Journal of Parkinson's Disease 12 (2022) 2601–2603
DOI 10.3233/JPD-223496
IOS Press

Letter

Parkinsonian Patients Requiring Proteasome Inhibitors for Multiple Myeloma: Exceptional Circumstances Call for Extra Caution

Pierre Rocanières[a], Sylvain Lamure[b], Christian Geny[c], Dominique Hillaire-Buys[a], Jean-Luc Faillie[a,d] and Virginie Bres[a,*]
[a]*Department of Medical Pharmacology and Toxicology, Pharmacovigilance Regional Centre, CHU Montpellier, Montpellier, France*
[b]*Department of Clinical Hematology, CHU Montpellier, IGMM UMR5535 CNRS, Univ Montpellier, Montpellier, France*
[c]*Department of Internal Medicine and Geriatrics, CHU Montpellier, Montpellier, France*
[d]*Desbrest Institute of Epidemiology and Public Health, Univ Montpellier, INSERM, Montpellier, France*

Accepted 12 September 2022
Pre-press 29 September 2022

Feedback on the management of patients with both Parkinson's disease (PD) and multiple myeloma (MM) is not common in the literature, and we would like to report an original possible adverse event (AE) of MM chemotherapy: an increased PD severity induced by ixazomib. The patient, a 68-year-old man with PD (Hoehn and Yahr (HY) stage 3) was effectively and stably treated for 14 years with dopaminergic therapy (levodopa equivalent daily dose (LEDD) 1275 mg). His symptomatic MM was first treated by lenalidomide (25 mg) with dexamethasone (Rd protocol) for 19 months. Then, a second-line therapy combined the proteasome inhibitor (PI) ixazomib (4 mg) with lenalidomide (20 mg) and dexamethasone (IRd protocol, 4-week cycle) due to MM progression.

After one month of IRd the patient described a significant poorer control of his PD with less effective L-dopa therapy, which continued to deteriorate over a 3-month period (progression to HY stage 4): severe nocturnal akinesia, amimia, hypophonia with palilalia, and daily walking time worsened from 45 to 10 min. There was neither distal bradykinesia, nor resting tremor. LEDD increased to 1350 mg with an extended-release levodopa/benserazide and the patient reported a more effective and durable control of PD, though not recovering his basal status. After 11 months of IRd, the patient was hospitalized for bronchitis, altered general condition, repetition of falls and sleepiness, imputed by clinicians to PD progression. IRd was withdrawn and antiparkinsonian treatment was reinforced by adding rasagiline (LEDD 1450 mg). Finally, 6 months after IRd inter-

*Correspondence to: Dr. Virginie Bres, Pharmacovigilance Regional Centre, Department of Medical Pharmacology and Toxicology, CHU Montpellier, 191 Avenue du Doyen Gaston Giraud, 34295 Montpellier, France. Tel.: +33 4 67 33 67 57; E-mail: v-bres@chu-montpellier.fr.

ISSN 1877-7171/$35.00

ruption, the patient showed a substantial general and neurologic status improvement with a resumption of walk and a much more satisfactory state of alertness, MM remaining in partial response.

We argue that ixazomib has a role in the increased PD severity, due to its mechanism of action. Cellular proteostasis is notably controlled by the ubiquitin-proteasome system, which ensures the elimination of proteins and the regulation of many essential cellular functions through the proteolysis of identified targets by ubiquitination [1]. Its proteolytic activity is decreased by about 33% to 42% in *substantia nigra* from postmortem samples of idiopathic parkinsonian patients, leading to the aggregation of misfolded amyloid proteins (including α-synuclein) into typical inclusions [2]. This fundamental discovery was elegantly explored in the early 2000s by McNaught et al. who successfully developed a model of PD involving proteasome inhibition. This inhibition leads to formation of intracytoplasmic inclusion bodies and death of dopaminergic neurons *in vitro* [3] and in rodent models [4, 5] but failed to show the same effect in non-human primate model, possibly because of a lack of cerebral penetrance [6].

Currently marketed PIs, including ixazomib, have little or no blood-brain barrier (BBB) crossing, which may partly explain their low toxicity on the central nervous system [7–9]. However, the permeability of BBB is increased in the postcommissural putamen of PD patients, suggesting the possibility of a brain diffusion of PIs in this population [10]. More specifically, dopaminergic neurons would be more sensitive to a decreased proteasome activity than other cells, due to physiologically high levels of oxidized proteins and dopamine [11]. In PD patients, these particular conditions may lead to the same observation as seen in various animal models: formation of inclusions, neurodegeneration and finally, progression of PD.

It is commonly challenging to establish the existence of an AE, except in the case of a positive rechallenge. A drug reintroduction is obviously unacceptable for the safety and interest of our patient. We must, therefore, admit the classical biases of this observation and notably the possible imputability of other drugs (especially lenalidomide and clozapine) or the influence of stress associated with the progression of MM. Symptoms improvement may also be due to adjustments in Parkinson medication. However, the increased PD severity following ixazomib initiation and the positive dechallenge evidenced by the remarkable recovery of the patient's general condition after its withdrawal, reinforce the causality assessment of this AE to the PI. Furthermore, while no such observations were found in the literature, we identified two additional cases of PD progression associated with the use of bortezomib, another PI, in VigiBase®, the WHO's global database of individual safety reports.

Finally, we propose the hypothesis that ixazomib, and more generally PIs, may have a role in the evolution of pre-existing PD. This scenario does not compromise the benefit/risk balance of ixazomib in the treatment of MM, which remains an indispensable medication even in parkinsonian patients. However, in this population, the initiation of PI therapy may accentuate a pre-existing clinical imbalance: thus, we are convinced that neurologists will have a prominent role in the follow-up of parkinsonian patients with MM, in close collaboration with hematologists.

REFERENCES

[1] Ciechanover A, Kwon YT (2015) Degradation of misfolded proteins in neurodegenerative diseases: Therapeutic targets and strategies. *Exp Mol Med* **47**, e147.

[2] McNaught KS, Jenner P (2001) Proteasomal function is impaired in substantia nigra in Parkinson's disease. *Neurosci Lett* **297**, 191–194.

[3] McNaught KSP, Mytilineou C, Jnobaptiste R, Yabut J, Shashidharan P, Jennert P, Olanow CW (2002) Impairment of the ubiquitin-proteasome system causes dopaminergic cell death and inclusion body formation in ventral mesencephalic cultures. *J Neurochem* **81**, 301–306.

[4] McNaught KSP, Björklund LM, Belizaire R, Isacson O, Jenner P, Olanow CW (2002) Proteasome inhibition causes nigral degeneration with inclusion bodies in rats. *Neuroreport* **13**, 1437–1441.

[5] Fornai F, Lenzi P, Gesi M, Ferrucci M, Lazzeri G, Busceti CL, Ruffoli R, Soldani P, Ruggieri S, Alessandrí MG, Paparelli A (2003) Fine structure and biochemical mechanisms underlying nigrostriatal inclusions and cell death after proteasome inhibition. *J Neurosci* **23**, 8955–8966.

[6] Kordower JH, Kanaan NM, Chu Y, Suresh Babu R, Stansell J, Terpstra BT, Sortwell CE, Steece-Collier K, Collier TJ (2006) Failure of proteasome inhibitor administration to provide a model of Parkinson's disease in rats and monkeys. *Ann Neurol* **60**, 264–268.

[7] Huehnchen P, Springer A, Kern J, Kopp U, Kohler S, Alexander T, Hiepe F, Meisel A, Boehmerle W, Endres M (2020) Bortezomib at therapeutic doses poorly passes the blood-brain barrier and does not impair cognition. *Brain Commun* **2**, fcaa021.

[8] Dao Trong P, Jungwirth G, Yu T, Pusch S, Unterberg A, Herold-Mende C, Warta R (2020) Large-scale drug screening in patient-derived IDHmut glioma stem cells identifies several efficient drugs among FDA-approved antineoplastic agents. *Cells* **9**, 1389.

[9] Quillin J, Patel R, Herzberg E, Alton D, Bikzhanova G, Geisler L, Olson J (2020) A phase 0 analysis of ixazomib in patients with glioblastoma. *Mol Clin Oncol* **13**, 1–1.

[10] Gray MT, Woulfe JM (2015) Striatal blood-brain barrier permeability in Parkinson's disease. *J Cereb Blood Flow Metab* **35**, 747–750.

[11] Jenner P, Olanow CW (1998) Understanding cell death in Parkinson's disease. *Ann Neurol* **44**, S72-84.