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COMMENTARY

Comment on: "A Single Dose-Escalation Study to Evaluate the Safety and Pharmacokinetics of Orally Administered Des-aspartate Angiotensin I in Healthy Subjects"

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Des-aspartate angiotensin I (DAA-I) is a short-acting peptide molecule comprising nine amino acids, whose main role is to block angiotensin II via agonistic activity on the angiotensin AT1 receptor [1]. Lee et al. recently reported the safety, tolerability and pharmacokinetics of DAA-1 in healthy subjects who received single escalating doses of DAA-1 in an extemporaneously prepared oral formulation [2]. This study in particular assumes importance primarily because hitherto no such human clinical pharmacology data pertaining to DAA-1 have been published [2].

The safety and tolerability data gathered in this study showed no inadvertent effects and/or adverse events associated with DAA-1. However, the lack of differentiation in the single-dose pharmacokinetics of the examined three active doses in relation to placebo [2] poses a challenge in developing a cohesive clinical development plan for the advancement of DAA-1. Because of the rapid degradation of DAA-1, it was not expected that the first exogenous dose of DAA-1 at 0.08 mg/kg would show appreciable plasma levels in the human subjects [2]. Interestingly, the other two higher doses of DAA-1 (i.e., 0.7 and 1.5 mg/kg) appeared to be equally rapidly metabolized, resulting in no appreciable systemic levels of DAA-1 [2]. Perhaps one limitation of the study, as pointed out by the authors, was related to the frequency of pharmacokinetic sample time

collection; perhaps, the inclusion of early time points after oral administration in a 2- to 3-min interval for the first 30 min after dosing may have provided a better opportunity to pick the transient elevated levels of DAA-1 in the systemic circulation.

On one hand, the development of exogenous DAA-1 is an exciting prospect from a clinical perspective, given the wide range of therapeutic interventions it could be applied to [3–5]. On the other hand, it represents an insurmountable challenge to develop DAA-1 from a clinical development perspective. The intent of this note is to provide some thoughts on developing DAA-1 as a potential drug candidate.

Peptide drug delivery via the oral route is a daunting task owing to instability of peptides in the local environment of the gastrointestinal tract [6, 7]. Therefore, the lack of any DAA-1 levels above and beyond the baseline levels in the systemic circulation observed in this study is testament to the extent of the problem that needs to be overcome. The occasional spikes in the mean systemic levels of DAA-1, especially observed in later time points, were merely a reflection of the variability of the endogenously occurring DAA-1, rather than absorption from the administered DAA-1 doses [2]. In addition, none of the observed parameters such as vital signs, aldosterone levels, liver function biomarkers and renal function biomarkers showed any differences to discern a clear DAA-1 effect versus placebo effect. Overall, the single-dose data for DAA-1, although suggestive of an excellent safety/tolerability profile, have failed to provide any clues that would aid the developmental aspects of DAA-1.

The key question is how would one design a multiple-dose escalation study of DAA-1 in humans to obtain meaningful data. What would be the starting dose and the

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frequency of multiple-dosing regimens? What would be the cap, if any, on the highest dose of DAA-1 to be administered in the study? These questions are rather difficult to answer, especially if the orally administered DAA-1 is rapidly metabolized and/or de-stabilized in the gastrointestinal tract.

Therefore, as a drug developer it may become important to find innovative ways to tackle such tricky issues. Prior to investment of resources for the whole clinical development program, it may be vital to ascertain the proof of concept of the desired effect of DAA-1. Although the authors' suggestion of using circulatory prostaglandin entities such as prostaglandin E2 (PGE_2) or prostaglandin I2 (PGI_2) as target biomarkers may be potentially considered [2], it would still fall short of the much desired confirmatory pharmacological activity of DAA-1 for allocation of resources for full-scale drug development. Hence, to better understand the pharmacodynamics of exogenous DAA-1 and obtain proof of concept of its pharmacological activity, one might consider DAA-1 given in a combination regimen with another agent, using an established surrogate marker such as blood pressure.

In order to establish the proof of concept of DAA-1, two other companion classes of drugs, namely, angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), may be potentially considered. The design may involve the addition of DAA-1 to either an ACEI- or ARB-stabilized regimen that may help in the reduction of the stable doses of either ACEI or ARB companion drug in the relevant patient population. Perhaps, the highest dose of DAA-1 tested in the single-dose escalating study (i.e., 1.5 mg/kg) could potentially be added to the stable dose regimen of either ACEI or ARB in a twice daily (bid) dosing regimen of DAA-1 with concomitant reduction in the respective dose of either the ACEI or ARB. Alternatively another design may be to randomize a group of patients on stable doses of either ACEI or ARB to two experimental groups: one group would continue to be on the stable dose of either of the two drugs, while the other group would receive approximately 50% of the stable dose of either of the two drugs along with the highest tested dose of DAA-1 (bid regimen). Regardless of the design adopted, after a specific time period, the measurement of blood pressure as the surrogate would establish the proof of concept of DAA-1.

Overall, development of peptide drugs via the oral route represents a considerable challenge as manifested for other drugs, most notably insulin [8]. Hence, as a first step it may be crucial to understand the proof of concept whether such a route (i.e., oral) is amenable for DAA-1 and what may be the minimal dose requirement/regimen to achieve the proof of concept.

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