IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ezetimibe for hypercholesterolaemia[1]

Executive Summary

[1] Translation of the executive summary of the final report "Ezetimib bei Hypercholesterinämie" (Version 1.0; Status: 18.07.2011). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Background

In its letter of 20 May 2010, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess ezetimibe (in mono- or combination therapy) in patients with hypercholesterolaemia.

Research question

The aim of this investigation is the benefit assessment of treatment with ezetimibe (in mono- or combination therapy) compared to treatment with placebo or other lipid-lowering drugs, as well as to non-drug treatment options in patients with hypercholesterolaemia. The focus of the assessment was on patient-relevant outcomes.

Methods

The assessment was conducted on the basis of randomized controlled trials (RCTs) on the research question outlined above. For this purpose, a systematic literature search was conducted in the following databases: MEDLINE, EMBASE, BIOSIS, and the Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, a search for relevant systematic reviews was performed in the databases MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). The systematic reviews were screened for further relevant studies. The literature search covered the period up to 28 April 2011. In addition, trial registries and publicly accessible regulatory documents were scrutinized. Moreover, relevant published and unpublished studies were requested from MSD SHARP & DOHME GmbH, the manufacturer of the drugs approved in Germany (Ezetrol®, Inegy®).

The literature screening was conducted by 2 reviewers independently of each other. After an assessment of the risk of bias, the results of the single studies were presented.

Results

Overall, 2 studies were identified as relevant for the research question of the present benefit assessment. On the basis of therapy with statins, the studies investigated the additional administration of ezetimibe versus placebo (ENHANCE) and versus niacin (ARBITER-6-HALTS). The 24-month ENHANCE study and the 14-month ARBITER-6-HALTS study included a total of 720 and 363 patients respectively. No relevant studies on ezetimibe monotherapy were available.

All-cause mortality and vascular mortality

No statistically significant difference was shown between ezetimibe and placebo (in each case in addition to simvastatin) for the outcomes “all-cause mortality” (2 / 357 vs. 1 / 363, p = 0.578) and “vascular cardiac mortality” (2 / 357 vs. 1 / 363, p = 0.578). No vascular cerebral and vascular non-cardiac / non-cerebral fatal events occurred.

For the comparison of ezetimibe and niacin (in each case in addition to a statin), a statistically significant difference between therapy options was shown to the disadvantage of ezetimibe (7 / 176 vs. 1 / 187, p = 0.028). The risk of bias of this outcome was classified as high, as it remained unclear whether the study discontinuations were considered in the analysis. In view of the fact that the proportion of study discontinuations in the niacin group was larger than in the ezetimibe group (27 patients [14%] vs. 9 patients [5%]), the results cannot be regarded as reliable. Due to the high risk of bias, no indication of a lower benefit of ezetimibe is inferred from the study. With regard to the outcome "vascular cardiac mortality", no statistically significant difference between treatment groups was shown (5 / 176 vs. 1 / 187, p = 0.110). The result for this outcome also carries a potentially high risk of bias, as study discontinuations were not considered in the analysis. Data on cerebral or non-cardiac/non-cerebral deaths were not available.

In summary, for the outcomes "all-cause mortality" and "vascular mortality" the data provide neither proof nor an indication of a benefit of ezetimibe versus placebo or of an additional benefit or lesser benefit of ezetimibe versus niacin.

Vascular morbidity

The comparison of ezetimibe and placebo (in each case in addition to simvastatin) showed no statistically significant difference for the analysed vascular cardiac events "myocardial infarction" (MI) (3 / 357 vs. 2 / 363 patients with an event, p = 0.666) and "revascularization" (6 / 357 vs. 5 / 363 patients with an event, p = 0.789). No resuscitations after cardiac arrest occurred. Likewise, no statistically significant difference between treatment options was shown with regard to vascular cerebral morbidity (stroke) (1 / 357 vs. 1 / 363, p > 0.999). Data on vascular non-cardiac/non-cerebral morbidity were not available.

The comparison of ezetimibe with niacin (in each case in addition to a statin) showed no statistically significant difference with regard to vascular cardiac morbidity (revascularization) (3 / 165 vs. 0 / 160 patients with an event, p = 0.091). In this context, the risk of bias was assessed as high, as study discontinuations were not considered in the analysis and, moreover, a notable difference between treatment groups was evident (study discontinuations in the ezetimibe group vs. niacin group: 5% vs. 14%). Data on cerebral as well as on non-cardiac/non-cerebral morbidity were not available.

In summary, for the outcome "vascular morbidity" the data provided neither proof nor an indication of a benefit of ezetimibe versus placebo nor of an additional or lesser benefit of ezetimibe versus niacin.

Composite outcome of mortality and cardiovascular morbidity

The comparison of ezetimibe with placebo (in each case in addition to simvastatin), showed no statistically significant difference for the composite outcome (10 / 357 vs. 7 / 363 patients with an event, p = 0.464) comprising death, MI, stroke, resuscitation after cardiac arrest and coronary revascularization.

In the comparison of ezetimibe with niacin (in each case in addition to a statin), more patients in the ezetimibe group than in the niacin group experienced an event of the composite outcome comprising death due to coronary disease, MI, myocardial revascularization and hospital admission due to acute coronary syndrome (9 / 165 vs. 2 / 160 patients with an event). In this context, the difference observed was statistically significant ($p = 0.04$). However, the data reported on this outcome show insufficient certainty of results. First of all, a single component of the composite outcome was not reported ("hospital admission due to acute coronary syndrome"). A query to the study centre responsible and the co-sponsor of the study (Abbott) produced no clarifying information. Secondly, the analysis must also be regarded as showing insufficient certainty of results, due to the large proportion of patients not considered in the analysis and to the notable differences in rates between the two treatment groups (higher proportion of study discontinuations in the niacin group). The results were therefore not considered in the benefit assessment.

In summary, for the composite outcome of mortality and cardiovascular morbidity, the data provided neither proof nor an indication of a benefit of ezetimibe versus placebo or of an additional or lesser benefit of ezetimibe versus niacin.

Health-related quality of life

Information on the outcome "health-related quality of life" was only available for the comparison of ezetimibe with niacin (in each case in addition to a statin). However, no detailed results on this outcome were presented; it was only reported that a statistically significant difference between groups was not observed either at the start or at the end of the study. The risk of bias at the outcome level was thus classified as high, as no information was available on the patients included and analyses conducted.

For the outcome "health-related quality of life" the data provided neither proof nor an indication of a benefit of ezetimibe versus placebo or of an additional or lesser benefit of ezetimibe versus niacin.

Adverse drug effects

For this benefit assessment, the outcome "adverse drug effects" was operationalized by means of "adverse events".

The comparison of ezetimibe with placebo (in each case in addition to simvastatin) showed no statistically significant difference for the overall rates of adverse events (338 / 357 vs. 338 / 363 patients with an event, $p = 0.391$), overall rates of serious adverse events (48 / 357 vs. 43 / 363 patients with an event, $p = 0.539$), and study discontinuations due to adverse events (29 / 357 vs. 34 / 363 patients, $p = 0.578$).

For the comparison of ezetimibe and niacin (in each case in addition to a statin), only data on study discontinuations due to adverse events were reported. A statistically significant difference between treatment options was shown in favour of ezetimibe (3 / 176 vs. 17 / 187

patients, p = 0.002). Due to the high risk of bias on a study level, the overall risk of bias was classified as high. For this reason no advantage of ezetimibe was inferred from the result.

In summary, for adverse events, serious adverse events, as well as study discontinuations due to adverse events, the data provide neither proof nor an indication of harm from ezetimibe versus placebo. Likewise, versus niacin, neither proof nor an indication of greater or lesser harm from ezetimibe was shown.

Subgroup characteristics and other effect modifiers

No different effects in subgroups were shown on the basis of the available data on subgroup characteristics.

Conclusions

In patients with hypercholesterolaemia there is no proof of a benefit or harm from ezetimibe therapy compared with placebo. This applies both to monotherapy and combination therapy. No studies on monotherapy were available. Likewise, there is no proof of an additional or lesser benefit, or for greater or lesser harm from ezetimibe compared with other lipid-lowering agents or with non-drug treatment interventions. This applies both to monotherapy and combination therapy. No studies on monotherapy were available.

Keywords: ezetimibe, simvastatin, anticholesteraemic agents, lipid lowering agents, cholesterol, hypercholesterolaemia, benefit assessment, systematic review

The full report (German version) is published under www.iqwig.de