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Up-To-Date Pharmacological Topics on the Medication of Statin and Inclisiran

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Abstract

Up-to-date pharmacological topics for inclisiran and statin for dyslipidemia are described. The efficacy of inclisiran has been reported for reduction of LDL-C values. Inclisiran has been involved in gene silencing, which brings selective inhibition of a protein by targeting its mRNA. For RCTs of inclisiran, ORION 10/11 studies were conducted, where inclisiran and control groups were followed 1.5 years. LDL-C reduced in 53.8%/49.2%. RCTs of 19 meta-analyses showed whether statins will prolong life and its degree. As a result, statin can delay onset of events compared to placebo for cardiovascular death 9.3 days, myocardial infarction 18 days, and stroke 6.1 days.

Keywords: Inclisrian statin dyslipidemia; LDL-C; Atherosclerotic cardiovascular disease (ASCVD)

Commentary Article

In actual clinical practice, metabolic syndrome is increasing worldwide. The underlying problem would be the presence of dyslipidemia. Concerning dyslipidemia, current topics can include inclisiran and other agents [1,2]. This paper introduces the latest reports and developments on dyslipidemia. As a new agent for dyslipidemia, the efficacy of inclisiran has been reported. It is used for patients associated with high LDL-C. For large studies, the ORION-10 and the ORION-11 tests were conducted. The former was intended for patients with atherosclerotic cardiovascular disease (ASCVD). The latter is intended for patients with ASCVD or at risk comparable to ASCVD. Both protocols were RCTs comparing two groups of inclisiran (284 mg) and placebo for 1.5 years. Regarding the protocols, inclisiran was given by subcutaneous injection on the 1st and 90th days, and every 6 months thereafter. For the evaluation, the changed ratio in LDL-C was measured as the primary outcome. As a result, the LDL-C after 1.5 years was found to decrease by 53.8% in the former and 49.2% in the latter. All data were significantly different from placebo ($p < 0.001$). In the light of adverse effects, some pain and swelling at the injection site were more common in the inclisiran group [2].

Inclisiran has been involved in gene silencing, which brings selective inhibition of a protein by targeting its mRNA [1]. As to the safety of inclisiran, pre-specified analysis of ORION-1 was conducted, especially from hematological parameters [3]. Inclisiran is a siRNAs (small interfering RNA molecules) directed against PCSK9. It is indeed that its benefit is with large efficacy for lowering LDL-C, but weak point is expensive. Then, its use has been often discontinued, that may leave the patients keeping higher cardiovascular risk [4]. Inclisiran is an interfering RNA targeting PCSK9 (proprotein convertase subtilisin-kexin type 9). As to inclisiran, pharmacodynamic property was investigated for subjects with renal impairment and normal function [5]. As a result, both groups showed similar data, indicating no necessity of dose adjustments for renal function. Inclisiran has an unknown effect on cardiovascular prognosis at this stage [2]. Therefore, we look forward to the accumulation of evidence in the future.

Conventionally, n-3 unsaturated fatty acids have been reported to have benefits for the cardiovascular system. Several systematic review meta-analyses in n-3 USFA have been reported. A recent review included a double-blind RCT 17 study (n=83,617) with a follow-up period of ≥1 year. When the dose of n-3 unsaturated fatty acids became higher, the benefits became greater. In other words, the risk reduction of cardiovascular disease was not

revealed at 1 g or less per day. Second, at 2 g daily, the rate of cardiac death was significantly reduced, with a relative risk (RR) 0.55. Furthermore, when 3 g or more was administered daily, a significant reduction in risk was observed. Regarding the detailed RR, the remarkable effects were shown: cardiac death 0.82, sudden death 0.70, and stroke 0.74 [6].

For elderly people with frailty, a systematic review was conducted on the cardiovascular prognosis of statins. Of these, 6 cohort studies were included and RCTs meeting the acceptance criteria were not included. In addition, the results for cardiovascular events and the effects on primary prevention were not included. This included a study of the secondary prophylaxis population, which showed a reduced risk of death as HR 0.28 [7].

There is an ASPREE (Aspirin in Reducing Events in the Elderly) study that investigated the efficacy of statins in healthy elderly people. The results of this secondary analysis have recently been reported. ASPREE has been an RCT that examines the effect of aspirin on healthy life expectancy. The subjects were 19,114 aged 65 and over, of which 18,096 aged 70 and over (median 74.2 years, 56.0% female) were extracted in the secondary analysis. Among them, two groups were compared, between who were taking statins at the beginning of the study and those who were not. The investigated factors were survival condition without disability (combined outcomes of total mortality, dementia, and persistent physical dysfunction). Follow-up of 4.7 years in median found no significant difference between statin use and unimpaired survival as Hazard ratio (HR) 0.92. Thus, secondary analysis of RCTs showed little benefit of statins on healthy life expectancy [8]. Judging from this, the effects of statins on the general elderly will not necessarily be significant. There is a cohort study investigating statin treatment in the elderly for primary prevention of cardiovascular disease. Among them, the subjects were 326 thousand US veterans aged 75 and over. The average age was 81.1 years, 97% male and 91% Caucasian, with an average follow-up of 6.8 years. As a result, cardiovascular deaths per 1000 man-years were 22.6 for statin users and 25.7 for non-users. Corrected by propensity score matching, HR was 0.75 total mortality, 0.80 cardiovascular mortality, and 0.92 arteriosclerotic cardiovascular event. All of them were found to be significantly lower in statin users [9]. The results of RCTs analyzed the extent to which statins could prolong life, associated with the publication of 19 meta-analysis. The degree of delayed onset of events compared to placebo showed cardiovascular death 9.3 days, non-cardiovascular death 1.5 days, myocardial infarction 18 days, and for stroke 6.1 days [10].

Various factors were investigated that affect cardiac statins for medication adherence. A review was conducted in a systematic review associated with the summary reported. From detail examination of nine reviews, factors with positive effects on medication adherence were found to be high social/economic status, high education level, and age of middle-aged people. On the other hand, there were many factors related to the decrease in medication adherence. They include older, younger, female subjects, lower economic and social levels, higher out-of-pocket costs, new statin users as medication history, dosage/dose complexity, and experience of reverse effects. Psychologically, distrust of medical care and lack of realization of clinical effects were included, and lifestyle habits included daily drinking and smoking [11].

Conflicts of Interest

The author declares that they have no conflicts of interest.

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