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Short communication

Effects of angiotensin type 1 receptor antagonists on Parkinson's disease progression: An exploratory study in the PPMI database

Lucas Udovin [a], Matilde Otero-Losada [a], Sofia Bordet [a,b], Guenson Chevalier [a], Cecilia Quarracino [a], Francisco Capani [a,c,d,e,1], Santiago Pérez-Lloret [a,f,g,1,*]

[a] Centro de Altos Estudios en Ciencias Humanas y de la Salud- Universidad Abierta Interamericana. Consejo Nacional de Investigaciones Científicas y Técnicas. CAECIHS-UAI. CONICET, Buenos Aires, Argentina
[b] Centro de Investigaciones en Psicología y Psicopedagogía (CIPP), Facultad de Psicología y Psicopedagogía, Pontificia Universidad Católica Argentina (UCA), Buenos Aires, Argentina
[c] Instituto Universitario de Ciencias de la Salud, Fundación H.A Barceló, Buenos Aires, Argentina
[d] Departamento de Biología, Universidad John F. Kennedy, Buenos Aires, Argentina
[e] Facultad de Medicina, Universidad Autónoma de Chile, Santiago, Chile
[f] Facultad de Ciencias Médicas, Pontificia Universidad Católica Argentina, Buenos Aires, Argentina
[g] Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires. Buenos Aires, Argentina

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ABSTRACT

Introduction: We explored the potential clinical effects of angiotensin-II AT1 receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) in patients from the Parkinson's Progress Marker Initiative (PPMI) study database.

Methods: We included 423 newly diagnosed PD patients, free from antiparkinsonian treatment, from the PPMI. We compared the proportion of patients starting on L-DOPA during the first year of follow-up, and the changes in MDS-UPDRS total score and sub-scores during the first five follow-up years for patients exposed or not to ARBs or ACEIs.

Results: Treatment with ARBs did not affect the proportion of patients on L-DOPA during the first year (adjusted OR, 95% CI = 0.26, 0.03–2.18, N.S.) while reduced MDS-UPDRS total score (0.85, 0.76–0.95, $p < 0.01$). Patients treated with ACEIs experienced no changes in either measure.

Conclusions: These results show potential signals for a beneficial effect with ARBs. Further clinical trials are warranted.

1. Introduction

Parkinson's disease (PD) is the second leading neurodegenerative disorder after Alzheimer's [1]. The many advances in the pathophysiology of PD have not yielded either preventing or progression-retarding treatments. The renin-angiotensin system (RAS) in the brain was reported in regulating dopaminergic neurotransmission and neuron survival. Angiotensin II AT1 receptor blockers (ARBs) and the angiotensin-converting enzyme inhibitors (ACEIs) prevented neuronal damage caused by dopaminergic neurotoxins in experimental PD cellular and animal models [2]. Furthermore, perindopril, an ACEI, reduced the latency of the motor response to L-DOPA and increased "on" periods during the waking day in a small double-blind, randomized, cross-over study [3]. We analyzed data of the Parkinson's Progression Markers Initiative (PPMI) study and evaluated the potential effects of ARBs and ACEIs on disease progression in PD patients.

2. Materials and methods

2.1. Study participants

This study included 423 untreated, newly diagnosed PD patients from the PPMI study [4]. The inclusion criteria were: 1) a 2-year PD history, 2) a Hoehn and Yahr stage I or II at enrollment, 3) a dopamine transporter-protein deficit measured by single-photon emission computed tomography (SPECT), 4) no clinical expectation of starting PD

* Corresponding author. CAECIHS-UAI. CONICET Av. Montes de Oca 745, C1270AAH ,Buenos Aires, Argentina.
E-mail address: santiagopl@conicet.gov.ar (S. Pérez-Lloret).
[1] shared authorship.

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medication until six months after the initial evaluation.

Institutional review boards at participating clinical sites approved the PPMI study protocol. Before being included in the study, all participants signed a written informed consent whereby the result would be shared with involved and non-involved investigators.

2.2. Study design

This study comprised two sub-studies: one case-control study and one cohort study.

For the first sub-study, cases were defined as PD patients requiring L-DOPA within the first year after diagnosis, unlike controls that did not. The index date was the date of the first L-DOPA prescription for cases or the closest visit in controls. Exposition to ARBs (valsartan, telmisartan, losartan, candesartan, irbesartan, olmesartan, eprosartan, azilsartan, filmasartan, tasosartan) or to an ACEis (hydrophilic: captopril, enalapril, imidapril, lisinopril; lipophilic: benazepril, cilazapril, fosinopril, delapril, moexipril, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, zofenopril) was considered when the drug had been prescribed for at least 2 years before entering the study. Drug doses were recorded and converted to Defined Daily Doses (DDD) [5].

The main outcome of the cohort sub-study was the change in MDS-UPDRS total score (i.e. the sum of parts I to IV) during the first five years after inclusion. Parts I to IV sub-scores were also analyzed. Motor examination (i.e. Part III) was assessed in the practically defined off-condition, without medication. A patient was considered as exposed to ARBs or ACEIs if he/she was receiving these drugs at one and all preceding visits and for two years before the baseline visit. For example, exposure at Year 1 visit meant that a patient had been taking these drugs for at least 2 years at baseline and over the entire year thereafter. Exposure at Year 2 visit meant that the patient had been on these drugs for at least 2 years at baseline and over the two years thereafter, and so forth for exposure in Years 3, 4, and 5. Then, a patient status could change from "exposed" to "non-exposed" during the follow-up, but not the other way.

2.3. Statistical analysis

For the case-control study, the chi-square or t-tests explored differences in drug exposure. Multivariate analyses with logistic regression adjusting for age and sex, disease severity at the time of inclusion (tested by the MDS-UPDRS II + III score), the Elixhauser comorbidity score, which reflects nonspecific effects on patients' general health [6], and the presence of cardiometabolic comorbidities. Cohen's d value, size effect estimate, was calculated as the between-means difference divided by the pooled standard deviation (SD) [7].

The evolution of the subjects exposed or not to ACEis or ARBs over the five years' follow-up was compared using General Estimation Equations (GEE). Sex, age, time from diagnosis to baseline visit, the presence of cardiometabolic comorbidities and the use of anti-parkinsonian medications were treated as confounding factors. Post-hoc comparisons of marginal means, calculated by the GEE model, were performed at each time point. The significance level was conventionally set at 0.05. SPSS v.23 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

3. Results

3.1. Case-control sub-study

Of the 423 subjects included in the study, 103 (24%) started treatment with L-DOPA (cases) during Year 1 of follow-up, while 320 patients (76%) did not (controls). The median time to start on L-DOPA was 6 months (interquartile range, IQR = 5–8 months). Cases were older than controls, had a later-onset disease with higher Hoehn and Yahr score at baseline (Table 1). By month 12, 273 out of the 423 patients (64%) were on at least one antiparkinsonian drug, 110/273 (40%) patients being treated with more than 1 drug at the same time. Five (1%) patients were on anticholinergics, 34 (8%) on amantadine, 103 (24%) on L-DOPA, 119 (28%) on dopamine agonists, and 135 (32%) on MAO-B inhibitors. The daily L-DOPA dose was 438.1 ± 274.8 mg.

In this sample, 29 (6.9%), 12 (2.8%), and 12 (2.8%) patients were exposed to hydrophilic ACEIs, lipophilic ACEIs, and ARBs, respectively, at baseline (Table 1). The most consumed drugs were: lisinopril for hydrophilic ACEIs (21/29 = 72%), ramipril for lipophilic ACEIs (5/12 = 41%), and valsartan for ARBs (4/12 = 33%). Table 1 shows the characteristics of and exposure to drugs of interest in cases and controls. There were no statistically significant differences in exposure. However, cases exposed to ARBs showed a trend to a lower risk of requiring L-

Table 1
Characteristics of patients that started with L-DOPA during the first year of follow-up or no.

	PD sample (n = 423)	Controls (n = 320)	Cases (n = 103)	p-value	Size effect (Cohen's d)
Patients' characteristics					
Males	277 (65%)	211 (66%)	66 (64%)	0.73	-
Age (years)	61.7 ± 9.7	60.6 ± 9.6	65.1 ± 9.4	<0.01	-
PD age at diagnosis	61.1 ± 9.7	60.1 ± 9.6	64.5 ± 9.3	<0.01	-
Disease duration (months)	6.7 ± 8.4	6.7 ± 8.6	6.6 ± 7.7	0.94	-
PD family history	103 (24%)	84 (26%)	19 (18%)	0.10	-
Elixhauser comorbidity score	0.6 ± 2.8	0.6 ± 2.8	0.6 ± 2.9	0.95	-
Cardiometabolic comorbidities					
Hypertension	136 (32%)	102 (32%)	34 (33%)	0.89	-
Diabetes	21 (5%)	16 (5%)	5 (5%)	0.93	-
Hypercholesterolemia	88 (21%)	65 (20%)	23 (22%)	0.70	-
Metabolic Syndrome	1 (<1%)	0	1 (1%)	0.80	-
Hoehn and Yahr score					
I	185 (44%)	157 (49%)	28 (27%)	<0.01	
II	236 (56%)	160 (51%)	76 (73%)		
MDS-UPDRS II + III scores at baseline	34.9 ± 14.6	34.5 ± 14.2	36.4 ± 15.9	0.32	-
Drug Exposure					
Hydrophilic ACEis	29 (6.9%)	20 (6.3%)	9 (8.7%)	0.38	0.21
Duration (years)	8.9 ± 7.0	10.6 ± 7.7	7.2 ± 3.0	0.22	0.01
DDD (mg)	1.8 ± 1.3	1.6 ± 1.3	2.4 ± 1.2	0.21	0.12
Lipophilic ACEis	12 (2.8%)	8 (2.5%)	4 (3.9%)	0.46	0.04
Duration (years)	9.9 ± 8.9	7.5 ± 4.3	14.3 ± 14.3	0.41	0.02
DDD (mg)	2.9 ± 2.1	4.9 ± 3.4	2.1 ± 0.8	0.10	0.05
ARBs	12 (2.8%)	10 (3.1%)	2 (1.9%)	0.52	0.74
Duration (years)	6.7 ± 3.2	7.1 ± 3.1	8.5 ± 3.1	0.57	0.11
DDD (mg)	1.5 ± 0.5	1.4 ± 0.7	1.5 ± 0.7	0.84	0.52

Data are expressed as mean ± standard deviation (SD) (continuous variables) or frequency and percentage (categorical variables). Bivariate comparisons were performed using a *t*-test or a Chi-square test. PD: Parkinson disease; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale; ACEis: Angiotensin-Converting Enzyme inhibitors; ARBs: Angiotensin Receptor Blockers.

DOPA compared with controls (adjusted OR: 0.26; 95% confidence interval CI: 0.03–2.18, Table 1) with a medium-high Cohen's d value of 0.74. These values remained unchanged when Hoehn and Yahr scores were taken into consideration as a confounding factor or when cardiometabolic comorbidities were considered in the place of the Elixhauser score.

3.2. Cohort sub-study

Of the 423 subjects included in the study, 344 (81%) were available in Year 1, 331 (79%) in Year 2, 329 (78%) in Year 3, 310 (73%) in Year 4, and 298 (70%) in Year 5. From the 125 patients missing at Year 5, 91 patients were discontinued from the study (73%) while the rest of the patients had not attained the fifth-year visit at the time of the analysis.

The cumulative number of patients exposed to hydrophilic ACEis at baseline and Years 1, 2, 3, 4 and 5 were 29 (8%), 27 (8%), 26 (8%), 19 (6%), and 19 (6%) respectively. Cumulative exposure to lipophilic ACEis was 11 (3%), 10 (3%), 10 (3%), 8 (3%), and 8 (3%), respectively. Finally, cumulative exposure to ARBs was 9 (3%), 8 (3%), 7 (3%), 7 (3%), and 7 (3%), respectively. Mean ± standard deviation MDS-UPDRS total scores at these visits were 32.3 ± 13.1 at baseline and 39.1 ± 16.2, 43.1 ± 17.4, 46.1 ± 19.0, 51.0 ± 21.7, and 51.5 ± 22.1 at Year 1, 2, 3, 4, and 5 respectively. The GEE revealed a significant association between MDS-UPDRS total score and exposure to AT1 antagonists (adjusted OR: 0.85; 95% confidence interval CI: 0.76–0.95; $p < 0.01$, Table 2).

MDS-UPDRS total score during the follow-up in patients, exposed or not to ARBs, are shown in Fig. 1. No significant associations were observed with exposure to hydrophilic ACEIs (0.91, 0.81–1.01; p = 0.08), or lipophilic ACEIs (1.04, 0.91–1.20; p = 0.56). As shown in Table 2, patients exposed to ARBs or hydrophilic ACEIs showed statistically significant lower MDS-UPDRS III sub-scores (evaluated in the practically defined OFF-state). An analysis stratified by age, which is a major confounder, showed that exposure to ARBs was related to lower MDS-UPDRS total values in all age categories (data not shown).

4. Discussion

While symptomatic control of PD motor symptoms can be achieved by using a variety of drugs or devices [8], disease-modifying treatments are still not available. Drug repurposing, using old well-known drugs with new indications, may offer the opportunity of developing PD-modifying treatments rapidly and cost-effectively. It also has the advantage of identifying signals of relevant effects in experimental models and observational studies for later translation into clinical trials. We explored the clinical effects of ARBs and ACEIs, which have shown

Table 2
Effects of ARBs and ACEIs on MDS-UPDRS total score and sub-scores evolution during the first five years after PD diagnosis.

MDS-UPDRS scores	ARBs	Lipophilic ACEIs	Hydrophilic ACEIs
Total	0.85, 0.76–0.95 (p < 0.01)	1.04, 0.91–1.20 (p = 0.56)	0.91, 0.81–1.01 (p = 0.08)
Part I	0.64, 0.29–1.43 (p = 0.28)	1.61, 0.26–10.1 (p = 0.61)	0.76, 0.39–1.51 (p = 0.44)
Part II	0.86, 0.70–1.07 (p = 0.17)	1.16, 0.92–1.48 (p = 0.21)	0.91, 0.77–1.07 (p = 0.25)
Part III (OFF-state)	0.87, 0.77–0.98 (p = 0.02)	1.01, 0.86–1.17 (p = 0.96)	0.89, 0.80–0.99 (p = 0.04)
Part IV[a]	0.68, 0.26–1.79 (p = 0.43)	0.84, 0.31–2.28 (p = 0.74)	0.90, 0.46–1.72 (p = 0.75)

Odds ratio, their 95% confidence intervals and (p-values) are shown. Drug effects were assessed by means of GEE, adjusting for time from diagnosis at baseline visit, age, gender, use of antiparkinsonian treatments and presence of cardiometabolic comorbidities.

[a] This variable was categorized as score = 0 (Reference) vs score≥1 to fit a meaningful GEE model.

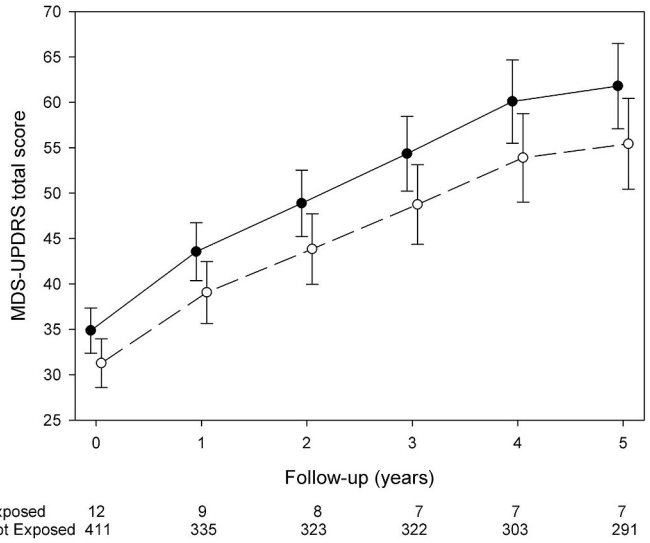

Fig. 1. Total MDS-UPDRS total score in patients exposed (○) or not (●) to Angiotensin Receptor Blockers. Shown are estimated marginal means and standard errors, adjusted for time from diagnosis at baseline visit, age, gender, use of antiparkinsonian treatments and presence of cardiometabolic comorbidities.

symptomatic and neuroprotective effects in experimental PD models of the disease [2] and reduced PD risk in one population-based cohort study with hypertensive patients [9]. Our results suggest that PD patients exposed to ARBs had comparatively lower MDS-UPDRS total score and Part III sub-scores (in the practically defined off-condition) during the first five follow-up years after the diagnosis. The change in the risk of requiring L-DOPA during the first follow-up year did not reach a statistical difference in these patients compared with the non-exposed controls. These observations are compatible with a potential symptomatic or disease-modifying effect of ARBs. Patients exposed to hydrosoluble ACEIs also showed a statistically significant reduction in Part III sub-score. Liposoluble ACEIs showed no effects. The action mechanism of ARBs and ACEIs in PD is not clear, and explaining the difference in the effects of these drugs observed here is difficult. The AT1 receptor can be activated in the absence of Ang II [10]. Therefore, ARBs may have a greater effect, for they stabilize the AT1 receptor and block its activation even in the absence of Ang II.

One upside of this study is having used two complementary approaches to increase the possibility of detecting a signal of efficacy. The first approach was a case-control study using the L-DOPA requirement during the first year of follow-up as the outcome. This outcome has been frequently used in the context of proof-of-concept phase II futility studies [10]. The main limitations of this outcome may be that it is influenced by sociocultural and economic factors (i.e., employment status and public healthcare system), as well as by differences in physicians' attitudes towards early management of PD patients. We used the same dataset to constitute a cohort of PD patients followed for up to 5 years after the PD diagnosis [4]. As the PPMI is rolling on, not all patients attained the end of this period, which forced us to use statistical techniques that could take into account censored data (i.e., the GEE technique). The outcome of this sub-study was the progression of MDS-UPDRS total scores. Although MDS-UPDRS scores have been used in some recent disease-modification trials in PD (NCT02168842), they may not be reliable measures of the underlying disease process once symptomatic treatment has been received. Furthermore, the practically defined-off state may be an unreliable measure of disease progression as the "long duration" response may be hard to exclude. Therefore, none of the outcomes may be reliable when considered alone, but considering them together might increase the validity of signals of drug efficacy.

Another plus-point is having applied a conservative definition of

exposure to ARBs or ACEIs. Treatment for at least two years before PD diagnosis and no interruptions during the five follow-up years after the diagnosis were both requirements to consider a patient as exposed to each one of these drugs. The GEE technique allowed us to handle missing data and changes in exposure status, without excluding the patient from the analyses. Using a less conservative definition of exposure would have yielded more exposed patients, at the cost of losing reliability.

This study poses certain limitations. The small number of patients exposed to the drugs under study may have concealed the statistical significance of between-group differences. For this and other reasons, we conducted the cohort sub-study. Combining multiple observations from single patients allowed characterizing and excluding within-subjects variability, thus increasing the statistical power. Notwithstanding, analyzing results from the two sub-studies altogether increased the experiment-wise alpha error. We did not correct for this to avoid further statistical power reduction. Bearing this in mind, we meant our study to be exploratory.

In summary, we observed a signal of potential clinical effects of the ARBs that deserves further attention in future clinical trials. The ARBs are commonly used in PD patients for treating hypertension. Then, Phase I studies may not be needed, and a proof-of-concept futility trial [10] seems warranted. The outcome of our study may lay the bases for the corresponding design.

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