Long-acting insulin analogues in type 2 diabetes: advantage over human insulin not proven

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It has so far not been proven that long-acting insulin analogues (LAIAs) have an advantage over conventional human insulin in the treatment of patients with type 2 diabetes. Even though the results of a 5-year study are available for one of the two LAIAs assessed (insulin glargine), the potential long-term benefits and harms of this drug class have still not been sufficiently investigated. This is the conclusion of a report by the German Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, which was published in March 2009 and for which an English-language summary is now available.

The final report is part of a comprehensive commission package awarded by the Federal Joint Committee, by means of which key therapy options for people with diabetes are to be assessed. The reports on rapid-acting insulin analogues in diabetes mellitus type 1 and 2 have already been completed.

Only one study lasting longer than 12 months was available

For the assessment of the LAIAs, IQWiG searched for studies that either compared one of the two currently approved LAIAs for the treatment of type 2 diabetes (insulin glargine and insulin detemir) with human insulin, or compared the benefits of the two LAIAs with each other. A precondition for study inclusion was that patients had been randomly

allocated to one of the treatment groups and that the treatment period had lasted at least 24 weeks, as the aim of the project was to assess the potential benefits and harms of long-term therapy.

A database search and queries to the manufacturers resulted in the retrieval of a total of 18 studies for inclusion in the evaluation. Of these studies, 15 (glargine: 9; detemir: 6) compared an LAIA with neutral protamine Hagedorn (NPH) insulin, a longer-acting (intermediate-acting) insulin based on human insulin. The other 3 studies compared the two LAIAs with each other. In 11 studies, insulin was used in addition to oral antidiabetics, in 6 studies within the framework of intensified insulin therapy. One study investigated various treatment schemes. This study on insulin glargine lasted 5 years; all the other studies lasted a maximum of 12 months.

It is notable that in 7 of the 9 studies comparing insulin glargine and human insulin, the drugs were not used as normally used in Germany. The study participants only injected the drugs once daily, even though in daily practice they are often injected more frequently. The relevance of these studies is therefore limited.

Conclusions about late complications of diabetes are hardly possible

It is not possible to draw reliable conclusions about the long-term advantages and disadvantages of the drugs investigated, solely due to the short duration of most studies. Even the 5-year study on insulin glargine, the results of which were not available at the time of the preparation of the preliminary report, only allows limited conclusions about late complications of diabetes. Regarding heart disease, the comparison with NPH insulin does not provide indications of a difference between treatment options. Similarly, the data do not provide indications that

insulin glargine is associated with a higher risk of damage to the ocular fundus. This suspicion had prompted the US regulatory authority FDA (Food and Drug Administration) to request a long-term study from the manufacturer (Sanofi-Aventis). This study has now been completed and is assessed in the IQWiG report.

Data provide an indication of less frequent severe hypoglycaemia in patients using insulin glargine

The data do not prove short-term advantages of LAIAs, either. However, the data do provide some indications: in certain treatment schemes, non-severe hypoglycaemia seems to occur less frequently with insulin detemir, in consideration of the individual lowering of HbA1c levels. However, this only applies to the use as basal insulin (once or twice daily) in patients who also use oral antidiabetics. In addition, the 5-year study provides an indication that in patients using insulin glargine, severe hypoglycaemia occurs less frequently than in those using NPH insulin.

In the direct comparison of the two LAIAs, neither drug was clearly better than the other. However, study participants who used insulin detemir discontinued the study more often due to adverse events than those using insulin glargine. On average, patients in the detemir group put on less weight than those in the glargine group. However, the differences were small (0.9-1.3 kg). As the studies only lasted 6-12 months, it is unclear anyway whether this effect is long term.

Manufacturers provide previously unpublished data

Both manufacturers of LAIAs, Sanofi-Aventis (insulin glargine) and Novo Nordisk (insulin detemir), agreed to provide IQWiG with previously unpublished data during the preparation of the report. Data subsequently requested by IQWiG were supplied. These data referred in

part to studies still completely unpublished and in part to additional information (clinical study reports) on comparative clinical trials already published. In addition, the manufacturers agreed that all of these data could be documented in the final report. A large amount of previously unpublished data could thus be incorporated in the final report.

During the course of the hearing procedure on the preliminary report, the manufacturers also supplied further analyses based on individual patient data (IPD). However, these data only changed the conclusions of the preliminary report in a few cases.

Procedure of report production

The preliminary results (preliminary report) were published by IQWiG at the end of March 2008 and interested parties were invited to submit comments. Following the commenting procedure, the preliminary report was revised and the final report sent to the contracting agency, the Federal Joint Committee, in January 2009. The documentation of the written comments, as well as the meeting minutes of the oral scientific debate, will be published in a separate document simultaneously with the final report.

Source: Institute for Quality and Efficiency in Health Care