ABSTRACT

Atherosclerotic cardiovascular diseases remained as the top killer in Malaysia for the past ten years. Simvastatin is a medication that can effectively reduce LDL-C level. Clinicians and practicing pharmacists usually advise patients to take simvastatin in the evening or night, due to de novo biosynthesis of cholesterol is peaking at the midnight (00.00 – 03.00) as well as relatively short half-life of simvastatin. Despite that, adherence to simvastatin therapy is crucial for the best societal benefit (reduce premature death and disability secondary to cardiovascular incidence that may lead to a national productivity loss) as non-adherence to simvastatin therapy had been proven to increase cardiovascular morbidity and mortality. This was a randomized, prospective, multi-center, open-labeled, active comparator study with a primary objective of investigating the efficacy of simvastatin administered at different timing, which was after breakfast, after dinner or before bedtime, in term of percentage reduction of low-density lipoprotein cholesterol (LDL-C). In addition, the percentage changes of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) when simvastatin being administered at different timing were also being explored. Despite that, the study also investigated the effect of administration time of simvastatin on subjects' adherence in local setting as well as the incidence rate of statin associated muscle symptoms (SAMS) in local population newly started with simvastatin. Subjects for this study was recruited from four public health clinics in Kedah State, two public health clinics each in Perak State and Sarawak State, and one public health clinics each in Penang State and Sabah State. All subjects recruited were being randomized into three intervention arms (after breakfast, after dinner or before bedtime) during baseline visit (week 0). Follow up visits was schedule on week 8 and week 16. Percentage of LDL-C reduction was calculated and compared between three interventional arms. Adherence to simvastatin therapy was assessed by using 8-items Morisky Medication Adherence Scale (MMAS-8) as well as

incidence of suspected SAMS was recorded on both follow up visit. A total of 160 subjects were randomized and 147 of them were completed the study with a dropout rate of approximately 8%. Median LDL-C reduction of 33%, 38% and 45% was recorded for after breakfast, after dinner and before bedtime arms respectively at the end of the study. The Kruskal-Wallis test showed the difference of LDL-C reduction was very highly statistical significant ($p < 0.001$) among three arms. Pairwise post-hoc analyses using bonferroni-corrected Man-Whitney U test showed that LDL-C reduction for both after breakfast and after dinner arm was statistically significant as compare to after dinner arms. Statistically significant and greater reduction of TC was observed when simvastatin was taken in the later timing of the day (22%, 27%, 29% reduction for after breakfast, after dinner and before bedtime arms respectively). The effect of administration time of simvastatin on TG was inconsistent and approximately 10% to 30% reduction of was observed throughout the study. HDL-C was remained plateau throughout the study when simvastatin was administered on after dinner and before bedtime. However, HDL-C was found to consistently increase from baseline throughout the study when simvastatin was taken after breakfast. At the end of study, better adherence was observed in before bedtime arm as compare to its counterpart. Suspected SAMS was observed in approximately 4% of the study sample and administration time of statins had no significant effect on suspected incidence of SAMS. In conclusion, simvastatin should be taken before bedtime as maximal reduction of LDL-C and TC level as well as better adherence was observed when simvastatin was being taken before bedtime.