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CKJX839A1CN07 Study Results Abstract for Public Disclosure

Title

A Retrospective, Observational Database Study to Assess the Real-World Effectiveness of Inclisiran and PCSK9 mAbs in Chinese Hypercholesterolemia Adult Patients

Keywords

Inclisiran, Proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs), Hypercholesterolemia, Low density lipoprotein cholesterol (LDL-C) reduction, Adherence, Real-world, Meta-analysis

Rationale and background

Inclisiran is a long-acting, subcutaneously delivered, double-stranded small interfering ribonucleic acid (siRNA) targeting PCSK9 messenger RNA (mRNA), thereby lowering circulating LDL-C by inhibiting hepatic PCSK9 synthesis. It was approved by the Center for Drug Evaluation (CDE) on August 22, 2023, as an adjunct to dietary management for adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia. After an initial injection, a reinforcement dose is given at 3 months, followed by dosing every 6 months (two injections per year) (Novartis, 2023). Inclisiran shows prolonged LDL-C pharmacodynamic effects (Inclisiran Clinical Application Chinese Expert Advice Development Group, 2024).

The efficacy and safety of inclisiran have been demonstrated in multiple Phase III trials and Chinese real-world studies. In the global Phase III ORION-9, -10, and -11 trials, inclisiran produced placebo-adjusted LDL-C reductions of 48-52% at Day 510, with sustained time-adjusted average reductions of 44-54% over 18 months and adverse event rates comparable to control (Raal et al., 2020; Ray et al., 2020; Wright et al., 2021). In mainland China, the Phase III ORION-18 study reported a placebo-adjusted LDL-C reduction of 57.2% at Day 330 with good tolerability (Yong Huo et al., 2023). A prospective real-world study in the Boao Lecheng Medical Pilot Zone showed a mean LDL-C reduction of 40.2% at Day 90, increasing to 53.3% among patients with unchanged background therapy, with acceptable tolerability (Y Huo et al., 2023).

The results of real-world studies suggest better adherence and persistence with inclisiran than with PCSK9 mAbs. A Komodo Health database study reported higher 12-month adherence and persistence for inclisiran compared with alirocumab and evolocumab (Xiaoli Niu, et al.,2024). Similarly, a Metro Infusion Center database analysis showed high early discontinuation of PCSK9 mAbs, whereas most patients initiating inclisiran received subsequent doses, indicating sustained lipid-lowering therapy (Nihar R Desai, et al.,2023).

Real-world data on PCSK9-targeted lipid-lowering therapies in China remain limited, and deviations from labeled use may affect clinical value. This study aims to use three regional electronic health record (rEHR) databases to describe the real-world effectiveness of inclisiran and PCSK9 mAbs in Chinese adults with primary hypercholesterolemia or mixed dyslipidemia.

Research question and objectives

The purpose of this study is to describe the real-world effectiveness of inclisiran and PCSK9 mAbs among China adult patients with primary hypercholesterolemia or mixed dyslipidemia.

Primary objective

1. To describe the real-world effectiveness of the Inclisiran Cohort and PCSK9 mAbs Cohort respectively in reducing LDL-C from baseline to 6 months.

Secondary objectives

1. To describe the real-world effectiveness of the Inclisiran Cohort and PCSK9 mAbs Cohort respectively in reducing LDL-C from baseline to 12 months.
2. To describe the real-world adherence and persistence to inclisiran and PCSK9 mAbs in the Inclisiran Cohort and PCSK9 mAbs Cohort in China.
3. To describe the real-world effectiveness in changing lipid levels other than LDL-C from baseline to 12 months in the Inclisiran Cohort and PCSK9 mAbs Cohort.
4. To describe the patient characteristics of the patients in the Inclisiran Cohort and PCSK9 mAbs Cohort.
5. To describe the stability of LDL-C level from baseline to 12 months in the Inclisiran Cohort and PCSK9 mAbs Cohort.

Study design

This study was a retrospective, observational database study conducted in a real-world setting in China. Data for this study was obtained from three rEHR databases.

Setting

The study period extended from April 1, 2023, to no later than the date of ethics committee (EC) approval (February 27, 2025).

The patient identification period was from October 1, 2023, to June 30, 2024. For each patient, the index date was defined as the date of the first injection of inclisiran or a PCSK9 mAb during the identification period. The baseline period was defined as the 6 months prior to the first injection of inclisiran or a PCSK9 mAbs.

Subjects and study size, including dropouts

The inclusion and exclusion criteria for this study include:

Inclusion criteria

1. Aged ≥ 18 years.
2. First received inclisiran or any PCSK9 mAbs during the indexing period.

Exclusion criteria

1. Participated in any interventional or observational study of inclisiran or PCSK9 mAbs anytime during the study period.
2. In Inclisiran Cohort, the first injection of inclisiran was in the index period, and patients were treated with PCSK9 mAbs within 3 months prior to first inclisiran.

Using real-world databases across three regions, this study constructed two treatment-specific real-world cohorts: the Inclisiran Cohort (N = 571) and the PCSK9 mAbs Cohort (N = 11420).

Variables and data sources

The study variables included patients' baseline demographics (within 6 months prior to the first inclisiran or PCSK9 mAbs), baseline clinical characteristics (within 6 months prior to the first inclisiran or PCSK9 mAbs), laboratory tests, treatment patterns (on or after the index date to the end of study), and vital signs (baseline).

The data were sourced from three rEHR databases.

Statistical methods

Independent analyses were conducted for each of the three rEHR databases. Descriptive statistical methods were mainly employed to analyze the primary and secondary endpoints.

Following the individual database analyses, a meta-analysis was performed on selected endpoint measures for these three databases. Both fixed-effect and random-effects models were fitted. Results from the random-effects model were primarily reported in cases of significant heterogeneity; otherwise, the fixed-effect model results were presented, with random-effects estimates included for robustness assessment.

Results

A total of 571 patients were included in the Inclisiran Cohort and 11420 patients in the PCSK9 mAbs Cohort. Patients treated with inclisiran had a mean age of approximately 55-59 years and were predominantly male (73.6%), whereas patients receiving PCSK9 mAbs were older, with a mean age of approximately 62 years and a lower proportion of males (61.3%).

At 6 months, the mean percentage change of LDL-C was -27.78% from baseline (95% confidence interval [CI]: -31.65%, -23.90%) in the Inclisiran Cohort (N = 69), with minimal

heterogeneity across databases (I^2 = 0.0%). The PCSK9 mAbs Cohort (N = 1780) achieved a comparable mean LDL-C change at 6 months (-28.64%; 95% CI: -42.96%, -14.33%), although with greater inter-database variability. LDL-C reductions were also observed at other assessed time points (3, 9, and 12 months) in both cohorts and across the subgroup, which only included patients who at baseline received either inclisiran or PCSK9 mAbs in combination with a statin or who were statin-intolerant.

At 12 months, adherence outcomes were descriptively summarized for each cohort. The mean proportion of days covered (PDC) was 58.73% (95% CI: 54.94%, 62.51%) in the Inclisiran Cohort (N = 251) and 17.25% (95% CI: 13.53%, 20.98%) in the PCSK9 mAbs Cohort (N = 3947). Over the 12 months follow-up period, patients treated with inclisiran received a mean of 1.91 injections (95% CI: 1.80, 2.02).

Discussion

The study demonstrated that, in a real-world setting, both inclisiran and PCSK9 mAbs effectively reduced LDL-C levels at 3, 6, 9, and 12 months in the Inclisiran Cohort and the PCSK9 mAbs Cohort, respectively. From a numerical perspective, the two cohorts exhibited similar percentage reductions in LDL-C from baseline at both 6 and 12 months.

Notably, the magnitude of LDL-C reduction from baseline observed in this study was numerically lower than that reported in previously published studies conducted in China, which may be attributable to several factors. First, dosing intervals and injection timing in routine clinical practice may not strictly adhere to prescribing information, thereby diminishing maximal LDL-C reduction. Second, differences in adherence and persistence between therapies—particularly the superior long-term dosing continuity observed with inclisiran—likely play a central role in shaping longitudinal LDL-C trajectories. Third, the retrospective, non-interventional design inherently limits data completeness and continuity, as laboratory measurements, medication records, and follow-up visits outside participating centers may not be fully captured, further influencing effectiveness estimates.

Overall, this study contributed more representative population data within the Chinese real-world context, elucidating the critical role of adherence in actual lipid-lowering efficacy. It provided evidence reference points that were more closely aligned with real-use scenarios for clinical practice and policy making.

Conclusion

The results of this study showed the effectiveness and adherence of both inclisiran and PCSK9 mAbs in a real-world setting, and especially inclisiran exhibited a more stable and sustained reduction in LDL-C levels, accompanied by a higher PDC.

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