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CADTH Reference List

Switching From Reference to Biosimilar Insulin Aspart for Patients With Diabetes Mellitus (Type 1 or 2)

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Summary of Abstracts

CADTH

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Key Message

- Two randomized controlled trials were identified regarding the clinical effectiveness of switching from reference to biosimilar insulin aspart 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 aspart 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 concepts were reference insulin aspart and biosimilars. No search filters were applied to limit retrieval by study type. Conference abstracts were excluded. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2016 and November 1, 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 aspart (i.e., NovoRapid) to biosimilar insulin aspart (i.e., Trurapi)
Comparator	Continuous use of reference insulin aspart; 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

Two randomized controlled trials[1,2] were identified regarding the clinical effectiveness of switching from reference to biosimilar insulin aspart in adult or pediatric patients with diabetes mellitus (Type 1 or 2). No 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

Two randomized controlled trials were identified regarding the clinical effectiveness of switching from reference to biosimilar insulin aspart in adult or pediatric patients with diabetes mellitus (Type 1 or 2).[1-2] One open-label randomized controlled trial (i.e., GEMELLI

1 study) transitioned adult participants with diabetes (Type 1 or 2) from Novolog/NovoRapid insulin aspart (NN-Asp) or Humalog R/Liprolog R to either NN-Asp or biosimilar insulin aspart SAR341402 (SAR-Asp).[1] In a subgroup analysis of the GEMELLI 1 trial, no differences in hemoglobin A1c change, changes in insulin doses, hypoglycemia, and safety outcomes were found between those transitioned to SAR-Asp and NN-Asp at 26 and 52 weeks within the subgroup of participants originally receiving NN-Asp.[1] An open-label cross-over trial randomized adult patients with type 1 diabetes to a self-administered treatment sequence of SAR-Asp to NN-Asp or SAR-Asp NN-Asp through an insulin pump.[2] Both treatments were well tolerated by participants, with no significant difference in infusion set occlusions over a four-week treatment period.[2] Additionally, no differences in hypoglycemia, adverse-events, hypersensitivity, and injection site reactions were detected between treatments.[2]

References

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

1. Shah VN, Franek E, Wernicke-Panten K, Pierre S, Mukherjee B, Sadeharju K. Efficacy, safety, and immunogenicity of insulin aspart biosimilar SAR341402 compared with originator insulin aspart in adults with diabetes (GEMELLI 1): a subgroup analysis by prior type of mealtime insulin diabetes therapy research, treatment and education of diabetes and related disorders. *Diabetes Ther.* Feb 2021; 12(2): 557-568. PubMed: PM33432547

   INTRODUCTION: **The biosimilar SAR341402 insulin aspart (SAR-Asp) was compared to its originator NovoLog R/NovoRapid R insulin aspart (NN-Asp) in terms of efficacy, safety, and immunogenicity, in adults with type 1 or type 2 diabetes switching from different rapid-acting insulin analogs**. METHODS: **This phase 3, randomized, open-label, multinational, 52-week study (GEMELLI 1) enrolled participants with type 1 or type 2 diabetes (n = 597). At randomization, participants transitioned from NovoLog/NovoRapid (n = 380) or Humalog R/Liprolog R (n = 217) to equivalent (1:1) doses (or a dose at the discretion of the investigator) of either SAR-Asp or NN-Asp (1:1 randomization).** Participants were treated with multiple daily injections in combination with insulin glargine 100 U/mL (Lantus R). **In this subgroup analysis, efficacy measures (change in hemoglobin A1c [HbA1c], insulin dose [total, basal and mealtime]), and safety outcomes (hypoglycemia incidence, adverse events, anti-insulin aspart antibodies) of SAR-Asp were compared with those of NN-Asp separately according to the participants' prestudy mealtime insulin**. RESULTS: **At week 26 (primary efficacy endpoint), change in HbA1c was similar between SAR-Asp and NN-Asp in those participants pre-treated with NovoLog/NovoRapid (least squares [LS] mean difference - 0.04%, 95% confidence interval [CI] - 0.182 to 0.106%)** or Humalog/Liprolog (LS mean difference - 0.15%, 95% CI - 0.336 to 0.043%) (P value for treatment by subgroup interaction = 0.36). **This HbA1c response persisted over the 52 weeks of the study similarly for both treatments within each subgroup**. **In both subgroups, changes in insulin doses were similar between treatments over 26 weeks and 52 weeks, as were the incidences of severe or any hypoglycemia, adverse events (including hypersensitivity and injection site reactions), and anti-insulin aspart antibodies**. CONCLUSIONS: **Efficacy and safety (including immunogenicity) profiles of SAR-Asp are similar to those of NN-Asp over 52 weeks in adults with diabetes irrespective of prior type of mealtime insulin**.

2. Thrasher J, Polsky S, Hovsepian L, et al. Safety and tolerability of insulin aspart biosimilar SAR341402 versus originator insulin aspart (NovoLog) when used in insulin pumps in adults with Type 1 diabetes: a randomized, open-label clinical trial. *Diabetes Technol Ther.* 09 2020; 22(9): 666-673. PubMed: PM31833801

   Background: **The aim was to assess the safety and tolerability of the insulin aspart biosimilar/follow-on product SAR341402 (100 U/mL solution; SAR-Asp) and originator insulin aspart (100 U/mL; NN-Asp; NovoLog R) self-administered through an insulin pump**. Materials and Methods: **This randomized, open-label, 2 x 4-week crossover study enrolled 45 adults with type 1 diabetes (T1D)**. **Participants were randomized 1:1 to the treatment sequence SAR-Asp/NN-Asp or NN-Asp/SAR-Asp.** The basal and prandial insulin doses were individually titrated. **The primary outcome was the number of participants with at least one infusion set occlusion (infusion set change due to failure-to-correct hyperglycemia [plasma glucose >=250 mg/dL] by insulin pump bolus) during the 4-week treatment. The main**

secondary outcome was the number of participants with at least one episode of unexplained hyperglycemia (regardless of correction by an insulin pump bolus without apparent material defect, medical, dietary, insulin dosing reason, or pump problem). Results: **The number of participants reporting >=1 infusion set occlusion were similar between treatments: 14/43 on SAR-Asp (33 events) and 12/43 on NN-Asp (24 events). The estimated difference in infusion set occlusion risk for SAR-Asp versus NN-Asp was 4.1% (95% confidence interval: -9.3% to 17.4%). The number of participants with >=1 episode of unexplained hyperglycemia was similar between treatments (31/43 on SAR-Asp [154 events]; 32/43 on NN-Asp [175 events]). Hypoglycemia, treatment-emergent adverse events, hypersensitivity, and injection site reactions were similar between treatments.** Conclusions**: SAR-Asp and NN-Asp were well tolerated and had similar infusion set occlusions over a 4-week period in insulin pump users with T1D.**

Non-Randomized Studies

No literature identified.

Appendix 1: References of Potential Interest

Randomized Controlled Trials

Alternative Comparator – Not Switching

3. Karonova TL, Mayorov AY, Magruk MA, et al. Safety and efficacy of GP40071 compared with originator insulin aspart (NovoRapid R Penfill R) in Type 1 diabetes mellitus. *J Comp Eff Res.* 06 2021; 10(9): 763-775. PubMed: PM33928797

   Aim: To compare safety and efficacy of GP40071 insulin aspart (GP-Asp) and NovoRapid R (NN-Asp). Materials & methods This randomized open-label, active-controlled, 26-week non-inferiority Phase III clinical trial enrolled 264 Type 1 diabetes mellitus patients (HbA1c: 7.1-12.0%) randomized 1:1 to once daily GP-Asp (n = 132) or NN-Asp (n = 132). The primary safety end point was immune response at week 26. Results: The groups were similar in frequency of immune response (p = 0.323) and in other safety end points. Mean HbA1c change from baseline was -0.57% for GP-Asp and -0.56% for NN-Asp and did not differ between groups (p = 0.955). Intergroup mean difference of HbA1c level change (95% CI) at week 26 from baseline was 0.00 (-0.26, 0.25) %. Insulin doses, fasting plasma glucose levels and seven-point glucose profiles were similar between groups (p > 0.05). The number of patients experiencing hypoglycemic episodes did not differ between the groups (p = 0.497). Conclusion: GP-Asp demonstrated similar safety and efficacy.

4. Garg SK, Wernicke-Panten K, Wardecki M, et al. Efficacy and safety of insulin aspart biosimilar SAR341402 versus originator insulin aspart in people with diabetes treated for 26 weeks with multiple daily injections in combination with insulin glargine: a randomized open-label trial (GEMELLI 1). *Diabetes Technol Ther*. 02 2020; 22(2): 85-95. PubMed: PM31804851

   Background: This study compared the efficacy, safety, and immunogenicity of insulin aspart biosimilar/follow-on biologic product SAR341402 (SAR-Asp) with originator insulin aspart-NovoLog R/NovoRapid R (NN-Asp) in people with type 1 diabetes (T1D) or type 2 diabetes (T2D) treated with multiple daily injections in combination with insulin glargine (Lantus R; Gla-100). Materials and Methods: This 6-month, randomized, open-label, phase 3 study (NCT03211858) enrolled 597 people with T1D (n = 497) or T2D (n = 100). Participants were randomized 1:1 to mealtime SAR-Asp (n = 301) or NN-Asp (n = 296) in combination with Gla-100. The primary objective was to demonstrate noninferiority (by 0.3% margin in the intent-to-treat population) of SAR-Asp versus NN-Asp in HbA1c change from baseline to week 26. Immunogenicity was also assessed in terms of anti-insulin aspart antibody (AIA) status (positive/negative) and titers during the study. Results: HbA1c was similarly improved in both treatment groups (SAR-Asp -0.38%; NN-Asp -0.30%); the least squares mean difference at week 26 for SAR-Asp minus NN-Asp was -0.08% (95% confidence interval: -0.192 to 0.039), thus meeting the criteria for noninferiority between SAR-Asp and NN-Asp and inverse noninferiority of NN-Asp versus SAR-Asp. Changes in fasting plasma glucose and seven-point self-monitored plasma glucose profile, including postprandial glucose excursions, and insulin dosages were similar in both groups at week 26. Safety and tolerability, including AIA responses (incidence, prevalence), hypoglycemia, and adverse events (including hypersensitivity events and injection site reactions), were similar between groups. Conclusions: SAR-Asp demonstrated effective glycemic control with a similar safety and immunogenicity profile to NN-Asp in people with diabetes treated for 26 weeks.

Intervention Not Specific to NovoRapid

5. Garg SK, Wernicke-Panten K, Wardecki M, et al. Safety, immunogenicity, and glycemic control of insulin aspart biosimilar SAR341402 versus originator insulin aspart in people with diabetes also using insulin glargine: 12-month results from the GEMELLI 1 trial. *Diabetes Technol Ther*. 07 2020; 22(7): 516-526. PubMed: PM32068436

   Background: SAR341402 (SAR-Asp) is a biosimilar/follow-on of the originator insulin aspart-NovoLogR/NovoRapid R (NN-Asp). This study investigated whether the efficacy, safety, and immunogenicity findings for SAR-Asp versus NN-Asp, observed over 6 months in people with type 1 (n = 497) or type 2 diabetes (n = 100) treated with multiple daily injections in combination with insulin glargine (Lantus R), are maintained after 12 months. Materials and Methods: GEMELLI 1 was a multicenter, randomized, open-label, phase 3 study. Participants completing the initial 6-month treatment period continued on SAR-Asp or NN-Asp, as randomized, for a 6-month safety extension. Results: Of the 597 participants randomized, 264 out of 301 (87.7%) and 263 out of 296 (88.9%) assigned to SAR-Asp and NN-Asp, respectively, completed 12 months of treatment. Improved glycemic control was sustained at 12 months in both treatment groups, with similar least-squares mean reductions in glycated hemoglobin (HbA1c) from baseline (SAR-Asp: -0.25%; NN-Asp: -0.26%). Fasting plasma glucose and seven-point self-monitored plasma glucose profile changes, including postprandial glucose excursions, and changes in mealtime and basal insulin dosages were similar between groups. Safety and tolerability, including anti-insulin aspart antibodies (AIAs; incidence, prevalence, titers, cross-reactivity to human insulin), neutralizing antibodies (incidence, prevalence), hypoglycemia, and treatment-emergent adverse events (including hypersensitivity events and injection site reactions), were similar between groups. No relationship was observed between maximum individual AIA titers and change in HbA1c or insulin dose, hypoglycemia, or hypersensitivity

reactions or between efficacy/safety measures and subgroups by presence or absence of treatment-emergent AIA.
Conclusions: SAR-Asp and NN-Asp demonstrated similar efficacy and safety (including immunogenicity) in people with diabetes over 12 months of treatment.