Cardiovascular Safety of Nilotinib in Alzheimer's Disease

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We read with interest the article by Turner et al on the use of Nilotinib for the treatment of mild-to-moderate Alzheimer's disease (AD)[1]. In this phase 2 trial, Nilotinib was found to reduce central nervous system amyloid burden, cerebrospinal fluid Aβ40 and Aβ42, hippocampal volume loss and phospho-tau-181 associated with AD at 12 months follow-up[1]. The authors reported the cardiac safety profile of Nilotinib, and demonstrated no QTc prolongation which can be associated with risk of sudden cardiac death[1].

We caution that the risk and incidence of cardiovascular events (CVE) while on Nilotinib may not have been fully accounted in this report. In the ENESTnd trial which investigated the efficacy and safety of Nilotinib in the treatment of chronic myeloid leukaemia, there was a dose- and duration-dependent association between Nilotinib and CVE, defined as a composite of ischaemic heart disease, ischaemic cerebrovascular events and peripheral vascular disease[2,3]. This trial initially described no CVE at 12 months[2], yet the 5-year CVE incidence was 7.5% in patients receiving Nilotinib 300mg twice daily and 13.4% with 400mg twice daily[3]. Patients' baseline Framingham cardiovascular risk score was found to be predictive for CVE[3]. Furthermore, Nilotinib was found to significantly increase low-density-lipoprotein cholesterol and glycated haemoglobin to above clinical thresholds[3].

Patients receiving Nilotinib in the study by Turner et. al. had a mean age of 72 years and were predominantly female. Baseline cardiovascular risk factors, scores and prevalence of known CVE prior to trial entry were not reported. Based on mean age of participants, it may be reasonable to assume a significant proportion of trial population may have moderate-to-high cardiovascular risk.

While the daily dose and duration of Nilotinib used in this trial (150mg for 6 months followed by 300mg for 6 months) were lower than that in ENESTnd trial, cardiovascular risk upon prolonged use in moderate/high cardiovascular risk patients remains unknown and should be considered in future trials. Finally, the authors suggested that these doses may be non-cardiotoxic based on previously reported lack of plasma Abelson inhibition using similarly low doses of Nilotinib[1]. It is worth noting that Nilotinib toxicity may result from both on-target and off-target kinase inhibition, hence may not be predicted by plasma Abelson inhibition alone[4].

In summary, low dose Nilotinib may be a promising treatment for AD, however assessment of cardiovascular risk and detailed description of acute and long term CVE should be considered in the future phase 3 trials.

Potential Conflicts of Interest

J.S. has received honoraria and served on advisory committee for Novartis, which manufactures Nilotinib that is discussed in this letter. J.S. has also received honoraria from Bristol Myer Squibb, which manufactures the tyrosine kinase inhibitor Dasatinib, and Specialised Therapeutics Australia, which manufactures the tyrosine kinase inhibitor Ponatinib.

B.K. has received honoraria and served on advisory committee for Novartis, which manufactures Nilotinib that is discussed in this letter. B.K. has also received honoraria from Bristol Myer Squibb, which manufactures the tyrosine kinase inhibitor Dasatinib, and Specialised Therapeutics Australia, which manufactures the tyrosine kinase inhibitor Ponatinib.

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The remaining authors have nothing to disclose.

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