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Research Article

Clinical Results of a New Formulation of Resveratrol (Residyn) in Glaucoma Patients

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Abstract

The medical treatment is mostly based on topical beta-blockers or selective prostaglandin agonist. When the patient suffers from allergic reaction or insufficient effect of the topical drops, we might consider using laser trabeculoplasty. When laser doesn't work, we get into the surgical options like MIGS (microinvasive glaucoma surgery) or trabeculectomy. Recent works have shown that nutritional preventive strategy could also be considered. In the early stage of the disease neuro-inflammation plays an important role with astrocytes, microglia and monocytic cells as critical players in the trabecular meshwork (TM) endothelial cells.

Keywords: chronic surgery; cancer; blood pressure; heart disease

1.Introduction

Visual impairment is a global major health issue. More than 285 million people worldwide suffer from visual loss, of whom 39 million are blind [5]. Polyphenols (RSV) may protect against numerous diseases like cancer, inflammatory disease and vascular disease. Due to its anti-inflammatory, anti-angiogenic and antioxidant power RSV can help fight the molecular events of ocular pathologies. In this review we will concentrate on the work mechanism of RSV on glaucoma.

2. What is the origin of Resveratrol?

RSV was first isolated in 1940 from the root of the flower Veratrum grandiflorum. The root powder has long been used in Japan, Asia and Northern Europe to treat rheumatism, hypertension and nervous disease. One of the richest sources of RSV is Japanese knotweed (barnbuo japonaise) Polygonum cuspidatum, root extract. The importance of RSV in plant biology lies in its ability to inhibit growth of fungal infection. This is why we may consider it as an antibiotic plant: phytoalexins. RSV is found in grapes and acts as a natural antifungal agent [6]. There are two forms: trans-RSV which blocks the development of the fungus Botrytis Cinerea and cis-RSV obtained by the action of light on trans-RSV. The grape skin contains about 50-100 microgram of RSV per gram so it is found in 20 mg/L of red wine. This brings us to the French paradox where French people, red wine drinkers, suffer less from coronary disease than other European inhabitants. The attention on the healing properties of RSV only grew after Pezzuto's team in 1997 published his paper on the ability of RSV to inhibit carcinogenesis at multiple stages [7]. The main properties of RSV were found to relate to its antioxidant power and its anti- inflammatory properties.

It modulates in various diseases like:

1. Coronary heart disease, via a reduction in platelet aggregation, a decrease in pro- inflammatory molecules and preventing the oxidation of low-density lipoproteins (LDL) [8,9].
2. Cancers, RSV is inhibiting in vivo models the initiation and progression of skin tumors. It acts through cell cycle arrest, induction of apoptosis and the inhibition of Angiogenesis [10,11].
3. Inflammatory diseases, RSV decreases the production of various cytokines in response to a large variety of exogenous stimuli [3].

4. Age-related degenerative diseases, through its capacity to activate Sirtuin-1, which exhibits down-regulated expression in multiple organs during aging [12].

Through all these mechanisms, RSV also works against ocular diseases like AMD, glaucoma, retinal degeneration, cataract, optic neuritis and retinoblastoma [13].

3. The action of RSV in glaucoma.

What is glaucoma?

It is a progressive optic neuropathy with the first lesions found in the retinal ganglion cell (RGC) layer causing visual field defects and subsequent possible blindness. More than 80 million people are affected by this neuro-degenerative disease expecting to attain 112 million patients by 2040 [14,15]. It is the second leading cause of blindness in the world after cataract. Which are the actors in glaucoma? Ocular hypertonia (OH) is the first known risk factor that contributes to the pathology. This is an accessible target for medical or surgical treatment. The pathological rise in intra-ocular pressure (IOP) is due to degeneration of the trabecular network or the excess in production of aqueous humor (AH). AH is eliminated for 90% by the trabecular network and for 10% by the uveoscleral route. Therapy of rise in IOP consists on medical, surgical or laser intervention. The medical treatment is mostly based on topical beta-blockers or selective prostaglandin agonist. When the patient suffers from allergic reaction or insufficient effect of the topical drops, we might consider using laser trabeculoplasty. When laser doesn't work, we get into the surgical options like MIGS (microinvasive glaucoma surgery) or trabeculectomy. Recent works have shown that nutritional preventive strategy could also be considered. In the early stage of the disease neuro-inflammation plays an important role with astrocytes, microglia and monocytic cells as critical players in the trabecular meshwork (TM) endothelial cells. When we induce inflammatory markers in TM cells and subject them to oxidative stress the mitochondriae produce intracellular reactive oxygen species (iROS). RSV can be used to reduce the iROS production (Luna et al.) (16). Razzali et al. showed that repeated topical application of RSV for 21 days in steroid-induced ocular hypertensive rats significantly reduced IOP and TM thickness. And RSV increased the thickness of the RGC, the linear cell density in this layer and the inner retinal thickness [17]. Several studies have shown that oxidative stress, ROS, play an important role in the damage to the RG layer. RSV has antioxidant properties through the hydroxyl groups. By several pathways RSV is downregulating ROS and gives higher hydroxyl levels leading to less apoptosis [18,19]. RSV is also able to increase the number of mitochondriae present in one cell, restoring protein levels that are decreased in glaucoma [20]. Zhang et al. have shown that RSV also modifies the quality of mitochondriae by decreasing the membrane potential depolarization induced by pressure [21]. RSV also decreases apoptosis in the RGCs. Furthermore pyroptosis, a pro-inflammatory cell programmed necrosis, plays a crucial role in RGC layer death, by acute IOP rise. RSV intervenes and reduces the cell death [22].

4. Which formulation of RSV to use?

We know that RSV dissolves badly in water and that it is a large molecule. This is why we decided in Eytelia to link RSV to a Silica carrier to enhance its bioavailabilty. We knew from former studies performed in a rabbit model that RSV lipid-based encapsulation formulation when given on a topical instillation base was shown to give a significant reduction of IOP by 4.3 +/- 0.5 mm Hg. for up to 8 hours [23,24]. The main reason for creating Residyn is to achieve better distribution of RSV in the circulation but also to lower possible toxic side effects of the molecule. We know that at a day dose of 2-gram patients can experience gastrointestinal symptoms [25]. In our study the drop out range was 27.5%. Longevity has become a major subject from the moment biogerontology emerged in the 1990s. Ageing is now considered to be a treatable disease. Several methods are studied to extend human lifespan going from dietary restriction (DR), DNA altering or the administration of food supplements. The antioxidant Resveratrol (RSV) is one of those supplements. It is a polyphenol that has a positive effect in cardiology [1,2], lowering platelet aggregation, lowering atheromatosis, LDL-Cholesterol and blood pressure. It also enhances immunity, has an antiviral power and diminishes NO. There are even compelling evidences that it acts against cancer, against degenerative disease and it has successfully being used in dermatology [3,4]. In ophthalmology it is known to prevent AMD (Age-related macular disease) and has a positive effect on glaucoma.

Materials and methods

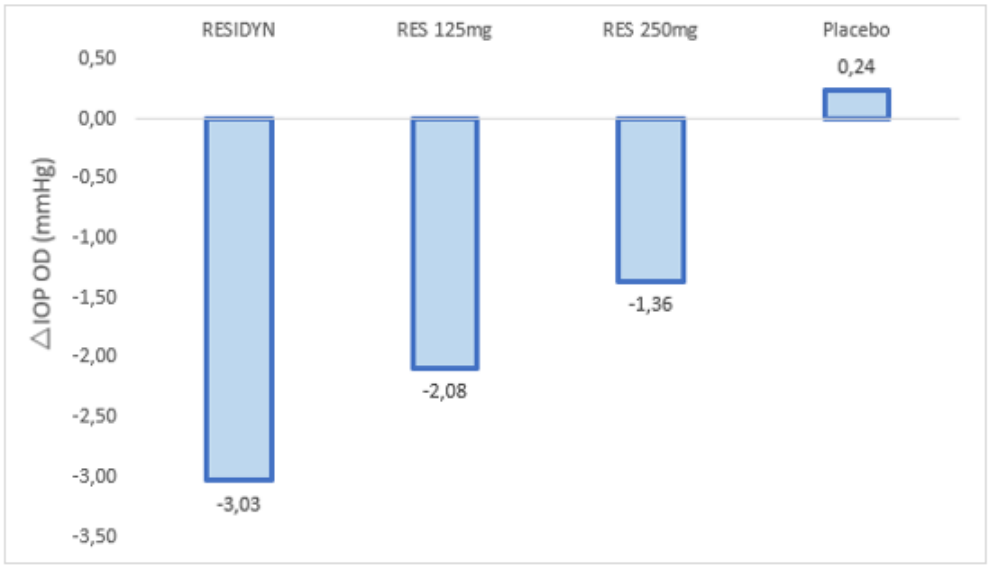
Resveratrol is a large molecule with a molecular weight of 228g/ml and has a very low solubility and only around 1% bioavailability. For this reason there was a need to search for a technology that can increase the solubility. Our collaborators in Eytelia created a unique combination of 30% RSV to a 70% Mesoporous silica-carrier to improve the solubility, absorbability and bioavailability. Residyn, being the result of a technology where mesoporous silica and resveratrol are combined, as a consequence, gives a better bioavailability with lower side effects because we will be able to give a lower dose of RSV for a similar clinical result. A randomized double-blinded clinical trial on 40 glaucoma patients was done and the patients were in 4 groups.

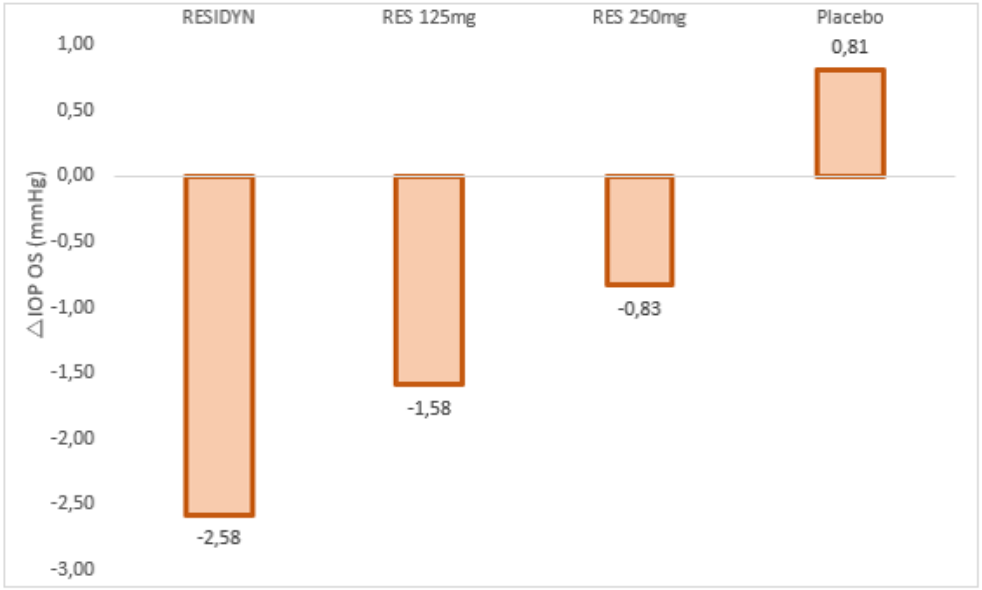
Based on the plasma data from preclinical trials, it was decided to split the dose over 4 time points. The patients took orally either 4x 1 250mg capsule of Resveratrol (total 1gr), 4x1 125mg capsule of Resveratrol (total 500mg), 4x1 capsule of Residyn 125mg (total 500mg) or 4x 1 placebo capsule containing MCC, for a period of 3 months. The capsules were spreaded over the day being before breakfast, lunch, dinner and before sleep. Before and after this period several exams were performed. We measured the intra ocular pressure (IOP) at the same hour of the day, did a visual field analysis and performed OCT to look at the average thickness of the retinal nerve fiber layer (rnfl), retinal ganglion cel (RGC) layer and Rim area in mm2. All patients were on concomitant topical anti-glaucomatous medication.

Results

After 3 months administration of Residyn we saw a significant mean drop in IOP by – 2.8 mmHg. The IOP drop with Residyn was significantly higher than in the RSV 1 gr group (-1.1 mmHg), RSV 500 mg group (-1.83 mmHg) or placebo group (+0.53 mmHg). In the right eye we even got a IOP drop of 3 mmHg in the Residyn group. In the other parameters we examined we saw no significant changes because of the relative short period of drug administration. The dropout rate due to gastro-intestinal complaints was 1 patient in the Residyn-group, 3 patients in the RSV 500 mg group and 1 patient in the RSV 1 gram group. 2 patients didn't start to take the supplement and 1 patient on placebo stopped taking the pills because he felt like gaining weight.


RESIDYN
RES 125mg
RES 250mg
Placebo
1,00
0,50
0,00
-0,50
-1,00
-1,50
-2,00
-2,50
-3,00
△IOP (mmHg)
-2,80
-1,83
-1,10
0,53


RESIDYN
RES 125mg
RES 250mg
Placebo
0,50
0,00
-0,50
-1,00
-1,50
-2,00
-2,50
-3,00
-3,50
△IOP OD (mmHg)
-3,03
-2,08
-1,36
0,24


RESIDYN
RES 125mg
RES 250mg
Placebo
1,00
0,50
0,00
-0,50
-1,00
-1,50
-2,00
-2,50
-3,00
△IOP OS (mmHg)
-2,58
-1,58
-0,83
0,81

5. Conclusion

There is evidence that Residyn is effective in reducing the IOP in patients who have glaucoma. The pathways to attain this result are multiple. RSV on one hand has the ability to act on reactive oxygen species being an anti-oxidant. It also acts on apoptosis and pro- inflammatory mediators. And Residyn has a positive effect on mitochondriae. Overall, the IOP drop in the Residyn group was better than in the RSV groups where there was no carrier used. In our study with Residyn we saw no significant side-effects of the product. Residyn could constitute a good novel candidate to enhance the efficacy of therapies currently used in patients with glaucoma. More clinical studies are required to provide further proof of the activity of Residyn in the treatment of glaucoma.

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