Efficacy and safety of saxagliptin and metformin as initial combination therapy in patients with type 2 diabetes: a meta-analysis

Xue-Ying Tan\(^1\), Yang Lu\(^1\), Li-Ping Xuan\(^1\), Yong-Min Huang\(^1\), Jing-Bo Hu\(^2\)

\(^1\)Department of Endocrinology, Ningbo University Affiliated Yuyao Yangming Hospital, Yuyao 315400, China; \(^2\)College of Pharmaceutical Science, Zhejiang University, 866 Yuhangtang Road, Hangzhou 310058, China

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Abstract: Purpose: This meta-analysis was performed to evaluate the efficacy and safety of saxagliptin and metformin as initial combination therapy in patients with type 2 diabetes. Methods: A meta-analysis was performed to identify randomized controlled trials (RCTs) of saxagliptin plus metformin as combination therapy in patients with type 2 diabetes whose glycaemic control was insufficient after metformin monotherapy. RCTs were retrieved from PubMed, Embase, the Cochrane Library and Clinical Trials Gov through May 2015. Two people independently extracted data, including haemoglobin A1C (HbA\(_1c\)), fasting plasma glucose (FPG), weight, and adverse events, assessed search results and appraised risk of bias. Results: Five RCTs were included in this meta-analysis. Compared with metformin monotherapy, saxagliptin combined with metformin could significantly reduce HbA\(_1c\) [MD=-0.44, 95% CI (-0.71, -0.17), P<0.00001] and FPG level [MD=-0.62, 95% CI (-1.09, -0.15), P<0.00001]. Meanwhile, this combination therapy did not further decrease cardiovascular events [MD=0.96, 95% CI (0.31, 2.92), P=1.00] and increased incidence risk of hypoglycaemia [MD=3.22, 95% CI (1.10, 9.40), P=0.75]. Conclusions: Saxagliptin combined with metformin can be effective in improving glycemic control in patients with type 2 diabetes and decreasing incidence of hypoglycemia.

Keywords: Saxagliptin, metformin, type 2 diabetes, meta-analysis

Introduction

Type 2 diabetes is believed to be a chronic, progressive, and multifactorial metabolic disease defined by the presence of chronic hyperglycemia [1]. Long-term elevated blood glucose levels will cause complications of various organs, including retinopathy [2], nephropathy [3], and peripheral neuropathy [4]. Control of blood glucose is fundamental to the management of diabetes. The American Diabetes Association recommends a glycemic target of a glycosylated hemoglobin (HbA\(_1c\))<7% [5]. Lifestyle changes such as diet, exercise, and weight loss are typically recommended for patients with type 2 diabetes, but most patients still require pharmacotherapy to achieve glycemic goals.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin, linagliptin, vildagliptin, saxagliptin, and alogliptin) provide new choices for oral pharmacological therapy [6, 7]. The incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) released from the small intestine, are released in a glucose-dependent manner after food intake [8, 9]. The enhancement of GLP-1 and GIP stimulates the pancreas to secrete insulin, as well as reduces glucagon secretion and glucose production in liver [10, 11]. Saxagliptin, a DPP-4 inhibitor, improves glucose control in patients with type 2 diabetes through contributing to the increased concentration of GLP-1 and GIP [9]. Metformin is used in the clinic more than 60 years and is still recommended as the first line therapy for patients with type 2 diabetes [12-15]. Metformin lowers glucose levels through suppressing hepatic glucose production [16]. Besides, it can reduce the absorption of glucose from the gastrointestinal tract (GIT), enhance peripheral glucose uptake and increase insulin sensitivity [17, 18].
By combining their different, complementary glucose-lowering activity, saxagliptin and metformin synergistic treatment benefits patients to achieve glucose target than individual component [19-21]. Hence, we conducted a meta-analysis to assess comparative change in HbA\(_1c\), FPG and risk of hypoglycaemia of saxagliptin as add-on therapy to metformin in patients with type 2 diabetes inadequately controlled with metformin monotherapy.

Methods

Information sources and search strategy

We identified eligible studies through electronic databases, including Medline, Embase, the Cochrane Library, and Clinical Trials Gov, from inception to March 2015 using pertinent terms (saxagliptin, metformin, dipeptidyl peptidase-4 inhibitors, DPP-4 inhibitors). In addition, we hand-searched abstracts of major scientific meetings in the field of diabetes along with any associated e-posters (American Diabetes Association, Canadian Diabetes Association, European Association for the Study of Diabetes, American Association of Clinical Endocrinologists and International Diabetes Federation) from 2010 to 2015.

Study selection

In this meta-analysis, we included randomized controlled trials (RCTs) with the follow-up duration ≥12 weeks (trials with follow-up duration <12 weeks excluded), enrolling subjects with type 2 diabetes, and comparing saxagliptin plus metformin as combination therapy to metformin monotherapy. The changes in HbA\(_1c\), FPG, body weight and adverse events, including cardiovascular events, hypoglycaemia and gastrointestinal events, were investigated. Eligible studies included were no limitation with respect to language, years of publication or publication status. Studies without a control group, non-randomized grouping and retrospective trials were excluded.

Data extraction and risk of bias assessment

Trial data were independently abstracted by two reviewers and any resulting discrepancies were resolved by discussion. For each eligible trial included, we extracted data on study characteristics, baseline characteristics of participants and key efficacy and safety outcomes. The quality of included trials was assessed through Jadad criteria [22]. Assessment included the following domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting.

Data synthesis and analysis

During the study, Cochrane Collaboration’s method was used for meta-analysis. Significant heterogeneities among the studies were resolved with the random-effects model (Der-Simonian-Laird method) [23]. Otherwise, the fixed-effects model (Mantel-Haenszel method) was applied [24]. The mean difference (MD), pooled odds ratio (OR) and their 95% confidence intervals (CI) were calculated for each outcome. Cochran’s chi-squared test was used to examine heterogeneity among the included studies and \( P \), which is the proportion of the total variation due to heterogeneity between studies, was computed to determine the degree of inconsistency across studies. Heterogeneity was assessed by using \( P \) statistics, with results
### Table 1. Characteristics of RCTs included in this meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean age (years)</th>
<th>Study size</th>
<th>Combination therapy</th>
<th>Monotherapy</th>
<th>Study duration (weeks)</th>
<th>Quality score (max 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White [27]</td>
<td>55</td>
<td>160</td>
<td>Saxagliptin 2.5 mg+Metformin ≥1500 mg</td>
<td>Metformin ≥1500 mg</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Hermans [28]</td>
<td>58</td>
<td>286</td>
<td>Saxagliptin 5 mg+Metformin 1500 mg</td>
<td>Metformin 2500 mg</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Yang [29]</td>
<td>54</td>
<td>570</td>
<td>Saxagliptin 5 mg+Metformin 1500 mg</td>
<td>Metformin ≥1500 mg</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Deffronzo [30]</td>
<td>54</td>
<td>371</td>
<td>Saxagliptin 2.5 mg+Metformin 1500~2000 mg</td>
<td>Metformin 1500~2000 mg</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Fonseca [31]</td>
<td>55</td>
<td>282</td>
<td>Saxagliptin 5 mg+Metformin 1500 mg</td>
<td>Metformin 2000 mg</td>
<td>18</td>
<td>4</td>
</tr>
</tbody>
</table>
Saxagliptin plus metformin combination therapy

![Graph](image)

Figure 2. Meta-analysis for HbA1c change from baseline between saxagliptin plus metformin as combination therapy and metformin monotherapy.

![Graph](image)

Figure 3. Meta-analysis for FPG change from baseline between saxagliptin plus metformin as combination therapy and metformin monotherapy.

![Graph](image)

Figure 4. Meta-analysis for hypoglycaemia between saxagliptin plus metformin as combination therapy and metformin monotherapy.

Ranging from 0 to 100% and values of 25, 50 and 75% representing low, moderate and high levels of heterogeneity, respectively 25. The random-effect model was used when \(I^2>50\%\), whereas the fixed-effect model was used in cases where heterogeneity was not significant (\(I^2<50\%\)). A sensitivity analysis was performed, for the main analysis and for the predefined separate analyses, including also trials with zero events, using continuity correction. Publication bias was assessed using visual inspection of funnel plots and Egger's weighted regression statistics, where asymmetrical funnel plot and Egger's \(p\)-value <0.05 indicate potential publication bias [26]. All statistical analyses were performed by RevMan5.0 from Cochrane Collaboration.

**Results**

Figure 1 presented the trial flow summary. A total of 5 trials fulfilling the inclusion criteria were ultimately included in this meta-analysis [27-31]. Characteristics of the studies included in the review are presented in Table 1.

Compared with metformin monotherapy, saxagliptin plus metformin combination therapy could significantly reduce HbA1c (MD=-0.44, 95% CI (-0.71, -0.17), \(P<0.00001\); heterogeneity \((I^2=100\%)\), Figure 2] and FPG [MD=-0.62, 95% CI (-1.28, -0.13), \(P<0.001\); heterogeneity \((I^2=100\%)\), Figure 3].
Saxagliptin plus metformin combination therapy

Figure 5. Meta-analysis for cardiovascular events between saxagliptin plus metformin as combination therapy and metformin monotherapy.

Figure 6. Meta-analysis for gastrointestinal adverse reactions between saxagliptin plus metformin as combination therapy and metformin monotherapy.

CI (-1.09, -0.15), P<0.00001, heterogeneity (I²=100%), Figure 3.

There was no statistical difference in the incidence rate of hypoglycaemia between saxagliptin plus metformin and metformin monotherapy [MD=3.22, 95% CI (1.10, 9.40), P=0.75, I²=0%, Figure 4]. Consistently, saxagliptin combined with metformin did not further reduce adverse cardiovascular events [MD=0.96, 95% CI (0.31, 2.92), P=1.00, I²=0%, Figure 5] compared to metformin monotherapy. Gastrointestinal adverse effects were also assessed in this meta-analysis, and it was found that no increased risk of gastrointestinal adverse reactions were seen between saxagliptin plus metformin as combination therapy and metformin monotherapy [MD=0.72, 95% CI (0.31, 1.64), P=0.70, I²=0%, Figure 6].

Discussion

This meta-analysis demonstrated that saxagliptin and metformin combination therapy significantly improves glucose control in patients with type 2 diabetes compared with metformin monotherapy. Combination therapy has greater reduction in HbA₁c and FPG than metformin monotherapy, and does not increase the incidence of various adverse reactions.

In summary, saxagliptin, a selective DPP-4 inhibitor, is recommended as an adjuvant therapy to achieve ideal glucose targets in patients with type 2 diabetes [32]. It has demonstrated that saxagliptin is weight neutrality and low risk for hypoglycemia when used as monotherapy [33]. Saxagliptin plus metformin combination therapy provides a complementary mechanism of action. This combination therapy provides further decrease in HbA₁c from baseline, and permit more patients to achieve HbA₁c goal than the individual component [19, 20, 34]. In addition, saxagliptin probably be suitable alternative for subjects with type 2 diabetes who cannot take metformin, and reduce cardiovascular risk, especially for patients with heart disease.

One randomized, double-blind, placebo-controlled study [30] was performed to assess the efficacy of saxagliptin, with different daily dose, plus a stable dose of metformin in subjects type 2 diabetes. This trial demonstrates that the therapy of saxagliptin combined with metformin was well tolerated and significantly improved glycemic indexes in patients inadequately controlled with metformin alone. Some other trials [27-29, 31] obtained the same conclusion that saxagliptin plus metformin combi-
Saxagliptin plus metformin combination therapy

nation therapy was an effective and safe treatment for patients not achieving glycemic goal.

Patients with diabetes usually have high cardiovascular risks and some antidiabetic agents also probably increased incidence rate of cardiovascular events in patients [35]. Recently, in consideration of certain antidiabetic agent with additional cardiovascular risks, the Food and Drug Administration asks for all the new developed diabetes drugs to present cardiovascular risks [36]. This study demonstrated that saxagliptin combined with metformin didn’t increase cardiovascular risks compared with metformin monotherapy, and even contributed to the reduced incidence of cardiovascular events. Compared with younger patients with type 2 diabetes, elderly patients usually are more likely to get hypoglycaemia [37]. DPP-4 inhibitors have good safety profile, such as low risk of hypoglycaemia [38]. Accordingly, there was no significant difference in reductions of HbA1c from baseline between elderly and younger patients receiving saxagliptin [39], which demonstrated good safety and tolerance in elderly patients.

There were some potential limitations in this study. Only five trials investigating efficacy and safety of saxagliptin combined with metformin were identified in this study [27-31]. Hence, more evidence is needed to further confirm clinical value of saxagliptin and metformin combination therapy. In addition, the efficacy of saxagliptin monotherapy and in combination with other oral antidiabetic agents was not considered in this study.

Conclusion

Saxagliptin combined with metformin can be effective in improving glycemic control in patients with type 2 diabetes and decreased incidence of hypoglycemia. More high-quality RCTs are demanded to evaluate long-term safety and efficacy of saxagliptin combination with metformin in future.

Disclosure of conflict of interest

None.

Address correspondence to: Xue-Ying Tan, Department of Endocrinology, Ningbo University Affiliated Yuyao Yangming Hospital, Yuyao 315400, China. E-mail: tanxueying@163.com; Jing-Bo Hu, College of Pharmaceutical Science, Zhejiang University, 866 Yuhangtang Road, Hangzhou 310058, China. E-mail: hujiaabo@zju.edu.cn

References

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[34] Boulton DW, Smith CH, Li L, Huang J, Tang A, LaCreta FP. Bioequivalence of saxagliptin/metformin extended-release (XR) fixed-dose combination tablets and single-component saxagliptin and metformin XR tablets in healthy

[35] Frederich R, Alexander JH, Fiedorek FT Dono-
van M, Berglind N, Harris S, Chen R, Wolf R,
Mahaffey KW. A systematic assessment of car-
diovascular outcomes in the saxagliptin drug
development program for type 2 diabetes.

[36] Goldfine AB. Assessing the cardiovascular
2008; 359: 1092-5.

[37] Rosenstock J. Management of type 2 diabetes
in the elderly: special considerations. Drugs
Aging 2001; 18: 31-44.

[38] Paolisso G, Monami M, Marfella R, Rizzo MR,
Mannucci E. Dipeptidyl peptidase-4 inhibitors
in the elderly: more benefits or risks? Adv Ther

[39] Doucet J, Chacra A, Maheux P Lu J, Harris S,
Rosenstock J. Efficacy and safety of saxagliptin
in older patients with type 2 diabetes mellitus.