Long acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus (Protocol)

Horvath K, Jeitler K, Berghold A, Plank J, Pieber TR, Siebenhofer A

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TABLE OF CONTENTS

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
To assess the advantages or disadvantages of long term treatment in patients with type 2 diabetes mellitus with long acting insulin analogues currently insulin glargine and insulin detemir compared to NPH Insulin (isophane insulin human).

BACKGROUND

Diabetes mellitus type 2 is a metabolic disorder characterised by relative insulin deficiency resulting from a reduced sensitivity of tissues to insulin and/or an impairment of insulin secretion by pancreatic beta cells. This in turn leads to chronic hyperglycaemia (i.e. elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy, neuropathy and increased risk of cardiovascular disease. For a detailed overview of diabetes mellitus, please see 'Additional information' in the information on the Metabolic and Endocrine Disorders Group in The Cochrane Library (see 'About the Cochrane Collaboration', 'Collaborative Review Groups (CRGs)'). For an explanation of methodological terms, see the main Glossary in *The Cochrane Library*.

Despite the unequivocal epidemiological evidence that higher blood glucose concentrations are associated with a higher risk for developing micro- and macrovascular complications (Stratton 2000) evidence for a beneficial effect of antihyperglycaemic therapy is conflicting. In the past, investigations of different pharmacological interventions showed results from a marked risk reduction of microvascular complications (Ohkubo 1995), a reduction of macrovascular risk without a difference in blood glucose concentrations (UKPDS 34 1998) to a statistically non significant (Abraira 1997) and even statistically significant (UKPDS 34 1998) risk increase for macrovascular complications. Following from these results, it has to be assumed that the different interventions carry different substance specific beneficial or adverse effects. As a consequence, firm conclusions on the effect of interventions on patient relevant outcomes can not be drawn from the effect of these interventions on blood glucose concentration alone.

Pharmacological anti-hyperglycaemic therapy in patients with type 2 diabetes mellitus can be done either by different oral agents or insulin. Insulin in itself is a group of heterogeneous preparations clinically differentiated by their course of action over time. While short acting insulin is used to mimic the response of endogenous insulin to food intake and to correct pre- or between-meal hyperglycaemia (bolus insulin), intermediate and long acting insulin is primarily used to provide a continuous supply of small amounts of insulin, independent of food intake, over a longer period of time to regulate lipolysis and the output of hepatic glucose (basal insulin). Long acting insulin preparations are obtained by crystallisation with either protamine (NPH type) or Zinc (Lente type). Treatment with these basal insulins however does show some drawbacks. Achieving lower blood glucose levels carries an increased risk for hypoglycaemia. Since NPH, the most widely used basal insulin, is associated with a pronounced insulin peak follow-

ing injection and variable absorption (Heinemann 2000, Lepore 2000), targeting for lower HbA1c levels often is difficult and leads to an increased rate of hypoglycaemic events.
In an effort to make insulin with a more physiological time course of action available to patients with diabetes mellitus so called insulin analogues have been developed. Insulin analogues are insulin-like molecules, engineered on the basis of the human insulin molecular structure by changing the amino acid sequence and the physiochemical properties. Two such long acting insulin analogues, insulin Detemir (Levemir®) and insulin Glargine (Lantus®) are currently available on the market.

Insulin Glargine is produced by substituting glycine for asparagine at position 21 of the A-region of the insulin molecule and the addition of two arginine molecules at position B30. This leads to a shift of the isoelectric point toward a neutral pH, resulting in a molecule which is less soluble at the injection site and forms an amorphous precipitate in the subcutaneous tissue which is gradually absorbed. From this depot insulin molecules are slowly released. Metabolic activity of insulin Glargine has been shown in pharmacodynamic studies to last for 22 (Lepore 2000) and 30 (Heinemann 2000) hours and to have no peak (Lepore 2000). Different from this time course of action, NPH Insulin, currently the most widely used basal-insulin, reaches a peak between 4 and 8 hours with a duration of action of 12 to 14 hours (Lepore 2000). Variation among subjects in the rates of glucose infusion required to maintain euglycaemia after injection has also been found to be lower with insulin Glargine than with both NPH and zinc insulin (Lepore 2000).
Compared to human insulin, the amino acid threonin at position 30 of the B-region has been omitted and a fatty acid acylated to lysin at position B 29 in insulin Detemir. These modifications lead to a self association at the injection site and allow insulin Detemir to reversibly bind to the fatty acid binding sites of albumin. Both of these mechanisms seem to be responsible for the slow absorption from the subcutaneous tissue and thus the protracted action of this insulin analogue (Havelund 2004). Also euglycaemic clamp studies in type 1 diabetic patients showed a lower degree of intra patient variability of action compared with NPH Insulin and Insulin Glargine (Heise 2004).
Based on the altered time-action profiles of these insulin analogues, different possible advantages in the therapy of diabetic patients were suggested. For instance it was proposed that a lower HbA1c could be achieved with a simultaneous lower risk of hypoglycaemia due to the longer action (lower fasting plasma glucose) and the less pronounced peak (less hypoglycaemia especially during the night). It was also hypothesised that use of Insulin Glargine or Detemir could improve the patient's quality of life and treatment satisfaction.

Comparing human insulin with insulin analogues has shown a higher mitogenic potency and IGF binding affinity for some representatives of the group of insulin analogues in in vitro and animal studies (Grant 1993; Jorgensen 1992; King 1985; Kurtzhals 2000). These effects differ among the individual insulin analogues and results provided from these studies cannot clarify the relevance for patients with diabetes mellitus. The American and the European pharmaceutical registration agencies FDA and EMEA (EMEA 2003; EMEA 2004; FDA 2000; FDA 2005) have commented on the mitogenic and carcinogenic potency of long-acting insulin analogues and conclude that the detrimental effects seems to be low; however; it must be noted that the clinical relevance for patients remains unknown.

Several studies have evaluated the clinical efficacy of insulin Glargine and insulin Detemir in the treatment of patients with type 2 diabetes mellitus. Also several reviews on this subject have been conducted. These reviews considered either only glargine (CCOHTA_Glargine 2004; Dunn 2003; National 2002; Rosenstock 2005) or insulin detemir (CCOHTA_Detemir 2004; Chapman 2004) or were published before new studies on these new insulin analogues became available.

While from their pharmacokinetic profile, long acting insulin analogues appear to be a big improvement in the insulin therapy of patients with diabetes mellitus, their superiority in the clinical setting has still to be proven. The aim of this work is to systematically review the clinical efficacy and safety of insulin glargine and detemir in the treatment of patients with type 2 diabetes mellitus.

OBJECTIVES

To assess the advantages or disadvantages of long term treatment in patients with type 2 diabetes mellitus with long acting insulin analogues currently insulin glargine and insulin detemir compared to NPH Insulin (isophane insulin human).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised controlled trials with parallel or cross-over design, blinded or open with a duration of 24 weeks or longer. Reports of which no full publication exists will only be considered for inclusion in this review if the information available would allow for a publication in accordance with all criteria of the CONSORT statement.

Types of participants

People with type 2 diabetes mellitus of either gender and any age.

Types of intervention

Comparison of long acting insulin analogues (insulin glargine and insulin detemir) to NPH insulin. In case of a combination therapy (long acting analogue combined with another anti hyperglycaemic drug) the additional anti hyperglycaemic agent has to be part of

each treatment arm. Only studies reporting on insulin schemata with subcutaneous application will be considered for inclusion in this review.

Types of outcome measures

Outcomes of interest are.

Primary outcome measure

"Number of overall, severe and nocturnal hypoglycaemia
"Glycaemic control as measured by HbA1c

Secondary outcome measure

"Mortality (total, diabetes specific and cardiovascular)
"Cardiovascular morbidity (e.g. myocardial infarction, stroke, heart failure, revascularization procedures)
"Diabetic late complications: renal failure, amputation, blindness or worsening of retinopathy
"Quality of life measured with a validated instrument
"Adverse events
"Costs

Co-Variants thought to be effect modifiers: Is the anti hyperglycaemic therapy scheme comparable?

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Published studies will be identified through a literature search using the Cochrane Library (including the Cochrane Controlled Trials Register), MEDLINE, EMBASE, and the CRD Databases (DARE, NH SEED, HTA) via Ov id Web Gateway. We will use the search strategy as listed below. The search strategies will be adapted for the other databases.

1. glargin$.ti,ab,ot,tn,sh.
2. (Gly$A21 or A21Gly$ or (gly$ adj1 A21)).ti,ab,ot.
3. (Arg$B31 or B31Arg$ or (arg$ adj1 B31)).ti,ab,ot.
4. (Arg$B32 or B32Arg$ or (arg$ adj1 B32)).ti,ab,ot.
5. (HOE-901 or HOE901).ti,ab,ot,tn.
6. Lantus$.ti,ab,ot,tn.
7. (glargin$ or 160337-95-1).rn.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. detemir$.ti,ab,ot,tn,sh.
10. (Lys$B29 or B29Lys$ or (lys$ adj1 B29)).ti,ab,ot.
11. (Ala$B30 or B30Ala$ or (ala$ adj1 B30)).ti,ab,ot.
12. (NN-304 or NN304).ti,ab,ot,tn.
13. Levemir$.ti,ab,ot,tn.
14. (detemir$ or 169148-63-4 or 201305-44-4 or 270588-25-5).rn.
15. 9 or 10 or 11 or 12 or 13 or 14
16. 8 or 15
17. (insulin$ adj6 (analog$ or derivat$)).ti,ab,ot.
18. (longacting adj6 insulin$).ti,ab,ot.
19. ((long$ or delayed$ or slow$ or ultralong$) adj1 (acting or action) adj6 insulin$).ti,ab,ot.
20. ((novel or new) adj6 insulin$).ti,ab,ot.
21. 17 or 18 or 19 or 20
22. exp insulin/aa
23. exp Insulin Derivative/
24. 22 or 23
25. 21 or 24
26. exp Diabetes Mellitus/
27. diabet$.ti,ab,ot.
28. mellitu$.ti,ab,ot.
29. IDDM.ti,ab,ot.
30. MODY.ti,ab,ot.
31. NIDDM.ti,ab,ot.
32. (T1DM or T2DM or ((T1 or T2) adj1 DM)).ti,ab,ot.
33. (insulin$ depend$ or insulin?depend$ or noninsulin$ or noninsulin?depend$).ti,ab,ot.
34. ((matury or late) adj onset$ adj6 diabet$).ti,ab,ot.
35. (typ$ adj6 diabet$).ti,ab,ot.
36. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. exp Diabetes Insipidus/
38. insipid$.ti,ab,ot.
39. 37 or 38
40. 26 or 36
41. 40 or (27 not (39 not 40))
42. controlled clinical trial.pt.
43. controlled clinical trials/
44. randomized controlled trial.pt.
45. randomized controlled trials/
46. random allocation/
47. cross-over studies/
48. double-blind method/
49. single-blind method/
50. 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51. ((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).ti,ab,ot.
52. ((random$ or cross-over or crossover) adj25 (trial$ or study or studies or intervention$ or investigat$ or experiment$ or design$ or method$ or group$ or evaluation or evidenc$ or data or test$ or condition$)).ti,ab,ot.
53. (random$ adj25 (cross over or crossover)).ti,ab,ot.
54. 51 or 52 or 53
55. 50 or 54
56. exp meta-analysis/
57. meta analysis.pt.
58. (metaanaly$ or meta analy$).ti,ab,ot.
59. 56 or 57 or 58
60. exp biomedical technology assessment/
61. hta.ti,ab,ot.
62. ((biomed$ or health$) adj6 technolog$ adj6 assessment$).ti,ab,ot.
63. 60 or 61 or 62
64. exp "Review Literature"/

65. ((review$ or search$) adj25 (medical databas$ or medline or pubmed or embase or cochrane or systemat$)).ti,ab,ot.
66. 64 or 65
67. addresses.pt.
68. bibliography.pt.
69. biography.pt.
70. "case reports".pt.
71. "clinical conference".pt.
72. comment.pt.
73. "conference abstract".pt.
74. "conference paper".pt.
75. congresses.pt.
76. "consensus development conference nih".pt.
77. "consensus development conference".pt.
78. dictionary.pt.
79. directory.pt.
80. editorial.pt.
81. festschrift.pt.
82. "historical article".pt.
83. interview.pt.
84. lectures.pt.
85. "legal cases".pt.
86. legislation.pt.
87. letter.pt.
88. "newspaper article".pt.
89. note.pt.
90. "patient education handout".pt.
91. "periodical index".pt.
92. "review of reported cases".pt.
93. "technical report".pt.
94. or/67-93
95. exp Animals/
96. exp animal/
97. exp animals/
98. "animal experiment".sh.
99. or/95-98
100. exp Humans/
101. exp human/
102. 100 or 101
103. 99 not 102
104. cn$.an.
105. (16 or 25) and 41
106. 55 not (94 or 103)
107. 59 or 63 or 66
108. 105 and (106 or 104)
109. 105 and 107

There will be no language restrictions.

Handsearches

Handsearching will be done by using cross-references from original articles and reviews.

Additional searches

Further searches for published or unpublished studies will be carried out in registries of clinical trials at http://www.clinicalstudyresults.org and http://www.clinicaltrials.gov.
We will also plan to search publicly accessible documents at the European Medicines Agency (EMEA) at http://www.emea.eu.int and the Food and Drug Administration (FDA) at http://www.fda.gov.

Information on unpublished trials will be sought from Sanofi-Aventis Pharmaceuticals (producer of insulin glargine) and Novo Nordisk (producer of insulin detemir)

METHODS OF THE REVIEW

Study selection

Two reviewers (out of KH, AS, KJ) will independently screen the title, abstract and key words of each reference identified by the search and apply the inclusion criteria. Articles that appear to fulfil the inclusion criteria will be retrieved in full. In case of disagreement between the two reviewers, the full article will be obtained and inspected independently by the two reviewers. Also, if there is doubt regarding the inclusion criteria from the information given in the title and abstract, the full article will be retrieved for clarification. Any differences in opinion will be resolved by discussion with a third reviewer. Interrater agreement will be calculated using the kappa-statistic (Cohen 1960).

Quality assessment of trials

Trials fulfilling the review inclusion criteria will be assessed independently by two reviewers to evaluate methodological quality. Interrater agreement will be calculated using the kappa-statistic (e.g. allocation concealment). Again any differences in opinion will be resolved by discussion with a third reviewer. Assessment for methodological quality will be done using a modification of the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions and the criteria of Jadad and Schulz (Jadad 1996; Schulz 1995) and will be made based on the following criteria:

1. Minimisation of selection bias: - a) was the randomisation procedure adequate? - b) was the allocation concealment adequate?
2. Minimisation of performance bias: - a) were the patients and people administering the treatment blind to the intervention?
3. Minimisation of attrition bias: - a) were withdrawals and dropouts completely described? - b) was analysis done by intention-to-treat?
4. Minimisation of detection bias: - a) were outcome assessors blind to the intervention?

Based on these criteria, studies will be subdivided into the following three categories as set forth by the Cochrane Handbook:
A - all quality criteria met: low risk of bias.

B - one or more of the quality criteria only partly met: moderate risk of bias.
C - one or more criteria not met: high risk of bias.

For the purpose of the analysis in this review, trials will be included if they meet the criteria A, B or C according to the Handbook (Clarke 1998; Kunz 1998) (see also sensitivity analysis below). Although individual quality criteria will be investigated.

Quality assessment of trials
Data from each included study will be extracted by two independent reviewers using a standard data extraction form. The data extraction form will be headed by the identification of the trial, the name of the first author, the year in which the trial was first published and will contain the following items:

(1) General Information:
a) Title of article
b) First Author
c) Publication date
d) Journal
e) Country / region in which the trial was conducted
f) Language of publication
g) Source of funding
h) Institutional affiliation
i) Contact information
j) Name of reviewer
k) Date of data extraction
l) Notes
m) Internal ID

(2) Verification of study eligibility

(3) Study characteristics
a) Question
b) Hypothesis
c) Design
d) Setting
e) Duration of observation
f) Primary Outcomes
g) Secondary outcomes
h) Power calculation
i) Statistical methods
j) Randomisation
k) Concealment of allocation
l) Blinding (participants, people administering treatment, outcome assessors)

(4) Intervention
a) Intervention
b) Intervention 2 (if applicable)
c) Control
d) Similarity of concomitant medication

(5) Patient characteristics
a) Inclusion and exclusion criteria
b) Baseline characteristics (age, sex, HbA1c, duration of diabetes, diabetes related complications, BMI)
c) Similarity of groups at baseline
d) Number of patients screened
e) Number of patients randomised
f) Number of patients lost to follow-up / withdrawals
g) Number of patients included in analysis
h) Planned subgroup analyses

(6) Comments

(7) Quality assessment (low, moderate, high risk of bias)

(8) Outcomes
The measures mentioned in the outcome section and any other outcomes measured in the study will be reported.
a) Continuous data
b) Dichotomous data

Differences between the reviewers will be resolved by consensus, referring back to the original article. When necessary, information will be sought from the authors of the primary studies.

Data analysis
Exploratory data analysis will be performed on all relevant data, and summary measures will be used where appropriate. Continuous data will be expressed as weighted mean differences (WMD) and an overall WMD will be calculated. Dichotomous data will be expressed as odds ratios (OR). NNT will be calculated in certain circumstances only, with appropriate caution (Cates 2002; Moore 1999).Data analysis will be performed using Review Manager 4.2 (Cochrane software). The meta-analysis will be carried out using a fixed effects model. Heterogeneity will be tested for using the Chi square statistic, with a level of significance of $P < 0.1$. Additionally I^2 will be used to describe the percentage of the variability in effect estimates due to heterogeneity (Higgins 2002). If heterogeneity is present and a meta-analysis seems appropriate, the assumptions of a fixed effects model no longer apply, and a random effects model will be used. Possible sources of heterogeneity will be assessed by subgroup and sensitivity analyses as described below. A funnel plot or other corrective analytical methods, depending on the number of clinical trials included in the systematic review, will be used to test for publication bias and small study effects.

Subgroup analysis
We plan to perform subgroup analysis to explore the possible effect size differences for:

1. Different types of insulin analogues (Glargine vs Detemir)
2. Different additional anti hyperglycaemic therapy such as OADs (oral antidiabetic drugs) vs. insulin
3. NPH once daily vs. NPH twice daily

Sensitivity analyses
We plan to perform sensitivity analyses in order to explore the influence of the following factors on effect size:

1. Repeating the analysis excluding unpublished studies (if there are any).
2. Repeating the analysis restricting for study quality
3. Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
4. Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry versus other).

The robustness of the results will also be tested by repeating the analysis using different measures of effect size (risk difference, odds ratio etc.) and different statistical models (fixed and random effects models).

FEEDBACK

Comment to the protocol by Horvath

Summary

Page 1: The general statement "evidence for the beneficial effect of antihyperglycemic therapy is conflicting" is out of date. It is generally accepted that microvascular complications are reduced by effective glycaemic control in diabetes type 2, and there is increasing evidence for reduction of macrovascular complications if glycaemic control is established early in the course of the disease (published type 1 diabetes, ongoing large clinical studies in type 2 diabetes). There is no evidence "that different interventions carry different substance specific beneficial or adverse effects". Establishing glycaemic control in diabetes type 2 is the essential element of preventing microvascular and macrovascular complications [by early insulin therapy, in suitable clinical conditions by oral antihyperglycemic agents, and by combination treament]. The substance specific beneficial or adverse effects of the two classes of compounds (insulins versus oral antidiabetic drugs, OAD) are entirely different. Within the pharmacological group of insulins, differences are related more to the dosage form (immediate acting insulin or intermediate acting insulin) than to the specific substances (animal insulins, human insulin or insulin analogues).
The statement "firm conclusions on the effect of interventions on patient relevant outcomes cannot be drawn from the effect.... on blood glucose concentrations alone" is ambiguous because treatment to glycaemic targets is the primary objective in type 2 diabetes, the effect of achieving glycaemic control on microvascular complications is firmly established.
The statement "insulin in itself is a group of heterogeneous preparations" needs to be changed to "the insulin drug substance is used in a number of presentations of different duration of action".

Page 2: It is useful to extend the definition of insulin analogues "changing the amino acid sequence, and the physicochemical properties", because the essential element is delayed absorption due to the physicochemical change.
The definition of insulin glargine needs to iinclude "which is less soluble at the injection site, and forms an amorphous precipitate in the subcutaneous tissue which is gradually absorbed (Sandow et al 2003)". Glargine does not form crystals or microprecipitates as quoted in outdated reviews.
The statement in the last paragraph refers to human insulin as well as insulin analogues and can be worded "structural homology of human insulin to insulin like growth factor (IGF-I) has caused concern..." because the findings with high (supraphysiological) doses of human insulin in experimental preclinical studies indicate that human insulin has mitogenic activity which is dose-related, when animals are treated with excessive doses of human insulin may cause effects similar to those of IGF-I [EPAR].
The references that "IGF-I may affect the progression of retinopathy" need to be updated in view of the clinical consensus that progression of retinopathy is related to the rapid normalisation of glycaemic control, whereas the systemic and local factors involved in progression of retinopathy are not completely resolved. The specific effect of IGF-I in clinical studies (Thrailkill et al 1999) on formation of macular edema is not found with insulin analogues.
The statement "modified insulin analogues have shown a carcinogenic effect in the mammary gland of female rats" is not correct, there is only one fast acting insulin analogue [B10-Asp]-insulin which has shown such an effect and was subsequently used as the comparator for all new insulin analogues. >From the publication of Kurtzhals 2000 it is evident that all clinically used insulin analogues differ from [B10-Asp]-insulin (which has markedly prolonged residence time on the insulin receptor) by a (rate of dissociation which is similar to human insulin or even shorter. It cannot be justified to quote the evidence for the current insulin analogues in this rudimentary form. No preclinical evidence has been brought forward for the "potentially adverse properties of insulin analogues", on the contrary extensive clinical testing and post-marketing surveillance reporting has shown no evidence for either increased mitogenic efficacy in patients, or for progression of retinopathy and related events (retinal bleeding).
The proposed aim of the Cochrane review is to review clinical efficacy and safety. In this context, reference to the "increased mitogenic potential" should be discontinued because the scientific evidence has been evaluated by the competent authorities (EMEA and FDA), and periodic safety updates are evaluated which do not provide evidence or support the contentions of "increased mitogenic potential" in the therapeutic dose range used for both type 1 diabetes and type 2 diabetes.
The inclusion criteria for studies with combination therapy should clearly state "long acting analogue combined with other antihyperglycemic drugs", and should not be limited to combination with one antihyperglycemic drug, because the clinical study protocols frequently included more than one orally active antihyperglycemic drug. There are also studies comparing combination treatment (NPH insulin plus OAD vs. long acting insulin analogue alone). Excluding such studies from the evaluation would create unnec-

essary bias and loss of evidence. The clinical relevance of combination treatment reflects the reality of present-day therapy. Comparing basal insulin therapy alone with combination therapy in RCT-24 studies is important for EBM assessment.
The statement "only studies reporting on insulin regiments (schemata) with subcutaneous application" should be omitted because the two long acting insulin analogues to be reviewed are approved for subcutaneous application only, both are contraindicated and unsuitable for CSII due to their physicochemical properties.

Page 3: In the primary outcome measure, it is surprising to find hypoglycaemia events first followed by glycaemic control. The clinical evidence is clearly that improving and maintaining glycaemic control is the key objective in type 2 diabetes (as well as in type 1 diabetes). Prevention or a delay of progression of microvascular and macrovascular complications follows from treatment to close hypoglycemic targets, as defined by IDF, ADA and National Diabetes Societies. The key issue is whether glycaemic control can be achieved to the same extent as by conventional NPH insulin, and whether the risk of hypoglycemic events can be reduced by new treatment regimens, using long acting insulins alone, combination with orally active antidiabetic drugs (OAD), and early insulinisation.
For the secondary outcome measure, it is suggested to evaluate first the evidence for reduced microvascular complications. This may be followed by evaluation of reduction of macrovascular complications, for which supporting evidence from studies of "duration of 24 weeks or longer" (Page 2) cannot be expected at the present time, because longer observation periods are clearly required, as is well-established from similar long term observations in diabetes type 1.

References: Concerning the "additional references" on pages 6 and 7 of the protocol, it is suggested to update this reference list considerably because much of the recent evidence for effective treatment of type 2 diabetes and related studies in type 1 diabetes and the effect on microvascular/macrovascular complications needs to be included.
It is proposed to omit reference to the "increased mitogenicity" arguments, or to include an updated and comprehensive discussion of the topic with relevant contemporary references. [Reference and reprints forwarded by separate mail]

Author's reply

Many thanks for your comments on this important topic.

Regarding the first comment, we will not make any changes because our interpretation of the statement that the "evidence for the beneficial effects of antihyperglycemic therapy is conflicting" is based on the currently published results of randomised controlled trials dealing with drugs that lower blood glucose.
According to your suggestions, we will extend the definition of insulin analogues and provide a more precise definition of insulin glargine.

Though the content of the paragraph about carcinogenicity and mitogenic potency is correct, we have rephrased it to make it more comprehensive.

Our review will aim to assess advantages or disadvantages of long-acting insulin analogues as compared to NPH insulin. To detect any differences between both treatment arms any additional antihyperglycaemic agents have to be part of each treatment group.

We do not understand the comment that our statement "only studies reporting on insulin regimens with subcutaneous application" should be omitted because e.g. studies using inhalative insulin as additional treatment in both groups will be excluded as well.

Concerning the criticism of the ranking of our outcome measures, it was the decision reached by consensus of all protocol authors in terms of patient-relevant endpoints.

Contributors

Prof Dr Juergen Sandow. Submitter has modified conflict of interest statement: I am a member of the diabetes research group at Sanofi Aventis.

POTENTIAL CONFLICT OF INTEREST

The research group performed several studies in short and long acting insulin analogues with the companies Sanofi-Aventis, Eli Lilly, Novo Nordisk. TR Pieber was or is currently a paid consultant for these companies.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Department of Internal Medicine, University Hospital Graz; Institute for Medical Informatics, Statistics and Documentation, University of Graz AUSTRIA

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COVER SHEET

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