SIMBA trial: reasons for failure despite sound principle

We read with interest the recent multicentre randomised controlled trial by Guilabert *et al*.[1] The authors tested the efficacy of simvastatin or placebo in patients with recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) in reducing the recurrence of pancreatitis. Statins have pleiotropic anti-inflammatory properties. Backed with robust observational data of a lower probability of having pancreatitis with simvastatin (adjusted risk ratio 0.626, 95% CI 0.588 to 0.668) in 4 million people by Wu *et al*, the drug held a firm promise to deliver in the simvastatin for the prevention of recurrent pancreatitis (SIMBA) trial.[2–4] However, the trial was terminated after the first interim analysis because there was no significant difference in the recurrence of pancreatitis between the groups, both in intention-to-treat and per-protocol analyses (46.2% vs 44.4% and 35.5% and 41.9%, respectively). We believe that a few comments are warranted to put the results of the SIMBA trial in perspective.

First, the success and failure of therapy is highly dependent on the study population and outcome assessment methods. The study population included both RAP (n=25 in the simvastatin group and n=24 in the placebo group) and CP with a median of two episodes of pancreatitis in the last 12 months. Of the patients in the placebo arm, 56% did not have recurrence of pancreatitis over the next 12 months. Probably, this preintervention event density was too low to expect a meaningful reduction with therapy. In addition to the recurrence and time to recurrence of pancreatitis, it is important to know whether the pancreatitis event was milder with a shorter duration and lesser requirement of analgesic drugs in the simvastatin arm. These parameters can be assessed by outcome measures such as number of painful days or number of workdays lost to disease or pain scores such as Izbicki's score and AIIMS (All India Institute of Medical Sciences) pain score.[5–7] These outcome measures might have provided additional information regarding the potential efficacy of simvastatin.

Second, alcohol and smoking are well-established risk factors of CP and a dose–response relationship has also been observed.[8 9] In this study, 27.05% and 35.29% of the study population were people who actively smoke or consumed alcohol actively (table 2s). Although the randomisation was stratified for aetiology of pancreatitis (alcohol vs others), the continued exposure to these risk factors could be a confounder. This is better highlighted by the fact that even in alcohol-related pancreatitis, there were no flares at the end of 1 year in the statin group in people who do not drink alcohol versus five in the placebo group, while there were seven flares in the statin group versus four flares in the placebo group among people who drink alcohol (table 10s). No subgroup analysis is available to assess if there was a similar trend among people who actively smoke.

Third, the study provided exploratory data in favour of a higher occurrence of diabetes with simvastatin (4 vs 0). This is in contrast to the findings of an observational study[10] of 118 479 patients, where regular statin users had a 42% lower risk of developing diabetes as compared with non-users after an acute pancreatitis episode over a median of 3.5 years of follow-up. In the current study, six patients had diabetes at baseline in the CP group—four in the simvastatin and two in the placebo group. Diabetes developed in three patients in the simvastatin group and none in the placebo group over 12 months (table 6s). But a total of six patients had diabetes in the CP group at 12 months—five in the simvastatin and one in the placebo group (tables 3s and 4s). Thus, it appears that two patients in the simvastatin and one in the placebo group recovered from diabetes, which is a rare clinical occurrence.

At the end, we congratulate the authors for conducting this clinical trial, overcoming the difficulties of the COVID pandemic, slow recruitment and patient attrition, and providing further insight on how to conduct future trials in patients with RAP and CP. We feel the trial opens more research opportunities to re-evaluate this drug in a population of recurrent pancreatitis with high preintervention event density before concluding the futility of statins.

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