IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Rapid-acting insulin analogues in children and adolescents with diabetes mellitus type 1[1] – follow-up commission

Executive Summary

[1] Translation of the executive summary of the final report "Kurzwirksame Insulinanaloga bei Kindern und Jugendlichen mit Diabetes mellitus Typ 1" (Version 1.0; Status: 24.09.2009). Please note that 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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Rapid-acting insulin analogues for children and adolescents with diabetes mellitus type 1 – follow-up commission

Executive summary

In its letter of 17 July 2008 the Federal Joint Committee (G-BA) commissioned the Institute of Quality and Efficiency in Health Care (IQWiG) to assess the benefit of rapid-acting insulin analogues (RAIs) in children and adolescents with diabetes mellitus type 1 as a follow-up commission to A05-02.

Research question

The aims of this investigation were

- to assess the benefit of long-term treatment with insulin aspart, insulin glulisine or insulin lispro, each compared to a treatment with short-acting human insulin, and
- to conduct a comparative benefit assessment of the 3 above-mentioned RAIs compared with each other,

in each case in children and adolescents with diabetes mellitus type 1, focusing on patient-relevant outcomes.

In addition to the benefit assessment, short-term effects of the interventions investigated were to be presented for the outcomes in the report.

Methods

The evaluation was performed on the basis of randomized controlled trials (RCTs) investigating the research questions outlined above. For this purpose, a systematic literature search was performed in the following databases: MEDLINE, EMBASE, and CENTRAL. Alongside the search for relevant primary studies, a search for relevant secondary publications was performed in MEDLINE and EMBASE. In addition, a search was undertaken in the following specialized databases: Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment Database (HTA Database). The period covered was up to 29.06.09. In addition, clinical study registries were screened and relevant published or unpublished trials requested from the manufacturers of insulin aspart (Novo Nordisk Pharma GmbH), insulin lispro (Lilly Deutschland GmbH) and insulin glulisine (Sanofi-Aventis Pharma Deutschland GmbH). Included were randomized controlled trials with a duration of at least 24 weeks and where at least 1 out of the 3 above-mentioned RAIs was investigated according to their valid European approval status.

The literature screening was conducted by 2 reviewers independently of each other. After assessing the bias potential, the results of the individual studies, classified according to

compared therapies, were compared against each of the therapy goals and outcomes, and described.

Results

A total of 4 trials were identified as being relevant to the research question in this benefit assessment. In one of the trials, adults were included as well as adolescents. Subgroup analyses were requested for the adolescent patient population, which was the focus of this report. None of the 4 trials were designed to investigate the long-term additional benefit of RAIs.

One of the included trials consisted of a 3-arm treatment trial: insulin aspart, insulin lispro and human insulin (Trial 2126). This trial provided data on the comparison of RAIs with human insulin as well as on the direct comparison of insulin analogues with each other. Overall, data were available on the following compared therapies:

- insulin aspart vs. human insulin (2 trials: 1507, 2126)
- insulin lispro vs. human insulin (2 trials: 2126, Z015)
- insulin aspart vs. insulin lispro (1 trial: 2126)
- insulin glulisine vs. insulin lispro (1 trial: D3001)

No relevant trials were identified that compared insulin glulisine with human insulin or insulin aspart with insulin glulisine.

All 4 included trials investigated the use of RAIs in intensified insulin therapy using multiple subcutaneous injections. No relevant long-term trial was found on the use of RAIs in insulin pump therapy.

The treatment period in the trials was 24 to 26 weeks (without run-in phase; 1507, 2126, D3001) and 12 months (Z015). The report's conclusions are therefore based exclusively on results of a comparatively short duration. A summary of the evidence for the patient-relevant outcomes mentioned in the report shows that there is a paucity of robust data on the treatment of children and adolescents even for those outcomes that can be investigated in trials of shorter duration.

Information on outcomes

There were no relevant trials available on the following previously defined outcomes: mortality, micro- and macrovascular late complications, physical or psychosocial development disorders. For all trials, there were data on deaths, inpatient treatments, ketoacidotic coma, and symptoms caused by hyperglycaemia, which were collated in the safety analyses on adverse events. However, due to the comparatively low patient numbers and the short duration of the trials, there were few such events. As a result, due not only to the

poor quality of the data but also the insufficient quantity of data, the additional benefit of RAIs for these outcomes remains unclear.

Data on health-related quality of life were only collected in 1 trial on the comparison of insulin lispro with human insulin (Z015). However, the measurement instrument used was not validated for the under-18 patient population. Thus, no reliable conclusions could be derived for this report from the data collected. Treatment satisfaction was measured in Trial 1507. However, because the measurement instrument used was not validated for children up to 7 years of age or for their parents, the results from this trial cannot be interpreted either.

All 4 trials contained information on hypoglycaemia, HbA1c values, serious adverse events and study discontinuations due to adverse events. However, even for these outcomes, the reporting of results was to a large extent inadequate, although the study report was provided by the trial sponsor concerned. Irrespective of the validity of the data collected, there was no statistically significant difference between insulin analogues and human insulin. With regard to the comparison of insulin analogues with each other, a statistically significant difference existed only for symptomatic nocturnal hypoglycaemia between insulin lispro and insulin glulisine. This difference was to the disadvantage of insulin glulisine. However, the measurement certainty of the results on these events was low. As a result, no indication could be derived from the existing data of a disadvantage of insulin glulisine when compared to insulin lispro.

Hypoglycaemia in conjunction with long-term blood glucose control

When blood glucose changes and serious hypoglycaemia (including nocturnal) were assessed together, there was no proof of a difference in the 3 RAIs compared to human insulin or in direct comparison with each other. However, the validity of the data was mostly inadequate as serious hypoglycaemia did not occur frequently. Moreover, there were few data available for these evaluations.

Non-severe, confirmed hypoglycaemia, comprising a combination of lowered blood glucose levels and hypoglycaemic symptoms, were not reported separately in any trial. The analyses of non-severe, confirmed hypoglycaemia provided for the subgroup of adolescents in trial Z015 (comparison of insulin lispro with human insulin) could not produce any adequately analysable information. As a result, none of the 4 trials provided sufficiently robust data on non-severe hypoglycaemia.

Harm potential

None of the relevant trials had the aim of investigating the long-term safety of RAIs in the treatment of children and adolescents. For the superordinate assessment of harm potential, data on serious adverse events and on study discontinuations due to adverse events were collected from the identified studies. The analysis of these events showed no statistically significant differences

between the RAIs and human insulin or between each of the insulin analogues. However, the results have only limited validity due to the size and duration of the trials.

In addition, deaths, the number of inpatient treatments, and the occurrence of diabetic ketoacidosis were reported in the safety analyses. Deaths did not occur in any of the included trials. With reference to diabetic ketoacidosis, the occurrence of such events was markedly more frequent in terms of numbers in the insulin aspart group than in the human insulin group. The difference between the treatment groups was not statistically significant. Overall, the available data provided no proof of an advantage in any of the therapy alternatives investigated for the above-mentioned outcomes.

Thus, in the summary of the results, there was no proof of greater or lesser harm from the 3 RAIs compared to human insulin or compared with each other.

Additional short-term effects

As a supplement to the benefit assessment of RAIs in long-term use, results were additionally presented from trials with a minimum duration of 12 weeks in order to test whether the short-term effects produced pointers for effect differences between RAI and human insulin. A total of 9 trials on children and adolescents were identified (of which 1 was a subgroup of a trial with adults and adolescents). All trials compared insulin aspart or insulin lispro with human insulin. These trials provided no proof of an advantage of RAIs when compared to human insulin when given pre-prandially in a basal bolus regimen. With regard to post-prandial administration, it could not be excluded – when evaluating blood glucose lowering and serious hypoglycaemia together – that RAIs have a disadvantage in certain patient subpopulations when compared to pre-prandial human insulin administration.

There was only one trial available on the use of RAIs in pump therapy. This produced no evidence of an advantage of RAIs compared to human insulin.

Conclusions

There is no proof of additional benefit of RAIs compared to human insulin or in direct comparisons with each other. In addition, there is no proof of greater or lesser harm from RAIs compared to human insulin or in direct comparisons with each other.

Only trials with a maximum treatment period of 1 year were available on the treatment of children and adolescents with RAIs. In all trials the RAIs were investigated in a basal bolus regimen; no relevant trials on their use in pump therapy were identified. There were no long-term trials identified that investigated micro- and macrovascular late complications or physical or psychosocial development disorders. Moreover, there is a lack of valid data on health-related quality of life and patient satisfaction.

Keywords: insulin aspart, insulin lispro, insulin glulisine, rapid-acting insulin analogues (RAIs), human insulin, children, adolescents, diabetes mellitus type 1, systematic review

The full report (in German) is available on www.iqwig.de/index.789.de.html