Accepted Manuscript

Title: Safinamide: a new hope for Parkinson's disease?

Authors: Fábio G. Teixeira, Miguel F. Gago, Paulo Marques, Pedro Silva Moreira, Ricardo Magalhães, Nuno Sousa, António J. Salgado

PII: S1359-6446(17)30426-9
DOI: https://doi.org/10.1016/j.drudis.2018.01.033
Reference: DRUDIS 2166

To appear in:

Received date: 1-9-2017
Revised date: 21-12-2017
Accepted date: 9-1-2018

Please cite this article as: Teixeira, Fábio G., Gago, Miguel F., Marques, Paulo, Moreira, Pedro Silva, Magalhães, Ricardo, Sousa, Nuno, Salgado, António J., Safinamide: a new hope for Parkinson's disease?.Drug Discovery Today https://doi.org/10.1016/j.drudis.2018.01.033

Safinamide: a new hope for Parkinson's disease?

Fábio G. Teixeira[1,2,*], Miguel F. Gago[1,2,3,*], Paulo Marques[1,2], Pedro Silva Moreira[1,2], Ricardo Magalhães[1,2], Nuno Sousa[1,2], and António J. Salgado[1,2]

[1]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal
[2]ICVS/3Bs – PT Government Associate Laboratory, Braga/Guimarães, Portugal
[3]Neurology Department, Hospital da Senhora da Oliveira, EPE, Guimarães, Portugal
*These authors contribute equally to this work.
Corresponding author: Teixeira F. (fabioteixeira@med.uminho.pt)
Keywords: Parkinson's disease; safinamide; neuroprotection; disease-modifying strategy.
Teaser: Safinamide is presented as a promising Parkinson's disease (PD) drug, which in addition to modulating dopaminergic transmission (through MAO-B inhibition), could have neuroprotective and disease-modifying effects, by preventing the formation of toxins and/or free radicals and inhibiting calcium channels and glutamate release.

Research Highlights

1. Safinamide is a novel MAO-B inhibitor and a Calcium channel blocker drug.
2. Safinamide improves OFF-time and ON-time with no-troublesome dyskinesia's in PD.
3. In PD rat models, blocking of calcium channels by safinamide, has been linked to neuroprotection.

The loss of dopaminergic neurons (DAn) and reduced dopamine (DA) production underlies the reasoning behind the gold standard treatment for Parkinson's disease (PD) using levodopa (L-DOPA). Recently licensed by the European Medicine Agency (EMA) and US Food and Drug Administration (FDA), safinamide [a monoamine oxidase B (MOA-B) inhibitor] is an alternative to L-DOPA; as we discuss here, it enhances dopaminergic transmission with decreased secondary effects compared with L-DOPA. In addition, nondopaminergic actions (neuroprotective effects) have been reported, with safinamide inhibiting glutamate release and sodium/calcium channels, reducing the excitotoxic input to dopaminergic neuronal death. Effects of safinamide have been correlated with the amelioration of non-motor symptoms (NMS), although these remain under discussion. Overall, safinamide can be considered to have potential antidyskinetic and neuroprotective effects and future trials and/or studies should be performed to provide further evidence for its potential as an anti-PD drug.

Introduction

PD is the second most-common chronic neurodegenerative disorder worldwide, characterized by the degeneration of DAn and deficient DA production in the nigrostriatal pathway [1,2]. Clinically, it is recognized by a core of motor symptoms, including bradykinesia, rigidity, tremor, and postural instability, which are used to establish its diagnosis [3]. Although it has been postulated that PD itself is not a primary cause of death, studies have proposed that death might occur as a secondary result of the progression of PD motor dysfunctions, for example, as a result of falls in patients with advanced-stage PD [4–6]. In addition, the development of NMS, such as sleep disturbances, depression, olfactory dysfunction, and behavioral and/or cognitive problems, has also been linked with functional disabilities [7–10]. Therefore, management strategies have been preferred, involving the diagnosis and evaluation of the condition of the patient, followed by the development and application of personalized strategies, aiming to ameliorate the patient's quality of life [11–13]. Still, as recently reviewed by Onofrj and colleagues [14], satisfactory approaches to relieve the symptoms, or slow down the progression, of PD by protecting DAn from premature death remain lacking. Promising results have been experimentally and clinically obtained with several drugs, yet the challenge remains to show a clinical proof of arrest of delay of DAn loss in PD.

The current symptomatic treatment relies on the use of pharmacological strategies, such as L-DOPA, which remains the gold standard treatment), DA agonists (DAAs; e.g., ropinirole or pramipexole), and MAO-B (e.g., rasagiline or selegiline) and catechol-*O*-methyltransferase (COMT; e.g., entacapone or tolcapone) inhibitors, to compensate for the deficits of DA in the nigrostriatal dopaminergic pathway [15–17] (Figure 1). Although efficacious, they have several adverse effects (AEs), which can limit their use over long periods of time [14]. In addition, although surgical interventions, such as deep brain stimulation (DBS), have also been used as strategies