IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports - Commission No. A05-02

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

Executive Summary

[1] Translation of the executive summary of the final report "Kurzwirksame Insulinanaloga zur Behandlung des Diabetes mellitus Typ 1" (Version 1.0; Status: 30.03.2007). Publication date of translation: 25.06.2007. 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Rapid-acting insulin analogues in the treatment of diabetes mellitus type 1

Contracting agency:

Federal Joint Committee

Commission awarded on:

22.02.2005

Internal Commission No.:

A05-02

Address of publisher:

Institute for Quality and Efficiency in Health Care
Dillenburger Str. 27
51105 Cologne
Germany

Tel: +49-(0)221/35685-0
Fax: +49-(0)221/35685-1
E-mail: berichte@iqwig.de
Website: www.iqwig.de

Rapid-acting insulin analogues in the treatment of diabetes mellitus type 1

Executive summary

Background

The German Federal Joint Committee commissioned the Institute for Quality and Efficiency in Health Care to conduct an evaluation of the benefits and harms of rapid-acting insulin analogues (RAIs) in the treatment of diabetes mellitus type 1.

Research question

The aims of this review were:

- the evaluation of the benefits and harms of long-term therapy with an RAI compared with short-acting human insulin,

as well as

- the evaluation of the benefits and harms of RAIs compared with each other,

in each case in patients with diabetes mellitus type 1.

The focus of the evaluation was on patient-relevant therapy goals (in particular, morbidity, mortality, quality of life, and adverse events).

All RAIs approved and available in Germany at the time of report production were evaluated (insulin aspart, insulin glulisine, and insulin lispro). The evaluation was conducted on the basis of the comparison and weighing of desired and undesired effects of the individual drugs (weighing of benefits and harms).

Methods

The evaluation was performed on the basis of randomised controlled trials (RCTs) investigating the research questions outlined above. For this purpose, a systematic literature search in the databases MEDLINE (including Pre-MEDLINE), EMBASE, and CENTRAL was performed (coverage up to August 2006). In addition, reference lists of relevant

secondary publications (systematic reviews, HTA reports), trial and trial results registries, as well as publicly accessible drug approval documents, were screened. The manufacturers of insulin aspart, insulin glulisine, and insulin lispro were asked to provide information on relevant published or unpublished studies.

Finally, in September and October 2006, persons and parties submitting comments on the preliminary version of the report (preliminary report) were also asked to provide relevant studies.

Studies lasting at least 24 weeks were included in which one of the 3 RAIs named above was investigated, either compared with short-acting human insulin (regular insulin) or with another of the 3 RAIs. The literature screening was conducted by 2 reviewers independently of one another.

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

IQWiG's preliminary evaluation, the preliminary report, was published on the Internet (www.iqwig.de). Interested persons and parties were asked to submit written comments, in particular on the following aspects:

- completeness of the literature screening,
- interpretation of the studies included,
- methodology specific to the report.

Unclear aspects of these written comments were discussed in a scientific debate. The final report was subsequently produced considering the comments submitted.

Results

Results of the literature search

The literature search identified 9 published relevant studies and 6 further potentially relevant studies that had either not been fully published (5 studies) or whose results were not interpretable due to the quality of the available publication (one study). A total of 8 of the 9 studies were comparative studies between RAIs and human insulin (insulin aspart: 2, insulin lispro: 6, insulin glulisine: 0); the ninth study was a direct comparative study between 2 RAIs (insulin glulisine vs. insulin lispro). None of the studies included in the evaluation were

blinded and all showed major deficiencies regarding study and/or publication quality. In all studies, the study medication was investigated within the framework of intensified insulin therapy with multiple subcutaneous injections (in addition to basal insulin). Studies on insulin pump therapy lasting ≥ 24 weeks were not identified. Likewise, no fully published studies in children and adolescents were found.

Long-term complications and mortality

No conclusions can be drawn from the studies about the long-term effects of the interventions on the risk of diabetes-related complications and overall mortality.

Hyperglycaemia

Serious hyperglycaemic events (including ketoacidotic coma) rarely occurred in any of the studies. The studies were neither designed nor suited to demonstrate the benefit of RAIs regarding the prevention of serious hyperglycaemic events.

Inpatient treatment

No conclusions can be drawn from the studies regarding the effects of RAIs on the necessity of inpatient treatment.

Reduction in blood glucose levels (HbA_{1c})

In both insulin aspart studies, a statistically significantly greater reduction in blood glucose levels with insulin aspart versus human insulin of about 0.1% (HbA_{1c}) was reported. Both studies were designed as non-inferiority studies. The observed difference, including the limits of the 95% confidence interval, lay below the predefined irrelevance margin. In both studies the basal insulin dose in the insulin aspart group was statistically significantly higher than in the human insulin group; therefore, adjusted analyses were presented in the publicly accessible drug approval documents. According to these analyses, there was no statistically significant difference between treatment groups in either study after adjustment. A further adjusted analysis was also presented in a publication of one of the studies; in this case, the difference remained significant. No such analysis was included in the (incomplete) clinical

study reports provided by the company Novo Nordisk within the framework of the submission of comments on the preliminary report. Overall, the observed differences according to the definition in the individual studies were not clinically relevant, and possibly, after adjustment for the basal insulin dose, not statistically significant either.

For insulin lispro, the meta-analytical summary of the 12-month studies regarding the change in HbA_{1c} showed no statistically significant difference between treatment groups. Likewise, in both 6-month studies no statistically significant difference was shown.

The direct comparative study between insulin glulisine and insulin lispro did not show a difference between treatment groups either.

Serious hypoglycaemic events

No statistically significant difference between treatment groups was shown in any of the 9 studies with regard to serious hypoglycaemic events. A meta-analytical summary of the 6-month studies on insulin aspart and the 12-month studies on insulin lispro showed no differences between either RAI versus human insulin. In a 6-month study on insulin lispro in patients with a high risk for serious hypoglycaemic events, a marked numerical (statistically non-significant) difference was shown in favour of insulin lispro regarding the event rate. However, the rate of patients who experienced at least one such event did not differ between groups. Overall, no evidence was available from the studies that one of the treatment options investigated was superior to another in respect of serious hypoglycaemic events.

No statistically significant difference between insulin aspart and human insulin was shown with regard to serious nocturnal hypoglycaemic events. The results between publications were inconsistent concerning the proportion of patients who had experienced at least one such event. Furthermore, the validity of these results is generally greatly limited, due to indications of a bias in favour of insulin aspart, caused by differences in therapy optimisation. No advantage of insulin aspart concerning the risk reduction for serious nocturnal hypoglycaemic events can be inferred from the available data.

Information on serious nocturnal hypoglycaemia rates under insulin lispro was only available for the subgroup of patients with an impaired awareness of hypoglycaemia. A marked numerical (statistically non-significant) difference in favour of insulin lispro was shown. This difference was qualified by a higher (also statistically non-significant) number of serious daytime hypoglycaemic events under insulin lispro.

In study 3001 comparing insulin glulisine and insulin lispro, a statistically significant difference between treatment groups was shown in favour of insulin lispro regarding serious nocturnal hypoglycaemic events. Certain evidence of a superiority of insulin lispro cannot be inferred from this single study alone, which was designed to investigate efficacy and not to compare serious hypoglycaemic events. However, an indication in this regard may be inferred.

Quality of life

Information on quality of life was only provided for a subgroup of patients in an insulin aspart study as well as for 2 insulin lispro studies.

A separate publication presented results on quality of life in a German-language subpopulation in one of the 2 insulin aspart studies. The publication did not provide information on essential methodological issues. A statistically significant difference between treatment groups was shown in favour of insulin aspart in one of the 3 primary outcome domains (diet restrictions), but not in the other 2 domains. Due to the different specifications for the injection-meal interval between treatment groups, the effect in the domain "diet restrictions" was not necessarily caused by the use of insulin aspart, but may possibly have been caused by these very specifications. In the overall score and in a post-hoc responder analysis, which was however of restricted use, no statistically significant difference between treatment groups was shown.

In 2 insulin lispro studies, no difference between treatment groups was shown for the quality of life parameters investigated. However, the information provided was insufficiently transparent to infer an equivalence of treatment options. It could therefore not be inferred that the specification of a fixed injection-meal interval for human insulin, as well as possibly for insulin lispro,[2] led to this result.

Treatment satisfaction

In a subgroup of patients from England, the main publication, as well as the study report on one of the insulin aspart studies, reported a statistically significant difference in the total score

[2] Fixed intervals for insulin lispro were reported in a publication on a pooled analysis from one study centre participating in 3 multicentre studies on insulin lispro; however, this information was not provided in the single clinical study reports.

of the Diabetes-Treatment-Satisfaction Questionnaire in favour of insulin aspart. For the German-language subpopulation, more detailed results were only provided in a supplementary publication. In this subgroup, a statistically significant difference in the total score to the advantage of insulin aspart was also shown.

For both subgroups, the difference in treatment satisfaction between both treatment groups was mainly based on outcomes describing the convenience and/or flexibility of treatment. It is therefore unclear whether the effect observed was caused by the specification of the fixed injection-meal interval in the human insulin group or can actually be attributed to insulin aspart.

In 2 insulin lispro studies, no difference between treatment groups was shown regarding treatment satisfaction. As for the information on quality of life, this information was also insufficiently transparent. It could not be clarified whether the specification of a fixed injection-meal interval for human insulin and (possibly also for insulin lispro[3]) led to this result.

In the direct comparative study between insulin glulisine and insulin lispro, no statistically significant difference was shown between treatment groups in respect of treatment satisfaction.

Other adverse events

With regard to non-hypoglycaemic adverse events, a clear advantage or disadvantage versus human insulin could be inferred neither for insulin aspart nor for insulin lispro. However, randomised controlled trials aiming to demonstrate long-term safety were not identified, in particular in respect of clarifying the clinical relevance of preclinical study results on mitogenicity. Nor did the direct comparative study between insulin glulisine and insulin lispro provide any indications in favour of either therapy option.

[3] As stated, fixed intervals for insulin lispro were reported in a publication on a pooled analysis from one study centre participating in 3 multicentre studies on insulin lispro; however, this information was not provided in the single clinical study reports.

Subgroup analyses

Gender- or age-specific conclusions can hardly be inferred from the available studies. No indications were available showing that the results varied for men or women or for different age groups of adult patients. Relevant, fully published studies including children younger than 12 years were not found. However, 2 potentially relevant unpublished studies on insulin aspart in children were identified.

No detailed analyses regarding concomitant diseases were provided in the available publications. As patients with serious concomitant diseases were generally excluded from most of the relevant studies, conclusions from the available studies can hardly be made for these patients.

One study specifically provided data on patients with a high risk of serious hypoglycaemic events due to an impaired awareness of hypoglycaemia (GVAD Study). No clear evidence of an advantage of either treatment option (insulin lispro or human insulin) was shown.

The Persson 2002 study investigated insulin lispro therapy in pregnant patients. This study also provided no evidence of an advantage of either insulin lispro or human insulin.

Conclusion

Adult patients

The benefit of insulin aspart compared with human insulin in adult patients is unclear due to a lack of data or poor-quality data; an additional benefit is therefore not proven.

In patients without a higher than usual risk of hypoglycaemia, overall, the studies show similar results between insulin lispro and human insulin. On the basis of the data available, it is unclear whether insulin lispro has an additional benefit in patients with an increased risk of serious hypoglycaemic events.

Due to a lack of data, there is no evidence of an additional benefit of insulin glulisine versus human insulin.

There is an indication of an additional benefit of insulin lispro versus insulin glulisine. This indication is solely based on a lower rate of serious nocturnal hypoglycaemic events under insulin lispro observed in one study. Other direct comparative studies between RAIs were not available.

The benefit of insulin analogues in insulin pump therapy is unclear. Only short-term studies were available, which cannot be used to evaluate the patient-relevant benefit of long-term therapy with insulin analogues.

Children and adolescents

Insulin aspart and insulin lispro are the only RAIs approved for the treatment of children and adolescents. The benefit of both of these RAIs in children and adolescents is unclear.

Only short-term studies were available as full-text publications, which cannot be used to evaluate the patient-relevant benefit of long-term therapy with insulin analogues. Long-term studies in children and adolescents were identified. However, due to the lack of full-text publications, and the fact that the sponsor Novo Nordisk did not provide the corresponding data, they could not be included in the evaluation. Therefore, no concluding statements can be made regarding the benefit of insulin analogues in children and adolescents.

The same applies to their use in insulin pump therapy.

Key words: insulin aspart, insulin lispro, insulin glulisine, insulin analogues, human insulin, diabetes mellitus type 1, systematic review