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LETTER TO THE EDITOR

Comment on: "Effect of Age and Renal Function on Idarucizumab Pharmacokinetics and Idarucizumab-Mediated Reversal of Dabigatran Anticoagulant Activity in a Randomized, Double-Blind, Crossover Phase Ib Study"

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This manuscript has incorrectly been tagged as a '**Commentary**'. It should be tagged as a '**Letter to the Editor**' We read with interest the study by Glund et al., which highlighted important pharmacological aspects of idarucizumab in the elderly and those with mild to moderate renal impairment [1]. This is pertinent as age ≥75 years and the presence of chronic kidney disease are independent risk factors for major bleeding with dabigatran treatment [2, 3].

We are interested in the unbound plasma dabigatran concentration and anticoagulation intensity (as measured by clotting assays) beyond the initial 24-h period. On visual inspection of Figs. 2–6, which illustrate the effect of idarucizumab during the initial 24-h period, there is a trend for the unbound dabigatran concentrations to rise in the second half of the treatment period. Pharmacodynamically, this is reflected by the changes in activated partial thromboplastin time (aPTT; Figs. 2c, 3c, 4c, 5c) and activated clotting time (ACT; electronic supplementary Fig. 4). Although the rise in unbound dabigatran concentrations did not reach the threshold set by the authors for concentrations associated with a significant anticoagulant effect (20 ng/mL), the trajectory of the data suggest that this threshold could eventually be reached. It would be informative to clarify this; we note the authors collected data up to 120 h following idarucizumab administration.

The duration of laboratory monitoring post-administration of reversal agents such as idarucizumab is worth further consideration. We note that the REVERSE-AD study monitored patients for 24 h [4]; however, there are clinical scenarios where it is crucial that anticoagulation remains reversed beyond this time period, such as intracranial haemorrhage. It is therefore important to establish the duration of the anticoagulation reversal achieved by idarucizumab, particularly in patients with moderate renal impairment, where the renal clearance of dabigatran is reduced. Recent case reports suggest a rebound phenomenon, where coagulation assays initially normalised by the administration of idarucizumab subsequently increased without readministration of dabigatran [5–7]. This was associated with renal failure [5], significantly elevated dabigatran concentrations secondary to overdose [6], and delayed gastrointestinal absorption [7]. Do the authors have information about whether dabigatran concentrations and coagulation assays should be monitored beyond 24 h, and whether a second dose of idarucizumab should be administered in case of recovery of dabigatran-mediated anticoagulation?

Furthermore, we seek clarification from the authors regarding the apparent correlation between idarucizumab dose and fraction of idarucizumab dose excreted in the urine between 0 and 6 h post-infusion (fe_6; shown in Table 2). This is notable when comparing idarucizumab 1 and 5 g doses, but less so between 2.5 and 5 g. The authors state that "in all treatment groups and with all idarucizumab doses, the largest proportion of idarucizumab excreted in urine was between 0 and 6 h post-infusion, with negligible amounts present in subsequent collection intervals". These observations suggest

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that renal clearance of idarucizumab makes a greater proportional contribution to total clearance at higher concentrations. This is consistent with previous reports suggesting that renal catabolism of idarucizumab is saturated at higher concentrations, and hence a greater fraction of idarucizumab is excreted unchanged in urine at higher doses [8, 9]; however, the contribution of non-renal catabolism is unclear.

Finally, we note that the creatinine clearance (mean ± standard deviation) in the moderate renal impairment group (defined as creatinine clearance 30–60 mL/min) is reported as 58.7 ± 10.2 mL/min (Table 1), which implies that there were subjects in the moderate renal impairment group whose creatinine clearance was >60 mL/min. Is this a typographic error or is there another explanation for this inconsistency?

Compliance with Ethical Standards

Conflict of interest Kirollos S. Kamel, Paul K. L. Chin, Matthew P. Doogue and Murray L. Barclay declare that they have no conflicts of interest.

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