LDL-cholesterol decrease by anti-PCSK9 monoclonal antibodies: systematic review, meta-analysis and meta-regression of randomized controlled trials

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Background: PCSK9 antibodies are novel potent and expansive lipid lowering agents that demonstrated clinical benefit in high risk patients. We hypothesized that optimization of dose and administration schedule, ideally adapted to the target population, could reduce costs while maintaining the clinical benefit.

Objective: To explore the relationship between LDL-Cholesterol (LDL-C) decrease by anti-PCSK9 monoclonal antibodies and several covariates such as drug dose, administration schedule, baseline LDL-C, population and statins.

Methods: We performed systematic review, meta-analysis and meta-regression of randomized controlled trials that compared alirocumab or evolocumab to placebo or no treatment and reported LDL-C decrease, with a minimum follow-up of 12 weeks and with a sample size of 30 patients or more. Electronic searches of MEDLINE, EMBASE, CENTRAL and ClinicalTrials.gov from inception to March 2019. We evaluated the quality of included studies and extracted aggregate data. We used random effect models and multivariate multilevel meta-regression to explore factors influencing LDL-C decrease. All analyses were performed with R.

Results: From 1479 references identified and screened on title/abstract, the full texts of 72 articles were screened. We included 32 studies (31 references.) Anti-PCSK9 mAbs decreased LDL-C by 53%, 95% CI (–56% to –50%), with no significant difference between the two drugs (p=0.07). In univariate meta-regressions, higher baseline LDL-C level, monthly administration, higher percentage of patients with high-dose statins were associated with a lower LDL-C decrease ($p<0.0001$, p=0.02 and p=0.006 respectively). Drug dose and population did not influence LDL-C decrease in univariate analysis, but with a significant statistical interaction between drug dose and administration schedule (p=0.03). In multivariate meta-regression, LDL-C decrease remained significantly and negatively influenced by baseline LDL-C level
($p<0.0001$) and the percentage of patients with high-dose statins (p=0.0009), and was significantly and positively influenced by drug dose ($p<0.0001$).

Conclusion: Alirocumab and evolocumab showed substantial LDL-C reductions in clinical trials, without significant differences in their biological efficacies. A higher baseline LDL-C, higher intensity of statin co-treatment and a lower dose seemed to negatively influence LDL-C decrease.