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

Jorge L. Grossi, James Rogers², Dan Polhamus², William Gillespie⁴, Sanjay Patel¹, Christian Friedrich¹, Yan Gong¹, Brigitta Monz¹, Alexander Staab⁵, Silke Retlich⁶
¹Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil; ²Metrum Research Group, Tariffville, CT, USA; ³Boehringer Ingelheim, Bracknell, UK; ⁴Boehringer Ingelheim, Biberach, Germany; ⁵Boehringer Ingelheim, Ingelheim, Germany.

INTRODUCTION

To develop a longitudinal statistical model to indirectly estimate the comparative efficacies of 2 drugs, using a recent meta-analysis of published studies. The model-based meta-analysis (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 ranging from 1 week to 2 years within model predictions, thus enabling less restrictive inclusion/exclusion criteria for study selection and more efficient use of data from the studies that are available.

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 cardiovascular interventions, the Australian and New Zealand Clinical Trial Registry, Cochran Review of DPP-4 inhibitors for T2DM, sitagliptin trials or FDA website to December 2011, and individual patient data from manufacture of drug. A systematic review was performed using double random, randomized, controlled, clinical trials 1-2 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.

RESULTS

For the indirect comparison, a population of 1000 patients was simulated, with a racial composition reflecting Australia and New Zealand. SITR, the Cochran Review of DPP-4 inhibitors for T2DM, was used as reference population. The simulations show that both linagliptin 5 mg and sitagliptin 100 mg reduce HbA1c when administered to patients with T2DM for 24 weeks (Figure 2). The results show that linagliptin and sitagliptin are virtually indistinguishable in their effects on HbA1c. A post hoc analysis was used to calculate the differences from placebo and 90% confidence intervals for the difference after fitting of the model to linagliptin and placebo. The authors state that the model is a new approach that addresses the limitations of comparing the efficacies of new oral antihyperglycemic agents, and has the potential to improve the comparison of new oral antihyperglycemic agents.

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 modeling 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.

ACKNOWLEDGMENTS

This work was supported by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, and had full access to all of the primary data. All authors have seen and approved the final manuscript.

REFERENCES


Scott R, et al. DPP-4 Inhibitors in Type 2 Diabetes Mellitus: An Updated Systematic Review and Meta-Analysis. 2017 in Diabetologia. [cited 2017 Nov;doi:10.1007/s00125-017-4428-z].


Table 1: Comparisons of sitagliptin and linagliptin in T2DM patients. Significantly different from placebo; *p<0.05. All comparisons are for T2DM patients with baseline HbA1c of 8.0%, regardless of background medication.

Figure 1: Difference from placebo (%) and change from baseline (%). Points are connected by lines with 90% confidence intervals. The shaded areas show 90% prediction intervals.

Figure 2: Change from baseline in HbA1c for 1000 patients simulate, with race composition reflecting Australia and New Zealand.