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Clinical Stabilization in Parkinson´s Disease: The Multi-Target Treatment Description and Results

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Abstract

Previous clinical trials designed to control the progression of Parkinson´s Disease (PD) have failed to demonstrate significant clinical stabilization. PD patients received a new oral Multi-Target Treatment to halt disease progression. The treatment consists of four substances that have a synergistic effect in controlling the most important known mechanisms of disease progression: aberrant apoptosis, oxidative damage, mitochondrial degeneration, caspase activation, syncytin-mediated neuroinflammation, and Mitogen-Activated Protein-Kinases activation.

Result: 40 patients with PD were studied, age 32 to 90 years (mean 62 years, SD +/-14.3), 23 female (57.5%), 17 male (42.5%). Initial United Parkinson´s Disease Rating Scale Sub-section 3 (UPDRS-3) score: 1-15 (mean 5, SD +/- 2.5). Maximum follow-up period was 84 months, mean 38 months (SD +/-24.5).

Results: There were 2 clinical remissions (5 %), 34 patients (85 %) improved their basal UPDRS-3 score and 37 patients (92.5%) had no increase in their UPDRS-3 score during the follow up period. The mean UPDRS-3 score at 51 months of follow-up was 3. The UPDRS-3 was worse in only 3 patients (7.5 %).

Conclusion: At present, there is no medication that has proven effective in controlling PD´s progression. The Multi-Target Therapy here described is a promising treatment that may control the progression of PD.

Keywords: Multi-Target therapy; Parkinson´s Disease; Disease modifying treatment; Clinical stabilization; Apoptosis; Aeuroprotection; Neurodegeneration

Background

It is necessary to have a safe and effective treatment to control the progression of Parkinson's disease (PD). Currently, no such therapy exists. As this neurodegenerative disease progresses, the patient's quality of life and productivity drastically decrease. The cost of available treatment also increases exponentially as the disease progresses. At the earlier stages, the annual cost is from $2,500 to $7,000 on medication alone; while long-term care costs about $47,000 per year [1].

Previous clinical trials designed to control Parkinson´s disease progression

Currently, the medical options available for PD are mainly for symptomatic treatment. The first clinical trial designed to evaluate a medication for disease-modifying potential was the Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP study) [2].

Patients with PD at an early stage were randomly assigned to take placebo or selegiline, the medication of interest, and the primary outcome was disease progression to disability such that the patient required levodopa therapy.

This study reported that patients who were treated with selegiline had about a 50% lower risk of reaching that endpoint, but this was likely due to symptomatic improvement rather than modification of disease progression.

The Sinemet vs Deprenyl in PD (SIN-DEP-PAR) [3] was the first study that used a wash out period after treatment with selegiline to try to differentiate between symptomatic improvement and true disease modification. Patients with very early PD were randomly assigned to treatment with selegiline or placebo, and to symptomatic treatment with bromocriptine or carbidopa/levodopa. Over 14 months of follow-up, selegiline was stopped 2 months prior to endpoint, and the bromocriptine and levodopa were stopped 1 week prior to endpoint. Patients treated with selegiline were clinically better at 14 months compared to those who received placebo, potentially consistent with a slowing of disease progression. However, monoamine oxidase-B (MAO-B) inhibitors like selegiline bind irreversibly to MAO-B in the brain and it takes the brain about 30 days to turn over half of its MAO-B; thus, there could have been a remnant symptomatic effect that was not sufficiently washed out by the study endpoint.

The Earlier vs Later Levodopa Therapy in Parkinson Disease (ELLDOPA) study [4] compared levodopa at various dosages to placebo for 40 weeks, followed by a 2-week washout period. After 40 weeks, symptom improvement was positively correlated with the dose of levodopa. After the 2-week washout, benefits of levodopa declined but treated patients still had fewer symptoms than those who received placebo. Thus, it was suspected that this treatment could provide disease modification. However, 2 weeks may not be enough time to eliminate the symptomatic effects of levodopa, which is hypothesized to induce compensatory changes to dopamine neurons, with an unknown duration of lasting effect. There were 2 delayed-start studies for rasagiline: TEMPO [TVP-1012 in Early Monotherapy for Parkinson's Disease Outpatients] [5,6] and ADAGIO [Attenuation of Disease progression with Azilect Given Once daily [7].

In the TEMPO study [5] about 400 patients were randomly assigned to 1 of 3 groups: rasagiline 1 mg/day for12 months, 2 mg/day for 12 months, or placebo for 6 months followed by rasagiline 2 mg/day for the second 6 months. The latter group is the delayed-start group. At the end of 12 months, a small but statistically significant difference was found, with the early-start groups clinically better than the delayed-start group.

The ADAGIO study [7] included approximately 1200 patients with a total follow-up of 18 months. It compared rasagiline 1 mg early start vs 1 mg delayed start, and 2 mg early start vs 2 mg delayed start. The delayed-start groups received placebo for 9 months followed by active medication for 9 months; the early-start groups received rasagiline for the full period of 18 months. Patients who received rasagiline 1 mg early did better than the 1 mg delayed group.

It was a small but statistically significant difference at 18 months, findings consistent with the TEMPO results. In the 2 mg group there was no difference between the early and delayed start groups.

Thus far, no symptomatic medication has proven to be neuroprotective or have a clear disease modifying effect. There is also no reason to support that they might achieve this goal based on their mechanisms of action as none of them has effect in syncytin-mediated neuroinflammation, free radical control, caspase inhibition, activation of Mitogen-Activated Protein-Kinases (MAPK), or other mechanism of PD progression.

As PD´s progression is a very complex process, with several simultaneous mechanisms of action, we postulate that it is necessary to combine more than one drug in order to effectively control the disease progression. We describe a new oral treatment, called Multi-Target Therapy (MTT), specifically designed to control neurodegenerative disease progression and to obtain clinical stabilization. Each one of its components has a different pathophysiologic target, and no symptomatic effect, different from what has been studied previously.

The pathological principle of protein propagation offers new disease-modifying therapeutic approaches to treating neurodegenerative diseases. It is well known, that in prion diseases, an infectious protein replicates by recruiting and inducing pathological conformational changes in its normal counterpart, resulting in the aggregation of pathological prions [8-10]. Prions thus act as corruptive templates that induce a chain-reaction-like process of protein misfolding and progressive aggregation. Recent studies have provided convincing evidence that a 'prion-like' self-propagating mechanism may apply to a wider range of proteins that are associated with neurodegenerative diseases, including misfolded Aβ, tau and α-synuclein, mutant huntingtin with polyglutamine repeats (characteristic of Huntington disease), mutant superoxide dismutase 1 (SOD1) and phosphorylated TDP43 [11].

Studies in vivo on individuals with PD who had received transplants of fetal mesencephalic dopaminergic neurons, show that α-synuclein pathology can propagate, as they developed α-synuclein-positive Lewy bodies and showed signs of neuronal degeneration [12-16]. Evidence from in vitro studies [17-19] and animal model experiments [17,18,20-27] confirmed seeded aggregation and transmission of α-synuclein [11].

Fluid-phase and receptor-mediated endocytosis have been implicated in the cellular uptake of mutant tau, mutant SOD1, and fibrils, oligomers and monomers of α-synuclein [19,28-32]. It is possible that these proteins could have synergistic deleterious effects on mitochondrial function [33].

The earliest lesions in PD and in dementia with Lewy bodies can be detected in the olfactory bulb and anterior olfactory nucleus, as well as in the dorsal motor nucleus of the vagus nerve in the medulla oblongata [11].

In PD and in dementia with Lewy bodies, with increasing burden of pathology, α-synuclein aggregate pathology is found in the pons and midbrain before being found in the basal forebrain and, ultimately, in the neocortex [11,34-39]. Thus, only in more advanced stages of PD does α-synuclein aggregation cause the loss of midbrain dopaminergic neurons in the pars compacta of the substantia nigra [11,34]. The accumulation of α-synuclein aggregates in the anterior olfactory nucleus [11,40] and olfactory bulb is clinically reflected by hyposmia, which is frequently observed before the onset of motor symptoms in PD [11,41]. It has been suggested that projection neurons with sparsely myelinated axons would require prodigious energy expenditure to maintain axonal function and transport [42], and that such high energy demands would result in continuously high levels of oxidative stress that could increase neuron vulnerability to α-synuclein aggregation in PD [11,43-46].

Template-directed replication and subsequent cell–cell transmission of pathology-associated proteins provides a common molecular pathway that could be targeted by novel therapeutic strategies with the aim of disrupting or delaying propagation. Moreover, agents that interfere with the release or uptake of neurodegenerative disease proteins could prevent transmission of pathology to neighboring neurons. Finally, many neurodegenerative diseases are likely to be non-cell autonomous, with an important part played by astroglia, oligodendroglia and microglia [11].

While designing the MTT we considered syncytin-mediated neuroinflammation a therapeutically important target. Even though increased Human Endogenous Retro-Virus (HERV) activity could be an epiphenomena, and association does not imply causality, there are increasing and stronger evidence that the presence of HERV-induced syncytin production is correlated to higher progression index in most of the neurodegenerative diseases studied. It also has a well-studied neuroinflammatory pathway, where the released tumor necrosis factor alpha (TNFα) bind to the Tumor Necrosis Factor Receptor (TNFR) that initiates necrosis factor κβ (NF-κβ) activation in an autocrine and paracrine manner. The signaling pathway downstream from TNFR leads to nuclear translocation of NF-κβ, where it binds to the promoters of syncytin1. Cytoplasmic accumulation of env proteins induces endoplasmic reticulum (ER) stress responses and extracellular or transmembrane env proteins can exert their properties: fusogenicity and capacity to activate the neuroimmune system, damage oligodendrocytes and interfere with myelin regeneration [47]. Additionally, the long terminal repeats (LTRs), which control retroviral gene expression, can also change host RNA levels [48] and the HERV-expression pattern has been shown to be altered in murine cell culture models for prion infection [49] and in the cerebrospinal fluid (CSF) of sporadic CJD patients [50,51].

The multi-target therapy to control neurodegenerative diseases´ progression

The Multi-Target Therapy treatment (patent MX329006 B), combines four substances that interact to produce a synergistic effect. As far as we know, this is the first treatment specifically designed to control the progression of neurodegenerative diseases such as PD. It contains ferulic acid 50 mg, apigenin 100 mg, gamma oryzanol (GO) 50 mg and sylimarin 150 mg. It is designed to preserve the brain's physiological micro-environment and to control the most active known pathophysiologic mechanisms involved in neurodegenerative disease progression. Because of the compound's antioxidant properties, it has a protective effect for myelin and neurons; thus it may also be useful in other neurodegenerative oxidative-mediated diseases, such as multiple sclerosis and Alzheimer´s disease, among others. The MTT is an oral treatment designed to be taken daily and long-term to continuously combat the active pathophysiologic mechanisms involved in disease progression. It is not designed to relieve the symptoms of PD, but to slow down and control the progression of the disease. All the components have been tested previously in humans and proven to be safe for consumption [52].

Ferulic acid

Ferulic Acid (FA) has shown protective effects against various inflammatory diseases [53]. It is an antioxidant that has proved highly effective in neutralizing free radicals such as superoxide, hydroxyl radical, and nitric oxide (NO). It acts synergistically with other antioxidants, giving them extra potency [54], and protects against nitrosamines [55]. Its structure is similar to catecholamines like norepinephrine. There are no documented side effects of ingestion of FA in humans. FA is a fenolcarboxilic acid [56] that has been shown in vitro and in vivo to decrease death of oligodendrocytes under cellular stress, which can improve neurological outcome [57]. Several mechanisms of disease can cause damage in the central nervous system that can modify the core expression of glial cells. Those effects can be produced by protein misfolding or by protein accumulation in the ER, which causes a cellular stress response and the production of neurotoxic molecules, including redox reactants like NO, reactive nitrogen-oxygen species, peroxinitrite anions and superoxide, which can cause encephalic damage [57]. FA acts against several potent cellular stress mechanisms mediated by Interleukin 1 (IL1), inducible nitric oxide synthase (iNOS) and redox reactant synthesis, among others.

Syncytin is a 518-amino-acid membrane glycoprotein that may exert biological action by binding to the receptor ASCT2 (alanine, serine, cysteine transporter 2), which is both an amino acid transporter and a retrovirus receptor [58]. Viral envelope glycoproteins are known to affect immune responses and syncytin is related to activation of lymphocytes and macrophages [59]. Overexpression of syncytin in astrocytes and macrophages is sufficient to cause the cells to produce high amounts of the proinflammatory cytokine IL-1β and reactive oxygen radicals. The overexpression of syncytin is toxic to oligodendrocytes, and this toxicity is prevented by FA [60].

FA also appears to encourage the proliferation of at least some types of nerve cells, such as retinal cells [61]. It has proven to be effective in several diseases in humans and in animals. In a model of iron-induced neuronal oxidative stress and neuronal apoptosis in granular cerebellar cells [62], an increase in caspase 3 activity and apoptosis related to gene p53 activity and of its gene effector p21 was demonstrated. In neurons treated with tetrametilpirazine and FA and then exposed to the iron-induced oxidative model, a significant decrease of caspase 3 activity and expression of p53 and p21 was documented, with less severe oxidative damage and apoptosis induced by iron. This suggests that tetrametilpirazine and FA can be used to treat neurological diseases associated to oxidative stress.

Macrophage activity also has been related to neurodegenerative disease progression. FA has been shown to specifically reduce the macrophage inflammatory protein-2 (MIP-2) in the RAW264.7 macrophage cell line. Its effect was superior to that of dexamethasone [63]. FA-related compounds have potential to produce NSAID-like effects [64,65], can inhibit NO production [66] and have radical scavenging activity [67].

Apigenin

Apigenin is a flavonoid found in its natural form in several fruits and vegetables. It is well known for its anti-oncogenic, antioxidant and anxiolytic properties, acting by several mechanisms. In cases of injury or disease, microglia are recruited to the site of damage and become ativated, as evidenced by morphological changes and expression of pro-inflammatory cytokines. Evidence suggests that microglia proliferate by cell division to create gliosis at the site of injury, such as the amyloid plaques in Alzheimer's disease and the substantia nigra in PD. The hyperactivation of microglia contributes to neurotoxicity. Anti-inflammatory compounds modulate the progression of the cell cycle and induce apoptosis of activated cells, and thus might inhibit microglial proliferation [68].

Apigenin, among its structural analogues, appears to be the most potent inhibitor of the production of pro-inflammatory cytokines by lipopolysaccharide-stimulated human peripheral blood mononuclear cells [69]. Apigenin inhibits phosphorylation pathways and is a potential inhibitor of cellular autoimmunity. Due to the inhibitory activity of flavonoids on IL-4 and IL-13 synthesis, it can be expected that the intake of flavonoids, depending on the quantity and quality, may ameliorate allergic symptoms or prevent the onset of allergic diseases [70]. Apigenin is a very potent inhibitor of xanthine oxidase activity. Prostaglandin biosynthesis and NO production have been implicated in the processes of neurodegeneration, carcinogenesis and inflammation. Apigenin may be the most potent inhibitor of transcriptional activation of both COX2 and iNOS. Western and northern blot analyses demonstrated that apigenin significantly blocked protein and mRNA expression of COX2 and iNOS in LPS-activated macrophages. Transient transfection experiments showed that LPS caused an approximately 4-fold increase in both COX2 and iNOS promoter activities, but these elevations were suppressed by apigenin. This suggests that modulation of COX2 and iNOS by apigenin may be important in the prevention of carcinogenesis and inflammation [71].

The chemical chain reaction initiated by NMDA receptors and by calcium influx causes an increase in the activity of the enzyme system known as the Mitogen-Activated Protein Kinases system (MAPK). Factors released in response to hypoxia (growth factors, inflammatory cytokines and free radicals) can also stimulate the MAPK system. MAPK activity can remain elevated long after cessation of the initial stimulus. Inhibiting MAPK activity has been shown to have a neuroprotective effect in cases of central nervous system insult; and apigenin has been shown to be a strong MAPK inhibitor [72].

Decreased activity of superoxide dismutase was strongly correlated with increased oxidative damage to plasma proteins at the individual level. Intervention with apigenin seemed to partly overcome this decrease and resulted in increased levels of glutathione reductase and superoxide dismutase [73].

Sylimarine

Sylimarine is an antioxidant found in several plants and types of food. It is estimated that its antioxidant effect is 10 times stronger than that of vitamin E. It increases the hepatic content of the antioxidant enzyme glutathione by 35% and decreases free radical-mediated cellular damage by inhibition of lipoxygenase. Lipoxygenase acts in polyunsaturated fatty acids and produces leukotrienes, which are involved in cellular membrane damage [74].

Gamma oryzanol

GO was discovered in the late 60s while experimenting with growth factors in animals. It was observed that GO accelerated animal growth with no collateral effects. It is a compound molecule made up of FA and estherol. When GO is taken orally, absorption is low (<10 %). Once absorbed by the digestive system, it is hydrolyzed by a non-specific esterase, separating it into free FA and estherol. When administered alone, FA absorption increases by a factor of 20 to 30 because it is a hydrosoluble compound, thus eliminating the issue of cellular transport. Also, free FA does not undergo first pass metabolism by the liver as GO does. Nevertheless, GO is an additional source of FA that increases the level of this antioxidant, providing additional effect [75].

Clinical stabilization treatment trial

The 4 different substances of the MTT, synergistically working against the most important known pathophysiologic mechanisms of disease progression, including pathophysiologic oxidation, mitochondrial degeneration, cellular damage mediated by macrophage free radicals, caspase activation, aberrant apoptosis, and MAPK cellular damage, could preserve the physical and functional integrity of the myelin-axon unit, the neurovascular unit, and the neurons and glial cells, achieving clinical stability in neurodegenerative disease. We have previously demonstrated that it is safe to use the MTT in humans [52]. It is the first, and as far as we know, the only therapy that combats the most known mechanisms of disease progression simultaneously. As the MTT has no effect on the clinical symptoms of PD, it does not replace standard symptomatic treatment.

Materials and Methods

We designed a cohort phase II/III trial. The primary endpoint was the United Parkinson´s Disease Rating Scale-3 (UPDRS-3) score during the follow up period (a lower score indicates better clinical condition). Before beginning the trial, we optimized the symptoms of each participant and recorded their basal UPDRS-3 score. Then, we added the MTT at a dose of 1 pill every 12 hours taken on an empty stomach. We evaluated all patients with clinical examination, UPDRS-3 scoring and laboratory testing every 3 months during the follow-up period of up to 84 months.

Results

We included 40 patients with PD. Age: 32 to 90 years (mean 62 years, SD +/- 14.3), 23 female (57.5%), 17 male (42.5%). Initial UPDRS-3 score: 1-15 (mean 5, SD +/- 2.5). Maximum follow-up period: 84 months, mean 38 months (SD +/- 24.5). During the follow up period, 7 patients (17.5 %) improved their basal UPDRS-3 score while there was no change in score for 37 patients (92.5 %). There were 2 clinical remissions (5 %). The UPDRS-3 was worse in 3 patients (7.5 %). Of these three patients, one discontinued the MTT for 18 months and deteriorated in that time. The mean UPDRS-3 score was 3 at 51 months of follow-up. Adverse effects: None.

Conclusions

One of the most important challenges in PD is controlling disease progression. The PD progression index has been established in a deterioration of 7.8 +/- 9.0 points in UPDRS at 42 weeks of follow-up [76] in the UPDRS. It is necessary to have new therapeutic resources to control disease progression and improve patient outcomes. As there is no medication that has previously demonstrated efficacy in controlling PD progression, it is justified to design and test new medications created for this purpose.

The MTT is the first treatment specifically designed to control the progression of neurodegenerative diseases. With this initial evidence, we believe that the MTT may be able to change the course of PD and control its progression. The MTT represents a new pharmacological strategy in PD treatment because it combines several agents with different mechanisms of action, which has never been done before in attempting to halt neurodegenerative disease, and particularly PD, progression.

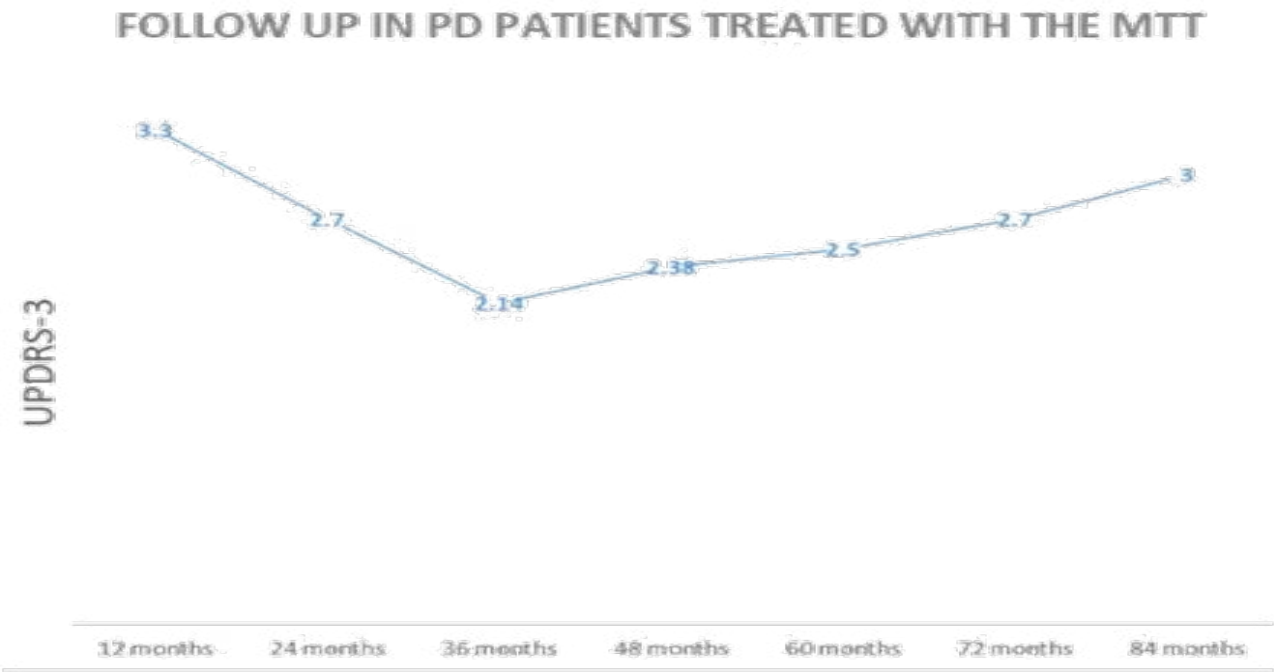

Figure 1: Disease progression control in PD patients using the Multi-Target Therapy. Historically, the score of PD patients treated only for symptomatic improvement would increase as time went on, affecting their quality of life. In PD patients treated with the Multi-Target Therapy, the disease has less clinical progression in most of the cases during the follow up period.

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