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CADTH Reference List

Switching from Reference to Biosimilar Insulin Lispro for Patients with Diabetes Mellitus (Type 1 or 2)

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Summary of Abstracts

CADTH

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Key Message

- One randomized controlled trial was identified regarding the clinical effectiveness of switching from reference to biosimilar insulin lispro in adult or pediatric patients with diabetes mellitus (Type 1 or 2).

Research Question

What is the clinical effectiveness of switching from reference to biosimilar insulin lispro in adult or pediatric patients with diabetes mellitus (Type 1 or 2)?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was insulin lispro biosimilars. No filters were applied to limit the retrieval by study type. Conference abstracts were excluded from the search results. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2016 and February 9, 2021. Internet links were provided, where available.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. The Overall Summary of Findings was based on information available in the abstracts of selected publications.

Table 1: Selection Criteria

Criteria	Description
Population	Patients (any age) with diabetes mellitus (Type 1 or 2)
Intervention	Switching from reference insulin lispro (i.e., Humalog) to biosimilar insulin lispro (i.e., Admelog)
Comparator	Continuous use of reference insulin lispro; pre/post switch comparisons
Outcomes	Effectiveness (e.g., change in disease severity, disease complications, health-related quality of life) and safety (e.g., adverse events, withdrawal due to adverse event)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

Results

One randomized controlled trial was identified regarding the clinical effectiveness of switching from reference to biosimilar insulin lispro in adult or pediatric patients with diabetes mellitus (Type 1 or 2).[1] No relevant health technology assessments, systematic reviews, or non-randomized studies were identified.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

Overall Summary of Findings

One crossover randomized controlled trial[1] assessed the safety of switching between reference insulin lispro and biosimilar insulin lispro administered by continuous subcutaneous insulin infusion pumps for patients with type 1 diabetes. Patients were randomized

to receive the reference or biosimilar for 4 weeks, then switched to the other treatment for 4 weeks.[1] The number of patients reporting at least one infusion set occlusion (ISO) was low in both treatment groups, and the estimated difference in ISO risk was not significantly different between groups.[1] The event rate of hypoglycemia and the percentage of patients who experienced any treatment-emergent adverse events were also similar between treatment groups.[1]

References

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

Crossover Study Assessing Insulin Lispro Administered by Continuous Subcutaneous Insulin Infusion Pump

1. Thrasher J, Surks H, Nowotny I, et al. Safety of insulin lispro and a biosimilar insulin lispro when administered through an insulin pump. *J Diabetes Sci Technol*. 2018 05;12(3):680-686.
PubMed: PM29359575

BACKGROUND: SAR342434 (U100; SAR-Lis; insulin lispro) is a biosimilar/follow-on to insulin lispro (U100; Ly-Lis). Similar pharmacokinetics/pharmacodynamics between the two products has been demonstrated in a hyperinsulinemic euglycemic clamp study. **The current study evaluated the safety of SAR-Lis and Ly-Lis when administered by continuous subcutaneous insulin infusion (CSII; insulin pumps).** METHODS: **This was a randomized, open-label, 2 x 4-week, two-arm crossover study in 27 patients with type 1 diabetes mellitus (NCT02603510). The main outcome was the incidence of infusion set occlusions (ISOs), defined as failure to correct hyperglycemia (plasma glucose >=>= 300 mg/dl) by 50 mg/dl within 60 minutes by insulin bolus via the pump. Secondary outcomes included intervals between infusion set changes, treatment-emergent adverse events (TEAEs) including infusion site, hypersensitivity reactions and hypoglycemic events, and safety.** RESULTS: **The number of patients reporting at least one ISO was small: 6/25 patients on SAR-Lis reported 14 ISOs and 4/27 on Ly-Lis reported nine ISOs. The estimated difference in ISO risk for SAR-Lis versus Ly-Lis was 7.9% (95% CI, -1.90 to 17.73).** Mean interval between infusion set changes for any reason was similar with SAR-Lis (3.09 days) and Ly-Lis (2.95 days). **The event rate (events/patient-month) of any hypoglycemia was similar with SAR-Lis (7.15) and Ly-Lis (7.98), as was the percentage of patients who experienced any TEAE (12.0% and 14.8%).** CONCLUSION: Both SAR-Lis and Ly-Lis were well tolerated by patients using insulin pumps. **The results do not suggest a clinically significant difference in the risk of ISO between SAR-Lis and Ly-Lis when used in CSII.**

Non-Randomized Studies

No literature identified.

Appendix 1: References of Potential Interest

Systematic Reviews and Meta-analyses

Alternative Intervention – Not Specific to Insulin Lispro and Not Switching

2. Ampudia-Blasco FJ. Biosimilars and novel insulins. *Am J Ther*. 2020 Jan/Feb;27(1):e52-e61.
PubMed: PM31764128

BACKGROUND: Insulin therapy is the mainstay of treatment for type 1 diabetes and may be necessary in type 2 diabetes. Current insulin analogues present a more physiological profile, are effective, and with less risk of hypoglycemia, but they are expensive. Biosimilar insulins should offer the advantages of insulin analogues at reduced costs. In addition, current rapid-acting insulin analogues are not fast enough to control excessive postprandial glucose excursions in many patients. AREAS OF UNCERTAINTY: Biosimilar insulins demonstrated that are safe and effective, but interchangeability and automatic substitution remain an issue. Ultrafast-acting insulins should reduce postprandial hyperglycemia and improve flexibility in insulin dosing. DATA SOURCES: This systematic review was conducted following widely recommended methods. We searched for each topic in Medline, Embase, the Cochrane Library, and SCISEARCH for relevant citations for the appropriate period. THERAPEUTIC ADVANCES: LY2963016 and MK-1293 are biosimilar insulins of insulin glargine, and SAR342434 is a biosimilar of insulin lispro. The abbreviated developed program demonstrated comparable efficacy and safety and supports their use for treatment of people with diabetes but no interchangeability. Faster-acting insulin aspart is a new formulation of insulin aspart with accelerated subcutaneous absorption. Faster aspart demonstrated noninferiority in reducing HbA1c as compared to insulin aspart with superiority in controlling postprandial hyperglycemia without increasing hypoglycemia, and flexible insulin dosing. CONCLUSIONS: Biosimilar insulins have comparable PK-PD profiles and equivalent efficacy and safety to original insulins at a lower price, making them available for more people with diabetes. Faster aspart is the first ultrafast-acting insulin. New upcoming clinical trials and more clinical experience with faster aspart will show the real potential of this new insulin.

3. Tieu C, Lucas EJ, DePaola M, Rosman L, Alexander GC. Efficacy and safety of biosimilar insulins compared to their reference products: a systematic review. *PLoS ONE*. 2018;13(4):e0195012.
PubMed: PM29668697

IMPORTANCE: For nearly a century, no generic form of insulin has been available in the United States. However, the first biosimilar insulin, Basaglar, was approved by the U.S. Food and Drug Administration in 2015, and subsequently Admelog and Lusduna in 2017. OBJECTIVE: To summarize the scientific evidence comparing the safety, efficacy, pharmacokinetics, and pharmacodynamics of biosimilar and reference insulin products. DATA SOURCES: We conducted a systematic review using PubMed, Cochrane, Embase, Latin America and Caribbean Health Sciences, South Asian Database of Controlled Clinical Trials, and IndiaMED from their inception through January 14, 2018. STUDY SELECTION: We included randomized controlled trials (RCTs) comparing safety, clinical efficacy, pharmacokinetics and pharmacodynamics of any biosimilar insulin with a reference product in adults regardless of sample size and location. DATA EXTRACTION AND SYNTHESIS: Two researchers independently reviewed all titles, abstracts and text; extracted data; and performed quality assessments. MAIN OUTCOMES AND MEASURES: Efficacy, safety, pharmacokinetics, and pharmacodynamics of biosimilar and reference insulin products. RESULTS: Of 6945 articles screened, 11 studies were included in the data synthesis. LY2963016, Basalog, Basalin, and MK-1293 were compared to Lantus while SAR342434 was compared to Humalog. Three trials enrolled healthy volunteers, five enrolled type 1 diabetics, and two enrolled type 2 diabetics. One study enrolled both healthy and type 1 diabetics. Of the eleven studies, six examined pharmacokinetic and/or pharmacodynamic parameters and five examined clinical efficacy and immunogenicity. All studies included adverse events. All PK and/or PD studies showed that comparable parameters of biosimilar and reference products were within the pre-specified equivalence margins. Clinical studies suggested similar clinical efficacy and immunogenicity. Adverse events were similar between the groups across all studies. CONCLUSIONS AND RELEVANCE: Few published studies have compared biosimilar and reference insulins, though those that did suggest that the biosimilars have comparable safety and clinical efficacy as its reference product.

4. Yamada T, Kamata R, Ishinohachi K, et al. Biosimilar vs originator insulins: systematic review and meta-analysis. *Diabetes Obes Metab*. 2018 07;20(7):1787-1792.
PubMed: PM29536603

Biosimilar insulins have expanded the treatment options for diabetes. We compared the clinical efficacy and safety of biosimilar insulins with those of originator insulins by conducting a meta-analysis. A random-effects meta-analysis was performed on randomized controlled trials comparing biosimilar and originator insulins in adults with diabetes. Studies were obtained by searching electronic databases up to December 2017. Ten trials, in a total of 4935 patients, were assessed (2 trials each on

LY2963016, MK-1293, Mylan's insulin glargine and SAR342434, and 1 trial each on FFP-112 and Basalog). The meta-analysis found no differences between long-acting biosimilar and originator insulins with regard to reduction in glycated haemoglobin at 24 weeks (0.04%, 95% confidence interval [CI] -0.01, 0.08; P for efficacy = .14, I² = 0%) or at 52 weeks (0.03%, 95% CI -0.04, 0.1), or reduction in fasting plasma glucose (0.08 mmol/L, 95% CI 0.36, 0.53), hypoglycaemia (odds ratio 0.99, 95% CI 0.96, 1.03), mortality, injection site reactions, insulin antibodies and allergic reactions. Analyses stratified by type of diabetes and prior insulin use yielded similar findings. Similarly, no significant differences were found between short-acting biosimilar and originator insulins. In summary, our meta-analysis showed no significant differences in clinical efficacy and safety, including immune reactions, between biosimilar and originator insulins. Biosimilar insulins can increase access to modern insulin therapy and reduce medical costs.

Randomized Controlled Trials

Alternative Intervention – Not Switching

5. Mayorov AY, Mosikian AA, Alpenidze DN, et al. Efficacy and safety of GP40021 insulin lispro biphasic compared with Humalog Mix 25 in type 2 diabetes mellitus patients. *J Comp Eff Res.* 2021 Jan;10(1):55-66.
PubMed: PM33355484

   Aim: To compare safety (immunogenicity) and efficacy of a biosimilar insulin GP-Lis25 and a reference insulin Ly-Lis25 (Humalog Mix 25) in Type 2 diabetes mellitus (T2D) patients. Materials & methods: This randomized open-label, 26-week clinical trial enrolled 210 T2D patients, randomized 1:1 to twice-daily GP-Lis25 or Ly-Lis25. The primary end point was immune response at 26th week. Noninferiority margin for HbA1c was 0.4%. Results: Immune response frequency was similar in GP-Lis25 and Ly-Lis25 groups both at week 12 (p = 0.651) and 26 (p = 0.164). The difference of HbA1c change at week 26 was (95% CI) 0.01 (-0.27-0.28)%. Fasting plasma glucose, seven-point glucose profile and insulin dose were similar between groups. Safety did not differ between groups. Conclusion: GP-Lis25 and Ly-Lis25 demonstrated similar safety and efficacy. ClincalTrials.gov identifier: NCT04023344.

6. Derwahl KM, Bailey TS, Wernicke-Panten K, Ping L, Pierre S. Efficacy and safety of biosimilar SAR342434 insulin lispro in adults with type 2 diabetes, also using insulin glargine: SORELLA 2 Study. *Diabetes Technol Ther*. 2018 01;20(1):49-58.
PubMed: PM29232162

   BACKGROUND: SAR342434 (SAR-Lis) is a biosimilar (follow-on) of insulin lispro (U100; Humalog^R; Ly-Lis). This study aimed to show similar efficacy, safety, and immunogenicity of SAR-Lis versus Ly-Lis in adult patients with type 2 diabetes mellitus (T2DM) treated with multiple daily injections, while using insulin glargine (GLA-100; Lantus^R) as basal insulin. METHODS: SORELLA 2 was a 6-month, randomized, open-label, Phase 3 study (NCT02294474). Insulin doses were adjusted to achieve fasting and 2-h postprandial glucose targets according to American Diabetes Association guidelines. Primary endpoint was the HbA_{1c} change from baseline to week 26 (tested for noninferiority of SAR-Lis vs. Ly-Lis with a margin of 0.3%). Secondary endpoints included fasting plasma glucose (FPG), seven-point self-monitored plasma glucose (SMPG) profiles, hypoglycemic events, treatment-emergent adverse events (TEAEs), and anti-insulin antibodies (AIA). RESULTS: A total of 505 patients were randomized (1:1) to multiple daily injections of SAR-Lis (n = 253) or Ly-Lis (n = 252) plus once-daily GLA-100. Least square (LS) mean (standard error) change in HbA_{1c} from baseline to week 26 was similar in both treatment groups (SAR-Lis, -0.92% [0.051] and Ly-Lis, -0.85% [0.051]). Noninferiority at prespecified 0.3% noninferiority margin was demonstrated (LS mean difference of SAR-Lis vs. Ly-Lis: -0.07% [95% CI: -0.215 to 0.067]) as was inverse noninferiority. Similar changes in FPG, seven-point SMPG profiles, including postprandial glucose excursions and mean glucose over 24 h, and insulin dosages were observed in the two groups. Hypoglycemia, TEAEs, and AIA (incidence and prevalence) did not differ between groups. CONCLUSIONS: Results from this controlled study in patients with T2DM also using GLA-100 support similar efficacy and safety (including immunogenicity) of SAR-Lis and Ly-Lis.

7. Home P, Derwahl KM, Ziemen M, et al. Anti-insulin antibodies and adverse events with biosimilar insulin lispro compared with humalog insulin lispro in people with diabetes. *Diabetes Technol Ther*. 2018 02;20(2):160-170.
PubMed: PM29355435

   BACKGROUND: SAR342434 (SAR-Lis) is a biosimilar (follow-on) of insulin lispro (Humalog^R; Ly-Lis). Two randomized, controlled, open-label, parallel-group, phase 3 studies were conducted to compare the efficacy and safety of SAR-Lis and Ly-Lis, both in combination with insulin glargine (Lantus^R). SORELLA 1 was a 12-month study in 507 people with type 1 diabetes mellitus (T1DM); SORELLA 2 was a 6-month study in 505 people with type 2 diabetes mellitus (T2DM). In this study, the impact of anti-insulin antibodies (AIA) to SAR-Lis and Ly-Lis on safety and glycemic control is reported. METHODS: AIA were measured regularly throughout both studies at a centralized laboratory blinded to treatment

groups using a drug-specific AIA assay. The AIA status (positive or negative), AIA titers, and cross-reactivity to human insulin, insulin glargine, and insulin glargine metabolite M1 were analyzed. The potential effect of AIA on safety, particularly as related to hypersensitivity reactions, hypoglycemia, and treatment-emergent adverse events, as well as on glycemic control (HbA_{1c}, insulin dose), was evaluated. RESULTS: AIA positive status at baseline was similar for the two insulins, but higher in T1DM than in T2DM. In both studies, the percentage of people newly developing AIA in the two treatment groups, or having a >=4-fold increase in AIA titers, did not differ. No relationship was observed between maximum individual AIA titers and change in HbA_{1c} or insulin dose, hypoglycemia, or hypersensitivity reactions or between efficacy/safety measures and subgroups by presence or absence of treatment-emergent AIA. Hypersensitivity events and events adjudicated as allergic reactions were few and did not differ between the two groups. CONCLUSION: Insulin lispro SAR342434 and the originator insulin lispro had a similar immunogenicity profile in people with T1DM or T2DM.

8. Garg SK, Wernicke-Panten K, Rojeski M, Pierre S, Kirchhein Y, Jedynasty K. Efficacy and safety of biosimilar SAR342434 insulin lispro in adults with type 1 diabetes also using insulin glargine-SORELLA 1 Study. *Diabetes Technol Ther*. 2017 09;19(9):516-526.
PubMed: PM28722480

   BACKGROUND: SAR342434 is a biosimilar follow-on of insulin lispro-Humalog^R. This study aimed to show similar efficacy, safety, and immunogenicity of SAR342434 (SAR-Lis) versus insulin lispro-Humalog (Ly-Lis) in adult patients with type 1 diabetes (T1DM) treated with multiple daily injections while using basal insulin glargine (Lantus^R; GLA-100). MATERIALS AND METHODS: SORELLA-1 was a randomized, open-label phase 3 study (NCT02273180). Patients completing the 6-month main study continued on SAR-Lis or Ly-Lis, as randomized, for a 6-month safety extension. Assessments included change in HbA_{1c}, fasting plasma glucose (FPG), seven-point self-monitored plasma glucose (SMPG) profiles, hypoglycemic events, treatment-emergent adverse events (TEAEs), and anti-insulin antibodies (AIAs). RESULTS: Five hundred seven patients were randomized (SAR-Lis n = 253; Ly-Lis n = 254). Least square (LS) mean (SEM) change in glycosylated hemoglobin (HbA1c) (baseline to week 26; primary endpoint) was similar in both treatment groups (SAR-Lis: -0.42% [0.051]; Ly-Lis: -0.47% [0.050]). Noninferiority at prespecified 0.3% noninferiority margin and inverse noninferiority were demonstrated (LS mean difference of SAR-Lis vs. Ly-Lis: 0.06% [95% confidence interval: -0.084 to 0.197]). At week 52 (end of extension period) versus week 26, a small HbA1c increase was observed in both groups. FPG and seven-point SMPG profile changes, including postprandial glucose excursions, were similar between groups. At week 52, similar changes in mean daily mealtime and basal insulin doses were observed. Hypoglycemia, TEAEs, and AIAs (incidence, prevalence) did not differ between groups. CONCLUSIONS: Results from this controlled study in patients with T1DM also using GLA-100 support similar efficacy and long-term safety (including immunogenicity) of SAR-Lis and Ly-Lis.

Alternative Outcomes – Pharmacokinetics and Pharmacodynamics

9. Kapitza C, Nowotny I, Lehmann A, et al. Similar pharmacokinetics and pharmacodynamics of rapid-acting insulin lispro products SAR342434 and US- and EU-approved Humalog in subjects with type 1 diabetes. *Diabetes Obes Metab*. 2017 05;19(5):622-627.
PubMed: PM27987252

   AIM: To compare the pharmacokinetics (PK) and pharmacodynamics (PD) of 3 rapid-acting insulin lispro products: SAR342434 solution, United States (US)-approved Humalog and European Union (EU)-approved Humalog. METHODS: In a single-centre, randomized, double-blind, 3-treatment, 3-period, 6-sequence, crossover, euglycaemic clamp study (NCT02273258), adult male subjects with type 1 diabetes were randomized to receive 0.3 U/kg of SAR342434 solution, US-approved and EU-approved Humalog under fasted conditions. PK and PD (glucose infusion rate [GIR]) were assessed up to 12 hours. RESULTS: Of the 30 subjects randomized, 28 completed all 3 treatment periods. Mean concentration and GIR vs time profiles were similar for all 3 products. Exposure (INS-C_{max} , INS-AUC_{last} and INS-AUC) and activity (GIR_{max} and GIR-AUC_{0-12h}) of SAR342434, US-approved and EU-approved Humalog were similar in all comparisons (point estimates of treatment ratios, 0.95-1.03 for PK parameters and 1.00-1.07 for PD parameters), with 90% confidence intervals for the ratios of geometric least squares means within the pre-specified bioequivalence limit (0.80-1.25) and no significant differences in time-related parameters. Within-subject variability of exposure and activity was low across the 3 clamps, indicating high day-to-day reproducibility in clamp performance, irrespective of the individual product. Adverse events were similar for all 3 products. No safety concerns were noted in vital signs or in laboratory and electrocardiogram data. CONCLUSIONS: The results of this study demonstrate similarity in insulin lispro exposure profiles and PD activity of SAR342434 solution to both US- and EU-approved Humalog, and between both US- and EU-approved Humalog, supporting the use of SAR342434 solution for injection as a follow-on product.

Review Articles

Alternative Intervention – Not Switching

10. Hu J, Wang M, Zhao Y. SAR342434 - an insulin biosimilar for the treatment of type II diabetes. *Expert Opin Biol Ther*. 2018 11;18(11):1107-1112.
PubMed: PM30295083

    INTRODUCTION: The global incidence of diabetes mellitus is increasing, with a concomitant rise in individual and overall treatment costs. The development of biosimilars contributes to the facilitation of greater access to treatment. SAR342434 is a biosimilar follow-on of insulin lispro, a key therapeutic for the treatment of diabetes mellitus, and it is currently under phase III clinical trials. Areas covered: In this review we discuss the recent updates on clinical data obtained from phase III trials to compare the equivalence and similarity of SAR342434 to insulin lispro, including pharmacokinetics (PKs), pharmacodynamics, clinical efficacy, safety and immunogenicity. Expert opinion: The rising treatment costs of diabetes mellitus poses a challenge to public health enterprises worldwide. The development of biosimilars is probably a good choice to solve this conundrum. Based on the available clinical trials, it is confirmed that SAR342434 is equivalent to the reference insulin lispro, with similar pharmacodynamics, PKs, anti-hyperglycemic efficacy and safety. These attributes show the good potential of SAR342434 for serving as an alternative to achieve the glycemic control in patients with diabetes mellitus.

Alternative Intervention – Not Specific to Insulin Lispro and Not Switching

11. White J, Goldman J. Biosimilar and follow-on insulin: the ins, outs, and interchangeability. *J Pharm Technol*. 2019 35(1): 25–35.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313268/

    Objective: To provide an overview of the differences between biosimilars and generics, and to summarize regulatory requirements and outstanding issues related to biosimilar insulins in the United States, including the issue of interchangeability. Data Sources: References were obtained using MEDLINE searches, the bibliographies of articles identified during the searches, review articles, and general Internet searches. Key words included the following: diabetes, insulin, biosimilar, regulatory, follow-on, and interchangeability. Study Selection and Data Extraction: Articles, studies, regulatory documents, and opinion pieces that addressed issues around biosimilar/follow-on insulins and interchangeability of insulins in people with diabetes were selected for inclusion in this narrative review. Data Synthesis: There is understandable interest in the potential for new copies of existing insulins—termed biosimilar insulins or follow-on insulins—to reduce the substantial and growing costs associated with managing the diabetes epidemic and to improve access, as has been achieved with conventional generic drugs. However, biosimilars or follow-on insulins are not generics. There are critical differences between biologic products and conventional chemical drugs, which present specific challenges to manufacturers, regulators, and clinicians. Conclusions: Health care providers and payers need to be aware of the issues surrounding biosimilar and follow-on insulins as they become more widely available in the coming years. In particular, in the face of limited data on comparative safety and efficacy, careful consideration needs to be given when interchanging between originator and biosimilar drugs, when switching patients from one biosimilar drug to the other.