IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Rapid-acting insulin analogues for the treatment of diabetes mellitus type 2[1]

Executive Summary

[1] Executive summary of the final report "Kurzwirksame Insulinanaloga zur Behandlung des Diabetes mellitus Typ 2" (Version 1.0; Status: 15.12.2005). Please note: This document is provided as a service by IQWiG to English-language readers. However, solely the German original full report is absolutely authoritative and legally binding.

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Executive summary

Background

The Federal Joint Committee commissioned the Institute of Quality and Efficiency in Health Care to evaluate the effects of rapid-acting insulin analogues in the treatment of diabetes mellitus type 2.

Research question

The aim of this benefit assessment was to compare the effects of long-term treatment with rapid-acting insulin analogues (RAIs) vs. short-acting regular human insulin (RHI) (and also compare the effects of different RAIs with each other) with regard to patient-relevant outcomes in patients with type 2 diabetes.

In this text, the term "rapid-acting insulin analogues" (or "RAIs") refers to all currently approved and available preparations of this type in Germany: insulin aspart, insulin glulisine, and insulin lispro. The term "short-acting insulin" refers to RHI; "longer-acting insulin" refers to intermediate-acting (e.g. Neutral Protamin Hagedorn [NPH]) and/or long-acting insulin (e.g. ultralente).

This benefit assessment was conducted on the basis of the comparison and weighing of desired and undesired effects of the respective drugs (weighing of benefits and harms).

Methods

A systematic literature search was performed in the databases MEDLINE, EMBASE, CENTRAL, and The Cochrane Library (CDSR, DARE, HTA) (coverage up to June 2005). In addition, reference lists were screened of relevant secondary publications (systematic reviews, HTA reports), trial registries, and publicly accessible drug approval documents. The manufacturers of the RAIs investigated were asked to provide information on relevant published or unpublished studies, and requests for additional information were also sent to the main authors of publications. The literature screening was conducted by 2 reviewers independently of one another.

Eligible studies were randomised controlled trials (RCTs) that investigated at least one of the three RAIs noted (either compared with another insulin of this type or with short-acting RHI) in patients with manifest diabetes mellitus type 2. If a combination therapy of an insulin analogue with additional blood glucose-lowering treatment was administered (e.g. insulin aspart combined with NPH insulin), this additional treatment also had to be part of the comparator treatment, as well as approved and available in Germany. Premixed formulations of insulin components were allowed for the test and comparator interventions. Outcomes of interest were patient-relevant outcomes such as mortality, morbidity, hypo- and

hyperglycaemic episodes, other adverse events, quality of life (QoL), and treatment satisfaction. The minimum study duration was 24 weeks. Only studies published in German, English, French, Dutch, Spanish or Portuguese were considered.

After an assessment of study quality, the results of the single trials were collated according to therapy goals and outcomes.

IQWiG's preliminary benefit assessment, the preliminary report, was published on the Internet (www.iqwig.de). Interested persons and parties were asked to submit written comments. Unclear aspects of these written comments were discussed in a scientific debate. The final report was subsequently produced.

Results

A total of seven relevant studies were identified. Sufficient transparent information was available for these studies and they were therefore included in the benefit assessment. In addition, a further potentially relevant study was found, but excluded, as a full-text publication was not available.

In five of the studies included, insulin lispro was compared with RHI (both in combination with longer-acting insulin); for three of these studies, study reports were available which provided substantially more information than the publications. In the other two studies, insulin glulisine was compared with RHI (both in combination with longer-acting insulin). For one of these studies, the results of which had not previously been published, the benefit assessment was mainly conducted on the basis of the study report provided by the manufacturer. No relevant and fully published study was found on insulin aspart. The results on one study (Study 037) were only published as an abstract in 1999. Novo Nordisk was not prepared to provide study data under the prerequisite that these data were to be published in the final report. Therefore no detailed, publicly accessible results were available on a randomised long-term intervention study in patients with type 2 diabetes mellitus treated with insulin aspart. Furthermore, no relevant studies were found on premixed formulations of rapid-acting and longer-acting insulin components or on direct comparisons between RAIs.

Overall, the quality of reporting in the publicly accessible publications was insufficient. In part, the information presented on study methods and results deviated substantially from the information presented in the study reports.

With a study period of between 5.5 and 12 months, none of the studies was designed to investigate the effect of RAIs with regard to the reduction of diabetic late complications or total mortality. Information on hospitalisations was only provided within the framework of safety evaluations.

The hypoglycaemia rate was recorded in all studies; however, due to the open-label study design and the lack of blinding of the endpoint evaluation, all studies were susceptible to systematic bias. Furthermore, the missing or unclear consideration of premature discontinuations of therapy, in particular in the studies on insulin glulisine, strongly limited

the informative value of the results. In summary, under consideration of these problems, no clear advantage was shown for any of the investigated treatment options, neither with regard to severe, symptomatic, nor nocturnal hypoglycaemia.

Only limited QoL data were available (only for two studies on insulin lispro). In the largest study on insulin lispro (approx. 350 patients), no difference was shown between treatment groups. In the shortest study included (5.5 months; approx. 150 patients), a statistically significant difference in favour of insulin lispro in a subcategory of the employed QoL instrument was shown; however, for the total score of this instrument, no statistically significant difference between groups was demonstrated. In summary, no clear advantage was shown for either treatment option.

Treatment satisfaction was assessed in both studies on insulin glulisine; however, the publication on one study (Study 3002) did not include information on the respective results. In the other study (Study 3005), the results provided in the study report are of little informative value due to substantial selection bias, methodological deficiencies, and inconsistent data. Therefore, no definite statements can be made on the effects of long-term therapy with RAIs (compared with RHI) on treatment satisfaction.

Information on adverse non-hypoglycaemia events was scarce in the publicly accessible publications, but was provided in the study reports. In the safety evaluation, no clear advantage or disadvantage was shown for insulin lispro or for insulin glulisine compared with RHI; however, there was a tendency towards more discontinuations due to adverse drug effects in patients treated with insulin glulisine and towards more serious adverse events in patients treated with insulin lispro compared with RHI.

In all studies, insofar as reported, similar weight increases occurred for both patients receiving the study drug (RAI) and the control (RHI): the weight gain ranged from approx. between 1.5 kg and 5 kg throughout the study periods.

With a maximum study period of 12 months, no study was suited to show the safety of long-term therapy with RAIs in patients with type 2 diabetes mellitus.

Conclusion

For patient-relevant outcomes, there is no convincing evidence of a superiority of rapid-acting insulin analogues compared with short-acting regular human insulin in diabetes mellitus type 2 therapy. Rapid-acting insulin analogues have not been sufficiently investigated with regard to their potential long-term beneficial and harmful effects.

Key words: insulin aspart, insulin lispro, insulin glulisine, insulin analogues, human insulin, diabetes mellitus type 2, systematic review

The full report (English version) is available under

http://www.iqwig.de/download/A05-04_Final_Report_Rapid-acting_insulin_analogues_for_the_treatment_of_diabetes_mellitus_type_2.pdf