A Novel Model-Based Meta-Analysis to Estimate Comparative Efficacies of 2 Drugs: an Example Using the DPP-4 Inhibitors Linagliptin and Sitagliptin in Type 2 Diabetes Mellitus

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INTRODUCTION

- It is not always feasible to conduct direct comparisons between all available treatment options for a given disease state. Indirect comparisons and network meta-analyses can be used to estimate relative efficacy when there are no direct comparative data[1,2]
- A novel approach, recently described as model-based meta-analysis (MBMA), has been developed to estimate the comparative efficacy of 2 medications. MBMA is distinguished from the methodology of conventional meta-analysis by the way in which it incorporates longitudinal and/or dose-response data. This allows the integration of information from trials of different durations/sampling timepoints, thus enabling less restrictive inclusion/exclusion criteria for study selection and more efficient use of data from the studies that are selected[3]
- The dipeptidyl peptidase (DPP)-4 inhibitors are a relatively new class of oral antihyperglycemic agents, developed for the treatment of type 2 diabetes mellitus (T2DM). Although several DPP-4 inhibitors are already available in many countries, to date only 1 published trial has been conducted to directly compare individual drugs within this class[4]

OBJECTIVE

- To develop a longitudinal statistical model to indirectly estimate the comparative efficacies of 2 drugs, using MBMA. Comparison of 2 oral DPP-4 inhibitors, sitagliptin and linagliptin, for the treatment of T2DM was used as an example

METHODS

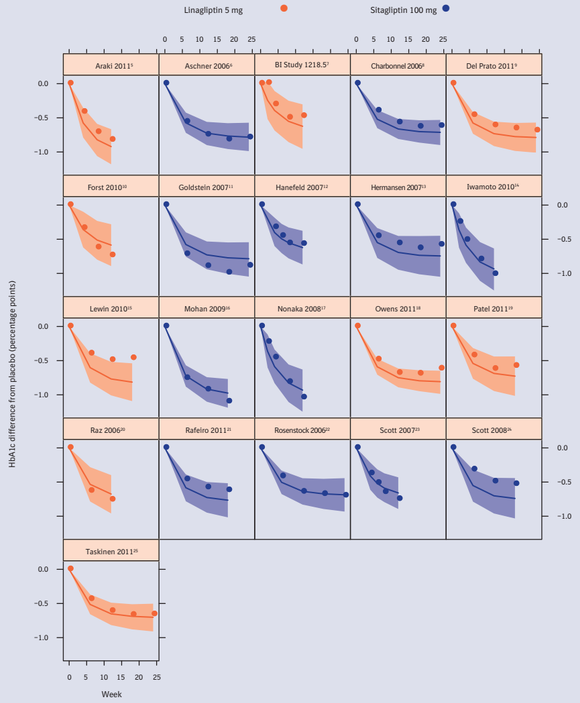
- The present study used recently proposed MBMA methodology that takes account of longitudinal correlations
- Data sources for study identification were: MEDLINE, EMBASE, publications on www.clinicaltrials.gov, the Australian and New Zealand Clinical Trial Registry, Cochrane Review of DPP-4 inhibitors for T2DM, sitagliptin trials on FDA website to December 2011, and individual patient data from manufacturer of linagliptin
- A systematic review was performed using double-blind, randomized, controlled, clinical trials of ≥12 weeks' duration. This review investigated the efficacy of sitagliptin or linagliptin, as indicated by changes in glycated hemoglobin (HbA1c), in adults with T2DM and HbA1c >7.0%, irrespective of background medication
- A Bayesian model was fitted using Markov Chain Monte Carlo methodology. The base model described HbA1c levels as function of time, dose, baseline HbA1c, washout status/duration, and race. Other covariates (e.g., age, body mass index, gender, antihyperglycemic background medication, duration of T2DM), showed no major impact on model parameters and were, therefore, not included in the final model
- For the indirect comparison, a population of 1000 patients was simulated, with a racial composition reflecting the average distribution of participants enrolled in the linagliptin trials, and a baseline HbA1c of 8.0%

RESULTS

- Initial searches returned 1066 sitagliptin and linagliptin references, of which 1005 were excluded
- After removal of duplicate records, a total of 31 sitagliptin studies were assessed for eligibility for inclusion in the analysis, and 16 were excluded on the basis that the study design did not meet the inclusion criteria. A further 10 linagliptin studies were identified
- Longitudinal mean data from 11,234 patients were included (from 15 sitagliptin and 10 linagliptin studies)
- Mean baseline HbA1c was 8.0%, with reported means for study groups ranging from 7.3% to 8.7%
- Model predictions for each individual study using the final model showed that the observed data from the studies fell mostly within the 90% prediction interval (between 5% and 95% prediction bounds), with no overall systematic over- or under-prediction (Figure 1)

RESULTS

Figure 1: *Difference from placebo values (percentage points) of the 21 studies with relevant treatment arms (i.e., studies with linagliptin 5 mg or sitagliptin 100 mg, and placebo arms) over time: comparison of observed and predicted HbA1c difference from placebo effect*

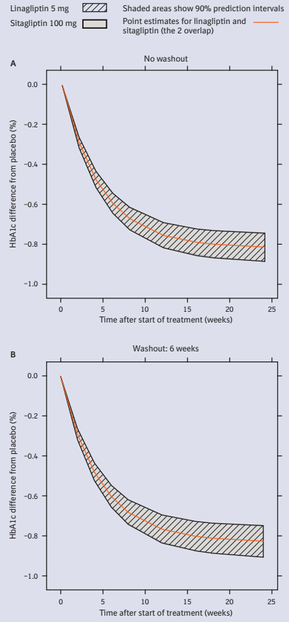


Filled dots represent observed data, shaded regions show the unconditional 90% prediction intervals, and the central line represents the median prediction

RESULTS

- Simulations generated by the model showed that both linagliptin 5 mg and sitagliptin 100 mg reduce HbA1c levels by 0.8% (placebo-adjusted) at Week 24 (credible intervals for patients without washout, −0.88 to −0.74 [both treatment groups]; and for patients with washout, −0.91 to −0.75 [linagliptin], and −0.90 to 0.75 [sitagliptin]) when administered to patients with T2DM for 24 weeks (Figure 2)
- A post hoc *t*-test was used to compare the HbA1c difference from placebo residuals (i.e., unexplained variations after fitting of the model) for linagliptin and placebo. A *P*-value of 0.14 was generated, suggesting no evidence of a systematic bias in favor of linagliptin by conventional thresholds ($P<0.05$)

Figure 2: *A. Estimated drug effects on HbA1c for reference population, with no pre-treatment washout, over 24 weeks (difference from placebo); B. Estimated drug effects on HbA1c for reference population, with 4-week washout plus 2-week placebo run-in period, over 24 weeks (difference from placebo)*



Reference population of 1000 patients, baseline HbA1c: 0.8%, racial composition: 61.5% white, 1.5% black, 37.0% Asian

CONCLUSIONS

- These findings suggest that this MBMA model provides a valid approach to indirect comparisons of the efficacy of 2 treatments, when head-to-head trials are not available
- This study represents a novel use of longitudinal MBMA in the field of diabetes treatment, being the only instance to date that adequately accounts for longitudinal correlations in each treatment arm, which is a prerequisite to the correct characterization of uncertainty in the estimation of drug effects
- The results show virtually indistinguishable efficacies of sitagliptin and linagliptin, both showing reduction in mean HbA1c of approximately 0.8%, following 24 weeks' treatment of patients with T2DM and baseline HbA1c of 8.0%, regardless of background medication
- Broadening the use of MBMA has the potential to improve the comparison of individual drug therapies, compared with older statistical methods, and could provide a new way of generating results for populations that have not been studied to date

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