor Emeritus at the Vita-Salute San Raffaele University, Milan, and CEO at Windtree Therapeutics, aims to explore the relationship between an individual’s genetic code and how they respond to rostafuroxin that ‘selectively’ targets them.

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ver the past 40 years, the drugs used for hypertension (high blood pressure) have shown their limitations, partly due to their inability to target the causal genetic mechanisms of the condition. The majority of patients (50–85% globally) still do not reach the therapeutic target of blood pressure control. In 20–25% of patients, this control is still not achieved when a combination of multiple drugs is used. These patients are therefore considered carriers of ‘resistant hypertension’.

In the US, the control of blood pressure decreased by 20% in all hypertensive individuals within four years (from 2015 to 2018). This decrease is slightly greater in White patients compared to African American patients. Alongside this, many drugs may fail to fully protect other organs from the damage that hypertension can cause. Dr Giuseppe Bianchi, Professor Emeritus at the Vita-Salute San Raffaele University, Milan, and CEO at Windtree Therapeutics, has conducted a study on rats infused with ouabain, and his findings cast doubts on the ability of current drugs to fully protect from cardiac and renal complications, even when they are able to normalise blood pressure. Ouabain is a steroid hormone which is able to improve the contraction of the heart muscle and increase blood pressure, making it a promising target for treating hypertension.

**PRECISION MEDICINE**

Drugs interact with other body molecules to exert their wanted or unwanted effects. These molecules are encoded by someone’s genetic makeup and may vary from person to person (gene variants). Some of these gene variants may trigger other body molecules. The molecular abnormalities can be caused by different gene variants in different people, hence the need for a personalised approach.

**THE ADVANTAGES OF ROSTAFUROXIN**

Dr Bianchi explains that one particular medication, rostafuroxin, may be important in taking the first steps towards precision medicine for hypertension. Unlike current drugs used to treat hypertension, rostafuroxin is able to address the genetic causal mechanisms underlying the condition in a subset of patients, and this has been demonstrated in animal and human trials. Genetic testing must be used to identify the patients who are most likely to respond to treatment. The drug works by selectively inhibiting a common step of the pathways leading to hypertension and organ damages, triggered by endogenous ouabain (EO) and mutant adducin. It disrupts the binding to the cSrc-SH2 domain of mutant Gα12/13 and of the ouabain-activated Na-K pump at 10-11 M, being ineffective on wild adducin or non-activated Na-K pump or on the other 34 receptors or proteins involved in cardiovascular regulation up to 105. In other words, it inhibits the effects of EO, a type of hormone produced by the body which is seen at higher levels in the blood of some people with hypertension. Levels of EO in the body tissues are controlled by certain variants of the genes (L55, HSD3B1 and MDR1) which affect both its synthesis and transport. Moreover, rostafuroxin inhibits the effects of mutations in the adducin gene, which are associated with body sodium and blood pressure changes both in rats and in patients.

There have already been many studies exploring the potential benefits of rostafuroxin in treating hypertensive patients. These include Phase I drug trials, which look at the safety and tolerability of medication, and Phase II trials, which are larger studies that investigate how well the treatment works and the risk of side effects. So far, six clinical studies have been conducted on animals and humans, together with an associated medicinal chemistry programme.

When EO is given to rats, they develop high blood pressure and cardiac and renal damage. All these conditions are prevented by administration of rostafuroxin, while amiodipine (a first-line drug treatment for hypertension) only normalises blood pressure.

Rostafuroxin has been developed with a series of studies across different settings in presence or absence of the above gene variants: animal models, isolated cells, and protein–protein interactions in animals and humans, together with an associated medicinal chemistry programme.

**Hypertension and its associated complications have significant health and economic costs.**

- Tubular reabsorption
- Cell volume
- ROS
- Sympathetic drive
- Cardiomyopathic cell (including cell proliferation, cardiomyocyte remodeling, cardiac and renal damages, mortality and metastasis)

Rostafuroxin antagonizes the mutant adducin and ouabain-activated Na-K pump. Src-mediated effects normalise blood pressure and prevent organ complications.
have been done, involving 84 healthy volunteers and 802 hypertensive patients.

**CLINICAL TRIALS**

Once Phase I trial was the OASS-HT trial. This was a double-blind, crossover study, meaning that patients are given either the test drug or the control drug for the first part of the study, before being swapped to the other group for the remainder of the study. Over 400 Caucasian people with hypertension were involved in the trial, and the results showed that rostafuroxin did reduce blood pressure only in a subset of patients carrying the above genetic variants either alone or group in what the researchers established as genetic profile 2. Profile 2 consists of variants of adducin (ADD3 rs3731566), 3β-hydroxysteroid dehydrogenase (HSD3B1) rs10923835, isomerase type 1 (HSDB1) n1092385, and ATP-binding cassettes subfamily B member 1 (ABCB1/MDR1) rs1045642, and in genes that regulate EO synthesis and in genes that regulate adducin gene and in genes that regulate EO synthesis and transport. The drug is able to

**Unlike current drugs used to treat hypertension, rostafuroxin is able to address the causal mechanisms underlying the condition in a subset of patients.**

that may offer a more effective and resource-efficient approach. Dr Bianchi emphasises that rostafuroxin is a more efficient treatment option on blood pressure and organ damage for about 25% of the hypertensive population who have mutations in the adducin gene and in genes that regulate EO synthesis and transport. The drug is able to

Many patients currently receive a combination of different drugs to achieve the desired response. Rostafuroxin has the potential to be a single-drug replacement for these combination therapies in people with specific gene variants, particularly for those with resistant hypertension, meaning better outcomes for patients and more cost-effective use of medications.

Extensive cardiac and renal damage protection in antihypertensive rats.

Rostafuroxin was found to reduce proteinuria in ouabain-treated rats. This effect was much less in Chinese participants before the drug has been evaluated in future studies.

**References**


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**Personal Response**

What will Phase III trials for rostafuroxin look like?

Phase III trials should look for the therapeutic benefit of rostafuroxin in two types of patients: those carrying the genetic profile 2 in comparison to (be discussed) with placebo (trial 1) and a standard treatment losartan or amlopidine (trial 2): type 1 – patients with so-called resistant hypertension; that is, blood pressure above the normal range after one month of treatment with these different types of drugs; and type 2 – newly discovered patients who do not respond to the first two separate treatments. Markers of cardiac and renal damage should also be measured. Composite primary endpoints include: number of patients with reported adverse events (AIE), therapy discontinuation, changes in their quality of life, in office (or home) systolic blood pressure, the number of drugs and, when possible, markers of kidney or heart damage.