

## Commentary

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# Nilotinib – Differentiating the Hope from the Hype

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**Abstract.** We discuss a report in the current issue on clinical and biochemical findings from a safety trial using the cAbl tyrosine kinase inhibitor Nilotinib (150 mg or 300 mg given daily for 24 weeks) in a small group of patients with either advanced Parkinson's disease or Dementia with Lewy Bodies. Despite some side effects (one serious), the authors claim that Nilotinib, which is normally used at much higher doses for treating leukemia, is safe and tolerated. Furthermore, they report a possible benefit on motor and cognitive outcomes. We debate the safety of Nilotinib and the reported efficacy signals. We emphasize that due to the small sample size, and lack of a control group, it is impossible to rule out a placebo effect. We briefly discuss a range of aspects surrounding the current and possible future use of this cAbl inhibitor in patients with alpha-synucleinopathy, and what must now be done to obtain definitive information about its safety and efficacy in this population of patients.

Keywords: Drug repositioning, neuroprotection, Nilotinib

## MAIN TEXT

The paper by Pagan et al. [1], published in this issue, was originally reported as a brief abstract at the Society for Neuroscience in Chicago in October 2015. The world's press and television news channels gave high coverage to this abstract, with some of the study patients shown worldwide in videos that focused on their purported clinical improvements. Many neurology experts felt that the global media exposure which followed the initial announcement of the results was an object lesson on how not to report a small clinical trial that has no placebo control. While patients suffering from Parkinson's disease (PD) and related alpha-synucleinopathies continue to feel an

urgent need for better therapies, this news story inappropriately fed their hope with hype. Following the global news story, the authors of this editorial were made aware that the off label use of Nilotinib in PD escalated. It is currently conservatively estimated that >200 PD patients across many countries are taking Nilotinib. Not only is Nilotinib extremely expensive, but it carries a black box warning at its leukemia doses and its safety at low doses in PD and has only been studied in the 12 patients suffering from PD or Dementia with Lewy Bodies (DLB) in the current trial. Unfortunately some side effects were noted amongst the 12 patients within the 6 month study period [1]. Therefore, definitive proof is now required, one way or the other and as quickly as possible, as to whether Nilotinib is safe in PD and DLB, and whether the hints of possible improvement are apparent in a larger group of patients when compared to placebo.

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Nilotinib is a brain penetrant tyrosine kinase cAbl inhibitor used for the treatment of chronic myeloid leukemia. It is approved for this condition at doses up to 1200 mg daily (EU) and up to 800 mg daily (USA) where it carries a black box warning for QT interval prolongation; sudden cardiac death has been reported in patients taking Nilotinib, and it can also cause myelosuppression. One patient of the twelve in the study had a serious cardiac event during the 6 month duration of the study, although the investigators felt it was partially related to an initial electrocardiogram (ECG) screening failure [1]. Two other patients in the study had QT prolongation. Emerging ECG abnormalities such as these occur in a considerable number of leukemia patients taking Nilotinib at the oncology doses [2, 3], and these can lead to fatal cardiac events. Taken together, these facts indicate a study reporting on the safety of Nilotinib in a small patient cohort during 6 months should be interpreted with caution. Pagan and collaborators had selected a group of advanced and relatively frail PD and DLB patients for their trial. Why this patient group was targeted is not clear, and indeed in the listing for this trial on the clinicaltrials.gov website it specifies that patients would be at Hoehn and Yahr stage <2 as an inclusion criterion [4]. Selecting these later stage patients generated a large number of screen failures but, paradoxically, may have helpfully given a tougher test of the safety and tolerability issues surrounding the use of low dose Nilotinib.

Preclinical studies had strongly suggested that cAbl inhibition by Nilotinib might interfere with pathogenic mechanisms that are relevant to PD and DLB and therefore could potentially modify the course of these diseases [5–16]. The biochemical basis for this hypothesis has multiple threads. cAbl is substantially activated (by phosphorylation) in brains of PD patients, as well as in MPTP and in alpha-synuclein preclinical models of PD. cAbl phosphorylation appears to be a consequence of mitochondrial dysfunction [17]. cAbl activation by phosphorylation is highly indicative of increased oxidative stress, and in dopaminergic neurons this is thought to contribute to the pathogenesis of PD. cAbl inhibition by Nilotinib has been shown both to protect against MPTP damage, and to reduce intracellular levels of alpha-synuclein by autophagic degradation. Also, given it is widely reported that Parkin function is compromised in sporadic PD, the observation that Nilotinib can also act as a Parkin agonist by preventing its phosphorylation also represents yet another important putative mode of action. By inhibiting the

phosphorylation of Parkin, Nilotinib may well offer protection against alpha-synuclein toxicity through a cytoprotective process that would be consistent with observations that overexpression of Parkin protects against the effects of  $\alpha$ -synuclein-induced toxicity [18]. In addition, there is evidence that some parallel Parkin-independent benefits of cAbl inhibition may also be clinically relevant [5].

In 2012, and again in 2013, an international committee of PD experts discussed in great detail the preclinical evidence for taking Nilotinib into a clinical trial in PD patients [19]. At the time, it was questioned whether a low, and potentially safer, dose of Nilotinib might be appropriate to test in PD. The conclusion was that, while the biological target (cAbl inhibition) is highly relevant in PD, given potential safety issues with Nilotinib it was not given top priority as a drug repurposing candidate [19]. Thus, the study reported in this issue became the first in-human testing of Nilotinib in patients with alpha-synucleinopathies. The daily doses of 150 mg and 300 mg of Nilotinib produced some adverse events, but helpfully opened the door on a lower dose range that might be appropriate to consider in the future definitive trial(s) of Nilotinib. The choice of these doses was not arbitrary; preclinical research would suggest efficacy in alpha-synuclein models at even lower doses than this, but Nilotinib is only available in capsules of 150 mg minimum size and it is impractical to divide these. Future PD trials involving Nilotinib will have to determine if this is an optimal dose in PD and DLB.

The value of measuring cerebrospinal fluid (CSF) levels of the dopamine metabolite homovanillic acid (HVA), as reported in this study, is unclear. Prior studies suggest that HVA levels in CSF vary greatly between patients at similar disease stages and track poorly with disease progression. Similarly, CSF levels of S100B and neuron-specific enolase (NSE), also used in the current study and which correlate with damage to neurons and glia, respectively, in stroke and in spinal & intracranial injuries, are not validated biomarkers for PD and DLB [20–22]. Finally, the changes or lack of changes in alpha-synuclein measures in the study are difficult to interpret given our current understanding of the different molecular forms of this protein and their relation to disease progression [23]. In short, substantial caution should be exercised when interpreting changes in CSF levels of HVA, S100B, NSE and alpha-synuclein.

So, what can we take from this small but innovative study? Given the publicity surrounding the trial

when it was initially announced, it is important (as published in this issue) to have the full results of this trial made widely available to the scientific community. But it is impossible to extract definitive safety and valid efficacy signals from a small open-label unblinded study (lacking a placebo control) in PD and DLB. This is especially poignant as even a placebo effect can be very large over the time period used in this study, particularly in advanced PD [24], and can even induce biochemical changes in the dopamine system [25, 26].

Perhaps the most important conclusions to be drawn from this study are that:

- 1) A future double-blinded study is definitely warranted. Given the importance of the next clinical study evaluating Nilotinib, we encourage the involvement of leaders in PD clinical trial design and the use of well-established multi-site clinical study protocols. All raw data from any future study should be made widely available to the research and patient communities to allow detailed evaluation without any restrictions.
- 2) The current study also helpfully gives us a first clue as to what dose(s) of Nilotinib might offer a sensible balance between safety concerns and the search for efficacy. As future definitive trials are designed, there is a need further to consider the most appropriate dose and also to determine which PD patients are most likely to benefit from this type of therapeutic approach.

In conclusion, the current paper by Pagan et al. substantiates a new direction, addressing a molecular pathway not previously targeted in a clinical trial in this context, for potential disease modification in PD and DLB. However, this study is just a first step and a major concerted effort is needed to determine whether there is still hope that can match the hype for Nilotinib in alpha-synucleinopathies.

## DISCLOSURES

RW None.

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TS None.

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